The Development of Novel Organocatalytic and Transition-Metal Catalysed Methodologies for Amide Bond Formation

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The Development of Novel Organocatalytic and Transition-Metal Catalysed Methodologies for Amide Bond Formation

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requirements for the degree of Doctor of Philosophy

By

Christopher G. McPherson

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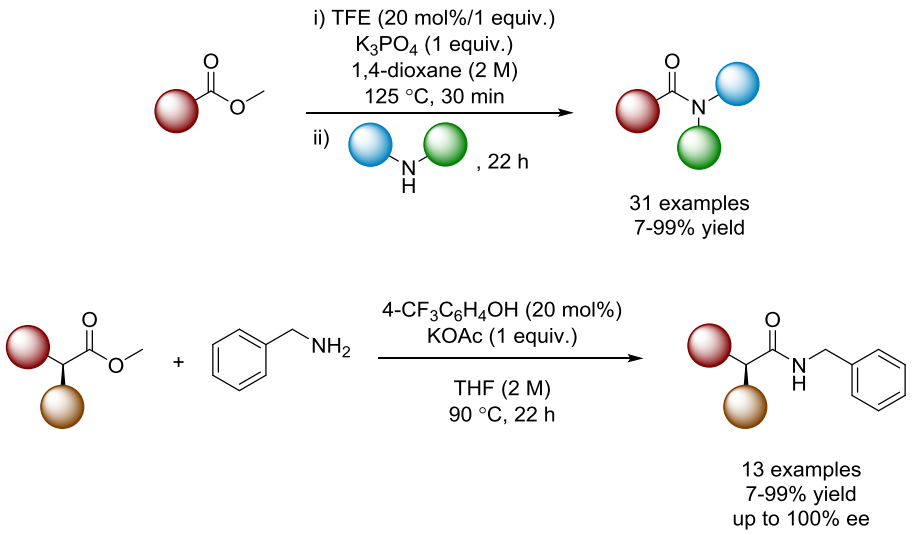
Abstract

With the formation of amide bonds being one of the most widely performed reactions within organic chemistry, highly efficient and atom economical approaches enabling the transformation are desired. Traditional methodologies, in which a stoichiometric coupling reagent is utilised, although efficient, have several inherent drawbacks hindering their general applicability, including stoichiometric by-product formation, low atom economy and poor cost effectiveness. Therefore, the development of atom economical catalytic approaches to facilitate the facile synthesis of amide bonds would successfully address the aforementioned outstanding issues.

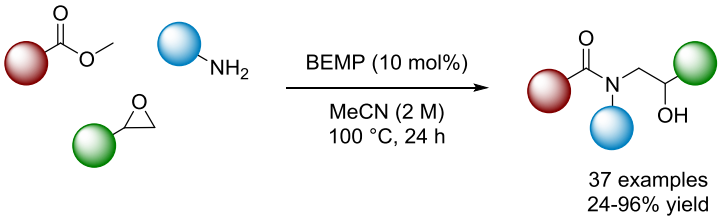
Building upon previous research performed within the Jamieson group, one such approach is the trifluoroethanol-catalysed amidation of unactivated ester derivatives. However, in the initial studies, the general applicability of this methodology was limited by the incompatibility of acyclic secondary amines under the reaction manifold, and additionally, stereoerosion when the use of α-stereogenic ester substrates was examined. Further optimisation of the progenitor conditions successfully addressed these limitations, allowing the synthesis of a diverse range of acyclic tertiary amides and chiral secondary amides, with the latter synthesised in good to excellent levels of stereoretention (Scheme 1.1).



Scheme 1.1: Formation of tertiary and chiral amides from unactivated esters using second generation conditions.

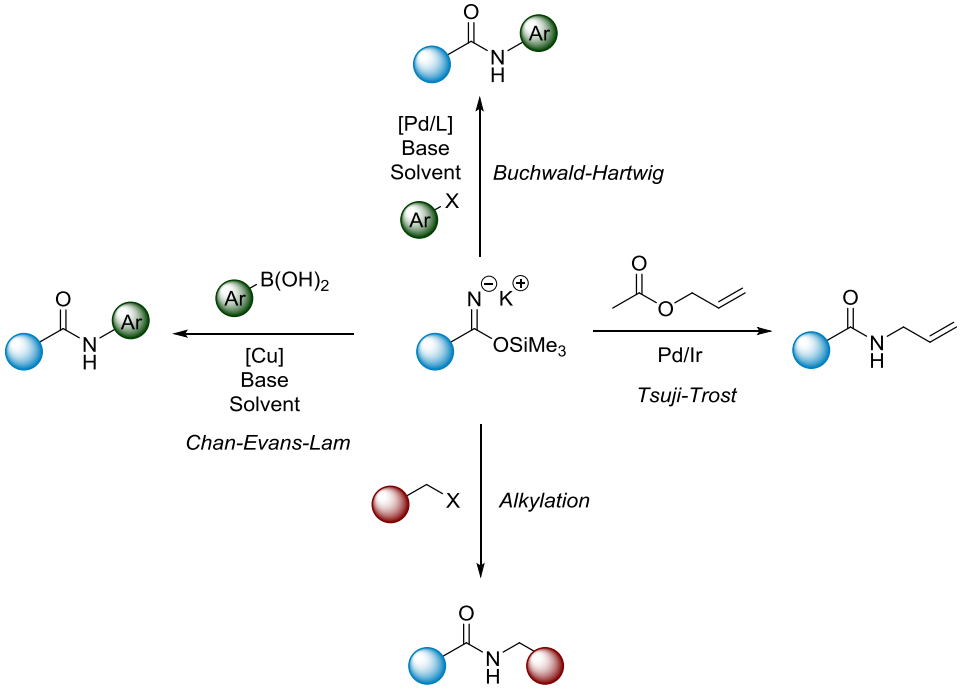
Additionally, a multicomponent approach enabling the formation of secondary amides from epoxides, amines and unactivated esters, mediated by the organobase BEMP, has also been

developed. The use of a multicomponent process, employing only catalytic quantities of base, limits by-product formation, thereby resulting in a highly atom efficient amide bond forming method (Scheme 1.2). This approach has also been further adapted to enable the synthesis of corresponding oxazolidinone moieties.



Scheme 1.2: BEMP-mediated multicomponent amidation.

The use of transition-metal catalysis has also been employed to facilitate amide bond formation. Utilising silanoate-derived imidate salt species, synthesised from the corresponding nitriles as amide surrogates, a Buchwald-Hartwig amidation methodology has been developed, enabling the synthesis of secondary amides (Scheme 1.3). Investigations into the use of these species in other amide bond forming transformations have also been carried out.



Scheme 1.3: Investigations into the use of the silanoate-derived imidate species as an amide surrogate.

Acknowledgements

Firstly, I would like to express my sincere gratitude to my PhD supervisor, Dr Craig Jamieson for the opportunity to not only work on this project, but also for all of his support, motivation and advice over the course of the last four years. Additionally, thank you for not treating me like a complete idiot when I have no doubt given you just cause at various points throughout my PhD!

I would also like to acknowledge Dr Allan Watson for all of his advice during the course of my PhD, particularly when investigating transition metal catalysis.

To all of the previous and current members of the Jamieson and Watson groups, thank you for all the advice, support, chat and entertainment in the office and in the lab. You have all made the last four years easier and more enjoyable than they would otherwise have been. It's been a privilege and a pleasure! Particular thanks must go to both Jennifer Clark and Keith Livingstone for proof reading the drafts of this thesis, and also ensuring that the majority of the commas contained within are there in the first place! Also, to my fellow final years Peter Campbell, Mairi Littleson, John Molloy and Ciaran Seath, it's been a pleasure completing the 8 year journey from undergraduate to PhD alongside you.

Finally, to my family and friends, your love and support has been invaluable throughout both the good and the bad days. Without it, none of this would have been possible.

Abbreviations

AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AOMP	5-(7-Azabenzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
AOP	(7-Azabenzotriazol-1-yl)oxytris(dimethylamino)phosphonium hexafluorophosphate
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BDMP	5-(1*H*-Benzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMMP	1-(1-(1*H*-Benzo[d][1,2,3]triazol-1-yloxy)ethyl-idene)pyrrolidinium hexachloroantimonate
BOMI	Benzotriazol-1-yloxy-*N*,*N*-dimethylmethaniminium hexachloroantimonate
BOP	Benzotriazolyl-*N*-oxytrisdimethylaminophosphonium hexafluorophosphate
BPMP	1-(1*H*-Benzotriazol-1-yloxy)phenylmethylenepyrrolidinium hexachloroantimonate
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
BroP	Bromotris(dimethylamino)phosphonium hexafluorophosphate
BTFFH	Bis(tetramethylene)fluoroformamidinium hexafluorophosphate
BTPP	*tert*-Butylimino-tri(pyrrolidino)phosphorane
Cat.	Catalyst
CDMT	2-Chloro-4,6-dimethoxy-1,3,5-triazine
CIC	*N*-Cyclohexyl–*N*-isopropylcarbodiimide
CloP	Chlorotris(dimethylamino)phosphonium hexafluorophosphate
Cod	Cyclooctadiene
COMU	(1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate
CPME	Cyclopentyl methyl ether
CuHMDS	Copper hexamethyldisilazide
CyJohnPhos	(2-Biphenyl)dicyclohexylphosphine
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAST	Diethylaminosulfur trifluoride
DCC	Diisopropylcarbodiimide
DavePhos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl

D*t*BPF	Bis(di-*tert*-butylphosphino)ferrocene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DCMT	2,4-Dichloro-6-methoxy-1,3,5-triazine
DFIH	1,3-Dimethyl-2-fluoro-4,5-dihydro-1*H*-imidazolium hexafluorophosphate
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DIC	Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMC	Dimethyl carbonate
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DoE	Design of Experiments
Dppb	1,4-Bis(diphenylphosphino)butane
Dppe	1,2-Bis(diphenylphosphino)ethane
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
EEDQ	*N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
Equiv.	Equivalent
er	Enantiomeric ratio
EWG	Electron-withdrawing group
GC-MS	Gas chromatography-mass spectrometry
HAPyU	1-(1-Pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene)pyrrolidinium hexafluorophosphate *N*-oxide
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*,*N*-tetramethyluronium hexafluorophosphate
HBTU	*O*-(Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCl	Hydrochloric acid
HF	Hydrofluoric acid

HFIP	Hexafluoroisopropanol
HMPA	Hexamethylphosphoramide
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	1-Hydroxy-1*H*-benzotriazole
HOCt	6-Chloro-1-hydroxy-1*H*-benzotriazole
HOPO	2-Hydroxypyridine-*N*-oxide
H-PGDS	Human prostaglandin-D synthase
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
HYP	Hydroxyproline
IIDQ	*N*-Isobutoxycarbonyl-2-isobutoxy-1,2-dihydroquinoline
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolium
IPA	Isopropyl alcohol
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
Kg	Kilogram
KHMDS	Potassium hexamethyldisilazide
KOAc	Potassium acetate
KO*t*Bu	Potassium *tert*-butoxide
KTFA	Potassium trifluoroacetate
LiHMDS	Lithium hexamethyldisilazide
MCR	Multicomponent reaction
MeCN	Acetonitrile
MePhos	2-Dicyclohexylphosphino-2′-methylbiphenyl
2-MeTHF	2-Methyltetrahydrofuran
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Molecular sieves
MW	Microwave
NHC	*N*-Heterocyclic carbene
NHS	*N*-Hydroxysuccinimide
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
PCy_3	Tricyclohexylphosphine
PFP	Pentafluorophenol
PNO	Pyridine *N*-oxide
PPh_3	Triphenylphosphine

PyAOP	[(7-Azabenzotriazol-1-yl)oxy]tris(pyrrolidino)phosphonium hexafluorophosphate
PyBOP	Benzotriazol-1-yloxytri(pyrrolidino)phosphonium hexafluorophosphate
PyBroP	Bromotri(pyrrolidino)phosphonium hexafluorophosphate
PyCloP	Chlorotri(pyrrolidino)phosphonium hexafluorophosphate
PyFloP	Fluorotri(pyrrolidino)phosphonium hexafluorophosphate
P_1-^{t}Bu	*tert*-Butylimino-tris(dimethylamino)phosphorane
Q-Phos	1,2,3,4,5-Pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene
RME	Reaction mass efficiency
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SET	Single electron transfer
SIPr	1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium
S_NAr	Nucleophilic aromatic substitution
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TAME	*tert*-Amyl methyl ether
TAPipU	1-(1-Pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-b]pyridin-1 ylmethylene)pyrrolidinium tetrafluoroborate *N*-oxide
TATU	*O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetra-methyluronium tetrafluoroborate
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBHP	*tert*-Butyl hydroperoxide
*t*BME	*tert*-Butyl methyl ether
TBTU	*O*-Benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate
*t*BuBrettPhos	2-(Di-tert-butylphosphino)-2′,4′,6′- triisopropyl-3,6-dimethoxy-1,1′-biphenyl
*t*BuOH	*tert*-Butanol
*t*BuXPhos	2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
TFFH	Tetramethylfluoroformamidinium hexafluorophosphate
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
Trop	5-*H*-dibenzo[a,d]cyclohepten-5yl
TTBP.HBF_4	Tri-*tert*-butylphosphonium tetrafluoroborate
TTMPP	Tris(2,4,6-trimethoxyphenyl)phosphine
T3P	2-Propanephosphonic acid anhydride

VRE	Vancomycin-resistant enterococci
VT	Variable temperature
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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1. Introduction

The amide functional group is extensively encountered in both nature and medicinal chemistry. Within nature, the occurrence of amides is crucial in sustaining a wide range of biological processes such as enzymatic processes, cell signalling, cell adhesion, and immune response, due their role in linking amino acid subunits through peptide bonds to form proteins.

Synthetically, approximately a quarter of all drugs or drug-like molecules contain the amide motif, a figure which clearly highlights the ubiquity of the amide functional group within the pharmaceutical industry.[1] Further to this, in 2011, Roughley and Jordan published a detailed analysis of reactions performed during drug candidate synthesis at AstraZeneca, GlaxoSmithKline, and Pfizer.[2] This investigation showed that amide bond formation was the most frequently performed class of reaction, comprising 16% of all the reaction types studied, which further emphasises the pervasiveness of the amide functional group. It is therefore unsurprising that the amide motif is found in many of the top-selling pharmaceuticals, examples of which are shown in Figure 1.1.

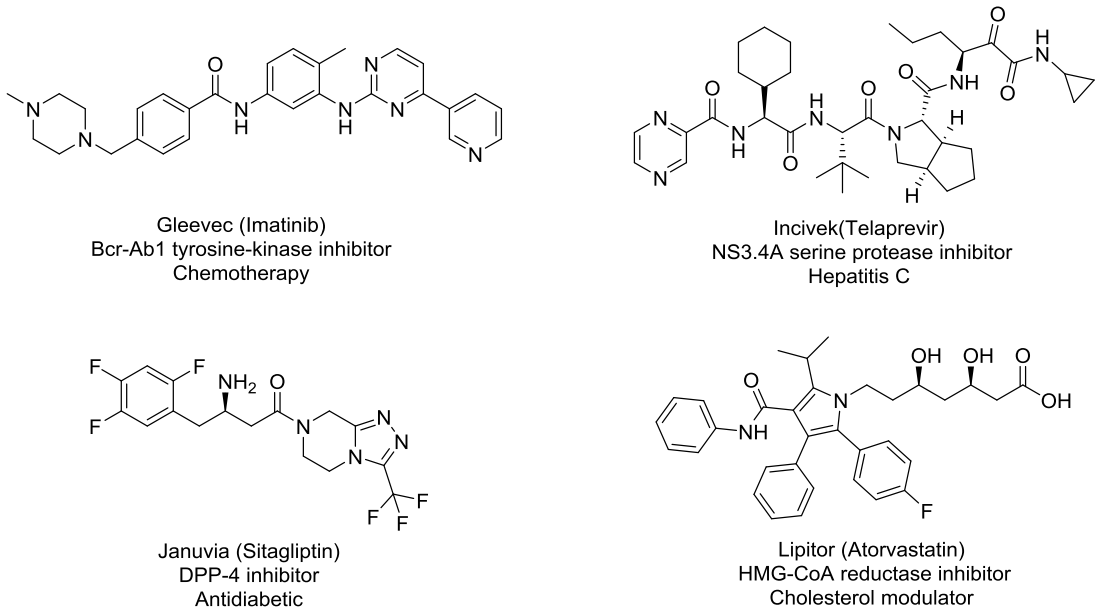
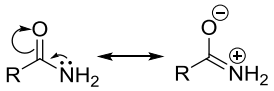


Figure 1.1: Marketed pharmaceuticals containing the amide functional group.

This prevalence of amide bonds in pharmaceuticals can be attributed to a number of favourable properties associated with the inclusion of the motif in a candidate molecule. Favourable interactions with the candidate's target receptor, which in turn enhance binding of the drug, can be established through the hydrogen bond accepting and donating capabilities of the amide motif.[3] The improved bioavailability of small molecule candidates incorporating an amide is a further advantage, with this effect a consequence of the chemical and metabolic stability of the amide functional group. From a practical perspective, this chemical stability results in easy handling of amides, which along with the ready availability of required starting materials and ease of purification allows the concise synthesis of amide containing small molecules.[4]

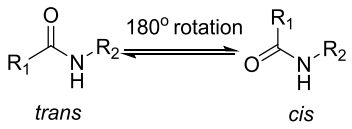
1.1 Nature of the Amide Bond

The amide functional group has two main resonance contributors (Scheme 1.4), resulting in a partial double bond effect. This effect is attributable to the lone pair of electrons present on the nitrogen atom delocalising into the adjacent carbonyl, resulting in the formation of a partial double bond between the nitrogen and carbon atoms. As a result of this effect, the amide bond is both strengthened and shortened in comparison to a single carbon-nitrogen bond, with a secondary amide having a bond length of 1.334 Å, whereas the bond length of a neutral amine is 1.469 Å.[5] Furthermore, this partial double bond effect prevents free rotation around the carbon-nitrogen bond.[6]



Scheme 1.4: Amide resonance contributors.

Despite the prevention of free rotation around the carbon-nitrogen single bond, slow rotation does occur and can be observed *via* NMR spectroscopy. This slow rotation results in two conformational isomers, or rotamers, of the amide, with one where R_1 is *trans* in respect to R_2 and the other with R_1 and R_2 *cis* (Scheme 1.5). The stability of these conformational isomers is determined by the precise nature of the substituents present in the amide.[6]



Scheme 1.5: Rotation around the carbon-nitrogen bond forms the *trans* and *cis* isomers.[6]

The resonance contributors of an amide also explain why it is a generally unreactive functional group. The orbital in which the lone pair is situated overlaps the vacant π* antibonding orbital of the carbonyl carbon, resulting in the energy of the system, and hence the lone pair, being lowered. This reduction in energy results in the lone pair having neither basic nor nucleophilic characteristics, and also raises the energy of the π* antibonding orbital. Therefore, the amide is unreactive towards nucleophiles (Figure 1.2).[7]

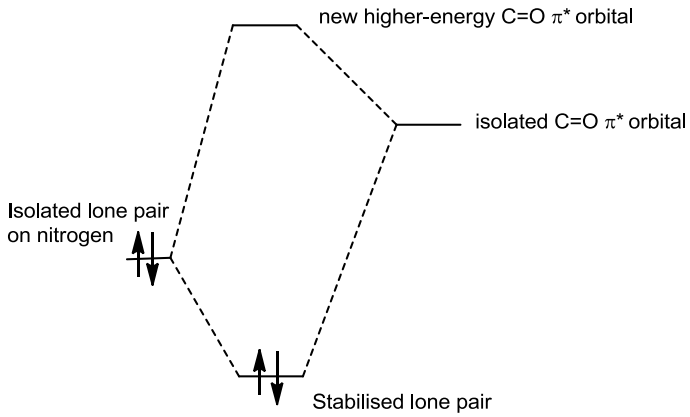
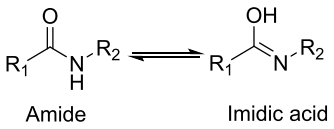


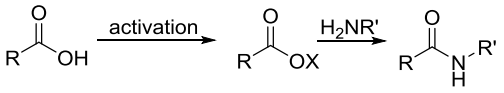
Figure 1.2: Molecular orbital diagram illustrating the stabilisation of the lone pair, resulting in a decrease in reactivity.[7]

Amides can also tautomerise to the corresponding imidic acid through the migration of a hydrogen atom and the transfer of a double bond (Scheme 1.6).



Scheme 1.6: Tautomerisation of an amide to an imidic acid.

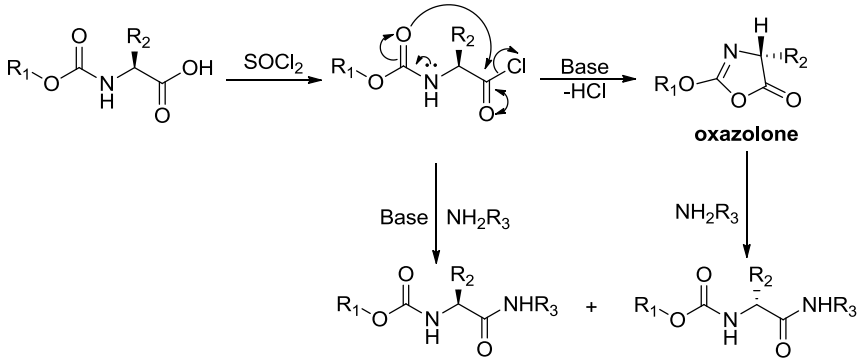
As a result of the above advantageous properties, methods allowing straightforward amide bond formation *via* the condensation of a carboxylic acid and an amine have been extensively developed. With the direct coupling reaction of an amine and carboxylic acid found to be unfavourable due to the high temperatures (≥ 200 °C) required to facilitate the elimination of water, most of the developed approaches involve activation of the carboxylic acid, which then readily undergoes the desired amidation reaction with the amine coupling partner (Scheme 1.7).[8] Methods in which an activated carbonyl species is formed are reviewed in subsequent sections.



Scheme 1.7: Activation of a carboxylic acid prior to condensation with an amine.

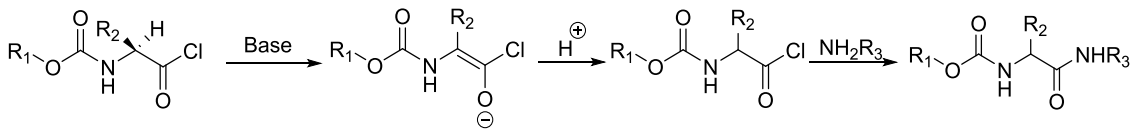
1.2 Acyl Halides in Amide Bond Formation

Activation of a carboxylic acid to form the corresponding acyl halide is a method commonly employed in amide bond formation. Formation of an acid chloride can be achieved by exposing the desired carboxylic acid to a variety of inexpensive, commercially available chlorinating reagents such as thionyl chloride ($SOCl_2$) (Scheme 1.8), oxalyl chloride $(COCl)_2$, phosphoryl chloride ($POCl_3$) and phosphorus pentachloride (PCl_5). [9,10]



Scheme 1.8: Amidation using thionyl chloride as an activating agent.

However, the application of acid chlorides in amide bond formation is hindered by several drawbacks. Firstly, the liberation of HCl in the process prevents substrates bearing acid sensitive functionalities, such as Boc-protected amines, from being activated with such reagents. Furthermore, racemisation of chiral substrates, e.g. amino acids, is a significant drawback of this approach. Racemisation can occur *via* the formation of an oxazolone species through a base-mediated intramolecular cyclisation, as shown in Scheme 1.8.[9] This oxazolone species, although still active towards amide bond formation, slowly reacts with amine coupling partner, allowing epimerisation to occur *via* exposure to the base present. Alternatively, racemisation can also occur *via* an enolisation pathway (Scheme 1.9), where deprotonation α to the acyl chloride leads to epimerisation.[10]



Scheme 1.9: Racemisation *via* enolisation.

In order to circumvent the issue of the application of acid sensitive moieties, several chlorinating methods in which HCl is not produced have been developed. Firstly, triazine reagents such as cyanuric chloride, CDMT and DCMT (Figure 1.3) can be utilised.[11,12] When cyanuric chloride is used, the reaction proceeds through a tri-acylated triazine intermediate (Scheme 1.10), hence allowing the amount of chlorinating reagent to be limited to 0.33 equivalents, limiting both expense and by-product formation.[12]

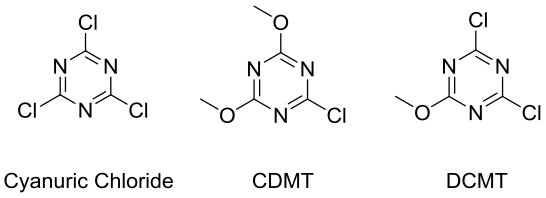
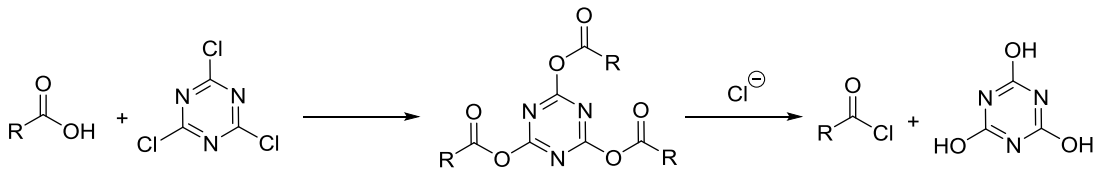
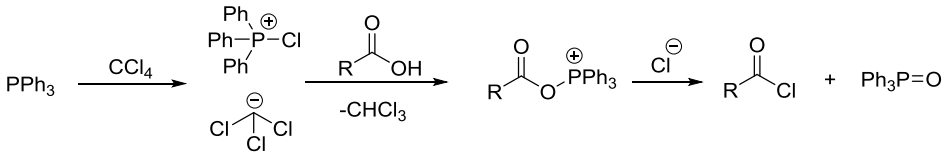


Figure 1.3: Triazine chlorinating reagents.



Scheme 1.10: Activation of a carboxylic acid using cyanuric chloride.[12]

Alternatively, HCl production can be mitigated by employing triphenylphosphine and carbon tetrachloride to form the acid chloride species through an Appel reaction (Scheme 1.11).[13] Adaptation of the Appel conditions has allowed catalytic quantities of triphenylphosphine to be employed through the addition of both diethoxymethylsilane and bis(4-nitrophenol)phosphate to the reaction which act to reduce the triphenylphosphine oxide by-product to triphenylphosphine.[14] However, although these approaches prevent HCl formation, safety concerns regarding the handling and use of chlorinating reagents and carbon tetrachloride have limited their effective use.[15]



Scheme 1.11: Acid chloride formation through an Appel reaction.

As an alternative to acyl chlorides, fluorinating agents such as cyanuric fluoride and DAST (Figure 1.4) can be used to form the corresponding acyl fluoride. With their increased reactivity and stability to hydrolysis, acyl fluorides can be an attractive alternative to acyl chlorides.[10] However, as with chlorinating reagents, there are significant safety concerns in the handling and use of fluorinating agents due to the potential for HF generation.

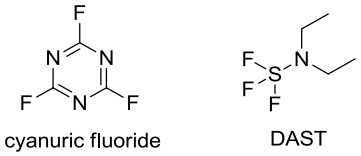


Figure 1.4: Fluorinating agents used in acyl fluoride formation.

1.3 Coupling Reagents

With the application of acyl halides limited due to the drawbacks detailed above, coupling reagents which activate the carboxylic acid *via* the *in situ* formation of an active ester have found widespread application in amide bond synthesis. A range of the most popular methods and reagents utilised in both small molecule chemistry and peptide coupling are described below.

1.3.1 Carbodiimides

The use of carbodiimides to facilitate amide bond formation represented the first approach that proceeded through the *in situ* formation of an active ester. Carbodiimides commonly employed include DCC, DIC, EDC and CIC (Figure 1.5), with the corresponding *O*-acyl intermediate formed from their reaction with the carboxylic acid undergoing condensation with an amine (Path A, Scheme 1.12).[10] Alternatively, amide formation can result through the reaction of an acid anhydride, formed from the reaction of the *O*-acylurea intermediate with excess carboxylic acid, and the amine. (Path B, Scheme 1.12).

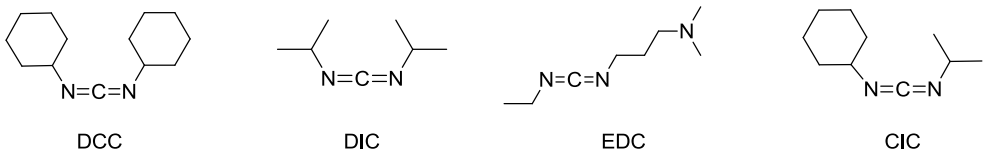
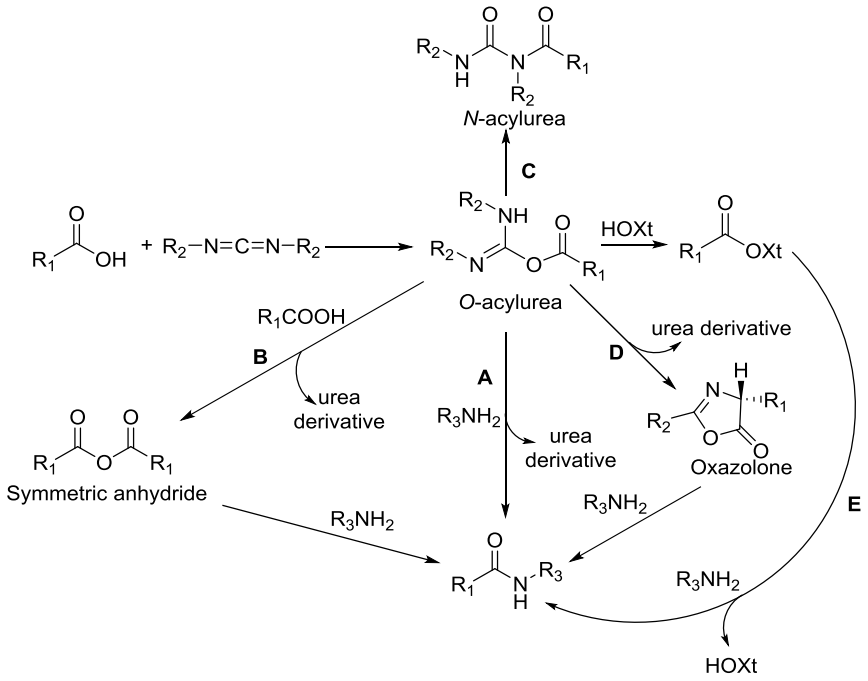


Figure 1.5: Carbodiimide reagents employed in amide bond formation.



Scheme 1.12: Amide bond formation using carbodiimide coupling reagents.

However, the use of carbodiimides have inherent drawbacks such as the formation of an *N*-acylurea, which is a stable and inert by-product, *via* the rearrangement of the highly reactive *O*-acylurea (Path C, Scheme 1.12).[10] Oxazolone formation can also occur (Path D, Scheme 1.12), *cf.* acyl chloride formation, resulting in epimerisation of any chiral centre present in the carboxylic acid substrate.[10]

In order to prevent racemisation occurring when using carbodiimide coupling reagents, the use of an additive can be incorporated. Hydroxybenzotriazole additives such as 1-hydroxybenzotriazole (HOBt) (Figure 1.6) react with the *O*-acylurea intermediate to form a subsequent activated ester species, which is less susceptible to side reactions and hence improving selectivity.[16,17] Reaction of this active ester with the amine substrate results in the formation of the desired amide (Path E, Scheme 1.12).

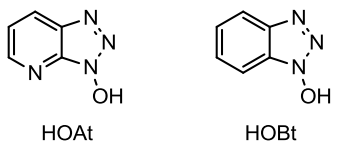
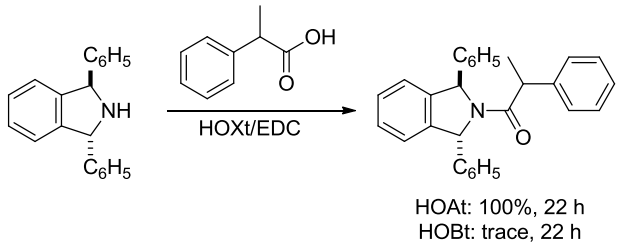


Figure 1.6: Hydroxybenzotriazole additives.

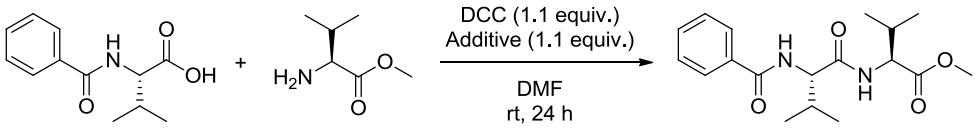
1-Hydroxy-7-azabenzotriazole (HOAt), first reported by Carpino, has shown to be a superior additive in comparison to HOBt in both the yield of amide formed, for example in the

acylation of secondary amines (Scheme 1.13), and the suppression of racemisation (Table 1.1).[17]



Scheme 1.13: Amidation of secondary amines with 2-phenylpropanoic acid with hydroxybenzotriazole additives.[17]

Table 1.1: Effect of hydroxybenzotriazole additives on observed levels of racemisation.[17]



Additive	D-L isomer (%)
No additive	61.5
HOAt	14.4
HOBt	41.9

The improved selectivity observed with the use of HOAt is hypothesised to be a result of a favourable neighbouring group effect between the active ester and the incoming amine substrate (Figure 1.7). Hydrogen bonding between a proton situated on the amine nitrogen and the heterocyclic nitrogen acts to direct nucleophilic attack of the amine onto the carbonyl of the active ester.[17] To support this hypothesis, when positional isomers of HATU were investigated, the 7-aza species was shown to be the superior isomer indicating that the neighbouring group effect that this isomer possesses is crucial to the improved reactivity over HOBt.[17]

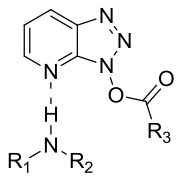
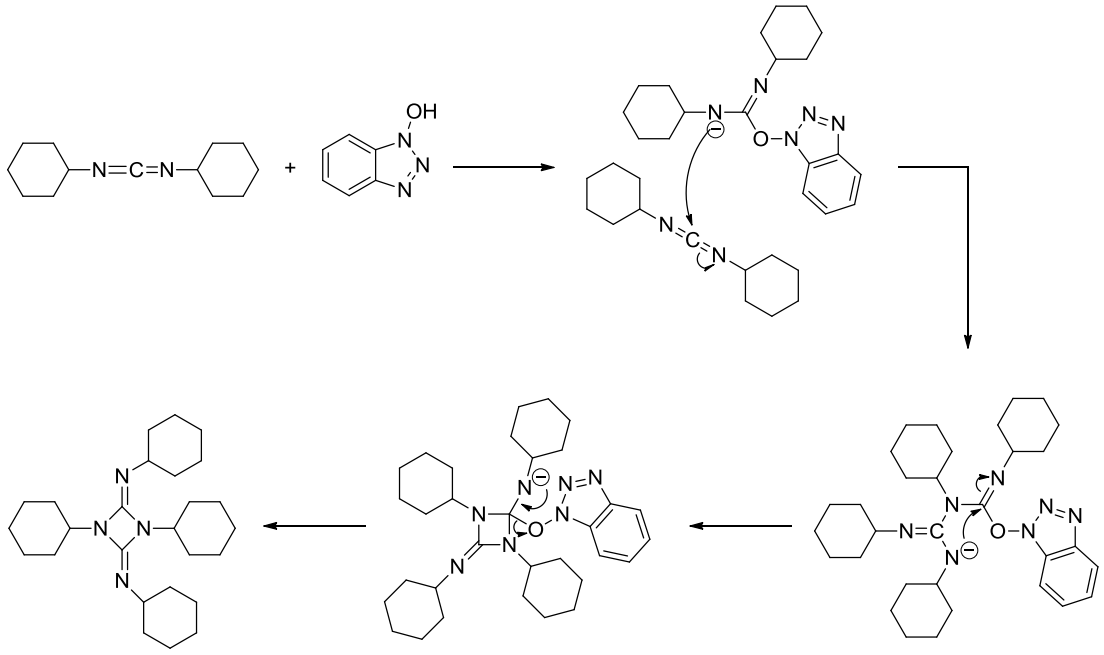


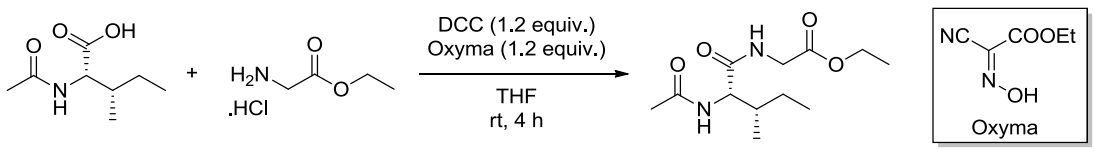
Figure 1.7: Origin of observed neighbouring effect between HOAt active ester and the incoming amine.

Although the introduction of hydroxybenzotriazole additives succeeded in improving the selectivity of carbodiimide-mediated amide bond formation, diazetidine by-product formation originating from the direct reaction of the carbodiimide and hydroxybenzotriazole species (Scheme 1.14) can prove problematic.[9,18] In addition, both HOAt and HOBt exhibit explosive tendencies, which may limit their application particularly on scale.[19]



Scheme 1.14: Formation of a diazetidine by-product when using DCC and HOBt.

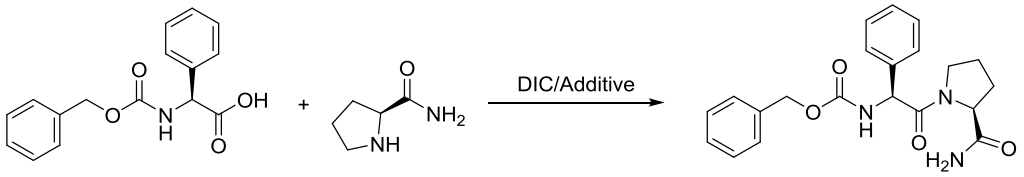
An alternative reagent found to possess greater thermal stability, and hence lowering the explosive risk, than both HOAt and HOBt is the oxime based reagent ethyl cyanohydroxyiminoacetate (Oxyma).[20] First reported as a viable coupling reagent in 1973 by Itoh, Oxyma in conjunction with DCC resulted in no observed racemisation when applied in the coupling of *N*-acetyl-L-isoleucine and ethyl glycinate hydrochloride forming the desired amide in 92% yield, whereas 8% racemisation was observed with no oxime additive (Scheme 1.15).[21]



Scheme 1.15: Racemisation suppression utilising Oxyma as an additive.[21]

In 2009, Albericio *et al*. directly compared Oxyma to both HOAt and HOBt, and a non-benzotriazole reagent 2-hydroxypyridine-*N*-oxide (HOPO), in a Z-PhgPro-NH_2 peptide model (Table 1.2). This study showed that Oxyma not only supressed racemisation to a greater extent than the other additives tested, but also led to a more efficient peptide coupling (Entry 3, Table 1.2).[20]

Table 1.2: Comparison of Oxyma to alternative additives in carbodiimide-mediated amide bond formation.[20]



Entry	Additive	Yield (%)	DL-isomer (%)
1	HOAt	86.1	2.1
2	HOBt	78.8	8.9
3	Oxyma	89.8	3.8
4	HOPO	88.5	45.1

1.3.2 Aminium/Uronium Coupling Reagents

With the application of the carbodiimide/additive approach to forming amide bonds limited due to the selectivity and handling problems discussed previously, a plethora of coupling reagents based upon the otherwise effective hydroxybenzotriazole scaffold have since been developed. Due to their ease of handling, stability, applicability and commercial availability, the use of these coupling reagents has largely supplanted the use of carbodiimides.[22]

One such class of coupling reagents are the aminium/uronium salts, which encompass reagents such as HATU, HBTU, TATU, TBTU, HAPyU and TAPipU (Figure 1.8). Uronium and aminium isomers of these reagents have been identified, with factors such as solvent, the species of base, counterion and isolation method determining which isomer is favoured (Figure 1.9).[23] It was initially believed that the reagents existed as the uronium or *O*-isomer but Carpino determined *via* X-ray crystallography that both HATU and HBTU existed as the aminium or *N*-isomer.[23] Comparative studies using HBTU and TBTU have shown that the counterion present in the coupling bears no influence on reaction progression.

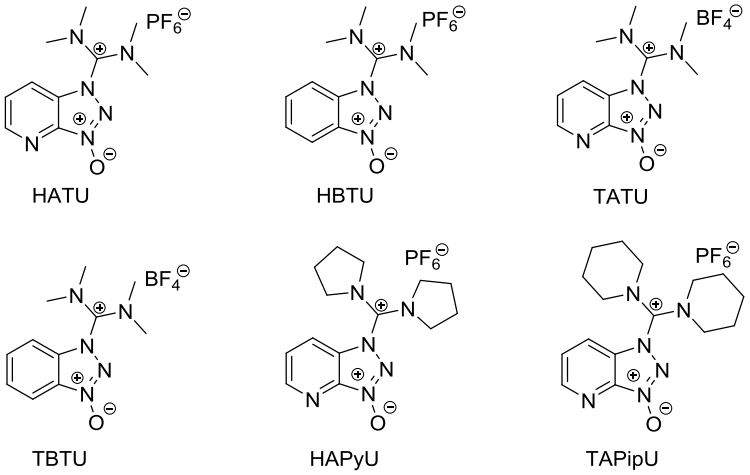


Figure 1.8: Examples of aminium/uronium coupling reagents.

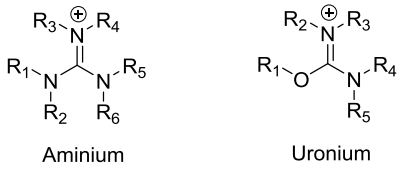
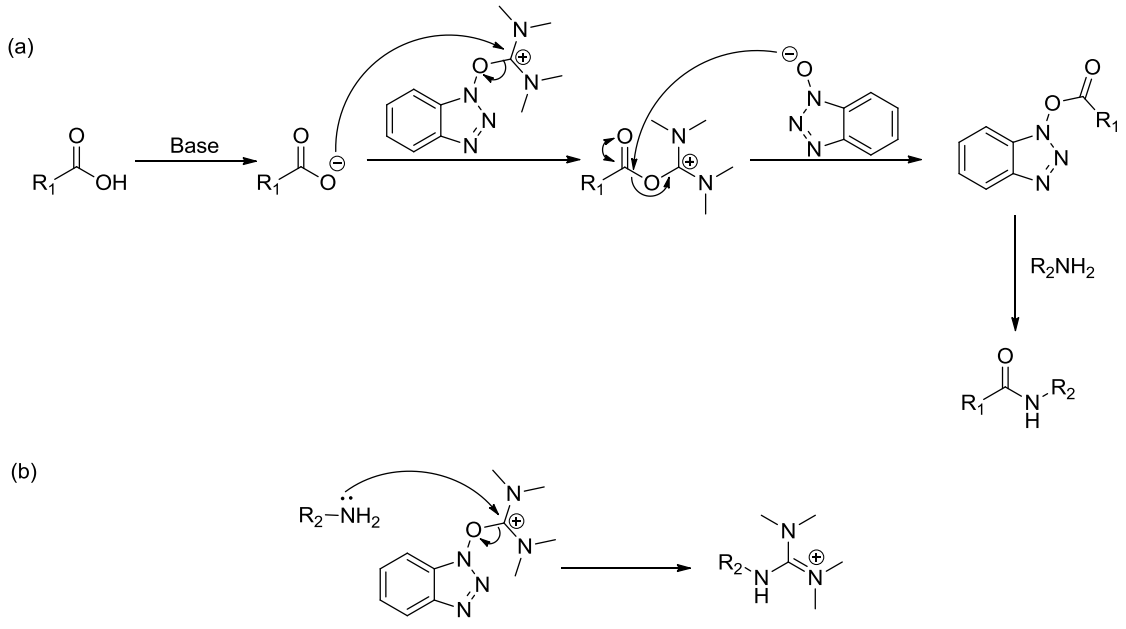


Figure 1.9: Aminium and uronium isomers.

Aminium/uronium reagents react with the carboxylic acid to form an active OAt or OBt ester, *via* the initial generation of the *O*-acylisourea which liberates an HOAt/HOBt anion, which in turn reacts with the *O*-acylisourea. The resulting OAt or OBt active ester is then nucleophilically attacked by an amine, in the case of HATU assisted by a neighbouring group effect synonymous with HOAt, to furnish the amide product (Scheme 1.16a). However, a potential side reaction can occur directly between the coupling reagent and the amine to form a guanidinium by-product (Scheme 1.16b).[9] The order of addition of the reagents can mitigate guanidinium formation, with the active ester preformed before addition of the amine.



Scheme 1.16: (a) Activation and amidation using an aminium/uronium coupling reagent. (b) Guanidinium by-product formation.

Although an efficient and effective approach to amide bond formation, the use of these coupling reagents, and those discussed in subsequent subsections, are hindered by several inherent drawbacks. Firstly, stoichiometric quantities of the reagents are required, therefore meaning that the atom economy of this approach is sub-optimal.[24] Also, as a result of this necessity for stoichiometric levels of the coupling reagent, any by-product generated in the process, e.g. a urea by-product formed from aminium/uronium reagents, is produced in stoichiometric amounts, potentially leading to difficult purification. A further disadvantage is the expense of using stoichiometric quantities of the coupling reagents.

1.3.3 Phosphonium Coupling Reagents

Another family of coupling reagents derived from HOAt/HOBt is the phosphonium salt reagents. These reagents, like aminium/uronium salts, react *via* the prior formation of an active -OAt or -OBt ester which then couples with the amine. However, the use of phosphonium coupling salts is advantageous over aminium/uronium salts as phosphonium reagents are unable to directly react with the amine, hence preventing guanidinium by-product formation.[9] The first HOAt/HOBt phosphonium coupling reagent to be developed was (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (Figure 1.10), however its successful use has been hindered due to the liberation of HMPA in the amidation process, which has both carcinogenic and toxic respiratory effects (Scheme 1.17).[25]

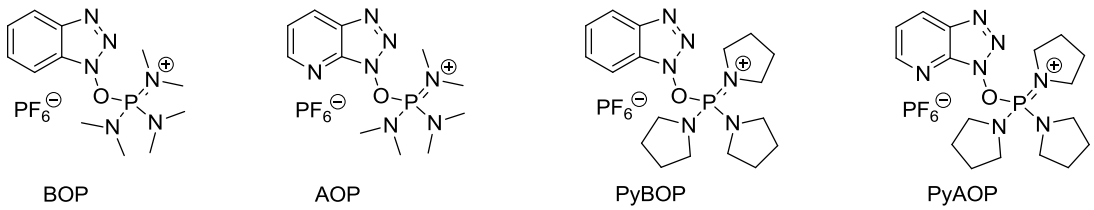
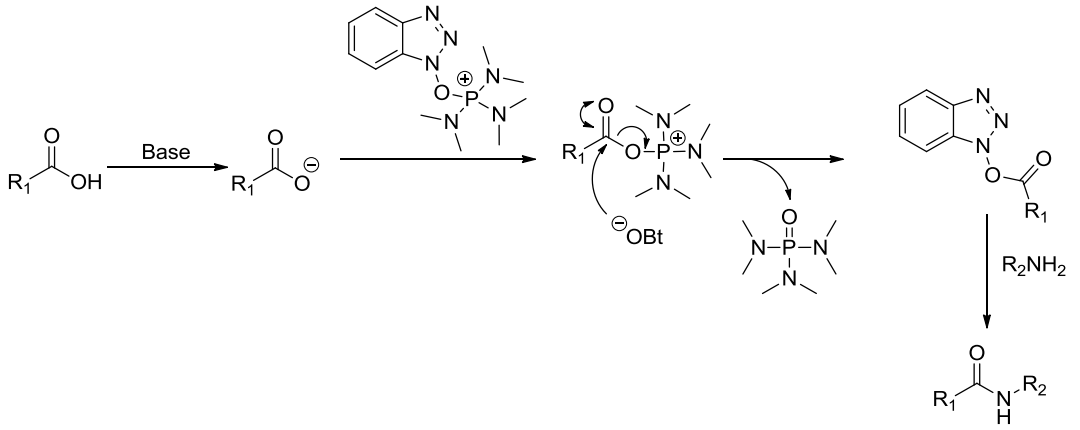


Figure 1.10: Examples of phosphonium coupling reagents.



Scheme 1.17: Mechanism of amidation using BOP with liberation of HMPA.

To counter this, the equally efficient pyrrolidino derivative PyBOP was developed, which instead liberates the less toxic 1,1',1''-phosphoryltripyrrolidine by-product.[26] Further advances in the field by Carpino resulted in the development of both AOP and PyAOP, which again liberate HMPA and 1,1',1''-phosphoryltripyrrolidine, respectively, as by-products.[22,27] When the efficiency of these aza-derivatives were compared to BOP and PyBOP in the coupling of Fmoc-diethylglycine and the fluorenylmethyl ester of the phenylalanine, both AOP and PyAOP were found to be more reactive coupling reagents (Figure 1.10), presumably as a consequence of the favourable neighbouring group effect.[22,27]

1.3.4 Immonium Coupling Reagents

The final class of coupling reagents derivatised from the prior HOAt/HOBt reagents are the immonium salt reagents. Mechanistically similar in their reaction with a carboxylic acid and an amine as both the aminium/uronium and phosphonium salts, Li designed the BOMI, BDMP, BPMP, BMMP and AOMP immonium reagents (Figure 1.11).[28–31] Of these immonium salts, BOMI and BDMP were the most effective reagents in the coupling of Z-Gly-Phe-OH with H-Val-OMe with the resulting amide formed in > 90% yield within 10 minutes. Racemisation of the amide product was also minimal, with BOMI and BDMP

resulting in 3.1 and 2.3% of the DL-isomer, respectively, however these reagents have yet to be directly compared to widely utilised coupling reagents such as HATU or PyBOP.[28–31]

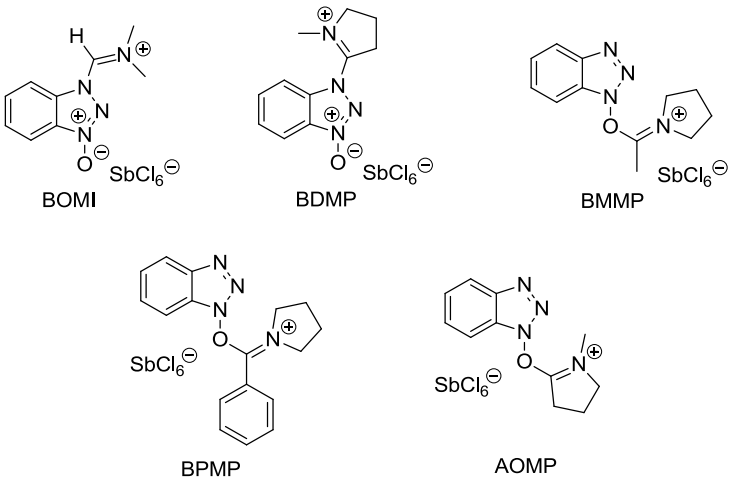


Figure 1.11: Iminium Coupling Reagents.

1.3.5 Halo-uronium and Halo-phosphonium Coupling Reagents

An alternative to hydroxybenzotriazole derived coupling reagents are the halo-uronium and halo-phosphonium reagents. Instead of activating the carboxylic acid *via* an OAt or OBt ester, the use of these reagents result in the carboxylic acid being activated in the form of an acyl halide. Acyl fluoride producing reagents such as TFFH and BTFFH and DFIH (Figure 1.12) have been successfully used to form acyl fluorides with amino acids such as histidine and arginine, which were unable to form shelf-stable aryl fluoride intermediates when treated with cyanuric fluoride.[32,33]

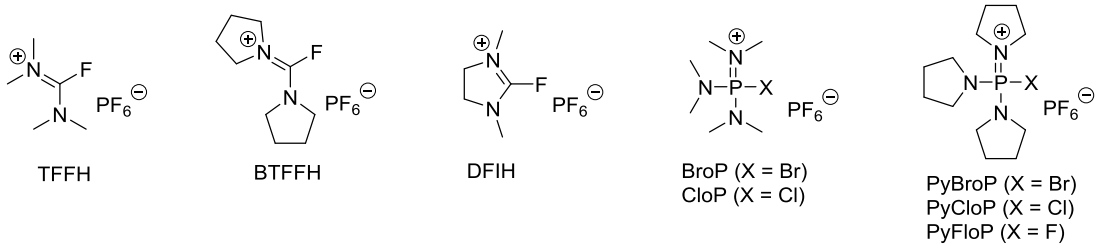
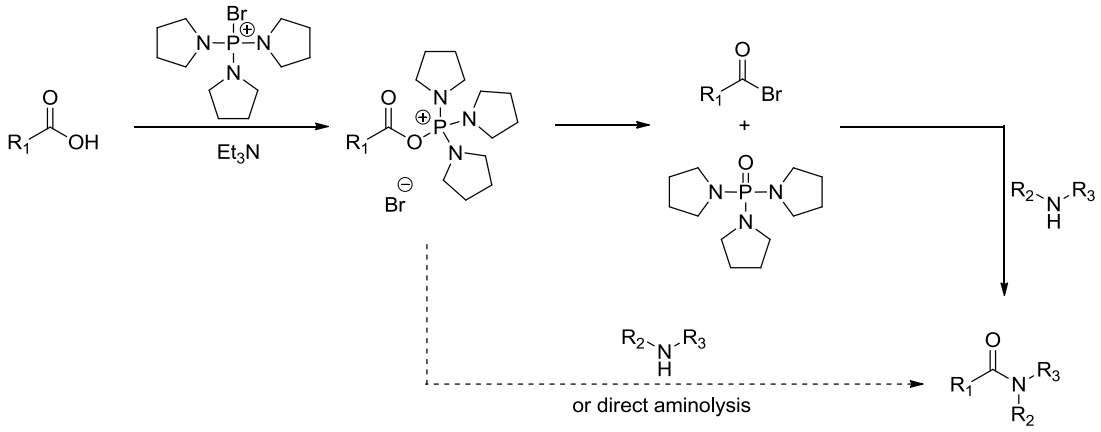


Figure 1.12: Halo-uronium and Halo-phosphonium coupling reagents.

Reagents generating acyl chlorides and acyl bromides have also been developed, with the relatively benign reaction conditions a distinct advantage over the harsh conditions associated with the use of thionyl chloride. Coste first synthesised the reagent BroP, and after further development, PyBroP and PyCloP (Figure 1.12), which when applied to the amide coupling of *N*-methyl amino acids were found to be more efficient than the

hydroxytriazole derived PyBOP (Scheme 1.18).[34,35] A drawback of both PyBroP and PyCloP however is their ability to form oxazolones which can lead to epimerisation of the amide product (*cf.* Section 1.2). Interestingly, the use of the fluorine derivative PyFloP (Figure 1.12) was found to not lead to the formation of any acyl fluoride.[32] CloP (Figure 1.12), another acyl chloride forming reagent, was also found to result in low levels of epimerisation.[36]



Scheme 1.18: Amidation *via* the formation of an acyl bromide using PyBroP.

1.3.6 Miscellaneous Coupling Reagents

1.3.6.1 COMU

After reporting the oxime-based coupling additive Oxyma as a viable alternative to HOAt and HOBt,[20] El-Faham and Albericio combined a morpholonium-based iminium moiety with an Oxyma leaving group to produce the uronium reagent COMU (Figure 1.13).[37] This combination of moieties led to a coupling reagent not only more hydrolytically stable than HATU and HBTU, but also resulted in a marked increase in solubility, allowing more concentrated solutions of COMU to be utilised to drive coupling reactions to completion if required.[37] Reaction progression is easily monitored *via* a simple colour change, with a change from a pink or orange-red solution, dependent on the basic species, to a colourless or yellow solution respectively, indicating reaction completion.[37] The efficiency of COMU was also investigated in the coupling of the hindered amino acid model of Z-Aib-OH (Z-2-methylalanine) and H-Val-OMe, with the results indicating that the use of one equivalent of COMU (97% after 2 hours) was more efficient than the use of 2 equivalents of both HATU (92% after 2 hours) and HBTU (83% after 2 hours).[37] This observed efficiency is proposed to be as a result of COMU solely existing as the more reactive *O*-isomer whereas HATU and HBTU can also exist as the less reactive *N*-isomer.

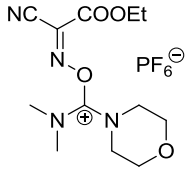
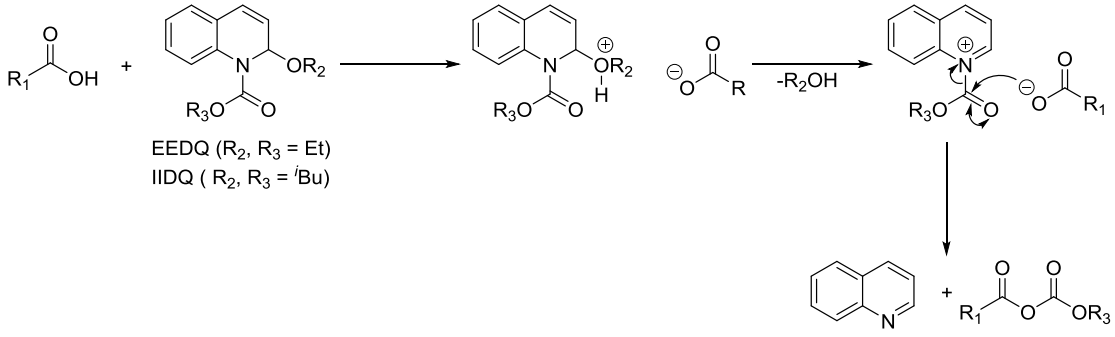


Figure 1.13: COMU.

1.3.6.2 Acid Anhydride Forming Reagents

The use of EEDQ (Scheme 1.19), first synthesised in 1967,[38] is advantageous over a range of uronium based coupling reagents as a guanidinium by-product is unable to be formed through direct attack of the amine onto the coupling reagent. Furthermore, slow formation and rapid consumption of the anhydride intermediate limits the potential for unwanted side reactions, such as epimerisation, to occur. Further derivatives such as IIDQ (Scheme 1.19) have since been developed, which, in the limited comparative studies performed, has been shown to be a marginally superior reagent than EEDQ.[39,40]

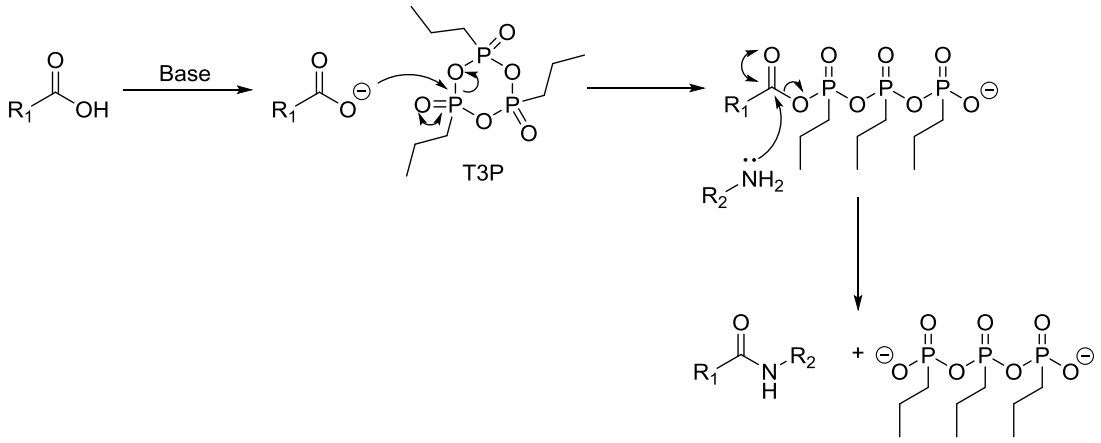


Scheme 1.19: Mixed anhydride formation using EEDQ or IIDQ.

1.3.6.3 T3P

T3P, an alkyl phosphonic acid reagent, (Scheme 1.20), is a highly soluble, bench-stable alternative to traditionally used coupling reagents. First reported by Kleiner, T3P is a commercially available reagent which is simply prepared from the reaction of propanephosphonic acid dichloride with water.[41] In comparison to carbodiimide reagents, T3P was proven to be just as efficient, if not superior, in terms of not only yield but also in the suppression of epimerisation, with the added advantage of easy extraction of any side products formed in the amidation process.[41] In a comparative study of T3P and HAPyU in investigating the cyclisation of *L*-pentapeptides and systems with a sterically hindered amino acid at the cyclisation centre, Carpino found that T3P again performs as well as, if not

better, than the established reagent with retention of the stereochemistry.[42] However in unhindered cyclisations, no clear superiority for T3P can be established.



Scheme 1.20: Amidation mediated by T3P.

1.4 Catalysis in Amide Bond Formation

In recent years, attention has turned to addressing the traditional problems associated with the use of stoichiometric quantities of coupling reagents, such as the production of equimolar by-products, and therefore the related expense in utilising the reagents. Emphasising the importance of developing such approaches, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable highlighted 'amide formation avoiding poor atom economy reagents' as a key objective for future research.[43] The successful development of catalytic approaches towards amide bond formation would be one approach which would successfully meet this research target. The application of catalysts could potentially lead to more benign reaction conditions than those widely employed, whilst also serving to address by-product formation and the atom economy concerns associated with the use of coupling reagents.

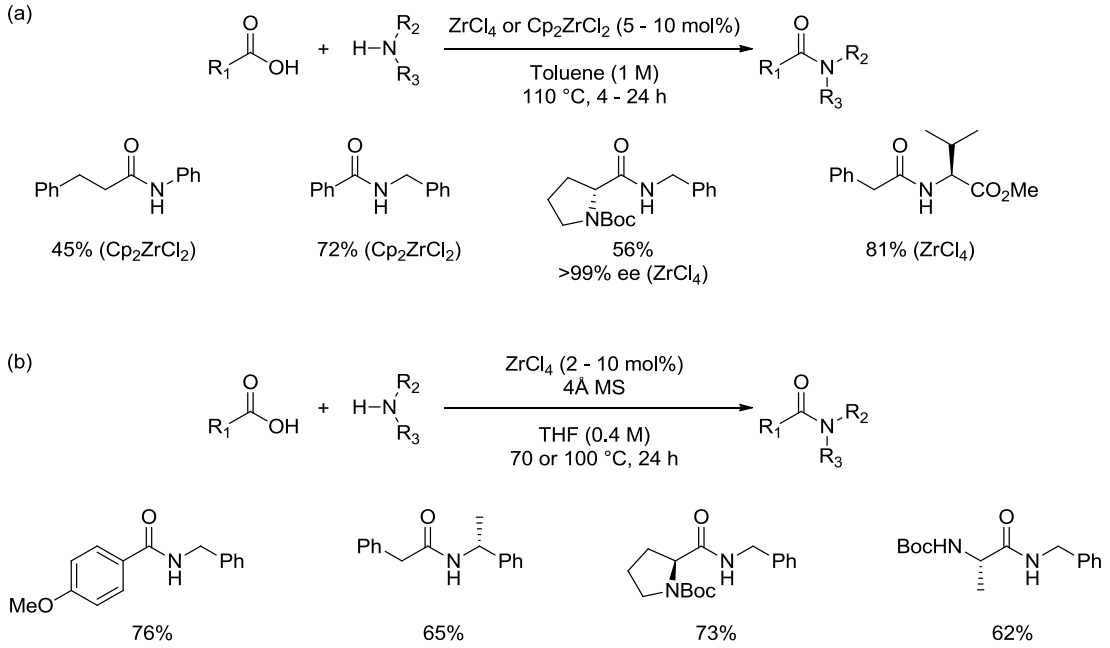
1.4.1 Metal Catalysis

A relatively underexplored approach to amidation, the application of metal catalysis in amide synthesis is an area which has received increasing attention within the last 10 – 20 years. With the direct reaction between a carboxylic acid and an amine disfavoured,[8] this approach has enabled amide bond formation to be performed on not only carboxylic acids, but also carboxylic acid derivatives such as esters. Redox and oxidative transition metal catalysed amidation procedures have further widened the scope of competent substrates to functionalities including alcohols, aldehydes and nitriles.

1.4.1.1 Metal Catalysed Amide Bond Formation from Carboxylic Acids

Lewis acids were first found to successfully promote the reaction of carboxylic acids and amines in an initial report from Wilson and Weingarten, where a slight excess of $TiCl_4$ was employed at -70 °C to furnish a small range of amides in moderate to good yield.[44] However, extended reaction times of up to 7 days were required to enable reaction completion. In 1988, Carlson reported the use of $TiCl_4$, $AlCl_3$, ZnI_2 and $ZnCl_2$ in stoichiometric quantities, and in a comparative study performed with the organocatalyst $BF_3.OEt_2$, $TiCl_4$ in refluxing toluene was found to give comparative yields.[45]

Following this, Williams *et al.* have shown that Lewis acids such as CuBr, $FeCl_2$, $Ni(NO_3)_2$, $TiCl_4$, $ZrCl_4$ and Cp_2ZrCl_2 can also efficiently promote the desired transformation.[46] $ZrCl_4$ and Cp_2ZrCl_2 were particularly effective, with 5 mol% of each Lewis acid in toluene at 110 °C furnishing a wide range of amides in high yield within 4 – 24 hours. (Scheme 1.21a).[46] Adolfsson *et al.* reported a similar procedure in which THF is used *in lieu* of toluene allowing the transformation to be performed at the lower temperature of 70°C (Scheme 1.21b).[47] However, both a higher temperature (100 °C) and a higher catalyst loading (10 mol%) were required to enable aromatic acids and secondary amines to be successfully coupled.[47] Further work in the Adolfsson group also highlighted the ability of Lewis acids such as $Ti(OiPr)_4$, $Zr(OEt)_4$, $Zn(OtBu)_4$, $Hf(OtBu)_4$, $Nb(OEt)_5$, and $Ti(OBn)_4$ to promote the coupling of phenylacetic acid and benzylamine in up to 88% yield.[48]



Scheme 1.21: (a) William's conditions.[46] (b) Adolfsson's conditions.[47]

The exact mechanism of the Zr-mediated amidation is unknown, with several possible coordination modes proposed for the Zr to activate the acid. Previous studies undertaken on the behaviour of Lewis acid catalysts in amidation reactions imply that the reaction progresses through a typical Lewis acid complex, with the metal accepting a lone pair from the carbonyl, thus forming an activated carbonyl complex (Figure 1.14a).[49,50] An alternative proposal is the activation of both the carbonyl and the leaving group by the Lewis acid, forming an electron deficient centre susceptible to attack by the amine whilst also facilitating the dissociation of the leaving group (Figure 1.14b).[50] Finally, sole activation of the leaving group may also lead to zirconium carboxylate formation (Figure 1.14c).[50]

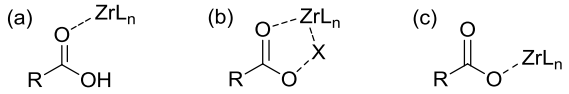


Figure 1.14: Proposed mechanisms for zirconium-mediated amide bond formation. (a) Carbonyl group activation by Zr. (b) Simultaneous carbonyl and leaving group activation by Zr. (c) Leaving group activation by Zr.[49,50]

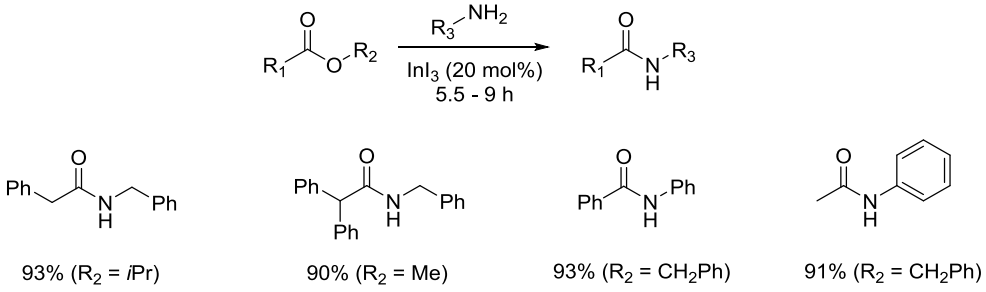
1.4.1.2 Metal Catalysed Amide Bond Formation from Esters

As the catalytic amidation of carboxylic acids can prove difficult due to inherent drawbacks such as the use of elevated temperatures, extended reaction times, limited scope and the requirement for strict anhydrous conditions, the use of corresponding ester derivatives has been explored as a viable alternative. The use of esters should promote the desired amidation reaction as a consequence of the increased electrophilicity of an ester carbonyl in comparison to that of a carboxylic acid. To this end, a range of metal- and organocatalysed procedures have been reported to date.

Successful amidation reactions employing esters have been known from as early as 1977, when Weinreb *et al.* reported the use of stoichiometric $AlMe_3$ to promote the reaction.[51] Upon reaction with an amine, the corresponding dimethylaluminium amide is formed, which can be stored as a 1M solution or reacted directly with an ester, which allowed 20 amides to be synthesised in high yield with only gentle heating (25 – 41 °C) required.[51] However, reaction times of up to 48 hours were required in some cases.[51] Similarly, Woodward *et al.* reported the use of the air stable, non-pyrophoric $AlMe_3$ adduct ($AlMe_3$).DABCO (DABAL–Me_3) in non-inert conditions to synthesise a range of amides from primary amines and esters in moderate to excellent yield (69 – 99%).[52]

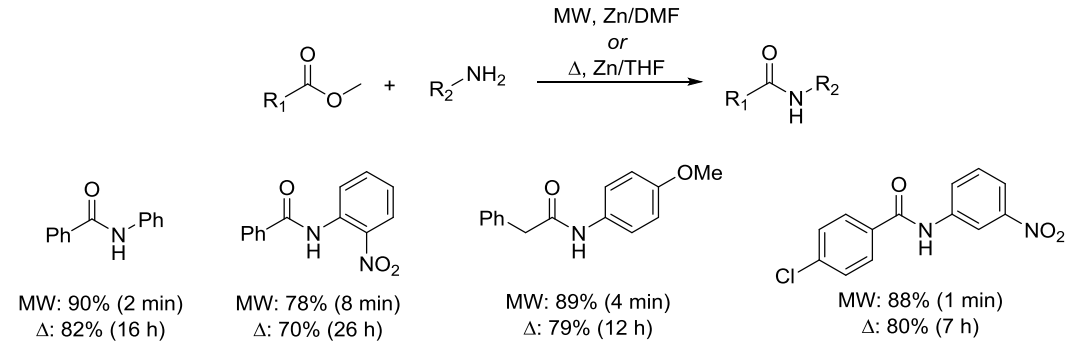
In one of the first reports using catalytic amounts of metal reagents, Ranu and Dutta employed the use of InI_3 (20 mol%) in a solvent-free process to facilitate amide bond

formation (Scheme 1.22).[53] Secondary amides were formed in up to 93% yield with benzyl, methyl, ethyl and isopropyl esters , however the use of secondary amines and ammonia were found to be incompatible with the reaction conditions.[53] Additionally, the use of elevated temperatures of 110 - 120 °C and a vast excess of the amine substrate were required.[53]



Scheme 1.22: In_3 catalysed amidation of esters.

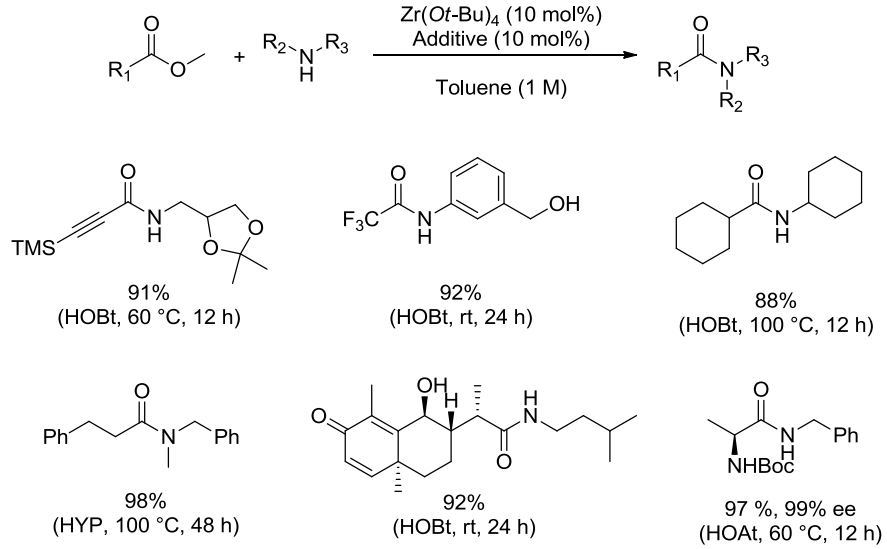
Zn dust has also been applied as a recoverable catalyst to couple anilines with aromatic and benzylic methyl esters under both conventional heating and microwave (MW) irradiation (Scheme 1.23).[54] Under microwave irradiation, the reaction is complete within 1 – 8 minutes, with yields between 70 and 91%.[54] Conventional heating at 70 °C requires vastly extended reaction times (11 – 30 h) with yields of 64 – 84%.[54] The catalyst can be recovered, upon washing with diethyl ether and diluted HCl, and reused a further 6 times without a deleterious effect on the yield.[54] However, the demonstrated scope is limited and again precludes formation of tertiary amides. The authors make no comment on the exact role of the zinc in the reaction, however, presumably it acts as a Lewis acid and activates the carbonyl centre of the ester, hence promoting the nucleophilic attack of the amine.



Scheme 1.23: Amidation of methyl esters catalysed by Zn dust.[54]

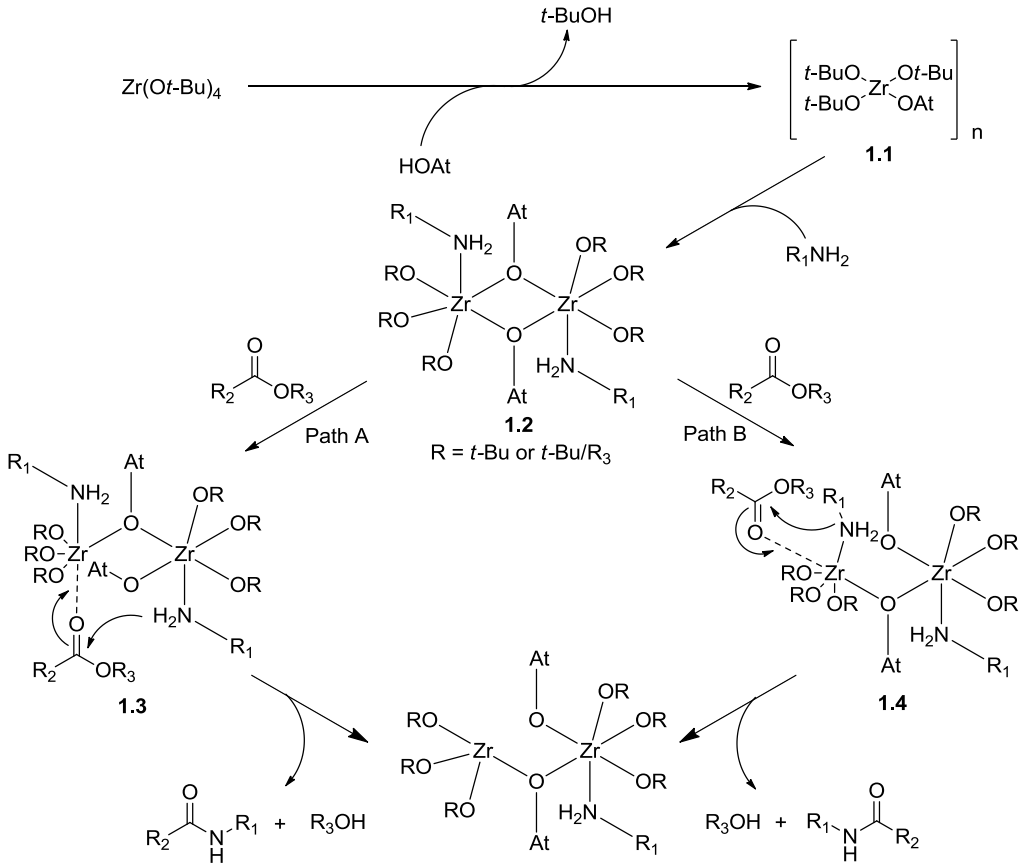
Porco *et al.* have reported the use of group IV metal alkoxides in combination with an additive to effect the amidation of esters (Scheme 1.24).[55] Comparing the efficiency of Ti(*Oi*-Pr)$_4$, Zr(O*t*-Bu)$_4$ and Hf(*Ot*-Bu)$_4$ alongside a range of additives (HOAt, HOBt, PFP,

2-hydroxypyridine and DMAP) demonstrated that Zr(O*t*-Bu)$_4$ (10 mol%) and HOAt (20 mol%) was the optimum catalyst/additive combination resulting in a 90% yield of a model substrate.[55] The ratio of catalyst to additive was then successfully reduced to 1:1, however this catalyst and additive system is not general, with the additive used altered according to the desired amidation reaction.[55] These conditions were then successfully applied to a diverse range of esters and amines achieving yields of 75 – 99%. Two optically pure substrates were also investigated, Boc-Ala-OMe and methyl (*S*)-mandelate, with little epimerisation observed (97 and 99% ee, respectively.)[55] Chemoselectivity was also demonstrated between lactones and ketones, and anilines and benzyl alcohols, while secondary amines could also be successfully applied in the reaction manifold to form the corresponding tertiary amide. However, as with other amidations, elevated temperatures of 100 °C can be required for some substrates.



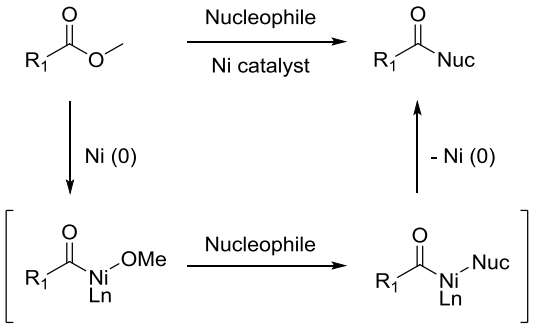
Scheme 1.24: Zr(*Ot*-Bu)$_4$/additive catalysed amidation of esters.[55]

Using X-ray crystallography, NMR and kinetic studies, a mechanism was proposed which suggests that initial ligand exchange of HOAt with *tert*-butyl alcohol forms a dynamic mixture of Zr-OAt species **1.1** that may afford a dimeric zirconium species **1.2**, which is the hypothesised catalytically active species (Scheme 1.25).[55] Coordination of an ester to one zirconium atom in the dimeric species forms a second dimeric species **1.3** or **1.4**, through the breaking of a Zn-O bridging bond.[55] The coordinated ester can then be attacked by the amine *via* a six- (Path A) or four-membered (Path B) transition state to afford the amide product.[55]

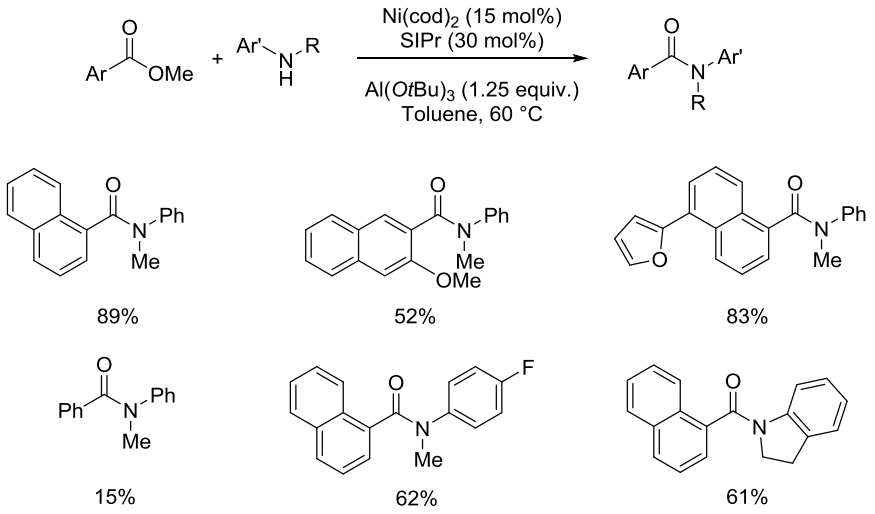


Scheme 1.25: Proposed catalytic cycle for Zr(*Ot*-Bu)$_4$/HOAt catalysed amidation of esters.[55]

Recently, Houk and Garg *et al.* have developed a catalytic method in which the acyl C-O bond of a methyl ester is activated through the oxidative addition of a nickel catalyst, avoiding decarbonylation (Scheme 1.26).[56] These activated adducts can then be trapped *in situ* with an aniline to form the corresponding tertiary amide product.[56] Using 15 mol% of Ni(cod)$_2$ and 15 mol% of the NHC SIPr in conjunction with a slight excess (1.25 equiv.) of Al(*O*tBu)$_3$, anilides can be formed in moderate to good yield (Scheme 1.27). However, no aliphatic amines were investigated, and reducing the size of the substituent on the ester moiety to a phenyl ring from a napthyl group hinders the reaction, with extended aromatic systems proposed to enable the nickel-mediated C-O bond cleavage.[56]



Scheme 1.26: Garg and Houk's amidation approach *via* Ni catalysed activation of the acyl C-O bond.[56]

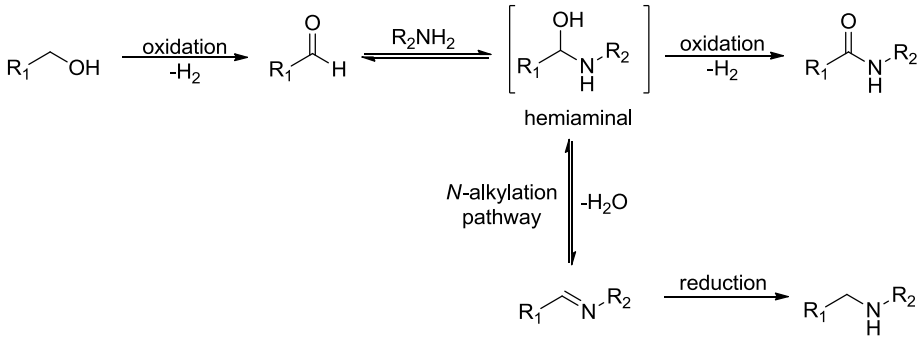


Scheme 1.27: Amidation *via* nickel catalysed activation of methyl esters.[56]

In the absence of Al(*O*tBu)$_3$, only trace amounts of amide was formed. DFT calculations showed that without Al(*O*tBu)$_3$ the reaction is endergonic, meaning that the amidation is thermodynamically unfavourable, whereas with Al(*O*tBu)$_3$, the reaction is thermoneutral.[56] Al(*O*tBu)$_3$ is also proposed to have a beneficial kinetic effect towards the rate-determining oxidative addition. Without the additive, the kinetic barrier for oxidative addition is calculated to be 33.2 kcal mol^{-1}, but this lowered to 26.8 kcal mol^{-1} when Al(*O*tBu)$_3$ is incorporated into the calculations.[56]

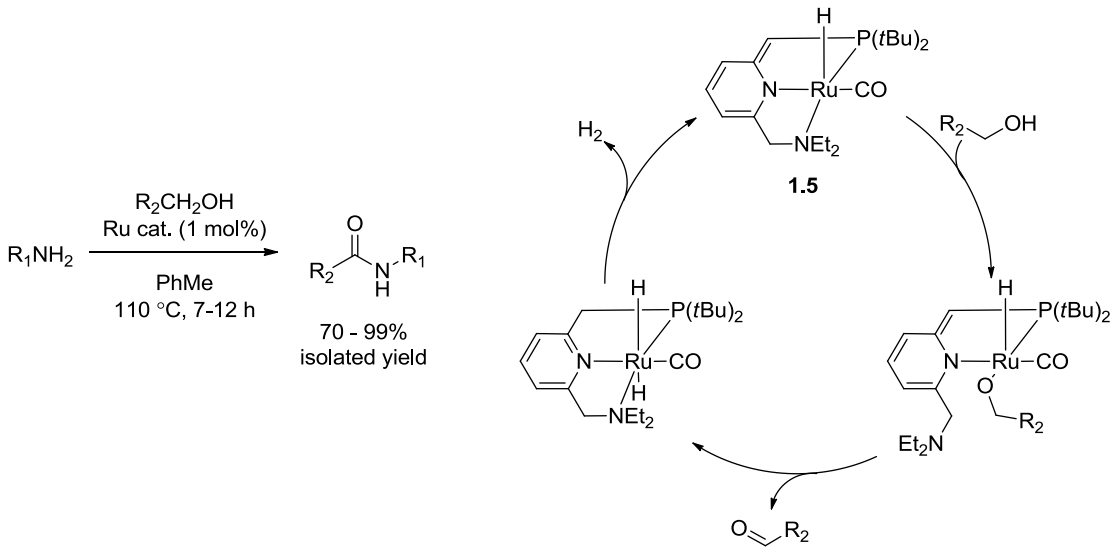
1.4.1.3 Metal Catalysed Amide Bond Formation from Alcohols

The ability to catalytically synthesise amides from alcohol substrates is a desirable transformation due to the wide range of potential alcohol starting materials that are commercially available. Additionally, the process is highly atom efficient and sustainable, with hydrogen gas the only by-product produced in the process. The reaction between alcohols and amines generally proceeds through the initial oxidation of the alcohol to an aldehyde, releasing one molecule of hydrogen (Scheme 1.28).[57] A hemiaminal is then formed through the reaction of this aldehyde and the amine component, which undergoes a second oxidation to the desired amide and releases a second molecule of hydrogen. If dehydration of the hemiaminal is faster than its dehydrogenation, a competing *N*-alkylation can instead occur, with this process more widely reported than the alternative amidation.[57–59] The use of ruthenium complexes in these processes has been extensively reported, however other transition metals including rhodium, gold, silver, iron, copper and zinc have also been shown to promote the desired amidation.



Scheme 1.28: General reaction pathway for the formation of amides from alcohols and amines.[57]

The first intermolecular procedure from Milstein *et al.* in 2007 utilised a ruthenium-pincer complex **1.5** (Scheme 1.29), with the production of hydrogen as the only by-product.[60] The pincer complex undergoes an aromatisation/dearomatisation process, with initial alcohol addition forming the corresponding pyridine complex. The loss of an aldehyde subsequently generates a *trans* ruthenium dihydride complex, from which the elimination of molecular hydrogen reforms the initial Ru-pincer complex. The aldehyde formed then reacts with amine to form an aminol, which is then oxidised by a similar cycle to the corresponding amide. Catalyst loadings as low as 0.1 mol% were shown to be able to effect the desired transformation, which also demonstrated high chemoselectivity, with substrates containing both a primary and secondary amine shown to react exclusively at the primary amine without any protection of the secondary amine required.[60]

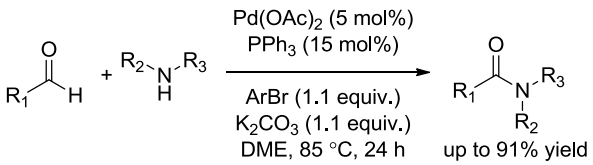


Scheme 1.29: Milstein's Ru-pincer complex mediated formation of amides.

Following Milstein's seminal report, the use of a variety of different ruthenium catalysts have been reported as mediators in amide bond forming process from alcohols, including the combination of $[Ru(p\text{-cymene})Cl_2]_2$ and phosphine ligands such as dppb as reported by Williams *et al.*,[61,62] the Rh(I)-diolefin amido complex $[Rh(trop_2N)(PPh_3)]$ as reported by Grützmacher,[63] and the use of NHCs in conjunction with $Ru(COD)Cl_2$ as reported by Madsen.[64]

1.4.1.4 Metal Catalysed Amide Bond Formation from Aldehydes

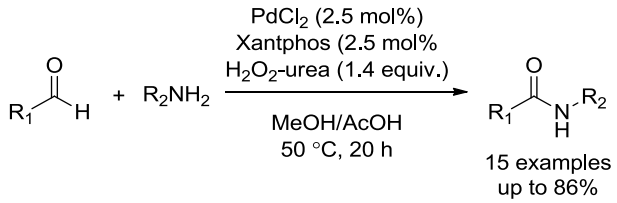
Metal catalysed oxidative amidation of aldehydes was first reported in the early 1980s and proceeds *via* the same mechanism as that for the amidation of alcohols (Scheme 1.28). The first catalyst system successfully employed in the transformation was $Pd(OAc)_2$ and triphenylphosphine utilising an aryl bromide (bromobenzene or 2,4,6-trimethylbromobenzene) as an oxidant, with a range of alcohols demonstrated to couple with morpholine, piperidine and di-*N*-propylamine (Scheme 1.30).[65,66]



Scheme 1.30: $Pd(OAc)_2$ catalysed oxidative amidation of aldehydes.[65,66]

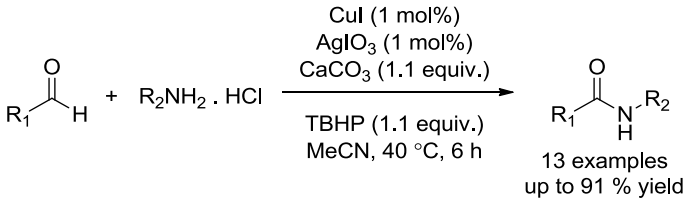
Improved conditions employing another palladium catalyst, $PdCl_2$, have since been reported by Torisawa *et al.* (Scheme 1.31).[67] Utilising H_2O_2 in urea as an oxidant and Xantphos as a

ligand allowed both the reaction temperature and time required to be lowered, whilst increasing the scope of amide substrates.



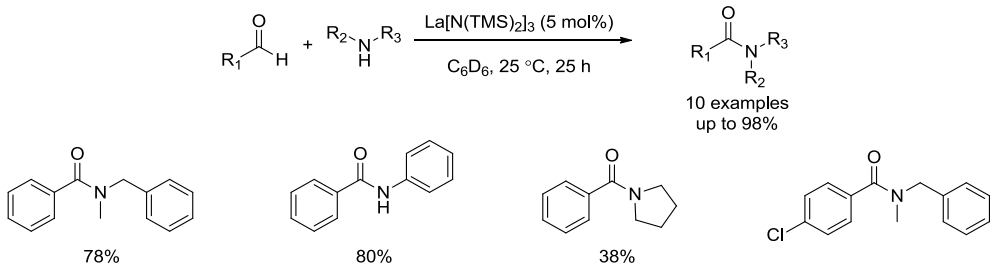
Scheme 1.31: $PdCl_2$ catalysed oxidative amidation of aldehydes.[67]

Copper catalysis can also be applied to oxidatively couple aldehydes and amine hydrochlorides. Using *tert*-butyl hydroperoxide, with a catalytic quantity of $AgIO_3$, Yoo and Li reported the synthesis of 13 amides using 1 mol% of CuI (Scheme 1.32).[68] The competing oxidative reaction of the amine was suppressed through the use of the amine hydrochloride salt instead of the free amine, with the authors rationalising that the salt form would be more resistant to oxidation. The process is also more suited to aromatic aldehydes with a marked decrease in yield observed when aliphatic aldehydes are applied (91% benzyl vs 39% cyclohexyl).[68] The coupling of a chiral amino acid derived substrate, *D*-valine methyl ester hydrochloride, was also reported in high yield (91%) with no observed racemisation.[68]



Scheme 1.32: Copper catalysed oxidative coupling of aldehydes.[68]

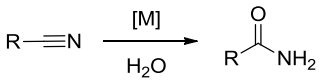
Lanthanide catalysts have also been recently utilised in the amidation of aldehydes. This approach is advantageous as it can be performed at room temperature without an exogenous oxidant, with the aldehyde presumed to act as the hydrogen acceptor. In 2008, Seo and Marks reported the use of lanthanum, samarium and yttrium to affect the transformation.[69] Lanthanum proved to be the superior metal, affording 78% of the amide product in the model reaction of benzaldehyde and *N*-methylbenzylamine, whereas samarium and yttrium only afforded 54 and 47%, respectively.[69] However, 3 equivalents of the aldehyde are required as a result of its role as the hydrogen acceptor. (Scheme 1.33).[69]



Scheme 1.33: Lanthanide catalysed amidation of aldehydes.[69]

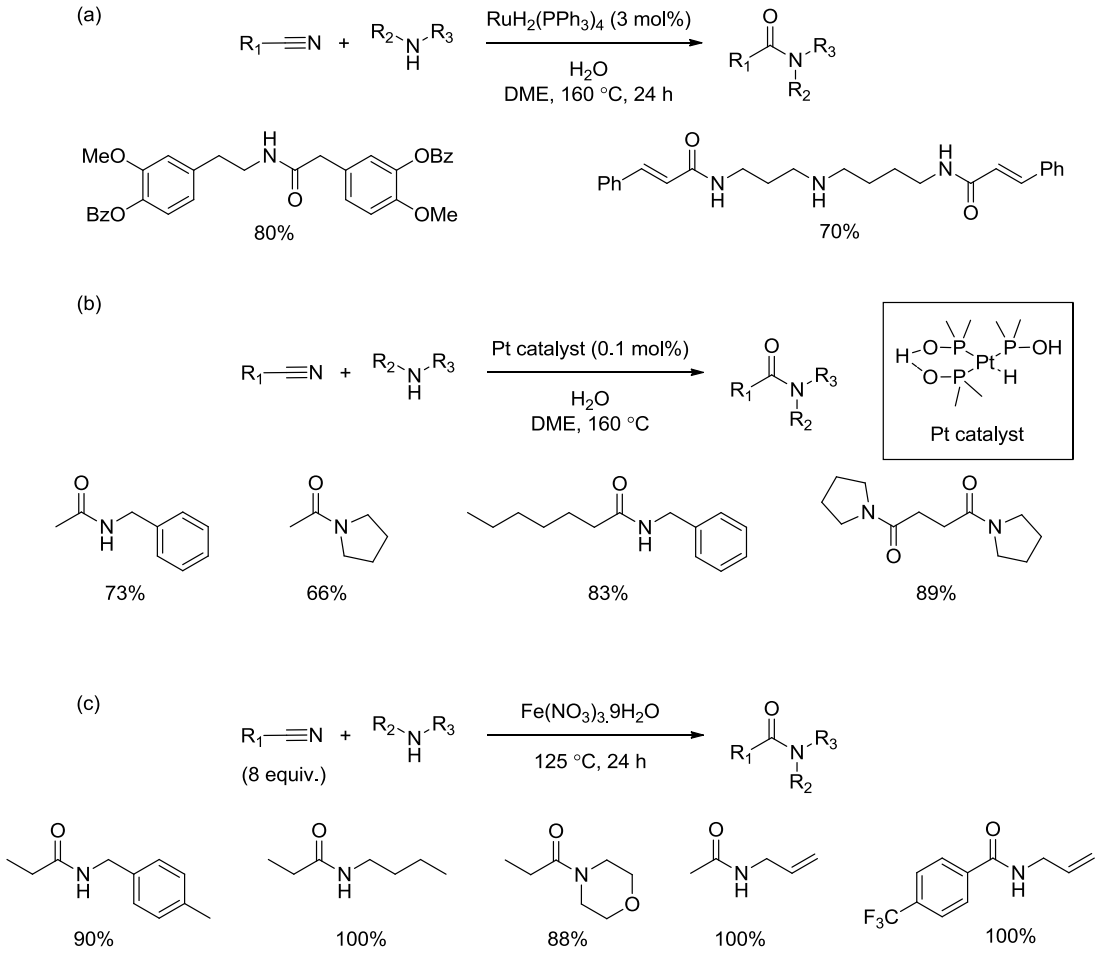
1.4.1.5 Metal Catalysed Amide Bond Formation from Nitriles

The use of nitriles in the formation of amides can be achieved both simply and efficiently through the metal catalysed hydration of the nitrile, with many catalysts including Cu, Ni, Rh, Ru, Ti and Zn (Scheme 1.34).[70–74]



Scheme 1.34: Metal catalysed hydration of nitriles to form primary amides.

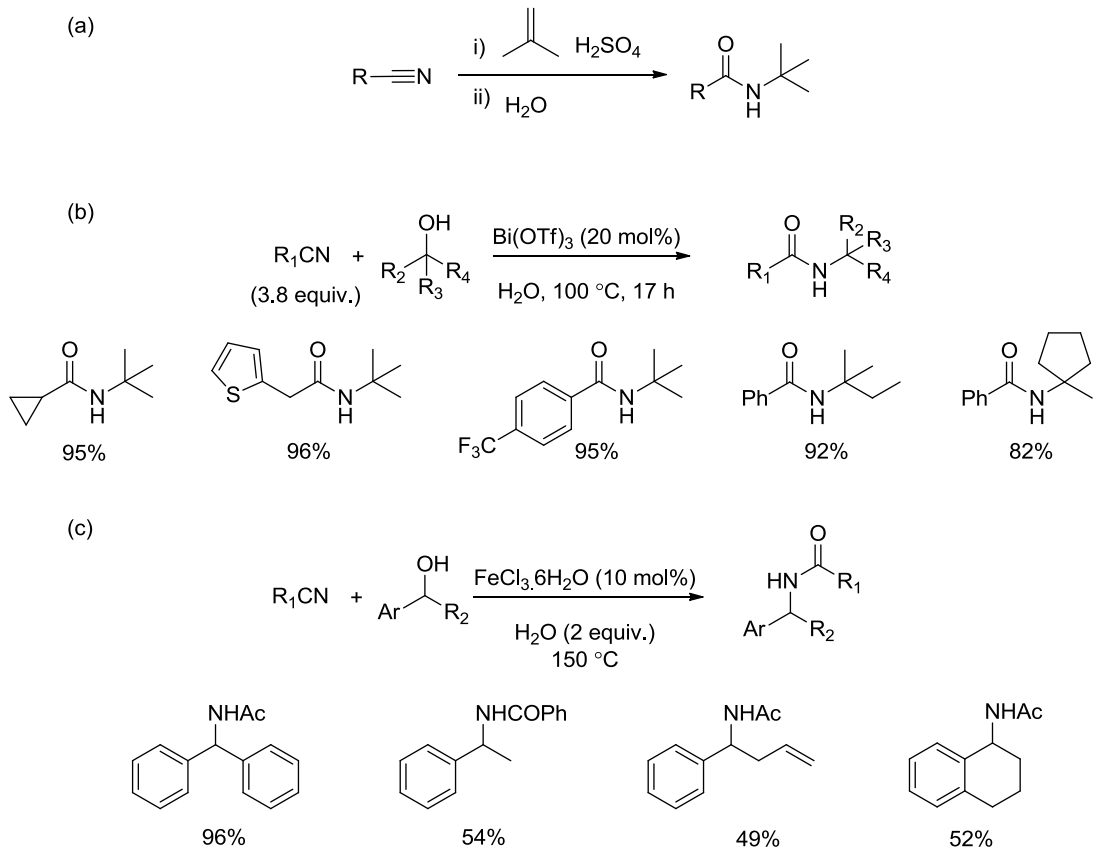
Alternatively, amides can be synthesised *via* the hydrolytic coupling of nitriles with amines. This was first reported by Murahashi in 1986 using ruthenium catalysis, where a range of amides were synthesised, including drug precursors (Scheme 1.35a).[75] However, elevated temperatures of 160 °C were required to facilitate the reaction. Further development of this transformation by De Vries in 2008 allowed the catalyst loading to be decreased further to loadings as low as 0.1 mol% of a platinum(II) complex (Scheme 1.35b).[76] However no reduction of the reaction temperature was achieved and extended reaction times of up to 60 hours were needed in some cases.[76] The use of iron catalysis, as demonstrated by Williams, did result in a slight reduction in the required reaction temperature to 125 °C, although the catalyst was required in a loading of 10 mol% along with a vast excess (8 equiv.) of the nitrile species (Scheme 1.35c).[77] The addition of water was not required, with the authors postulating that a sufficient amount of water is present in the reaction from the hydrated form of the catalyst and the undried nitrile reagent.[77]



Scheme 1.35: Selected examples of metal catalysed hydrolytic coupling of nitriles and amines.[75–77]

Alcohols can also be coupled to nitriles *via* the Ritter reaction (Scheme 1.36a). *In lieu* of the traditional use of sulfuric acid, transition metals have been successfully applied as catalysts. One such example is the use of bismuth triflate to couple a range of nitriles and tertiary alcohols (Scheme 1.36b).[78] 20 mol% of the catalyst species is required to ensure reaction completion, with a 20% decrease in yield observed when using a loading of 5 mol%.[78] The use of elevated temperatures is also required with the reaction performed at reflux in water, as well as a large excess (4.8 equiv.) of the nitrile species.[78]

Iron catalysis has also been used in the Ritter procedure, widening the scope of the transformation (Scheme 1.36c).[79] The loading of the catalytic species was able to be lowered to 10 mol%, however the reactions required a more forcing temperature of 150 °C to ensure reaction completion.[79] The substrate scope was also limited, investigating only three nitrile species alongside four aryl substituted tertiary alcohols.[79]

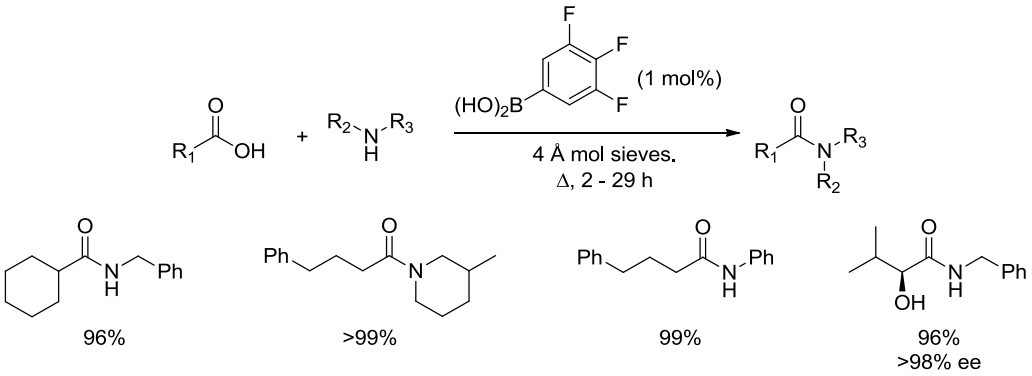


Scheme 1.36: (a) Typical Ritter conditions and mechanism. (b) $Bi(OTf)_3$ catalysed Ritter reaction.[78] (c) $FeCl_3$ catalysed Ritter reaction.[79]

1.4.2 Organocatalytic Amide Bond Formation

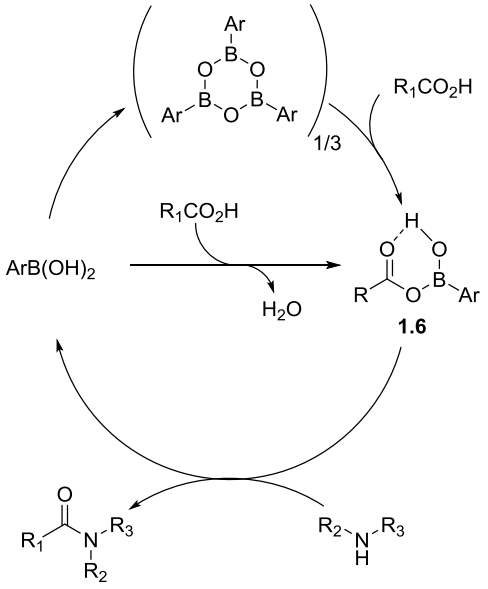
1.4.2.1 Organoboron Catalysed Amidation of Carboxylic Acids

The ability to form amide bonds through the use of boron catalysis was initially reported by Yamamoto *et al.*, with electron-deficient boronic acids species applied as the catalyst. Electron-deficient moieties enhance the Lewis acidity of the boron species, thus allowing its use in catalytic quantities, whereas previous boron-mediated procedures required the boron species to be applied in stoichiometric amounts.[80] With 3,4,5-trifluorobenzeneboronic acid shown to be the most effective catalyst with only 1 mol% required, the transformation of both primary and secondary amines with carboxylic acids was shown to proceed in excellent yield and with low levels of epimerisation in relevant chiral examples (Scheme 1.37).[81] However, a limited scope of substrates was detailed. In conjunction with the requirement of high temperatures (110 - 160°C) and in some cases extended reaction times, this may prove to limit the potential applicability of the methodology.



Scheme 1.37: Boronic acid catalysed amide bond formation with selected examples.[81]

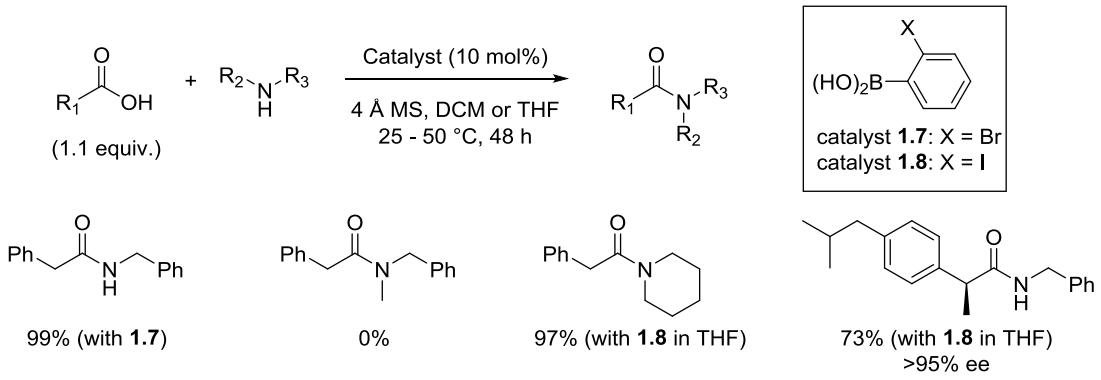
The use of 4 Å molecular sieves in the reaction to remove the water formed from the condensation of the proposed mono(acyloxy)boronic acid intermediate **1.6** and the amine was found to be critical. The reaction was found to only afford 50% of the desired amide product in their absence, with hydrolytic decomposition of the intermediate acyloxyboronic acid **1.6** inhibiting further reaction (Scheme 1.38).[81] Interestingly, the reaction between this intermediate and the amine was found to proceed at room temperature. [81]



Scheme 1.38: Proposed catalytic cycle for boronic acid catalysed amide bond formation.[81]

Hall *et al.* have reported the use of *ortho* halo-substituted aryl boronic acids to facilitate amide bond formation (Scheme 1.39).[82] It was found that *ortho*-bromophenylboronic acid (**1.7**) and *ortho*-iodophenylboronic acid (**1.8**) both allowed the desired amidation reaction to proceed at 25 °C in good yield, albeit requiring a catalyst loading of 10 mol% and an extended reaction time of 48 h.[82] However, in order for aromatic carboxylic acids to couple,

a catalyst loading of 20 mol% and an elevated reaction temperatures of 50 °C were required, whilst it was also noted that acyclic secondary amines were incompatible coupling partners.[82]



Scheme 1.39: Amide bond formation utilising *ortho* halo-substituted boronic acids.[82]

Continuing their focus on boronic acid catalysed amidation protocols, Hall *et al*. have since reported a range of second generation catalysts, with the most effective catalyst found to incorporate an electron-donating methoxy substituent *para* to the iodine substituent.[83] This adaptation to the catalytic species allowed a wider range of carboxylic acid substrates to be applied to the reaction manifold, efficiently affording 20 amide products in as little as 2 hours.[83] However, aromatic carboxylic acids again required elevated reaction temperatures (50 °C) and extended reaction times of 48 h.[83]

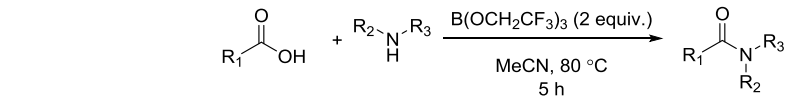
The successful application of boronic acid catalysis in amide bond formation has proven advantageous over more traditional approaches utilised in amide synthesis. Firstly, as the reagents can be applied in catalytic quantities, the atom efficiency is vastly increased in comparison to coupling reagent-promoted amide bond formation, which is furthered again by the ability to incorporate the boronic acids into solid supported coupling reagents. In addition to this, no stoichiometric by-products are formed in the processes allowing simple purification of the amide products.

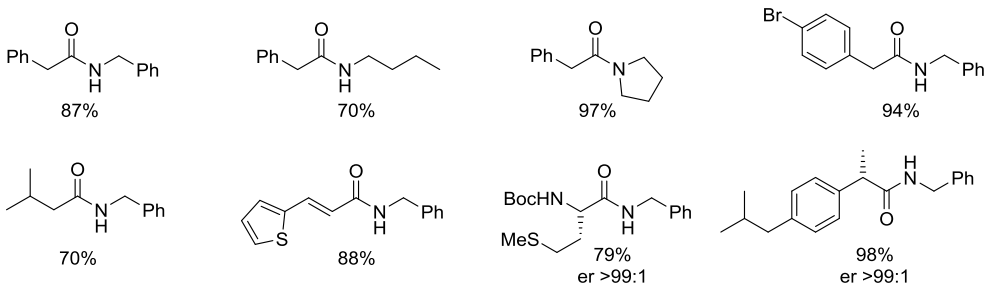
However, the requirement of high temperatures and extended reaction times is a drawback of these methodologies. Substrates such as aromatic carboxylic acids also require more forcing conditions to ensure reaction completion and, additionally, the amidation of acyclic secondary amines was found to be unachievable in all the catalytic protocols. In addition to this, the complete removal of water, *via* azeotropic reflux or the addition of molecular sieves, is imperative to prevent the hydrolytic decomposition of the catalyst.

In an effort to overcome these drawbacks, Sheppard and Starkov have recently reported the use borate esters such as tris(2,2,2-trifluoroethyl) borate, $B(OCH_2CF_3)_3$, to promote amide bond formation.[84] Although superstoichiometric quantities (2 equivalents) of the borate were employed, a range of amides were able to be synthesised at a temperature of 80 °C in MeCN, without the need for rigorous anhydrous conditions or the addition of an exogenous drying reagent.[84] Furthermore, the pure amide products were obtained after a simple aqueous work-up.[84] This methodology was further refined and extensively exemplified in 2013, with 68 amide products reported (Scheme 1.40a).[85] The reaction time was decreased from 15 to 5 hours with negligible effects on the yield observed.[85] The already operationally simple purification was also improved, resulting in the use of commercially available resins to remove any residual starting materials and reagents, creating a solid-phase work-up procedure.[85] Chiral carboxylic acids were also found to be competent substrates in the reaction, with minimal epimerisation observed in most cases.[85] In addition to the reported amidation procedure, the use of $B(OCH_2CF_3)_3$ in the transamidation of DMF was reported. The addition of DMF to the standard reaction conditions *in lieu* of a carboxylic acid allowed ten formylation products to be synthesised (Scheme 1.40b).[85]

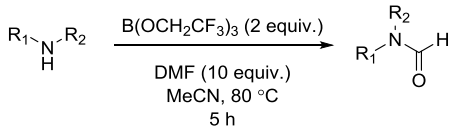
Further development of this approach towards amide bond formation by the Sheppard group has enabled $B(OCH_2CF_3)_3$ to be applied in catalytic quantities.[86] Previously, decomposition of the partially hydrolysed borate ester, formed upon amidation, to an oligomeric boron species had hindered catalytic turnover. However, the use of Dean-Stark apparatus was able to effect efficient turnover in refluxing *tert*-amyl methyl ether (TAME), with the amidation of primary and secondary amines, in addition to unprotected amino acids, found to proceed in good to excellent yield (Scheme 1.40c).[86] ^{19}F NMR studies of the Dean-Stark trap indicated that one equivalent of trifluoroethanol was removed from the reaction mixture, with further kinetic studies showing that the reaction was first-order in catalyst, 0.5 order in acid concentration and independent of amine concentration.[86] These observations resulted in acyloxyboron species **1.9** being proposed as the active acylating species (Scheme 1.40d).[86] However, ^{11}B NMR studies indicated that only tetrahedral boron species are present in the reaction, indicating that **1.9** exist as a Lewis base adduct with the amine or solvent (**1.10**).[86]

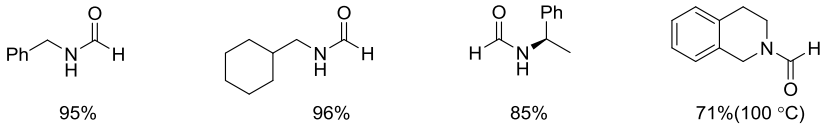
(a)


B(OCH2CF3)3 (2 equiv.)
MeCN, 80 °C
5 h

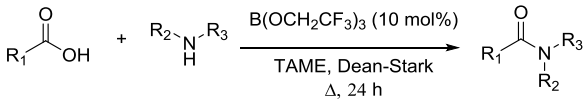

87%
70%
97%
94%
70%
88%
79%
er >99:1
98%
er >99:1

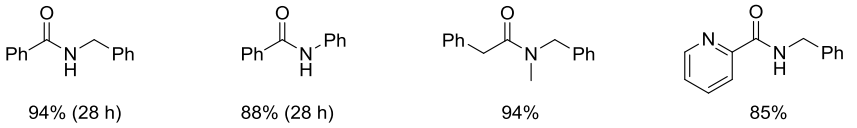
(b)

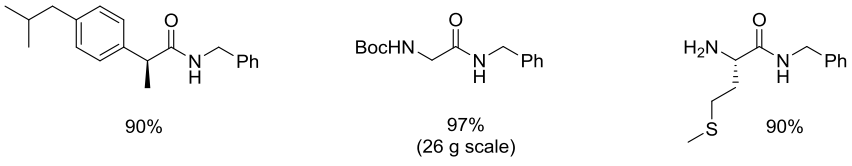

B(OCH2CF3)3 (2 equiv.)
DMF (10 equiv.)
MeCN, 80 °C
5 h


95%
96%
85%
71%(100 °C)

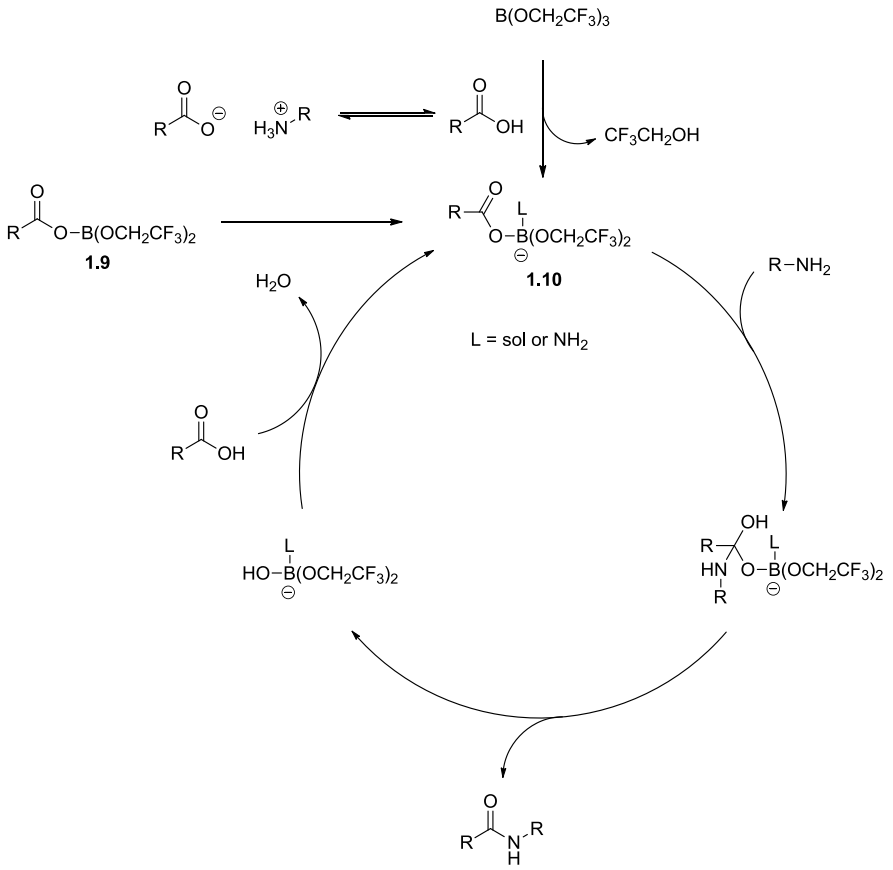
(c)


B(OCH2CF3)3 (10 mol%)
TAME, Dean-Stark
Δ, 24 h


94% (28 h)
88% (28 h)
94%
85%


90%
97%
(26 g scale)
90%

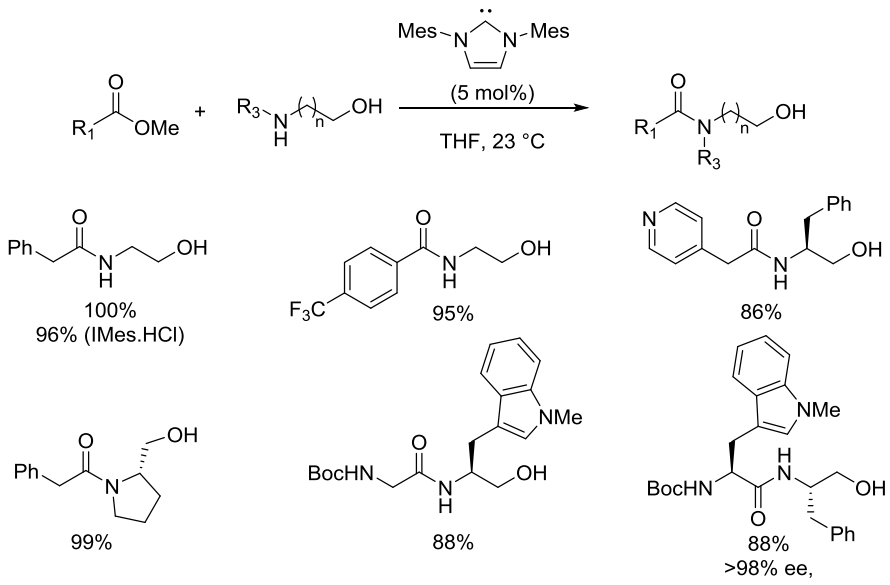
(d)



Scheme 1.40: (a) Selected examples of $B(OCH_2CF_3)_3$-mediated amidation.[85] (b) Selected examples of $B(OCH_2CF_3)_3$-mediated transamidation of DMF.[85](c) Selected examples of $B(OCH_2CF_3)_3$ catalysed amidation.[86] (d) Proposed mechanism for $B(OCH_2CF_3)_3$ catalysed amidation.[86]

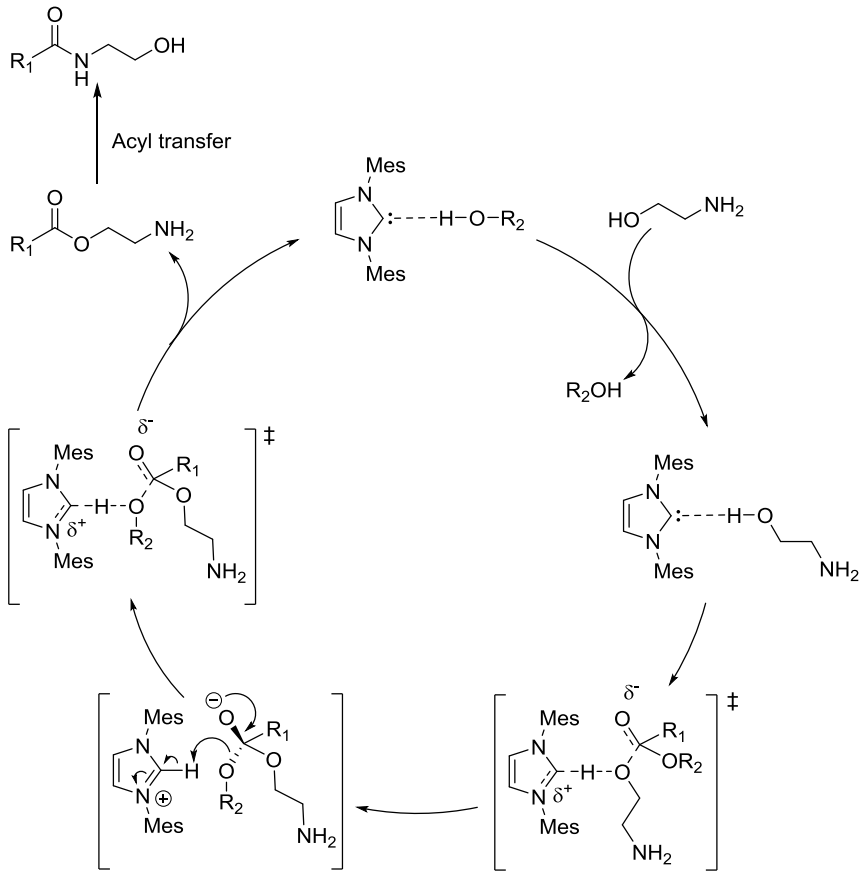
1.4.2.2 Organocatalysed Amidation of Esters

In 2005, Movassaghi and Schmidt utilised the NHC IMes to efficiently promote the reaction.[87] Using 5 mol% of the NHC, a diverse range of amides were synthesised under ambient conditions, without any requirement for an excess of reagents or drying agents (Scheme 1.41).[87] Additionally, the reaction proceeds as efficiently when the IMes catalyst is generated *in situ* from the corresponding HCl salt upon treatment with 10 mol% of potassium *tert*-butoxide.[87] Aliphatic and aromatic esters were found to be competent substrates, as were esters and amino alcohols bearing heterocycles. For substrates with unfavourable electronic or steric properties, the addition of 5 mol% of LiCl was found to increase the rate and yield.[87]



Scheme 1.41: IMes catalysed coupling of amino alcohols with unactivated esters.[87]

Following X-ray and solution-based spectroscopic studies, carbene-alcohol complexes were shown to be surprisingly stable as a result of hydrogen bonding.[87] The authors propose that in the reaction, an initial transesterification occurs followed by an acyl transfer to form the desired amide product (Scheme 1.42).[87]

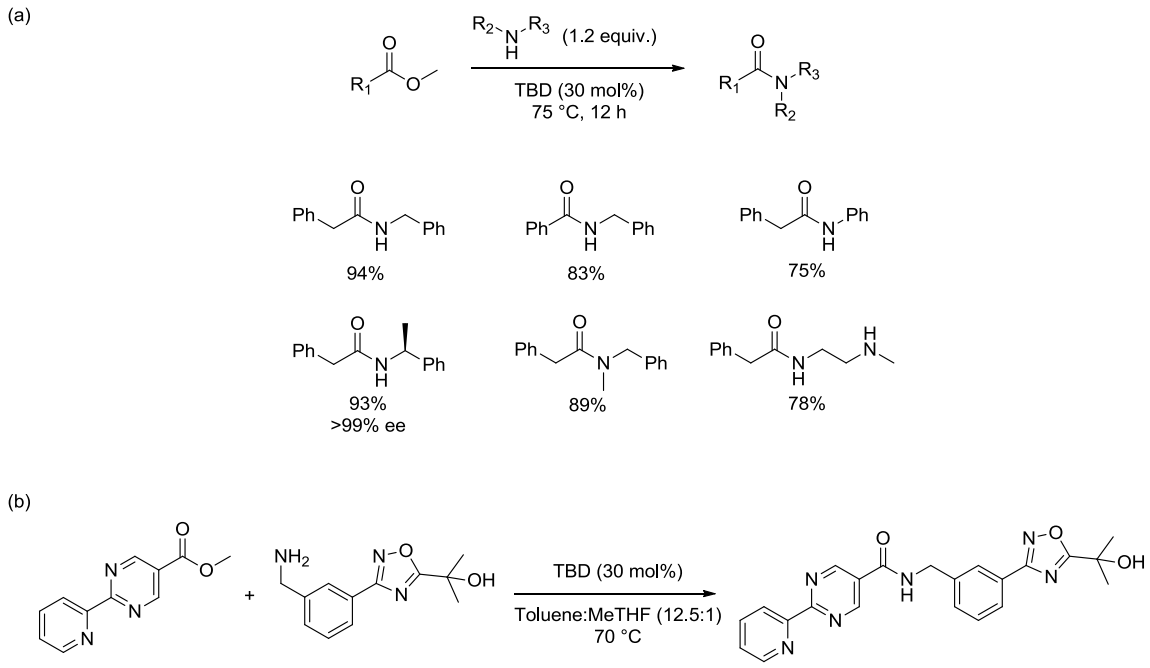


Scheme 1.42: Proposed mechanism for IMes catalysed coupling of amino alcohols and unactivated esters.[87]

Alternatively, the coupling of esters and amines can be facilitated by a nucleophilic catalytic species. In 2007, Mioskowski *et al.* facilitated this transformation through the use of 30 mol% of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).[88] A range of primary and secondary aliphatic amines alongside anilines were successfully coupled with both aliphatic and aromatic esters under solvent-free conditions at 75 °C (Scheme 1.43a).[88] Primary amines were found to be more reactive than secondary amines, as demonstrated through the coupling of *N*-methyl-ethylenediamine and methyl phenylacetate, which exclusively afforded 78% of the primary amide.[88] The reaction was also performed at ambient conditions however, a drop in yield of ~20% was observed.[88]

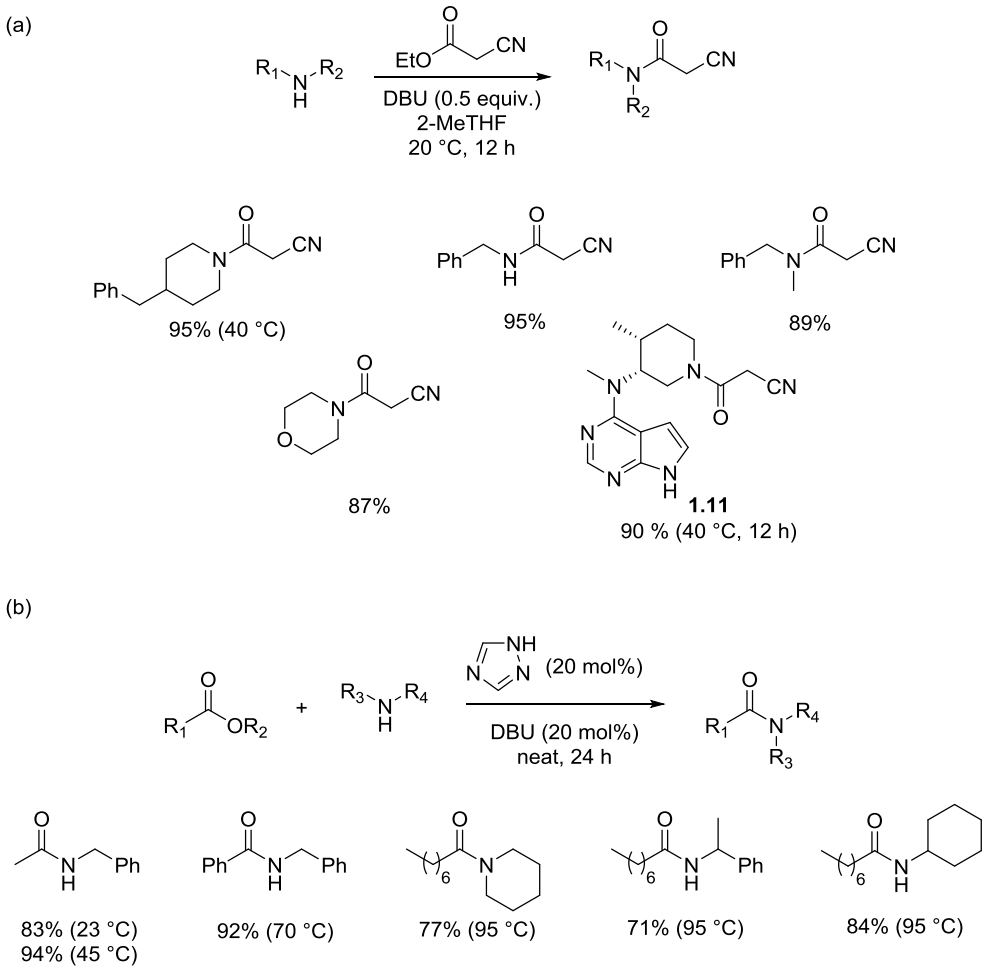
This methodology has since been successfully applied on a pilot-plant scale by Weiberth *et al.* in the synthesis of a human prostaglandin-D synthase inhibitor (H-PGDS) (Scheme 1.43b).[89] The reaction was performed on a 9 kg scale in a toluene/2-MeTHF (12.5:1) co-solvent system to afford the desired amide product in 82% isolated yield

(12.5 kg).[89] Application of this methodology eliminated 2 steps from the progenitor plant process (saponification of the ester followed by activation of the carboxylic acid).[89]



Scheme 1.43: (a) Selected examples of TBD catalysed amidation of esters.[88] (b) Application of TBD amidation to pilot-plant scale synthesis of an H-PGDS inhibitor.[89]

In 2009, both Vaidyanathan and co-workers, as well as Yang and Birman reported the use of DBU in catalytic amide synthesis. Vaidyanathan *et al*. reported the coupling of cyanoacetate moieties with amines promoted by 0.5 equiv. of DBU under ambient conditions or mild heating.[90] The coupling of a small range of primary and secondary amines was investigated, alongside the synthesis of a potent immunosuppressant **1.11** (Scheme 1.44a).

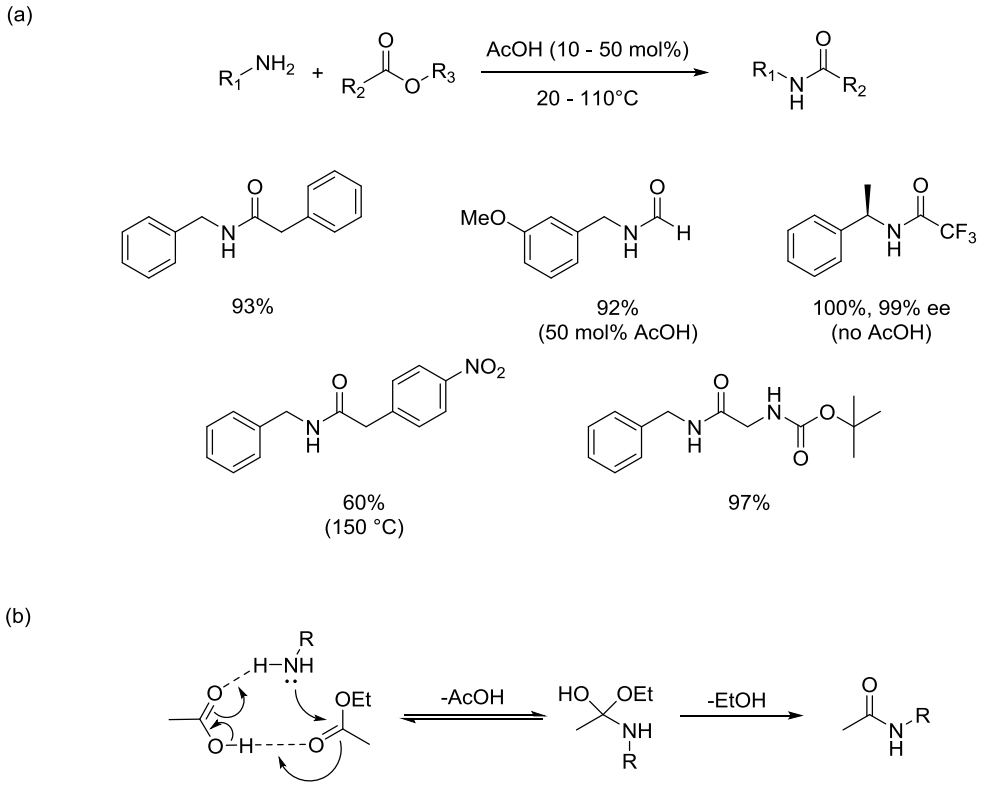


Scheme 1.44: (a) Amide coupling of cyanoacetates catalysed by DBU.[90] (b) Amide coupling of esters catalysed by 1,2,4-triazole.[91]

Yang and Birman demonstrated the use of catalytic quantities of both DBU and 1,2,4-triazole to facilitate the neat aminolysis of aliphatic and aromatic methyl or ethyl esters with benzylamine, piperidine, α-methylbenzylamine and cyclohexylamine (Scheme 1.44b).[91] Use of DBU without the triazole resulted in diminished yields of product, even when the temperature of the reaction was increased.[91] Poorer yields were also observed when the amidation was performed at room temperature, with heating to 90 – 95 °C required in some cases to ensure an efficient transformation.[91]

More recently, Sanz Sharley and Williams have reported the use of acetic acid as a catalyst in the amidation of esters. Using this methodology, a range of methyl and ethyl esters were coupled with benzylamine in good to excellent yields (Scheme 1.45a).[92] However, in the case of ethyl trifluoroacetate, the reaction was found to proceed at room temperature without the requirement of the acid catalyst, and when used in conjunction with

(*R*)-(+)-α-methylbenzylamine, was found to lead to no stereoerosion.[92] Methyl benzoate proved to be unreactive under the reaction conditions, however methyl 4-nitrobenzene was successfully coupled, albeit requiring an elevated temperature of 150 °C.[92] Competition studies and ^{13}C-labelling NMR studies suggested that the acetyl moiety in the amide products originated from the ester component and not the acid catalyst. With the reaction unsuccessful in H_2SO_4, therefore suggesting that the acid is not behaving as a proton transfer reagent, a mechanism was proposed, involving acetic acid rather than just a proton in the transition state (Scheme 1.45b).[92]

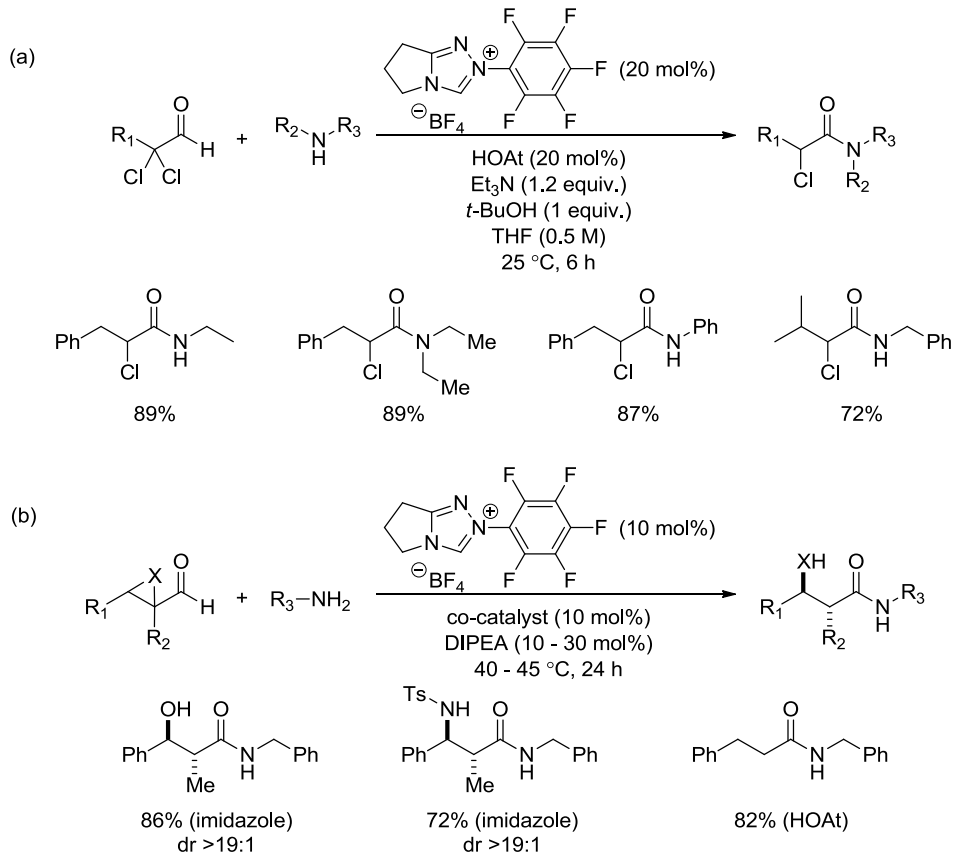


Scheme 1.45: (a) Selected examples of AcOH catalysed amidation of esters. (b) Proposed mechanism using ethyl acetate as the acyl source.[92]

1.4.2.3 Organocatalytic Amidation of Aldehydes

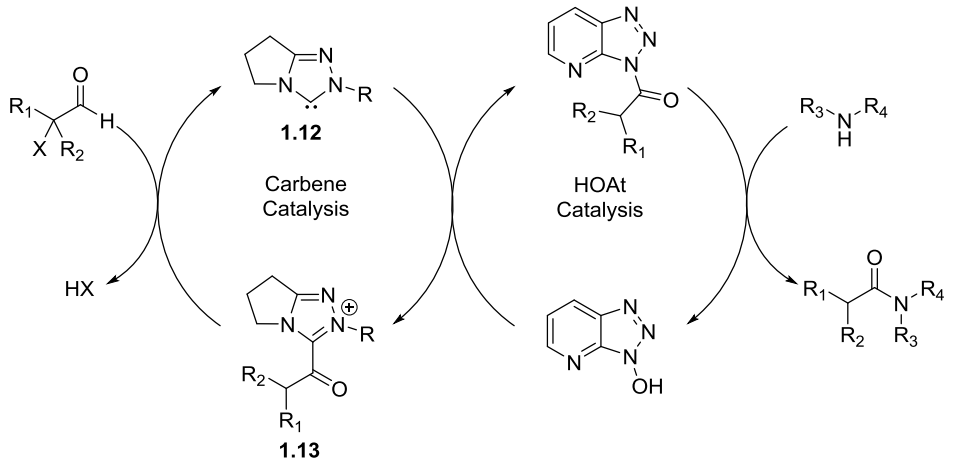
Similarly to the metal catalysed oxidative amidation of aldehydes discussed in Section 1.5.1.3, N-heterocyclic carbenes (NHCs) can also be utilised to form amide bonds. In 2007, the groups of Rovis and Bode independently reported their use of NHC catalysis to promote the formation of amide bonds. Rovis applied an NHC catalyst and a co-catalyst in a relay catalysed internal redox process furnishing amides from α-reducible aldehydes and amines. A range of co-catalysts were screened, from which, HOAt, HOBt, imidazole, DMAP and PFP found to be effective in promoting the reaction.[93] Using 20 mol% of both a

pentafluorophenyl-triazolium NHC precatalyst and HOAt, α-haloaldehydes and primary and secondary alkyl or aryl amines were transformed into 12 amides in good to excellent yields at ambient temperature within 6 hours (Scheme 1.46a).[93] Interestingly, α,β-epoxy, α,β-aziridino and α,β-unsaturated aldehydes could also be applied to the reaction manifold, resulting in the formation of β-hydroxy, β-amino and alkanamides, respectively, in both good yield and diastereoselectivity (Scheme 1.46b).[93]



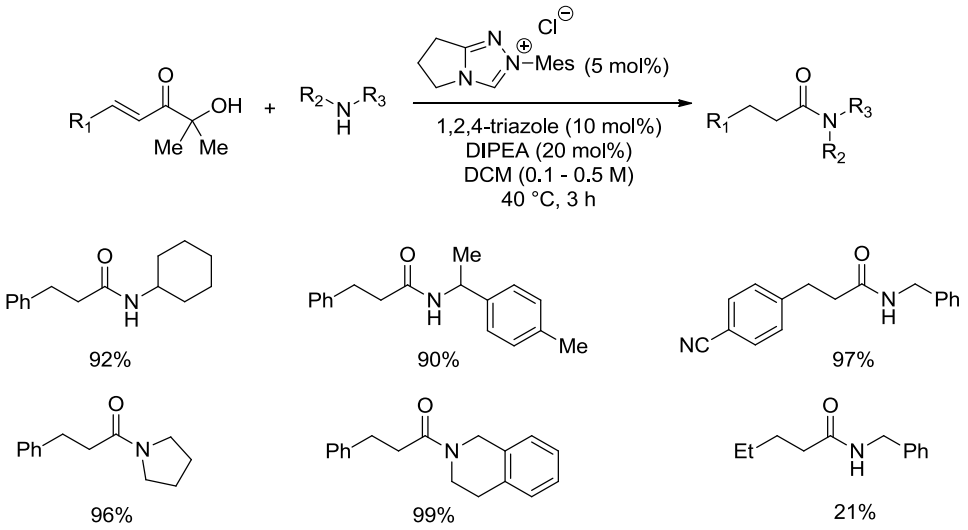
Scheme 1.46: (a) NHC catalysed internal redox process forming amides. (b) Application of the methodology to form β-hydroxy, β-amino and alkanamides.[93]

The proposed catalytic cycle initiates upon the formation of carbene **1.12** which nucleophilically adds to the α-haloaldehyde, forming a Breslow intermediate in the form of an acyl azolium intermediate **1.13**.[93] This intermediate can then undergo an acyl transfer with the hydroxybenzotriazole additive to form an active ester species.[93] Nucleophilic attack of the amine then furnishes the desired amide product and regenerates the additive (Scheme 1.47).[93]



Scheme 1.47: Proposed catalytic cycle for NHC/HOAt catalyst system.[93]

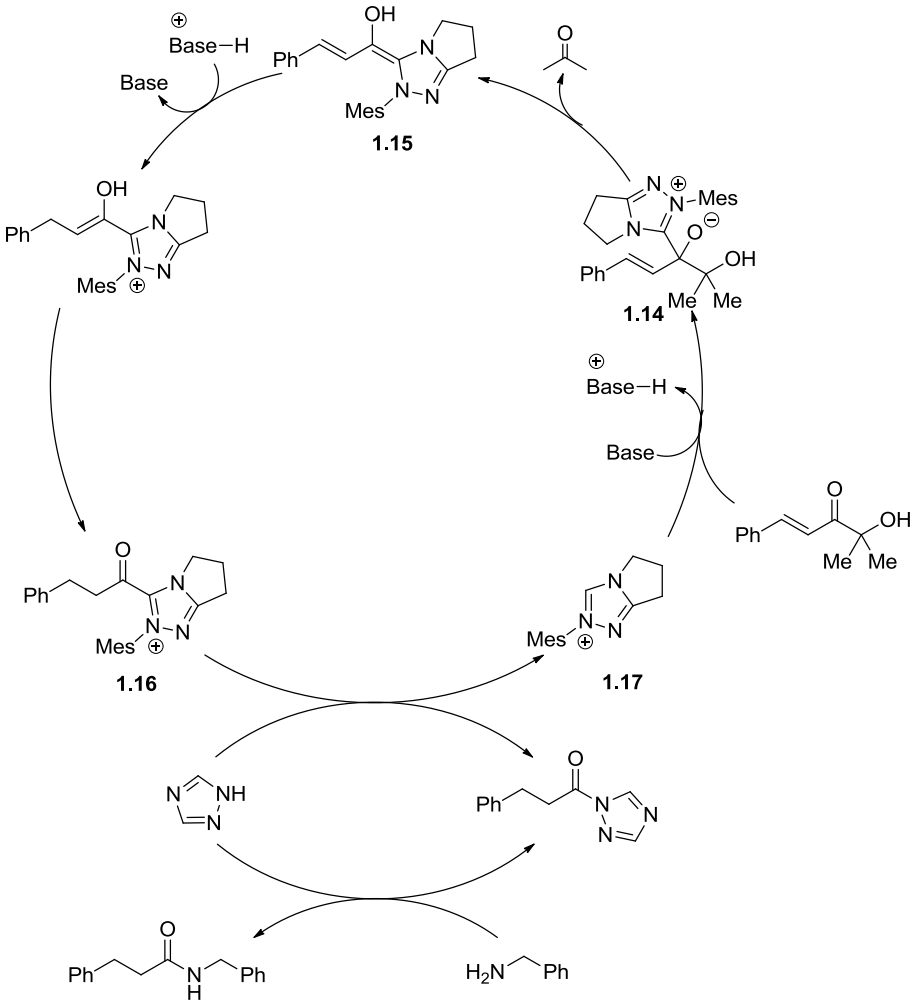
Bode *et al.* employed a triazole precatalyst in conjunction with a triazolium NHC, to enable the catalytic amidation of α′-hydroxyenones (Scheme 1.48).[94] The ability to catalytically amidate these species is desirable due to their use as α,ß-unsaturated aldehydes surrogates that are unable to undergo the competing imine formation which was found to be previously problematic. As before, the transformation was achieved using a lower catalyst loading than Rovis.[94]



Scheme 1.48: NHC catalysed amidation using a triazole precatalyst.[94]

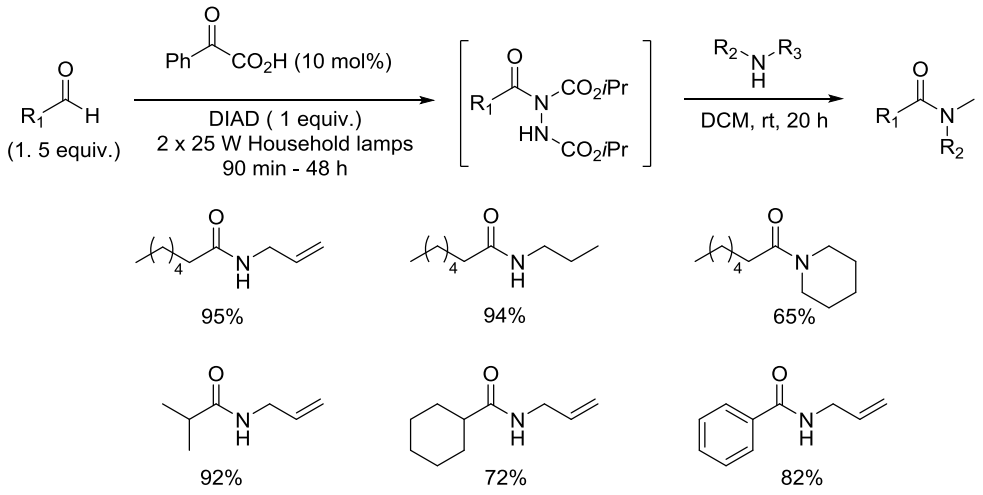
The NHC-catalysed redox amination is proposed to proceed as shown in the tandem catalytic cycle (Scheme 1.49), with initial attack of the NHC onto the α′-hydroxyenone to give **1.14**.[94] Acetone is then expelled to form the Breslow intermediate **1.15**, which is then protonated and tautomerises to form carboxylate **1.16**.[94] This is then turned over by the triazole

co-catalyst, forming the acyl triazole **1.17** and regenerating the NHC precatalyst.[94] This acyl triazole is then activated towards nucleophilic attack by the amine component.



Scheme 1.49: Proposed catalytic cycle for NHC/triazole catalysed amidation.[94]

An alternative approach towards the amidation of aldehydes has recently been reported by Papadopoulos and Kokotos utilising photoorganocatalysis to activate the aldehyde.[95] Using 10 mol% of the photocatalyst phenylglyoxylic acid to promote the formation of an intermediary carbonyl imide from a corresponding aldehyde and DIAD, a diverse range of secondary amides can be formed in moderate to excellent yields at ambient conditions upon the addition of an amine (Scheme 1.50).[95] This methodology is advantageous as a result of the inexpensiveness and commercial availability of the photocatalyst, and, additionally, the use of low-cost household lamps to promote the reaction. However, in some cases, protracted reaction times of up to 48 h are required for the initial carbomyl imide intermediate formation.[95]



Scheme 1.50: Photoorganocatalysed approach to the amidation of aldehydes.[95]

In summary, a plethora of amidation approaches have been developed focussing on addressing the inherent issues associated with coupling-reagent mediated amide bond formation. With the development of metal- and organocatalysed amidations, the poor atom economy of amidation reactions can be mitigated. Furthermore, finite, expensive and toxic metal reagents are avoided through the use of organocatalysts. Highly efficient and chemoselective approaches to amide bond formation in peptides have also been developed addressing the issues in both solution- and solid-phase peptide synthesis. However thus far, no one contemporary approach to amide bond formation has emerged as a general amidation methodology. Drawbacks such as reaction scope, harsh conditions, toxic and finite metal reagents and the requirement of stoichiometric of additives limit the effective application of reported methodologies. Therefore, further development of these existing amidation techniques, or for the existing library of approaches to be further augmented *via* research in to state-of-the-art amide bond forming methodologies, is a necessity. This future research should aim to fully address the aforementioned outstanding issues and result in a general, mild, atom economical and highly efficient amidation methodology.

2. Chapter 2 – Organocatalytic and Organobase Mediated Amidation of Unactivated Esters

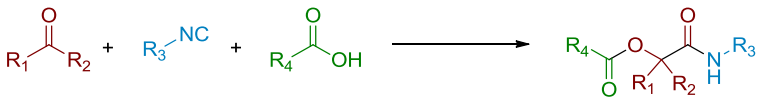
2.1 Introduction

2.1.1 Multicomponent Approaches to Amide Bond Formation

A multicomponent reaction (MCR) is a reaction in which 3 or more reactants combine *in situ* to form a single product. This combination occurs in a sequential manner to give highly selective products which retain the majority of atoms present in the starting materials, minimising waste and thus making MCRs highly atom economical. A single purification process is required, minimising the time and cost associated in isolating the desired product. Accordingly, if MCRs can be successfully applied in amide bond formation, this would create a highly expedient, efficient and cost effective route towards amide synthesis. Classical MCR approaches to forming amides such as the Passerini and Ugi reactions employ the use of isocyanides, and these are further exemplified below.

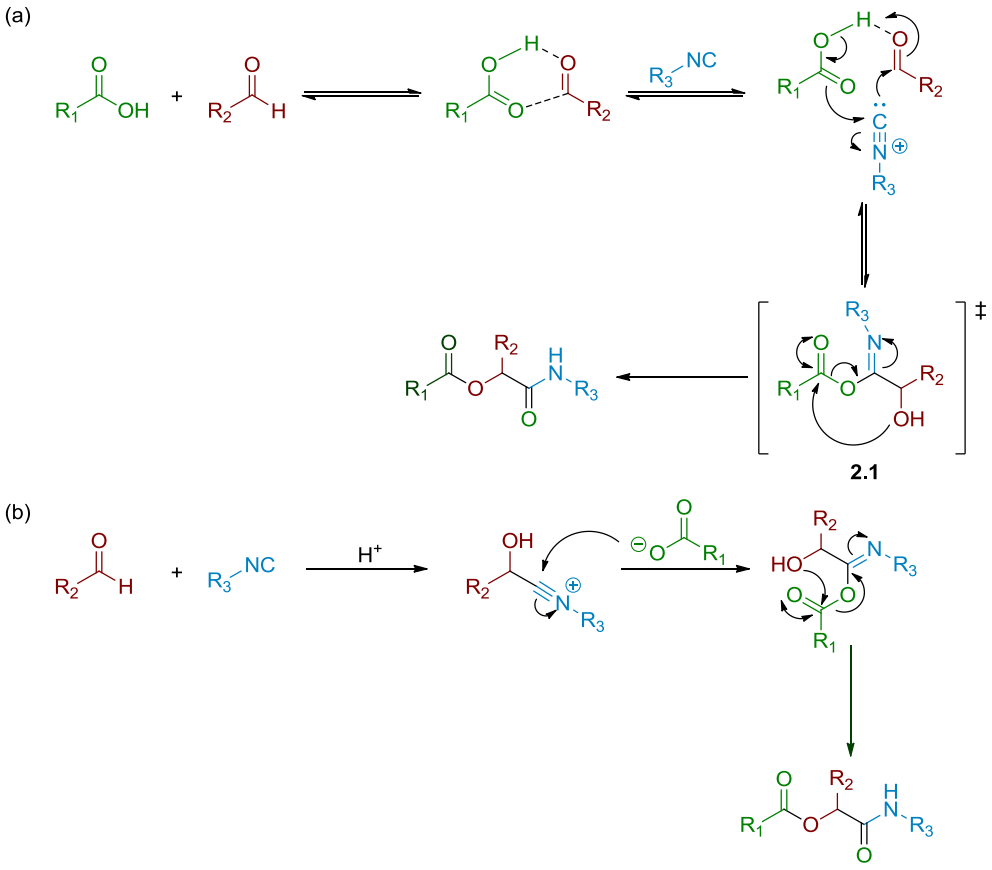
2.1.1.1 Passerini Reaction

First reported in 1921, the Passerini reaction was the first MCR to employ an isocyanide.[96] The reaction of a ketone or aldehyde with the isocyanide and a carboxylic acid results in the formation of an α-acyloxycarboxamide in one step (Scheme 2.1).



Scheme 2.1: General Passerini reaction.

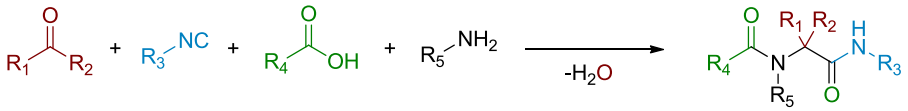
Two mechanisms for the formation of the α-acyloxycarboxamide have been proposed. Ugi has proposed a non-ionic, concerted trimolecular pathway, as a result of the reaction being accelerated in aprotic solvents and kinetic studies showing a dependency on all three reactants (Scheme 2.2a).[97,98] Electrophilic activation of the carbonyl group is followed by nucleophilic attack by the isocyanide, resulting in the formation of the nitrilium transition state **2.1**.[97] Acyl transfer to the hydroxyl group then forms the desired α-acyloxycarboxamide.[97] Alternatively, in polar solvents, the reaction is postulated to occur *via* initial protonation of the carbonyl with subsequent nucleophilic attack of the isocyanide to form the nitrilium intermediate (Scheme 2.2b).[99] Acyl transfer and tautomerisation then furnish the α-acyloxycarboxamide.[99]



Scheme 2.2: Proposed Passerini mechanisms: (a) Non-ionic pathway.[97] (b) Ionic pathway.[99]

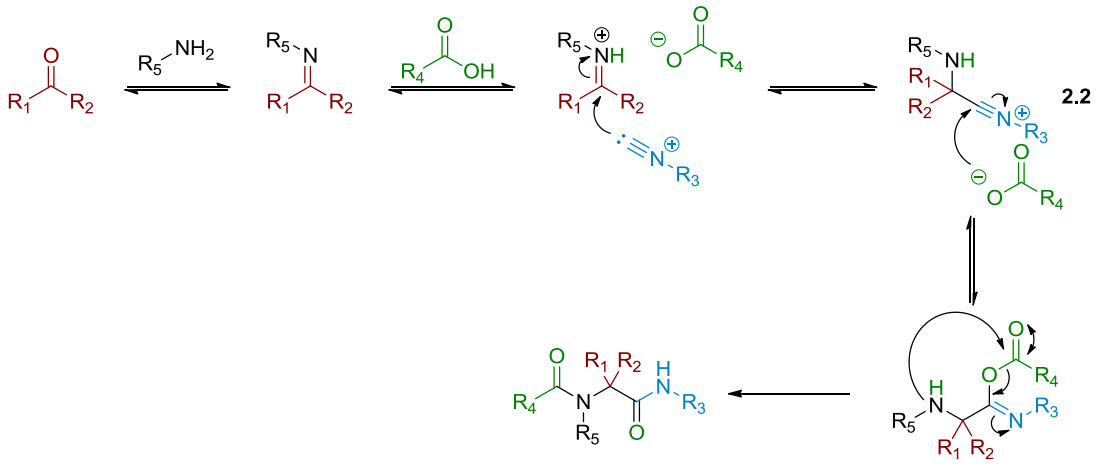
2.1.1.2 Ugi Reaction

First reported in 1959, the Ugi reaction is similar to the Passerini reaction, but incorporates a fourth component in the form of an amine species. This results in the formation of an α-aminoacyl amide (Scheme 2.3), with the liberation of water the sole by-product.[100] The reaction can be performed in polar, aprotic solvents, however recent research has shown that the reaction is accelerated in water.[101]



Scheme 2.3: General Ugi reaction.

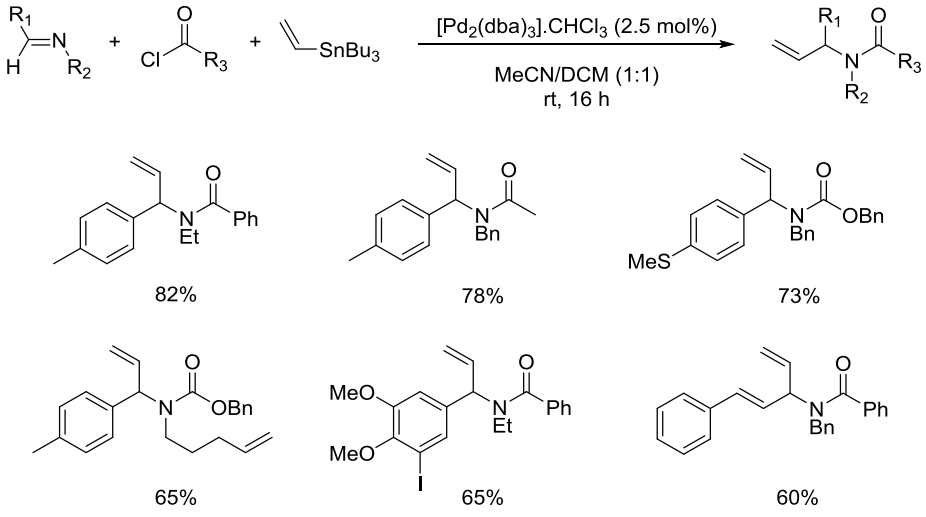
Initial imine formation from the ketone or aldehyde and the amine, with subsequent nucleophilic attack of the isocyanide, forms the nitrilium intermediate **2.2** (Scheme 2.4). This is then attacked by the carboxylic acid, with a subsequent Mumm rearrangement transferring the acyl group from the oxygen to the nitrogen.[102] Alternatively, a preformed imine can be used in the reaction.



Scheme 2.4: Ugi Mechanism.

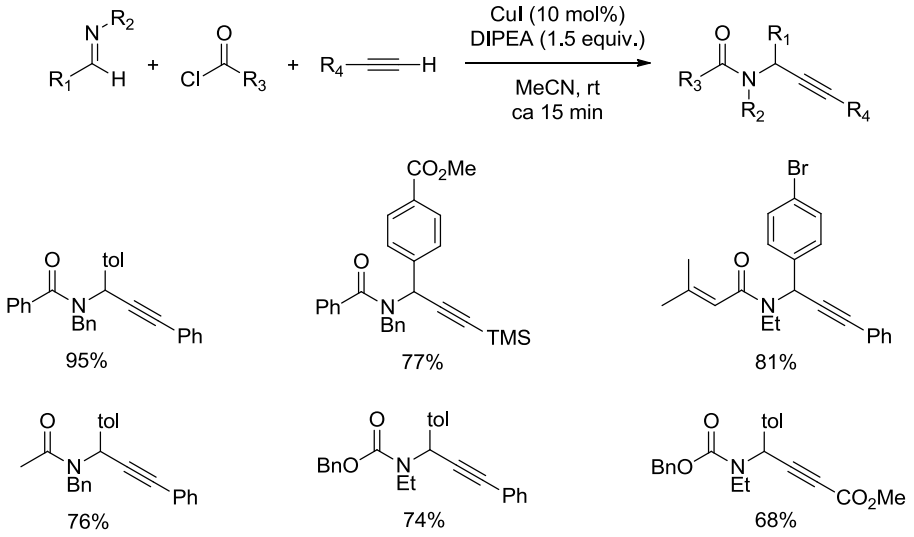
2.1.1.3 Contemporary MCR Approaches to Amide Bond Formation

In recent years, the combination of MCR approaches to amide synthesis with transition metal catalysis has been explored. In 2004, Arndtsen *et al.* reported a palladium catalysed Stille-type cross coupling of imines, acid chlorides (or chloroformates) and organotin reagents to synthesise α-branched amides in high selectivity and under mild conditions. (Scheme 2.5)[103] The reaction displays a good degree of generality with both alkyl and aryl acid chlorides tolerated, as well as functional groups such as ethers, thioethers and esters. Enolisable C-alkyl imines, however, were found to be incompatible.[103] Chemoselectivity is also displayed through the use of imines with terminal alkenes, which exclusively furnish the desired amide over the possible competing Heck product.[103]



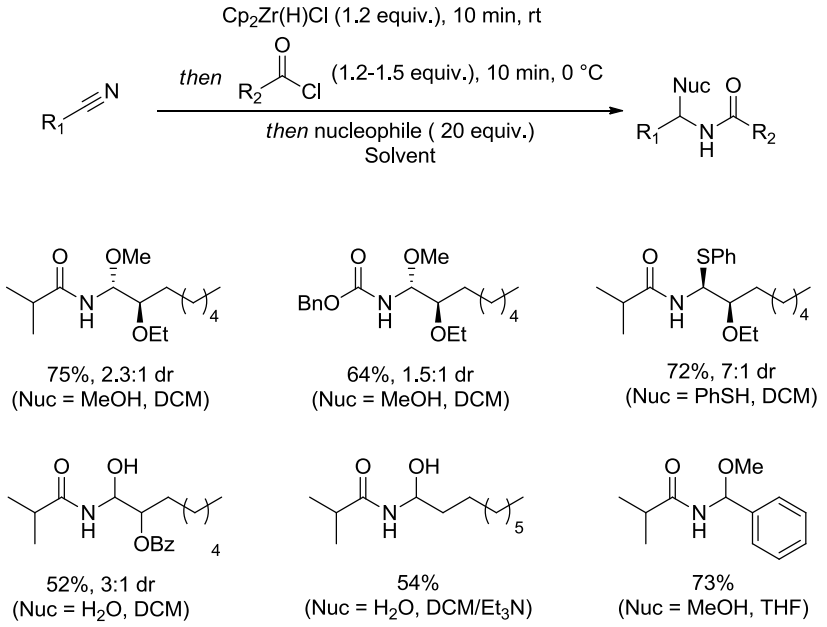
Scheme 2.5: Palladium-catalysed 3-component synthesis of α-branched amides.

In the same year, Arndtsen and co-workers reported a copper catalysed variant coupling imines and acid chlorides/chloroformates with terminal alkynes forming propargylamides (Scheme 2.6).[104] Using 10 mol% of CuI, a diverse range of substituted imines were coupled in good to excellent yields with alkyl and aryl substituted acid chlorides and alkynes in rapid reaction times (15 min) at ambient temperatures.[104]



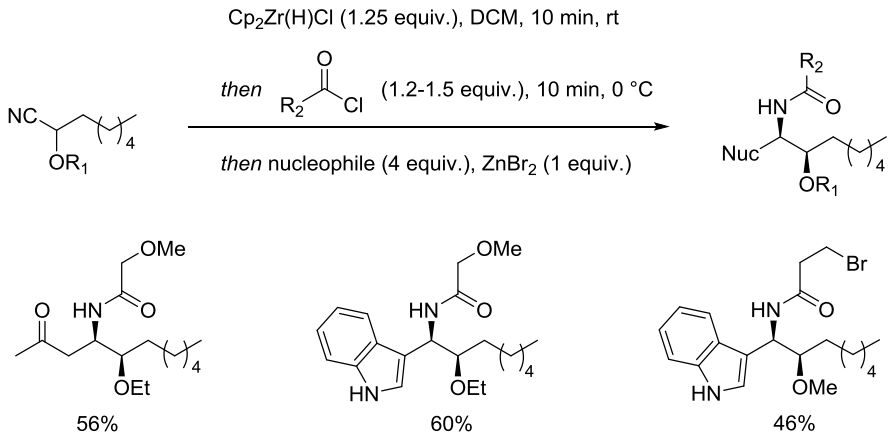
Scheme 2.6: Selected examples of Cu catalysed 3-component synthesis of propargylamides.[104]

In 2007, the Floreancig group reported a multicomponent approach to acyl aminals and hemiaminals through nitrile hydrozirconation.[105] After hydrozirconation of the nitrile, reaction with an acid chloride followed by nucleophile addition to the resulting acylimine results in the formation of the acyl aminal or hemiaminal (Scheme 2.7).[105] However, a slight excess of the zirconium reagent is required as well as a vast excess of the nucleophile.[105] Additionally, poor diastereoselectivities of the obtained products are achieved. Also, as the reagents are added sequentially (Zr, acyl chloride then nucleophile), whether this can be classed as a true multicomponent reaction is debatable.



Scheme 2.7: Multicomponent approach to acyl aminals and hemiaminals.[105]

Similarly, further work by Floreancig *et al.* led to the development of a protocol allowing the synthesis of α-branched amines through the hydrozirconation of nitriles.[106] As before, an acylimine is formed through the reaction of an acyl chloride with the metalated nitrile, before activation of the acylimine with a Lewis acid ($ZnBr_2$) and subsequent nucleophilic attack by a π-nucleophile (Scheme 2.8).[106] Again, a slight excess of the Zr reagent is utilised with an equimolar amount of $ZnBr_2$ required.[106] The nucleophile is again required in excess, although this is reduced to 4 equiv. in comparison to the progenitor process.[105] Sequential addition of the reagents again raises the issue as to whether this methodology can be termed a multicomponent reaction.

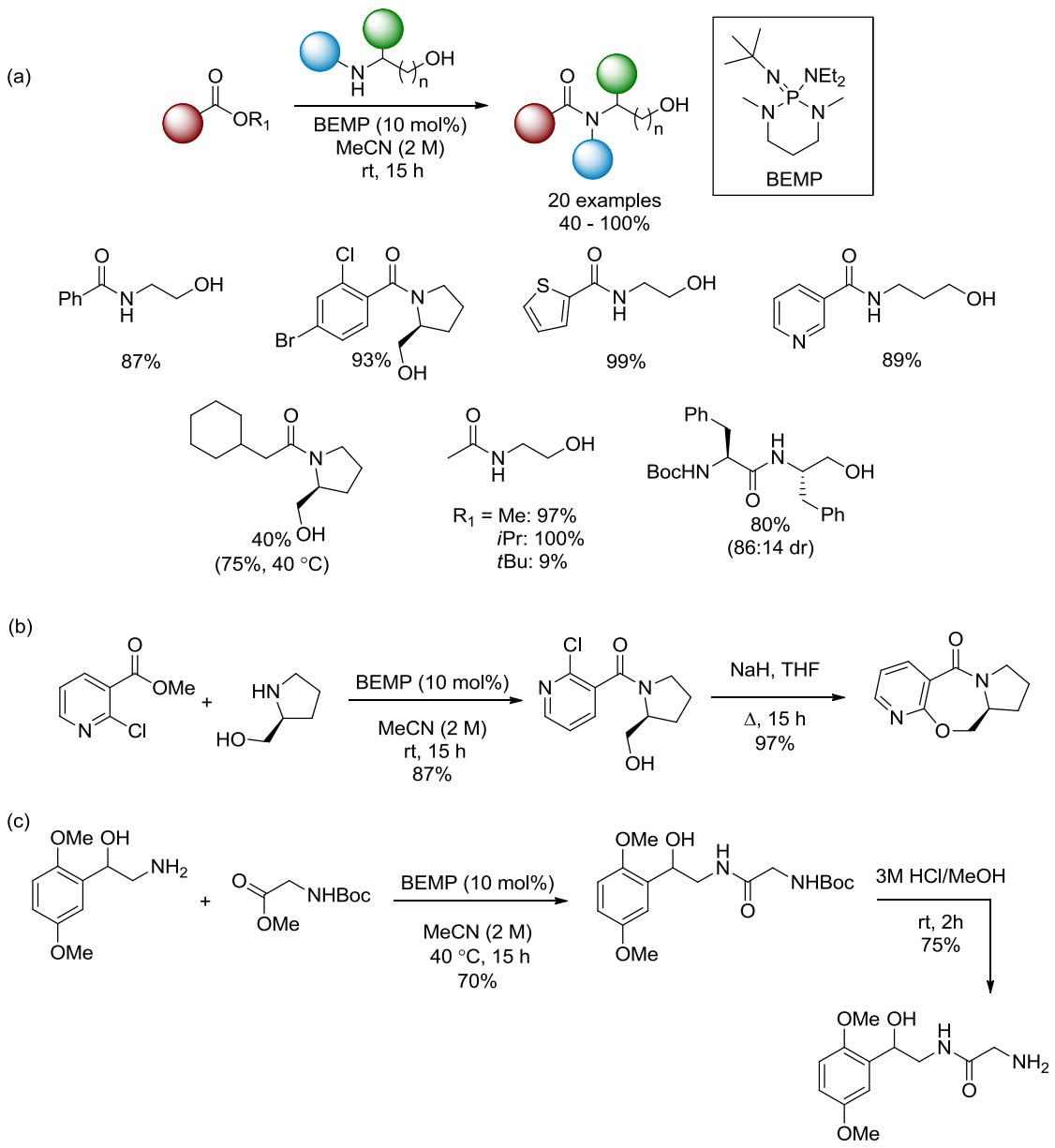


Scheme 2.8: Hydrozirconation multi-component approach to α-branched amides.[106]

Since the development of the classical multi-component approaches to amide bond formation, limited examples of catalysed methodologies have been reported. Although, in the case of Arndtsen, mild and efficient protocols have been reported, the use of transition metal catalysis has inherent drawbacks such as the associated cost, toxicity and sustainability. Alternatively, zirconium reagents can also be utilised, but these are applied in excess which again raises similar issues to the other transition metal catalysed approaches. Additionally, the approaches reported by Floreancig require the use of reagents in excess severely reducing their atom economy. With these drawbacks in mind, there is therefore scope for the development of efficient organocatalysed multicomponent reaction approaches to amide bond formation.

2.1.2 Prior Development of Catalytic Amidation Approaches within the Jamieson Group

In recent years within our laboratories, a programme focused on catalytic amide bond formation has been developed, with a view to addressing some of the outstanding issues associated with the transformation. In 2013, an organobase-mediated procedure was reported for the amidation of unactivated esters with amino alcohols. Using 10 mol% of the phosphazene BEMP as the basic species, 20 amide products were furnished in 40 – 100 % yield at ambient temperatures (Scheme 2.9a).[107] Additionally, two medicinally relevant compounds, an AMPA receptor potentiator (Scheme 2.9b) and the α_1 receptor agonist midodrine (Scheme 2.9c), were synthesised with the amidation steps proceeding in 87% and 70%, respectively.[107] Substrates bearing methyl, ethyl and isopropyl leaving groups on the ester were coupled in good yields, however the use of a *tert*-butyl group significantly hindered the reaction as a result of the increased steric bulk.[107] Enantiopure esters were also competent substrates, however erosion of chirality was observed (dr = 86:14).[107] The use of alternative, more cost effective phosphazene bases were also demonstrated with P_1-^{t}Bu and BTPP catalysing the reaction of methyl benzoate and ethanolamine to 93 and 82% yield, respectively (Figure 2.1).[107]



Scheme 2.9: (a) Selected examples of BEMP-mediated amidation of esters and amino alcohols. (b) Synthesis of AMPA potentiator. (c) Synthesis of midodrine.[107]

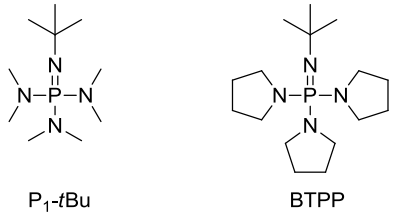
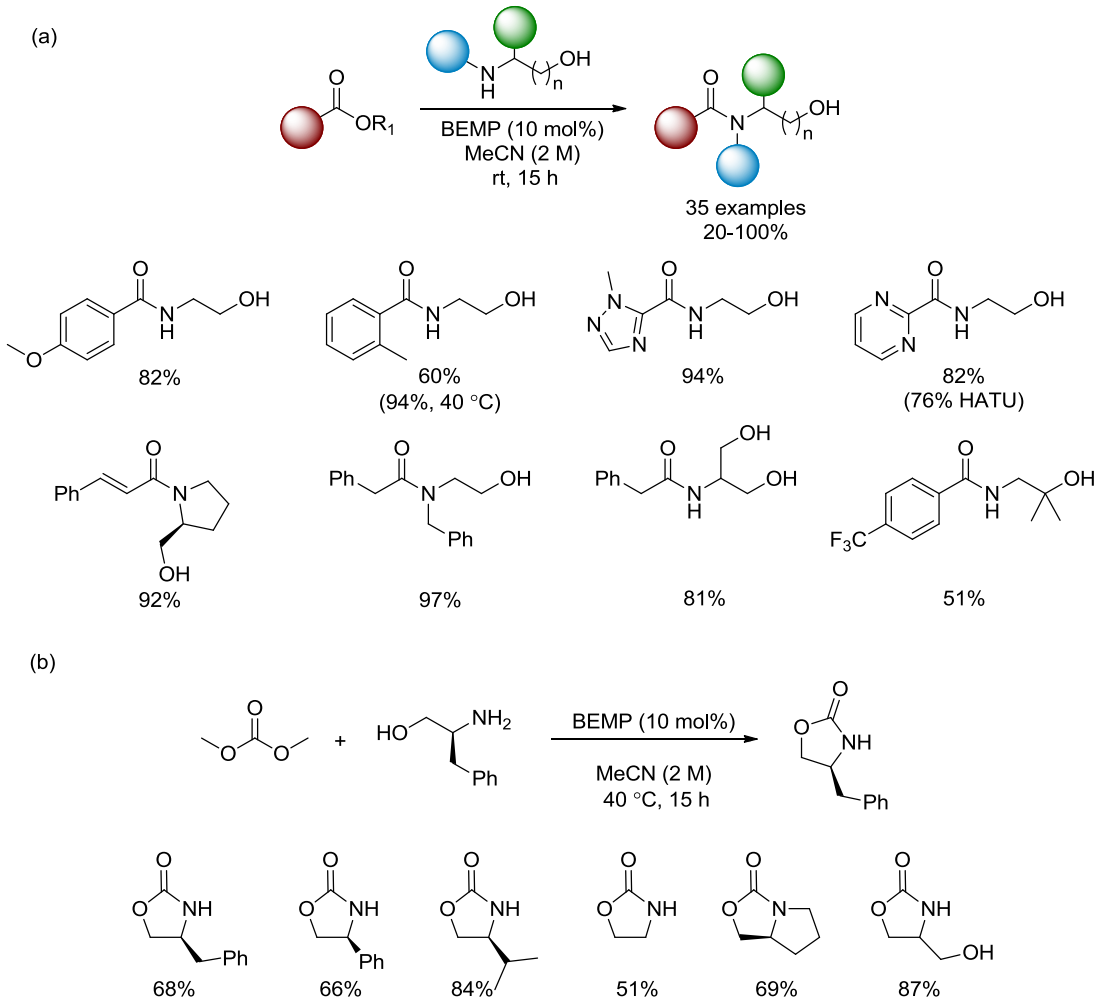


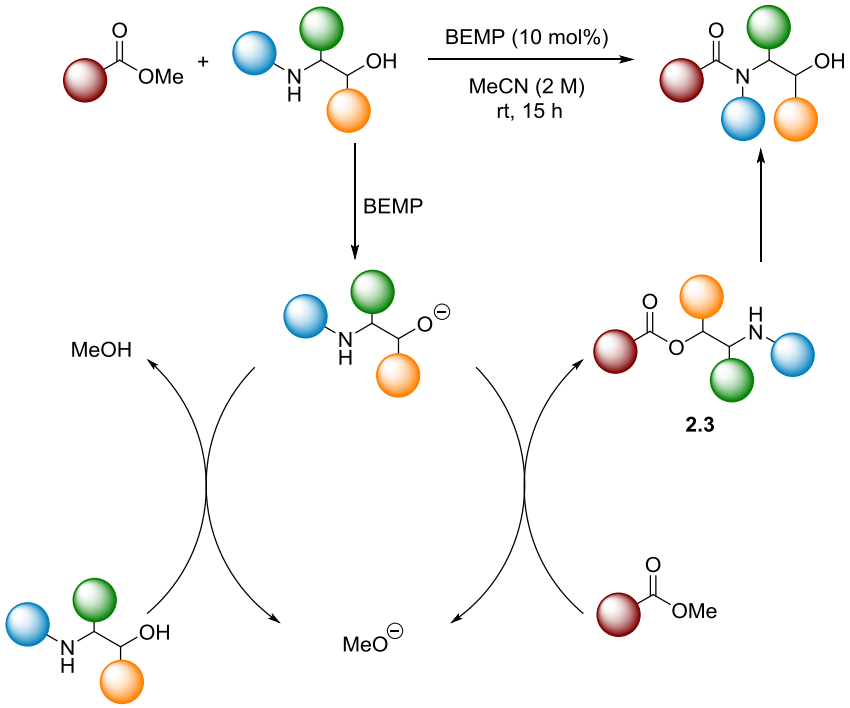
Figure 2.1: Alternative phosphazene bases.

Further investigation into this transformation allowed the scope and limitations to be further exemplified (Scheme 2.10a).[108] A range of substituted aryl esters were tolerated in the reaction, in addition to aliphatic and heterocyclic esters.[108] Straight chain amino alcohols, prolinol, other amino acid derivatives and secondary amines were shown to be competent coupling partners.[108] A comparative study using HATU to couple methyl pyrimidine-2-carboxylate ethanolamine demonstrated that the novel BEMP catalysed approach furnished the corresponding amide in an improved yield, whilst avoiding the use of stoichiometric coupling reagents and the formation of related by-products.[108] Additionally, this methodology was extended to the synthesis of oxazolidinone derivatives under mild heating, with dimethyl carbonate (DMC) mimicking the role of the ester component (Scheme 2.10b).[108]



Scheme 2.10: (a) Selected examples of exemplified BEMP-mediated amidation of esters and amino alcohols. (b) Adaption of methodology towards oxazolidinone synthesis.[108]

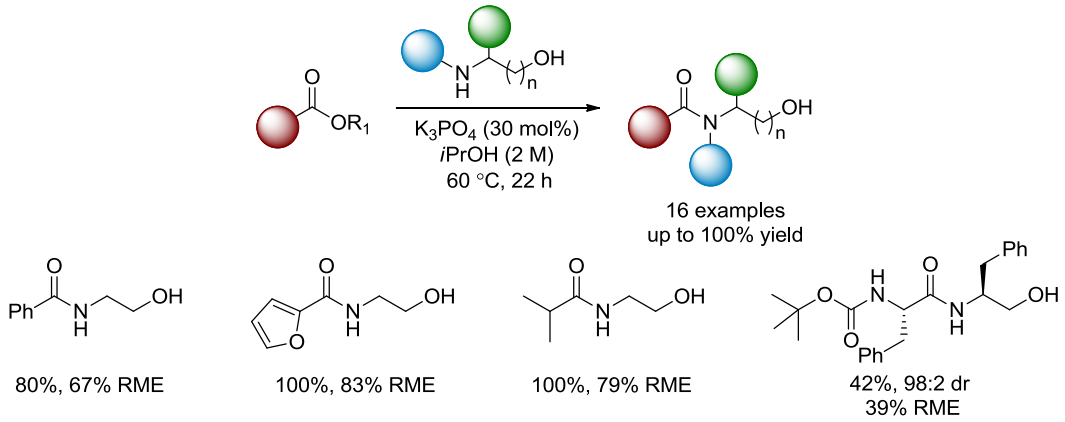
Investigations into the elucidation of the mechanism were also undertaken. It was proposed that the reaction proceeded through an initial transesterification, yielding an intermediate ester **2.3**, followed by an intramolecular rearrangement to afford the thermodynamically more stable amide product (Scheme 2.11).[108] Independent synthesis of this intermediate, which was subsequently exposed to base, demonstrated that this rearrangement is indeed feasible.[108] To further support this proposition, probing the chain length of the amino alcohol was investigated, with the proposed increases in flexibility and size of the cyclic transition state, and therefore an increase in the associated ring strain, hypothesised to hinder the reaction. When ethanolamine, propanolamine, butanolamine and pentanoloamine were subjected to the conditions, the decrease in yields obtained (95, 80, 20 and 0%, respectively) support this hypothesis and hence the proposed mechanism of reaction.[108] This also elucidates why only 10 mol% of BEMP is required to efficiently promote the reaction, with the BEMP deprotonating the first 10 mol% of the amino alcohol. The subsequent transesterification liberates methoxide which then deprotonates the remaining amino alcohol.



Scheme 2.11: Mechanism for BEMP catalysed amidation of amino alcohols and esters.[108]

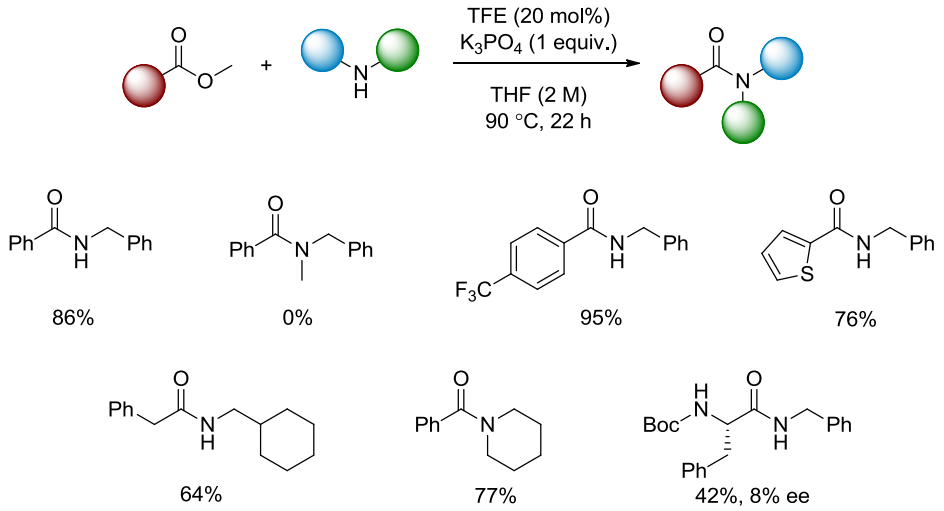
With a view to addressing the cost, sustainability and stereoerosion issues associated with the use of BEMP as the basic species, the reaction conditions were successfully adapted to create a sustainable approach to the amidation of esters with amino alcohols. K_3PO_4 was found to be a viable alternative to BEMP, with a loading of 30 mol% the optimal amount.[109]

Isopropanol was also introduced as the reaction solvent, which is a highly sustainable alternative to acetonitrile.[109] However, to ensure efficiency on par with the progenitor BEMP conditions, both the temperature and reaction time were extended to 60 °C and 22 hours, respectively.[109] These new conditions were applied to a subset of coupling partners investigated under the first generation process so as to allow ready comparison of the procedures. A range of amides were synthesised in both good yield and reaction mass efficiency (RME) (Scheme 2.12).[109]



Scheme 2.12: Selected examples of the sustainable catalytic conditions allowing the amide coupling of esters and amino alcohols.[109]

In relation to the coupling of amino alcohols, studies have also centred on the formation of amide bonds *via* the coupling of unactivated esters with amines. With the BEMP-mediated coupling of amino alcohols shown to proceed through an active ester intermediate *via* transesterification of the ester with the amino alcohol, it was proposed that the catalytic amidation of amines could be achieved *via* the *in situ* formation of an active ester through a base-mediated transesterification with an exogenous alcohol additive. Investigating the effect of common peptide coupling reagents promoting the desired amidation, an equimolar amount of 2,2,2-trifluoroethanol (TFE) was found to be the sole additive leading to any appreciable conversion to product.[110] Further condition screening *via* a Design of Experiments (DoE) approach found the combination of K_3PO_4 and THF at 90 °C to be optimal.[110] Analysis of the DoE results also indicated that a decrease in the amount of TFE to catalytic quantities, whilst retaining a full equivalent of K_3PO_4, would catalyse the reaction without a deleterious effect to yield.[110] This was indeed found to be the case with 20 mol% of TFE able to facilitate the amidation of a diverse range of amines and methyl esters (Scheme 2.13).[110]



Scheme 2.13: Selected examples of TFE catalysed amidation of esters and amines.[110]

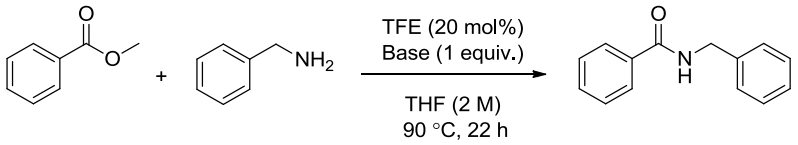
The reaction was tolerant of both electron-rich and electron-deficient aryl esters, as well as aliphatic and heterocyclic esters. However, the coupling of α-chiral amino acid derived esters was again found to proceed with significant erosion of the stereochemistry, resulting in a product with only 8% ee.[110] For the amine component, secondary cyclic amines were successfully coupled, in addition to benzylamine and cyclohexanemethylamine. However, acyclic secondary amines were incompatible substrates under the reaction manifold.

Additional mechanistic studies were also undertaken. With the reaction proposed to proceed through a trifluoroethyl active ester intermediate, this moiety was synthesised independently and subjected to the optimised conditions. HPLC analysis of the reaction indicated consumption of the active ester species with concomitant formation of the desired amide product, therefore supporting the postulated mechanism.[110] Additionally, LCMS analysis of the reaction mixture showed trace amounts (4%) of the active ester intermediate.[110]

2.2 Aims

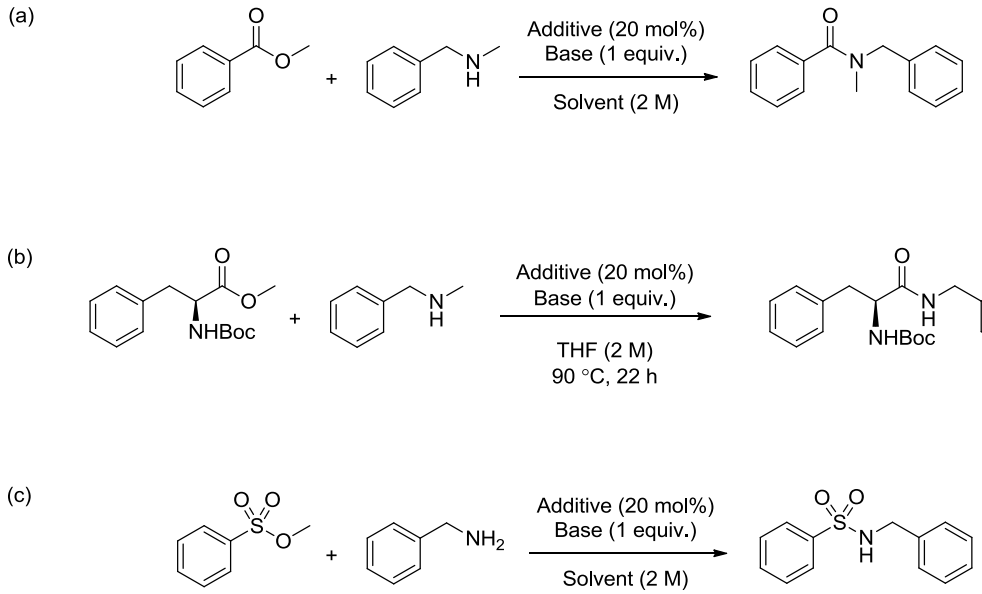
Continuing the established programme concerning the development of efficient organocatalytic approaches to amide bond formation within our laboratory, the aims of this project are to address the outstanding issues of the progenitor processes and further exemplify both their scope and limitations.

Initial efforts focused on the TFE-mediated amidation of unactivated esters. Since the development of the methodology, it has been noted that the pK_a values of the trifluoroethanol additive and the K_3PO_4 base species are extremely similar (12.4 and 12.3 respectively). To elucidate whether this alignment in pK_a is a prerequisite for the reaction to proceed efficiently, a wide range of alternative base species, representing a broader range of both pK_a values and counterions, will be investigated on a model substrate (Scheme 2.14).



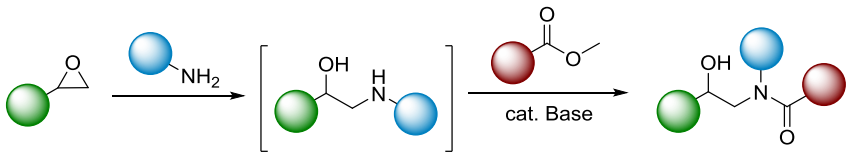
Scheme 2.14: Model reaction to investigate the nature of the base species.

Major limitations affecting the generality of the first generation process were the incompatibility of acyclic secondary amines as viable coupling partners and the erosion of stereochemistry observed when enantiopure starting materials were applied. With a view to addressing the use of acyclic secondary amines, it was proposed that altering the base, additive and solvent combination may overcome the problematic application of the methodology towards the synthesis of acyclic tertiary amides (Scheme 2.15a). In order to prevent the erosion of enantiopurity, the effect of the pKa of suitable base and additive species on the observed level of stereoerosion will be investigated using the protected amino acid Boc-Phe-OMe as a model substrate, with conditions preventing epimerisation applied in order to fully exemplify the scope of the reaction (Scheme 2.15b). Additionally, investigations will be performed to elucidate the point at which epimerisation occurs in the reaction. Finally, with the aim to further widen the applicability of the methodology, the effect of using an exogenous alcohol additive to mediate the synthesis of sulfonamides will be investigated, with the optimised conditions employed to fully assess the scope of the process (Scheme 2.15c).



Scheme 2.15: (a) Model reaction for screening conditions towards the synthesis of acyclic tertiary amides. (b) Model reaction for epimerisation studies. (c) Model reaction for the extension of the methodology towards sulfonamide formation.

As discussed in Section 2.1.1, the development of an organocatalysed multicomponent approach to amide bond formation would represent an efficient and atom economical route to synthesising amides. With the successful application of contemporary amide bond-forming multicomponent methodologies limited as a result of the use of finite, expensive and potentially toxic metals, or the use of reagents in excess, the development of a base-mediated methodology successfully promoting the desired amidation would represent a significant advance in the field. Drawing inspiration from the prior developed BEMP-mediated coupling of esters with amino alcohols, it was proposed that the amino alcohol could be synthesised *in situ via* the nucleophilic opening of an epoxide with an amine, which, when exposed to the ester component, would form the desired amide species following our established reaction manifold (Scheme 2.16). Following optimisation of the reaction conditions, the scope of each component will be examined with a view to creating a versatile, efficient and atom-economical multi-component amide bond formation.



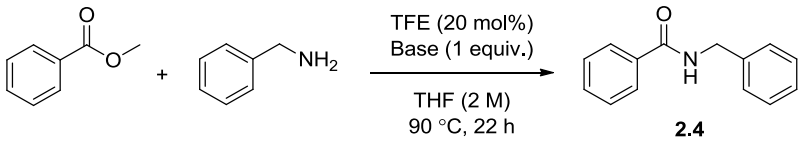
Scheme 2.16: Proposed multicomponent approach to the synthesis of amides.

2.3 Results and Discussion

2.3.1 Nature of the Base Species in the TFE-Mediated Amidation of Unactivated Esters

In an effort to extend the utility of the TFE-mediated amidation methodology to substrates that had previously proven challenging, the relationship between the base species and the TFE additive was initially investigated. Specifically, the role of the pK_a of the conjugate acid associated with the base species was investigated in order to ascertain whether the similar pK_a values of the K_3PO_4 (pK_a = 12.3) and TFE (pK_a = 12.4) combination previously utilised is essential to ensure an efficient reaction.[111] A selection of bases encompassing a wider range of pK_a values was therefore evaluated in the model amidation reaction of methyl benzoate and benzylamine (Table 2.1).

Table 2.1: Investigation of the nature of the base species.



2.4

Entry	Base	pK_a of conjugate acid[111]	Conversion (%)[a]
1	KTFA	0	1
2	KH_2PO_4	2	1
3	KOAc	5	1
4	K_2HPO_4	7	1
5	K_2CO_3	10	2
6	K_3PO_4	12	78 (77)[b]
7	KOH	16	5
8	KO*t*Bu	18	47
9	$Ca_3(PO_4)_2$	13	1
10	Cs_3PO_4	13	1
11	Li_3PO_4	13	<1%
12	$Mg_3(PO_4)_2$	13	16
13	Na_3PO_4	13	1
14	Cs_2CO_3	10	11
15	NMM	7	13
16	DABCO	9	4
17	Et_3N	11	1
18	DBU	12	61
19	BEMP	16.2[c]	8

[a]Conversion determined by HPLC with reference to an internal standard. [b]Isolated yield. [c]pK_a of conjugate acid of BEMP in DMSO, pK_a in MeCN = 27.6.[112,113]

The initial investigation focused on retaining the potassium counterion and evaluating the role of pK_a (Table 2.1, Entries 1 – 8). Consistent with the progenitor methodology, K_3PO_4 (Entry 6) was found to be the optimum base furnishing the desired amide **2.4** in 78% conversion. Other potassium bases screened in the model reaction led to negligible conversions to the amide product, aside from KO*t*Bu (Entry 8) which furnished the amide in a moderate conversion of 47%. The poor conversions observed from the use of bases with a pK_a value <12 is unsurprising considering the requirement for initial deprotonation of the trifluoroethanol in order to facilitate the formation of the active ester intermediate. The effect of altering the metal counterion was then examined by retaining the phosphate moiety of the base (Table 2.1, Entries 9 – 13), with $Mg_3(PO_4)_2$ (Entry 12) resulting in the only measurable conversion to the amide at 16%, an observation which is attributed to poor solubility of alternative phosphate species in the reaction milieu. Additionally, Cs_2CO_3 (Entry 14) was also found to lead to a poor conversion, again attributable to a sub-optimal basicity to enable active ester formation. However, it was found to lead to a greater conversion than achieved through the use of K_2CO_3 (Entry 5), again attributed to the increased solubility of Cs_2CO_3. Therefore, these results clearly indicate the importance of both the potassium counterion and the phosphate species in ensuring an efficient amidation reaction. Organic bases were also screened in the model system (Entries 15 – 19), with all but DBU (Entry 18) resulting in no or minimal amide formation.

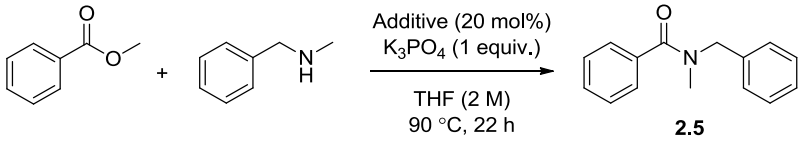
Analysis of this extended base screen clearly shows that bases with a pK_a comparable to that of TFE (K_3PO_4 and DBU) are markedly superior in promoting the amidation process. The use of KO*t*Bu is an exception to this observation, however its application only affords moderate amide formation when compared to the original K_3PO_4 conditions. Furthermore, the choice of counterion is clearly critical, as shown through the examination of other phosphate bases, with the alternatives all proving comparatively ineffective to the potassium variant. This observation can be attributed to the lower solubility of these bases versus K_3PO_4.

2.3.2 Tertiary Amide Formation *via* the Amidation of Unactivated Esters with Acyclic Secondary Amines

2.3.2.1 Optimisation of Reaction Conditions Allowing the Application of Acyclic Secondary Amines

With an increased understanding into the choice of the base species used in the amidation methodology, attention was turned to addressing the incompatibility of acyclic secondary amines in the first generation process. The previously optimised conditions were first applied to investigate the effect of altering the additive species. A range of additive species previously demonstrated to have utility in amide bond formation were therefore selected and screened under a model reaction (Table 2.2). However, no measurable conversion to the desired amide **2.5** was achieved in each case.

Table 2.2: Additive screening for acyclic tertiary amide synthesis.

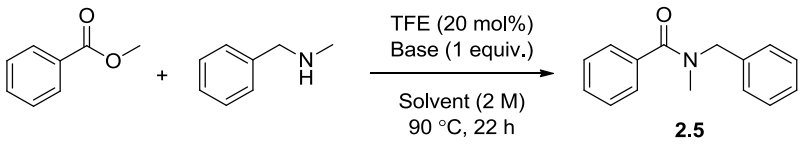


Entry	Additive	Conversion (%)[a]
1	Picoline *N*-oxide	<1
2	HOAt	<1
3	HOBt	<1
4	HOCt	<1
5	NHS	<1
6	Oxyma	<1
7	TFE	1
8	4-$CF_3C_6H_4OH$	1

[a]Conversion determined by HPLC with reference to a 0.05 M caffeine standard.

The combination of base and solvent used in the reaction was investigated, with the TFE additive retained. With the knowledge that for a base species to be a viable alternative it has to have a pK_a of approximately 12, a small selection of bases with pK_as around this value were selected to be examined in the model reaction (Table 2.3). Accordingly, DBU and K_3PO_4 were selected as a result of these bases performing well in the extended base screen. DABCO and KO*t*Bu were also investigated as these bases possess pK_a values either side of the TFE additive, and additionally KO*t*Bu showed moderate amide formation in the expanded base screen.

Table 2.3: Base and solvent screen for acyclic tertiary amide synthesis.



2.5

Entry	Base	Solvent	Conversion (%)[a]
1	DABCO	*n*-butanol	<1
2	K_3PO_4	*n*-butanol	3
3	DBU	*n*-butanol	2
4	KO*t*Bu	*n*-butanol	22
5	DABCO	CPME	0
6	K_3PO_4	CPME	37
7	DBU	CPME	4
8	KO*t*Bu	CPME	96 (99)[b]
9	DABCO	DCE	<1
10	K_3PO_4	DCE	<1
11	DBU	DCE	<1
12	KO*t*Bu	DCE	<1
13	DABCO	1,4-dioxane	<1
14	K_3PO_4	1,4-dioxane	12
15	DBU	1,4-dioxane	3
16	KO*t*Bu	1,4-dioxane	37
17	DABCO	DMC	<1
18	K_3PO_4	DMC	<1
19	DBU	DMC	<1
20	KO*t*Bu	DMC	<1
21	DABCO	DMF	<1
22	K_3PO_4	DMF	8
23	DBU	DMF	3
24	KO*t*Bu	DMF	21
25	DABCO	IPA	<1
26	K_3PO_4	IPA	9
27	DBU	IPA	2
28	KO*t*Bu	IPA	<1
29	DABCO	2-MeTHF	1
30	K_3PO_4	2-MeTHF	43
31	DBU	2-MeTHF	5
32	KO*t*Bu	2-MeTHF	2
33	DABCO	MeCN	<1
34	K_3PO_4	MeCN	2
35	DBU	MeCN	4
36	KO*t*Bu	MeCN	32
37	DABCO	THF	2
38	K_3PO_4	THF	62, <1, 1
39	DBU	THF	8
40	KO*t*Bu	THF	56

[a]Conversion determined by HPLC with reference to a 0.05 M caffeine standard. [b]Isolated yield.

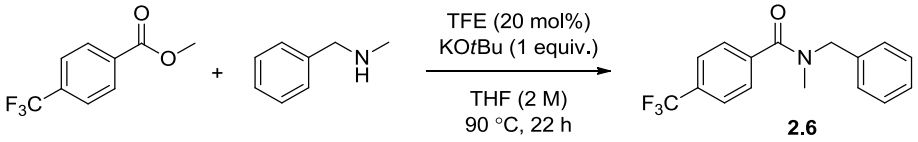
From this investigation of the base and solvent applied in the reaction, it can be clearly seen that DABCO is not a competent base in this context, independent of the solvent used, leading to no measurable conversion to amide **2.5**. This is an unsurprising observation when the pK_a values of DABCO and TFE are considered (9 and 12.4, respectively). Perhaps more surprising is the ineffectiveness of DBU in promoting the reaction, considering it led to a good conversion of 61% when examined in the widened base screen for the formation of secondary amide **2.5**. Under this model reaction, however, a maximum conversion of only 8% is observed when DBU is used in conjunction with THF (Table 2.3, Entry 39). However, a white precipitate was observed to form immediately upon heating, which precluded stirring of the reaction mixture.

Pleasingly, the use of K_3PO_4 in CPME (Entry 6), 1,4-dioxane (Entry 14) and 2-MeTHF (Entry 30) was found for the first time to lead to the formation of the desired amide in moderate conversion. Again, a white precipitate was found to form in all cases hindering stirring. Interestingly, re-examination of the combination of K_3PO_4 and THF as the base and solvent species led to a conversion of 62% (Entry 38). However, when this experiment was repeated, no measurable conversion was once again observed, with precipitation of a white solid again occurring. This contrast in reaction outcome can be attributed to a longer period of time elapsing between the addition of the amine to the reaction mixture when first performed, hence allowing pre-formation of the active ester. When repeated, the reactants were added concomitantly and, upon addition of the amine, formation of precipitate was again observed. Therefore, it is proposed that this white precipitate is a result of the preferential formation of a quaternary ammonium salt between trifluoroethanol and the amine, which sequesters the trifluoroethanol and hinders the transesterification event and, therefore, the overall amidation process.

The effect of this observed precipitate formation, in conjunction with the use of DBU and K_3PO_4, was initially dismissed at this stage of the investigation due to the superiority of KO*t*Bu as the base species, which led to a 96% conversion to the amide in CPME, with an isolated yield of 99% (Entry 8). When the ester component was altered to methyl 4-(trifluoromethyl)benzoate however, the reaction was only found to proceed in 48% isolated yield, which is contradictory to the more favourable electronic characteristic of this ester (Table 2.4, Entry 1). Therefore, before applying these conditions to a wider substrate scope, the relevant controls were performed to confirm that both the base and additive components were required to promote the reaction. As expected, in the absence of base, no desired amide product **2.6** was furnished in the reaction (Table 2.4, Entries 2 and 4). However, when

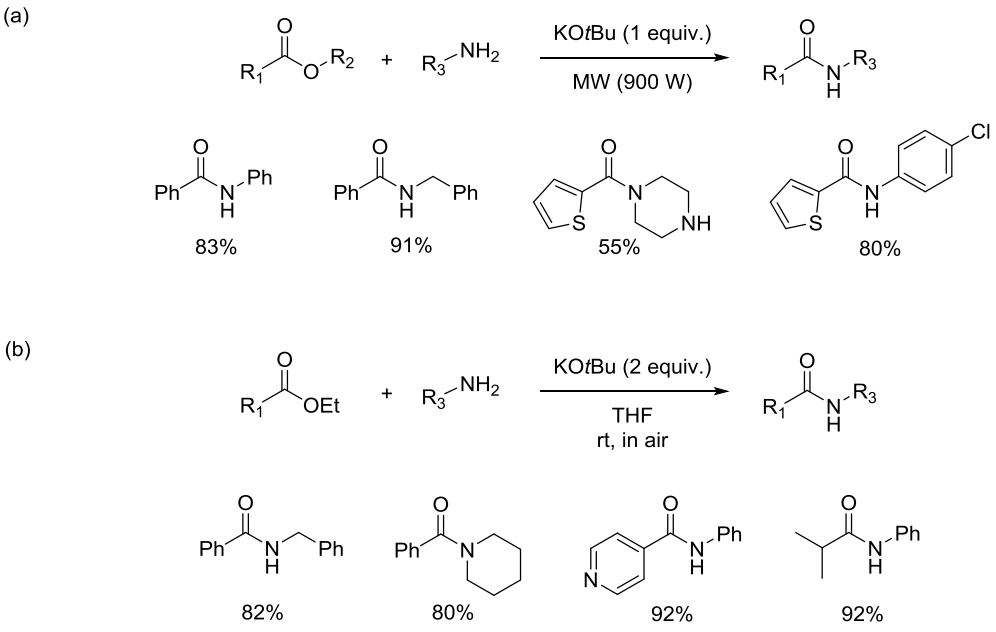
performed in the absence of the trifluoroethanol additive, **2.6** was found to form in a moderate but yet improved yield of 58% (Table 2.4, Entry 3).

Table 2.4: Control reactions for the KO*t*Bu/TFE-mediated amidation.



Entry	TFE	Base	Yield (%)
1	Yes	Yes	48
2	Yes	No	0
3	No	Yes	58
4	No	No	0

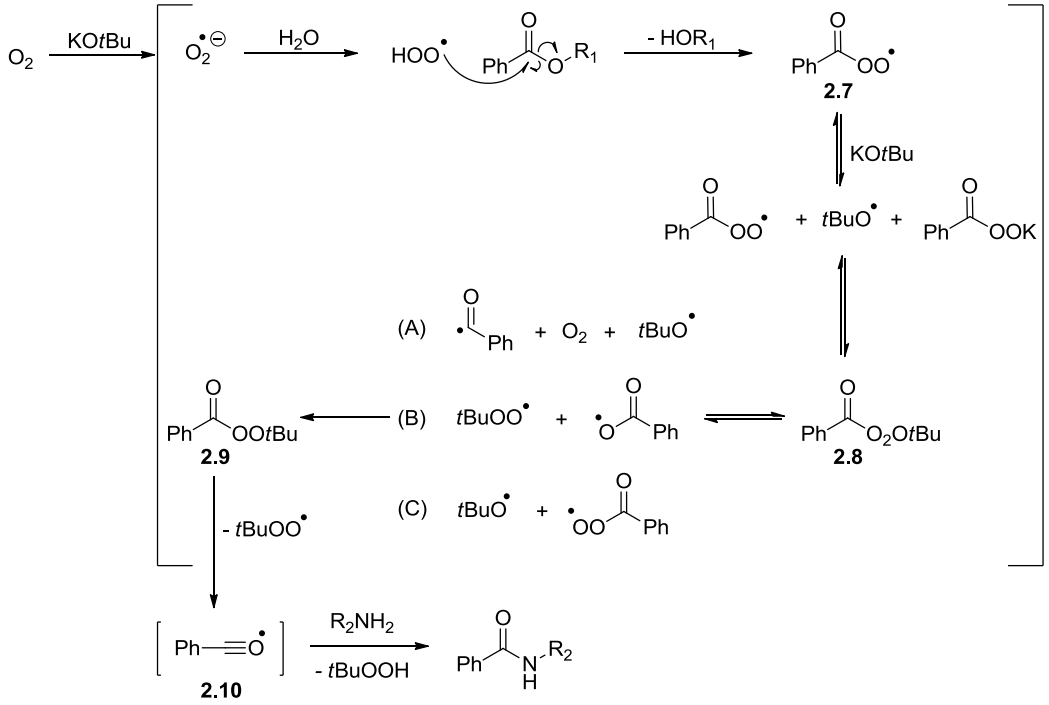
Examination of the literature indicated that KO*t*Bu could be used to promote the amidation of a range of methyl and ethyl esters *via* either a solvent-free microwave irradiation process (Scheme 2.17a), or through the use of THF as a solvent at ambient conditions (Scheme 2.17b).[114,115]



Scheme 2.17: (a) Solvent-free KO*t*Bu-mediated amidation.[114] (b) KO*t*Bu-mediated amidation in THF.[115]

Yoon, Park and co-workers proposed that the reaction proceeds through a radical pathway (Scheme 2.18), with superoxide radicals initially formed from the reaction of oxygen and

KO*t*Bu.[115] Reaction of the superoxide radical with water forms the corresponding peroxy radical, which upon reaction with the ester results in the formation of peroxy radical species **2.7**.[115] Further reaction of this peroxy radical with KO*t*Bu may form the trioxide species **2.8**.[115] Decomposition of this intermediate to *tert*-butyl peroxybenzoate **2.9** may occur *via* 3 pathways (A-C), with calculated energy potentials indicating the process may favour pathways B or C.[115] Decomposition of *tert*-butyl peroxybenzoate to the radical species **2.10**, followed by nucleophilic attack of the amine furnishes the desired amide product.[115]



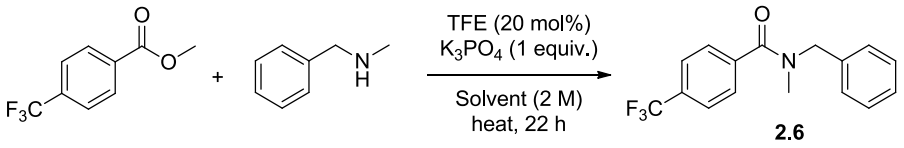
Scheme 2.18: Proposed mechanism for KO*t*Bu-mediated amidation of esters.[115]

However, this proposed mechanism does not explain the origin of the KO*t*Bu-mediated amidation observed in the optimisation process. As the reaction is performed using distilled solvent under a nitrogen atmosphere, neither oxygen nor water should be present to facilitate this radical pathway.

As a result of this competing KO*t*Bu-promoted amidation reaction, focus was returned to further optimising the use of K_3PO_4 in the methodology. In an attempt to circumvent the possible requirement of preforming the active ester species *in situ*, methyl 4-(trifluoromethyl)benzoate was retained as the model ester, with the inherent electron-withdrawing character associated with this ester species anticipated to make the desired amidation reaction more amenable. However, when the reaction was performed in THF at 90 °C, no conversion to the desired amide **2.6** was achieved (Table 2.5, Entry 1). The

proposed pre-formation of the active ester was then investigated, allowing a 30 minute period for the active ester to form before addition of the amine to the reaction. Pleasingly, this afforded a 70% conversion to the desired amide (Entry 2). This pre-formation approach was then applied to the amidation of methyl benzoate (Entry 3) with a 62% conversion achieved, consistent with the result observed in the previous base and solvent screening.

Table 2.5: Reaction optimisation using methyl 4-(trifluoromethyl)benzoate.



Entry	Solvent	Temperature (°C)	Conversion (%)
1	THF	90	0
2[a]	THF	90	70
3[a,b]	THF	90	62
4[a]	CPME	125	77[c]
5[a]	1,4-dioxane	125	93[c]
6[a]	2-MeTHF	100	72[c]
7[a,d]	1,4-dioxane	125	0[c]
8[a,e]	1,4-dioxane	125	0[c]
9[a,f]	1,4-dioxane	125	0[c]

[a]30 min pre-formation of active ester at reaction temperature. [b]Methyl benzoate used as ester substrate. [c]Isolated yield. [d]Performed in the absence of K_3PO_4. [e]Performed in the absence of TFE. [f]Performed in the absence of both K_3PO_4 and TFE.

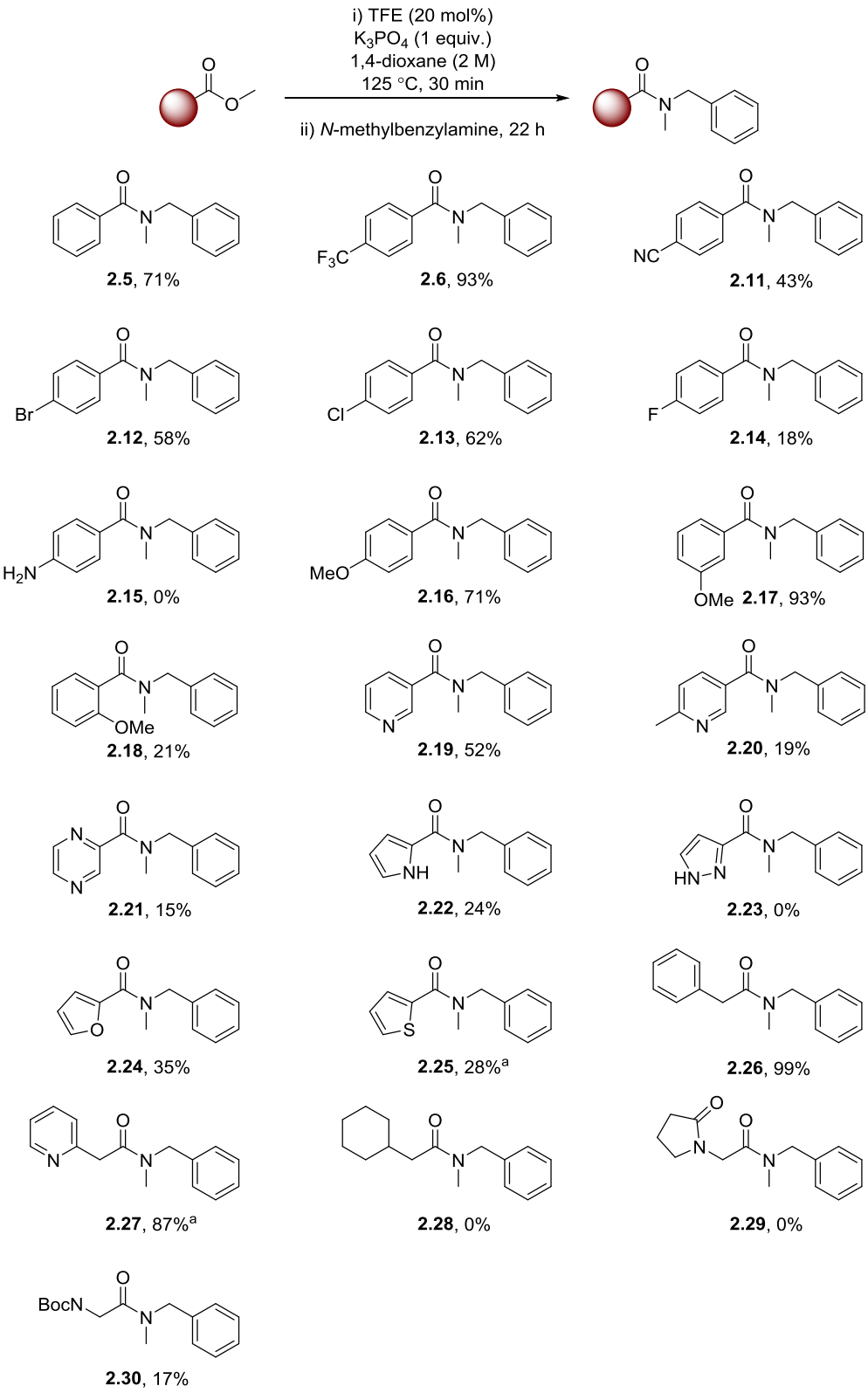
With CPME, 1,4-dioxane and 2-MeTHF all found to furnish the desired amide product in the base and solvent investigation performed at 90 °C, the higher boiling points of the solvents allowed higher temperatures to be investigated (Table 2.5, Entries 4 – 6). Pleasingly, this increase in reaction temperature resulted in the formation of amide **2.6** in an isolated yield of 93% when performed in 1,4-dioxane at 125 °C (Entry 5). To confirm that the reaction was not proceeding through direct aminolysis of the ester species, the corresponding control reactions were performed (Entries 7 – 9). As no amide formation was observed, this indicates that the reaction proceeds *via* the formation of the desired TFE-active ester species opposed to direct aminolysis.

2.3.2.2 Scope of the TFE-Mediated Amidation of Unactivated Esters with Acyclic Secondary Amines

With optimum conditions allowing the coupling of acyclic secondary amines with esters successfully developed, attention was subsequently turned to investigating the scope of the transformation. Initial studies focused on altering the ester component of the reaction (Scheme 2.19). Pleasingly, a range of aryl esters containing both electron-withdrawing and electron-donating groups were coupled successfully, furnishing the corresponding amides in good to excellent yields (**2.5**, **2.6**, **2.11 - 2.18**). Exceptions to this include the coupling of methyl (4-amino)benzoate **2.15**, and substituents bearing *ortho* substituents, for example, compound **2.18**. Surprisingly, the *para* fluoro substrate **2.14** also performed poorly in the reaction manifold, furnishing the corresponding amide in only 18% yield. Initially, this poor yield was reasoned to be a result of a possible competing S_NAr reaction, however GC-MS analysis of the reaction mixture indicated that no corresponding mass for the proposed side reaction was observed.

Heteroaryl esters were also tolerated when applied to the reaction conditions, with the pyridyl, furan and thiophene derivatives formed in moderate yields (**2.19**, **2.24** and **2.25** respectively). However, the addition of a methyl substituent *para* to the ester functionality on the pyridine ring (**2.20**), as well as the addition of a second nitrogen into the aromatic system (**2.21**) had a deleterious effect on the isolated yields. This latter effect was also observed when the analogous 5-membered ring species were examined, with the pyrrole derivative furnished in a poor yield of 24% (**2.22**), whereas pyrazole **2.23** was found to be an incompatible substrate.

Alkyl esters were also compatible substrates with **2.26** and **2.27** afforded in excellent yields. However, substrates featuring fully saturated cyclic systems (e.g. **2.28** and **2.29**) were found to be incompatible. Additionally, a glycine-derived alkyl ester was found to undergo the desired amidation reaction to form **2.30**, albeit in a poor yield of 17%.

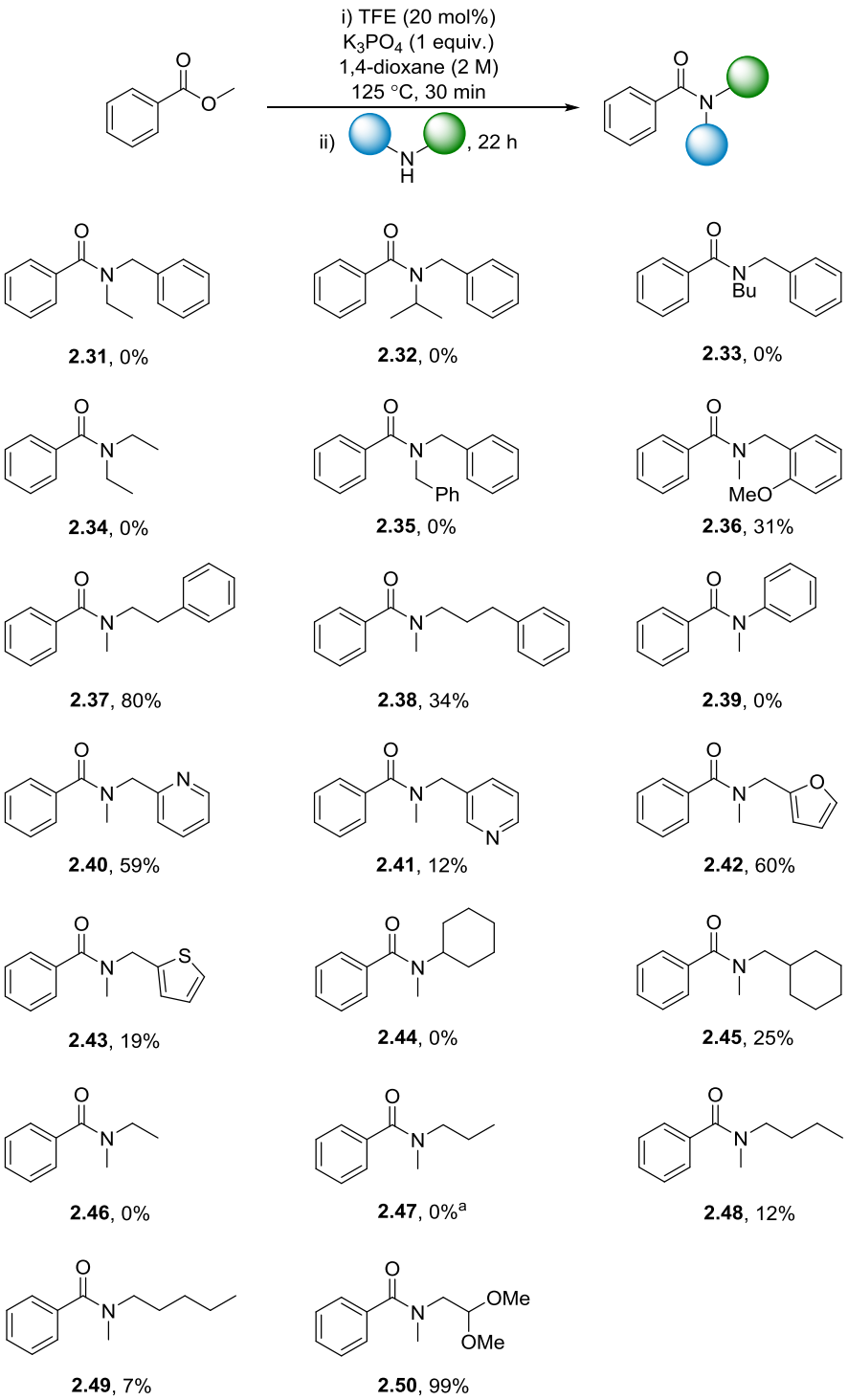


Scheme 2.19: Investigating the scope of the ester component. [a]Synthesised from the corresponding ethyl ester.

Having investigated the scope of the ester component of the reaction with the model acyclic secondary amine *N*-methylbenzylamine, variation of the amine coupling partner was then examined (Scheme 2.20). This scope was found to be somewhat more limited, with increasing the size of the substituent from *N*-methylbenzylamine to the corresponding ethyl, isopropyl, butyl, diethyl and dibenzyl-derivatives (**2.31 – 2.35**) not tolerated, which is attributed to the increased steric hindrance.

Returning to amines bearing a methyl substituent, substitution, in the form of an *ortho* methoxy group, was tolerated on the aromatic ring with a modest yield of 31% of amide **2.36** formed. Homologation of the amine was also tolerated in moderate to good yield (**2.37** and **2.38**), however aniline derivatives (e.g. **2.39**) were not competent substrates under these optimum conditions, which can be imputed to the lower nucleophilicity of anilines compared to non-aromatic amines. A range of benzylic amines containing heteroaryl moieties were found to be useful coupling partners within the reaction manifold (**2.40** – **2.43**), however the amidation of the 3-pyridyl derivative (**2.41**) was found to be less efficient than that of the 2-pyridyl derivative (**2.40**).

In contrast, alkyl amines were generally found to be inefficient coupling partners (**2.44 – 2.49**). In the case of **2.46** and **2.47**, this observation was initially ascribed to the volatility of the corresponding amine starting materials under the high temperature required to promote the desired amidation reaction. However, increasing the equivalents of amine used to 2 and 3 equivalents in order facilitate the formation of **2.47** resulted in no formation of the desired product. As expected due to the electron rich nature of the corresponding amine, amide **2.50** was found to be a competent substrate with a near quantitative yield obtained.



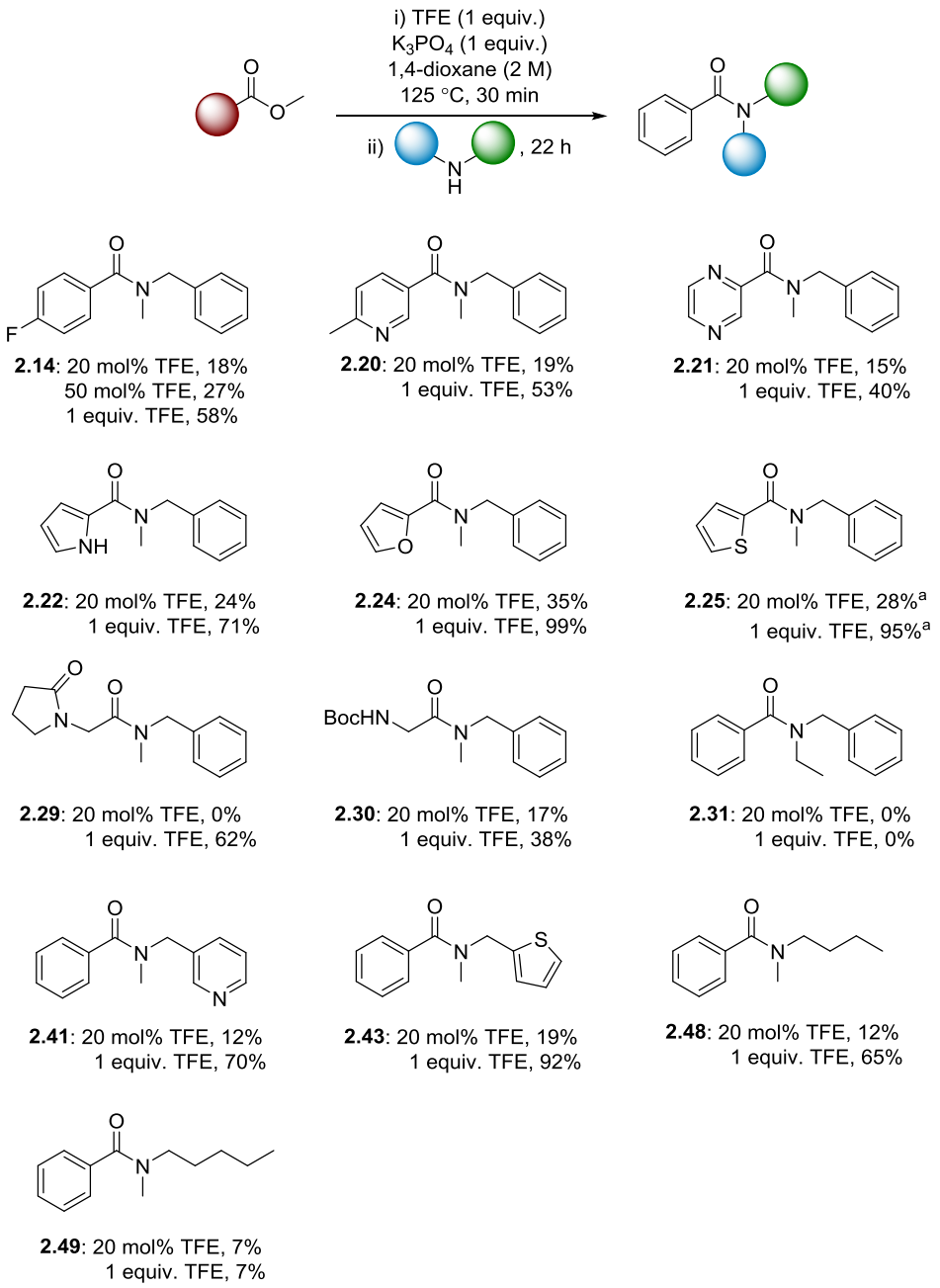
Scheme 2.20: Investigation of the scope of the amine component. [a]2 and 3 equivalents of propylamine results in no formation of corresponding amide.

Upon evaluation of the reaction scope under the optimised conditions, it was noted that several of the coupling partners investigated underwent the amidation process inefficiently, affording sub-optimal yields of the corresponding amide products. It was proposed that

increasing the quantity of the trifluoroethanol additive utilised in the reaction from a catalytic amount (20 mol%) to an equimolar amount may lead to increased yields for these substrates. Using methyl 4-fluorobenzoate to investigate this proposal, the amount of TFE was raised firstly to 0.5 equiv. and then an equimolar amount (Scheme 2.21, **2.14**). Pleasingly, this resulted in an increase in yield in both cases, furnishing the desired amide in a good yield of 58% when a full equivalent of TFE was used.

To fully evaluate whether this increase in the quantity of TFE would efficiently promote the amidation of previously difficult substrates, a subset of the amides which did not perform well under the catalytic conditions was re-investigated (Scheme 2.21). Pleasingly, a range of heteroaryl esters (**2.20** – **2.22**, **2.24** and **2.25**) exhibited a similar improvement in yield, and in the case of the furan (**2.24**) and thiophene (**2.25**) derivatives, almost quantitative conversion of the ester to the corresponding amide is obtained. Increased yields are also observed for alkyl esters, with the pyrrolidinone derivative (**2.29**), a previously unsuccessful substrate, furnished in a good yield of 62%. However, for the glycine derived ester (**2.30**), a more modest increase in yield from 17 to 38% was observed.

Unfortunately, the ethyl-substituted amine **2.31** remained an unsuccessful substrate, which further supports the postulated steric hindrance reasoning. However, the heteroaryl derivatives **2.41** and **2.43** reflect the improvement in yield achieved when the ester component was varied. Alkyl amines were also re-evaluated using a full equivalent of TFE, with the butyl derivative **2.48** previously isolated in only 12% now furnished in 65% yield. However, by contrast, the pentyl variant **2.49** was only isolated in 7% yield, consistent with the catalytic conditions.



Scheme 2.21: Application of an equimolar amount of TFE to sub-optimal substrates.

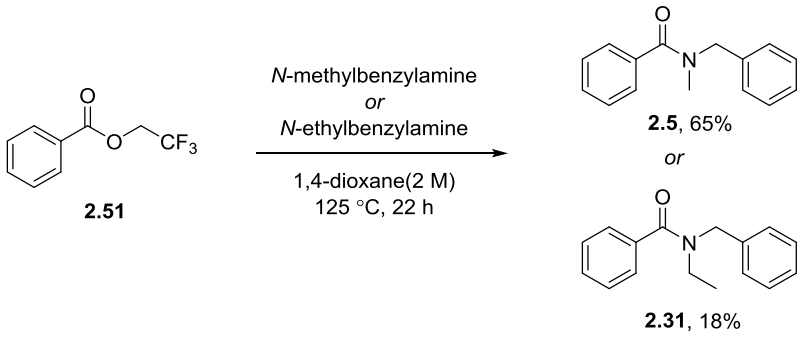
[a]Synthesised from corresponding ethyl ester.

Increasing the quantity of TFE has therefore been demonstrated as a generally successful alteration to the optimised conditions, allowing the efficient coupling of ester and amines substrates that performed sluggishly under the catalytic variant. Although the catalytic nature of the reaction is lost in this approach when coupling demanding substrates, the stoichiometric conditions compare favourably to other established methods of amide bond formation, making the use of a full equivalent of TFE a viable approach. In terms of atom

economy, the use of the stoichiometric TFE-mediated amidation conditions remains advantageous over the use of coupling reagent chemistry, where the reagents are typically larger than trifluoroethanol and result in the formation of both urea and hydroxybenzotriazole derived by-products. The low cost of TFE is a further advantage, with commercial availability from £37/mol, therefore making this a comparatively inexpensive methodology towards the formation of amides.

2.3.2.3 Steric Limitations of the TFE-Mediated Amidation of Unactivated Esters with Acyclic Amines

With the investigation into the scope of the amidation process demonstrating that amines bearing two substituents larger than a methyl group are unsuccessful coupling partners, a brief study was performed to further elucidate whether this observation was a result of increasing steric hindrance. The amidation of both *N*-methyl and *N*-ethylbenzylamine with the trifluoroethyl ester intermediate derived from methyl benzoate, **2.51**, was examined in order to ascertain whether the increase in steric bulk would impact the required nucleophilic attack of the amine (Scheme 2.22).



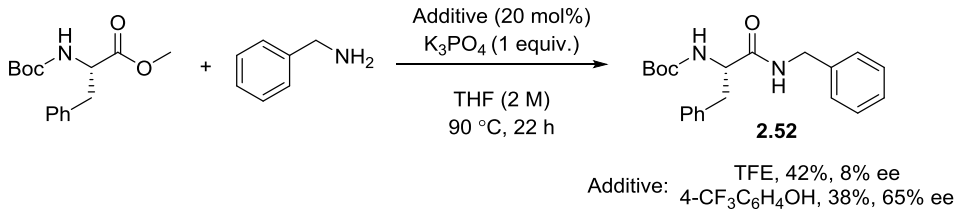
Scheme 2.22: Investigating the steric limits of the amidation methodology.

From this investigation, the amidation of *N*-methylbenzylamine with the ester species was found to proceed in a comparable yield to the amidation of *N*-methylbenzylamine under the TFE-mediated conditions (65 and 71%, respectively). However, *N*-ethylbenzylamine was found to perform significantly worse with only an 18% yield of the corresponding ethyl substituted amide **2.31** observed. Therefore, this deleterious effect on the amidation reaction further supports the proposition that the reduction in reactivity is a result of increasing steric hindrance.

2.3.3 Chiral Secondary Amide Synthesis from Enantiopure Ester Starting Materials

2.3.3.1 Optimisation of Base and Additive Combinations to Enhance Reaction Efficiency and Stereoretention

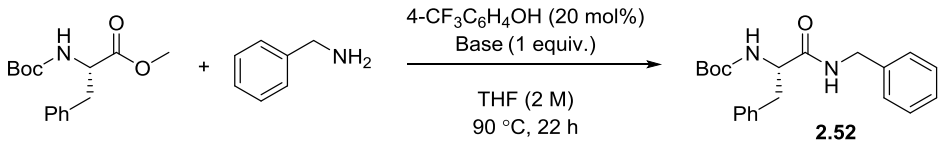
With the issue of reactivity of acyclic secondary amides in the progenitor methodology successfully addressed, efforts were then focused on developing conditions allowing chiral ester substrates to be utilised without erosion of the enantiopurity. In the first generation process, the coupling of Boc-phenylalanine methyl ester proceeded in 42% yield but with an ee of only 8%.[110] Further research within our laboratory led to the use of the alternative additive 4-(trifluoromethyl)phenol, which promoted the desired amidation in a comparable yield but with an improved ee of 65% (Scheme 2.23).[116]



Scheme 2.23: Previously developed conditions for the amidation of Boc-Phe-OMe.

With 4-(trifluoromethyl)phenol possessing a lower pK_a than trifluoroethanol (8.7 and 12.4 respectively),[111] it was reasoned from the initial base screen performed on the coupling of methyl benzoate and benzylamine that realigning the pK_a of the base species with the phenol additive may lead to both a more efficient reaction and superior retention of the stereochemistry. To investigate this hypothesis, a range of suitable bases were selected to be investigated in conjunction with 4-(trifluoromethyl)phenol (Table 2.6).

Table 2.6: Effect of altering the base species on the yield and ee obtained.



Entry	Base	pK_a[111]	Yield (%)	ee (%)[a]
1	KTFA	0	46	93
2	KH_2PO_4	2	62	87
3	KOAc	5	55	92
4	NMM	7	36	92
5	K_2HPO_4	7	48	92
6	DABCO	9	40	85
7	K_2CO_3	10	46	75
8	Cs_2CO_3	10	34	40
9	DBU	12	69	16

[a]Determined by chiral HPLC.

Analysis of the results obtained from this investigation indicates a clear trend between the strength of the base and the extent of the observed racemisation (Figure 2.2). The use of KTFA (pK_a = 0) through to K_2HPO_4 (pK_a = 7) (Table 2.6, Entries 1 – 5) result in minimal racemisation, with a slight decrease observed when DABCO (Entry 6) is utilised. If a base with a p*K*a of ≥ 10 is used (Table 2.6, Entries 7 – 9), significant levels of racemisation are observed, with DBU (Entry 9) leading to the most efficient coupling but also the greatest erosion in enantiopurity. From the results obtained, it was determined that the use of KOAc offered the most suitable combination of isolated yield relative to enantiomeric excess and was therefore retained for use in further studies.

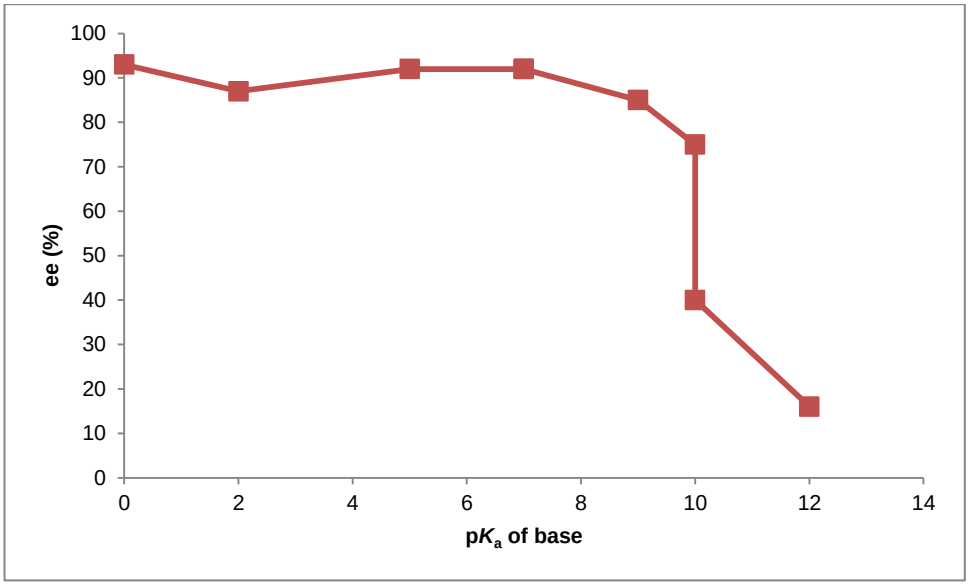
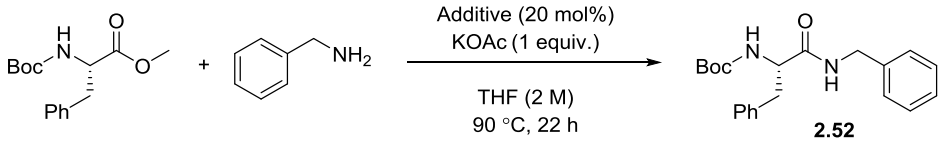


Figure 2.2: Effect of the pK_a of the base species on the ee of the obtained amide product.

Alteration of the additive species has little effect on the ee of the corresponding amide product (Table 2.7 and Figure 2.3), with NHS (Entry 6) the only additive investigated resulting in an ee below 87%. The use of HOCt[117] (Entry 2) performed comparatively to 4-$CF_3C_6H_4OH$ (Entry 7) with a yield and ee of 54 and 91% obtained, respectively. However, the use of 4-$CF_3C_6H_4OH$ was selected as the optimal additive due to the marginally superior balance between yield and ee than that obtained from HOCt.

Table 2.7: Effect of altering the additive species on the yield and ee obtained.



Entry	Additive	pK_a[111,118]	Yield (%)	ee (%)[a]
1	Picoline *N*-oxide	-	28	87
2	HOCt	2	54	91
3	HOAt	3	32	89
4	HOBt	5	47	91
5	Oxyma	5	50	93
6	NHS	8	58	79
7	4-$CF_3C_6H_4OH$	9	55	92
8	HFIP	9	35	89
9	TFE	12	31	89

[a]Determined by chiral HPLC.

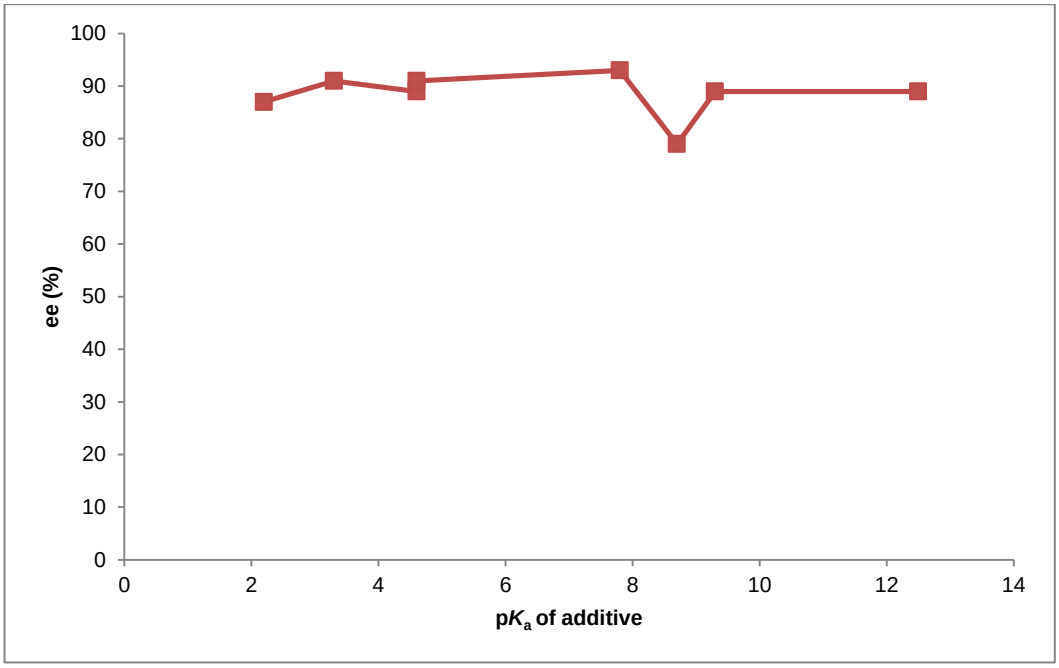
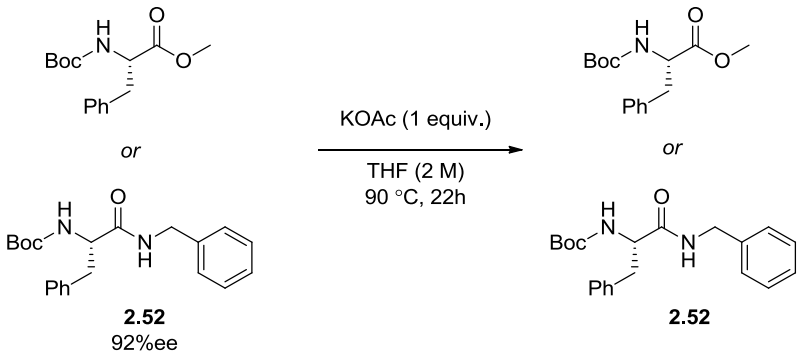


Figure 2.3: Effect of the pK_a of the additive species on the ee of the obtained amide product.

With excellent levels of stereoretention achieved for the model substrate, a study was undertaken to elucidate the point in the transformation at which epimerisation occurred. Boc-Phe-OMe and the corresponding amide product **2.52** were subjected to the optimised conditions, with no erosion of enantiopurity observed in either experiment (Table 2.8). It is therefore hypothesised that the observed epimerisation occurs *via* the active ester intermediate, potentially through oxazolone formation.

Table 2.8: Epimerisation study.



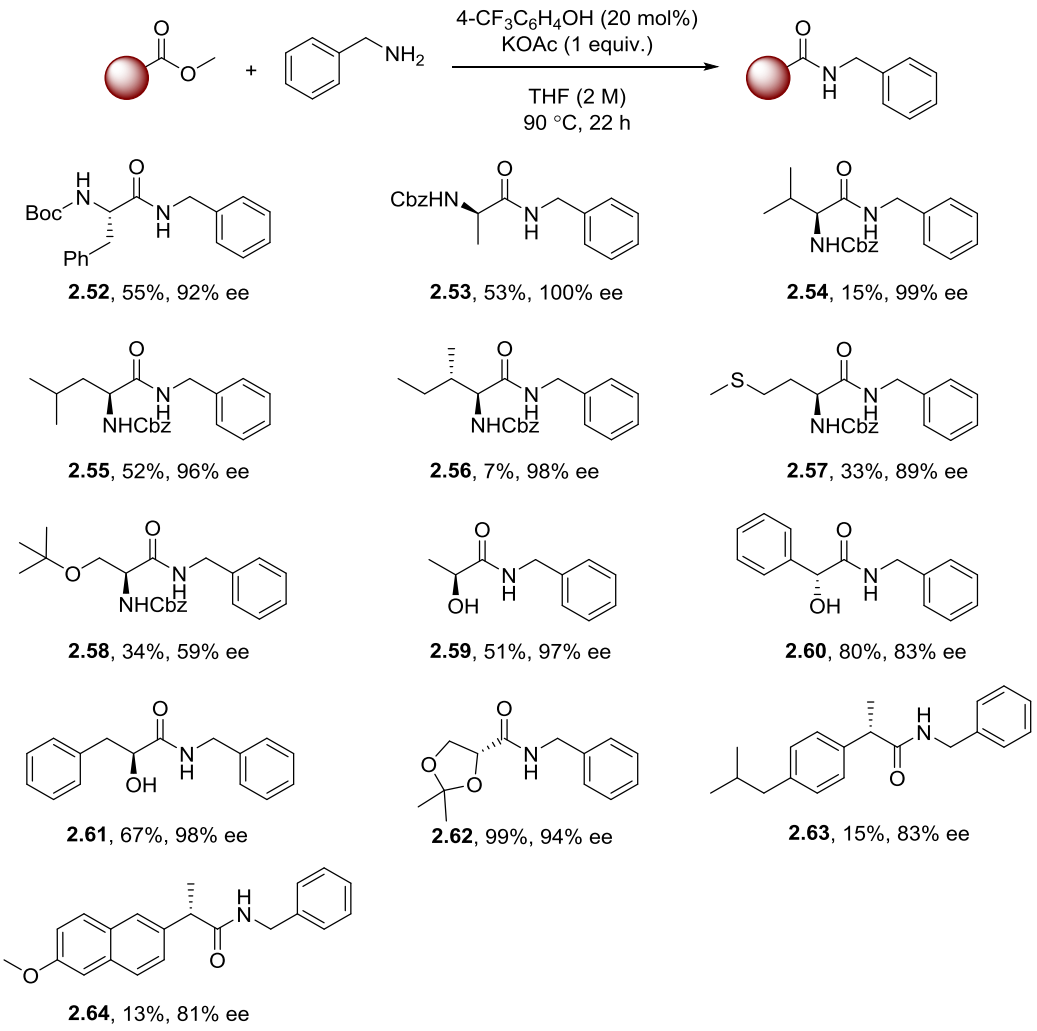
Entry	Substrate	Initial ee (%)	ee upon reaction completion (%)
1	Boc-Phe-OMe	100%	100%
2	**2.52**	92%	92%

2.3.3.2 Exemplification of Chiral Ester Scope

With conditions providing an excellent level of stereoretention successfully developed, a range of α-chiral esters were subjected to the optimum conditions to investigate the generality of the transformation (Scheme 2.24). Pleasingly, good to excellent levels of stereoretention were observed across the range of esters examined, with only the serine derivative **2.58** exhibiting significant erosion of stereochemistry. Other amino acid derivatives (**2.43** – **2.57**) investigated under the reaction conditions were successfully synthesised in low to moderate yields with ee ≥ 89%.

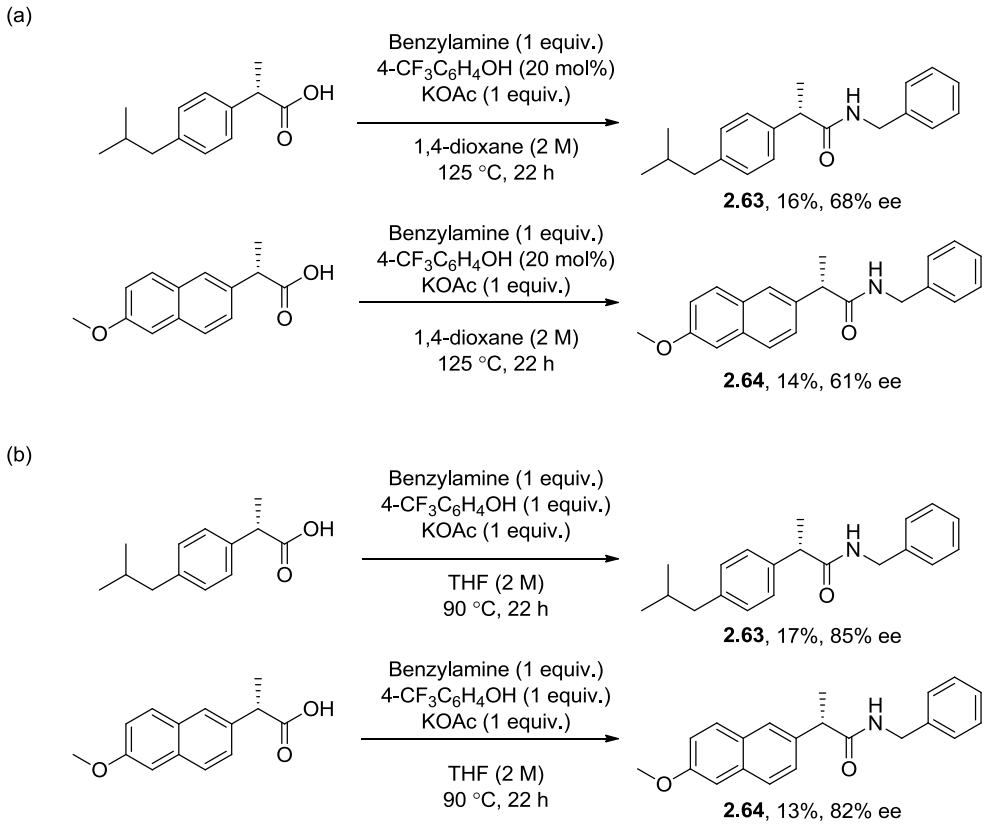
The incorporation of a hydroxyl group at the α-position was also tolerated in the transformation, with α-hydroxy amides **2.59** – **2.61** synthesised in moderate to good yield. Excellent retention of enantiopurity was observed for the lactic and phenyllactic derived amides (**2.59** and **2.61**, respectively), however the use of mandelic acid as a substrate led to a higher degree of stereoerosion, furnishing amide **2.60** with an ee of 83%. A dioxolane ester **2.62** was also found to be a competent substrate, undergoing the desired amidation in excellent yield and stereoretention.

The methyl esters of ibuprofen and naproxen could also be successfully amidated under the reaction manifold, however the corresponding amides (**2.33** and **2.64**, respectively) were furnished in poor yields but with good retention of stereochemistry.



Scheme 2.24: Substrate scope of enantiopure esters.

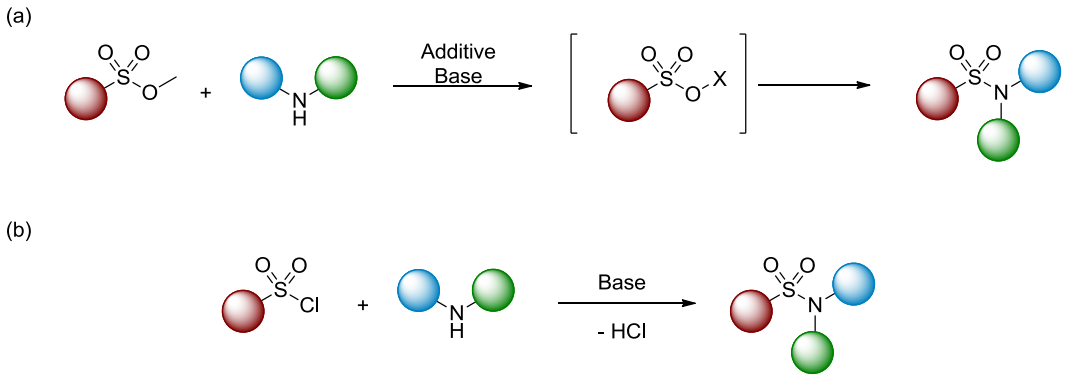
With a view to increasing the yield and the stereoretention for poorer performing substrates, insights gained from the amidation of acyclic secondary amines were applied to the transformation. Accordingly, the amidation of the ibuprofen and naproxen derived esters were selected for further examination. Applying the elevated temperature of 125 °C, which successfully promoted the amidation of acyclic secondary amines, was found to yield the corresponding amides in comparable yields to the optimised conditions (Scheme 2.25a). However, the observed enantiomeric excesses were found to significantly decrease for both the ibuprofen (**2.63**) and naproxen (**2.64**) derived amides to 68 and 61%, respectively. Increasing the quantity of the 4-(trifluoromethyl)phenol additive from 20 mol% to an equimolar amount was also investigated, however no improvement in isolated yield was achieved and comparable enantiomeric excesses observed (Scheme 2.25b).



Scheme 2.25 (a) Investigating the effect of elevated temperature on obtained yield and ee. (b) Investigating the effect of an equimolar amount of additive on obtained yield and ee.

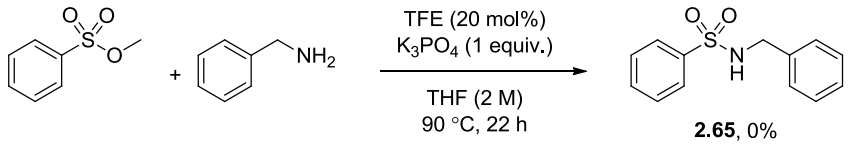
2.3.4 Extension of the TFE-Mediated Amidation Methodology to the Synthesis of Sulfonamide Derivatives

With the main limitations of the progenitor TFE-mediated amidation methodology successfully addressed and the corresponding scopes and drawbacks exemplified, focus centred on further extending the applicability of the methodology. Accordingly, the formation of sulfonamide derivatives from methyl sulfonates was identified as a viable extension (Scheme 2.26a). Commonly synthesised from the corresponding sulfonyl chloride species (Scheme 2.26b), sulfonamide formation therefore experiences similar drawbacks to the use of acid halides in amide bond formation, namely the inability to use acid labile functionalities due to HCl formation and racemisation when using chiral starting materials (*cf.* Section 1.2), in addition to the poor stability of sulfonyl chlorides. Therefore, the application of an exogenous alcohol to mediate the reaction would circumvent the inherent drawbacks associated with sulfonyl chloride use, and offer a mild and facile approach to sulfonamide synthesis.



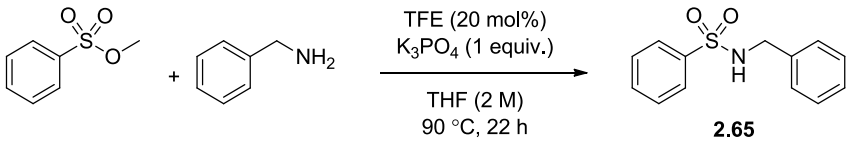
Scheme 2.26: (a) Proposed approach to sulfonamide formation. (b) Classical approach to sulfonamide synthesis from a sulfonyl chloride.

Initial application of the first generation amidation conditions to a model reaction between methyl benzenesulfonate and benzylamine resulted in no formation of the desired sulfonamide product **2.65**, however a white precipitate, attributed to be a quaternary ammonium salt, was formed, impacting the stirring of the reaction (Scheme 2.27). In an effort to facilitate the desired sulfonamidation, the effect of altering the base and additive combination utilised in the model reaction was investigated accordingly (Table 2.9).



Scheme 2.27: Application of first generation amidation condition to model reaction of methyl benzenesulfonate.

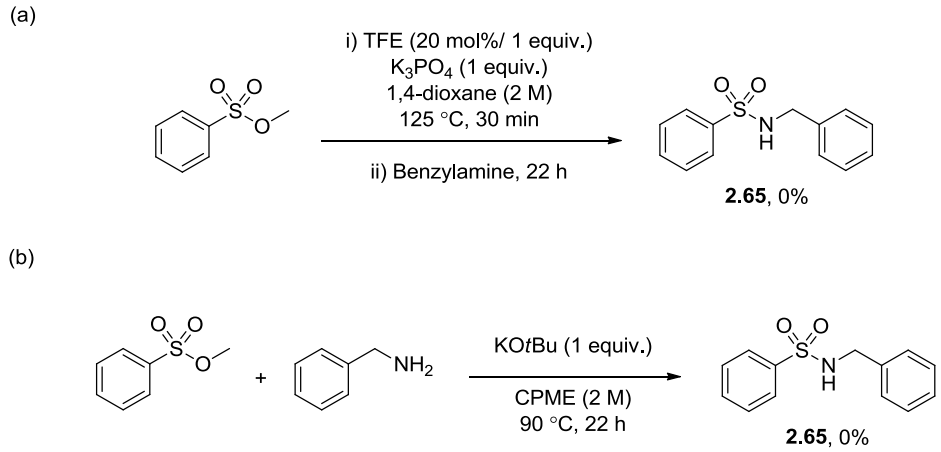
Table 2.9: Additive and base screen towards the TFE-mediated sulfonamidation of sulfonates.



Entry	Base	Additive	Conversion (%)[a]
1	K_3PO_4	HOAt	<1
2	K_3PO_4	NHS	<1
3	K_3PO_4	NHS	<1
4	K_3PO_4	Picoline *N*-oxide	<1
5	K_3PO_4	4-$CF_3C_6H_4OH$	<1
6	K_3PO_4	TFE	<1
7	K_3PO_4	No additive	<1
8	DBU	HOAt	<1
9	DBU	NHS	<1
10	DBU	NHS	<1
11	DBU	Picoline *N*-oxide	<1
12	DBU	4-$CF_3C_6H_4OH$	<1
13	DBU	TFE	<1
14	DBU	No additive	<1
15	KO*t*Bu	HOAt	<1
16	KO*t*Bu	NHS	<1
17	KO*t*Bu	NHS	<1
18	KO*t*Bu	Picoline *N*-oxide	<1
19	KO*t*Bu	4-$CF_3C_6H_4OH$	<1
20	KO*t*Bu	TFE	<1
21	KO*t*Bu	No additive	<1
22	BEMP	HOAt	<1
23	BEMP	NHS	<1
24	BEMP	NHS	<1
25	BEMP	Picoline *N*-oxide	<1
26	BEMP	4-$CF_3C_6H_4OH$	<1
27	BEMP	TFE	<1
28	BEMP	No additive	<1
29	NaH	HOAt	<1
30	NaH	NHS	<1
31	NaH	NHS	<1
32	NaH	Picoline *N*-oxide	<1
33	NaH	4-$CF_3C_6H_4OH$	<1
34	NaH	TFE	<1
35	NaH	No additive	<1
36	No base	HOAt	<1
37	No base	NHS	<1
38	No base	NHS	<1
39	No base	Picoline *N*-oxide	<1
40	No base	4-$CF_3C_6H_4OH$	<1
41	No base	TFE	<1
42	No base	No additive	<1

[a]Conversion determined by HPLC with reference to an internal standard.

In all combinations of base and additive screened, no desired sulfonamide formation was detected with ammonium salt formation observed in each case. In an attempt to overcome this, the more forcing conditions successfully developed for the amidation of acyclic secondary amines were applied to the desired transformation (Scheme 2.28a). Unfortunately, no desired sulfonamide was formed with salt formation inhibiting the reaction. Therefore, it can be inferred that no activated sulfonate intermediate required for the coupling reaction to proceed was successfully forming, with the TFE sequestered by the amine. Additionally, the KO*t*Bu-mediated amidation conditions discovered in the optimisation process for the amidation of acyclic amines were also investigated however no desired sulfonamide was again formed in the reaction (Scheme 2.28b). Based on this, no further work was attempted in sulfonamide formation and attention then turned to another area of study.



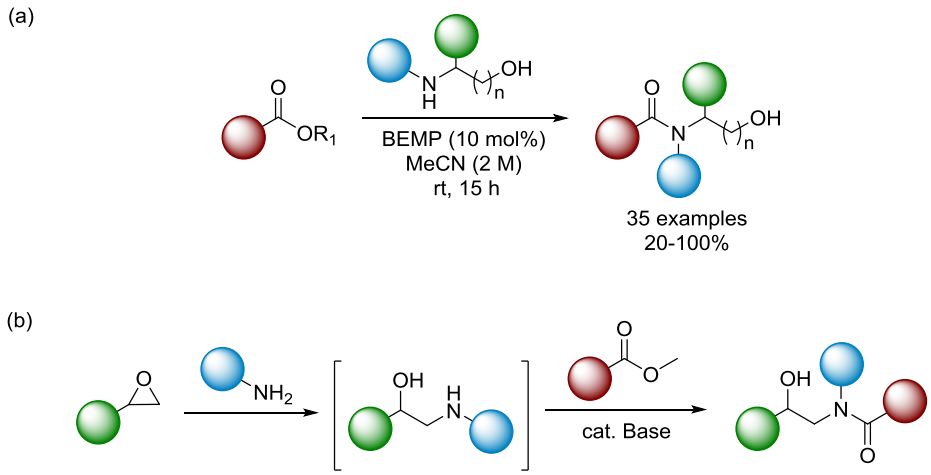
Scheme 2.28: Further attempts towards sulfonamide formation.

2.3.5 Development of an Organobase-Mediated Multicomponent Reaction for the Formation of Functionalised Amides

With the utility of the TFE-mediated amidation methodology successfully expanded, attention was then turned to the creation of an MCR approach to amide bond formation. As discussed in Section 2.13, the development of an MCR methodology would grant an atom economical approach to the synthesis of amides, and, in conjunction with a base-mediated approach, would mitigate both the use of finite, toxic metal reagents and the requirement for vast excesses of reagents associated with previously reported MCR amidation procedures.

Identifying that the amino alcohol component utilised in the previously reported BEMP-mediated amidation of esters (Scheme 2.29a) could be readily synthesised *via* the direct aminolysis of an epoxide, it was proposed that *in situ* formation of the required amino

alcohol followed by the addition of an ester and a base species to this reaction could facilitate the formation of the corresponding amide species (Scheme 2.29b)

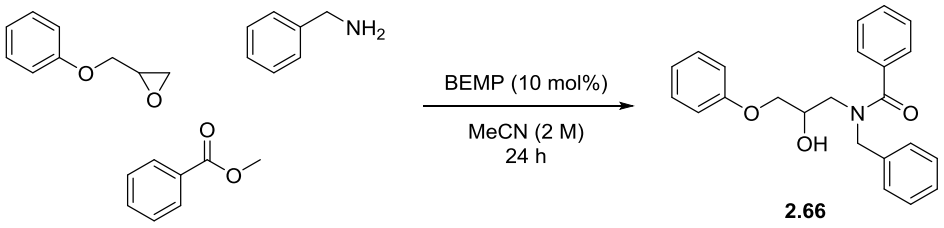


Scheme 2.29: (a) Progenitor BEMP-mediated amidation of unactivated esters and amino alcohols. (b) Proposed base mediated MCR formation of amides.

2.3.5.1 Optimisation of MCR Approach to Amide Bond Formation

An optimisation procedure of the desired MCR approach to amide bond formation previously undertaken by another member of our laboratories indicated that increasing the reaction temperature from room temperature, as utilised in the first generation process, to 100 °C promoted formation of amide **2.66** in 58% yield (Table 2.10).[119]

Table 2.10: Previously performed optimisation procedure towards the desired MCR amidation reaction.[119]

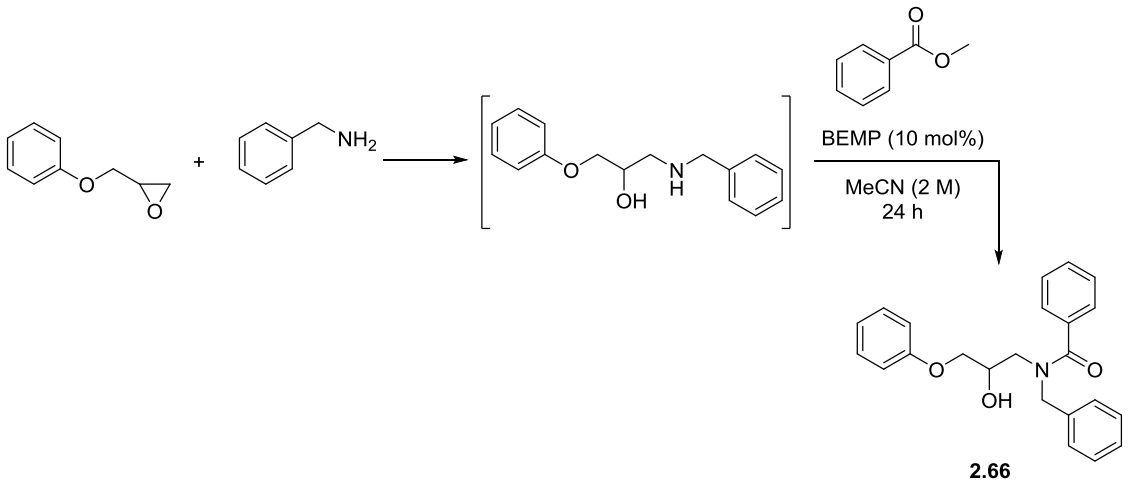


Entry	Temperature (°C)	Conversion (%)[a]
1	20	<1
2	40	17
3	60	41
4	70	52
5	100	58

[a]Conversion determined by HPLC with reference to an internal standard.

With a view to further optimise this MCR reaction, the effect of altering the order of addition on the reaction efficiency was investigated (Table 2.11). When reactions featuring concomitant addition of all reactants, thereby representing a true multicomponent reaction, were performed at 60 and 100 °C (Table 2.11, Entries 1 and 3), an improvement in yield of **2.66** was observed in both cases, 64 and 71%, respectively, when compared to the prior optimisation procedure. Allowing the pre-formation of the amino alcohol over a 5 hour period, prior to the addition of the ester and BEMP, was also investigated at both room temperature and 100 °C (Table 2.11, Entries 2, 4 and 5). In these cases, the desired amidation reaction was found to perform comparatively to the concomitant addition of reactants at 100 °C. Therefore with the pre-formation of the amino alcohol extending the required reaction time whilst leading to no improvement in the observed yield, the concomitant addition of reactants at a reaction temperature of 100 °C were selected as the optimum reaction conditions (Table 2.11, Entry 3).

Table 2.11: Investigating the order of addition in nascent MCR amidation reaction.

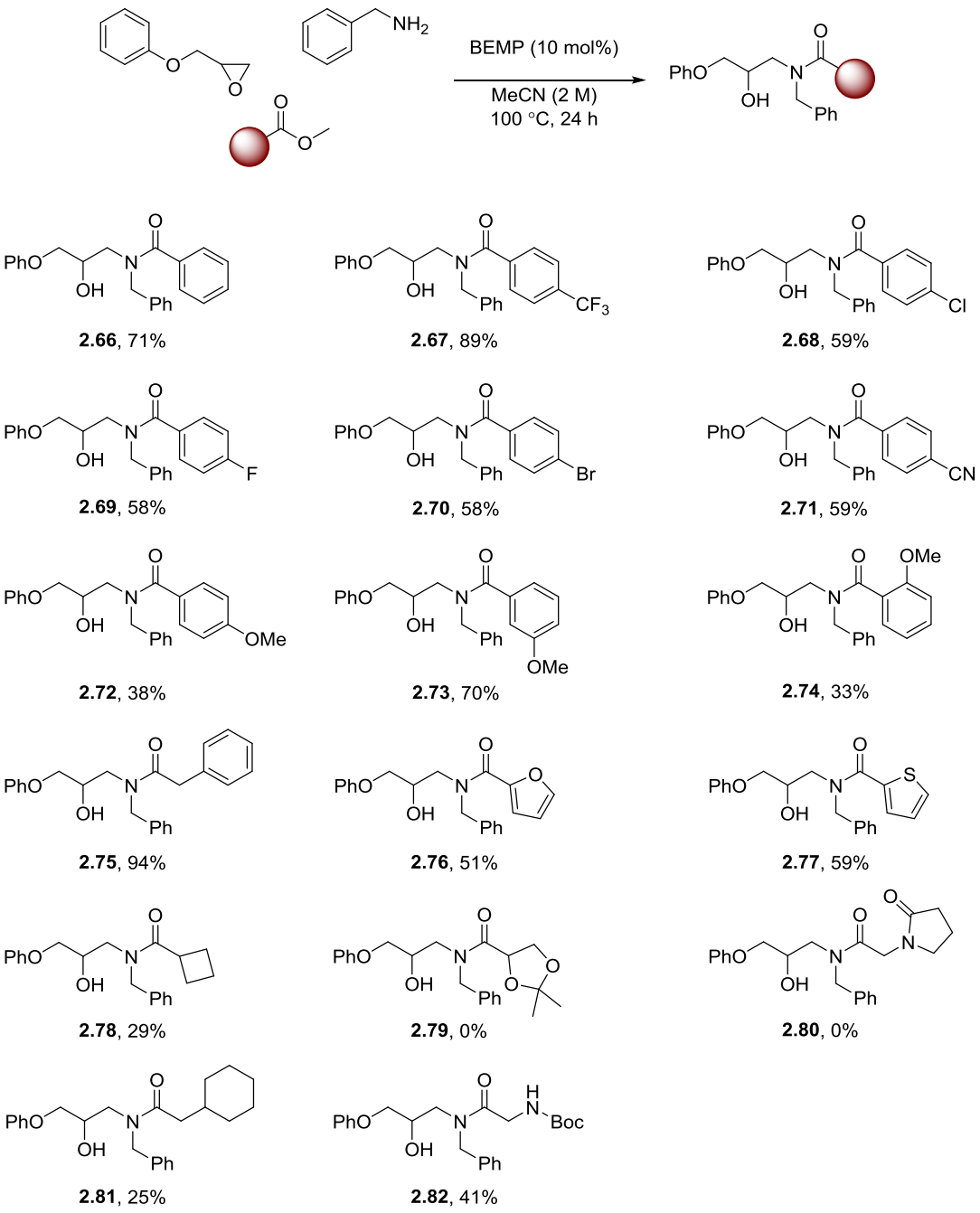


Entry	Conditions	Temperature (°C)	Yield (%)
1	Concomitant addition of reactants	60	64
2	5 hour pre-formation of amino alcohol at rt	60	73
3	Concomitant addition of reactants	100	71
4	5 hour pre-formation of amino alcohol at rt	100	72
5	5 hour pre-formation of amino alcohol at 100 °C	100	69

2.3.5.2 Scope of the Optimised MCR Approach to Amide Bond Formation.

With conditions allowing the efficient MCR amidation reaction of epoxides, amines and esters successfully developed, the scope of each component was then investigated (Scheme 2.30). Initially, the ester component of the MCR was examined, with the incorporation of both electron-withdrawing and electron-donating groups tolerated in moderate to excellent yields (**2.67** – **2.74**). Homologation of the ester component to methyl phenylacetate afforded the corresponding amide **2.75** in excellent yield, with this improvement expected as a result of the increased electrophilicity of the carbonyl centre. Heteroaryl esters are also competent substrates, with furan (**2.76**) and thiophene (**2.77**) derivatives coupled in 51 and 59%, respectively.

Cyclobutane (**2.78**), cyclohexyl (**2.81**) and glycine (**2.82**) derived aliphatic esters are tolerated under the reaction manifold, albeit in only comparatively modest yields. Other cyclic aliphatic esters, for example dioxolane **2.79** and pyrrolidinone **2.80**, are found to be incompatible substrates.

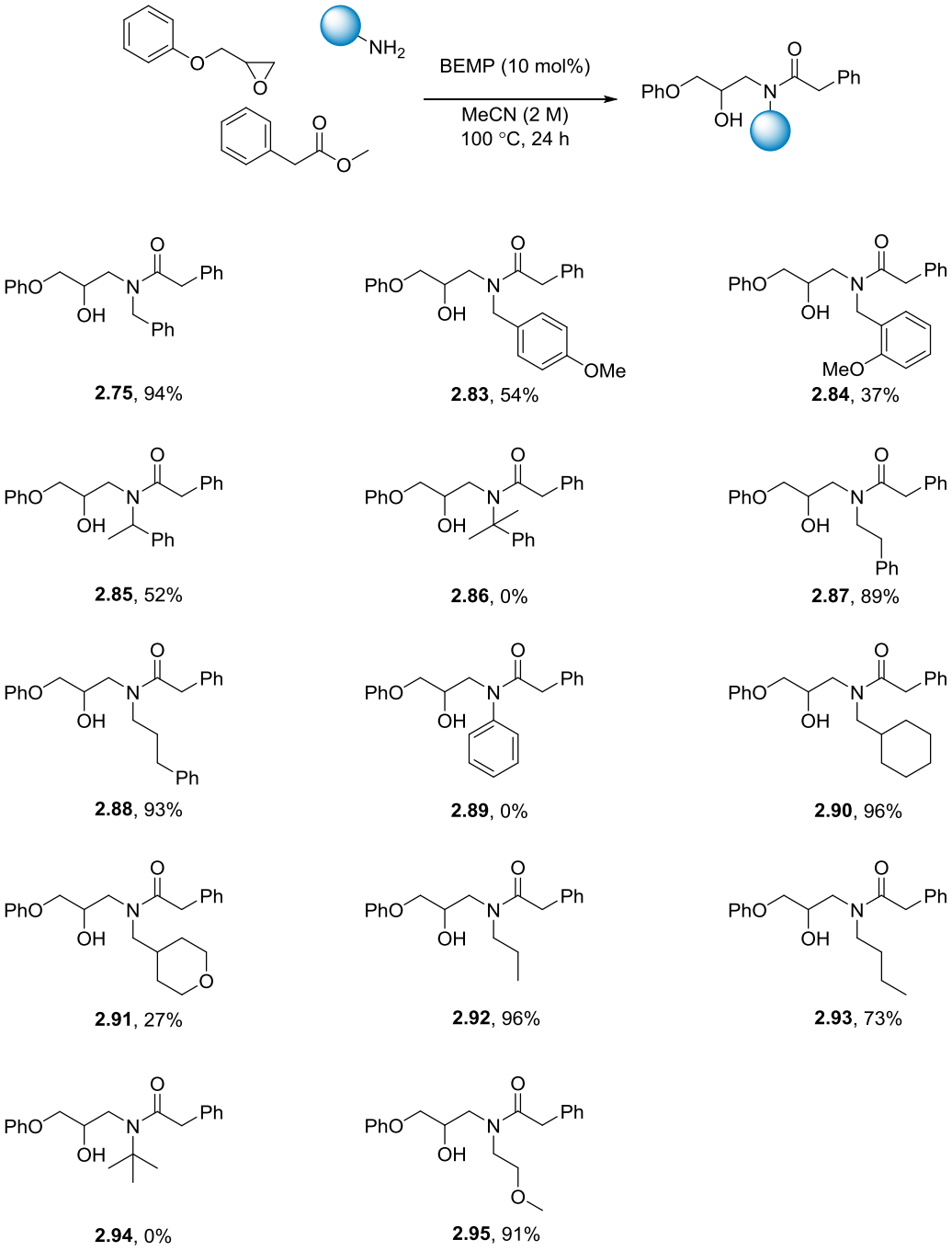


Scheme 2.30: Scope of the ester component in the developed amide bond forming MCR.

With the scope of the ester component successfully exemplified, focus was switched to examining the tolerance of the reaction towards variation of the amine component (Scheme 2.31). Due to the superior reactivity of methyl phenylacetate (**2.75**) compared to methyl benzoate (**2.66**), it was retained as the model ester in the investigation of the amine scope. Substitution on the aromatic ring in the form of a methyl ether substituent is tolerated in moderate yields, with *ortho* substitution (**2.84**) found to proceed less efficiently than *meta*

(**2.83**) which is ascribed to the increased steric hindrance of substitution at the *ortho* position. Substitution at the α-position leads to a significant decrease in the efficiency of the amidation process with the methyl substituted amine furnishing the corresponding amide (**2.85**) in only 52% yield. Further increasing the substitution at the α-position further to the gem-dimethyl **2.86** resulted in no formation of the desired amide, implying that only limited substitution at the α-position is tolerated before the reaction is impeded as a result of steric encumbrance.

Homologation of the amine component furnished amides **2.87** and **2.88** in excellent yields of 89 and 93%, respectively. The use of aniline (**2.89**) as a substrate was found to be unsuccessful, with the reduced nucleophilicity of aromatic amines reasoned to be the cause of the observed lack of reactivity. A range of alkyl amines were also prosecuted under the optimised reaction conditions with cyclohexylamine **2.90**, propylamine **2.92**, butylamine **2.93** and 2-methoxyethylamine **2.95** found to react in good to excellent yields. However, the tetrahydropyran derivative led to the formation of amide **2.91** in a comparatively poor yield of 27%, and *tert*-butylamine (**2.94**) was found to be an incompatible substrate, which is attributed to the steric bulk associated with the *tert*-butyl group.



Scheme 2.31: Scope of the amine component in the developed amide bond forming MCR.

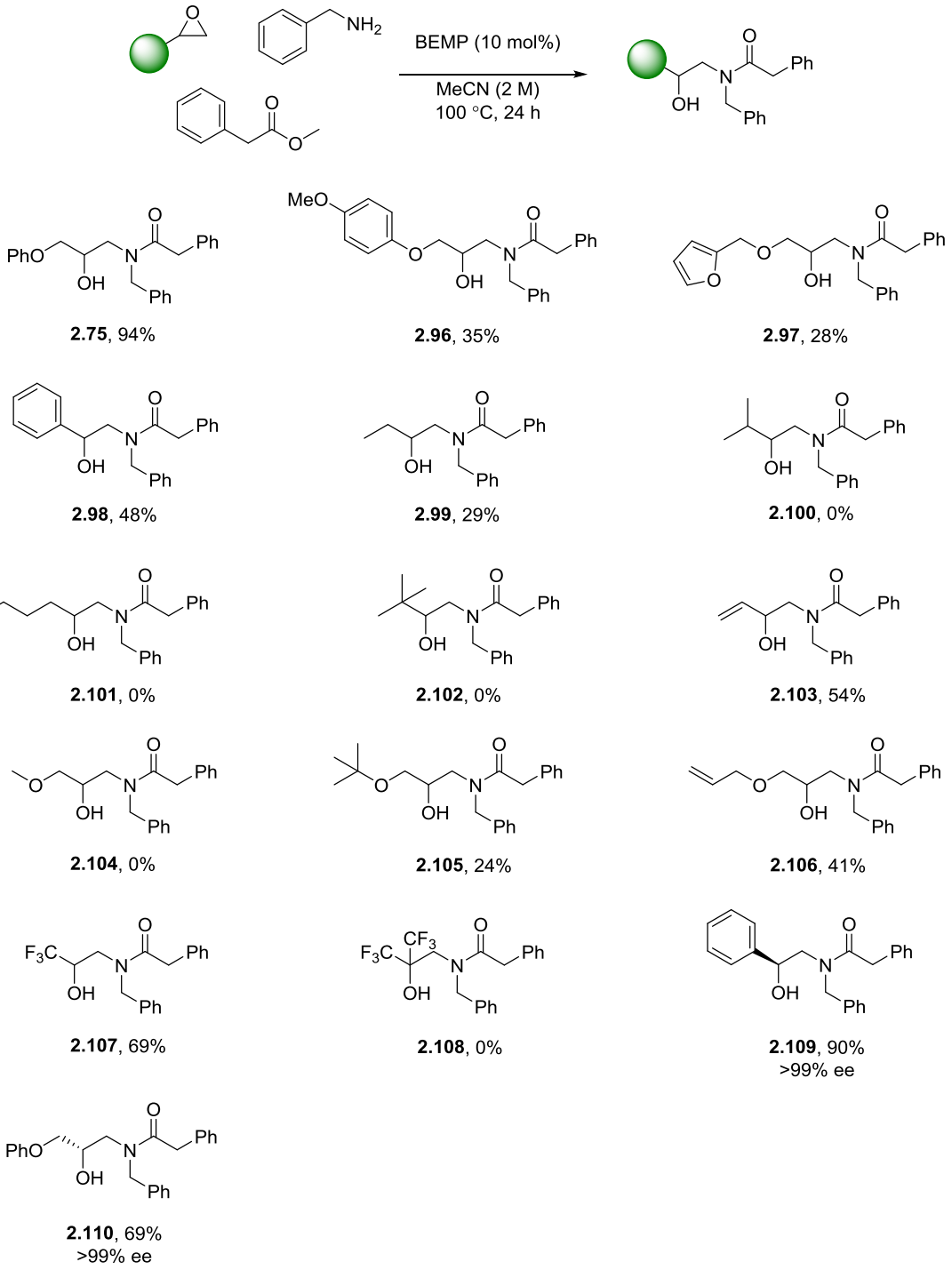
With the scope of the ester and amine components of the reaction successfully investigated and exemplified, the last phase of the study examined the nature of the epoxide substrate utilised in the MCR (Scheme 2.32). The application of further epoxides comprising an aromatic component, **2.96**, **2.97** and **2.98**, were found to lead to a decrease in reaction efficiency affording the corresponding amide products in 35, 28 and 48% yields, respectively. A range of aliphatic epoxides were then examined with an epoxide bearing an

ethyl substituent, **2.99**, successfully coupled in 29% yield. Further increasing the substitution to isopropyl (**2.100**), *n*-butyl (**2.101**) and *tert*-butyl (**2.102**) groups proved to have a deleterious effect with no formation of the corresponding amides observed. However, amide **2.103** was found to be a successful substrate, with the desired amidation from the corresponding vinyl epoxide proceeding in a moderate yield of 54%.

Aliphatic epoxides containing ether moieties were also investigated under the reaction manifold, with *tert*-butyl (**2.105**) and allyl ether substituents (**2.106**) found to be competent, albeit in low to moderate yields. The successful formation of **2.105** compared to other failed substrates containing *tert*-butyl substitution (**2.94** and **2.102**) is reasoned to be a result of the *tert*-butyl group being remote from the oxygen and nitrogen centres involved in the transesterification/rearrangement events, thereby limiting the effect of the increased steric bulk. In contrast with the prior observation that smaller substituents perform better in the amidation process, an epoxide bearing a methyl ether (**2.104**) was found to be an incompatible substrate.

As expected, the incorporation of a trifluoromethyl group directly bonded to the epoxide ring was found to furnish the corresponding amide product **2.107** in a good yield of 69%, with the electron-withdrawing inductive effects of the trifluoromethyl group promoting the nucleophilic attack of the amine at the carbon centre of the epoxide. However, the addition of a further trifluoromethyl group (**2.108**) was found to render the desired amidation unsuccessful, presumably as a result of the increased steric bulk associated with the tertiary amino alcohol intermediate preventing transesterification.

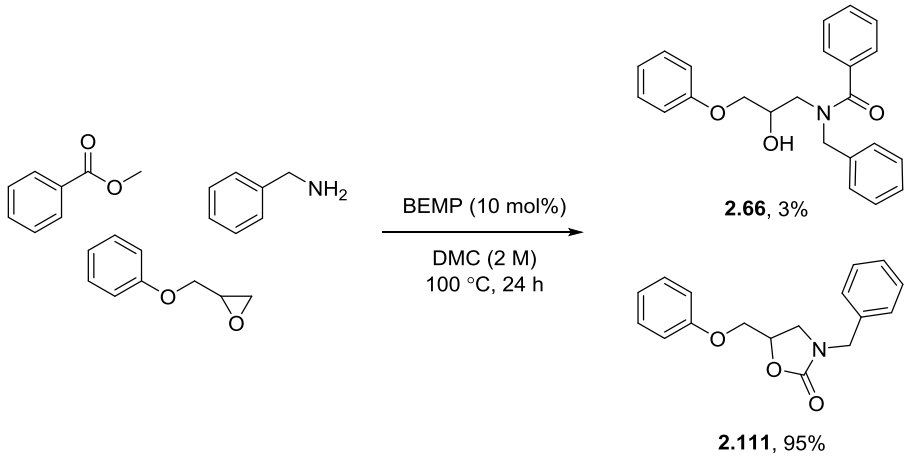
Enantiopure epoxide substrates were also subjected to the optimised conditions, with (*S*)-styrene oxide, **2.109**, and (*S*)-glycidyl phenyl ether, **2.110**, found to undergo the amidation process in good to excellent yields, with no erosion of chirality observed in either case.



Scheme 2.32: Scope of the epoxide component in the developed amide bond forming MCR.

2.3.5.3 Development of an MCR Reaction towards Oxazolidinone Synthesis

During the optimisation process of the MCR amidation process, it was found by another member of our laboratory that the use of dimethylcarbonate (DMC) as a solvent *in lieu* of acetonitrile led to only a 3% conversion to the desired amide (**2.66**).[119] However, HPLC analysis of the reaction mixture indicated full consumption of the amine and epoxide starting materials, and the intermediary amino alcohol species, had occurred forming a previously unobserved product, with little consumption of methyl benzoate observed.[119] Upon isolation, the observed by-product was identified as oxazolidinone species **2.111**, formed *via* the preferential reaction of the amino alcohol with the DMC solvent in a 95% yield (Scheme 2.33).[119]



Scheme 2.33: Preferential formation of oxazolidinone 2.111 when DMC is used as the solvent.[119]

With this process representing a second MCR proceeding through a similar transesterification-type/rearrangement process, as well as oxazolidinone scaffolds comprising an important class of antimicrobial and anticoagulant agents (Figure 2.4), this complimentary MCR process was optimised to further adapt the methodology towards the synthesis of oxazolidinones. Additionally, this approach would perhaps offer an advantage over a recently reported organocatalysed synthesis of oxazolidinones from epoxides and aryl isocyanates. Employing tetraarylphosphonium salts as the catalytic species, in loadings as low as 0.5 mol%, a range of oxazolidinone species were synthesised in moderate to excellent yields (Scheme 2.34).[120] However, the use of isocyanates is undesirable as a result of their nature as potential respiratory inhibitors.[121] Therefore, the nascent BEMP-mediated oxazolidinone formation would be preferential over this approach as it mitigates the necessity for isocyanate starting materials.

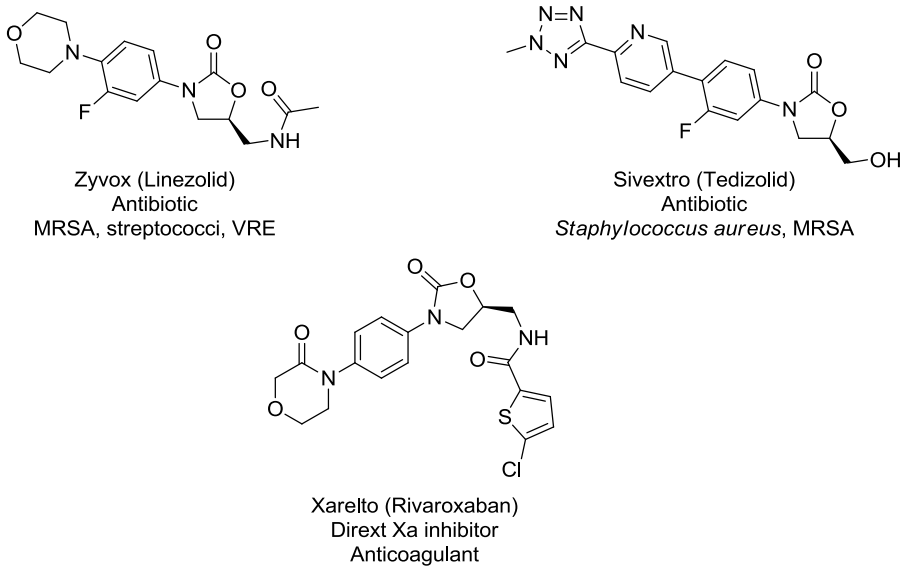
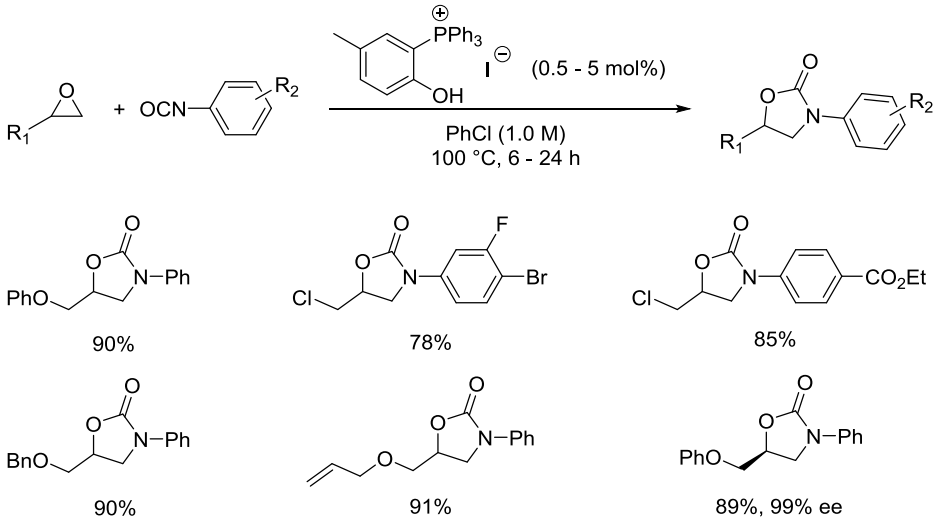


Figure 2.4: Marketed pharmaceuticals containing an oxazolidinone moiety.

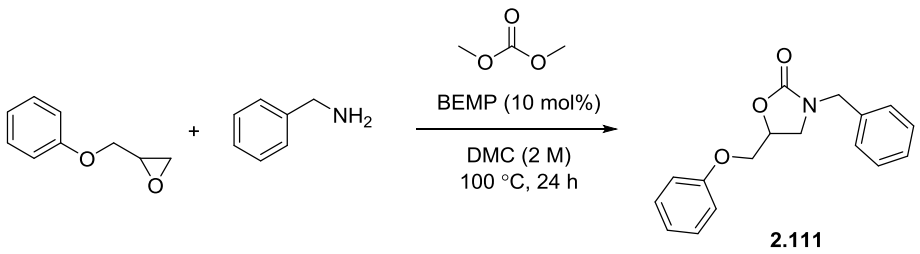


Scheme 2.34: Selected examples of oxazolidinone formation catalysed by a tetraarylphosphonium salt.[120]

A focused optimisation performed elsewhere in our laboratories identified that temperature was again the key factor influencing reaction efficiency, with a minimum reaction temperature of 70 °C required to ensure moderate formation of the desired oxazolidinone in 16 hours (Table 2.12, Entries 1 and 3).[122] In order to avoid the use of elevated reaction temperatures, extending the reaction time from 16 to 24 hours enabled a near quantitative yield of oxazolidinone **2.111** (Table 2.12, Entry 4).[122] Lowering the quantity of base used from 10 mol% to 5 mol% resulted in a significant decrease in yield at both 70 °C and 120 °C (Table 2.12, Entries 2 and 5). The reaction conditions of 10 mol% BEMP at 70 °C for 24

hours (Table 2.12, Entry 4) were therefore selected as the optimum conditions for the reaction.[122]

Table 2.12: Optimisation of MCR methodology towards oxazolidinone formation performed previously within the Jamieson group.[122]



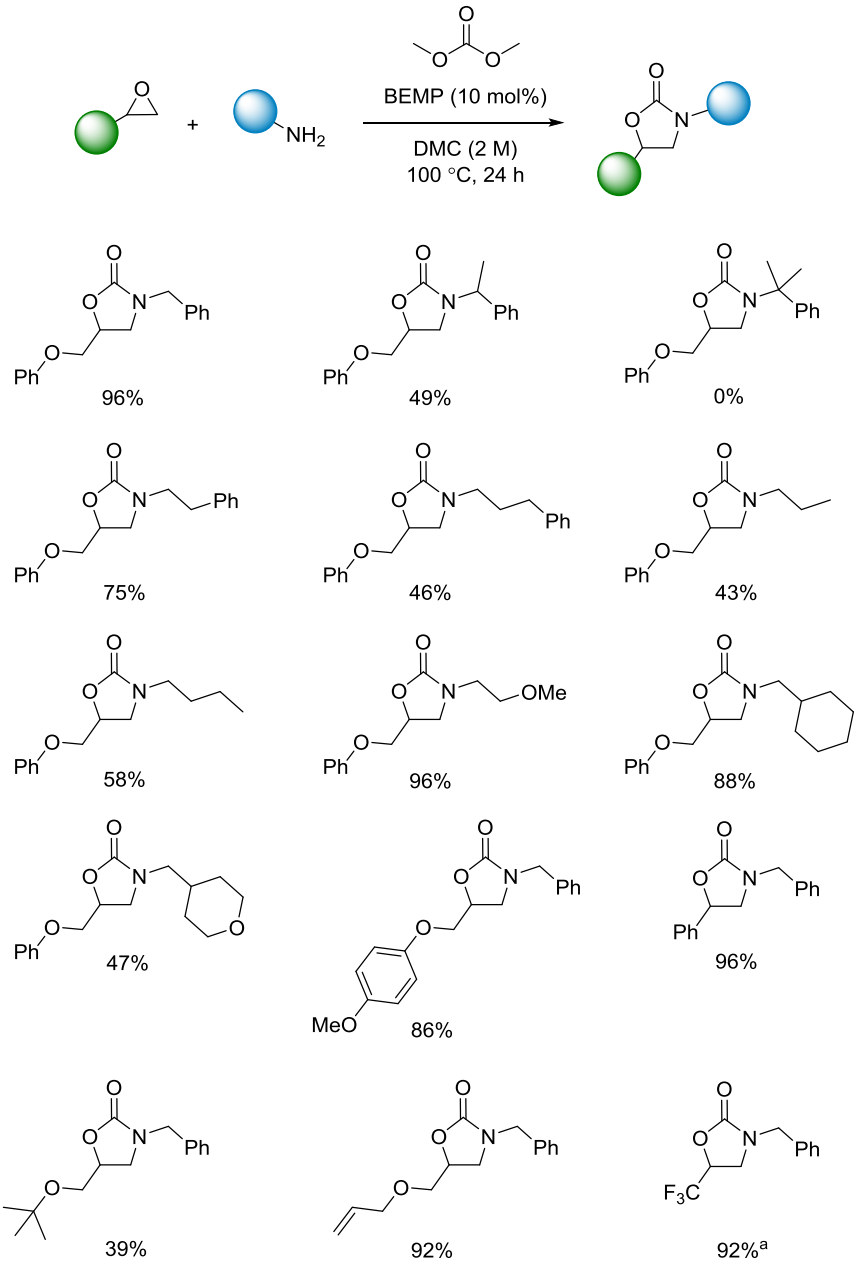
2.111

Entry	Reaction Temperature (°C)	BEMP (mol%)	Reaction Time (h)	Yield (%)
1	120	10	16	94
2	120	5	16	78
3	70	10	16	48
4	70	10	24	96
5	70	5	24	13
6	40	10	24	12

With the optimum conditions in hand, the scope of the amine and epoxide components was exemplified (Scheme 2.35).[122] A subset of the amines and epoxides screened under the amidation conditions were shown to be successful substrates in the formation of oxazolidinones, with similar reactivity profiles observed, for example, the decrease in reaction efficiency with increasing substitution alpha to the nitrogen in amines.[122]

However, an enantiopure exemplar was not examined within this previous

study, therefore (*S*)-glycidyl phenyl ether was examined by the author under the optimised conditions. Pleasingly, the corresponding oxazolidinone **2.112** was synthesised in a comparative yield to the racemate with complete retention of stereochemistry (Figure 2.5).



Scheme 2.35: Exemplification of the scope of the oxazolidinone forming MCR. [a]Reaction performed in neat DMC.[122]

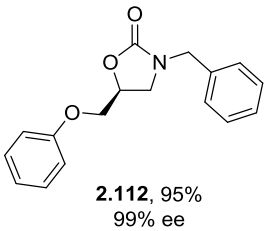
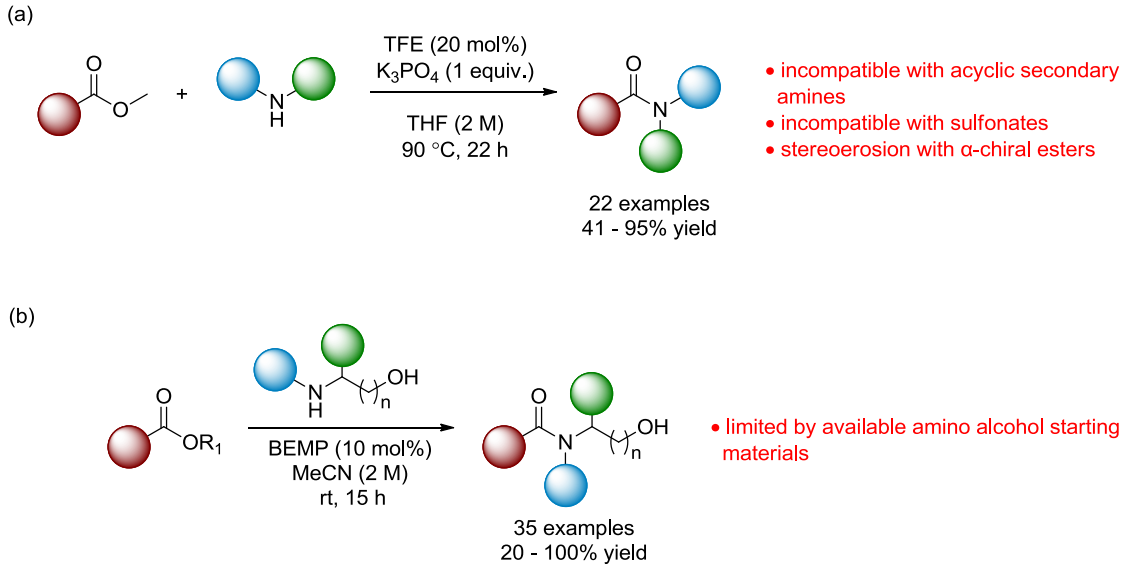


Figure 2.5: Chiral oxazolidinone synthesised from (*S*)-glycidyl phenyl ether.

2.4 Conclusions

At the outset of this study into organocatalytic mediated amidation, our laboratories had already successfully demonstrated the use of TFE and BEMP to facilitate the amidation of esters with amines and amino alcohols, respectively (Scheme 2.36). However, the general utility of these methodologies was hindered by a range of limitations. In the TFE-mediated amidation of unactivated esters (Scheme 2.36a), it was found that both acyclic secondary amines and sulfonates were incompatible coupling partners, and, the application of α-chiral ester starting materials was hindered by significant erosion of the enantiopurity. Under the first generation BEMP-mediated amidation of amino alcohols and unactivated esters (Scheme 2.36b), the scope of the reaction was limited by the general commercial availability of amino alcohol starting materials. Therefore, the aims of this project were to address these outstanding issues *via* further optimisation studies followed by full exemplification of the scope of the reactions and any inherent limitations associated with the methodologies.



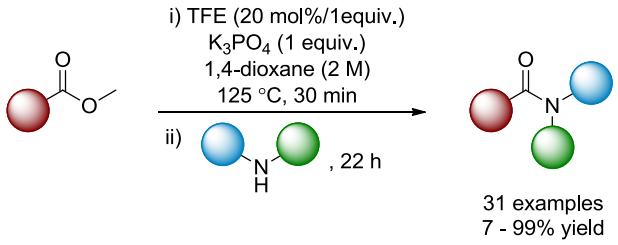
Scheme 2.36: First generation amidation methodologies and their limitations.

Initial investigations of the TFE-mediated amidation of unactivated esters and amines focused on gaining a further understanding into the relationship between the nature of the base species utilised in the reaction manifold and the TFE additive. Based on our previous observation that the pK_a values of the K_3PO_4 and TFE utilised in the progenitor conditions align (12.3 and 12.4, respectively), a variety of bases encompassing a range of pK_a values and counterions were examined to probe whether this alignment was a prerequisite for an efficient amidation reaction to proceed. From this study, it was observed that the K_3PO_4/TFE

combination was indeed optimal for reaction progression, with DBU (pK_a = 12) also promoting the reaction in a good, but albeit moderate, conversion of 61%. KO*t*Bu was also found to successfully promote the amidation reaction, but is proposed to proceed through a competing radical pathway.[115]

This greater understanding of the requirements for the base and additive combination was then applied in addressing the incompatibility of acyclic secondary amines in the first generation process. Additive and base studies, although hindered by the formation of quaternary ammonium salts, indicated that K_3PO_4 and TFE could facilitate the amidation of acyclic secondary amines. Further optimisation indicated that an increase in reaction temperature, and accordingly a change in solvent to 1,4-dioxane, alongside a 30 minute pre-formation of the active ester intermediate prior to addition of amine could allow efficient amide synthesis and circumvent salt formation.

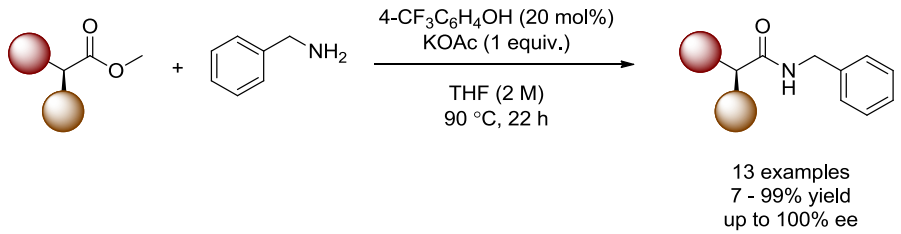
The scope of the reaction was then investigated by applying these optimum conditions to a diverse range of ester and amine coupling partners (Scheme 2.37). It was found that substrates which proved challenging could be improved by utilising an equimolar quantity of TFE. Unfortunately, one outstanding limitation of the process is the requirement for the acyclic secondary amine to possess a methyl substituent, with any larger moiety found to prohibit the desired amidation, an effect which is ascribed to increased steric bulk.



Scheme 2.37: TFE-mediated amidation of acyclic secondary amines.

A base and additive screen was also employed to address the observed stereoerosion when coupling α-chiral esters in the first generation process. This optimisation process indicated a strong correlation between the strength of base applied and the degree of stereoerosion observed, with bases with a pKa ≥ 10 resulting in a significant degradation of enantiopurity. The combination of KOAc and 4-(trifluoromethyl)phenol was found to lead to the optimum ratio of yield to ee, and therefore these conditions were applied in the examination of a range of α-chiral esters with good to excellent retention of stereochemistry generally observed

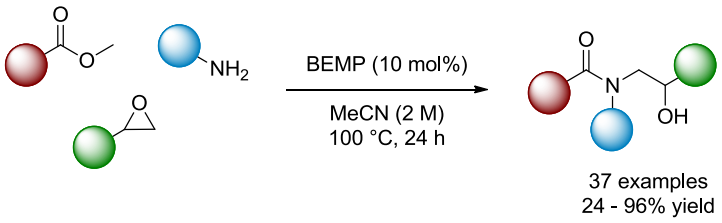
(Scheme 2.38). Additionally, investigations into the origin of the observed loss in chiral integrity suggested that stereoerosion occurred through the activated ester intermediate.



Scheme 2.38: TFE-mediated amidation of α-chiral esters.

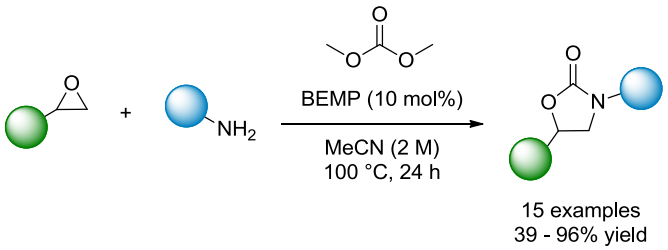
Broadening the scope of the methodology to incorporate the synthesis of sulfonamides proved unsuccessful, with the observed formation of a quaternary ammonium salt implying that no formation of the required activated sulfonate species was occurring under the reaction conditions.

In an effort to broaden the applicability of the BEMP-mediated amidation of amino alcohols, it was proposed that *in situ* formation of the amino alcohol could be achieved through the nucleophilic ring opening of an epoxide. If successfully achieved in a one-pot process, this would represent a highly atom economical multicomponent approach to amide bond formation. Optimisation of the progenitor conditions showed that a simple elevation of the reaction temperature from room temperature to 100 °C successfully promoted the desired amidation reaction.[119] Applying these optimised conditions to a palette of ester, amine and epoxide starting materials permitted a range of functionalised amides to be successfully synthesised, including two chiral exemplars with enantiomeric excesses >99% (Scheme 2.39).



Scheme 2.39: BEMP-mediated MCR for the synthesis of amide bonds.

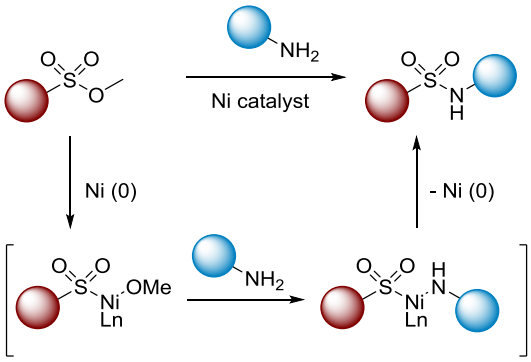
Further development and adaption of this BEMP-mediated amidation methodology elsewhere in our laboratories has allowed dimethyl carbonate to be employed *in lieu* of an ester species, resulting in the formation of oxazolidinone moieties, including an example synthesised from a chiral epoxide in 99% ee (Scheme 2.40).[122]



Scheme 2.40: BEMP-mediated MCR for the synthesis of oxazolidinone scaffolds.[122]

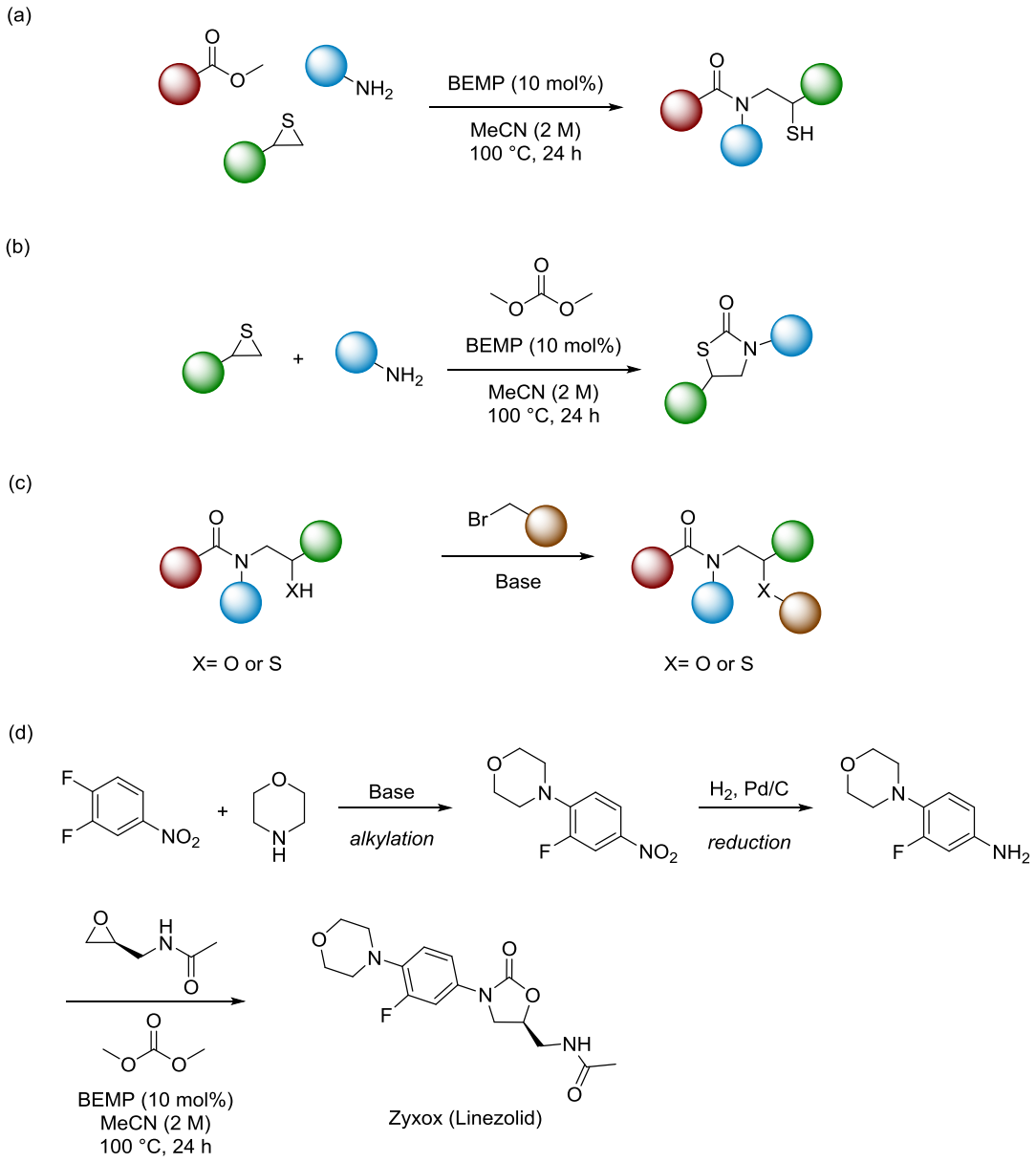
2.5 Future Work

With the successful formation of sulfonamides *via* the application of sulfonates as starting materials in the TFE-mediated amidation methodology remaining elusive, the investigation of alternative catalytic manifolds may successfully overcome this limitation. The application of metal catalysis is less desirable than organocatalysis as a result of expensive, finite metals, the use of which can have related toxicity concerns. However, the use of low catalyst loadings or abundant metal catalysts could provide one approach to successful catalytic sulfonamide synthesis. Activation of the sulfonate S-O bond, analogous to Houk and Garg's activation of the acyl C-O bond in esters, could offer one approach to activating the sulfonate starting material (Scheme 2.41).[56] Using a nickel catalyst, cost and sustainability concerns would be minimised, although the toxicity of nickel complexes could still be viewed as a potential drawback. Additionally, the atom economy of the process would be reduced if an NHC and additional metal additive is required as in Houk and Garg's methodology.



Scheme 2.41: Proposed nickel catalysed activation of a sulfonate S-O bond towards the formation of sulfonamide derivatives.

With a view to further enhancing the scope of the BEMP-mediated amide and oxazolidinone syntheses, the epoxide component could be substituted for an episulfide, forming functionalised amides with free thiol groups and thiazolidinones respectively (Scheme 2.42a and Scheme 2.42b). Additionally, the amides synthesised *via* this methodology could undergo further derivatisation, with the hydroxyl and thiol groups providing further functional handles, enabling the synthesis of moieties such as ethers and thioethers (Scheme 2.42c). Furthermore, with the oxazolidinone moiety present in an important class of antimicrobial and anticoagulant agents, the BEMP-mediated multicomponent methodology could therefore be utilised to synthesise relevant examples in an atom economical fashion. One such pertinent antimicrobial agent is Linezolid, which could be synthesised in 3 steps by utilising the MCR approach to oxazolidinone formation (Scheme 2.42d).



Scheme 2.42: (a) Proposed application of an episulfide in the BEMP-mediated MCR amide bond formation. (b) Proposed formation of thiazolidinones. (c) Further derivatisation of amide products bearing a free hydroxyl or thiol group. (d) Proposed synthesis of Linezolid utilising the BEMP-mediated multicomponent oxazolidinone formation.

2.6 Experimental

2.6.1 General Techniques

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[123] When purification was carried out *via* distillation, the relevant desiccants are indicated in brackets.

2.6.1.1 Purification of Solvents

i) Anhydrous THF was obtained from a PureSolv SPS-400-5 solvent purification system.

ii) DCE (CaH_2), MeCN (CaH_2), 2-MeTHF (CaH_2), DMC (4 Å molecular sieves) and IPA (KOH) were purified by fractional distillation.

iii) CPME (Na metal), 1,4-dioxane ($LiAlH_4$) and DMF ($MgSO_4$) were purified by vacuum distillation.

iv) *n*-Butanol was purified by stirring over 4 Å molecular sieves for 24 hours.

v) Purified solvents were transferred to and stored in septum-sealed oven-dried flasks over activated 4 Å molecular sieves and purged with and stored under nitrogen.

vi) Acetone, dichloromethane, ethyl acetate, methanol, and petroleum ether 40–60 °C for purification purposes were used as obtained from suppliers without further purification.

2.6.1.2 Purification of Reagents

i) BEMP (CaH_2), benzylamine (KOH), *N*-methylbenzylamine (KOH) and methyl benzoate (KOH) were purified by vacuum distillation.

ii) DBU, Et_3N (CaH_2), NMM (Na metal) and TFE (Na_2SO_4) were purified by fractional distillation.

iii) $Ca_3(PO_4)_2$, Cs_2CO_3, Cs_3PO_4, K_2CO_3, KH_2PO_4, K_2HPO_4, K_3PO_4, Li_3PO_4, $Mg_3(PO_4)_2$ and Na_3PO_4 were stored in a vacuum oven at 60 °C.

iv) DABCO purified by recrystallisation from IPA/MeOH (1:1).

v) KOAc, KOH and KTFA stored in a desiccator under P_2O_5.

vi) KO*t*Bu purified by sublimation.

vii) NaH purified by washing with petroleum ether 40 – 60 °C.

2.6.1.3 Experimental Details

i) All reactions were carried out using oven-dried (150 °C) glassware, which was evacuated and purged with N_2 before use.

ii) Purging refers to a vacuum/nitrogen-refilling procedure.

iii) TFE catalysed amidation reactions were performed using 25 mL Schlenk reaction vessels.

iv) BEMP-mediated amidation reactions were performed using 0.5 – 2 mL microwave vials.

v) Room temperature was generally *ca.* 20 °C.

vi) Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

vii) TFE catalysed amidation reactions at elevated temperatures were carried out using a STEM heating block.

viii) Reactions requiring the use of Radleys tubes with elevated temperatures were performed in a carousel resting on a temperature-regulated hotplate/stirrer.

2.6.1.4 Purification of Products

i) Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light or developed using potassium permanganate solution.

ii) Flash chromatography was carried out using ZEOprep 60 HYD 40-63 µm silica gel.

iii) Strong cation exchange chromatography was carried out using Silicycle SiliaPrepTM Propylsulfonic Acid (SCX-2) cartridges.

2.6.1.5 Analysis of Products

i) Fourier Transformed Infra-Red (FTIR) spectra were obtained using an A2 Technologies ATR 32 machine.

ii) ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX 500 spectrometer at 500 and 126MHz, respectively or on a Bruker AV3 400 at 400 and 101 MHz, respectively, or on a Bruker AVANCE 400 spectrometer at 400 and 101 MHz respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.16 ppm (^{13}C), and DMSO-d6 referenced at 2.50 (^{1}H) and 39.52 ppm (^{13}C).

iii) Variable temperature NMR experiments were obtained using a Bruker AVANCE 400 spectrometer at 400 and 100 MHz respectively, or a Bruker DRX 500 spectrometer at 500 and 126MHz, respectively at 333 K.

iv) High-resolution mass spectra were obtained on a Thermofisher LTQ Orbitrap XL instrument at the EPSRC National Mass Spectrometry Service Centre (NMSSC), Swansea.

v) Reverse phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column.

vi) Chiral HPLC data was obtained on an Agilent 1260 Infinity HPLC using a Chiralpak IA column.

vii) Optical rotations were measured at 589 nm using a Perkin Elmer 341 Polarimeter.

2.6.1.6 Reversed Phase HPLC Methods

i) For *N*-Benzylbenzylamide **2.4**: Reversed phase HPLC analysis was performed using a gradient method, eluting with 5 – 80% MeCN/H_2O over 5 minutes at a flow rate of 2 mL/min, with methyl benzoate, 2,2,2-trifluoroethyl benzoate intermediate, *N*-benzylbenzamide product , and iodobenzene internal standard eluting at 2.0, 2.5, 1.9 and 2.9 minutes, respectively.

Time (min)	Concentration of MeCN (%)
0	5
1	55
3.9	60
4.1	80
4.3	5
5	5

For *N*-Benzyl-*N*-methylbenzamide **2.5**: Reversed phase HPLC analysis was performed using a gradient method, eluting with 5 – 60% MeCN/H_2O over 8 minutes at a flow rate of 2 mL/min, with methyl benzoate, *N*-methylbenzylamine, N-benzyl-*N*-methylbenzamide product, and caffeine internal standard eluting at 4.7, 1.0, 5.1 and 2.0, respectively.

Time (min)	Concentration of MeCN (%)
0	5
5.5	60
5.8	5
8	5

ii) For *N*-Benzylbenzylamide **2.4**: For reactions using an internal standard, prior HPLC calibration was carried out using samples containing varying molarities of product and iodobenzene, allowing calculation of the response factor by substituting values into the following equation:

$$Response\ Factor = \frac{(\frac{Area}{Molarity})Product}{(\frac{Area}{Molarity})Standard}$$

Screening reactions were carried out using a known molarity of iodobenzene internal standard as indicated in the relevant general experimental procedures.
Unknown molarities of product were calculated by rearranging the above equation, using the average value for the response factor as determined during calibration.
Conversion to product was calculated as a percentage of the theoretical molarity for the reaction.

For *N*-Benzyl-*N*-methylbenzamide **2.5**: Conversion factor established by running 3 samples with a ratio of 0.25:1 caffeine:analyte, with the average conversion factor calculated by substituting values for each sample into the following equation:

$$Conversion\ factor = \frac{Peak\ Area\ Analyte}{Peak\ Area\ Caffeine}$$

For standard sampling of reaction mixtures, the ratio of caffeine:analyte is 0.25:1. Therefore, when calculating the % conversion:

$$\frac{Peak\ Area\ Analyte}{Peak\ Area\ Caffeine\ \times 4} = X$$

$$\frac{X}{Average\ Conversion\ Factor} = \%\ Conversion$$

iii) For *N*-Benzylbenzylamide **2.4**: Samples for HPLC analysis were prepared by diluting a 10 μL aliquot from the reaction mixture to 1 mL with MeCN.

For *N*-Benzyl-*N*-methylbenzamide **2.5**: Samples for HPLC analysis were prepared through the addition of 7 mL of a 0.05 M caffeine standard to the completed reaction mixture. The resulting solution was then stirred before the removal of a 200 μL aliquot. The aliquot was diluted to 1 mL with MeOH, a 200 μL aliquot of the diluted solution was then further diluted with 800 μL MeOH and then filtered for HPLC analysis against established conversion factors.

2.6.1.7 Normal Phase HPLC Methods

i) For compounds **2.52**, **2.59**, **2.61**, **2.62**, **2.63** and **2.121**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 10% IPA/hexanes over 20 minutes with a flow rate of 1 mL/min.

For compound **2.53**, **2.116** and **2.118**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 5% IPA/hexanes over 1 hour with a flow rate of 1 mL/min.

For compounds **2.55**, **2.57** and **2.109**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 10% IPA/hexanes over 1 hour with a flow rate of 1 mL/min.

For compound **2.54**, **2.56**, **2.58** and **2.60**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 10% IPA/hexanes over 40 min with a flow rate of 1 mL/min.

For compounds **2.110** and **2.112**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 5% IPA/hexanes over 2 hours with a flow rate of 1 mL/min.

For compounds **2.115**, **2.117** and **2.119**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 5% IPA/hexanes over 40 min with a flow rate of 1 mL/min.

For compound **2.123**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 5% IPA/hexanes over 20 min with a flow rate of 1 mL/min.

The major and minor enantiomers were found to elute as follows:

Product	Major enantiomer retention time (min)	Minor enantiomer retention time (min)
2.52	8.44	11.78
2.53	38.34	N/A
2.54	11.16	19.69
2.55	11.16	17.24
2.56	11.93	21.92
2.57	24.78	51.32
2.58	22.73	20.50
2.59	9.38	8.87
2.60	15.34	24.06
2.61	11.91	10.12
2.62	8.79	10.31
2.63	9.13	16.91
2.64	20.25	31.63
2.109	29.34	20.50
2.110	84.74	61.30
2.112	62.85	52.8
2.115	34.01	N/A
2.116	13.79	N/A
2.117	18.17	N/A
2.118	25.78	34.00
2.119	50.66	N/A
2.121	9.37	N/A
2.123	6.69	6.89

2.6.2 General Experimental Procedures

2.6.2.1 General Experimental Procedures for the TFE Catalysed Amidation of Acyclic Secondary Amines

General Experimental Procedure A for Investigating the Nature of the Base Species

To an oven-dried, purged and suba-sealed Schlenk tube containing trifluoroethanol (20 μL, 0.28 mmol, 0.2 equiv.), base (1.42 mmol, 1 equiv.) and THF (700 μL) was added methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to iodobenzene (1.4 M), which was used as an internal standard.

Entry	Base	pK_a	Conversion (%)
1	KTFA	0	1
2	KH_2PO_4	2	1
3	KOAc	6	1
4	K_2HPO_4	7	1
5	K_2CO_3	10	2
6	K_3PO_4	12	78 (77)[a]
7	KOH	16	5
8	KOtBu	18	47
9	Ca_3PO_4	13	1
10	Cs_3PO_4	13	1
11	Li_3PO_4	13	<1
12	Mg_3PO_4	13	16
13	Na_3PO_4	13	1
14	Cs_2CO_3	10	11
15	NMM	7	13
16	DABCO	9	4
17	Et_3N	11	1
18	DBU	12	61
19	BEMP	19	8

[a]Isolated yield.

General Procedure B for the Optimisation of the TFE Catalysed Tertiary Amide Formation: Additive Screen

To an oven-dried, purged and suba-sealed Schlenk tube containing additive (0.28 mmol, 0.2 equiv.), K_3PO_4 (301 mg, 1.42 mmol, 1 equiv.) and THF (700 µL) was added methyl benzoate (178 µL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and the reaction mixture was heated at 90 °C for 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to a 0.05 M caffeine solution.

Entry	Additive	Conversion (%)
1	4-$CF_3C_6H_4OH$	1
2	HFIP	<1
3	HOAt	<1
4	HOBt	<1
5	HOCt	<1
6	N-Hydroxysuccinimide	<1
7	Oxyma	<1
8	2-Picoline *N*-oxide	<1
9	TFE	1

General Procedure C for Optimisation of the TFE Catalysed Tertiary Amide Formation: Base and Solvent Screen

To an oven-dried, purged and suba-sealed Schlenk tube containing trifluoroethanol (20 µL, 0.28 mmol, 0.2 equiv.), base (1.42 mmol, 1 equiv.) and solvent (700 µL) was added methyl benzoate (178 µL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and the reaction mixture was heated at 90 °C for 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to a 0.05 M caffeine solution.

Entry	Base	Solvent	Conversion (%)
1	DABCO	*n*-butanol	<1
2	K_3PO_4	*n*-butanol	3
3	DBU	*n*-butanol	2
4	KO*t*Bu	*n*-butanol	22
5	DABCO	CPME	<1
6	K_3PO_4	CPME	37
7	DBU	CPME	4
8	KO*t*Bu	CPME	96 (99)[a]
9	DABCO	DCE	<1
10	K_3PO_4	DCE	<1
11	DBU	DCE	<1
12	KO*t*Bu	DCE	<1
13	DABCO	1,4-Dioxane	<1
14	K_3PO_4	1,4-Dioxane	12
15	DBU	1,4-Dioxane	3
16	KO*t*Bu	1,4-Dioxane	37
17	DABCO	DMC	<1
18	K_3PO_4	DMC	<1
19	DBU	DMC	<1
20	KO*t*Bu	DMC	<1
21	DABCO	DMF	<1
22	K_3PO_4	DMF	8
23	DBU	DMF	3
24	KO*t*Bu	DMF	21
25	DABCO	IPA	<1
26	K_3PO_4	IPA	9
27	DBU	IPA	2
28	KO*t*Bu	IPA	<1
29	DABCO	2-MeTHF	1
30	K_3PO_4	2-MeTHF	43
31	DBU	2-MeTHF	5
32	KO*t*Bu	2-MeTHF	2
33	DABCO	MeCN	<1
34	K_3PO_4	MeCN	<1
35	DBU	MeCN	4
36	KO*t*Bu	MeCN	32

37	DABCO	THF	2
38	K_3PO_4	THF	62, <1, 1
39	DBU	THF	8
40	KO*t*Bu	THF	56

[a]Isolated yield.

General Procedure D for Investigating the TFE Catalysed Tertiary Amide Formation with KO*t*Bu.

To an oven-dried, purged and suba- sealed Schlenk tube containing trifluoroethanol (20 µL, 0.28 mmol, 0.2 equiv.), KO*t*Bu (1.42 mmol, 1 equiv.) and CPME (700 µL) was added methyl 4-(trifluoromethyl)benzoate (229 µL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and the reaction mixture was heated at 90 °C for 22 h. Reaction was then diluted with EtOAc (10 mL), washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (1% MeOH/CH_2Cl_2).

Entry	**TFE**	**KO*t*Bu**	**Yield (%)**
1	Yes	Yes	48
2	Yes	No	0
3	No	Yes	58
4	No	No	0

General Procedure E for Optimisation of the TFE Catalysed Tertiary Amide Formation: Elevated Temperature Screen

To an oven-dried, purged and suba-sealed Schlenk tube containing trifluoroethanol (20 µL, 0.28 mmol, 0.2 equiv.), K_3PO_4 (301 mg, 1.42 mmol, 1 equiv.) and solvent (700 µL) was added methyl 4-(trifluoromethyl)benzoate (229 µL, 1.42 mmol, 1 equiv.) and the reaction heated at the desired temperature for 30 min. *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) was then added and the reaction mixture was heated at the desired temperature for a further 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to a 0.05 M caffeine solution.

Entry	Solvent	Temperature (°C)	Conversion (%)
1	THF	90	<1
2[a]	THF	90	70
3[a,b]	THF	90	62
4[a]	CPME	125	77[c]
5[a]	1,4-dioxane	125	93[c]
6[a]	2-MeTHF	100	72[c]
7[a,d]	1,4-dioxane	125	0[c]
8[a,e]	1,4-dioxane	125	0[c]
9[a,f]	1,4-dioxane	125	0[c]

[a]Pre-formation of the active ester intermediate for 30 min at reaction temperature. [b]Methyl benzoate used as ester substrate. [c]Isolated Yield. [d]Performed in the absence of K_3PO_4. [e]Performed in the absence of TFE. [f]Performed in the absence of both K_3PO_4 and TFE.

General Procedure F for Investigation of the Scope of the TFE Catalysed Tertiary Amide Formation: Ester Scope

To an oven-dried, purged and suba-sealed Schlenk tube containing trifluoroethanol (20 μL, 0.28 mmol, 0.2 equiv.), K_3PO_4 (301 mg, 1.42 mmol, 1 equiv.) and 1,4-dioxane (700 μL) was added ester (1.42 mmol, 1 equiv.) and the reaction heated at 125 °C for 30 min. *N*-methylbenzylamine (183 μL, 1.42 mmol, 1 equiv.) was then added and the reaction mixture was heated at 125 °C for a further 22 h. Reaction was then diluted with EtOAc (10 mL), washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography ($MeOH/CH_2Cl_2$).

General Procedure G for Investigation of the Scope of the TFE Catalysed Tertiary Amide Formation: Amine Scope

To an oven-dried, purged and suba-sealed Schlenk tube containing trifluoroethanol (20 μL, 0.28 mmol, 0.2 equiv.), K_3PO_4 (301 mg, 1.42 mmol, 1 equiv.) and 1,4-dioxane (700 μL) was added methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and the reaction heated at 125 °C for 30 min. Amine (1.42 mmol, 1 equiv.) was then added and the reaction mixture was heated at 125 °C for a further 22 h. Reaction was then diluted with EtOAc (10 mL), washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography ($MeOH/CH_2Cl_2$).

General Procedure H for Investigation of the Scope of the TFE Catalysed Tertiary Amide Formation: Effect of Using a Full Equivalent of TFE on Challenging Substrates

To an oven-dried, purged and suba-sealed Schlenk tube containing trifluoroethanol (100 μL, 1.42 mmol, 1 equiv.), K_3PO_4 (301 mg, 1.42 mmol, 1 equiv.) and 1,4-dioxane (700 μL) was added ester (1.42 mmol, 1 equiv.) and the reaction heated at 125 °C for 30 min. Amine (1.42 mmol, 1 equiv.) was then added and the reaction mixture was heated at 125 °C for a further 22 h. Reaction was then diluted with EtOAc (10 mL), washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography ($MeOH/CH_2Cl_2$).

General Procedure I for the Investigation of the Steric Limitation of the TFE Catalysed Tertiary Amide Formation

To an oven-dried, purged and suba-sealed Schlenk tube containing 2,2,2-trifluoroethyl benzoate (290 mg, 1.42 mmol, 1 equiv.) and 1,4-dioxane (700 μL) was added amine (1.42 mmol, 1 equiv.) and the reaction mixture was heated at 125 °C for 22 h. Reaction was then diluted with EtOAc (10 mL), washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography ($MeOH/CH_2Cl_2$).

General Procedure J for the Synthesis of Secondary Amine Starting Materials

To a round-bottomed flask containing a solution of amine (1 equiv.) in DCM (10 mL) at 0 °C was added Et_3N (2 equiv.) and a solution of di-tert-butyl dicarbonate (1.2 equiv.) in DCM (5 mL). Reaction warmed to room temperature and stirred for 16 h, at which point it was washed sequentially with 2M HCl (10 mL), 5% $NaHCO_3$ (aq.) (10 mL) and water (10 mL). Organics dried over Na_2SO_4 and concentrated to a residue *in vacuo*, to which was added THF (10 mL) and NaH (1.1 equiv.). Reaction stirred until effervescence had ceased, at which point methyl iodide (1.2 equiv.) was added and the reaction heated at 45 °C for 72 hours. THF removed *in vacuo* and the resulting crude product dissolved in EtOAc (10 mL), washed with water (3 x 10 mL), dried over Na_2SO_4 and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (5% EtOAc/Pet. ether 40–60 °C).

To a solution of the resulting *N*-methylated Boc-protected amine in DCM (10 mL) was added TFA (10 mL). Reaction stirred at room temperature for 16 h, at which point the reaction mixture was concentrated to a residue *in vacuo*. Resulting crude product dissolved in EtOAc (10 mL) and washed with 2M NaOH (aq.) until pH ≥ 9. Organics extracted with

EtOAc (3 x 20 mL), dried over Na_2SO_4 and concentrated in vacuo to afford the desired *N*-methyl amine.

2.6.2.2 General Experimental Procedures for the 4-trifluoromethyl phenol Catalysed Amidation of Chiral Esters

General Procedure K for Optimisation of the 4-trifluoromethyl phenol Catalysed Amidation of Chiral Esters: Base Screen

To an oven-dried, purged and suba-sealed Schlenk tube containing 4-(trifluoromethyl)phenol (46 mg, 0.28 mmol, 0.2 equiv.), base (1.42 mmol, 1 equiv.), Boc-L-phenylalanine methyl ester (397 mg, 1.42 mmol, 1 equiv.) and THF (700 μL) was added benzylamine (155 μL, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (1% MeOH/CH_2Cl_2).

Entry	Base	Base pK_a	Yield (%)	ee (%)
1	KTFA	0	46	93
2	KH_2PO_4	2	62	87
3	KOAc	5	55	92
4	NMM	7	36	92
5	K_2HPO_4	7	48	92
6	DABCO	9	40	85
7	K_2CO_3	10	46	75
8	Cs_2CO_3	10	34	40
9	DBU	12	69	16

General Procedure L for Optimisation of the 4-trifluoromethyl phenol Catalysed Amidation of Chiral Esters: Additive Screen

To an oven-dried, purged and suba-sealed Schlenk tube containing additive (0.28 mmol, 0.2 equiv.), KOAc (139 mg, 1.42 mmol, 1 equiv.), Boc-*L*-phenylalanine methyl ester (397 mg, 1.42 mmol, 1 equiv.) and THF (700 μL) was added benzylamine (155 μL, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (1% MeOH/CH_2Cl_2).

Entry	Additive	Additive pK_a	Yield (%)	ee (%)
1	Picoline *N*-oxide	-	28	87
2	HOCt	2.2	54	91
3	HOAt	3.3	32	89
4	HOBt	4.6	47	91
5	Oxyma	4.6	50	93
6	NHS	7.8	58	79
7	4-$CF_3C_6H_4OH$	8.7	55	92
8	HFIP	9.3	35	89
9	TFE	12.5	31	89
10[a]	4-$CF_3C_6H_4OH$	8.7	44	92
11	No additive	-	17	89
12[a]	No additive	-	28	88

[a]Performed in the absence of KOAc.

General Procedure M for Investigating the Point of Racemisation in the 4-trifluoromethyl phenol Catalysed Amidation of Chiral Esters

To an oven-dried, purged and suba-sealed Schlenk tube containing KOAc (1 equiv.), Boc-*L*-phenylalanine methyl ester (397 mg, 1.42 mmol, 1 equiv.) **or** amide **2.52** (150 mg, 0.43 mmol, 1 equiv.) was added THF (700/210 μL respectively). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo*. The ee of the resulting products was then determined by HPLC.

Entry	Substrate	Initial ee (%)	ee upon reaction completion (%)
1	Boc-Phe-OMe	100	100
2	**2.52**	92	92

General Procedure N for Investigating the Scope of the 4-trifluoromethyl phenol Catalysed Amidation of Chiral Esters

To an oven-dried, purged and suba-sealed Schlenk tube containing 4-(trifluoromethyl)phenol (46 mg, 0.28 mmol, 0.2 equiv.), KOAc (139 mg, 1.42 mmol, 1 equiv.), ester (1.42 mmol, 1 equiv.) and THF (700 μL) was added benzylamine (155 μL, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (MeOH/CH_2Cl_2 or acetone/pet. ether 40 – 60 °C).

General Procedure O for Investigating the Effect of Elevated Temperature on the 4-trifluoromethyl phenol Catalysed Amidation of Chiral Esters

To an oven-dried, purged and suba-sealed Schlenk tube containing 4-(trifluoromethyl)phenol (46 mg, 0.28 mmol, 0.2 equiv.), KOAc (139 mg, 1.42 mmol, 1 equiv.), ester (1.42 mmol, 1 equiv.) and 1,4-dioxane (700 μL) was added benzylamine (155 μL, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 125 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (MeOH/CH_2Cl_2 or acetone/pet. ether 40 – 60 °C).

General Procedure P for Investigating the Effect of Equimolar Quantities of Additive on the 4-trifluoromethyl phenol Catalysed Amidation of Chiral Esters

To an oven-dried, purged and suba-sealed Schlenk tube containing 4-(trifluoromethyl)phenol (230 mg, 1.42 mmol, 1 equiv.), KOAc (139 mg, 1.42 mmol, 1 equiv.), ester (1.42 mmol, 1 equiv.) and THF (700 μL) was added benzylamine (155 μL, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (MeOH/CH_2Cl_2 or acetone/pet. ether 40 – 60 °C).

General Procedure Q for the Synthesis of Chiral Ester Starting Materials *via* Esterification

To an oven-dried, purged Radleys tube containing carboxylic acid (1 equiv.) was added MeOH (20 mL), and the solution cooled to 0 °C. $SOCl_2$ (1.2 equiv.) added dropwise and the reaction refluxed for 16 h. Reaction mixture washed with saturated $NaHCO_3$ (aq.) until the pH ≥ 8, extracted with DCM (3 x 20 mL), dried over Na_2SO_4 and concentrated to a residue *in vacuo*. Resulting crude product was purified by silica gel chromatography (EtOAc/Pet. ether 40–60 °C).

General Procedure R for the Synthesis of Chiral Ester Starting Materials *via* Cbz Protection

To a round-bottomed flask was added ester hydrochloride salt (1 equiv.), *N*-(benzyloxycarbonyloxy)succinimide (1.1 equiv.), $NaHCO_3$ (2.5 equiv.), THF (7 mL) and water (7 mL). Reaction stirred for 16 h at room temperature, at which point the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). Organics

dried over Na_2SO_4 and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (EtOAc/pet. ether 40–60 °C).

General Procedure S for the Synthesis of Chiral Ester Starting Materials *via* Esterification and Cbz Protection

To an oven-dried purged Radleys tube containing carboxylic acid (1 equiv.), was added MeOH (20 mL), and the solution cooled to 0 °C. $SOCl_2$ (1.2 equiv.) added dropwise and the reaction heated at reflux for 16 h. Reaction mixture concentrated to a residue in vacuo, affording the corresponding crude hydrochloride salt, to which was added *N*-(benzyloxycarbonyloxy)succinimide (1.1 equiv.), $NaHCO_3$ (3 equiv.), THF (7 mL) and water (7 mL) and the reaction stirred at room temperature for a further 16 h. Reaction mixture diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). Organics dried over Na_2SO_4 and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (EtOAc/pet. ether 40–60 °C).

2.6.2.3 General Experimental Procedures for the Attempted Optimisation of an Organocatalytic Approach to the Formation of Sulfonamides

General Experimental Procedure T for the Attempted Optimisation of an Organocatalytic Approach to the Formation of Sulfonamides: Additive and Base Screen

To an oven-dried, purged and suba-sealed Schlenk tube containing additive (0.28 mmol, 0.2 equiv.), base (1 mmol, 1 equiv.) and THF (700 μL) was added methyl benzenesulfonate (193μL, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to iodobenzene (1.4 M), which was used as an internal standard.

Entry	Base	Additive	Conversion (%)
1	K_3PO_4	HOAt	<1
2	K_3PO_4	NHS	<1
3	K_3PO_4	NHS	<1
4	K_3PO_4	Picoline *N*-oxide	<1
5	K_3PO_4	4-$CF_3C_6H_4OH$	<1
6	K_3PO_4	TFE	<1
7	K_3PO_4	-	<1
8	DBU	HOAt	<1
9	DBU	NHS	<1
10	DBU	NHS	<1
11	DBU	Picoline *N*-oxide	<1
12	DBU	4-$CF_3C_6H_4OH$	<1
13	DBU	TFE	<1
14	DBU	-	<1
15	*t*BuOK	HOAt	<1
16	*t*BuOK	NHS	<1
17	*t*BuOK	NHS	<1
18	*t*BuOK	Picoline *N*-oxide	<1
19	*t*BuOK	4-$CF_3C_6H_4OH$	<1
20	*t*BuOK	TFE	<1
21	*t*BuOK	-	<1
22	BEMP	HOAt	<1
23	BEMP	NHS	<1
24	BEMP	NHS	<1
25	BEMP	Picoline *N*-oxide	<1
26	BEMP	4-$CF_3C_6H_4OH$	<1
27	BEMP	TFE	<1
28	BEMP	-	<1
29	NaH	HOAt	<1
30	NaH	NHS	<1
31	NaH	NHS	<1
32	NaH	Picoline *N*-oxide	<1
33	NaH	4-$CF_3C_6H_4OH$	<1
34	NaH	TFE	<1
35	NaH	-	<1
36	No base	HOAt	<1
37	No base	NHS	<1
38	No base	NHS	<1
39	No base	Picoline *N*-oxide	<1
40	No base	4-$CF_3C_6H_4OH$	<1
41	No base	TFE	<1
42	No base	-	<1

2.6.2.4 General Experimental Procedures for the BEMP-Mediated MCR Approach to Amide Bond Formation

General Procedure U for Investigating the Order of Addition for the BEMP mediated MCR Amide Formation

To an oven-dried, purged and sealed 2 – 5 mL microwave vial was added MeCN (0.5 mL), glycidyl phenyl ether (135 μL, 1 mmol, 1 equiv.) and benzylamine (109 μL, 1 mmol, 1 equiv.). BEMP (29 μL, 0.1 mmol, 0.1 equiv.) and methyl benzoate (126 μL, 1 mmol, 1 equiv.) added to the reaction at the required time. The reaction mixture was then heated at the desired reaction temperature for 24 h, at which point the reaction was concentrated *in vacuo* and the resulting residue purified by silica column chromatography (EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH).

Entry	Reaction Conditions	Temperature (°C)	Yield (%)
1	Concomitant addition of reactants	60	64
2	5 hour pre-formation of amino alcohol at rt	60	73
3	Concomitant addition of reactants	100	71
4	5 hour pre-formation of amino alcohol at rt	100	72
5	5 hour pre-formation of amino alcohol at 100 °C	100	69

General Procedure V for Investigating the Scope of the BEMP-Mediated MCR Amide Formation: Ester Scope

To an oven-dried, purged and sealed 2 – 5 mL microwave vial was added MeCN (0.5 mL), glycidyl phenyl ether (135 μL, 1 mmol, 1 equiv.), benzylamine (109 μL, 1 mmol, 1 equiv.), BEMP (29 μL, 0.1 mmol, 0.1 equiv.) and ester (1 mmol, 1 equiv.). The reaction mixture was then heated at 100 °C for 24 h, at which point the reaction was concentrated *in vacuo* and the resulting residue purified by silica column chromatography (EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH).

General Procedure W for Investigating the Scope of the BEMP-Mediated MCR Amide Formation: Amine Scope

To an oven-dried, purged and sealed 2 – 5 mL microwave vial was added MeCN (0.5 mL), glycidyl phenyl ether (135 μL, 1 mmol, 1 equiv.), amine (1 mmol, 1 equiv.), BEMP (29 μL, 0.1 mmol, 0.1 equiv.) and methyl phenylacetate (145 μL, 1 mmol, 1 equiv.). The reaction mixture was then heated at 100 °C for 24 h, at which point the reaction was concentrated *in*

vacuo and the resulting residue purified by silica column chromatography (EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH).

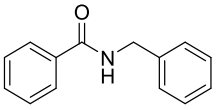
General Procedure X for Investigating the Scope of the BEMP-Mediated MCR Amide Formation: Epoxide Scope

To an oven-dried, purged and sealed 2 – 5 mL microwave vial was added MeCN (0.5 mL), epoxide (1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.), BEMP (29 µL, 0.1 mmol, 0.1 equiv.) and methyl phenylacetate (145 µL, 1 mmol, 1 equiv.). The reaction mixture was then heated at 100 °C for 24 h, at which point the reaction was concentrated *in vacuo* and the resulting residue purified by silica column chromatography (EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH).

2.6.3 Characterisation Data

2.6.3.1 Characterisation Data for TFE Catalysed Amidation: Amide Products

Compound 2.4. *N*-Benzylbenzamide



Synthesised according to General Procedure A using methyl benzoate (178 µL, 1.42 mmol, 1 equiv.) and benzylamine (155 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a white solid (231 mg, 77%).

ν_{max} (neat) 3356, 3092, 3036, 2932, 1636, 1560, 1261 cm^{-1}

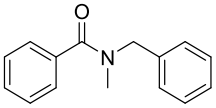
^{1}H NMR (400 MHz, DMSO-d6): δ 9.06 (t, *J* = 5.9 Hz, 1H), 7.91 – 7.88 (m, 2H), 7.54 (dt, *J* = 7.2, 1.9 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.36 – 7.30 (m, 4H), 7.27 – 7.22 (m, 1H), 4.48 (d, *J* = 6.0 Hz, 2H)

^{13}C NMR (101 MHz, DMSO-d6): δ 166.2, 139.7, 134.3, 131.2, 128.3, 128.2, 127.2, 127.1, 126.7, 42.6

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}NO$ 212.1070, Found 212.1069.

Consistent with previously reported data.[124]

Compound 2.5. *N*-Benzyl-*N*-methylbenzamide.



Synthesised according to General Procedure C using methyl benzoate (178 µL, 1.42 mmol, 1 equiv.), *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and KO*t*Bu (159 mg, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (317 mg, 99%).

Synthesised according to General Procedure F using methyl benzoate (178 µL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (226 mg, 71%).

ν_{max} (neat) 3060, 3029, 2921, 1629, 1398, 1264, 1068, 698 cm^{-1}

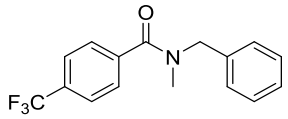
^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.45 – 7.42 (m, 5H), 7.39 – 7.36 (m, 2H), 7.31 – 7.27 (m, 3H), 4.60 (s, 2H), 2.86 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4, 171.7, 137.2, 136.7, 136.4, 129.7, 128.9, 128.5, 128.3, 127.7, 127.1, 126.9, 55.3, 50.9, 37.1, 33.3 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{16}NO$ 226.1226, found 226.1224.

Consistent with previously reported data.[125]

Compound 2.6. *N*-Benzyl-*N*-methyl-4-(trifluoromethyl)benzamide



Synthesised according to General Procedure D using methyl 4-(trifluoromethyl)benzoate (229 µL, 1.42 mmol, 1 equiv.), *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (202 mg, 48%).

Synthesised according to General Procedure D using methyl 4-(trifluoromethyl)benzoate (229 µL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) in the absence of trifluoroethanol and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (243 mg, 58%).

Synthesised according to General Procedure F using methyl 4-(trifluoromethyl)benzoate (229 µL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (386 mg, 93%).

ν_{max} (neat) 3066, 3032, 2926, 1634, 1407, 1325, 1167, 1109, 1072, 852, 700 cm^{-1}

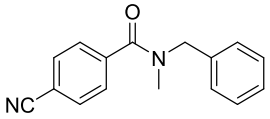
^{1}H NMR (500 MHz, 333 K, DMSO-d6): δ 7.79 (d, J = 7.5 Hz, 2H), 7.66 (d, J = 7.7 Hz, 2H), 7.39 – 7.28 (m, 5H), 4.69 – 4.44 (br. s, 2H), 2.85 (s, 3H)

^{13}C NMR (126 MHz, 333 K, DMSO-d6): δ 169.0, 140.3, 136.8, 129.5 (q, $^{2}J_{CF}$ = 32.0 Hz), 128.4, 127.3, 127.0, 125.1 (q, $^{3}J_{CF}$ = 3.6 Hz), 123.7 (q, $^{1}J_{CF}$ = 272.4 Hz), 53.8, 49.8, 36.4, 32.5 (mixture of rotamers, peak relating to one aromatic carbon not observed)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{15}F_3NO$ 294.1100, found 294.1096.

Consistent with previously reported data.[126]

Compound 2.11. *N*-Benzyl-4-cyano-*N*-methylbenzamide



Synthesised according to General Procedure F using methyl 4-cyanobenzoate (229 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (153 mg, 43%).

ν_{max} (neat) 3060, 3030, 2924, 2230, 1632, 1402, 1264, 1070, 850, 700 cm^{-1}

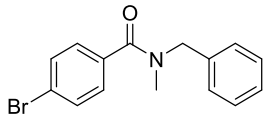
^1H NMR (400 MHz, 333 K, DMSO-d6): δ 7.89 (d, *J* = 7.9 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.39 – 7.28 (m, 5H), 4.66 (s, 2H), 2.85 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 169.7, 140.8, 140.7, 136.6, 136.0, 132.5, 129.2, 129.0, 128.4, 128.1, 127.9, 127.8, 127.6, 126.6, 118.2, 113.6, 55.1, 51.0, 36.9, 33.5 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{15}N_2O$ 251.1179, found 251.1178.

Consistent with previously reported data.[126]

Compound 2.12. *N*-Benzyl-4-bromo-*N*-methylbenzamide



Synthesised according to General Procedure F using methyl 4-bromobenzoate (305 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow solid (251 mg, 58%).

ν_{max} (neat) 3062, 3029, 2921, 1629, 1400, 1251, 1074, 1012, 837, 700 cm^{-1}

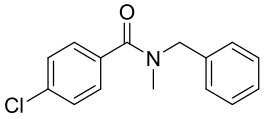
^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.29 (m, 7H), 4.59 (s, 2H), 2.86 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.4, 170.6, 136.9, 136.4, 135.2, 131.8, 129.0, 128.9, 128.7, 128.3, 127.8, 126.7, 124.1, 55.2, 51.0, 37.1, 33.5 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{15}BrNO$ 304.0332, found 304.0334

Consistent with previously reported data.[126]

Compound 2.13. *N*-Benzyl-4-chloro-*N*-methylbenzamide



Synthesised according to General Procedure F using methyl 4-chlorobenzoate (242 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow solid (229 mg, 62%).

ν_{max} (neat) 3055, 3030, 2913, 1632, 1409, 1087, 1074, 1016, 843, 739, 698 cm^{-1}

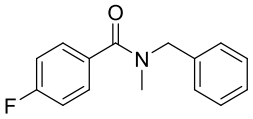
^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.50 – 7.45 (m, 4H), 7.39 – 7.35 (m, 2H), 7.31 – 7.27 (m, 3H), 4.59 (s, 2H), 2.86 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 170.7, 136.9, 136.5, 135.9, 134.7, 128.9, 128.7, 128.5, 128.4, 127.8, 126.7, 55.3, 51.1, 37.1, 33.5 (mixture of rotamers, peaks relating to two aromatic carbons occluded by broad carbon peaks)

HRMS (ESI) *m/z*: $[M+ H]^+$ calcd for $C_{15}H_{15}ClNO$ 260.0837, found 260.0831.

Consistent with previously reported data.[126]

Compound 2.14. *N*-Benzyl-4-fluoro-*N*-methylbenzamide



Synthesised according to General Procedure F using methyl 4-fluorobenzoate (184 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow solid (64 mg, 18%).

Synthesised according to General Procedure H using methyl 4-fluorobenzoate (184 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow solid (227 mg, 58%).

ν_{max} (neat) 3064, 3029, 2922, 1630, 1604, 1400, 1225, 1068, 847, 700 cm^{-1}

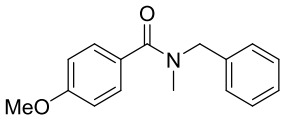
^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.53 – 7.49 (m, 2H), 7.39 – 7.35 (m, 2H), 7.31 – 7.22 (m, 5H), 4.60 (s, 2H), 2.87 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.7, 163.5 (d, $^{1}J_{CF}$ = 249.5Hz), 137.0, 136.7, 132.4, 129.4, 129.0, 128.4, 127.8, 126.7, 115.6 (d, $^{2}J_{CF}$ = 21.8 Hz), 55.4, 51.1, 37.2, 33.6 (mixture of rotamers, peaks relating to one carbon occluded by broad carbon peaks)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{15}FNO$ 244.1132, found 244.1127.

Consistent with previously reported data.[127]

Compound 2.16. *N*-Benzyl-4-methoxy-*N*-methylbenzamide



Synthesised according to General Procedure F using methyl 4-methoxybenzoate (236 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (258 mg, 71%).

ν_{max} (neat) 2958, 2919, 2839, 1625, 1608, 1396, 1249, 1174, 1029, 841, 700 cm^{-1}

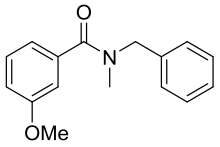
^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.43 – 7.35 (m, 4H), 7.30 – 7.26 (m, 3H), 6.99 – 6.96 (m, 2H), 4.60 (s, 2H), 3.80 (s, 3H), 2.88 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 160.8, 137.2, 129.1, 128.9, 128.4, 127.6, 126.9, 113.8, 55.4, 51.2, 37.3, 33.6 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{18}NO_2$ 256.1332, found 256.1325.

Consistent with previously reported data.[126]

Compound 2.17. *N*-Benzyl-3-methoxy-*N*-methylbenzamide



Synthesised according to General Procedure F using methyl 3-methoxybenzoate (236 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (338 mg, 93%).

ν_{max} (neat) 3062, 3029, 3004, 2935, 2835, 1630, 1580, 1398, 1269, 1042, 750, 698 cm^{-1}

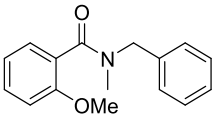
^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.39 – 7.27 (m, 6H), 7.01 – 6.95 (m, 3H), 4.58 (s, 2H), 3.76 (s, 3H), 2.86 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 159.7, 129.7 (2), 128.9 (2), 128.3, 127.7, 126.8, 119.2, 119.0, 115.9, 115.5, 112.6, 112.1, 55.5, 55.4, 50.9 (2), 37.1, 33.4 (mixture of rotamers, peaks relating to one aromatic carbon occluded by broad carbon peaks)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{18}NO_2$ 256.1332, found 256.1328.

Consistent with previously reported data.[128]

Compound 2.18. *N*-Benzyl-2-methoxy-*N*-methylbenzamide



Synthesised according to General Procedure F using methyl 2-methoxybenzoate (236 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (78 mg, 21%).

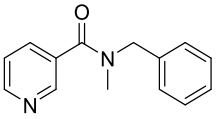
ν_{max} (neat) 3062, 3029, 3004, 2922, 2837, 1629, 1601, 1400, 1247, 1024, 754, 700 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.42 – 6.95 (m, 9H), 4.69 – 4.30 (br. s, 2H), 3.83 – 3.78 (m, 3H), 2.88 – 2.68 (m, 3H) (mixture of rotamers)

^{13}C NMR (101 MHz, 333 K, DMSO-d6): δ 168.2, 154.7, 137.1, 136.7, 129.9 (2), 128.2, 127.4, 127.1, 127.0, 126.8, 126.7, 126.2, 126.0 120.5, 120.3, 111.4 (2), 55.4, 55.2, 53.3, 49.1, 35.1, 31.6 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{18}NO_2$ 256.1332, found 256.1330.

Compound 2.19. *N*-Benzyl-*N*-methylnicotinamide



Synthesised according to General Procedure F using methyl nicotinate (195 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (2% MeOH/DCM) to afford the title compound as a yellow oil (166 mg, 52%).

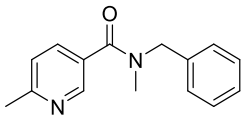
ν_{max} (neat) 3026, 2919, 1627, 1400, 1074, 1026, 734, 699 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 8.64 – 8.63 (m, 2H), 7.86 (d, *J* = 7.3Hz, 1H), 7.47 – 7.28 (m, 6H), 4.62 (s, 2H), 2.90 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 169.1, 150.9, 148.1, 147.9, 136.7, 136.1, 135.1, 134.8, 132.2, 129.1, 129.0, 128.4, 128.0, 127.9, 126.7, 123.5, 55.3, 51.1, 37.1, 33.7 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M+ H]^+$ calcd for $C_{14}H_{15}N_2O$ 227.1179, found 227.1173.

Compound 2.20. *N*-Benzyl-*N*,6-dimethylnicotinamide



Synthesised according to General Procedure F using methyl 6-methyl nicotinate (215 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (2% MeOH/DCM) to afford the title compound as a yellow oil (66 mg, 19%).

Synthesised according to General Procedure H using methyl 6-methyl nicotinate (215 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (2% MeOH/DCM) to afford the title compound as a yellow oil (181 mg, 53%).

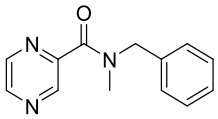
ν_{max} (neat) 3030, 2922, 1629, 1599, 1402, 1074, 754, 700 cm^{-1}

^1H NMR (500 MHz, 333 K, DMSO-d6): δ 8.53 (s, 1H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.40 – 7.37 (m, 2H), 7.32 – 7.29 (m, 4H), 4.62 (s, 2H), 2.90 (s, 3H), 2.51 (s, 3H)

^{13}C NMR (101 MHz, CDCl3): δ 170.1, 169.4, 160.1, 147.6, 147.3, 136.7, 136.2, 135.5, 135.2, 129.2, 129.0, 128.9, 128.3, 127.8, 126.6 123.0, 55.3, 51.1, 37.1, 33.6, 24.5 (mixture of rotamers, peak related to one aromatic carbon occluded by broad carbon peaks)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{17}N_2O$ 241.1335, found 241.1330.

Compound 2.21. *N*-Benzyl-*N*-methylpyrazine-2-carboxamide



Synthesised according to General Procedure F using methyl 2-pyrazinecarboxylate (196 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (50 mg, 15%).

Synthesised according to General Procedure H using methyl 2-pyrazinecarboxylate (196 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (130 mg, 40%).

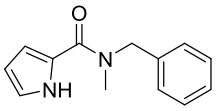
ν_{max} (neat) 3058, 3025, 2924, 1632, 1085, 1019, 701 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 8.89 – 8.85 (m, 1H), 8.73 – 8.71 (m, 1H), 8.67 – 8.64 (m, 1H), 7.37 – 7.26 (m, 5H), 4.73 – 4.60 (m, 2 H), 2.96 – 2.93 (m, 3H) (mixture of rotamers)

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 166.8, 150.0, 149.9, 145.7, 145.6, 145.4, 142.7 (2), 136.5, 136.4, 128.9, 128.4, 128.0, 127.8, 127.5, 54.8, 51.6, 36.6, 33.8 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{12}N_3O$ 226.0986, found 226.0976.

Compound 2.22. *N*-Benzyl-*N*-methyl-1H-pyrrole-2-carboxamide



Synthesised according to General Procedure F using methyl 2-pyrrolecarboxylate (178 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as an orange solid (72 mg, 24%).

Synthesised according to General Procedure H using methyl 2-pyrrolecarboxylate (178 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 µL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as an orange solid (218 mg, 71%).

ν_{max} (neat) 3231, 1589, 1400, 1134, 788, 730, 721, 691 cm^{-1}

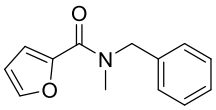
^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 11.31 (s, 1H), 7.38 – 7.34 (m, 2H), 7.29 – 7.26 (m, 3H), 6.91 – 6.89 (m, 1H), 6.48 (s, 1H), 6.12 – 6.10 (m, 1H) 4.75 (s, 2H), 3.11 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0, 137.3, 128.9, 127.5, 124.9, 121.5, 112.8, 109.8, 52.5, 36.2

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{15}N_2O$ 215.1179, found 215.1179.

Consistent with previously reported data.[129]

Compound 2.24. *N*-Benzyl-*N*-methylfuran-2-carboxamide



Synthesised according to General Procedure F using methyl 2-furoate (179 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as an orange oil (108 mg, 35%).

Synthesised according to General Procedure H using methyl 2-furoate (179 mg, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as an orange oil (349 mg, 99%).

ν_{max} (neat) 3112, 3062, 3030, 2922, 1621, 1493, 1400, 1070, 746, 700 cm^{-1}

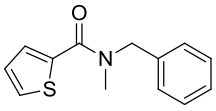
^{1}H NMR (500 MHz, 333 K, DMSO-d6): δ 7.80 (app. s, 1H), 7.38 – 7.35 (m, 2H), 7.30 – 7.26 (m, 3H), 7.00 (app. s, 1H), 6.61 – 6.60 (m, 1H), 4.72 (s, 2H), 3.06 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.6, 148.1, 144.1, 137.0, 128.8, 128.3, 127.6, 127.1, 116.6, 116.3, 111.4, 54.3, 52.0, 35.9, 34.4 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{14}NO_2$ 216.1019, found 216.1015.

Consistent with previously reported data.[126]

Compound 2.25. *N*-Benzyl-*N*-methylthiophene-2-carboxamide



Synthesised according to General Procedure F using ethyl 2-thiophenecarboxylate (191 μL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (93 mg, 28%).

Synthesised according to General Procedure H using ethyl 2-thiophenecarboxylate (191 μL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (313 mg, 95%).

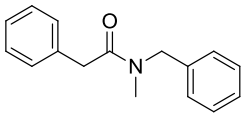
ν_{max} (neat) 3086, 3029, 2921, 1608, 1396, 1029, 700 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.74 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.41 – 7.36 (m, 2H), 7.31 – 7.27 (m, 3H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.73 (s, 2H), 3.08 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9, 137.9, 136.9, 129.2, 129.0, 127.7, 126.9, 53.5, 35.7 (peak relating to one aromatic carbon not observed)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{14}NOS$ 232.0791, found 232.0786.

Compound 2.26. *N*-Benzyl-*N*-methyl-2-phenylacetamide



Synthesised according to General Procedure F using methyl phenylacetate (200 μL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (336 mg, 99%).

ν_{max} (neat) 3062, 3029, 2921, 1640, 1400, 1109, 731, 698 cm^{-1}

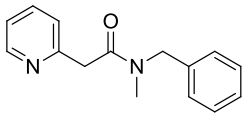
^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.31 – 7.20 (m, 10H), 4.62 – 4.53 (m, 2H), 3.77 (s, 2H), 2.94 – 2.82 (br. s, 3H) (mixture of rotamers)

^{13}C NMR (101 MHz, 333 K, DMSO-d6): δ 170.2, 137.5, 135.5, 128.7, 128.1, 127.9, 127.2, 126.7, 126.0, 52.6, 49.9, 34.8

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{18}NO$ 240.1383, found 240.1382.

Consistent with previously reported data.[64]

Compound 2.27. *N*-Benzyl-*N*-methyl-2-(pyridin-2-yl)acetamide



Synthesised according to General Procedure F using ethyl 2-pyridylacetate (216 μL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (2% MeOH/DCM) to afford the title compound as an orange oil (293 mg, 87%).

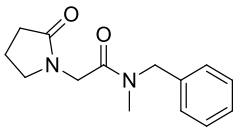
ν_{max} (neat) 3060, 3029, 3008, 2924, 1642, 1435, 1400, 1111, 756, 733, 700 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 8.50 – 8.47 (m, 1H) 7.75 – 7.71 (m, 1H), 7.36 – 7.23 (m, 7H), 4.69 – 4.54(m, 2H), 3.94 – 3.91 (m, 2H), 2.99 – 2.82 (br. s, 3H) (mixture of rotamers)

^{13}C NMR (101 MHz, 333 K, DMSO-d6): δ 169.5, 156.0, 148.6, 136.0, 128.3, 128.1, 127.2, 126.9, 126.6, 126.4, 123.5, 121.4, 52.7, 49.9, 42.6, 42.4, 35.0, 33.1 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{17}N_2O$ 241.1335, found 241.1335.

Compound 2.29. *N*-Benzyl-*N*-methyl-2-(2-oxopyrrolidin-1-yl)acetamide



Synthesised according to General Procedure H using methyl 2-oxo-1-pyrrolidineacetate (197μL, 1.42 mmol, 1 equiv.) and N-methylbenzylamine (183 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow solid (216 mg, 62%).

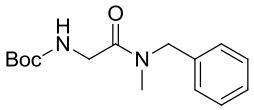
ν_{max} (neat) 2954, 2917, 2876, 1684, 1645, 754, 705 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.36 – 7.22 (m, 5H), 4.57 – 4.51 (m, 2H), 4.12 (s, 2H), 3.42 – 3.39 (m, 2H), 2.92 – 2.82 (br. s, 3H), 2.27 – 2.19 (m, 2H), 1.99 – 1.95 (m, 2H) (mixture of rotamers)

^{13}C NMR (101 MHz, 333 K, DMSO-d6): δ 174.0, 167.1, 137.2, 128.4, 128.1, 127.3, 127.0 126.8, 126.4, 51.5, 50.1, 47.0, 43.5, 33.6, 33.3, 29.7, 17.3 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_2$ 247.1441, found 247.1445.

Compound 2.30. *tert*-Butyl (2-(benzyl(methyl)amino)-2-oxoethyl)carbamate



Synthesised according to General Procedure F using *N*-(tert-butoxycarbonyl)glycine methyl ester (249 μL, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (67 mg, 17%).

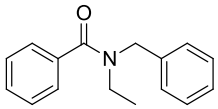
Synthesised according to General Procedure H using *N*-(tert-Butoxycarbonyl)glycine methyl ester (249 μL, 1.42 mmol, 1 equiv.) and N-methylbenzylamine (183 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow solid (152 mg, 38%).

ν_{max} (neat) 3406, 2978, 2934, 1711, 1653, 1368, 1163, 1052, 702 cm^{-1}

^1H NMR (500 MHz, 333 K, DMSO-d6): δ 7.33 – 7.22 (m, 5H), 4.52 (s, 2H), 3.85 – 3.84 (m, 2H), 3.69 – 3.67 (m, 1H), 2.90 – 2.78 (br. s, 3H), 1.39 (s, 9H) (mixture of rotamers)
^{13}C NMR (126 MHz, 333 K, DMSO-d6): δ 170.5, 168.7, 155.4, 137.3, 136.9, 128.4, 128.1, 128.0, 127.3, 127.0 (2), 126.7, 126.4, 78.0, 77.1, 51.2, 50.2, 41.6, 33.4, 27.9 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M+ H]^+$ calcd for $C_{15}H_{23}N_2O_3$ 279.1703, found 279.1696.

Compound 2.31. *N*-Benzyl-*N*-ethylbenzamide



Synthesised according to General Procedure I using 2,2,2-trifluoroethyl benzoate (290 mg, 1.42 mmol, 1 equiv.) and *N*-ethylbenzylamine (211 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow solid (60 mg, 18%).

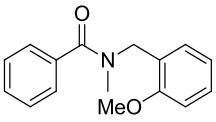
ν_{max} (neat): 3059, 3026, 2966, 2931, 1627, 1422, 697 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.44 – 7.26 (m, 10H), 4.61 (s, 2H), 3.29 – 3.26 (m, 2H), 1.05 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (101 MHz, 333 K DMSO-d6): δ 170.4, 136.7, 128.8, 128.2, 127.8, 127.0, 126.8, 126.3, 125.9, 56.9, 46.3, 11.3

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{18}NO$ 240.1383, found 240.1381

Compound 2.36. *N*-(2-Methoxybenzyl)-*N*-methylbenzamide



Synthesised according to General Procedure G using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and 2-Methoxy-*N*-methylbenzylamine (212 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow solid (113 mg, 31%).

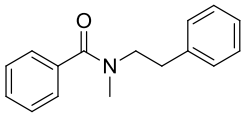
ν_{max} (neat) 3017, 2924, 2842, 1629, 1241, 1024, 756, 728 cm^{-1}

^{1}H NMR (500 MHz, 333 K, DMSO-d6): δ 7.45 – 7.39 (m, 5H), 7.30 – 7.26 (m, 1H), 7.19 – 7.18 (m, 1H), 7.01 – 6.96 (m, 2H), 4.54 (s, 2H), 3.76 (s, 3H), 2.86 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7, 171.7, 157.8, 157.3, 136.8, 136.6, 129.6, 129.3, 128.8, 128.4, 127.8, 127.0, 125.1, 124.8, 120.8, 120.7, 110.4, 55.5, 55.2, 50.7, 45.5, 37.5, 33.4 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{18}NO_2$ 256.1332, found 256.1332.

Compound 2.37. *N*-Methyl-*N*-phenethylbenzamide



Synthesised according to General Procedure G using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and *N*-methylphenethylamine (206 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (271 mg, 80%).

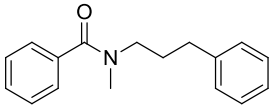
ν_{max} (neat) 3060, 3027, 2928, 1629, 1400, 1070, 700 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.43 – 7.38 (m, 3H), 7.28 – 7.19 (m, 7H), 3.54 – 3.49 (m, 2H), 2.89 – 2.86 (m, 5H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 171.4, 139.2, 138.0, 136.7, 129.5, 129.3, 129.0 (2), 128.9, 128.7, 128.4, 127.0, 126.8, 126.6, 53.1, 49.5, 38.4, 34.9, 33.6, 33.2 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{18}NO$ 240.1383, found 240.1379.

Compound 2.38. *N*-Methyl-*N*-(3-phenylpropyl)benzamide



Synthesised according to General Procedure G using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and (3-phenylpropyl)methylamine (212 mg, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (121 mg, 34%).

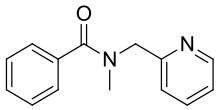
ν_{max} (neat) 3060, 3027, 2930, 2861, 1629, 1400, 1072, 700 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.42 – 7.37 (m, 3H), 7.35 – 7.33 (m, 2H), 7.27 – 7.23 (m, 2H), 7.18 – 7.14 (m, 3H), 3.35 – 3.32 (m, 2H), 2.92 (s, 3H), 2.54 – 2.51 (m, 2H), 1.89 – 1.85 (m, 2H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 171.5, 141.8, 140.9, 136.8, 129.5, 128.6, 128.5, 128.2, 127.0, 126.7, 126.2, 51.0, 47.4, 37.6, 33.4, 32.9, 32.8, 29.9, 28.8 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{20}NO$ 254.1539, found 254.1533.

Compound 2.40. *N*-Methyl-*N*-(pyridin-2-ylmethyl)benzamide



Synthesised according to General Procedure G using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and 2-[(methylamino)methyl]pyridine (175 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (190 mg, 59%).

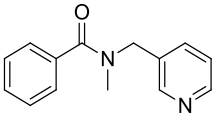
ν_{max} (neat) 3058, 3010, 2926, 1629, 1398, 1072, 702 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 8.57 – 8.55 (m, 1H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.46 – 7.41 (m, 5H), 7.31 – 7.28 (m, 2H), 4.66 (s, 2H), 2.95 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7, 171.7, 157.3, 156.9, 150.0, 149.4, 137.0, 136.2, 129.8, 128.5, 127.2, 127.0, 122.6, 122.3, 121.0, 57.1, 53.1, 38.0, 33.8 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{15}N_2O$ 227.1179, found 227.1175.

Compound 2.41. *N*-Methyl-*N*-(pyridin-3-ylmethyl)benzamide



Synthesised according to General Procedure G using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and 3-[(methylamino)methyl]pyridine (175 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (40 mg, 12%)

Synthesised according to General Procedure H using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and 3-[(methylamino)methyl]pyridine (175 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (225 mg, 70%)

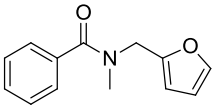
ν_{max} (neat) 3057, 3030, 2924, 1627, 1400, 1070, 1027, 787, 715, 702 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 8.52 – 8.50 (m, 2H), 7.70 (s, 1H), 7.46 – 7.43 (m, 5H), 7.41 – 7.37 (m, 1H), 4.64 (s, 2H), 2.89 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 149.6, 149.2, 148.8, 136.2, 135.9, 134.6, 132.8, 130.0, 128.6, 127.1, 123.9, 52.9, 48.6, 37.2, 33.2 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{15}N_2O$ 227.1179, found 227.1176.

Compound 2.42. *N*-(Furan-2-ylmethyl)-*N*-methylbenzamide



Synthesised according to General Procedure G using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and *N*-methylfurfurylamine (161 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a brown oil (183 mg, 60%).

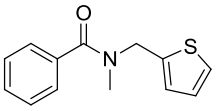
ν_{max} (neat) 3116, 3060, 2922, 1630, 1400, 1068, 1014, 700 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.61 – 7.60 (m, 1H), 7.47 – 7.40 (m, 5H), 6.43 – 6.42 (m, 1H), 6.35 – 6.34 (m, 1H), 4.54 (s, 2H), 2.89 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 171.5, 150.9, 150.3, 142.8, 142.5, 136.2, 129.8, 128.5, 127.2, 110.5, 108.8, 108.6, 48.5, 43.8, 37.3, 33.0 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{14}NO_2$ 216.1019, found 216.1016.

Compound 2.43. *N*-Methyl-*N*-(thiophen-2-ylmethyl)benzamide



Synthesised according to General Procedure G using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and *N*-methyl-1-(2-thienyl)methanamine (165 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (63 mg, 19%)

Synthesised according to General Procedure H using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and *N*-methyl-1-(2-thienyl)methanamine (165 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (304 mg, 92%)

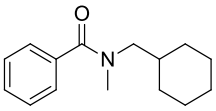
ν_{max} (neat) 3062, 2924, 1629, 1398, 1068, 700 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.47 – 7.40 (m, 6H), 7.04 – 6.99 (m, 2H), 4.74 (s, 2H), 2.90 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1, 139.8, 136.2, 129.8, 128.6, 127.1, 126.1, 125.7, 50.6, 45.9, 37.0, 32.9 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{14}NOS$ 232.0791, found 232.0787.

Compound 2.45. *N*-(Cyclohexylmethyl)-*N*-methylbenzamide



Synthesised according to General Procedure G using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and (cyclohexylmethyl)(methyl)amine (181 mg, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (83 mg, 25%).

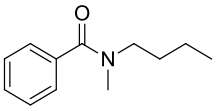
vmax (neat) 2921, 2850, 1629, 1448, 1402, 1288, 1070, 700 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.44 – 7.40 (m, 3H), 7.35 – 7.32 (m, 2H), 3.30 – 3.20 (m, 2H), 2.90 (s, 3H), 1.70 – 1.55 (m, 7H), 1.22 –1.17 (m, 4H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.5, 171.8, 167.7, 137.2, 137.1, 135.1, 131.4, 129.4, 129.2, 128.7, 128.5, 127.2, 127.0, 57.7, 53.7, 38.5, 38.2, 36.5, 36.0, 33.3, 31.1, 30.9, 30.6, 26.6, 26.5, 26.4, 26.1, 26.0, 25.9 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{22}NO$ 232.1696, found 232.1693.

Compound 2.48. *N*-Butyl-*N*-methylbenzamide



Synthesised according to General Procedure G using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and *N*-butylmethylamine (168 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (33 mg, 12%).

Synthesised according to General Procedure H using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and *N*-butylmethylamine (168 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (176 mg, 65%).

ν_{max} (neat) 2958, 2932, 2872, 1629, 1402, 1072, 702 cm^{-1}

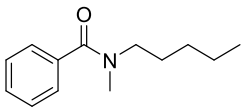
^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.44 – 7.41 (m, 3H), 7.36 – 7.33 (m, 2H), 3.35 – 3.25 (m, 2H), 2.91 (s, 3H), 1.54 – 1.51 (m, 2H), 1.32 – 1.16 (m, 2H), 0.93 – 0.85 (m, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 171.4, 137.0, 129.4, 128.5, 127.0, 126.8, 51.2, 47.3, 37.6, 32.8, 30.5, 29.2, 20.2, 19.7, 14.0, 13.7 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{18}NO$ 192.1383, found 192.1379.

Consistent with previously reported data.[130]

Compound 2.49. *N*-Pentyl-*N*-methylbenzamide



Synthesised according to General Procedure G using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and *N*-pentylmethylamine (195 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (20 mg, 7%).

Synthesised according to General Procedure H using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and *N*-pentylmethylamine (195 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (21 mg, 7%).

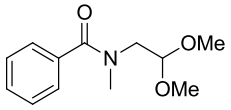
ν_{max} (neat) 2951, 2925, 2856, 1627, 1400, 1071, 701 cm^{-1}

^{1}H NMR (400 MHz, 333 K, DMSO-d6): δ 7.44 – 7.41 (m, 3 H), 7.36 – 7.33 (m, 2H), 3.31 – 3.24 (m, 2H), 2.91 (s, 3H), 1.55 – 1.53 (m, 2H), 1.33 – 1.16 (m, 4H), 0.91 – 0.81 (m, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.1, 171.4, 137.0, 129.4, 128.5, 127.0, 126.8, 51.4, 47.6, 37.6, 32.8, 29.2, 28.6, 28.0, 26.8, 22.6, 22.3, 14.2, 14.0 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{20}NO$ 206.1539, found 206.1536

Compound 2.50. *N*-(2,2-Dimethoxyethyl)-*N*-methylbenzamide



Synthesised according to General Procedure G using methyl benzoate (178 μL, 1.42 mmol, 1 equiv.) and (Methylamino)acetaldehyde dimethyl acetal (182 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow oil (314 mg, 99%).

ν_{max} (neat) 2935, 2835, 1632, 1400, 1126, 1072, 1027, 702 cm^{-1};

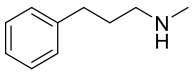
^{1}H NMR (500 MHz, 333 K, DMSO-d6): δ 7.44 – 7.43 (m, 3H), 7.38 – 7.36 (m, 2H), 4.65 – 4.45 (m, 1H), 3.57 – 3.39 (m, 2H), 3.30 (s, 6H), 2.96 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.6, 171.8, 136.5, 129.7, 129.5, 128.5, 127.1, 103.5, 103.1, 54.8, 53.2, 50.0, 39.6, 34.5 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{18}NO_3$ 224.1281, found 224.1281.

2.6.3.2 Characterisation Data for TFE Catalysed Amidation: Starting Materials

Compound 2.113. *N*-Methyl-3-phenylpropan-1-amine



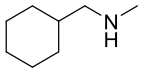
Synthesised according to General Experimental Procedure J using 3-phenylpropan-1-amine (500 mg, 3.7 mmol) to afford the title compound as a pale yellow liquid (372 mg, 67%).

ν_{max} (neat): 3027, 2932, 2857, 2794, 1673, 1455, 1033, 748, 700 cm^{-1}
^{1}H NMR (500 MHz, DMSO-d_6): δ 7.28 – 7.25, (m, 2H), 7.19 – 7.14 (m, 3H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.26 (s, 3H), 1.71 – 1.65 (m, 2H)

^{13}C NMR (126 MHz, DMSO-d_6): δ 142.2, 128.2, 128.2, 125.6, 50.9, 36.1, 32.9, 31.0

HRMS *m/z*: $[M+H]^+$ Calcd for $C_{10}H_{16}N$ 150.1277, found 150.1275

Compound 2.114. **1-Cyclohexyl-*N*-methylmethanamine**



Synthesised according to General Experimental Procedure J using cyclohexylmethanamine (1 g, 8.8 mmol) to afford the title compound as a pale yellow liquid (404 mg, 44%).

ν_{max} (neat): 2919, 2850, 2788, 1448, 1126, 1150, 742 cm^{-1}

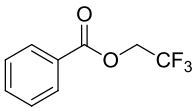
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.42 – 2.40 (m, 4H), 1.74 – 1.64 (m, 5H), 1.49 – 1.42 (m, 2H), 1.28 – 1.10 (m, 3H), 0.95 – 0.87 (m, 2H)

^{13}C NMR (126 MHz,$CDCl_3$): δ 54.3,

35.5, 34.4, 29.7, 25.6, 25.0

HRMS *m/z*: $[M+H]^+$ calcd for $C_8H_{18}N$ 128.1434, found 128.1429

Compound 2.51. 2,2,2-Trifluoroethyl benzoate



To a round-bottomed flask containing TFE (525 µL, 7.5 mmol, 1 equiv.) and Et_3N (1.275 mL, 9 mmol, 1.2 equiv.) in DCM (15 mL) was added benzoyl chloride (1.275 mL, 11.25 mmol, 1.5 equiv.) and the reaction refluxed for 60 hours. The reaction mixture was then concentrated *in vacuo*, re-dissolved in EtOAc (20 mL), washed with sat. $NaHCO_3$ (aq.) (25 mL) and brine (25 mL), and dried (Na_2SO_4). Organics concentrated *in vacuo* and the resulting residue purified by flash column chromatography (100% petroleum ether 40 – 60 °C to 2% EtOAc/ petroleum ether 40 – 60 °C) to afford the title compound as a colourless liquid (1.182g, 77%)

ν_{max} (neat): 1737, 1290, 1249, 1160, 1110, 708 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 – 8.07 (m, 2H), 7.64 – 7.60 (m, 1H), 7.50 – 7.46 (m, 2H), 4.70 (q, $^{3}J_{CF}$ = 8.4 Hz, 2H)

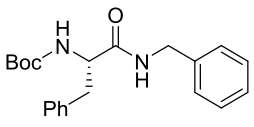
^{13}C NMR (101 MHz,$CDCl_3$): δ 165.1, 134.0, 130.2, 128.6, 128.5, 126.8 (q, $^{1}J_{CF}$ = 277.1 Hz), 61.0 (q, $^{2}J_{CF}$ = 36.7 Hz)

HRMS *m/z*: $[M+H]^+$ calcd for a $C_9H_8F_3O_2$ 205.0471, found 205.0475

Consistent with previously reported data.[110]

2.6.3.3 Characterisation Data for 4-(trifluoromethyl)phenol Catalysed Amidation of Chiral Esters: Chiral Amide Products

Compound 2.52. ***tert*-Butyl(*S*)-(1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamate**



Synthesised according to General Procedure N using Boc-*L*-phenylalanine methyl ester (397 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a white solid (276 mg, 55%).

ν_{max} (neat) 3317, 3256, 3064, 3036, 2999, 2926, 1662, 1530, 1163, 716, 700, 650 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.27 – 7.22 (m, 6H), 7.18 – 7.17 (m, 2H), 7.09 – 7.08 (m, 2H), 6.08 (s, 1H), 5.05 (s, 1H), 4.35 – 4.34 (m, 3H), 3.11 – 3.02 (m, 2H), 1.38 (s, 9H)

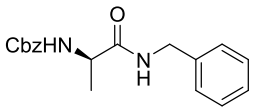
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 137.8, 136.8, 129.5, 128.9, 128.8, 127.8, 127.6, 127.1, 80.4, 56.2, 43.6, 38.7, 28.4

HRMS *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{27}N_2O_3$ 355.2016, found 355.2017.

ee = 92%

Consistent with previously reported data.[110]

Compound 2.53. **Benzyl (*R*)-(1-(benzylamino)-1-oxopropan-2-yl)carbamate**



Synthesised according to General Procedure N using methyl ((benzyloxy)carbonyl)-*D*-alaninate (337 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (0.5 – 1% MeOH/DCM) to afford the title compound as a white solid (235 mg, 53%).

ν_{max} (neat) 3284, 3060, 3034, 2978, 2932, 1684, 1644, 1526, 1258, 1228, 1048, 698 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.22 (m, 10H), 6.55 (s, 1H), 5.43 (s, 1H), 5.08 – 5.01 (m, 2H), 4.46 – 4.36 (m, 2H), 4.29 – 4.26 (m, 1H), 1.42 – 1.37 (m, 3H)

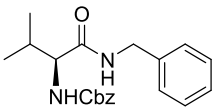
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 156.2, 138.0, 136.2, 128.9, 128.7, 128.4, 128.2, 127.8, 127.7, 67.2, 50.8, 43.7, 18.8

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{21}N_2O_3$ 313.1547, found 313.1545

ee = 100%

$[\alpha]_D^{20}$ −10.2 (c = 1.0, EtOH)

Compound 2.54. **Benzyl (*S*)-(1-(benzylamino)-3-methyl-1-oxobutan-2-yl)carbamate**



Synthesised according to General Procedure N using methyl ((benzyloxy)carbonyl)-*L*-valinate (377 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (0.5 % MeOH/DCM) to afford the title compound as a white solid (71 mg, 15%).

ν_{max} (neat) 3277, 3055, 3031, 2953, 2867, 1685, 1642, 1532, 1246, 1041, 695 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.24 (m, 10 H), 6.27 (s, 1H), 5.37 – 5.35 (m, 1H), 5.11 – 5.04 (m, 2H), 4.50 – 4.33 (m, 2H), 4.04 – 4.01 (m, 1H), 1.91 – 1.90 (m, 1H), 0.94 – 0.88 (m, 6H)

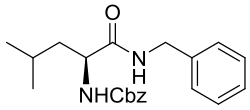
^{13}C NMR (126 MHz, $CDCl_3$): δ 171.3, 156.5, 138.0, 136.3, 128.9, 128.7, 128.4, 128.2, 127.9, 127.7, 43.7, 37.5, 24.9, 15.8, 11.5

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_3$ 341.1860, found 341.1860

ee = 99%

$[\alpha]_D^{20}$ -1.3 (c = 1.21, $CHCl_3$)

Compound 2.55. **Benzyl (*S*)-(1-(benzylamino)-4-methyl-1-oxopentan-2-yl)carbamate**



Synthesised according to General Procedure N using methyl ((benzyloxy)carbonyl)-*L*-leucinate (397 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1 % MeOH/DCM) to afford the title compound as a white solid (262 mg, 52%).

ν_{max} (neat) 3315, 3271, 3066, 2958, 2932, 1684, 1645, 1530, 1236, 1055, 696 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 –7.25 (m, 10H), 6.52 (s, 1H), 5.30 (m, 1H), 5.13 – 5.05 (m, 2H), 4.49 – 4.38 (m, 2H), 4.25 – 4.24 (m, 1H), 1.75– 1.65 (m, 2H), 1.58 – 1.54 (m, 1H), 0.99 – 0.94 (m, 6H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2, 156.4, 138.0, 136.2, 128.9, 128.7, 128.4, 128.2, 127.8, 127.7, 67.2, 53.8, 43.7, 41.6, 24.8, 23.1

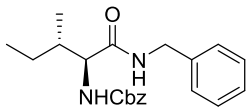
HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{27}N_2O_3$ 355.2016, found 355.2016

ee = 96%

$[\alpha]_D^{20}$ −16.0 (c = 1.2, EtOH), lit $[\alpha]_D^{22}$ −14.1 (c = 1.2, EtOH).

Consistent with previously reported data.[131]

Compound 2.56. **Benzyl ((2*S*,3*S*)-1-(benzylamino)-3-methyl-1-oxopentan-2-yl)carbamate**



Synthesised according to General Procedure N using methyl ((benzyloxy)carbonyl)-*L*-isoleucinate (397 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (0.5 % MeOH/DCM) to afford the title compound as a white solid (35 mg, 7%).

ν_{max} (neat) 3280, 3057, 3029, 2960, 2927, 2873, 1688, 1644, 1532, 1240, 695 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.24 (m, 10H), 6.34 (s, 1H), 5.40 – 5.39 (m, 1H), 5.06 (s, 2H), 4.48 – 4.29 (m, 2H), 4.02 – 3.99 (m, 1H), 3.74 – 3.65 (m, 1H), 2.16 – 2.14 (m, 1H), 1.67 – 1.60 (m, 1H), 0.97 – 0.87 (m, 6H)

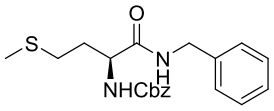
^{13}C NMR (126 MHz, $CDCl_3$): δ 171.2, 156.6, 138.0, 136.3, 128.9, 128.7, 128.4, 128.2, 127.9, 127.7, 67.2, 60.8, 43.7, 31.2, 19.4, 19.1, 18.0

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{27}N_2O_3$ 355.2016, found 355.2018

ee = 98%

$[\alpha]_D^{20}$ −14.3 (c = 0.5, EtOH)

Compound 2.57. **Benzyl (*S*)-(1-(benzylamino)-4-(methylthio)-1-oxobutan-2-yl) carbamate**



Synthesised according to General Procedure N using ethyl ((benzyloxy)carbonyl)-*L*-methioninate (442 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (0.5 % MeOH/DCM) to afford the title compound as a white solid (174 mg, 33%).

ν_{max} (neat) 3280, 2915, 1690, 1642, 1534, 1256, 1238, 1050, 1029, 698 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.23 (m, 10H), 6.52 (s, 1H), 5.55 – 5.53 (m, 1H), 5.11 – 5.08 (m, 2H), 4.49 – 4.35 (m, 3H), 2.61 – 2.45 (m, 2H), 2.15 – 1.95 (m, 6H)

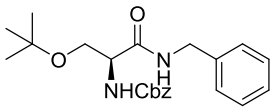
^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 156.2, 137.9, 136.2, 128.9, 128.7, 128.4, 128.3, 127.9, 127.8, 67.3, 54.1, 43.8, 31.7, 30.3, 15.30

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_3S$ 373.1580, found 373.1580

ee = 89%

$[\alpha]_D^{20}$ 12.4 (c = 1.0, EtOH).

Compound 2.58. **Benzyl (*S*)-(1-(benzylamino)-3-(*tert*-butoxy)-1-oxopropan-2-yl)carbamate**



Synthesised according to General Procedure N using methyl *N*-((benzyloxy)carbonyl)-*O*-(*tert*-butyl)-*L*-serinate (439 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (0.5 % MeOH/DCM) to afford the title compound as a white solid (186 mg, 34%).

ν_{max} (neat) 3297, 2970, 1646, 1510, 1218, 697 cm^{-1}

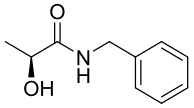
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.30 (m, 7H), 7.28 – 7.26 (m, 3H), 6.90 (s, 1H), 5.74 (s, 1H), 5.16 – 5.09 (m, 2H), 4.53 – 4.42 (m, 2H), 4.28 – 4.27 (m, 1H), 3.87 – 3.82 (m, 1H), 3.41 (t, *J* = 7.9 Hz, 1H), 1.13 (s, 9H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 156.2, 138.1, 136.2, 128.8, 128.7, 128.4, 128.3, 127.7, 127.6, 74.2, 67.3, 61.9, 54.9, 43.6, 27.5

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{29}N_2O_4$ 385.2122, found 385.2120

ee = 59%

Compound 2.59. **(*S*)-*N*-Benzyl-2-hydroxypropanamide**



Synthesised according to General Procedure N using methyl lactate (136 μL, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1 % MeOH/DCM) to afford the title compound as a yellow oil (129 mg, 51%).

ν_{max} (neat) 3310, 1644, 1532, 1273, 1122, 698 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.24 (m, 5H), 7.04 (s, 1H), 4.42 (d, *J* = 5.9 Hz, 2H), 4.27 – 4.21 (m, 1H), 3.54 – 3.53 (m, 1H), 1.42 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 138.0, 128.8, 127.8, 127.7, 68.5, 43.2, 21.4

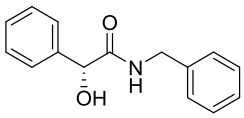
HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{14}NO_2$ 180.1019, found 180.1015

ee = 97%

$[\alpha]_D^{20}$ −4.2 (c = 0.25, $CHCl_3$), lit $[\alpha]_D^{26}$ −21.5 (c = 0.25, $CHCl_3$).

Consistent with previously reported data.[132]

Compound 2.60. **(*R*)-*N*-Benzyl-2-hydroxy-2-phenylacetamide**



Synthesised according to General Procedure N using methyl (*R*)-2-hydroxy-2-phenylacetate (236 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1 % MeOH/DCM) to afford the title compound as a white solid (273 mg, 80%).

ν_{max} (neat) 3406, 3285, 3183, 1647, 1539, 1455, 1068, 758, 707 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.24 (m, 8H), 7.18 – 7.16 (m, 2H), 6.67 (s, 1H), 5.02 – 5.01 (m, 1H), 4.44 – 4.34 (m, 2H), 3.89 – 3.86 (m, 1H)

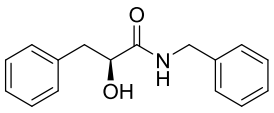
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2, 139.6, 137.8, 128.9, 128.8 (3), 127.7, 126.9, 74.3, 43.5

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{16}NO_2$ 242.1176, found 242.1174

ee = 83%

$[\alpha]_D^{20}$ −26.6 (c = 0.23, MeOH)

Compound 2.61. **(*S*)-*N*-Benzyl-2-hydroxy-3-phenylpropanamide**



Synthesised according to General Procedure N using methyl (*S*)-2-hydroxy-3-phenylpropanoate (256 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1 % MeOH/DCM) to afford the title compound as a white solid (241 mg, 67%).

ν_{max} (neat) 3366, 2919, 1629, 1534, 1091, 1074, 702 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.23 (m, 8H), 7.20 – 7.18 (m, 2H), 6.82 (br. s, 1H), 4.49 – 4.33 (m, 3H), 3.27 – 3.23 (m, 1H), 2.97 – 2.91 (m, 1H), 2.70 – 2.67 (m, 1H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.6, 138.0, 136.9, 129.7, 128.9, 128.8, 127.9, 127.7, 127.2, 73.0, 43.2, 41.0

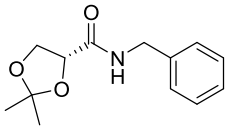
HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{18}NO_2$ 256.1332, found 256.1333

ee = 98%

$[\alpha]_D^{20}$ −55.7 (c = 3.4, EtOAc)

Consistent with previously reported data.[133]

Compound 2.62. **(*R*)-*N*-Benzyl-2,2-dimethyl-1,3-dioxolane-4-carboxamide**



Synthesised according to General Procedure N using methyl (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (206 μL, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (15 % acetone/petroleum ether 40 – 60 °C) to afford the title compound as a white solid (329 mg, 99%).

ν_{max} (neat) 3332, 2988, 2932, 1649, 1537, 1221, 1029, 839, 735, 702 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.32 (m, 2H), 7.30 – 7.26 (m, 3H), 6.89 (br. s, 1H), 4.55 – 4.52 (m, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.34 – 4.29 (m, 1H), 4.17 – 4.13 (m, 1H), 1.44 (s, 3H), 1.38 (s, 3H)

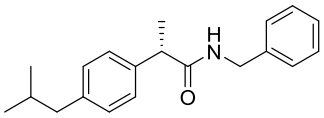
^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 137.9, 128.9, 127.7, 127.7, 111.1, 75.21, 67.9, 43.1, 26.3, 25.1

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{18}NO_3$ 236.1281, found 236.1280

ee = 94%

$[\alpha]_D^{20}$ +16.0 (c = 1.0, EtOH).

Compound 2.63. **(*S*)-*N*-Benzyl-2-(4-isobutylphenyl)propanamide**



Synthesised according to General Procedure N using methyl (*S*)-2-(4-isobutylphenyl)propanoate (313 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow solid (61 mg, 15%).

Synthesised according to General Procedure O using methyl (*S*)-2-(4-isobutylphenyl)propanoate (313 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow solid (66 mg, 16%).

Synthesised according to General Procedure P using methyl (*S*)-2-(4-isobutylphenyl)propanoate (313 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as a yellow solid (61 mg, 72%).

ν_{max} (neat) 3299, 3030, 2950, 2921, 2867, 1640, 1537, 1454, 1230, 737, 696 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.19 (m, 5H), 7.14 – 7.10 (m, 4H), 6.61 (s, 1H), 4.39 (d, *J* = 5.8 Hz, 2H), 3.58 (q, *J* = 7.2 Hz, 1H), 2.45 (d, *J* = 7.2 Hz, 2H), 1.91 –1 .78 (m, 1H), 1.55 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.5, 141.0, 138.6, 138.5, 129.9, 129.8, 128.7, 127.5, 127.5, 47.0, 45.1, 43.7, 30.3, 22.5, 18.6

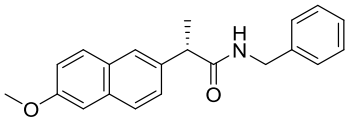
HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{26}NO$ 296.2009, found 296.2005

ee = 83%

$[\alpha]_D^{20}$ +3.0 (c = 0.88, DCM)

Consistent with previously reported data.[85]

Compound 2.64. **(*S*)-*N*-Benzyl-2-(6-methoxynaphthalen-2-yl)propanamide**



Synthesised according to General Procedure N using methyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate (347 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as an orange solid (57 mg, 13%).

Synthesised according to General Procedure O using methyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate (347 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as an orange solid (69 mg, 14%).

Synthesised according to General Procedure P using methyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate (347 mg, 1.42 mmol, 1 equiv.) and benzylamine (155 μL, 1.42 mmol, 1 equiv.) and purified by flash column chromatography (1% MeOH/DCM) to afford the title compound as an orange solid (60 mg, 13%).

ν_{max} (neat) 3290, 2968, 2933, 1638, 1534, 1026, 857, 693 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 – 7.66 (m, 3H), 7.39 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.26 – 7.21 (m, 3H), 7.14 – 7.12 (m, 3H), 5.67 (s, 1H), 4.45 – 4.34 (m, 2H), 3.92 (s, 3H), 3.74 (q, *J* = 7.2 Hz, 1H), 1.63 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3, 157.9, 138.5, 136.5, 133.9, 129.4, 129.1, 128.7, 127.8, 127.6, 127.5, 126.4, 126.3, 119.3, 106.8, 55.5, 47.3, 43.7, 18.7

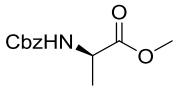
HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{22}NO_2$ 320.1645, found 320.1645

ee = 81%

$[\alpha]_D^{20}$ -2.8 (c = 0.5, EtOH)

2.6.3.4 Characterisation Data for 4-(trifluoromethyl)phenol Catalysed Amidation of Chiral Esters: Chiral Ester Starting Materials

Compound 2.115. **Methyl ((benzyloxy)carbonyl)-*D*-alaninate**



Synthesised according to General Experimental Procedure R, using methyl *D*-alaninate hydrochloride (500 mg, 3.58 mmol, 1 equiv.) and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a pale yellow oil (581 mg, 68%).

ν_{max} (neat): 3336, 3036, 2993, 2958, 1753, 1684, 1526, 1215, 1174, 1076, 754, 702 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 5.31 (s, 1H), 5.11 (m, 2H), 4.43 – 4.46 (m, 1H), 3.75 (s, 3H), 1.42 (d, *J* = 7.2 Hz, 3H)

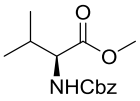
^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6, 155.7, 136.4, 128.6, 128.3, 128.2, 67.0, 52.5, 49.7, 18.8

HRMS *m/z*: $[M+H]^+$ calcd for $C_{12}H_{16}NO_4$ 238.1074, found 238.1076

ee = 100%

Consistent with previously reported data.[134]

Compound 2.116. Methyl ((benzyloxy)carbonyl)-*L*-valinate



Synthesised according to General Experimental Procedure S, using *L*-valine (750 mg, 6.40 mmol, 1 equiv.) and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a white solid (1.497 g, 88%).

ν_{max} (neat): 3345, 2951, 1746, 1692, 1534, 1222, 753 cm^{-1}

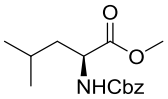
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.29 (m, 5H), 5.28 – 5.26 (m, 1H), 5.11 (s, 2H), 4.32 – 4.29 (m, 1H), 3.74 (s, 3H), 2.20 – 2.12 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7, 156.4, 136.4, 128.7, 128.3 (2), 67.2, 59.2, 52.3, 31.4, 19.1, 17.7

HRMS *m/z*: $[M+H]^+$ calcd for $C_{14}H_{20}NO_4$ 266.1387, found 266.1386

ee = 100%

Compound 2.117. Methyl ((benzyloxy)carbonyl)-*L*-leucinate



Synthesised according to General Experimental Procedure R, using of methyl *L*-leucinate hydrochloride (500 mg, 2.75 mmol, 1 equiv.) and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a colourless oil (683 mg, 89%).

ν_{max} (neat): 3339, 2956, 1699, 1526, 1262, 1208, 1171, 1046, 739, 700 cm^{-1}

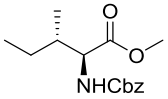
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.30 (m, 5H), 5.14 – 5.11 (m, 3H), 4.42 – 4.38 (m, 1H), 3.74 (s, 3H), 1.74 – 1.61 (m, 2H), 1.55 – 1.49 (m, 1H), 0.96 – 0.93 (m, 6H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8, 156.1, 136.4, 128.7, 128.3, 128.3, 67.1, 52.6, 52.4, 24.9, 23.0, 22.0

HRMS *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{22}NO_4$ 280.1543, Found 280.1541

ee = 100%

Compound 2.118. **Methyl ((benzyloxy)carbonyl)-*L*-isoleucinate**



Synthesised according to General Experimental Procedure S, using *L*-isoleucine (750 mg, 5.72 mmol, 1 equiv.) and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a white solid (1.0046 g, 63%).

ν_{max} (neat): 3342, 2960, 1703, 1514, 1207, 1041, 699 cm^{-1}

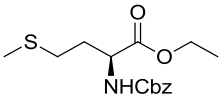
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.29 (m, 5H), 5.31 (s, 1H), 5.11 (s, 2H), 4.36 – 4.33 (m, 1H), 3.73 (s, 3H), 1.92 – 1.85 (m, 1H), 1.47 – 1.37 (m, 1H), 1.22 – 1.11 (m, 1H), 0.93 – 0.89 (m, 6H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.6, 156.2, 136.4, 128.7, 128.3 (2), 67.1, 58.5, 52.2, 38.2, 25.1, 15.6, 11.7

HRMS *m/z*: $[M+H]^+$ calcd for $C_{15}H_{22}NO_4$ 280.1543, found 280.1543

ee = 100%

Compound 2.119. **Ethyl ((benzyloxy)carbonyl)-*L*-methioninate**



Synthesised according to General Experimental Procedure R, using ethyl *L*-methioninate hydrochloride (600 mg, 2.81 mmol, 1 equiv.), and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a pale yellow oil (629 mg, 72%).

ν_{max} (neat): 3326, 2980, 2917, 1705, 1521, 1210, 1046, 1029, 700 cm^{-1}

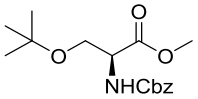
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.29 (m, 5H), 5.42 (s, 1H), 5.11 (s, 2H), 4.50 – 4.45 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.58 – 2.47 (m, 2H), 2.20 – 2.09 (m, 4H), 2.01 – 1.92 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.1, 156.0, 136.3, 128.7, 128.3, 128.3, 67.2, 61.8, 53.4, 32.2, 30.0, 15.6, 14.3

HRMS *m/z*: $[M+H]^+$ calcd for $C_{15}H_{22}NO_4S$ 312.1264, found 312.1261

ee = 100%

Compound 2.120. **Methyl *N*-((benzyloxy)carbonyl)-*O*-(*tert*-butyl)-*L*-serinate**



N-carbobenzoxy-*O*-*tert*-Butyl-*L*-serine (800 mg, 2.71 mmol, 1 equiv.) was dissolved in DMF (10 mL), to which was added K_2CO_3 (561 mg, 4.06 mmol, 1.5 equiv.) and methyl iodide (194 µL, 3.12 mmol, 1.7 equiv.) and the reaction stirred at 30 °C for 90 h. The reaction mixture was concentrated *in vacuo*, and the resulting residue dissolved in EtOAc (20 mL) and washed with water (3 x 20 mL) and brine (3 x 20 mL). Organics were dried (Na_2SO_4) and concentrated *in vacuo* and the resulting residue purified by flash chromatography (50% EtOAc/petroleum ether 40 – 60 °C) to afford the title compound as a yellow oil (716 mg, 85%).

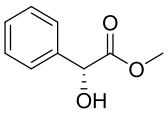
ν_{max} (neat): 3401, 2968, 1722, 1493, 1199, 1058, 703 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 5.61 (d, *J* = 8.6 Hz, 1H), 5.13 (s, 2H), 4.48 – 4.44 (m, 1H), 3.81 (dd, *J* = 9.0, 2.8 Hz, 1H), 3.74 (s, 3H), 3.58 (dd, *J* = 9.0, 3.2 Hz, 1H), 1.12 (s, 9H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 156.3, 136.5, 129.9, 128.7, 128.3, 73.6, 67.1, 62.1, 54.8, 52.5, 27.4

HRMS *m/z*: $[M+H]^+$ calcd for $C_{16}H_{24}NO_5$ 310.1649, found 310.1648

Compound 2.121. **Methyl (*R*)-2-hydroxy-2-phenylacetate**



Synthesised according to General Experimental Procedure Q, using mandelic acid (600 mg, 2.81 mmol, 1 equiv.), and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a colourless oil (643 mg, 78%).

ν_{max} (neat): 3434, 1738, 1206, 1191, 1068, 977, 739, 696 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 -7.31 (m, 5H), 5.18 (d, *J* = 5.3 Hz, 1H), 3.76 (s, 3H), 3.49 – 3.43 (m, 1H)

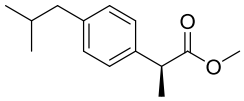
^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3, 138.4, 128.8, 128.7, 126.7, 73.0, 53.2

HRMS *m/z*: $[M+H]^+$ calcd for $C_9H_{11}O_3$ 167.0703, found 167.0701

ee = 100%

Consistent with previously reported data.[135]

Compound 2.122. Methyl (*S*)-2-(4-isobutylphenyl)propanoate



Synthesised according to General Experimental Procedure Q, using (*S*)-2-(4-isobutylphenyl)propanoic acid (750 mg, 3.64 mmol, 1 equiv.), and purified by flash column chromatography (10% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a pale yellow oil (583 mg, 73%).

ν_{max} (neat): 2954, 2870, 1738, 1206, 1163, 1066 cm^{-1}

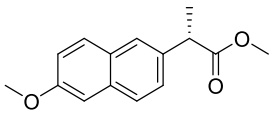
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.18 (m, 2H), 7.11 – 7.09 (m, 2H), 3.70 (q, *J* = 7.2 Hz, 1H), 3.66 (s, 3H), 2.45 (d, *J* = 7.2 Hz, 2H), 1.92 – 1.76 (m, 1H), 1.49 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.4, 140.7, 137.9, 129.5, 127.3, 52.1, 45.2, 30.3, 22.5, 18.8 (peak relating to one alkyl carbon not observed, presumed coincident)

HRMS *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{21}O_2$ 221.1536, Found 221.1533

Consistent with previously reported data.[136]

Compound 2.123. **Methyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate**



Synthesised according to General Experimental Procedure Q, using (*S*)-2-(6-methoxynaphthalen-2-yl) propanoic acid (750 mg, 3.26 mmol, 1 equiv.), and purified by flash column chromatography (10% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a white solid (792 mg, 99%).

ν_{max} (neat): 3003, 2973, 2931, 1731, 1173, 1028, 857, 824 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 – 7.66 (m, 3H), 7.40 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.16 – 7.11 (m, 2H), 3.91 (s, 3H), 3.86 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 1.58 (d, *J* = 7.2 H, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.3, 157.8, 135.8, 133.8, 129.4, 129.1, 127.3, 126.3, 126.1, 119.1, 105.7, 55.4, 52.2, 45.5, 18.7

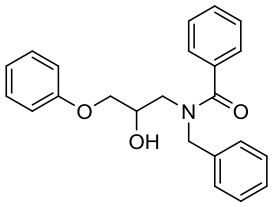
HRMS *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_3$ 245.1172, found 245.1174

ee = 100%

Consistent with previously reported data.[137]

2.6.3.5 Characterisation Data for BEMP-Mediated MCR Approach to Amide Bond Formation

Compound 2.66. ***N*-Benzyl-*N*-(2-hydroxy-3-phenoxypropyl)benzamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl benzoate (126 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a white solid (258 mg, 71%).

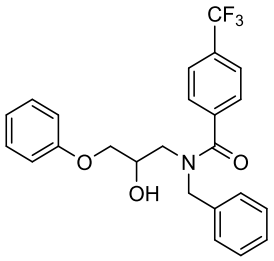
ν_{max} (neat): 3367, 3056, 3025, 2924, 1599, 1242, 693 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.47 (m, 2H), 7.42 – 7.26 (m, 8H), 7.19 – 7.17 (m, 2H), 6.98 – 6.95 (m, 1H), 6.89 – 6.87 (m, 2H), 4.70 – 4.58 (m, 2H), 4.39 (br. s, 1H), 4.26 (s, 1H), 4.04 – 3.83 (m, 3H), 3.71 – 3.67 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7, 158.5, 136.4, 135.6, 130.2, 129.7, 129.1, 128.7, 128.0, 127.2, 127.0, 121.3, 114.6, 70.2, 69.4, 54.9, 50.1

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{24}NO_3$ 362.1751, found 362.1753

Compound 2.67. ***N*-Benzyl-*N*-(2-hydroxy-3-phenoxypropyl)-4-(trifluoromethyl)benzamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl 4-(trifluoromethyl)benzoate (161 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (20% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as an off-white solid (384 mg, 89%).

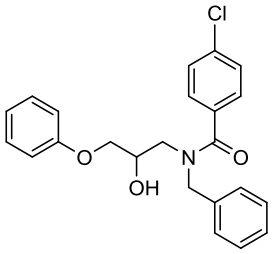
ν_{max} (neat): 3395, 3056, 3030, 2922, 1600, 1323, 1125, 753 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.36 (m, 5H), 7.17 – 7.15 (m, 2H), 6.99 – 6.96 (m, 1H), 6.90 – 6.88 (m, 2H), 4.65 – 4.58 (m, 2H), 4.33 (br. s, 1H), 4.03 – 3.97 (m, 2H), 3.85 (dd, *J* = 14.2, 7.5 Hz, 1H), 3.77 – 3.70 (m, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9, 158.4, 139.3, 136.0, 132.1 (q, $^2J_{CF}$ = 32.8 Hz), 129.7, 129.2, 127.3, 127.0, 125.8, 123.7 (q, $^1J_{CF}$ = 272.8 Hz) 121.4, 114.6, 69.9, 69.6, 54.6, 49.8 ($^3J_{CF}$ splitting not observed)

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{23}F_3NO_3$ 430.1625, found 430.1623

Compound 2.68. ***N*-Benzyl-4-chloro-*N*-(2-hydroxy-3-phenoxypropyl)benzamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl 4-chlorobenzoate (171 mg, 1 mmol, 1 equiv.), and purified by flash column chromatography (20% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow solid (234 mg, 59%).

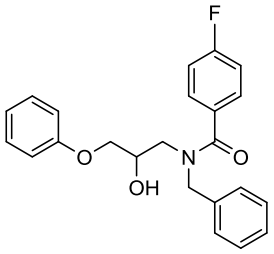
ν_{max} (neat): 3369, 3030, 2913, 1597, 1253, 1046, 753, 699 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.39 – 7.26 (m, 7H), 7.17 – 7.16 (m, 2H), 6.98 – 6.95 (m, 1H), 6.88 – 6.87 (m, 2H), 4.70 – 4.62 (m, 2H), 4.27 (br. s, 1H), 4.01 – 3.95 (m, 2H), 3.84 (dd, *J* = 13.8, 7.2 Hz, 1H), 3.73 – 3.70 (m, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.5, 158.4, 136.4, 136.2, 134.0, 129.7, 129.2, 129.0, 128.5, 128.1, 127.0, 121.4, 114.6, 70.1, 69.5, 54.8, 50.1

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{23}ClNO_3$ 396.1361, found 396.1361

Compound 2.69. ***N*-Benzyl-4-fluoro-*N*-(2-hydroxy-3-phenoxypropyl)benzamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl 4-fluorobenzoate (129 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (221 mg, 58%).

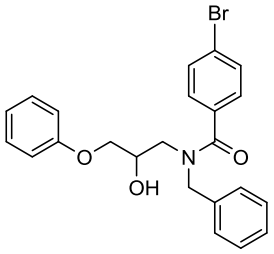
ν_{max} (neat): 3283, 3028, 2924, 1589, 1074, 1048, 842, 758, 697 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 – 7.47 (m, 2H), 7.39 – 7.36 (m, 2H), 7.33 – 7.26 (m, 3H), 7.18 – 7.17 (m, 2H), 7.08 – 7.04 (m, 2H), 6.98 – 6.95 (m, 1H), 6.88 – 6.86 (m, 2H), 4.69 – 4.61 (m, 2H), 4.26 (br. s, 1H), 4.01 – 3.95 (m, 2H), 3.88 – 3.82 (m, 1H), 3.70 – 3.67 (m, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.7, 158.4, 136.3, 131.6, 129.7, 129.4 (d, $^{3}J_{CF}$ = 8.7 Hz), 129.2, 128.1, 127.0, 121.4, 115.8 (d, $^{2}J_{CF}$ = 21.8 Hz), 114.6, 70.1, 69.5, 54.9, 50.3 ($^{1}J_{CF}$ splitting not observed; peak relating to one aromatic carbon not observed).

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{23}FNO_3$ 380.1656, found 380.1656

Compound 2.70. ***N*-Benzyl-4-bromo-*N*-(2-hydroxy-3-phenoxypropyl)benzamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl 4-bromobenzoate (215 mg, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a white solid (257 mg, 58%).

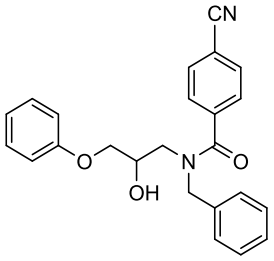
ν_{max} (neat): 3370, 3030, 2915, 1599, 1253, 1046, 751, 699 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 – 7.50 (m, 2H), 7.38 – 7.26 (m, 7H), 7.17 – 7.15 (m, 2H), 6.98 – 6.95 (m, 1H), 6.88 – 6.86 (m, 2H), 4.65 – 4.57 (m, 2H), 4.26 (br. s, 1H), 4.00 – 3.95 (m, 2H), 3.86 – 3.82 (m, 1H), 3.68 – 3.66 (m, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.6, 158.4, 136.2, 134.5, 132.0, 129.7, 129.2, 128.7, 128.1, 127.0, 124.7, 121.4, 114.6, 70.1, 69.5, 54.8, 50.1

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{23}BrNO_3$ 440.0856, found 440.0855

Compound 2.71. ***N*-Benzyl-4-cyano-*N*-(2-hydroxy-3-phenoxypropyl)benzamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl 4-cyanobenzoate (161 mg, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow oil (229 mg, 59%).

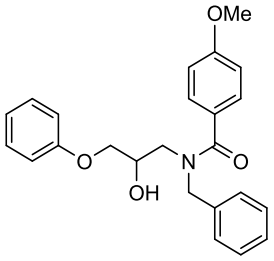
ν_{max} (neat): 3376, 3058, 3028, 2924, 2229, 1619, 1599, 1242, 755, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.39 – 7.26 (m, 5H), 7.14 – 7.13 (m, 2H), 6.99 – 6.96 (m, 1H), 6.89 – 6.87 (m, 2H), 4.59 (app. br. s, 2H), 4.31 (br. s, 1H), 4.00 – 3.99 (m, 2H), 3.83 (dd, *J* = 14.3, 7.4 Hz, 1H), 3.73 (dd, *J* = 14.3, 2.3 Hz, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 158.4, 140.1, 135.8, 132.6, 129.8, 129.3, 128.3, 127.6, 126.9, 121.5, 118.1, 114.6, 114.0, 69.9, 69.6, 54.6, 49.8

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_3$ 387.1703, found 387.1703

Compound 2.72. ***N*-Benzyl-*N*-(2-hydroxy-3-phenoxypropyl)-4-methoxybenzamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl 4-methoxybenzoate (166 mg, 1 mmol, 1 equiv.), and purified by flash column chromatography (40% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (150 mg, 38%).

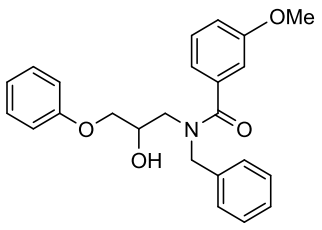
ν_{max} (neat): 3378, 2932, 1597, 1251, 1232, 1026, 725, 693 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.44 (m, 2H), 7.39 – 7.35 (m, 2H), 7.32 – 7.25 (m, 5H), 6.98 – 6.93 (m, 1H), 6.89 – 6.84 (m, 4H), 4.73 – 4.68 (m, 3H), 4.23 (br. s, 1H), 4.00 (br. s, 1H), 3.91 (br. s, 1H), 3.85 – 3.80 (m, 4H), 3.65 – 3.63 (m, 1H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6, 158.5, 136.7, 132.1, 129.7, 129.2, 129.1, 127.9, 127.1, 121.3, 114.6, 114.0, 70.2, 69.4, 55.5, 54.9, 50.6 (peak relating to one aromatic carbon not observed)

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{26}NO_4$ 392.1856, found 392.1853

Compound 2.73. ***N*-Benzyl-*N*-(2-hydroxy-3-phenoxypropyl)-3-methoxybenzamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl 3-methoxybenzoate (145 µL,1 mmol, 1 equiv.), and purified by flash column chromatography (40% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (273 mg, 70%).

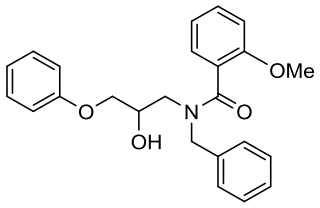
ν_{max} (neat): 3348, 2928, 1599, 1586, 1234, 1039, 753, 693 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.26 (m, 6H), 7.19 – 7.18 (m, 2H), 7.05 – 7.03 (m, 1H), 6.98 – 6.93 (m, 3H), 6.89 – 6.87 (m, 2H), 4.69 – 4.58 (m, 2H), 4.26 (br. s, 1H), 4.04 – 3.83 (m, 3H), 3.71 – 3.67 (m, 5H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.4, 159.8, 136.5, 129.9, 129.7, 129.1, 128.9, 128.0, 127.1, 121.4, 119.1, 116.4, 114.6, 112.1, 70.2, 69.4, 55.4, 54.8, 50.2 (peak relating to one aromatic carbon not observed)

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{26}NO_4$ 392.1856, found 392.1854

Compound 2.74. ***N*-Benzyl-*N*-(2-hydroxy-3-phenoxypropyl)-2-methoxybenzamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl 2-methoxybenzoate (145 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (40% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow oil (130 mg, 33%).

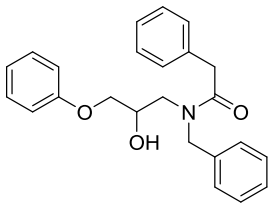
ν_{max} (neat): 3356, 3058, 3026, 2932, 1599, 1240, 753, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.22 (m, 7H), 7.15 – 7.14 (m, 2H), 7.00 – 6.91 (m, 5H), 4.52 – 4.26 (m, 3H), 4.03 – 4.02 (m, 2H), 3.88 – 3.87 (m, 1H), 3.81 (s, 3H), 3.65 – 3.62 (m, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.6, 158.6, 136.7, 136.5, 130.9, 129.7, 128.9, 128.8, 128.3, 127.9, 127.7, 121.2, 114.9, 114.6, 111.2, 69.9, 55.7, 54.7, 50.3, 49.7

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{26}NO_4$ 392.1856, found 392.1849

Compound 2.75. ***N*-Benzyl-*N*-(2-hydroxy-3-phenoxypropyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow oil (354 mg, 94%).

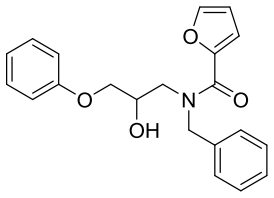
ν_{max} (neat): 3374, 3060, 3026, 1621, 1599, 1244, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.30 (m, 5H), 7.29 – 7.24 (m, 5H), 7.14 – 7.12 (m, 2H), 6.97 – 6.94 (m, 1H), 6.87 – 6.83 (m, 2H), 4.69 – 4.58 (m, 2H), 4.22 – 4.14 (m, 1H), 3.96 – 3.94 (m, 1H), 3.86 – 3.83 (m, 1H), 3.78 – 3.72 (m, 3H), 3.66 – 3.63 (m, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.6, 158.4, 136.2, 134.6, 129.8, 129.7, 129.2, 129.0, 128.9, 128.0, 127.6, 127.2, 126.6, 70.3, 69.2, 53.6, 51.3, 41.0,

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{26}NO_3$ 376.1907, found 376.1905

Compound 2.76. ***N*-Benzyl-*N*-(2-hydroxy-3-phenoxypropyl)furan-2-carboxamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl 2-furoate (107 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as an orange oil (178 mg, 51%).

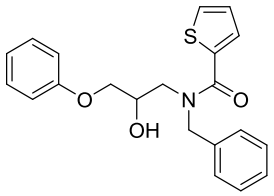
ν_{max} (neat): 3365, 3058, 3026, 2922, 1599, 1487, 1244, 753, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (br. s, 1H), 7.39 – 7.36 (m, 2H), 7.33 – 7.26 (m, 5H), 7.06 (br. s, 1H), 6.94 – 6.91 (m, 1H), 6.85 – 6.83 (m, 2H), 6.48 – 6.47 (m, 1H), 4.97 (br. s, 2H), 4.27 (br. s, 1H), 3.98 – 3.89 (m, 2H), 3.80 (dd, *J* = 14.4, 7.4 Hz, 1H), 3.66 – 3.64 (m, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.7, 158.3, 144.4, 136.5, 129.6, 128.9, 127.8, 127.1, 121.2, 117.6, 114.6, 114.5, 111.6, 69.8, 69.2, 53.5, 51.4

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{22}NO_4$ 352.1543, found 352.1544

Compound 2.77. ***N*-Benzyl-*N*-(2-hydroxy-3-phenoxypropyl)thiophene-2-carboxamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and ethyl 2-thiophenecarboxylate (134 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a yellow oil (218 mg, 59%).

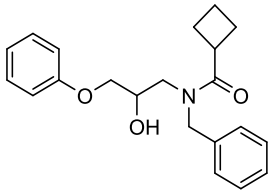
ν_{max} (neat): 3363, 3060, 3026, 2924, 1597, 1242, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.43 – 7.40 (m, 2H), 7.35 – 7.26 (m, 6H), 6.98 – 6.94 (m, 2H), 6.87 – 6.86 (m, 2H), 4.99 – 4.91 (m, 2H), 4.32 – 4.27 (m, 1H), 4.04 – 4.01 (m, 1H), 3.93 (dd, *J* = 9.4, 6.7 Hz, 1H), 3.86 (dd, *J* = 14.5, 7.5 Hz, 1H), 3.69 (dd, *J* = 14.5, 2.5 Hz, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 137.1, 136.4, 130.3, 129.7, 129.5, 129.3, 128.0, 127.3, 126.8, 121.4, 114.6, 69.9, 69.3, 54.6, 51.7 (peak relating to carbonyl carbon not observed)

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{22}NO_3S$ 368.1315, found 368.1314

Compound 2.78. ***N*-Benzyl-*N*-(2-hydroxy-3-phenoxypropyl)cyclobutanecarboxamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl cyclobutanecarboxylate (116 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (98 mg, 29%).

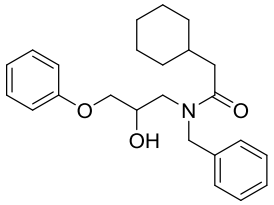
ν_{max} (neat): 3354, 3060, 3026, 2935, 2867, 1619, 1599, 1495, 1244, 1041, 755, 693 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.25 (m, 5H), 7.15 – 7.13 (m, 2H), 6.98 – 6.93 (m, 1H), 6.87 – 6.85 (m, 2H), 4.58 – 4.47 (m, 2H), 4.15 – 4.13 (m, 1H), 3.97 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.84 (dd, *J* = 9.4, 7.2 Hz, 1H), 3.68 (dd, *J* = 14.5, 6.9 Hz, 1H), 3.60 – 3.56 (m, 1H), 3.37 – 3.29 (m, 1H), 2.45 – 2.34 (m, 2H), 2.17 – 2.06 (m, 2H), 1.97 – 1.86 (m, 2H) (exchangeable proton not observed)

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.2, 158.5, 136.6, 129.7, 129.1, 127.9, 126.7, 121.2, 114.6, 70.4, 69.1, 52.7, 51.1, 37.3, 25.5, 18.1

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{26}NO$ 340.1907, found 340.1908

Compound 2.81. ***N*-Benzyl-2-cyclohexyl-*N*-(2-hydroxy-3-phenoxypropyl)acetamide**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl cyclohexylacetate (164 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (97 mg, 25%).

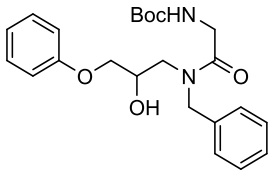
ν_{max} (neat): 3370, 3060, 3028, 2919, 2848, 1600, 1244, 755, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.36 (m, 2H), 7.32 – 7.26 (m, 3H), 7.16 – 7.15 (m, 2H), 6.97 – 6.94 (m, 1H), 6.88 – 6.86 (m, 2H), 4.68 – 4.58 (m, 1H), 4.18 – 4.14 (m, 1H), 3.99 (dd, *J* = 9.4, 5.2 Hz, 1H), 3.86 – 3.83 (m, 1H), 3.72 (dd, *J* = 14.5, 6.9 Hz, 1H), 3.62 – 3.59 (m, 1H), 2.28 (d, *J* = 6.9 Hz, 2H), 1.93 – 1.86 (m, 1H), 1.78 – 1.75 (m, 2H), 1.70 – 1.64 (m, 3H), 1.34 – 1.25 (m, 3H), 1.17 – 1.08 (m, 1H), 0.96 – 0.88 (m, 2H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.3, 158.5, 136.5, 129.7, 129.2, 127.9, 126.5, 121.3, 114.6, 70.5, 69.2, 53.5, 51.3, 41.0, 35.3, 33.5, 26.4, 26.3

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{32}NO_3$ 382.2377, found 382.2366

Compound 2.82. ***tert*-Butyl (2-(benzyl(2-hydroxy-3-phenoxypropyl)amino)-2-oxoethyl)carbamate**



Synthesised according to General Experimental Procedure V using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and *N*-(*tert*-butoxycarbonyl)glycine methyl ester (175 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow oil (169 mg, 41%).

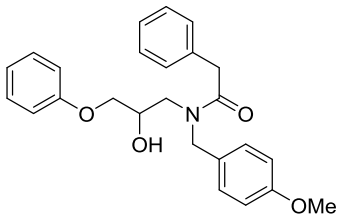
ν_{max} (neat): 3413, 2974, 2930, 1643, 1496, 1244, 1165, 755, 732, 693 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.23 (m, 6H), 7.17 – 7.15 (m, 1H), 6.98 – 6.95 (m, 1H), 6.88 – 6.86 (m, 2H), 5.46 (br. s, 1H), 4.65 – 4.53 (m, 2H), 4.21 – 4.17 (m, 1H), 4.06 – 4.04 (m, 2H), 3.97 – 3.88 (m, 2H), 3.73 – 3.63 (m, 2H), 1.45 (br. s, 9H) (exchangeable proton not observed)

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 157.7, 155.2, 134.9, 129.1, 128.7, 127.5, 126.0, 120.8, 114.0, 69.4, 68.7, 79.3, 51.6, 50.4, 41.9, 27.8

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{31}N_2O_5$ 415.2227, found 415.2222

Compound 2.83. ***N*-(2-Hydroxy-3-phenoxypropyl)-*N*-(4-methoxybenzyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure W using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), 4-methoxybenzylamine (131 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (220 mg, 54%).

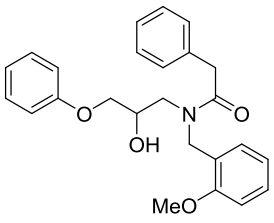
ν_{max} (neat): 3378, 3058, 3026, 2930, 2833, 1612, 1599, 1244, 755, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.25 (m, 7H), 7.03 – 7.01 (m, 2H), 6.96 – 6.93 (m, 1H), 6.88 – 6.86 (m, 2H), 6.84 – 6.82 (m, 2H), 4.61 – 4.49 (m, 2H), 4.40 – 4.39 (m, 1H), 4.16 – 4.10 (m, 1H), 3.93 (dd, *J* = 9.4, 5.2 Hz, 1H), 3.80 – 3.79 (m, 5H), 3.72 (dd, *J* = 14.4, 7.1 Hz, 1H), 3.60 (dd, *J* = 14.4, 2.6 Hz, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 158.8, 157.8, 135.9, 134.1, 129.1, 129.0, 128.4, 128.3, 127.4, 126.6, 120.6, 113.9, 69.8, 68.5, 54.8, 52.5, 50.4, 40.4

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{28}NO_4$ 406.2013, found 406.2008

Compound 2.84. ***N*-(2-Hydroxy-3-phenoxypropyl)-*N*-(2-methoxybenzyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure W using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), 2-methoxybenzylamine (131 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a yellow oil (152 mg, 37%).

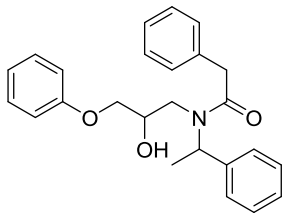
ν_{max} (neat): 3378, 3060, 3026, 2930, 1599, 1493, 1240, 753, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.30 (m, 3H), 7.28 – 7.24 (m, 5H), 7.09 – 7.07 (m, 1H), 6.98 – 6.90 (m, 3H), 6.85 – 6.83 (m, 2H), 4.67 – 4.55 (m, 2H), 4.48 – 4.47 (m, 1H), 4.11 (br. s, 1H), 3.93 (dd, *J* = 9.4, 5.2 Hz, 1H), 3.83 (s, 3H), 3.82 – 3.80 (m, 2H), 3.76 (dd, *J* = 14.3, 7.1 Hz, 1H), 3.59 (dd, *J* = 14.3, 2.4 Hz, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.0, 158.5, 157.4, 135.0, 129.6, 129.3, 129.1, 128.9, 127.9, 127.1, 124.2, 121.2, 120.9, 114.6, 110.6, 70.5, 69.3, 55.4, 51.3, 49.5, 40.7

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{28}NO_4$ 406.2013, found 406.2009

Compound 2.85. ***N*-(2-Hydroxy-3-phenoxypropyl)-2-phenyl-*N*-(1-phenylethyl)acetamide**



Synthesised according to General Experimental Procedure W using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), α-methylbenzylamine (129 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (20% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow oil (204 mg, 52%).

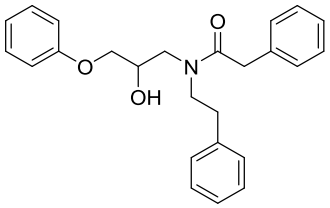
ν_{max} (neat): 3341, 3058, 3026, 2928, 1599, 755, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 – 7.21 (m, 10H), 7.12 – 7.10 (m, 1H), 7.04 – 7.03 (m, 1H), 6.95 – 6.90 (m, 1H), 6.84 – 6.83 (m, 1H), 6.72 – 6.70 (m, 1H), 5.25 – 5.20 (m, 1H), 4.07 – 4.00 (m, 1H), 3.97 – 3.96 (m, 1H), 3.93 – 3.91 (m, 1H), 3.71 – 3.56 (m, 2.5 H), 3.39 – 3.35 (m, 0.5 H), 3.28 – 3.20 (m, 1H), 1.52 – 1.48 (m, 3H) (1:1 mixture of diastereoisomers, exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.8, 174.3, 158.5, 158.3, 139.6, 138.7, 134.7, 134.5, 129.5, 129.3, 129.1, 129.0, 128.9, 128.8, 128.7 (2), 128.1, 127.9, 127.4, 127.3, 127.2, 126.5, 121.0, 120.8, 114.4, 114.3, 72.5, 70.9, 69.6, 69.4, 56.6, 56.2, 48.9, 47.7, 41.9, 41.6, 18.3, 17.0 (1:1 mixture of diastereoisomers)

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{28}NO_3$ 390.2064, found 390.2061

Compound 2.87. ***N*-(2-Hydroxy-3-phenoxypropyl)-*N*-phenethyl-2-phenylacetamide**



Synthesised according to General Experimental Procedure W using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), phenethylamine (126 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (348 mg, 89%).

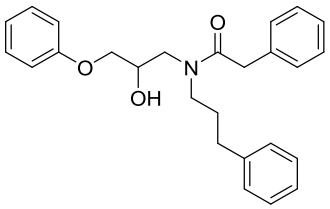
ν_{max} (neat): 3357, 3058, 3025, 2922, 1619, 1599, 1244, 753, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.30 (m, 5H), 7.29 – 7.26 (m, 3H), 7.17 – 7.16 (m, 2H), 7.12 – 7.11 (m, 2H), 6.98 – 6.95 (m, 1H), 6.90 – 6.98 (m, 2H), 4.53 (br. s, 1H), 4.23 – 4.19 (m, 1H), 4.00 (dd, *J* = 9.4, 5.2 Hz, 1H), 3.87 – 3.84 (m, 1H), 3.74 (dd, *J* = 14.4, 6.9 Hz, 1H), 3.66 – 3.54 (m, 3H), 3.50 (s, 2H), 2.87 – 2.75 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 158.3, 137.8, 134.6, 129.7, 129.6, 128.9, 128.8 (2), 127.0, 126.9, 121.2, 114.5, 70.5, 69.0, 51.9, 51.2, 40.5, 35.0

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{28}NO_3$ 390.2064, found 390.2066

Compound 2.88. ***N*-(2-Hydroxy-3-phenoxypropyl)-2-phenyl-*N*-(3-phenylpropyl)acetamide**



Synthesised according to General Experimental Procedure W using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), 3-phenylpropylamine (142 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (375 mg, 93%).

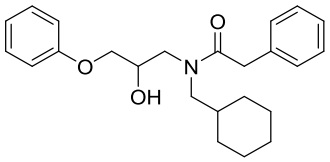
ν_{max} (neat): 3346, 3058 3025, 2924, 1619, 1599, 1244, 753, 693 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.26 (m, 8H), 7.14 – 7.10 (m, 4H), 7.00 – 6.97 (m, 1H), 6.87 – 6.85 (m, 2H), 4.62 – 4.61 (m, 1H), 4.18 – 4.14 (m, 1H), 3.99 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.85 – 3.81 (m, 1H), 3.74 – 3.70 (m, 1H), 3.63 (s, 2H), 3.60 – 3.57 (m, 1H), 3.40 – 3.34 (m, 1H), 3.31 – 3.24 (m, 1H) 2.59 (t, *J* = 7.3 Hz, 2H), 1.96 – 1.83 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.0, 158.4, 140.7, 134.7, 129.7, 128.9, 128.8 (2), 128.4, 127.1, 126.5, 121.3, 114.6, 70.7, 69.2, 51.4, 50.0, 41.0, 33.0, 30.2

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{30}NO_3$ 404.2220, found 404.2215

Compound 2.90. ***N*-(Cyclohexylmethyl)-*N*-(2-hydroxy-3-phenoxypropyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure W using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), cyclohexylmethylamine (130 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (20% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (366 mg, 96%).

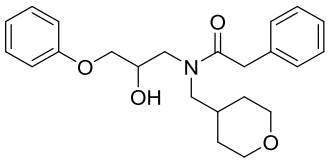
ν_{max} (neat): 3359, 3060, 3026, 2921, 2848, 1619, 1599, 1496, 1450, 1244, 753, 693 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.31 (m, 2H), 7.29 – 7.24 (m, 5H), 6.97 – 6.94 (m, 1H), 6.88 – 6.86 (m, 2H), 4.73 – 4.72 (m, 1H), 4.16 – 4.14 (m, 1H), 3.99 (dd, *J* = 9.4, 5.0 Hz, 1H), 3.82 – 3.74 (m, 4H), 3.58 – 3.55 (m, 1H), 3.24 (dd, *J* = 14.7, 7.8 Hz, 1H), 3.15 (dd, *J* = 14.7, 6.7 Hz, 1H), 1.77 – 1.68 (m, 6H), 1.24 – 1.14 (m, 3H), 0.95 – 0.83 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.5, 158.5, 134.9, 129.7, 129.0, 128.9, 127.1, 121.3, 114.6, 70.7, 69.2, 56.9, 52.3, 40.8, 37.6, 31.1, 26.4, 26.0

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{32}NO_3$ 382.2377, found 382.2380

Compound 2.91. ***N*-(2-Hydroxy-3-phenoxypropyl)-2-phenyl-*N*-((tetrahydro-2H-pyran-4-yl)methyl)acetamide**



Synthesised according to General Experimental Procedure W using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), 4-(aminomethyl)tetrahydropyran (113 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (60% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (104 mg, 27%).

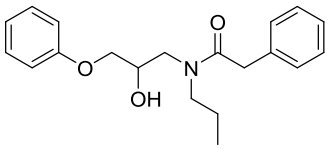
ν_{max} (neat): 3363, 3058, 3026, 2922, 2841, 1619, 1599, 1240, 1093, 756, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 7H), 6.98 – 6.95 (m, 1H), 6.87 – 6.86 (m, 2H), 4.57 – 4.54 (m, 1H), 4.18 (br. s, 1H), 4.03 – 3.96 (m, 3H), 3.86 – 3.82 (m, 1H), 3.79 – 3.75 (m, 3H), 3.60 – 3.57 (m, 1H), 3.35 – 3.30 (m, 3H), 3.27 – 3.21 (m, 1H), 1.89 (br. s, 1H), 1.59 – 1.55 (m, 2H), 1.35 – 1.22 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.4, 158.4, 134.7, 129.8, 129.0, 128.9, 127.3, 121.4, 114.5, 70.6, 69.1, 67.6, 56.2, 52.2, 40.9, 35.1, 30.9

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{30}NO_4$ 384.2169 , found 384.2171

Compound 2.92. ***N*-(2-Hydroxy-3-phenoxypropyl)-2-phenyl-*N*-propylacetamide**



Synthesised according to General Experimental Procedure W using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), 1-propylamine (82 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (313 mg, 96%).

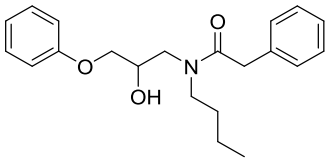
ν_{max} (neat): 3361, 3060, 3026, 2960, 2930, 2872, 1619, 1599, 1244, 1043, 755, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.30 (m, 2H), 7.28 – 7.24 (m, 5H), 6.97 – 6.94 (m, 1H), 6.87 – 6.85 (m, 2H), 4.64 – 4.63 (m, 1H), 4.16 – 4.13 (m, 1H), 3.98 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.82 (dd, *J* = 9.4, 7.3 Hz, 1H), 3.74 – 3.68 (m, 3H), 3.55 (dd, *J* = 14.4, 2.5 Hz, 1H), 3.36 – 3.30 (m, 1H), 3.28 – 3.22 (m, 1H), 1.62 – 1.49 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 158.5, 134.9, 129.7, 128.9 (2), 127.2, 121.3, 114.6, 70.7, 69.3, 52.2, 51.5, 40.9, 22.1, 11.3

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{26}NO_3$ 328.1907, found 328.1909

Compound 2.93. ***N*-Butyl-*N*-(2-hydroxy-3-phenoxypropyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure W using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), 1-butylamine (99 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a cloudy white oil (251 mg, 73%).

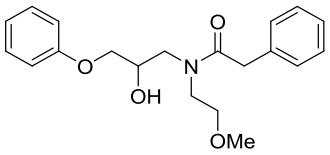
ν_{max} (neat): 3318, 3060, 3026, 2954, 2928, 2870, 1619, 1599, 1244, 755, 693 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.28 (m, 2H), 7.25 – 7.21 (m, 5H), 6.98 – 6.94 (m, 1H), 6.87 – 6.86 (m, 2H), 4.64 (br. s, 1H), 4.15 – 4.10 (m, 1H), 3.96 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.79 (dd, *J* = 9.4, 7.4 Hz, 1H), 3.72 – 3.66 (m, 3H), 3.56 – 3.51 (m, 1H), 3.37 – 3.20 (m, 2H), 1.53 – 1.43 (m, 2H), 1.31 – 1.25 (m, 2H), 0.89 – 0.85 (m, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0, 158.3, 134.7, 129.5, 128.8, 128.7, 127.0, 121.1, 114.4, 70.6, 69.0, 51.4, 50.3, 40.7, 30.8, 20.0, 13.7

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{28}NO_3$ 342.2064, found 342.2066

Compound 2.95. ***N*-(2-Hydroxy-3-phenoxypropyl)-*N*-(2-methoxyethyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure W using glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), 2-methoxyethylamine (87 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (50% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a cloudy yellow oil (312 mg, 91%).

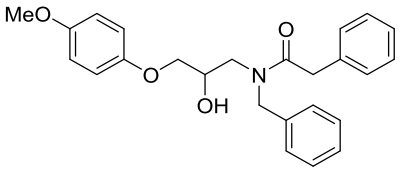
ν_{max} (neat): 3367, 3060, 3026, 2924, 2876, 1621, 1599, 1244, 1113, 756 693 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d6): δ 7.31 – 7.27 (m, 4H), 7.23 – 7.19 (m, 3H), 6.96 – 6.89 (m, 3H), 5.25 (br. s, 0.5H), 4.98 (br. s, 0.5 H) 4.06 (br. s, 1H), 3.93 – 3.72 (m, 4H), 3.61 – 3.47(m, 5H), 3.27 – 3.23 (m, 3H) (mixture of rotamers, exchangeable proton not observed)

^{13}C NMR (101 MHz, DMSO-d6): δ 171.0, 170.6, 158.5, 158.3, 135.9, 134.9, 129.2 (2), 128.8 (2), 128.7, 127.9, 125.9 (2), 120.5, 120.3, 114.4 (2), 70.5, 70.1, 69.7, 69.4, 67.6, 67.5, 58.0, 57.7, 51.2, 49.2, 48.3, 45.4 (mixture of rotamers, peaks relating to one alkyl carbon not observed – presumed coincident with DMSO-d6)

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{26}NO_4$ 344.1856, found 344.1860

Compound 2.96. ***N*-Benzyl-*N*-(2-hydroxy-3-(4-methoxyphenoxy)propyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure X using glycidyl 4-methoxyphenyl ether (180 mg, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a colourless oil (141 mg, 35%).

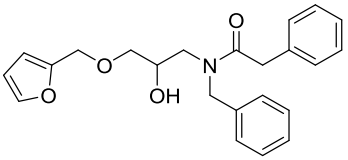
ν_{max} (neat): 3389, 3026, 2928, 2831, 1619, 1508, 1230, 1032, 825, 697 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.31 (m, 5H), 7.28 – 7.24 (m, 3H), 7.14 – 7.12 (m, 2H), 6.82 – 6.75 (m, 4H), 4.68 – 4.58 (m, 2H), 4.29 – 4.28 (m, 1H), 4.16 – 4.14 (m, 1H), 3.89 (dd, *J* = 9.4, 5.3 Hz, 1H), 3.81 – 3.70 (m, 7H), 3.64 (dd, *J* = 14.4, 2.7 Hz, 1H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.6, 154.2, 152.6, 136.3, 134.6, 129.2, 129.0, 128.9, 128.0, 127.2, 126.6, 115.5, 114.8, 70.4, 70.0, 55.9, 53.6, 51.3, 41.0

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{28}NO_4$ 406.2013, found 406.2008

Compound 2.97. ***N*-Benzyl-*N*-(3-(furan-2-ylmethoxy)-2-hydroxypropyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure X using furfuryl glycidyl ether (137 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (35% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as an orange oil (106 mg, 28%).

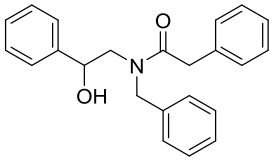
ν_{max} (neat): 3387, 3026, 2900, 2857, 1621, 1076, 734, 697 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.18 (m, 9H), 7.11 – 7.10 (m, 2H), 6.32 – 6.31 (m, 1H), 6.27 – 6.26 (m, 1H), 4.62 – 4.53 (m, 2H), 4.47 – 4.38 (m, 2H), 3.98 (br. s, 2H), 3.72 (s, 2H), 3.58 – 3.50 (m, 2H), 3.45 – 3.38 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.3, 151.5, 143.0, 136.6, 134.8, 129.1, 128.9, 128.9, 127.8, 127.1, 126.5, 110.5, 109.7, 71.6, 70.5, 65.2, 53.3, 51.2, 41.0

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{26}NO_4$ 380.1856, found 380.1858

Compound 2.98. ***N*-Benzyl-*N*-(2-hydroxy-2-phenylethyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure X using phenyl oxirane (114 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a white oil (166 mg, 48%).

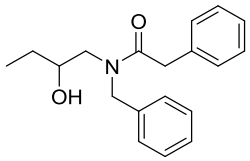
ν_{max} (neat): 3382, 3058, 3026, 1619, 1452, 697 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.32 (m, 4H), 7.31 – 7.25 (m, 9H), 7.06 – 7.05 (m, 2H), 4.93 (dd, *J* = 7.7, 2.7 Hz, 1H), 4.52 – 4.49 (m, 1H), 4.21 – 4.18 (m, 1H), 3.76 (s, 2H), 3.73 – 3.68 (m, 1H), 3.63 – 3.57 (m, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.3, 142.4, 136.1, 134.6, 129.2, 129.0 (2), 128.5, 128.0, 127.7, 127.2, 126.6, 125.9, 74.2, 56.0, 53.5, 41.0

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{24}NO_2$ 346.1802, found 346.1804

Compound 2.99. ***N*-Benzyl-*N*-(2-hydroxybutyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure X using 1,2-epoxybutane (87 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow oil (87 mg, 29%).

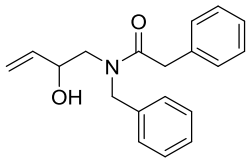
ν_{max} (neat): 3387, 3060, 3026, 2960, 2930, 2874, 1621, 1452, 697 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.32 (m, 6H), 7.25 – 7.23 (m, 2H), 7.13 – 7.11 (m, 2H), 4.66 – 4.56 (m, 2H), 3.75 (s, 2H), 3.71 – 3.68 (m, 1H), 3.66 – 3.63 (m, 1H), 3.22 (dd, *J* = 13.8, 1.7 Hz, 1H), 1.44 – 1.39 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H) (exchangeable proton not observed)

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0, 136.2, 134.6, 129.0, 128.8, 128.7, 127.8, 127.0, 126.4, 73.0, 53.6, 53.2, 40.9, 28.5, 9.7

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{24}NO_2$ 298.1802, found 298.1801

Compound 2.103. ***N*-Benzyl-*N*-(2-hydroxybut-3-en-1-yl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure X using butadiene monoxide (81 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow oil (161 mg, 54%).

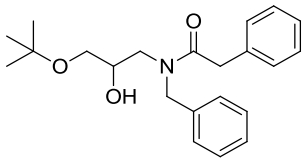
ν_{max} (neat): 3376, 3060, 3026, 2930, 1621, 1452, 697 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.29 (m, 6H), 7.25 – 7.23 (m, 2H), 7.13 – 7.11 (m, 2H), 5.82 – 5.76 (m, 1H), 5.32 – 5.29 (m, 1H), 5.13 – 5.11 (m, 1H), 4.67 – 4.56 (m, 2H), 4.35 (br. s, 1H), 3.83 (br. s, 1H), 3.75 (s, 2H), 3.59 (dd, *J* = 14.3, 7.9 Hz, 1H), 3.45 (dd, *J* = 14.3, 2.9 Hz, 1H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.3, 138.4, 136.3, 134.7, 129.2, 128.9, 128.9, 128.0, 127.2, 126.5, 115.9, 72.7, 53.6, 53.5, 41.0

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{22}NO_2$ 296.1645, found 296.1646

Compound 2.105. ***N*-Benzyl-*N*-(3-(*tert*-butoxy)-2-hydroxypropyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure X using *tert*-butyl glycidyl ether (142 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow solid (86 mg, 24%).

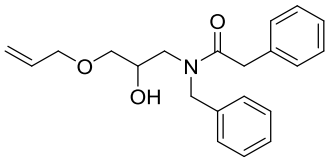
ν_{max} (neat): 3365, 3062, 3030, 2969, 2921, 2870, 1627, 1072, 699 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.35 (m, 2H), 7.31 – 7.30 (m, 4H), 7.24 – 7.23 (m, 2H), 7.15 – 7.13 (m, 2H), 4.66 (s, 2H), 3.90 (br.s, 2H), 3.74 (s, 2H), 3.56 – 3.53 (m, 1H) 3.32 – 3.26 (m, 2H), 1.13 (s, 9H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.7, 171.9, 137.7, 136.6, 135.4, 134.8, 129.0 (2), 128.8, 128.7, 128.6, 128.5, 128.1, 127.7, 127.3, 127.0, 126.8, 126.4 73.6, 73.2, 71.1, 69.1, 63.4, 62.9, 53.2, 50.8, 49.8, 48.9, 40.9, 40.8, 27.5, 27.5 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{30}NO_3$ 356.2220, found 356.2221

Compound 2.106. ***N*-(3-(Allyloxy)-2-hydroxypropyl)-*N*-benzyl-2-phenylacetamide**



Synthesised according to General Experimental Procedure X using allyl glycidyl ether (119 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow oil (128 mg, 41%).

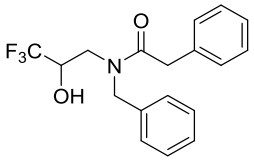
ν_{max} (neat): 3385, 3026, 2915, 2848, 1621, 1078, 697 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.30 (m, 5H) 7.26 – 7.22 (m, 3H), 7.14 – 7.12 (m, 2H), 5.88 – 5.80 (m, 1H), 5.24 – 5.14 (m, 2H), 4.68 – 4.60 (m, 2H), 4.00 – 3.88 (m, 5H), 3.74 (s, 2H), 3.60 – 3.52 (m, 1H), 3.40 – 3.37 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 172.1, 137.7, 136.5, 135.5, 134.8, 134.5, 134.2, 129.1 (2), 128.9 (2), 128.8, 128.7, 128.2, 127.8, 127.5, 127.1, 126.9, 126.5, 117.8, 117.3, 72.5, 72.4, 72.0, 71.6, 70.6, 69.1, 53.4, 51.2, 49.8, 49.1, 41.0, 40.9 (mixture of rotamers)

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{26}NO_3$ 340.1907, found 340.1906

Compound 2.107. ***N*-Benzyl-2-phenyl-*N*-(3,3,3-trifluoro-2-hydroxypropyl)acetamide**



Synthesised according to General Experimental Procedure X using 2-(trifluoromethyl)oxirane (86 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (20% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow oil (233 mg, 69%).

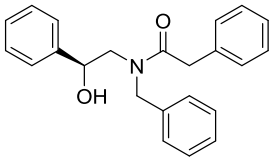
ν_{max} (neat): 3322, 3028, 1623, 1268, 1165, 1119, 695 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.33 (m, 5H), 7.30 – 7.27 (m, 1H), 7.24 – 7.23 (m, 2H), 7.11 – 7.09 (m, 2H), 5.11 (d, *J* = 5.0 Hz, 1H), 4.69 – 4.53 (m, 2H), 4.05 – 4.00 (m, 1H), 3.91 (dd, *J* = 14.6, 8.5 Hz, 1H), 3.80 (s, 2H), 3.48 (dd, *J* = 14.6, 2.1 Hz, 1H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.4, 135.2, 133.9, 129.3, 129.0, 128.8, 128.3, 127.3, 126.5, 125.5 (q, $^{1}J_{CF}$ = 282.6 Hz), 70.5 (q, $^{2}J_{CF}$ = 30.6 Hz), 53.6, 48.3, 40.8

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{19}F_3NO_2$ 338.1362, found 338.1362

Compound 2.109. **(*S*)-*N*-Benzyl-*N*-(2-hydroxy-2-phenylethyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure X using (*S*)-phenyloxirane (114 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a clear oil (310 mg, 90%).

ν_{max} (neat): 3374, 3056, 3025, 1619, 1452, 697 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.33 (m, 4H), 7.31 – 7.22 (m, 9H), 7.06 – 7.05 (m, 2H), 4.95 – 4.92 (m, 1H), 4.57 – 4.49 (m, 1H), 4.22 – 4.18 (m, 1H), 3.76 (s, 2H), 3.71 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.59 (dd, *J* = 14.3, 2.8 Hz, 1H) (exchangeable proton not observed)

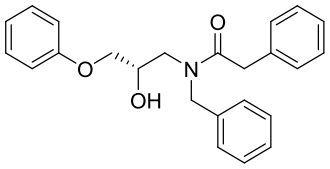
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7, 142.4, 136.1, 134.6, 129.2, 129.0 (2), 128.5, 128.0, 127.7, 127.2, 126.6, 125.9, 74.2, 56.0, 53.5, 41.0

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{24}NO_2$ 346.1802, found 346.1802

ee: >99%

$[\alpha]_D^{20}$ = 51.6 (c = 1, DCM)

Compound 2.110. **(*S*)-*N*-Benzyl-*N*-(2-hydroxy-3-phenoxypropyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure X using (*S*)-glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.) and methyl phenylacetate (140 µL, 1 mmol, 1 equiv.), and purified by flash column chromatography (30% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a pale yellow oil (260 mg, 69%).

ν_{max} (neat): 3361, 3058, 3025, 2924, 1621, 1599, 1495, 1242, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.31 (m, 5H), 7.30 – 7.24 (m, 5H), 7.14 – 7.12 (m, 2H), 6.97 – 6.94 (m, 1H), 6.84 – 6.83 (m, 2H), 4.71 – 4.60 (m, 2H), 4.19 – 4.15 (m, 1H), 3.95 (dd, *J* = 9.5, 5.3 Hz, 1H), 3.84 (dd, *J* = 9.5, 6.9 Hz, 1H), 3.78 – 3.72 (m, 3H), 3.66 – 3.63 (m, 1H) (exchangeable proton not observed)

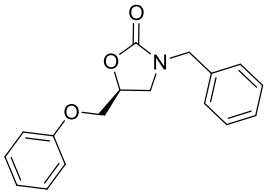
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.5, 158.3, 136.1, 134.5, 129.5, 129.1, 128.9, 128.8, 127.9, 127.1, 126.5, 121.2, 114.5, 70.3, 69.1, 53.5, 51.2, 40.9

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{26}NO_3$ 376.1907, found 376.1908

ee: >99%

$[\alpha]_D^{20}$ = -9.26 (c = 1, DCM)

Compound 2.112. **(*S*)-3-Benzyl-5-(phenoxymethyl)oxazolidin-2-one**.



To an oven-dried, purged and sealed 2 – 5 mL microwave vial was added dimethylcarbonate (84 µL, 1 mmol, 1 equiv.), glycidyl phenyl ether (135 µL, 1 mmol, 1 equiv.), benzylamine (109 µL, 1 mmol, 1 equiv.), BEMP (29 µL, 0.1 mmol, 0.1 equiv.) and MeCN (0.5 mL). The reaction mixture was then heated at 70 °C for 24 h, at which point the reaction was concentrated *in vacuo* and the resulting residue purified by silica column chromatography (25% EtOAc/Petroleum ether 40 – 60 °C) and strong cation exchange chromatography (MeOH) to afford the title compound as a white solid (270 mg, 95%).

ν_{max} (neat): 3057, 3040, 2959, 2923, 2866, 1733, 1447, 1244, 1063, 755, 740 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.35 (m, 2H), 7.33 – 7.26 (m, 5H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.86 – 6.84 (m, 2H), 4.84 – 4.79 (m, 1H), 4.51 – 4.43 (m, 2H) , 4.12 – 4.07 (m, 2H), 3.57 (t, *J* = 8.9 Hz, 1H), 3.44 (dd, *J* = 8.8, 6.0 Hz, 1H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.2, 157.8, 135.7, 129.7, 129.0, 128.3, 128.2, 121.7, 114.7, 71.0, 68.2, 48.5, 46.2

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{18}NO_3$ 284.1281, found 284.1281

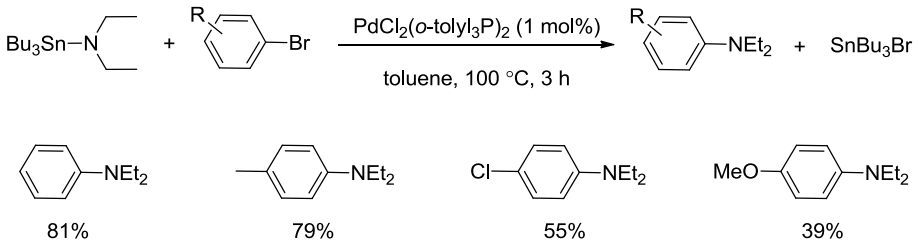
ee: 99%

$[\alpha]_D^{20}$ = 69.67 (c = 1, DCM)

3. Chapter 3 - Transition Metal Catalysed Synthesis of Aryl Amides *via* the Silanoate-Mediated Hydrolysis of Nitriles

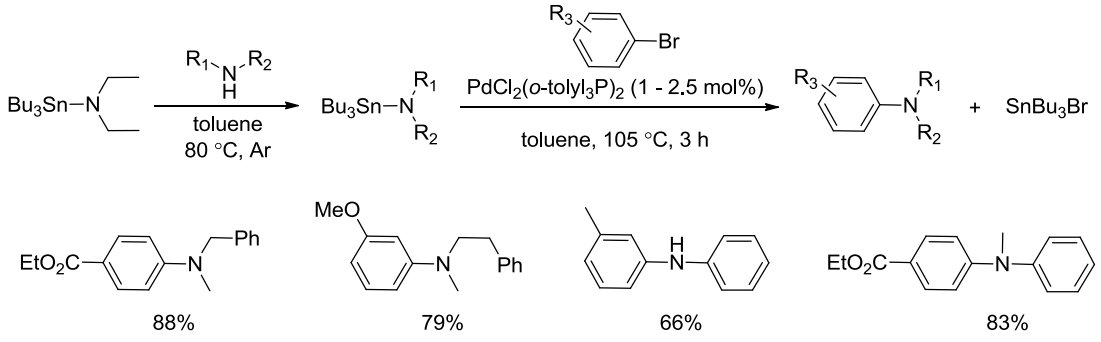
3.1 Introduction

The use of palladium to catalyse the cross-coupling of an amine and an aryl halide was first reported by Migita *et al* in 1983.[138] The formation of a new carbon-nitrogen bond between *N*,*N*-diethylaminotributyltin and an aryl bromide to generate the corresponding *N*,*N*-diethylaniline species was successfully demonstrated, with tributyltin bromide formed as a stoichiometric by-product (Scheme 3.1).[138] However, this methodology was limited by the small range of aminostannanes commercially available, in addition to the thermal and moisture sensitive nature of these reagents. Furthermore, efficient amination reactions were limited to electron-neutral aryl bromides with both electron-deficient and electron-rich aryl halides found to give poor yields.



Scheme 3.1: The first reported palladium catalysed cross coupling forming C-N bonds.[138]

Some of these limitations were overcome by Buchwald and Guram *via* the transamination of *N*,*N*-diethylaminotributyltin to form aminotin reagents *in situ* (Scheme 3.2).[139] However, the application of this process was still hindered by the requirement for stoichiometric organotin reagents.

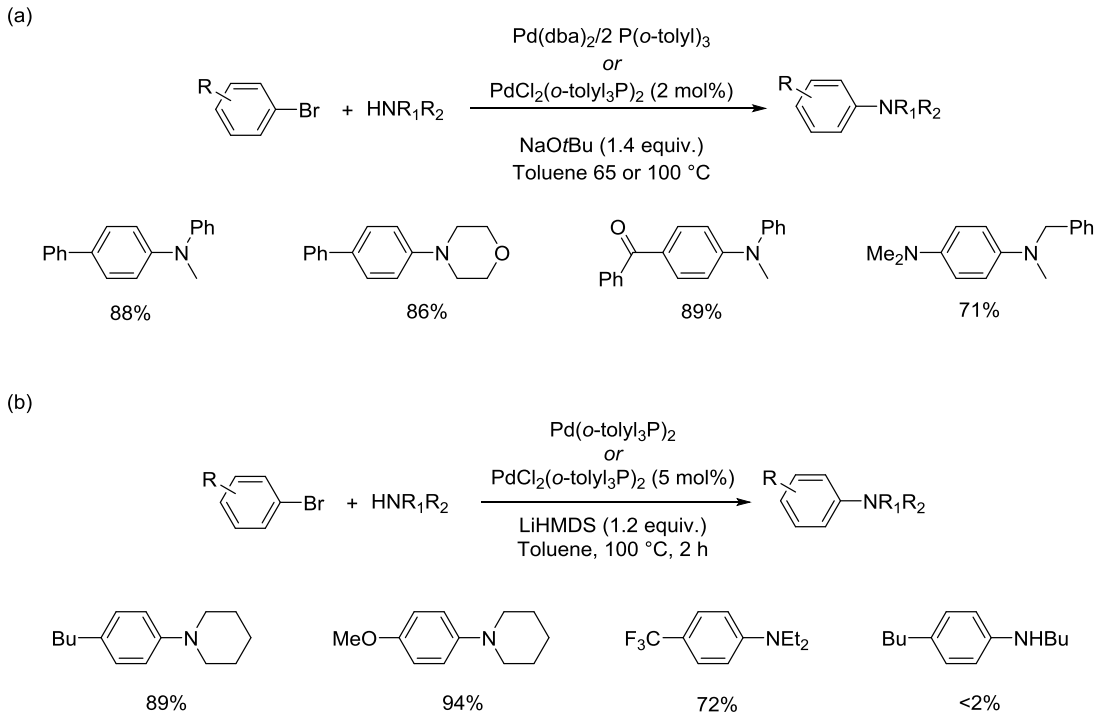


Scheme 3.2: *In situ* formation of aminotin reagents followed by Pd catalysed cross-coupling.[139]

3.1.1 Development of the Buchwald-Hartwig Amination

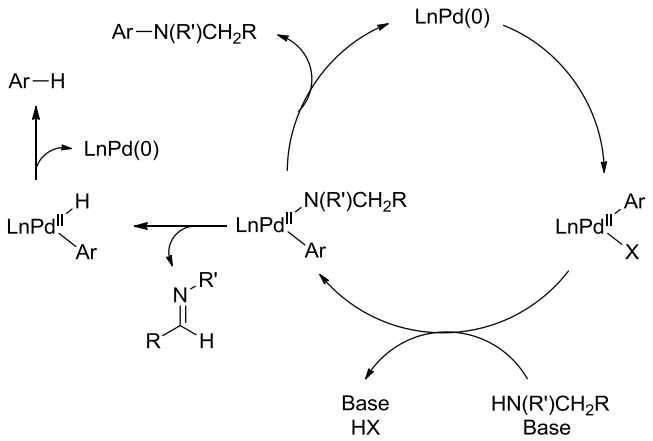
3.1.1.1 Initial Tin-free Coupling Conditions

The amination of aryl halides in the absence of tin reagents was reported concurrently by the Buchwald and Hartwig groups in 1995, with both groups employing the use of P(*o*-tolyl)$_3$ as the ligand species in conjunction with either an alkoxide or silylamide base (Scheme 3.3).[140,141] Secondary amines were shown to be competent coupling partners, however little corresponding product was observed when the coupling of primary amines was attempted using the reaction conditions.



Scheme 3.3: (a) Buchwald and co-workers tin-free cross-coupling of aryl halides and amines.[140] **(b) Louie and Hartwig's tin-free cross-coupling of aryl halides and amines.**[141]

A catalytic cycle for the reaction was postulated, with a Pd(0) species proposed to be the active catalyst. The cycle was suggested to involve oxidative addition of the aryl halide, followed by coordination and deprotonation of the amine, with a reductive elimination step furnishing the amine product and regenerating the catalyst (Scheme 3.4).[140] An alternative pathway, in competition with the reductive elimination of the desired product, is the formation of an arene and an imine *via* a β-hydride elimination process.[140] This competing pathway becomes increasingly prevalent when using electron-rich halides as these species undergo reductive elimination less readily than electron-poor halides.[140]

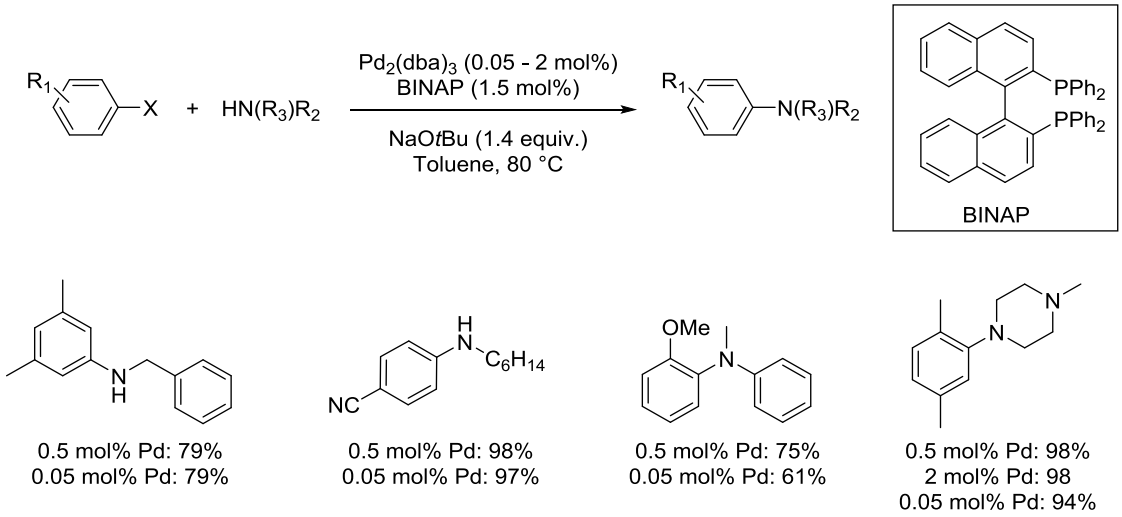


Scheme 3.4: Proposed catalytic cycle for the tin-free cross-coupling of amines and aryl halides.[140]

3.1.1.2 Second Generation Buchwald-Hartwig Catalysts

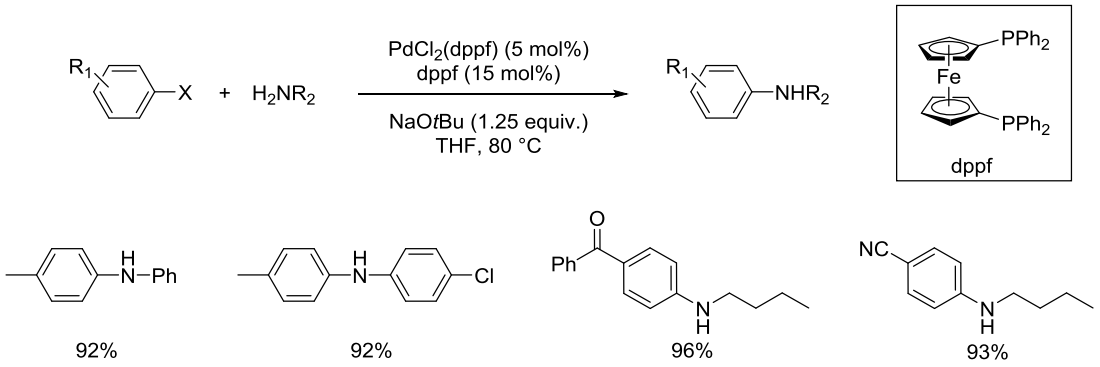
With the scope of the first generation cross-coupling conditions relatively narrow, efforts in both the Buchwald and Hartwig groups focused on moving away from the use of the sterically hindered P(*o*-tolyl)$_3$ ligand and towards the development of further catalyst systems.

Buchwald *et al.* reported the use of BINAP as the ligand species in conjunction with NaO*t*Bu and $Pd_2(dba)_3$ to facilitate the cross-coupling of aryl bromides with both primary and secondary amines (Scheme 3.5).[142] Additionally, catalyst loadings as low as 0.05 mol% were found to efficiently facilitate the desired cross-coupling reaction using suitable substrates.[142]



Scheme 3.5: Selected examples of Pd catalysed cross-couplings of aryl bromides and amines using BINAP.[142]

The Hartwig group reported the use of the ligand 1,1'-bis(diphenylphosphino)ferrocene (dppf), also in conjunction with NaO*t*Bu, in the amination of aryl halides with anilines, with near quantitative yields achieved (Scheme 3.6).[143] Electron-poor and electron-rich aryl bromides and iodides were shown to be competent substrates within the reaction manifold, with both sterically hindered and unhindered substrates also compatible.[143] Alkyl amines were also demonstrated to couple in good to excellent yields with both electron-neutral and electron-poor aryl halides.[143]

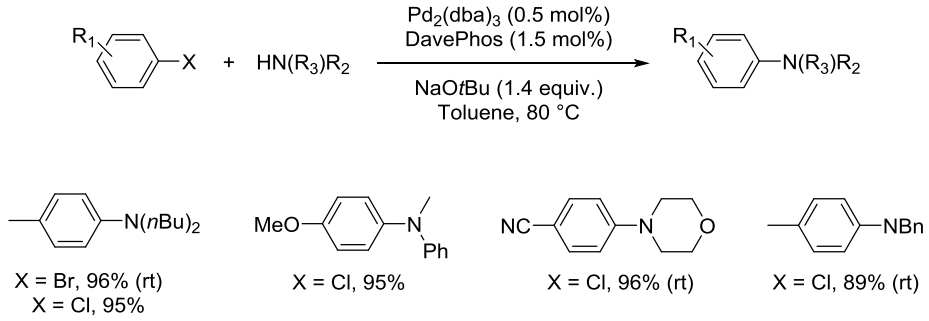


Scheme 3.6: Selected examples of the Pd catalysed cross-coupling of aryl bromides and amines using dppf.[143]

3.1.1.3 Third Generation Buchwald-Hartwig Catalysts

With a view to extending the ubiquity of the cross-coupling process, further development of the ligand species was reported by the Buchwald and Hartwig groups.

^{1}H NMR studies indicated that the oxidative addition of aryl bromides within BINAP catalyst systems was rate-limiting, the Buchwald group explored the use of more electron-rich phosphine ligands in an effort to overcome this issue.[144] Efforts focused on the air-stable dialkylbiaryl phosphine ligand scaffold, with 2,2′-bis(dicyclohexylphosphino)-1,1′-binaphthyl (**3.1,** Figure 3.1) and DavePhos initially found to efficiently promote the coupling of aryl bromides and chlorides (Scheme 3.7).[144,145]



Scheme 3.7: Amination of aryl bromides and chlorides using DavePhos as the ligand species.[144]

Further investigation into this class of ligand since the initial report has led to the development of a wide number of commercially available dialkylbiaryl phosphine ligands (Figure 3.1). The development of ligands such as XPhos, SPhos and RuPhos have enabled the scope of the process to be expanded to the coupling of amines with thiophenes, 5-bromopyrimidines, benzoxazoles, benzothiazoles, 5-bromoindole and 6-chloroindole, as well as being applicable under previously reported reaction conditions.[146] The scope was further extended by the development of BrettPhos, which improves the compatibility of aryl mesylates as substrates, as well as facilitating the monoarylation of primary amines in excellent yields whilst minimising potential bisarylation.[147]

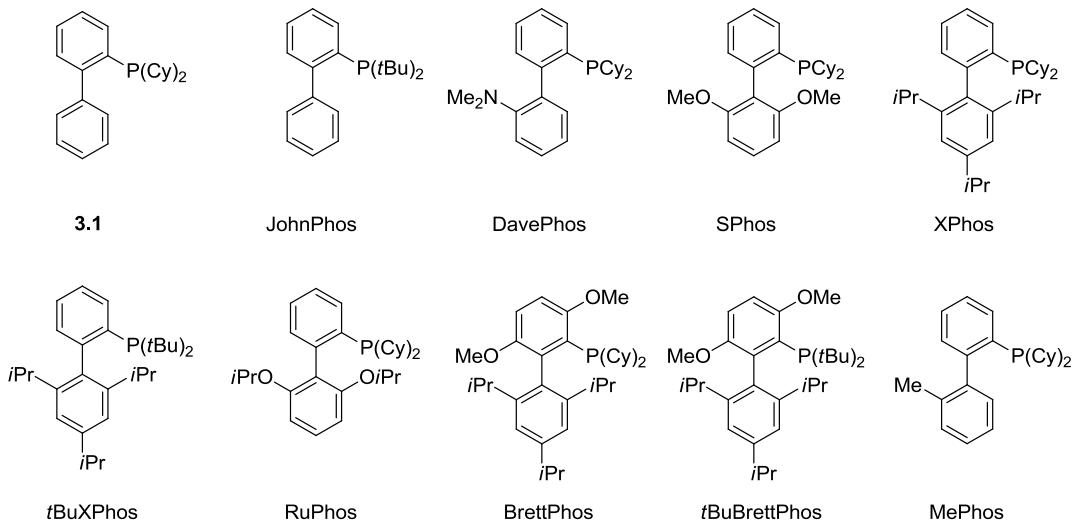


Figure 3.1: Examples of commercially available dialkylbiaryl phosphine ligands to promote the Buchwald-Hartwig amination reaction.

When using dialkylbiaryl phosphine ligands, the active catalyst species is believed to be the reactive monoligated Pd(0) species, which exists in equilibrium with the bis-ligated Pd(0) species.[148,149] The steric bulk and electron-donating character of the ligands is proposed to encourage formation of the monoligated palladium species, and hence readily promote oxidative addition.[148,149] Further studies have also shown that the size of substituents on the lower ring of the ligand species play a significant role in the rate of reaction by promoting the formation of the monoligated catalytic species, with ligands featuring bulkier substituents, for example XPhos and BrettPhos, shown to be more efficient than ligands with no substitution present on this ring.[150]

A palladium-arene interaction between the metal and the *ipso* position of the lower aryl ring of the ligand is also proposed to aid the stability of the catalyst and increase electron density at the metal centre (Figure 3.2).[148] DFT calculations have also indicated that this potential palladium-arene complex promotes the reductive elimination of the desired amine product through stabilisation of the amidopalladium intermediate and a reduction in energy of the transition state when the metal centre is proximal to lower ring of the ligand.[151,152]

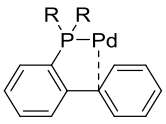
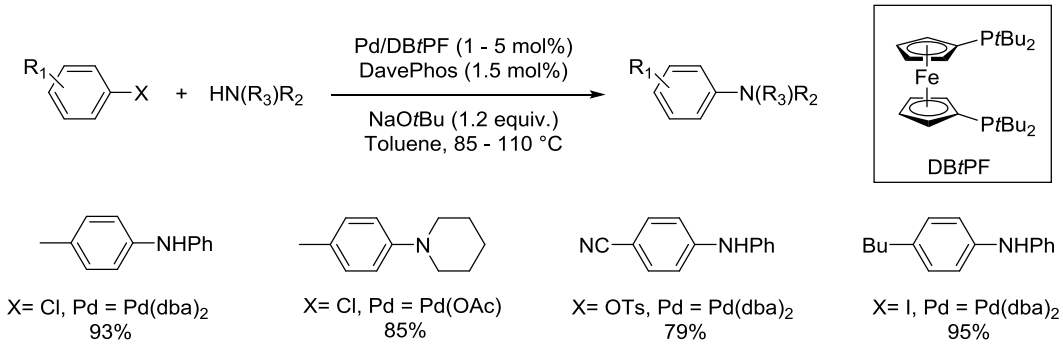


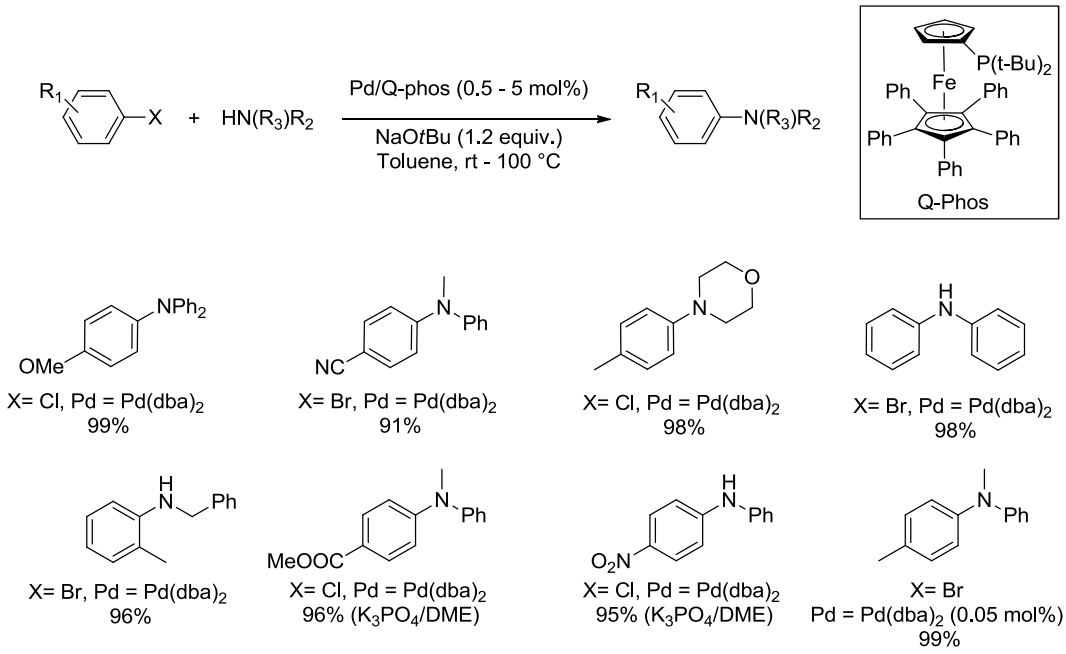
Figure 3.2: Proposed palladium-arene interaction.

In contrast to the development of dialkylbiaryl phosphine ligands by Buchwald *et al*., the Hartwig group instead focused on the development of ferrocene-derived ligands. Similarly to the Buchwald group, Hartwig and co-workers proposed that the use of these ligands would increase electron density at the metal centre, and hence promote oxidative addition. Initial studies focused on DB*t*PF, which, although air sensitive over time in solution, is easily handled in air (Scheme 3.8).[153] The use of DB*t*PF as the ligand species enabled aryl chlorides, bromides and iodides to be efficiently coupled to anilines, primary amines and cyclic secondary amines.[153] Additionally, aryl tosylates provided good yields under the cross-coupling conditions, substrates which had previously proven challenging.



Scheme 3.8: Initial report of alkyl phosphine ligands in the Buchwald-Hartwig amination.[153]

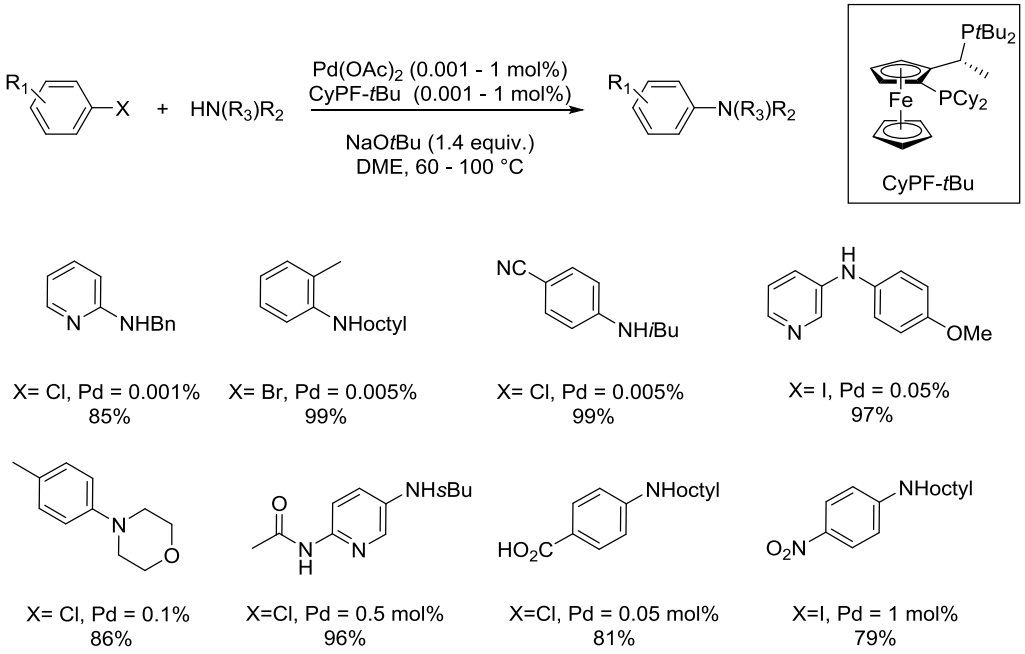
Further investigation into the effect of ferrocene based ligands in the Buchwald-Hartwig amination led to the development of the di-*tert*-butylphosphino pentaphenylferrocene ligand, Q-Phos, by Hartwig *et al*. in 2002.[154] Q-Phos, an air and solution stable ligand, was shown to be an extremely general and efficient ligand enabling the coupling of aryl bromides and chlorides with both primary and secondary aliphatic and aromatic amines (Scheme 3.9).[154] Furthermore, cross-coupling reactions with base-sensitive aryl halides, for example those with an ester or nitro substituent, could be successfully achieved when using Q-Phos in conjunction with K_3PO_4 and DME as the base and solvent respectively.[154] Loadings as low as 0.1 mol% of the corresponding catalyst species were also found to furnish arylated amines in excellent yields.[154]



Scheme 3.9: Selected Buchwald-Hartwig amination exemplars employing Q-Phos.[154]

3.1.1.4 Fourth Generation Buchwald-Hartwig Catalysts

In 2008, with the aim of extending the application of the cross-coupling amination process towards pharmaceutically relevant processes by limiting the amount of catalyst required, Hartwig *et al.* investigated the use of Josiphos ligand CyPF-*t*Bu.[155] This ligand contains two phosphine moieties which are proposed to bind strongly to the metal centre, thereby preventing ligand replacement on the catalyst and hence extending its lifespan in the reaction.[155] In addition to this, the steric and strong electron-donating characteristics of CyPF-*t*Bu should readily promote both the oxidative addition and reductive elimination steps of the catalytic cycle. It was found that the use of CyPF-*t*Bu efficiently catalysed the amination of heteroaryl and aryl chlorides, bromides and iodides with only part-per-million quantities of the palladium and ligand species required (Scheme 3.10).[155]

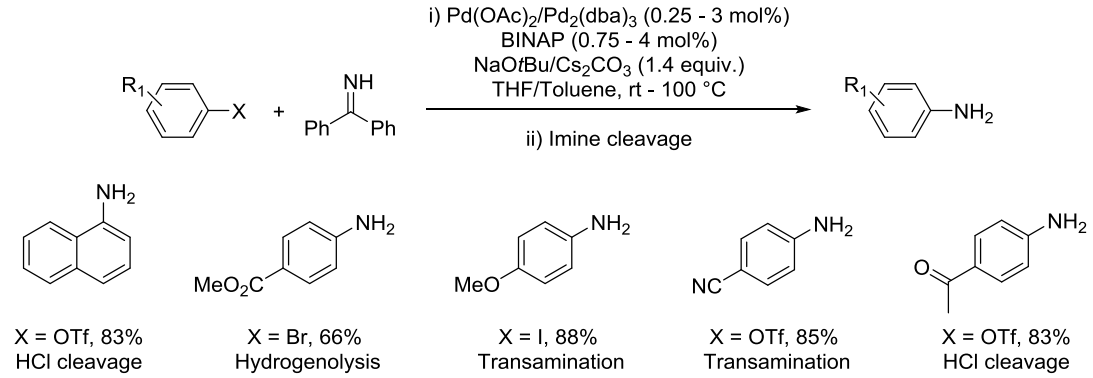


Scheme 3.10: Selected examples of the amination of aryl halides utilising the CyPF-*t*Bu ligand.[155]

3.1.2 Buchwald-Hartwig Coupling of Ammonia Surrogates

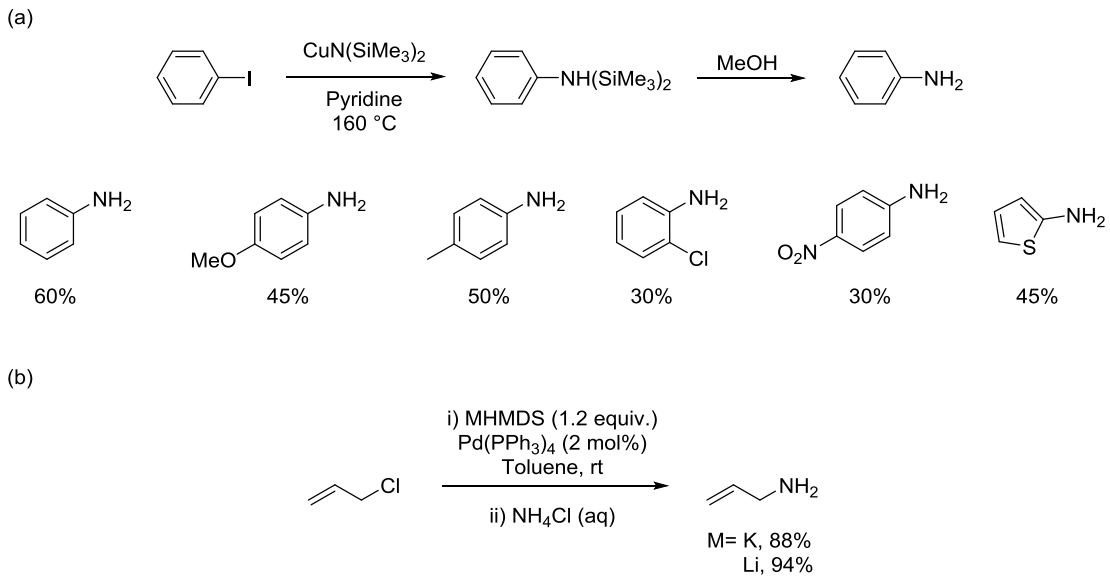
The continued development of catalyst species in the Buchwald-Hartwig amination has successfully enabled the efficient coupling of aromatic and aliphatic primary amines with aryl halides, mesylates, tosylates and triflates. However, although a readily available and inexpensive reagent, the application of ammonia to form corresponding primary arylamine derivatives has been largely neglected or has proven challenging under previously developed amination conditions. To overcome this limitation, both the Buchwald and Hartwig groups have demonstrated the use of ammonia surrogates within the cross-coupling reaction, which, after a deprotection step, furnishes the primary aryl amide species.

In 1997, Buchwald *et al*. reported that benzophenone imine could undergo the desired cross-coupling process with aryl halides and triflates in good to excellent yields (Scheme 3.11).[156] Following the coupling step, the resulting aryl imine species could be cleaved to the primary arylamine *via* several methods including transamination with hydroxylamine, hydrogenolysis and acidic hydrolysis.[156]



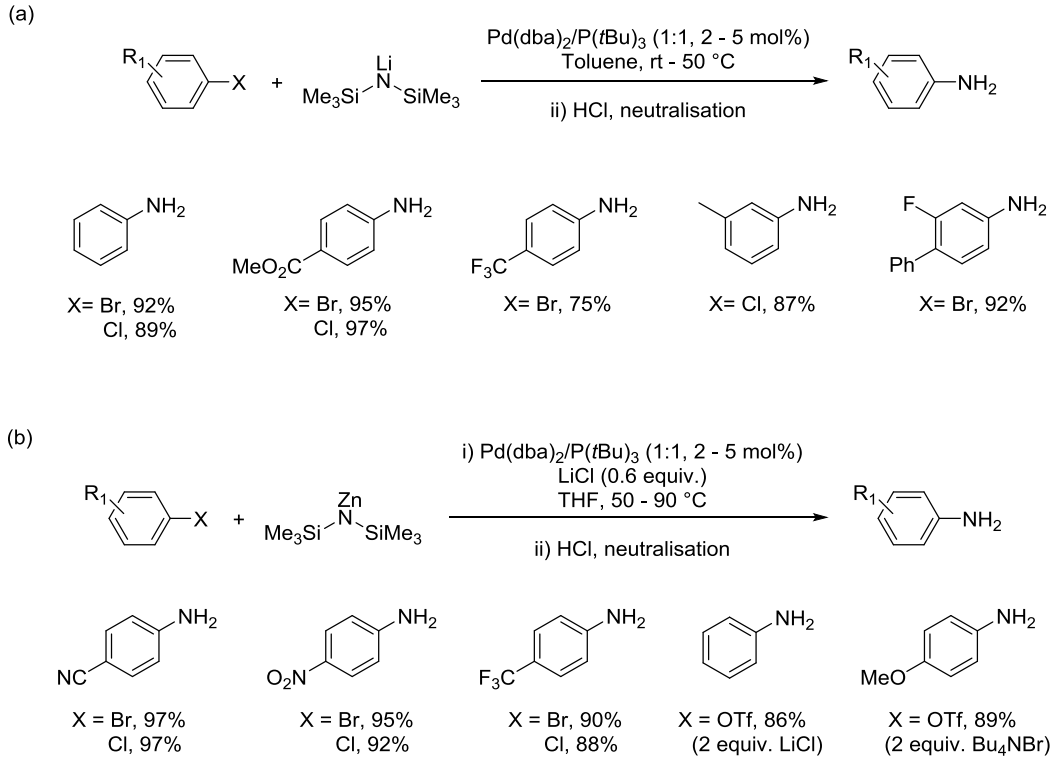
Scheme 3.11: Buchwald-Hartwig amination employing benzophenone imine as an ammonia surrogate.[156]

Metal bis(trimethylsilyl)amides, such as the lithium, sodium and potassium derivatives, have been extensively applied as a base species in the palladium catalysed amination of aryl halides. However, their application as an ammonia surrogate in metal catalysed amination reactions was limited before studies performed by Buchwald and Hartwig. In 1974, the formation of primary arylamines from aryl iodides was found to be promoted by CuHMDS in moderate yields, however a limited scope of only 6 arylamines was reported with the required formation of the protected aniline species performed at 160 °C in pyridine (Scheme 3.12a).[157] LiHMDS and KHMDS were also successfully utilised in the Pd(0) catalysed coupling of allyl chloride (Scheme 3.12b).[158]



Scheme 3.12: (a) CuHMDS as an ammonia surrogate in the amination of aryl iodides.[157] **(b) LiHMDS and KHMDS as ammonia surrogates in the amination of allyl chloride.**[158]

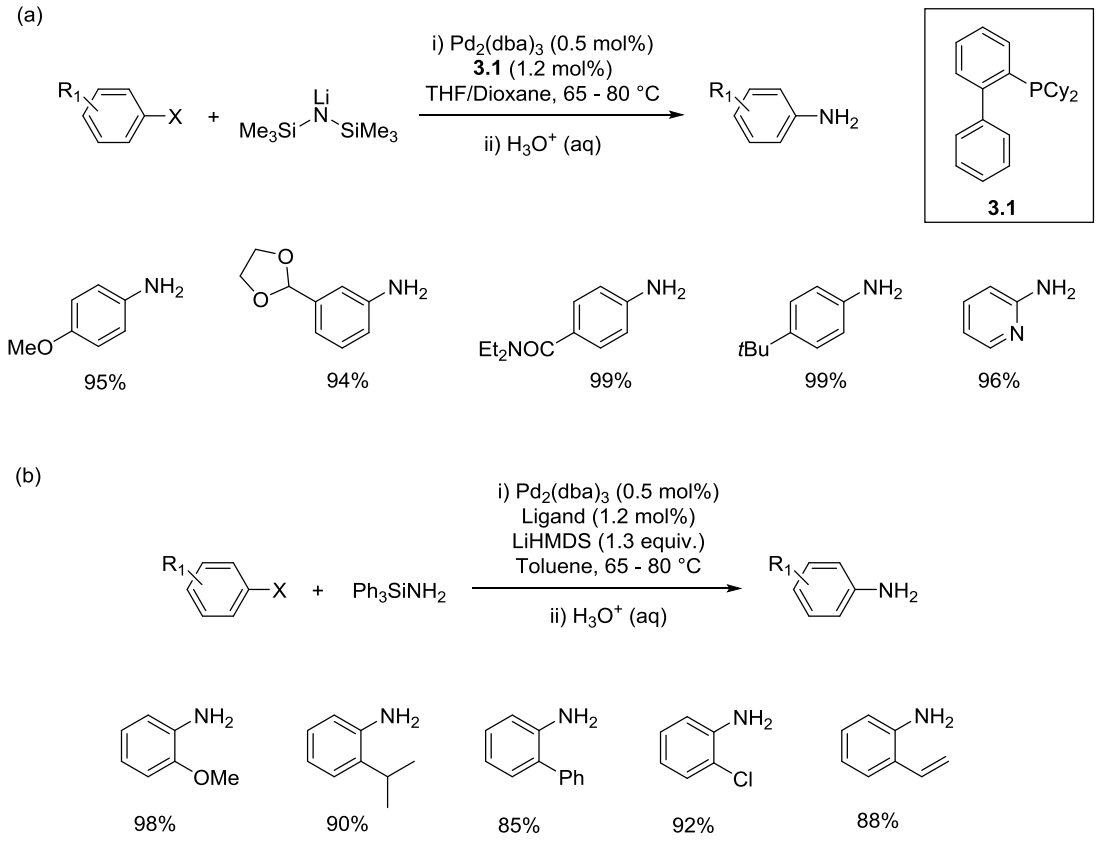
In 2001, Hartwig reported the use of LiHMDS to form anilines from the corresponding aryl bromides and chlorides using a $Pd_2(dba)_3$ and P(*t*Bu)$_3$ catalyst and ligand combination, and subsequent acid hydrolysis (Scheme 3.13a).[159] Previous attempts to use LiHMDS under catalyst conditions developed in the Hartwig group, such as using arylphosphine or dppf ligands, had proven unsuccessful in promoting the desired amination reaction, with consumption of the aryl halide resulting in poor yields at elevated temperatures and formation of two regioisomers of the silylamide product.[159] This observation was proposed to be a result of competing redox processes and benzyne formation.[159] Aryl halides featuring electron donating and withdrawing groups at the *meta* and *para* positions were found to couple efficiently, however *ortho* substitution, highly electron-withdrawing groups, and functional groups containing an enolisable centre were not tolerated under the reaction conditions.[159] More recently, the Hartwig group have also demonstrated the applicability of ZnHMDS, in conjunction with LiCl, in forming primary anilines containing base sensitive functionalities (Scheme 3.13b).[160]



Scheme 3.13: (a) Use of LiHMDS as an ammonia surrogate by Hartwig *et al.*[159] (b) Extension of the methodology to ZnHMDS.[160]

Also in 2001, Buchwald and co-workers reported their efforts in using LiHMDS as an ammonia equivalent. Using 2,2′-bis(dicyclohexylphosphino)-1,1′-binaphthyl (**3.1**) as the

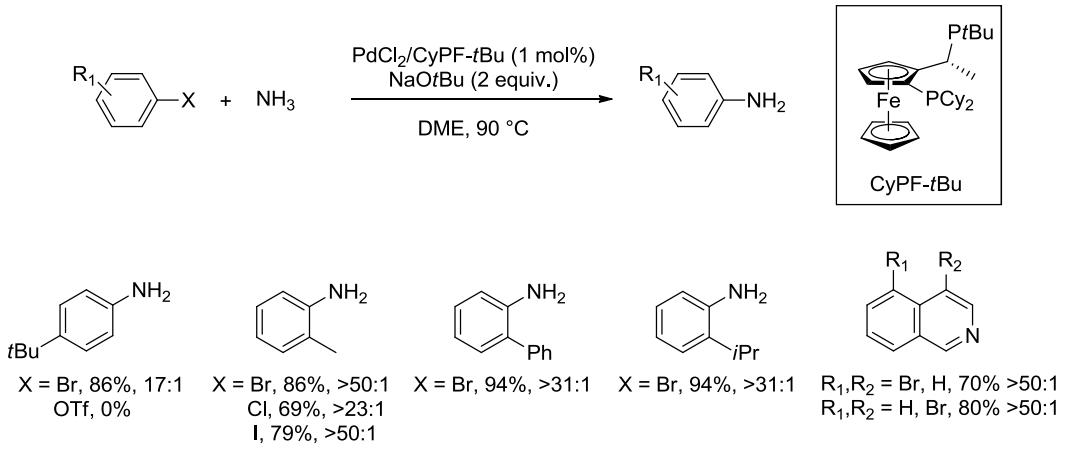
ligand species and cleaving the intermediary silylamide *via* an acidic work-up, the coupling of 5 aryl halide species was demonstrated in excellent yield using commercially available solutions of LiHMDS (Scheme 3.14a).[161] Solid LiHMDS could also be used in the reaction, however the use of a glovebox was required.[161] Buchwald *et al*. also demonstrated the use of aminotriphenylsilane as an ammonia surrogate, with a small range of anilines synthesised in excellent yields (Scheme 3.14b).[161] Aryl halides bearing *ortho* substituents were found to be compatible substrates using this latter methodology, a class of substrate that was found to be unsuited to the coupling conditions employing the use of LiHMDS as the ammonia surrogate.[161]



Scheme 3.14: (a) Use of LiHMDS as an ammonia surrogate by Buchwald *et al.* (b) Use of aminotriphenylsilane as an ammonia surrogate.[161]

In 2006, the Hartwig group successfully developed conditions to enable the direct use of ammonia in cross-coupling amination reactions with aryl bromides, chlorides, triflates and tosylates (Scheme 3.15). Utilising the fourth generation Josiphos ligand CyPF-*t*Bu, primary anilines were furnished in good to excellent yields and with good to excellent selectivities over the potential competing bis-arylated amine product.[162] *Ortho* substitution on the aryl halide was also found to be tolerated, which is an advantage over the use of LiHMDS as an

ammonia surrogate.[162] However, an excess of ammonia is required to ensure efficient coupling, with the reaction performed in DME saturated with ammonia in a bomb.[162]

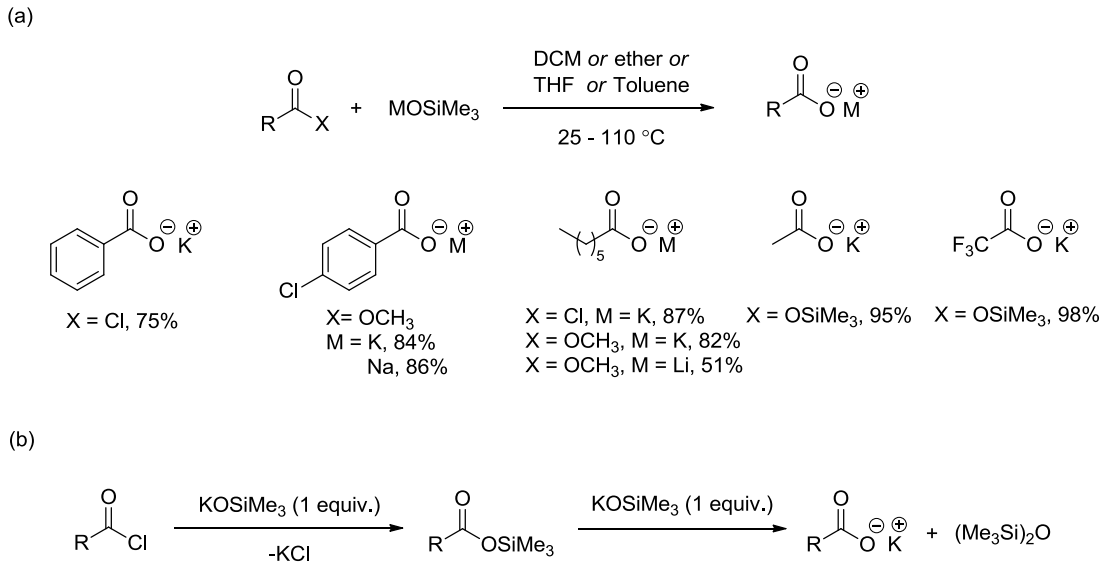


Scheme 3.15: Application of ammonia as the amine substrate in the Buchwald-Hartwig amination.[162]

3.1.3 Formation of Primary Amides *via* the Hydrolysis of Nitriles with Potassium trimethylsilanolate

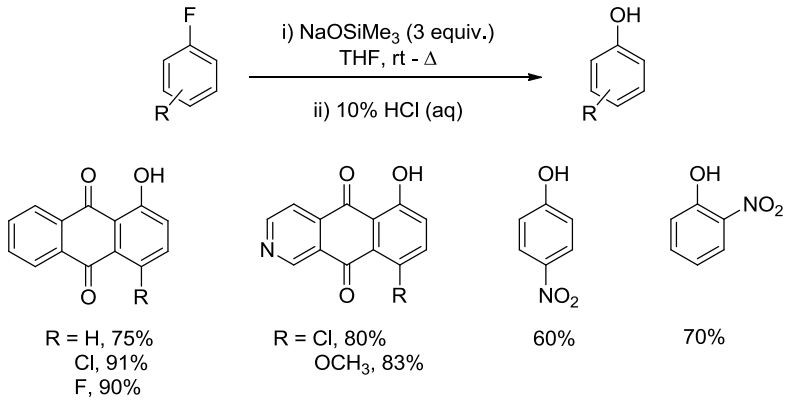
3.1.3.1 The Use of Alkali Trimethylsilanolates in Organic Chemistry

Featuring desirable characteristics such as solubility in organic solvents and an easily-cleaved silicon-oxygen bond, alkali trimethylsilanolates have been successfully applied as a hydroxyl anion equivalent in organic chemistry. However, despite these desirable properties, reports utilising alkali trimethylsilanolates in this role are somewhat limited. Their initial use, as reported by Laganis and Chenard in 1984, allowed the formation of anhydrous carboxylate salts from the corresponding esters and acid halides (Scheme 3.16a).[163] Both acid chlorides and fluorides perform competently, however in the case of acid chlorides, 2 equivalents of the alkali trimethylsilanolate are required to facilitate the transformation of an intermediary trimethylsilyl ester to the desired carboxylate salt (Scheme 3.16b).[163] With esters containing α-protons, the alkali trimethylsilanolate species behaves as a nucleophile as desired, instead of potentially behaving as a base.[163]



Scheme 3.16: Application of alkali trimethylsilanolates in the formation of carboxylate salts.[163]

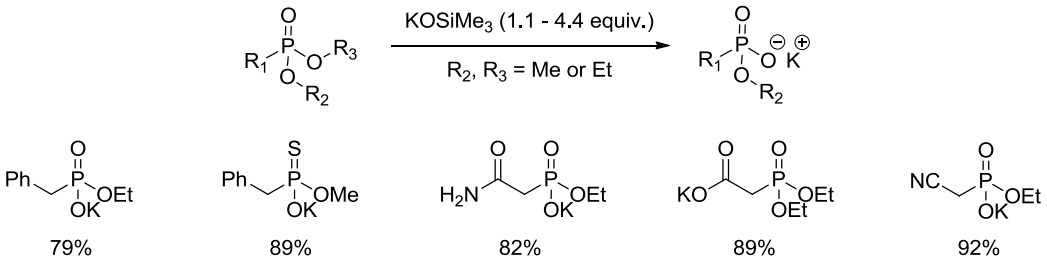
Sodium trimethylsilanolate has been utilised as a hydroxyl synthon in fluoride S_NAr *ipso* displacements. In a limited investigation undertaken by Krapcho and Waterhouse, hydroxyl groups were incorporated on fluoro substituted anthracene-9,10-diones, related aza-derivatives, and nitrobenzenes in good to excellent yields (Scheme 3.17).[164] Selectivity for the displacement of fluoride over chloride was also demonstrated, with 1-chloro-4-fluoro-anthracene-9,10-dione undergoing the desired hydroxylation reaction in 91% yield.[164]



Scheme 3.17: S_NAr displacement of aryl fluorides with sodium trimethylsilanolate.[164]

In 2004, Rachon *et al*. applied potassium trimethylsilanolate in the transformation of dialkylphosphonates to the corresponding potassium monoalkyl phosphonates (Scheme 3.18).[165] With previously established methods requiring extremely forcing conditions, this

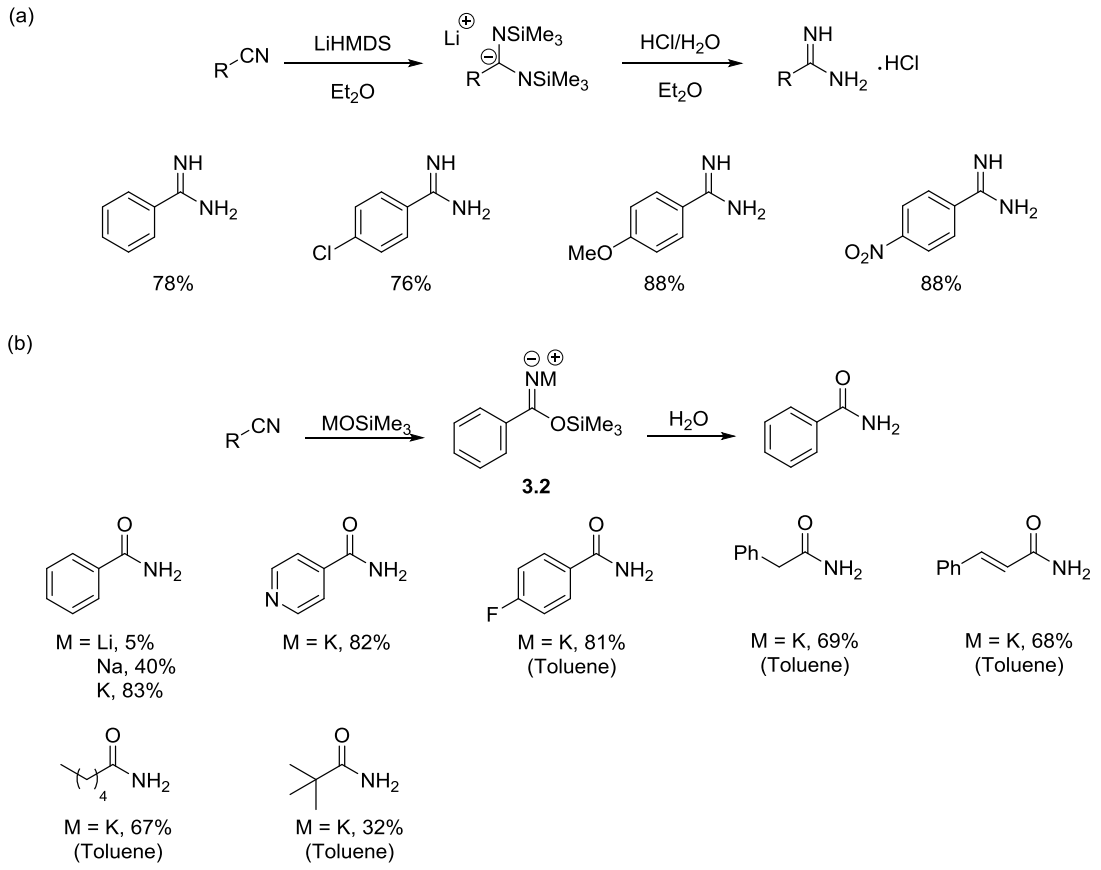
methodology allows the desired transformation to occur at ambient conditions with the incorporation of base sensitive functionalities.[165]



Scheme 3.18: Selected examples of potassium trimethylsilanolate-mediated formation of potassium monoalkyl phosphonates.[165]

3.1.3.2 Alkali Trimethylsilanolate-Mediated Hydrolysis of Nitriles

In 1987, Boeré *et al*. reported that the treatment of nitriles with LiHMDS forms the corresponding lithiated amidine derivative, with a subsequent acidic work-up furnishing the related unsubstituted amidine (Scheme 3.19a).[166] Proposing that substitution of the LiHMDS with the oxygen analogue lithium trimethylsilanolate would provide a route towards the formation of amides opposed to amidines from nitrile starting materials, Merchant successfully reported the synthesis of a range of both aromatic and aliphatic primary amides (Scheme 3.19b).[167]



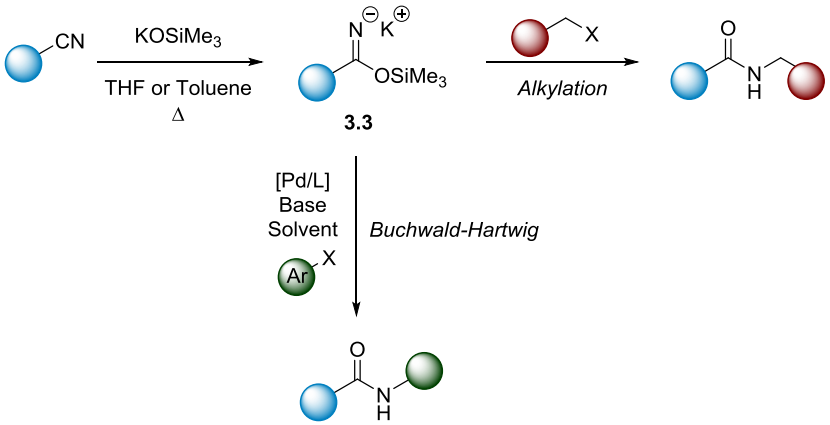
Scheme 3.19: (a) LiHMDS-mediated formation of amidines. (b) Alkali trimethylsilanolate-mediated formation of primary amides.

Upon refluxing the nitrile derivative with lithium, potassium or sodium trimethylsilanolate in anhydrous THF or toluene, an intermediate salt **3.2** precipitates from solution, halting the reaction at the amide stage and thus allowing any impurities to be removed *via* simply washing the intermediate with further volumes of the organic solvent.[167] An aqueous work-up of this intermediary salt with water yields the desired amide product.

Potassium trimethylsilanolate was found to consistently afford the amide products in greater yields than the lithium and sodium variants, an observation ascribed to the increased solubility of the lithium and sodium intermediate salts.[167] Increasing the temperature of the reaction, as required for non-activated nitriles, increased the rate of the reaction without a deleterious effect on yield.[167] Acrylonitrile derivatives, providing the potential for competing 1,4-addition, were found to undergo the desired transformation, as did fluorobenzonitriles in the absence of any fluoride S_NAr displacement.[167]

3.2 Aims

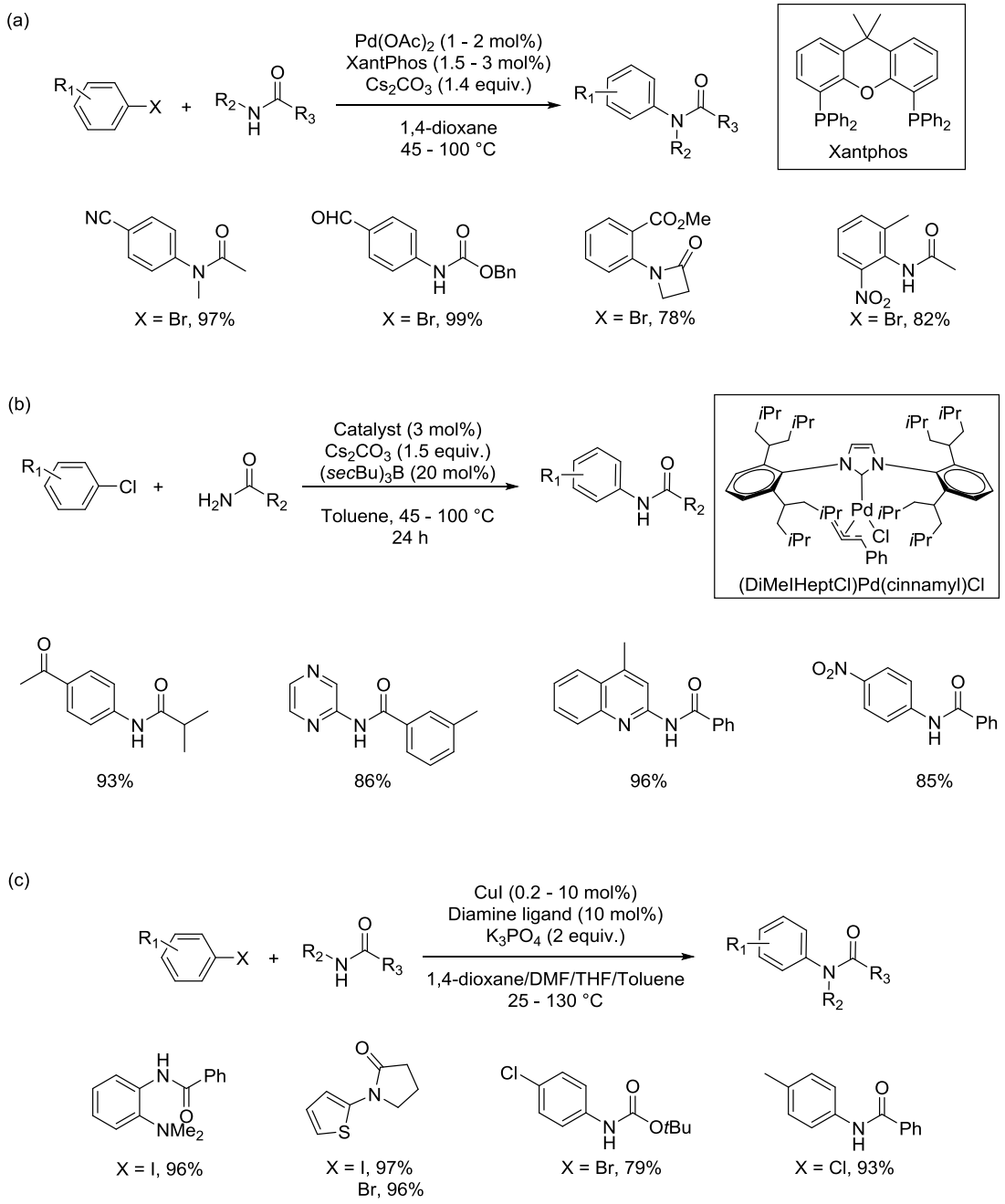
The aim of this project is to investigate whether the isolable intermediate salt (**3.3**) from the reaction of a nitrile species and potassium trimethylsilanolate, as reported by Merchant,[167] can act as an amide surrogate, with a view to synthesising secondary amide derivatives. This will be assessed *via* direct S_N2-based alkylation, and, by analogy with the palladium catalysed Buchwald-Hartwig coupling of LiHMDS (*cf.* Section 3.1.2),[159,161] through a palladium-mediated process with aryl halides (Scheme 3.20).



Scheme 3.20: Proposed routes to the formation of secondary amides utilising the silanoate-derived imidate salts and an amide surrogate.

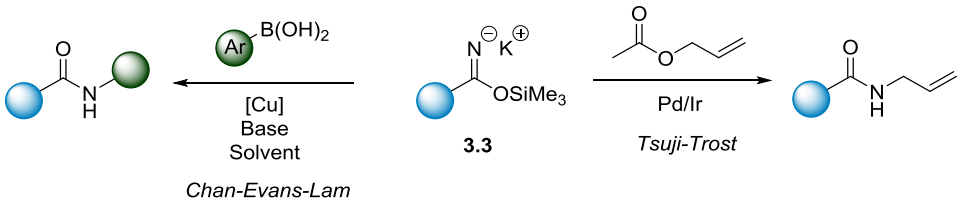
The applicability of the above processes to be performed *via* the *in situ* formation of the intermediate salt followed by an alkylation or arylation reaction, i.e. a one-pot procedure, will also be investigated. This would obviate prior isolation of the intermediate salt and increasing the practicality and sustainability of the reaction. Following optimisation, the scope of the alkylation/arylation reactions will be investigated through variation of the benzonitrile and halide components.

A Buchwald-Hartwig cross-coupling of the silanoate-derived imidate salt would represent a novel catalytic approach to amide bond formation, mitigating the requirement for the use of stoichiometric coupling reagents and, therefore, result in an atom economical amidation procedure. This approach would also be complimentary to existing procedures utilising copper and palladium to catalyse the arylation of primary and secondary amide derivatives, examples of which are shown in Scheme 3.21.



Scheme 3.21: Selected examples of: (a) $Pd(OAc)_2$ catalysed coupling of primary and secondary amides;[168] (b) Palladium catalysed coupling of primary amides and aryl chlorides;[169] (c) CuI catalysed coupling of primary and secondary amides.[170]

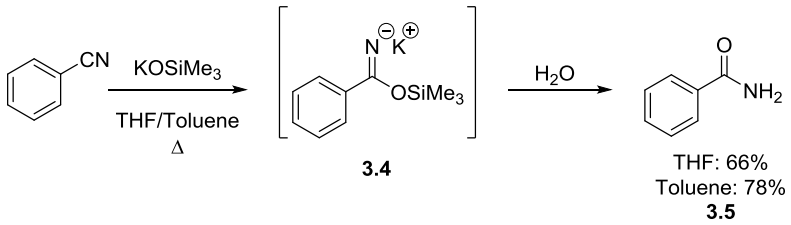
If the imidate salt intermediate proves to be a competent amide surrogate in the Buchwald-Hartwig process, its use will then be examined in further metal catalysed reaction manifolds, for example, Chan-Evans-Lam and Tsuji-Trost procedures (Scheme 3.22).



Scheme 3.22: Further catalytic process in which the silanoate-derived imidate salt could be applied as an amide surrogate.

3.3 Results and Discussion

Before commencing the investigations into the ability of the silanoate-derived imidate intermediate salt to act as an amide surrogate in the formation of secondary amides, the underpinning reaction, as reported by Merchant,[167] was validated using benzonitrile (Scheme 3.23). Potassium trimethylsilanolate was selected as the nucleophilic species instead of the lithium or sodium variants as a result of the decreased solubility of the intermediate potassium salt, therefore aiding isolation of the imidate.[167] Using both THF and toluene, the corresponding primary amide **3.5** was furnished in good yields of 66 and 78%, respectively.



Scheme 3.23: Replication of the formation of benzamide as reported by Merchant.

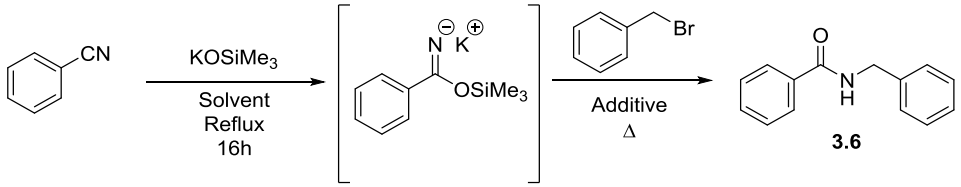
Having confirmed the reproducibility of the procedure, the applicability of the imidate salt as a nucleophilic amide surrogate was then investigated.

3.3.1 The use of the Silanoate-derived Imidate Species as an Amide Surrogate in Alkylation Reactions.

To investigate whether the nucleophilicity of the imidate salt was sufficient to enable its application in alkylation reactions, a one-pot procedure was initially examined using benzonitrile and benzyl bromide as the nitrile and electrophilic species, respectively (Table 3.1). An initial attempt, performed in refluxing THF, resulted in only an 8% conversion to the desired amide **3.6** (Entry 1). This poor conversion was proposed to be a result of the low solubility of the imidate in the reaction milieu. In an attempt to overcome this, the effect of the phase transfer catalyst TBAI on the desired amidation reaction was investigated. Unfortunately, this was found to prohibit any conversion to the amide (Entry

2). Increasing the quantity of the benzyl bromide utilised to a large excess of 5 equivalents was found to have a deleterious effect on reaction conversion, as did exchanging the solvent to DMF in an attempt to increase the solubility of the imidate salt (Entries 3 and 4). The use of microwave irradiation was also investigated, however only a 6% conversion to amide **3.6** was observed after a reaction time of 1 hour at 140 °C (Entry 5).

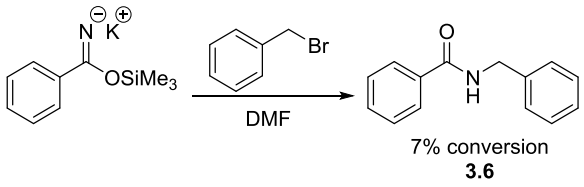
Table 3.1: One-pot alkylation reactions using the silanoate-derived imidate salt as a nucleophile.



Entry	Solvent	Additive	Time (h)	Conversion (%)[a]
1	THF	-	4	8
2	THF	TBAI	4	0
3[b]	THF	-	4	3
4	DMF	-	2	0
5[c]	Toluene	-	1	6

[a]Conversion determined by HPLC with reference to an internal standard. [b]Reaction performed using 5 equiv. of benzyl bromide. [c]Reaction performed in a microwave reactor at 140 °C.

In an attempt to prevent any potential by-products formed during the formation of the imidate salt from inhibiting the alkylation reaction, isolation of the imidate salt prior to subjecting it to the alkylation conditions was also examined. Again, in an effort to maximise the solubility of the salt, the alkylation reaction was performed in refluxing DMF (Scheme 3.24). However, unfortunately, no improvement was observed, with a conversion of only 7% to the desired amide achieved.



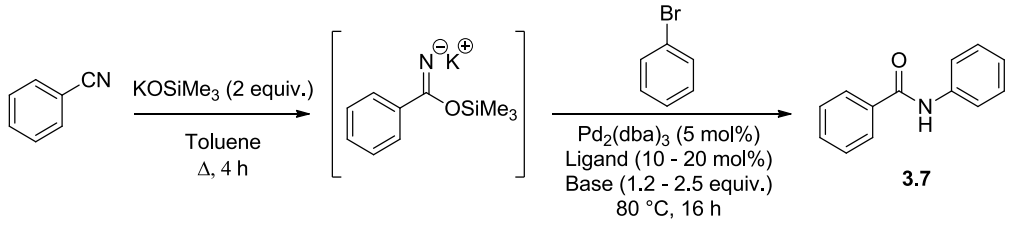
Scheme 3.24: Attempted alkylation on the isolated imidate salt.

With the attempted alkylation using the imidate salt as an amide surrogate proving to be less than tractable, focus was shifted to investigating its compatibility in a Buchwald-Hartwig process.

3.3.2 Investigating the use of the Silanoate-derived Imidate Species as an Amide Surrogate in a Buchwald-Hartwig Cross-Coupling Process.

The proposed Buchwald-Hartwig reaction was examined using bromobenzene in a model reaction to determine the effect of a range of different base and ligand combinations. Toluene was selected as the reaction solvent to maximise conversion of the nitrile to the imidate intermediate, and therefore potentially the efficiency of the overall reaction. In order to avoid the necessary reduction of Pd(II) to Pd(0), the required oxidation state of Pd in the Buchwald-Hartwig amination, the Pd(0) catalyst $Pd_2(dba)_3$ was selected as the palladium catalyst for the screening procedure, at an initial loading of 5 mol%. A range of ligands and bases were selected through the examination of previous literature and drawing from prior experience within our laboratories (Table 3.2). Conditions employing no basic species were also examined to assess whether the negative charge residing on the nitrogen of the intermediate was sufficient to enable the desired cross-coupling reaction (*cf.* the coupling of LiHMDS by Buchwald and Hartwig in Section 3.1.2).[159,161]

Table 3.2: Screening ligand and base conditions in a one-pot Buchwald-Hartwig Process.



Entry	Ligand	Ligand Loading (mol%)	Base	Conversion (%)[a]
1	JohnPhos	15	-	0
2	DavePhos	15	-	0
3	d*t*bpf	10	-	0
4	SPhos	15	-	0
5	XPhos	20	-	1
6	*t*BuXPhos	20	-	3
7	JohnPhos	15	KO*t*Bu	0
8	DavePhos	15	KO*t*Bu	0
9	d*t*bpf	10	KO*t*Bu	0
10	SPhos	15	KO*t*Bu	0
11	XPhos	20	KO*t*Bu	1
12	*t*BuXPhos	20	KO*t*Bu	4

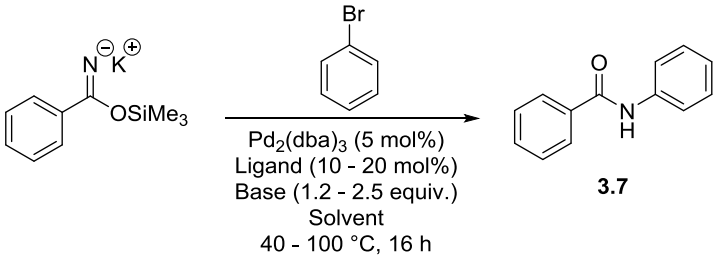
13	JohnPhos	15	NaO*t*Bu	0
14	DavePhos	15	NaO*t*Bu	0
15	d*t*bpf	10	NaO*t*Bu	1
16	SPhos	15	NaO*t*Bu	0
17	XPhos	20	NaO*t*Bu	0
18	*t*BuXPhos	20	NaO*t*Bu	1
19	JohnPhos	15	K_3PO_4	0
20	DavePhos	15	K_3PO_4	3
21	d*t*bpf	10	K_3PO_4	2
22	SPhos	15	K_3PO_4	0
23	XPhos	20	K_3PO_4	0
24	*t*BuXPhos	20	K_3PO_4	2

[a]Conversion determined by HPLC with reference to an internal standard.

From this screening study, all the ligand and base combinations examined resulted in minimal conversion to the desired secondary amide **3.7**. The combination of *t*BuXPhos and KO*t*Bu (Table 3.2, Entry 12) resulted in the highest conversion to **3.7** at 4%. However, as this was deemed insufficient to take forward to further optimisation studies, employing the isolated intermediate in a Buchwald-Hartwig amination with bromobenzene was instead investigated.

In assessing the compatibility of the isolated imidate salt to act as a nucleophilic amide surrogate in this procedure, the range of ligands and bases examined in the previous screening procedure were retained. However, as the choice of solvent used in the reaction now does not have to effect efficient formation of the imidate, the solvents and various temperatures examined were selected with respect to the ligand and base combination (Table 3.3).

Table 3.3: Buchwald-Hartwig reactions performed on the isolated imidate salt.



3.7

Entry	Ligand	Ligand Loading (mol%)	Base	Solvent	Temperature (°C)	Conversion (%)[a]
1	JohnPhos	15	-	DME	40	0
2	DavePhos	15	-	Toluene	80	0
3	d*t*bpf	10	-	THF	80	1
4	SPhos	15	-	Toluene	100	2
5	XPhos	20	-	1,4-Dioxane	100	12
6	*t*BuXPhos	20	-	THF	40	0
7	JohnPhos	15	KO*t*Bu	DME	40	0
8	DavePhos	15	KO*t*Bu	Toluene	80	1
9	d*t*bpf	10	KO*t*Bu	THF	80	0
10	SPhos	15	KO*t*Bu	Toluene	100	0
11	XPhos	20	KO*t*Bu	1,4-Dioxane	100	3
12	*t*BuXPhos	20	KO*t*Bu	THF	40	0
13	JohnPhos	15	NaO*t*Bu	DME	40	0
14	DavePhos	15	NaO*t*Bu	Toluene	80	0
15	d*t*bpf	10	NaO*t*Bu	THF	80	0
16	SPhos	15	NaO*t*Bu	Toluene	100	1
17	XPhos	20	NaO*t*Bu	1,4-Dioxane	100	0
18	*t*BuXPhos	20	NaO*t*Bu	THF	40	0
19	JohnPhos	15	K_3PO_4	DME	40	0
20	DavePhos	15	K_3PO_4	Toluene	80	0
21	d*t*bpf	10	K_3PO_4	THF	80	0
22	SPhos	15	K_3PO_4	Toluene	100	0
23	XPhos	20	K_3PO_4	1,4-Dioxane	100	17
24	*t*BuXPhos	20	K_3PO_4	THF	40	0

[a]Conversion determined by HPLC with reference to an internal standard.

As in the investigation of the one-pot Buchwald-Hartwig process, minimal conversion to the desired amide **3.7** was observed in the majority of conditions screened. However, pleasingly when using XPhos in both the presence and absence of an exogenous base, conversions of 12 and 17% are observed, respectively (Table 3.3, Entries 5 and 23). With these conditions resulting in no observed amide formation when examined under the previous screen towards a one-pot process, this implies that the choice of solvent utilised in the reaction is critical. In the one-pot process, using toluene as the reaction solvent could inhibit transmetallation of the $Pd_2(dba)_3$ and the XPhos ligand, preventing formation of the catalytically active palladium species. Alternatively, K_3PO_4 may not be sufficiently soluble in toluene, therefore preventing catalytic turnover. However, as the use of XPhos without a base is unsuccessful in promoting the desired reaction in the one-pot process, this suggests that the nature of the solvent affects the outcome of the reaction through further factors other than solubilisation of the base.

The observed differences in conversion between the Buchwald-Hartwig processes performed in a one-pot fashion and on the isolated imidate salt could also be attributed to the other components present within the reaction mixture. Residual benzonitrile or by-products formed *via* the *in situ* formation of the imidate intermediate could inhibit the desired cross-coupling reaction. Also, as an excess of potassium trimethylsilanolate is used in the reaction, residual quantities could preferentially coordinate to the palladium catalyst instead of the desired imidate intermediate. However, as the other ligand and base conditions screened result in, at best, minimal conversion to amide **3.7** in both the one-pot process and direct use of the imidate intermediate, this would suggest that the above reasoning cannot be solely accountable for the differences in conversion observed between the two processes investigated.

3.3.2.1 Optimisation of the Buchwald-Hartwig Amidation Methodology *via* a Design of Experiments Approach.

With the use of XPhos resulting in measurable formation of desired amide **3.7**, these conditions were taken forward to a further optimisation process *via* a Design of Experiments (DoE) approach, utilising the Design Expert® software.[171] The use of a DoE approach to optimisation is advantageous as it allows all factors under investigation to be varied simultaneously, hence allowing any relationships between factors to be elucidated. An alternative linear screening approach would only allow an individual factor be varied at any one time, therefore assuming that each factor acts independently of the other factors under

investigation. Furthermore, the data generated from a DoE approach can then be used to influence future experimentation on the process under investigation.

To illustrate this difference in approach to an optimisation procedure, consider an experiment investigating the effects of both the temperature and pH on the conversion of a reaction. Optimising *via* a linear approach, where the factors are assumed to act independently of one another, could result in a local optimum conversion being achieved (Figure 3.3a). However, this assumption has led to a greater conversion for the reaction to be missed, which could be exploited if the optimisation was performed utilising a DoE approach (Figure 3.3b).

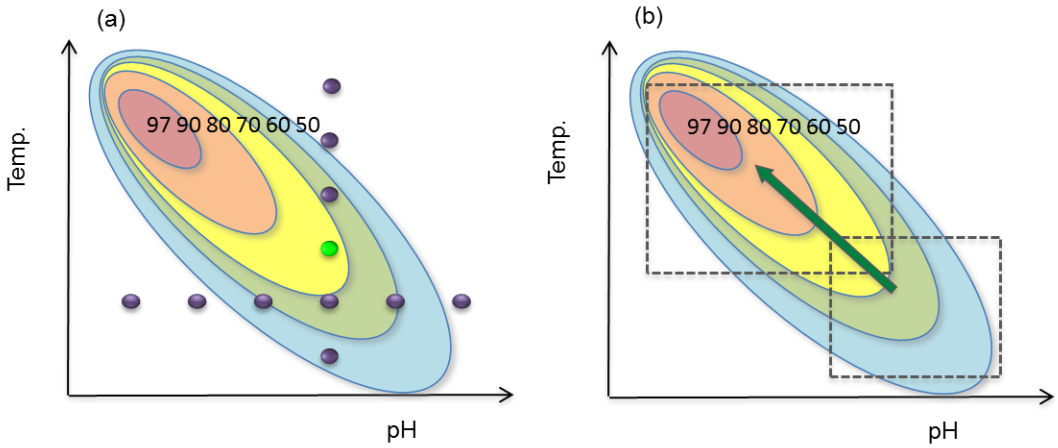


Figure 3.3: (a) Optimum conditions found *via* linear optimisation. (b) Potential area of conversion accessible *via* a DoE approach to reaction optimisation.

The experimental designs used in DoE incorporate both the factors under investigation as well as the levels of the factors, for example, a two-level design investigates pre-determined minimum and maximum values of the factors. Relevant control reactions, centre points of the maximum and minimum values, are also performed to ensure that the reactions are reproducible and to establish any error in the method. For example, a three factor, two level design would therefore result in 8 reactions, plus any controls, to be performed (Figure 3.4). However, as the number of factors under investigation increases, so does the number of reactions to be performed, with the relationship 2^n, where n = number of factors under investigation. For example, an 8 factor, 2 level design would result in 256 reactions, plus relevant controls, to be carried out. As this level of experimentation would be time consuming, a half-fractional design can instead be employed, which reduces the number of reactions to be performed by half whilst maximising the design space covered through the use of aliasing, which is where the software combines factors. Therefore, a 3 factor, 2 level

half-fractional design would result in 4 experiments to be performed (Figure 3.4), whereas the 8 factor variant would result in 128 reactions.

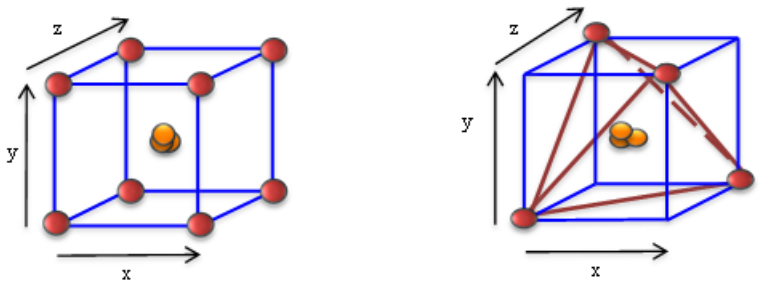


Figure 3.4: A 3 factor, 2 level design vs a 3 factor, 2 level half-fractional design.

Three levels of aliasing can be performed by the software: Resolution III, where the main effects are aliased with two-factor interactions; Resolution IV, where the main effects are aliased with three-factor interactions; and Resolution V, where all the main effects and 2-factor interactions can be estimated and third-factor interactions are assumed to be negligible. Resolutions IV and V are normally selected for designs as they offer a good balance between the number of reactions required to be performed and the accuracy of the results obtained. The use of Resolution III, however, can produce results which are difficult to interpret when two factor interactions affect the response. When a suitable design has been selected for the process under investigation, the software produces the reactions to be performed in a random order, which should ideally be followed to minimise any systematic error in the final response.

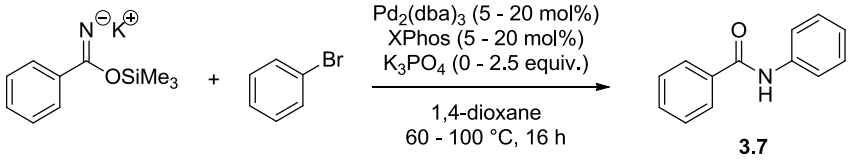
Once the experimentation has been completed and the corresponding data obtained, a half-normal plot and/or a Pareto chart can be created by the Design Expert®[172] software, which can be used to identify any factors having a significant effect on the outcome of the reaction. In a half-normal plot, a line of best-fit is placed through the points, with any points substantially deviating from this line deemed to have a significant effect on the reaction. For a Pareto chart, the factors are plotted in a bar graph with any factors crossing the Bonferroni limit, a statistical correction for multiple comparisons, deemed to have a significant effect on the reaction. A 3D plot can then be generated, representing the obtained results in the form of a response factor.

For the optimisation of the Buchwald-Hartwig process, a two-level half-fractional design evaluating five factors was selected, investigating: equivalents of base (0 – 2.5 equiv.); catalyst loading (5 – 20 mol%); ligand loading (5 – 20 mol%); reaction concentration

(0.1 – 0.2 M); and reaction temperature (60 – 100 °C). Two control reactions, representing the centre points of the factors under investigation, were also performed to ensure reaction reproducibility.

Although it is suggested that the chemistry is performed in the random order produced by the Design Expert® software, for ease of practical execution, the reactions were performed according to the temperature required (Table 3.4). Upon completion of the suggested reactions, initial analysis of the results indicated that the use of $Pd_2(dba)_3$ and XPhos, both at the maximum loading of 20 mol%, in conjunction with 2.5 equivalents of K_3PO_4 at a concentration of 0.2 M (Table 3.4, Entry 8) resulted in a 51% conversion to amide **3.7**, which represents a significant increase when compared to the maximum conversion achieved from the previous reaction screening (see Table 3.3). However, the use of the same loading of catalyst and ligand in the absence of an exogenous base and at a concentration of 0.1 M resulted in a higher conversion of 59% (Table 3.4, Entry 9). Upon isolation, a yield of 77% of amide **3.7** was obtained, with the discrepancy between conversion and isolated yield attributed to the limited solubility of **3.7** in the reaction milieu. Having shown that the use of an exogenous basic species is unnecessary to facilitate efficient catalytic turnover, this therefore offers an increase in the atom economy of the catalytic process.

Table 3.4: DoE optimisation approach for the Buchwald-Hartwig process utilising the imidate salt.



3.7

Entry	Base equiv.	Catalyst Loading (mol%)	Ligand Loading (mol%)	Concentration (M)	Temperature (°C)	Conversion (%)[a]
1	1.25	12.50	12.50	0.15	80	28
2	1.25	12.50	12.50	0.15	80	25
3	0	5.00	20.00	0.2	100	14
4	2.50	20.00	5.00	0.2	60	2
5	0	20.00	5.00	0.1	60	3
6	0	20.00	5.00	0.2	100	16
7	0	5.00	20.00	0.1	60	0
8	2.50	20.00	20.00	0.2	100	51

9	0	20.00	20.00	0.1	100	59 (77%)[b]
10	2.50	5.00	5.00	0.1	60	0
11	2.50	20.00	5.00	0.1	100	11
12	2.50	5.00	5.00	0.2	100	1
13	2.50	20.00	20.00	0.1	60	24
14	0	20.00	20.00	0.2	60	20
15	2.50	5.00	20.00	0.1	100	7
16	0	5.00	5.00	0.2	60	0
17	2.5	5.00	20.00	0.2	60	1
18	0	5.00	5.00	0.1	100	1

[a]Conversion determined by HPLC with reference to an internal standard. [b]Isolated yield

The conversions obtained were then analysed *via* a half-normal plot so as to determine the factors bearing the most significant effect on the efficiency of the reaction (Figure 3.5). From this plot, it could clearly be established that loadings of both the $Pd_2(dba)_3$ catalyst and the XPhos ligand, as well as reaction temperature (Figure 3.5, Points B, C and E, respectively) were the factors having a pronounced effect on the reaction outcome. This was further emphasised upon analysis of the corresponding 3D response surface (Figure 3.6).

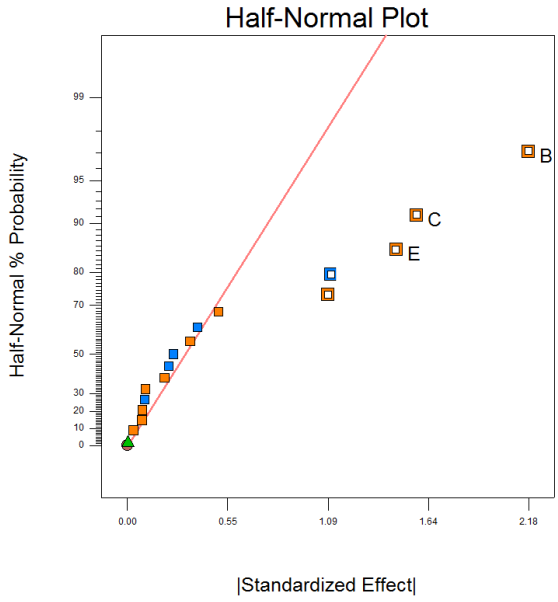


Figure 3.5: Half-normal plot indicating the influence of both catalyst and ligand loading, in addition to temperature.

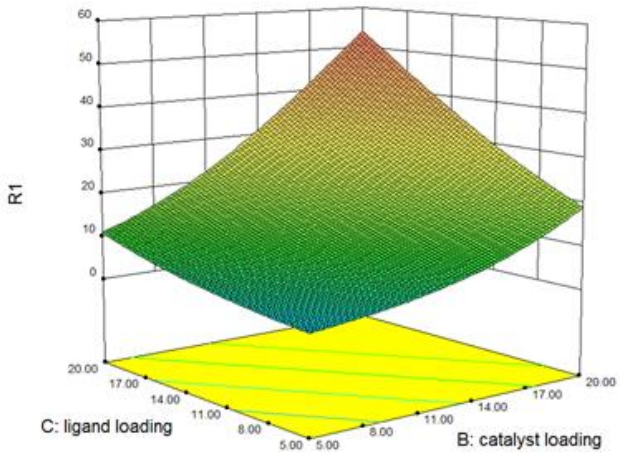
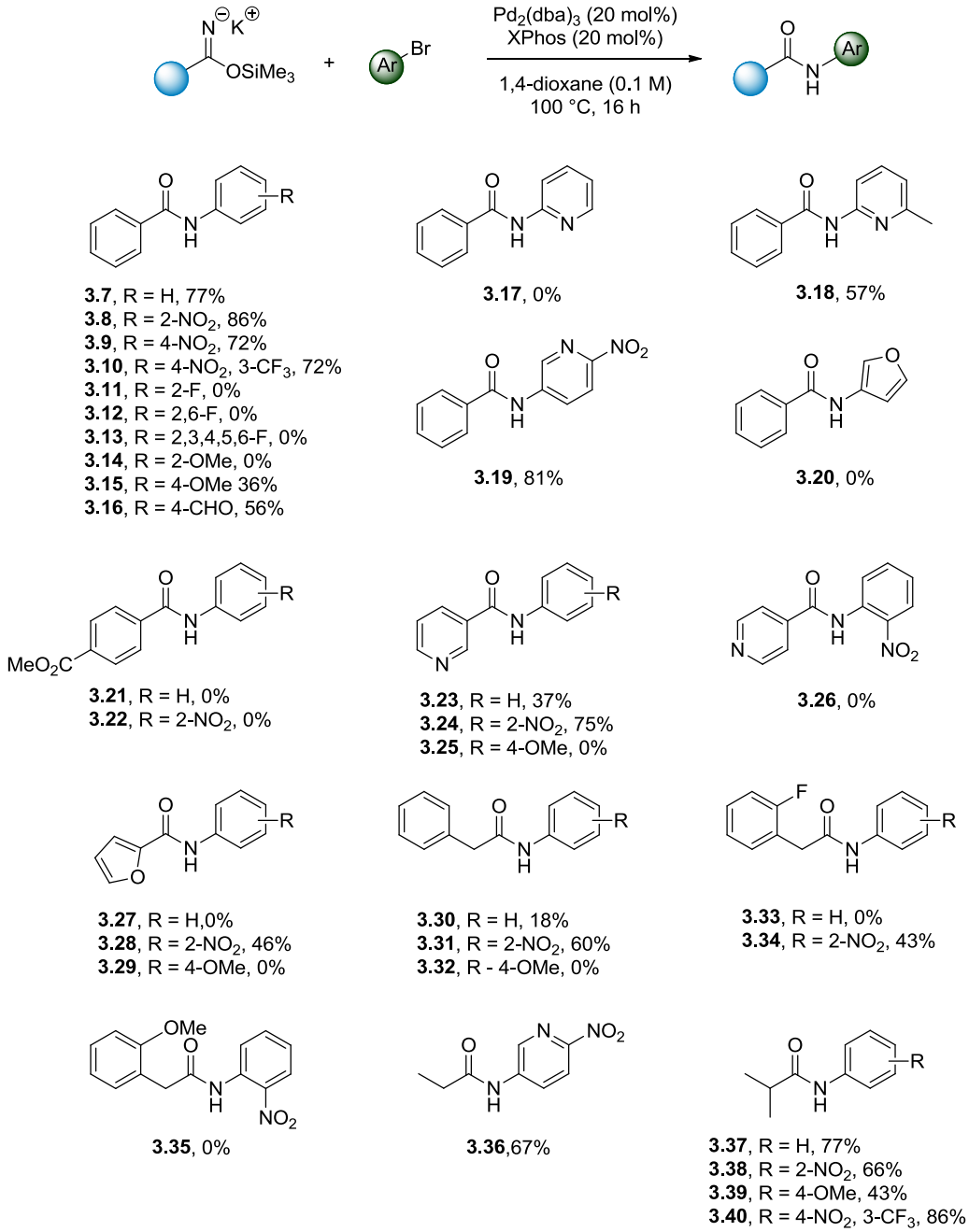


Figure 3.6: 3D response surface indicating the pronounced effect of 20 mol% of both $Pd_2(dba)_3$ and XPhos at 100°C.

3.3.2.2 Investigating the scope of the Buchwald-Hartwig Process

With the use of 20 mol% of both $Pd_2(dba)_3$ and XPhos in the absence of an exogenous base at 100 °C found to lead to a 77% isolated yield of amide **3.7**, these conditions were taken forward to investigate the scope of both the aryl bromide and imidate salt components of the reaction (Scheme 3.25).

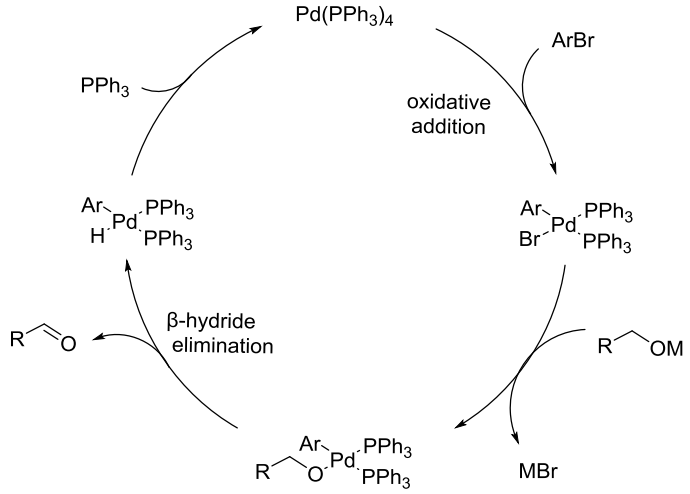
Using the imidate salt derived from benzonitrile as the nucleophilic coupling partner, the effect of varying the substitution on the aryl bromide was investigated (**3.7** – **3.16**). Incorporation of a nitro group at the *ortho* and *para* positions of the aryl bromide yielded amides **3.8** and **3.9** in good to excellent yields of 86 and 72%, respectively. This observed increase in yield is unsurprising as the electron withdrawing nitro group promotes the oxidative addition step of the Buchwald-Hartwig reaction. The formation of these amide products *via* the Buchwald-Hartwig methodology is also advantageous over established amide-bond formation approaches. Given the corresponding nitro-substituted aniline species are poor nucleophiles as a result of the electron-withdrawing substituents, forcing conditions (e.g. the use of acid chlorides) are required to enable preparation of the amide products. To further highlight the utility of this methodology, the highly electron-deficient anilide **3.10** was synthesised in a good yield of 72%, which would again require more forcing reagents in order to be coupled *via* the corresponding aniline. However, incorporation of fluorine substituents on the aryl ring was found to inhibit the reaction (**3.11** – **3.13**).



Scheme 3.25: Investigation of the scope of the Buchwald-Hartwig amidation.

Conversely, the use of electron-donating substituents on the aryl halide would be expected to result in less competent coupling partners as a result of the reduced propensity of the electron-rich aryl bromide towards oxidative addition. As expected, using a methoxy substituted aryl bromide was found to result in lower yields of the respective amide products (**3.14** & **3.15**), with the *ortho*-methoxy being incompatible in the reaction manifold, presumably as a result of the increased steric bulk inhibiting reductive elimination. The reduced efficiency of the coupling of electron-rich aryl halides therefore represents a

limitation of the Buchwald-Hartwig amidation methodology. When 4-bromobenzyl alcohol was subjected to the reaction conditions, the corresponding anilide with an aldehyde substituent (**3.16**) was obtained in a yield of 56%, which can be attributed to the precedented oxidation of primary benzylic alcohols by aryl bromides which is catalysed by palladium(0) species (Scheme 3.26).[173]



Scheme 3.26: Oxidation of primary alcohols by aryl bromides catalysed by Pd(0).[173]

A range of heterocyclic aryl bromides were also examined, with the methyl and nitro substituted pyridyl halides furnishing the corresponding amides **3.18** and **3.19** in good to excellent yields. However, 2-bromopyridine (**3.17**) and the π-excessive furan (**3.20**) were found to be incompatible when subjected to the reaction conditions.

The silanoate-derived imidate salt component was also varied, with the trends in yields for the Buchwald-Hartwig process consistent with the electronic characteristics of the aryl bromide coupling partner, as observed when using the benzonitrile-derived imidate species. When applying the imidate species derived from methyl 4-cyanobenzoate to the Buchwald-Hartwig amidation process, it was found that the coupling between both the electron-neutral bromobenzene (**3.21**), and the electron-withdrawing 1-bromo-2-nitrobenzene (**3.22**) was unsuccessful. This can perhaps be ascribed to the electron-poor nature of the imidate, hence reducing its nucleophilicity. Heterocyclic imidate species were also examined, with electron-neutral and electron-poor 3-pyridyl and 2-furyl variants found to couple in moderate to good yields (**3.23**, **3.24** & **3.28**). The electron-rich methoxy-substituted aryl halide derivatives were again found to be incompatible substrates (**3.25** & **3.29**), as was the coupling of the imidate derived from 4-cyanopyridine with bromobenzene (**3.26**).

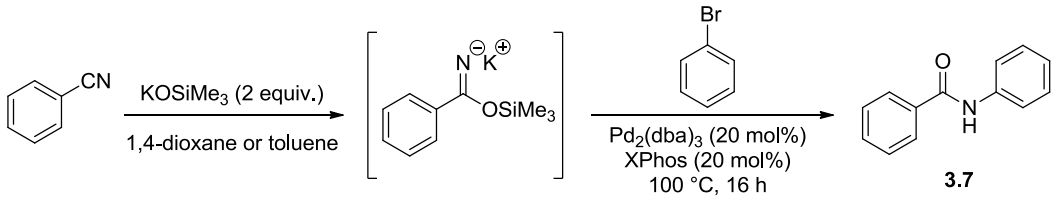
The coupling of benzyl-derived imidates was also examined, with the efficiency of the reactions again dictated by the electronic characteristic of the aryl bromide component. Applying the imidate derived from benzyl cyanide to the amidation conditions with 1-bromo-2-nitrobenzene, furnished the desired amide **3.31** in a good yield of 60%. The corresponding coupling reaction with bromobenzene was found to perform less efficiently, with the corresponding amide **3.30** formed in 18% yield, whereas 4-methoxybromobenzene (**3.32**) was found to be incompatible. Incorporation of a fluoro (**3.34**) substituent at the *ortho* position of the imidate aryl ring was also tolerated in moderate yield when coupled with the electron-withdrawing aryl bromide species, however the corresponding methoxy derivative (**3.35**) was found to be incompatible, presumably as a result of the increased steric bulk.

Finally, the compatibility of alkyl-derived imidate species in the amidation methodology was assessed. The coupling of an ethyl substituted imidate was found to couple in a good yield of 67% with 5-bromo-2-nitropyridine (**3.36**). An isopropyl substituted imidate species was also a competent substrate, successfully undergoing the desired coupling reaction with electron-neutral, poor and rich aryl bromides (**3.37** – **3.39**) in moderate to good yields. Of particular note is the efficient preparation of the anti-androgen agent Flutamide (**3.40**), which is used in the treatment of prostate cancer,[174] in an excellent yield of 86%.

3.3.2.3 Development of a One-Pot Buchwald-Hartwig Amidation Approach Utilising Isolated Imidate Species,

With the scope of the Buchwald-Hartwig coupling of aryl bromides with isolated imidate species furnishing secondary amides successfully delineated, attention was re-focused on the development of a corresponding one-pot procedure. With previous attempts at enabling such a process proving unsuccessful (*cf.* Table 3.2, Section 3.3.2), the optimised conditions for performing the Buchwald-Hartwig reaction directly on the imidate species were re-evaluated to enable the incorporation of the nitrile species in the reaction, and thereby obviating the required isolation of the imidate (Table 3.5).

Table 3.5: Adaptation of the optimised Buchwald-Hartwig conditions to enable a one-pot amidation process.

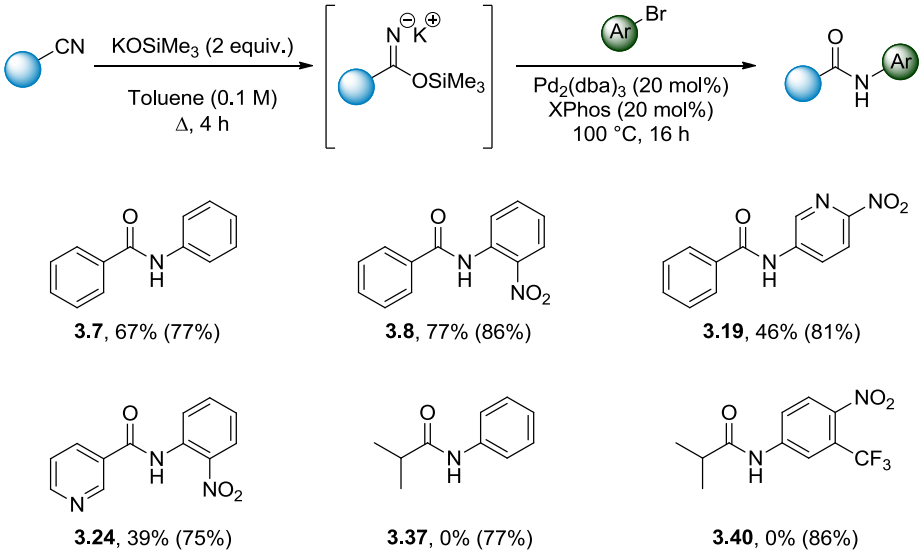


Entry	Conditions	Solvent	Yield (%)
1	Concomitant addition of reagents	1,4-dioxane	12
2	4 hour preformation of imidate at reflux	1,4-dioxane	39
3	Concomitant addition of reagents	Toluene	21
4	4 hour preformation of imidate at reflux	Toluene	67

When using 1,4-dioxane as the reaction solvent, in accordance with the previously optimised conditions, amide **3.7** was formed in a poor yield of 12% when the reactants were added concomitantly (Table 3.5, Entry 1). With a view to promoting efficient cross-coupling, the imidate was pre-formed *in situ* over a 4 hour period in 1,4-dioxane, before addition of the remaining reagents (Entry 2). The desired amide was formed in an improved yield of 39%, however, when compared to the yield obtained from the coupling using the isolated intermediate, this was a significantly less efficient amidation process. This observation is proposed to be as a result of the reduced ability of the imidate to form when using 1,4-dioxane as the reaction solvent.

In an attempt to overcome the poor formation of the required imidate species, the solvent utilised in the reaction was altered from 1,4-dioxane to toluene, which is optimal for isolating the imidate salt. When concomitant addition of the reagents was re-investigated, a slight increase in the yield to 21% of **3.7** was achieved (Entry 3). Pleasingly, allowing pre-formation of the imidate furnished **3.7** in a 67% yield, comparable to the yield obtained for the hyphenated Buchwald-Hartwig process.

With a one-pot Buchwald-Hartwig amidation process successfully developed for the coupling of the benzonitrile-derived imidate species with bromobenzene, the generality of the process was examined by prosecuting a subset of the substrates that proved successful in the previous scope (Scheme 3.27).



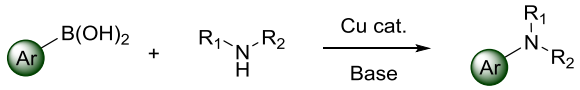
Scheme 3.27: Scope of the one-pot Buchwald-Hartwig amidation process.

Subjecting the coupling of benzonitrile and 1-bromo-2-nitrobenzene to the one-pot Buchwald-Hartwig procedure furnished the desired amide **3.8** in a comparable yield of 77%. However, formation of the pyridyl derivative **3.19** was found to proceed less efficiently when examined under the one-pot protocol, in comparison to prior isolation of the imidate species (46% *vs* 81%, respectively). Unfortunately, the generality of the one-pot process was also found to be less tolerant to variation of the imidate species, with the pyridine derivative **3.24** furnished in only 39%, whereas the isopropyl imidate species was found to be incompatible, even in the formation of the electron-deficient anilide **3.40**. Therefore, although comparable to the hyphenated methodology in selected examples, the general reduction in yields and compatibility associated with this one-pot process renders it an inferior approach.

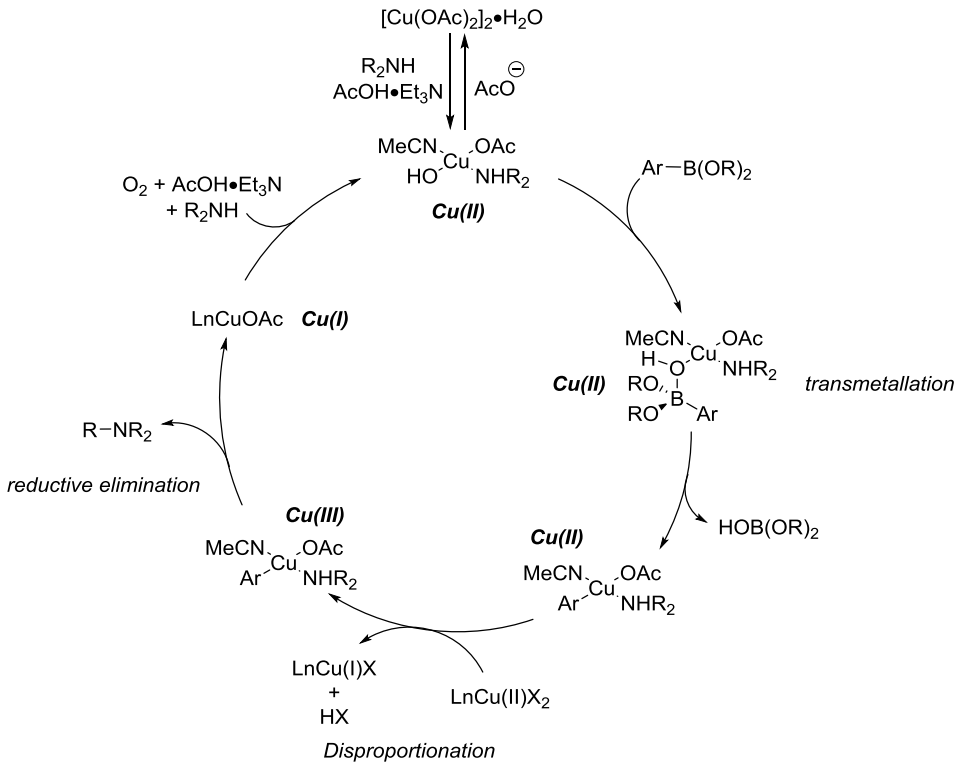
With imidate species furnished from the silanoate-mediated hydrolysis of nitriles shown to be competent amide surrogates in the formation of secondary amides *via* a Buchwald-Hartwig process, and the scope of the process exemplified, attention was then turned to alternative transition metal catalysed reaction manifolds.

3.3.3 Investigating the use of the Silanoate-derived Imidate Species as an Amide Surrogate in a Chan-Evans-Lam Cross-Coupling Process

Despite the demonstrated efficiency of the Buchwald-Hartwig process in the formation of secondary amides, the requirement of both high catalyst and ligand loadings, and the reduced propensity of electron-rich aryl bromides to undergo the desired amidation, are significant limitations that can detract from the generality of the process. In recent years, the Chan-Evans-Lam arylation has emerged as an efficient means of preparing aryl amine derivatives from the corresponding aryl amine and boronic acid coupling partners *via* copper catalysis (Scheme 3.28).[175–177] With copper a more abundant and less toxic metal than palladium, the successful application of imidates salts as amide surrogates in a Chan-Evans-Lam process would potentially represent a more sustainable catalytic approach to secondary amide formation.[178] Additionally, with the Chan-Lam process proceeding through an initial transmetallation event between the catalytically active copper species and the boronic acid, opposed to an initial oxidative addition event in the Buchwald-Hartwig, electron-rich boronic acids should be efficient coupling partners, therefore creating a coupling procedure complimentary to the Buchwald-Hartwig methodology (Scheme 3.29).[179] Following the transmetallation, oxidation of the copper species occurs *via* disproportionation to form a Cu(III) species.[179] Reductive elimination furnishes the desired amine product, and liberates a Cu(I)OAc species which is oxidised to the corresponding Cu(II) species to complete the catalytic cycle.[179]



Scheme 3.28: General Chan-Evans-Lam reaction for the arylation of amines.

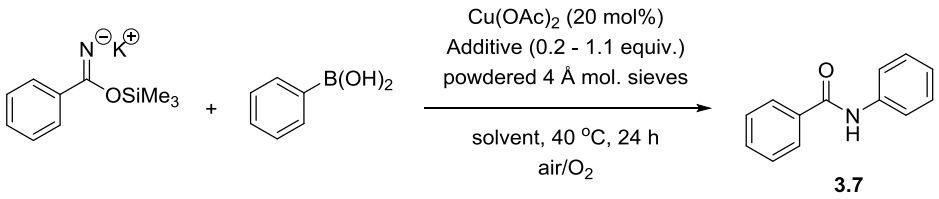


Scheme 3.29: Mechanism of Chan-Evans-Lam amination.[179]

3.3.3.1 Initial Optimisation of the Chan-Evans-Lam Process Using the Isolated Imidate

For initial reaction screening, $Cu(OAc)_2$, which is widely applied in Chan-Evans-Lam coupling processes, was selected as the copper catalyst at a loading of 20 mol% so as to investigate the choice of solvent in the reaction of the benzonitrile-derived imidate salt with phenylboronic acid (Table 3.6). Additionally, with Evans demonstrating that an oxygen atmosphere promotes the reaction, the use of an oxygen atmosphere and the exogenous oxidising additives pyridine *N*-oxide (PNO) and TEMPO were also examined.[176,180] The use of myristic acid was also investigated as an additive, following a report by Antilla and Buchwald which indicated that loadings of 10 – 40 mol% may aid the solubility of the copper catalyst in the reaction milieu.[181]

Table 3.6: Screening solvent, additive and atmosphere conditions for the Chan-Evans-Lam process.



3.7

Entry	Solvent	Additive	Conversion (%)[a]
1	DCM	-	1
2	1,4-dioxane	-	17
3	THF	-	3
4	*t*BME	-	16
5	CPME	-	3
6	2-MeTHF	-	42
7	DCM	PNO[b]	33
8	1,4-dioxane	PNO[b]	37
9	THF	PNO[b]	42
10	*t*BME	PNO[b]	13
11	CPME	PNO[b]	24
12	2-MeTHF	PNO[b]	41
13	DCM	TEMPO[b]	5
14	1,4-dioxane	TEMPO[b]	3
15	THF	TEMPO[b]	2
16	*t*BME	TEMPO[b]	16
17	CPME	TEMPO[b]	8
18	2-MeTHF	TEMPO[b]	8
19	DCM	Myristic Acid[c]	3
20	1,4-dioxane	Myristic Acid[c]	8
21	THF	Myristic Acid[c]	13
22	*t*BME	Myristic Acid[c]	4
23	CPME	Myristic Acid[c]	3
24	2-MeTHF	Myristic Acid[c]	9
25	DCM[d]	-	4
26	1,4-dioxane[d]	-	16
27	THF[d]	-	22
28	*t*BME[d]	-	19
29	CPME[d]	-	9
30	2-MeTHF[d]	-	22

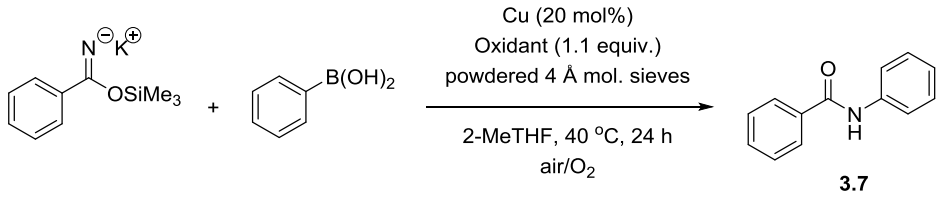
[a]Conversion determined by HPLC with reference to an internal standard. [b]1.1 equivalents of additive used. [c]0.2 equiv. of additive used. [d]Performed under an O_2 atmosphere.

From this initial investigation, it was observed that the conditions utilising an air atmosphere in the absence of an exogenous oxidant (Entries 1 – 6) generally resulted in a poor conversion to the model amide **3.7**. An exception to this is when the reaction was performed in 2-MeTHF, which resulted in a moderate conversion of 42% (Entry 6). The use of PNO as

an oxidant was found to lead to an increase in conversion across the range of solvents under investigation (Entries 7 – 12), with both THF and 2-MeTHF (Entries 9 & 12) resulting in a comparable conversion of 42 and 41%, respectively. However, the use of both TEMPO and myristic acid (Entries 13 – 24) were found to result in poor conversion to the desired amide. Using an oxygen atmosphere *in lieu* of an exogenous oxidant was found to result in a slight increase in conversion across the range of solvents examined, when compared to the use of an air atmosphere, but was inferior when compared to the use of PNO.

With the initial screening resulting in a promising conversion of 42%, using both 2-MeTHF and THF, the effect of altering the copper catalytic species was then examined (Table 3.7). A range of Cu(I) and Cu(II) species were investigated, with 2-MeTHF retained as the solvent due to its increased sustainability compared to THF.[182] The use of PNO and TEMPO, as well as an air and oxygen atmosphere, were also examined further.

Table 3.7: Investigating the copper species under varying oxidative conditions.



3.7

Entry	Catalyst	Atmosphere	Oxidant	Conversion (%)[a]
1	$Cu(OAc)_2$	Air	-	42
2	$Cu(OAc)_2$	O_2	-	22
3	$Cu(OAc)_2$	Air	PNO	41
4	$Cu(OAc)_2$	Air	TEMPO	8
5	CuOAc	Air	-	1
6	CuOAc	O_2	-	6
7	CuOAc	Air	PNO	2
8	CuOAc	Air	TEMPO	2
9	CuCl	Air	-	35
10	CuCl	O_2	-	44
11	CuCl	Air	PNO	40
12	CuCl	Air	TEMPO	45
13	$CuCl_2$	Air	-	27
14	$CuCl_2$	O_2	-	25
15	$CuCl_2$	Air	PNO	15
16	$CuCl_2$	Air	TEMPO	18
17	CuBr	Air	-	37
18	CuBr	O_2	-	45
19	CuBr	Air	PNO	59
20	CuBr	Air	TEMPO	27

21	$CuBr_2$	Air	-	28
22	$CuBr_2$	O_2	-	29
23	$CuBr_2$	Air	PNO	26
24	$CuBr_2$	Air	TEMPO	14
25	CuI	Air	-	0
26	CuI	O_2	-	1
27	CuI	Air	PNO	0
28	CuI	Air	TEMPO	2
29	Cu_2O	Air	-	0
30	Cu_2O	O_2	-	0
31	Cu_2O	Air	PNO	0
32	Cu_2O	Air	TEMPO	0
33	CuO	Air	-	0
34	CuO	O_2	-	4
35	CuO	Air	PNO	0
36	CuO	Air	TEMPO	0
37	$CuCO_3$	Air	-	8
38	$CuCO_3$	O_2	-	16
39	$CuCO_3$	Air	PNO	13
40	$CuCO_3$	Air	TEMPO	3
41	$Cu(OTf)_2$	Air	-	2
42	$Cu(OTf)_2$	O_2	-	3
43	$Cu(OTf)_2$	Air	PNO	2
44	$Cu(OTf)_2$	Air	TEMPO	3
45	$Cu(BF_4)_2.H_2O$	Air	-	5
46	$Cu(BF_4)_2.H_2O$	O_2	-	15
47	$Cu(BF_4)_2.H_2O$	Air	PNO	8
48	$Cu(BF_4)_2.H_2O$	Air	TEMPO	4
49	$[Cu(OH).TMEDA]_2Cl_2$	Air	-	39
50	$[Cu(OH).TMEDA]_2Cl_2$	O_2	-	64
51	$[Cu(OH).TMEDA]_2Cl_2$	Air	PNO	29
52	$[Cu(OH).TMEDA]_2Cl_2$	Air	TEMPO	28

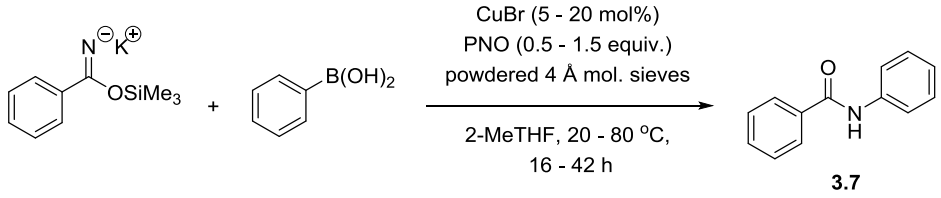
[a]Conversion determined by HPLC with reference to an internal standard.

Analysis of these results indicated general trends in the conversions obtained. Firstly, the use of an oxygen atmosphere generally led to a greater conversion than when using an air atmosphere, which contrasts with the previous screening procedure, and secondly, the use of TEMPO as an exogenous oxidant hinders the reaction, with the exception of its use in conjunction with CuCl (Entry 12). The use of CuBr and PNO under an atmosphere of air (Entry 19), and $[Cu(OH).TMEDA]_2Cl_2$ under an atmosphere of oxygen (Entry 50), were found to give comparable optimum conversions (59 and 64%, respectively) for this study. Further optimisation of the CuBr conditions was performed by the author, whereas optimisation of the $[Cu(OH).TMEDA]_2Cl_2$ conditions was performed by another member of our laboratory.[183]

3.3.3.2 Further Optimisation of the Chan-Evans-Lam Amidation Methodology

Further optimisation of the CuBr/PNO Chan-Evans-Lam amidation conditions was initially performed using a DoE approach, with a two-level half-fractional design selected, evaluating the following five factors: loading of CuBr (5 – 20 mol%); equivalents of phenylboronic acid (1 – 3 equiv.); equivalents of PNO (0.5 – 1.5 equiv.); reaction temperature (20 – 80 °C) and reaction time (16 – 48 h) (Table 3.8). Initial analysis of the results indicated that the use of 20 mol% CuBr and 1.5 equiv. of PNO, when the reaction was performed for 48 hours at 20 °C, resulted in a conversion of 90% to amide **3.7**. Good correlation of the HPLC assay was confirmed by obtaining an isolated yield of 84%. Interestingly, the use of 5 mol% CuBr and 0.5 equivalents of PNO, also at 20 °C for 48 hours, resulted in a good conversion of 74%, implying that reaction time was the dominant factor in the reaction.

Table 3.8: DoE optimisation approach for the Chan-Evans-Lam amidation process utilising the imidate salt.



3.7

Entry	CuBr (mol%)	Boronic acid (equiv.)	PNO (equiv.)	Temperature (°C)	Time (h)	Conversion (%)[a]
1	5	1	1.5	80	48	2
2	20	3	0.5	80	16	1
3	12.5	2	1	50	32	16
4	20	3	0.5	20	48	2
5	20	3	1.5	80	48	3
6	5	1	0.5	80	16	5
7	5	3	1.5	80	16	0
8	20	1	0.5	80	48	53
9	5	1	1.5	20	16	0
10	20	1	1.5	20	48	90 (84)[b]
11	12.5	2	1	50	32	18
12	5	3	0.5	20	16	0
13	5	3	0.5	80	48	6
14	20	1	0.5	20	16	1
15	5	1	0.5	20	48	74 (68)[b]
16	5	3	1.5	20	48	15
17	20	1	1.5	80	16	3
18	20	3	1.5	20	16	1

[a]Conversion determined by HPLC with reference to an internal standard. [b]Isolated yield.

The conversions obtained were then analysed *via* a half-normal plot and a Pareto Chart using the Design Expert® software so as to determine the factors bearing an effect on the efficiency of the reaction (Figures 3.7 and 3.8). From these, it could clearly be established that reaction time (Point E) was indeed the sole factor having a pronounced effect on the reaction outcome.

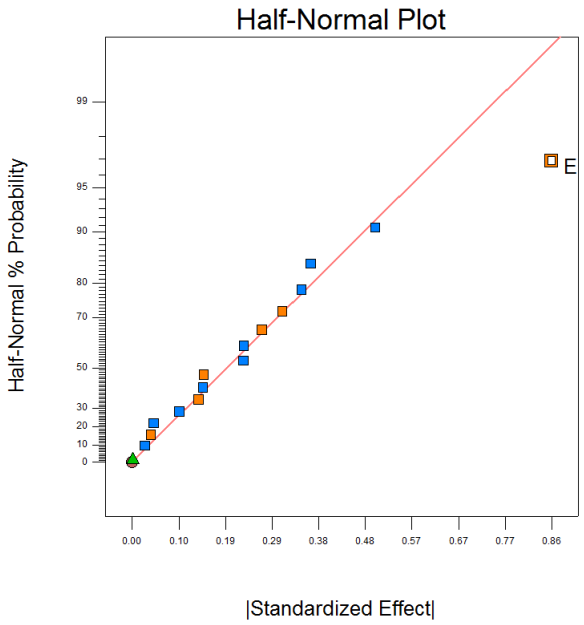


Figure 3.7: Half-normal plot indicating the pronounced effect of reaction time on the outcome of the Chan-Evans-Lam amidation reaction.

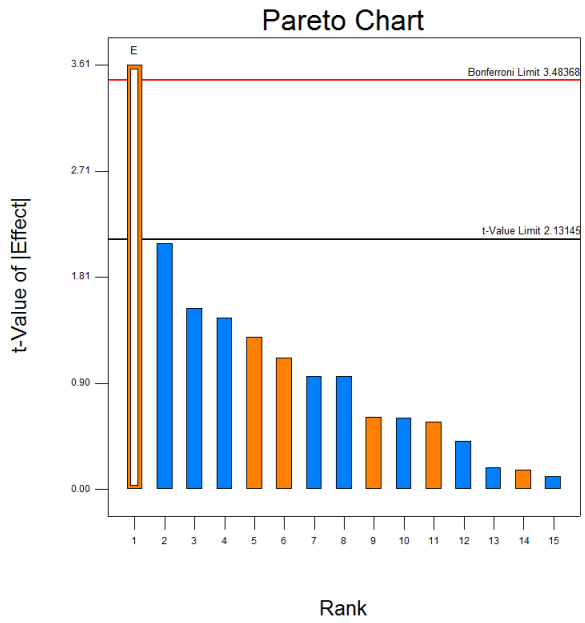


Figure 3.8: Pareto chart indicating the pronounced effect of reaction time on the outcome of the Chan-Evans-Lam amidation reaction.

With time found to be the sole factor influencing the outcome of the reaction, the 3D plot generated by the Design Expert® software was unable to accurately portray the conversions obtained. The results from the control reactions performed were higher in conversion than predicted in the 3D plot (Figure 3.9), thereby residing above the response surface produced. Therefore, this indicates that the model does not fully represent the data obtained.

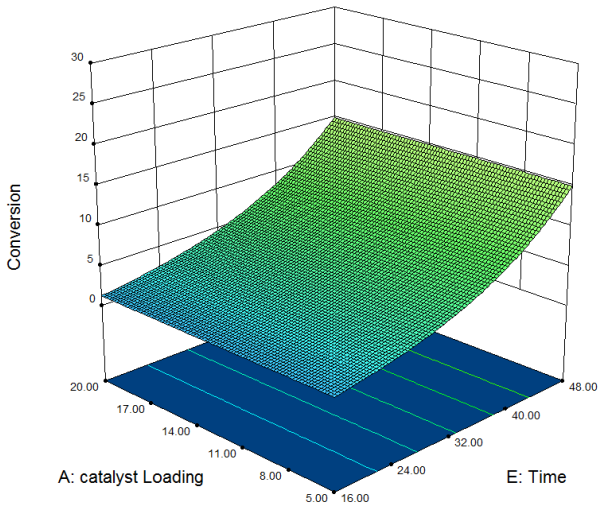
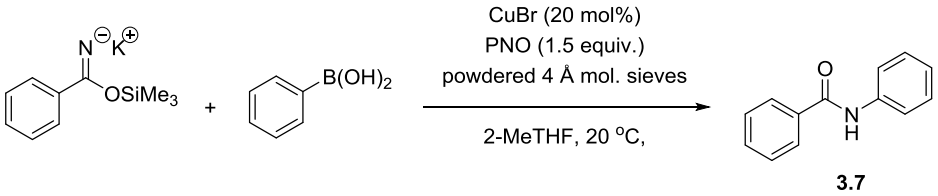


Figure 3.9: 3D response surface of the Chan-Evans-Lam amidation process.

As reaction time was indicated to have such a pronounced effect on the conversion of the Chan-Evans-Lam amidation procedure, a study was performed to investigate the time at which the reaction reached completion. Using the optimum conditions indicated by the DoE optimisation procedure, the yield of the Chan-Evans-Lam process was analysed after 8, 24, 30 and 48 hours (Table 3.9). From this initial time study, a comparable yield of **3.7** was obtained after only 8 hours. Therefore, a further time study was undertaken from 1 – 8 hours (Table 3.10).

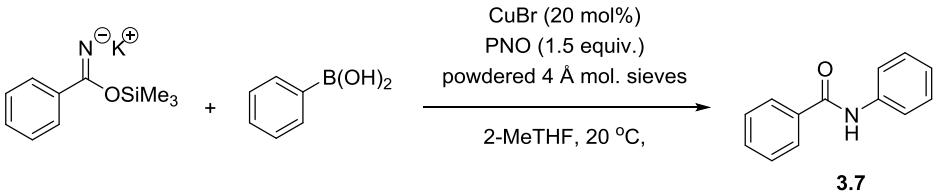
Table 3.9: Initial time study from 8 – 24 hours.



3.7

Entry	Time (h)	Yield (%)
1	8	91
2	24	91
3	30	84
4	48	84

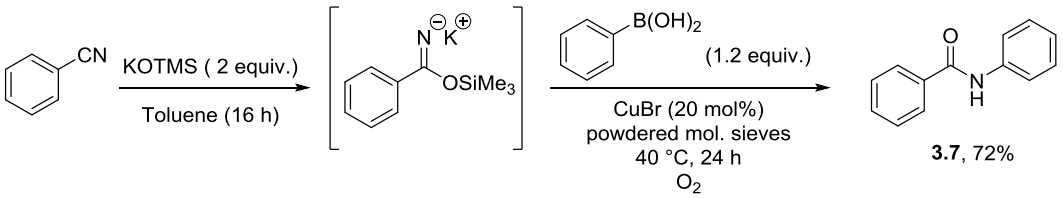
Table 3.10: Investigating reaction progression from 1 to 8 hours.



3.7

Entry	Time (h)	Yield (%)
1	1	2
2	2	4
3	3	3
4	4	3
5	5	5
6	6	0
7	7	0
8	8	0
9	24	9
10	24	2

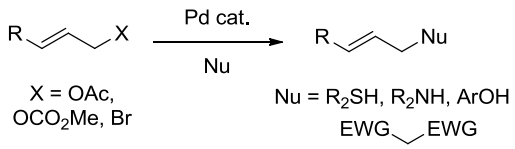
However, it was found when performing this additional time study that the process became unreproducible, even when performing the reaction over 24 hours, with benzamide the major product formed *via* hydrolysis of the imidate species (Table 3.10). Concurrently, the alternative Chan-Evans-Lam amidation conditions, using $[Cu(OH).TMEDA]_2Cl_2$ and an oxygen atmosphere, being optimised elsewhere in our laboratories, also experienced similar irreproducibility. Further studies undertaken on this catalyst system, with a view to elucidating the origin of the sudden irreproducible nature of the reaction, proved inconclusive.[183] However, a one-pot methodology akin to the one-pot Buchwald-Hartwig amidation process was found to still be a potential approach to utilising the imidate species an amide surrogate in a Chan-Evans-Lam process (Scheme 3.30).[183]



Scheme 3.30: One-pot Chan-Evans-Lam amidation process from benzonitrile.[183]

3.3.4 Investigating the use of the Silanoate-derived Imidate Species as an Amide Surrogate in a Tsuji-Trost Allylation Process

With the use of silanoate-derived imidate species as amide surrogates in a Chan-Evans-Lam process proving inconsistent, attention was turned to their application in an alternative catalytic manifold. The Tsuji-Trost reaction, in which a nucleophile such as an amine, phenol, thiol, enolate or active methylene, undergoes a palladium(0)-catalysed allylation with an allylic moiety such as an allylic acetate, carbonate or halide, was identified as one such catalytic transformation in which the imidate may successfully act as a nucleophilic species (Scheme 3.31).

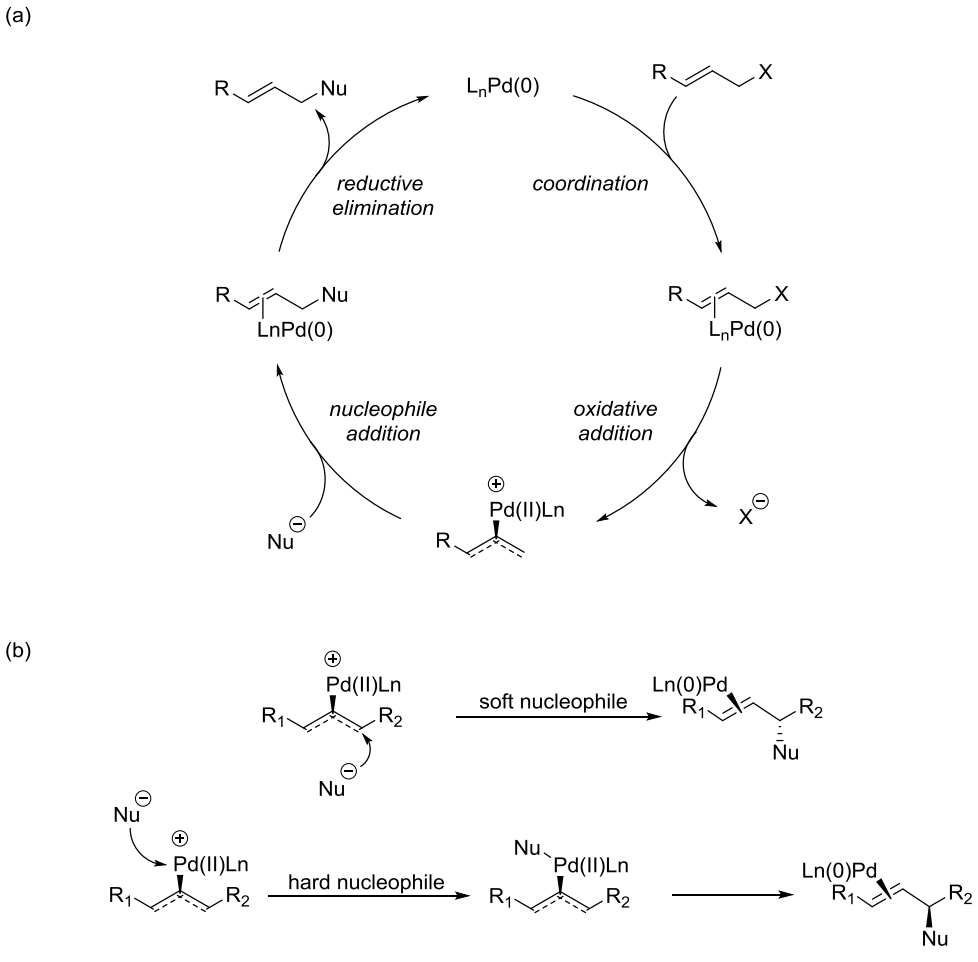


Scheme 3.31: General Tsuji-Trost reaction.

First reported in 1965 by Tsuji, and later adapted by Trost, who elucidated the mechanism and incorporated the use of phosphine ligands, the reaction begins with initial coordination of the palladium(0) catalyst to the alkene, forming an η^2 π-allyl complex (Scheme 3.32a).[184–187] Subsequent oxidative addition, eliminating the leaving group with inversion of configuration, forms the corresponding η^3 π-allyl palladium(II) complex.[186] Addition of the

nucleophile to the η^3 complex, forming a second η^2 π-allyl complex can occur *via* two pathways, dependent on the pK_a of the nucleophile. Soft nucleophiles (pK_a < 25) undergo direct addition to the allyl group, whereas hard nucleophiles (pK_a > 25) attack the palladium centre, with subsequent reductive elimination from the η^2 π-allyl complex furnishing the allylated product (Scheme 3.32b).[186,187] In asymmetric substrates, soft nucleophiles invert the stereochemistry of the π-allyl complex, which in conjunction with an inversion in the oxidative addition step, results in overall retention of stereochemistry in the process.[187,188] On the other hand, the addition of hard nucleophiles retains the stereochemistry of the π-allyl complex, and hence results in an overall inversion of stereochemistry in the reaction.[186,188]

With the structurally similar benzophenone imine possessing a pK_a of 31.0,[189] the imidate derived from benzonitrile is proposed to have a pKa > 25. Accordingly, it is hypothesised that the imidate would nucleophilically attack the palladium centre, based on the established precedent discussed above.



Scheme 3.32: (a) Tsuji-Trost catalytic cycle. (b) Mechanisms of nucleophile addition.[186–188]

3.3.4.1 Initial Optimisation of the Tsuji-Trost Allylation Process Using the Isolated Imidate

For initial optimisation of the Tsuji-Trost allylation, the effect of a range of palladium catalysts and solvents on the reaction of the benzonitrile-derived imidate with allyl acetate was initially investigated (Table 3.11).[190] The use of $[Ir(cod)Cl]_2$, a widely applied catalyst used to furnish branched regioisomers of allylamines, was also investigated.[191,192] From this catalyst and solvent screen, the majority of the conditions screened did not lead to formation of the desired allyl amide **3.41**. However, the use of $Pd(PPh_3)_4$, in CPME and toluene, and $[Ir(cod)Cl]_2$ in toluene resulted in appreciable conversion to the allyl amide (Entries 4, 49 & 54).

Table 3.11: Tsuji-Trost Catalyst and Solvent Screen.

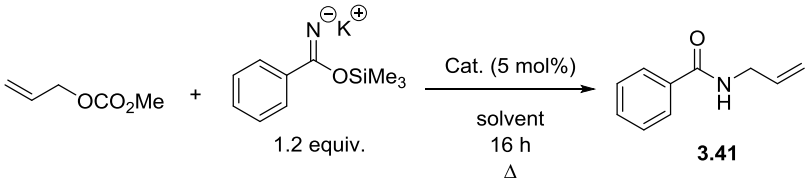
Entry	Catalyst	Solvent	Conversion (%)[a]
1	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	CPME	0
2	$Pd_2(dba)_3$	CPME	0
3	$Pd(dba)_2$	CPME	0
4	$Pd(PPh_3)_4$	CPME	19
5	$Pd(OAc)_2$	CPME	0
6	$PdCl_2$	CPME	0
7	$Pd(t\text{-}Bu_3P)_2$	CPME	1
8	$Pd(cod)Cl_2$	CPME	0
9	$[Ir(cod)Cl]_2$	CPME	9
10	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	DCM	0
11	$Pd_2(dba)_3$	DCM	0
12	$Pd(dba)_2$	DCM	0
13	$Pd(PPh_3)_4$	DCM	5
14	$Pd(OAc)_2$	DCM	0
15	$PdCl_2$	DCM	0
16	$Pd(t\text{-}Bu_3P)_2$	DCM	0
17	$Pd(cod)Cl_2$	DCM	0
18	$[Ir(cod)Cl]_2$	DCM	1
19	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	1,4-Dioxane	0
20	$Pd_2(dba)_3$	1,4-Dioxane	0
21	$Pd(dba)_2$	1,4-Dioxane	0
22	$Pd(PPh_3)_4$	1,4-Dioxane	2
23	$Pd(OAc)_2$	1,4-Dioxane	0
24	$PdCl_2$	1,4-Dioxane	0
25	$Pd(t\text{-}Bu_3P)_2$	1,4-Dioxane	0

26	$Pd(cod)Cl_2$	1,4-Dioxane	0
27	$[Ir(cod)Cl]_2$	1,4-Dioxane	2
28	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	2-MeTHF	0
29	$Pd_2(dba)_3$	2-MeTHF	0
30	$Pd(dba)_2$	2-MeTHF	0
31	$Pd(PPh_3)_4$	2-MeTHF	0
32	$Pd(OAc)_2$	2-MeTHF	0
33	$PdCl_2$	2-MeTHF	0
34	$Pd(t\text{-}Bu_3P)_2$	2-MeTHF	0
35	$Pd(cod)Cl_2$	2-MeTHF	0
36	$[Ir(cod)Cl]_2$	2-MeTHF	4
37	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	THF	0
38	$Pd_2(dba)_3$	THF	0
39	$Pd(dba)_2$	THF	0
40	$Pd(PPh_3)_4$	THF	0
41	$Pd(OAc)_2$	THF	0
42	$PdCl_2$	THF	0
43	$Pd(t\text{-}Bu_3P)_2$	THF	1
44	$Pd(cod)Cl_2$	THF	0
45	$[Ir(cod)Cl]_2$	THF	3
46	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	Toluene	0
47	$Pd_2(dba)_3$	Toluene	0
48	$Pd(dba)_2$	Toluene	0
49	$Pd(PPh_3)_4$	Toluene	12
50	$Pd(OAc)_2$	Toluene	0
51	$PdCl_2$	Toluene	0
52	$Pd(t\text{-}Bu_3P)_2$	Toluene	4
53	$Pd(cod)Cl_2$	Toluene	0
54	$[Ir(cod)Cl]_2$	Toluene	12

[a]Conversion determined by HPLC with reference to an internal standard.

With poor conversions obtained when using allyl acetate, the effect of altering the allylic species used in the screening process was investigated. Accordingly, the corresponding allyl methyl carbonate was instead applied in the Tsuji-Trost process, using catalyst and solvent combinations which were previously successful when using allyl acetate (Table 3.12). Pleasingly, comparable or improved conversions were observed in all catalyst and solvent combinations, with the use of $Pd(PPh_3)_4$ in CPME (Entry 1) the only exception. Therefore, the highest yielding conditions using the different metal species, $[Ir(cod)Cl]_2$ in CPME (Entry 3) and $Pd(t\text{-}Bu_3P)_2$ in toluene (Entry 12), were advanced for further optimisation studies.

Table 3.12: Tsuji-Trost catalyst and solvent screen using allyl methyl carbonate.



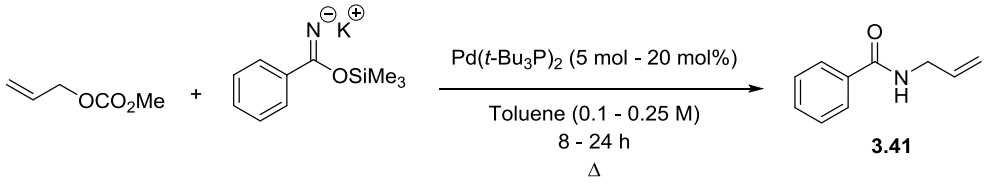
Entry	Catalyst	Solvent	Allyl acetate conversion (%)[a]	Allyl methyl carbonate conversion (%)[a]
1	$Pd(PPh_3)_4$	CPME	19	6
2	$Pd(t\text{-}Bu_3P)_2$	CPME	1	22
3	$[Ir(cod)Cl]_2$	CPME	9	40
4	$Pd(PPh_3)_4$	DCM	5	4
5	$[Ir(cod)Cl]_2$	DCM	1	2
6	$Pd(PPh_3)_4$	1,4-Dioxane	2	1
7	$[Ir(cod)Cl]_2$	1,4-Dioxane	2	33
8	$[Ir(cod)Cl]_2$	2-MeTHF	4	14
9	$Pd(t\text{-}Bu_3P)_2$	THF	1	8
10	$[Ir(cod)Cl]_2$	THF	3	10
11	$Pd(PPh_3)_4$	Toluene	12	13
12	$Pd(t\text{-}Bu_3P)_2$	Toluene	4	23
13	$[Ir(cod)Cl]_2$	Toluene	12	29

[a]Conversion determined by HPLC with reference to an internal standard.

3.3.4.2 Optimisation of the $Pd(t\text{-}Bu_3P)_2$ Catalysed Tsuji-Trost Allylation Process *via* Design of Experiments

Further optimisation of the $Pd(t\text{-}Bu_3P)_2$ catalysed Tsuji-Trost allylation process was initially performed using a DoE approach, with a two-level half-fractional design selected, evaluating the following 5 factors: loading of $Pd(t\text{-}Bu_3P)_2$ (5 – 20 mol%); equivalents of allyl methyl carbonate (1 – 3 equiv.); equivalents of imidate (0.5 – 1.5 equiv.); reaction concentration (0.1 – 0.25 M) and reaction time (8 – 24 h) (Table 3.13). Initial analysis of the conversions obtained showed no improvement on the 23% conversion to allyl amide **3.41** achieved in the prior catalyst and solvent screen. However, several of the experiments performed at a concentration of 0.1 M for 24 hours did result in comparable conversions (Entries 7, 15 & 17).

Table 3.13: DoE optimisation of Pd(*t*-$Bu_3P)_2$ catalysed Tsuji-Trost.



3.41

Entry	Pd(*t*-$Bu_3P)_2$ (mol%)	Allyl methyl carbonate (equiv.)	Imidate (equiv.)	Concentration (M)	Time (h)	Conversion (%)[a]
1	12.5	2	1	0.175	16	13
2	5	3	0.5	0.1	8	18
3	5	1	1.5	0.25	24	5
4	5	1	0.5	0.25	8	13
5	20	3	0.5	0.25	8	4
6	5	1	1.5	0.1	8	7
7	5	1	0.5	0.1	24	22
8	12.5	2	1	0.175	16	13
9	20	3	1.5	0.1	8	17
10	20	1	1.5	0.1	24	7
11	12.5	2	1	0.175	16	13
12	5	3	0.5	0.25	24	9
13	20	1	0.5	0.1	8	18
14	5	3	1.5	0.25	8	9
15	20	3	0.5	0.1	24	22
16	20	1	1.5	0.25	8	4
17	5	3	1.5	0.1	24	23
18	12.5	2	1	0.175	16	14
19	20	3	1.5	0.25	24	6
20	20	1	0.5	0.25	24	9

[a]Conversion determined by HPLC with reference to an internal standard.

The conversions obtained were then analysed *via* a half-normal plot and a Pareto Chart using the Design Expert®[172] software so as to determine the factors bearing an effect on the efficiency of the reaction (Figure 3.10). From these, it could clearly be established that concentration (Point D) was the sole factor having a pronounced effect on the reaction outcome.

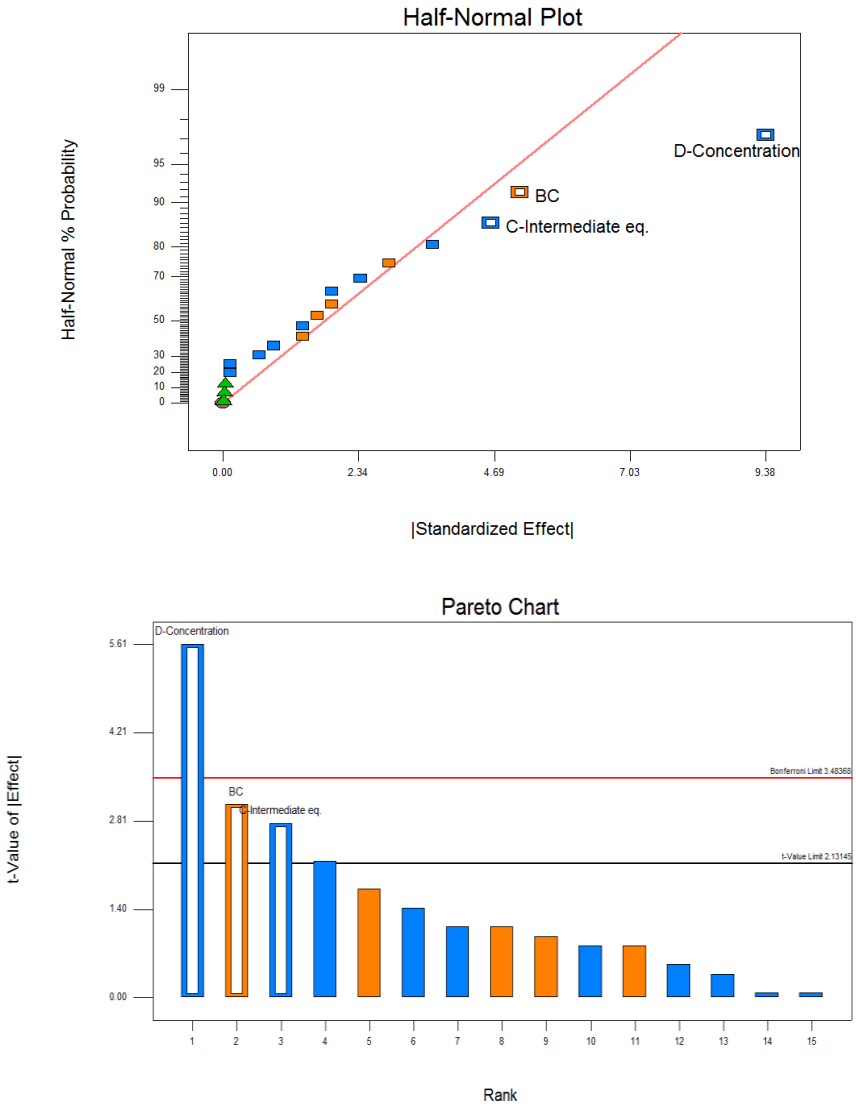


Figure 3.10: Half-normal plot and Pareto chart indicating the pronounced effect of reaction concentration on the Tsuji-Trost allylation process.

Again, as noted in the DoE optimisation of the Chan-Evans-Lam process, the sole dependency on reaction concentration resulted in an inaccurate portrayal of the obtained data in the 3D response surface (Figure 3.11). With no further improvement in the conversion of the Tsuji-Trost process to allyl amide **3.41** achieved, alternative optimisation procedures were therefore undertaken.

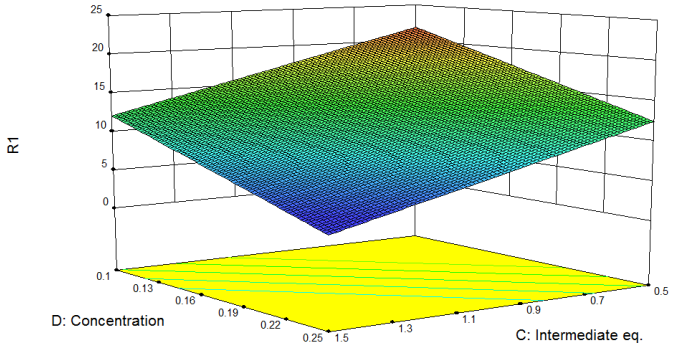
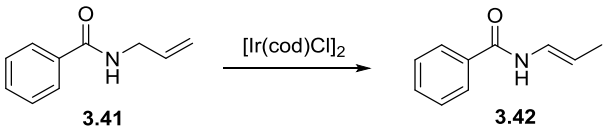


Figure 3.11: 3D response surface generated from obtained conversions.

3.3.4.3 Investigating the Effect of Exogenous Ligands on the Tsuji-Trost Allylation

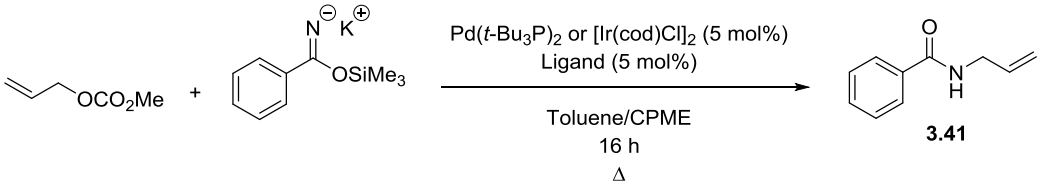
Upon NMR analysis of the isolated product from the $[Ir(cod)Cl]_2$ catalysed process performed in CPME, it was established that a complex mixture was formed in the reaction. This observation is perhaps a result of isomerisation of **3.41**, resulting in an isomeric mixture (Scheme 3.33) Additionally, with the DoE optimisation procedure using $Pd(t\text{-}Bu_3P)_2$ found to be unsuccessful in further improving the conversion, the addition of a range of phosphine ligands to both catalyst conditions was investigated (Table 3.14).



3.41 **3.42**

Scheme 3.33 Potential isomerisation of amide 3.41.

Table 3.14: Effect of exogenous phosphine ligands on the Tsuji-Trost allylation.

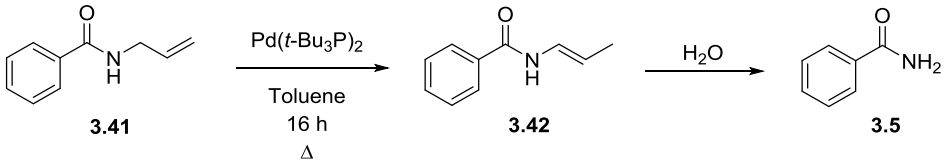


Entry	Ligand	Catalyst	Conversion (%)
1	PPh_3	$[Ir(cod)Cl]_2$	42
		$Pd(t\text{-}Bu_3P)_2$	7
2	PCy_3	$[Ir(cod)Cl]_2$	42
		$Pd(t\text{-}Bu_3P)_2$	7
3	TTMPP	$[Ir(cod)Cl]_2$	20
		$Pd(t\text{-}Bu_3P)_2$	12
4	Dppe	$[Ir(cod)Cl]_2$	28
		$Pd(t\text{-}Bu_3P)_2$	8
5	Di-*tert*-butylphenylphosphine	$[Ir(cod)Cl]_2$	41
		$Pd(t\text{-}Bu_3P)_2$	14
6	$TTBP.HBF_4$	$[Ir(cod)Cl]_2$	28
		$Pd(t\text{-}Bu_3P)_2$	12
7	CyJohnPhos	$[Ir(cod)Cl]_2$	33
		$Pd(t\text{-}Bu_3P)_2$	12
8	DavePhos	$[Ir(cod)Cl]_2$	40
		$Pd(t\text{-}Bu_3P)_2$	9
9	RuPhos	$[Ir(cod)Cl]_2$	34
		$Pd(t\text{-}Bu_3P)_2$	14
10	SPhos	$[Ir(cod)Cl]_2$	38
		$Pd(t\text{-}Bu_3P)_2$	17
11	XantPhos	$[Ir(cod)Cl]_2$	38
		$Pd(t\text{-}Bu_3P)_2$	5
12	XPhos	$[Ir(cod)Cl]_2$	37
		$Pd(t\text{-}Bu_3P)_2$	9

[a]Conversion determined by HPLC with reference to an internal standard.

Unfortunately, the addition of any exogenous phosphine ligand to the $Pd(t\text{-}Bu_3P)_2$ allylation conditions was found to have a deleterious effect on reaction efficiency (Entries 1 - 12). Comparable conversions were obtained, however, for the $[Ir(cod)Cl]_2$ catalysed allylation conditions when using PPh_3, PCy_3, di-*tert*-butylphosphine and DavePhos (Entries 1, 2, 5 & 8 respectively). Disappointingly, NMR analysis of the products formed in the reactions with these respective catalysts, showed no improvement in the unquantifiable reaction mixture.

One plausible explanation for the poor conversions observed, and the inability to further optimise the process, is the potential for enamide **3.42** to degrade, resulting in the formation of benzamide (Scheme 3.34). With benzamide formed, it would therefore be difficult to ascertain whether the benzamide observed by HPLC analysis of the reaction mixture is formed *via* hydrolysis of the imidate, or *via* this potential competing pathway.

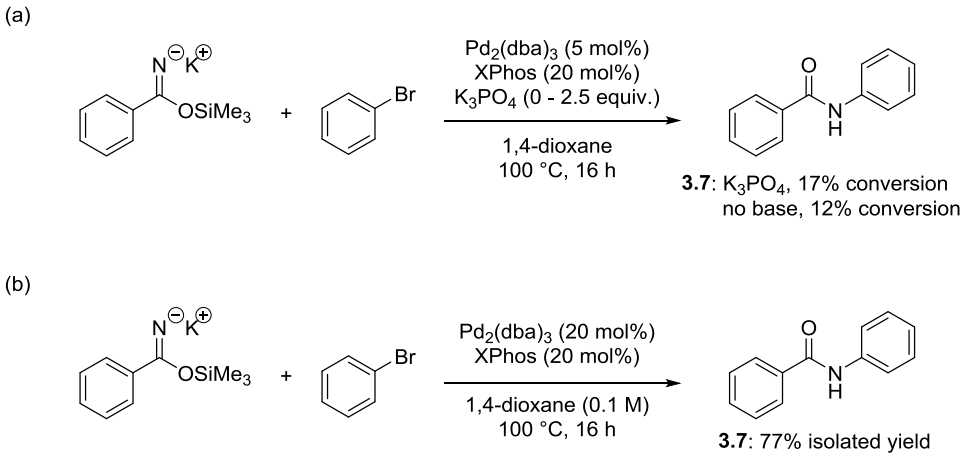


Scheme 3.34: Potential degradation of 3.42 to benzamide *via* isomerisation to an enamide.

3.4 Conclusions

Following Merchant's report detailing the formation of primary amides *via* the potassium silanolate-mediated hydrolysis of nitriles, it was proposed that the intermediary silanoate-derived imidate salt could be utilised as an amide surrogate in a range of different transformations. With initial attempts at developing an alkylation methodology proving to be low yielding, potentially as a result of the poor solubility or nucleophilicity of the imidate, attention was instead focused on alternative catalytic processes.

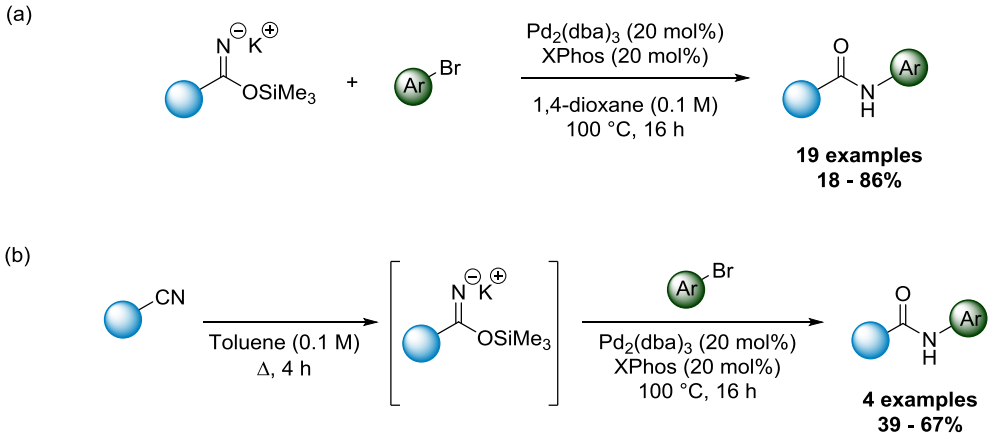
Pleasingly, inspired by the use of LiHMDS as an amide surrogate in Buchwald-Hartwig amination process, prior isolation of the imidate species enabled its use in a Buchwald-Hartwig amidation reaction, initially furnishing the desired secondary amide **3.7** in 17% conversion (Scheme 3.35a).[159,161] Further optimisation of the process *via* a Design of Experiments approach investigating the levels of catalyst, ligand and base used in the reaction, alongside reaction concentration and reaction temperature, allowed the efficiency of the process to be further improved, with amide **3.7** isolated in 77% isolated yield (Scheme 3.35b).



Scheme 3.35: (a) Initial conversions from ligand screen. (b) Optimised reaction conditions.

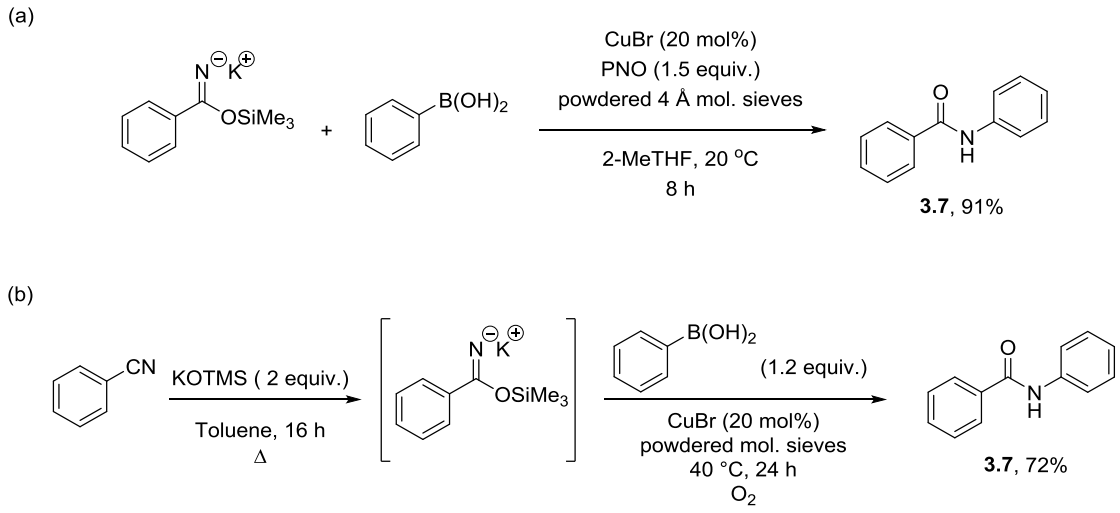
The scope of the Buchwald-Hartwig amidation process was then exemplified, with a diverse range of nitrile-derived imidate species and aryl halides successfully coupled, furnishing 19 secondary amides (Scheme 3.36a). However, electron-deficient aryl halides were found to couple more efficiently than electron-neutral or electron-rich halides, which is in line with the propensity of these species to undergo oxidative addition to the palladium metal. The optimum conditions were also successfully adapted to enable a one-pot process, with the required imidate species formed *in situ*, *via* substitution of the reaction solvent from 1,4-dioxane to toluene, in which imidate formation is promoted (Scheme 3.36b). The scope

of the one-pot process is, however, more limited, as demonstrated by the unsuccessful coupling of alkyl nitrile species which were found to be competent substrates when the intermediary imidate is isolated. Although it employs the use of transition metals, the current methodology represents a catalytic approach to amide bond formation, therefore can be considered more atom economical than traditional amide bond forming methodologies which require the use of stoichiometric coupling reagents. Additionally the wide commercial availability, and stability, of nitrile compounds is advantageous when compared to the use of substrates such as aldehydes in amidation processes.



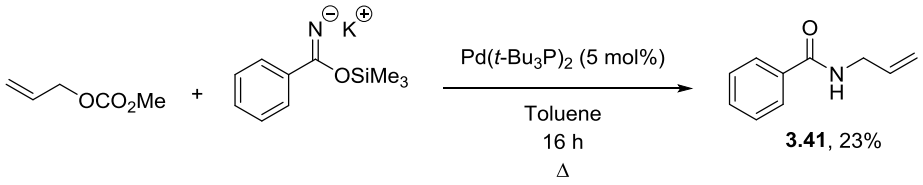
Scheme 3.36: **Buchwald-Hartwig amidation processes.**

With a view to widening the scope of the transition metal catalysed formation of secondary amides, and to also mitigate the high loadings of palladium required, the application of the silanoate-derived imidates species in a Chan-Evans-Lam amidation process was investigated. Screening a range of copper catalysts and oxidative conditions, followed by a DoE optimisation process, enabled amide **3.7** to be synthesised in 91% isolated yield (Scheme 3.37a). However, this process proved to be capricious in nature, with further studies unable to elucidate the source of the observed inconsistencies.[183] Pleasingly, a comparable one-pot process was still found to efficiently afford the desired secondary amide (Scheme 3.37b).



Scheme 3.37: (a) Optimised Chan-Evans-Lam amidation conditions. (b) One-pot Chan-Evans-Lam amidation conditions.

The final catalytic manifold in which the use of the silanoate-derived imidate species was examined as an amide surrogate was the Tsuji-Trost allylation reaction. Initial screening of appropriate ligand and solvent conditions using allyl acetate resulted in only low conversion to the desired amide **3.41**. Altering the alkene species to allyl methyl carbonate resulted in moderate conversions to **3.41** using both Pd(*t*-$Bu_3P)_2$ and $[Ir(cod)Cl]_2$ (Scheme 3.38). However, neither catalytic conditions could be successfully further optimised.



Scheme 3.38: Tsuji-Trost allylation using imidate species.

3.5 Future Work

The use of silanoate-derived imidate species as amide surrogates in a Buchwald-Hartwig cross coupling amidation protocol has been successfully exemplified. However, thus far, they have proven to be challenging substrates in further catalytic manifolds, as well as alkylation reactions. Therefore, future work should focus on further optimising their use in these transformations.

When applied in alkylation reactions, it is proposed that the insolubility and poor nucleophilicity of the imidate species hindered its effective use. With the Buchwald-Hartwig approach shown to successfully proceed in 1,4-dioxane, it is apparent that the imidate has a degree of solubility in this reaction media, and therefore the use of this as the solvent in alkylation reactions may prove successful. Alternatively, to improve the nucleophilicity of the imidate species, the use of 18-crown-6 (Figure 3.12) could be investigated. With an affinity for a range of small cations, this would bind to the potassium counterion present in the imidate salt species, thereby leaving the naked nitrogen anion, which may improve the competency of the imidate as a nucleophile. However, this approach would compromise the atom efficiency of the process.

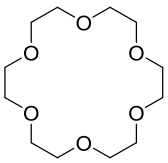
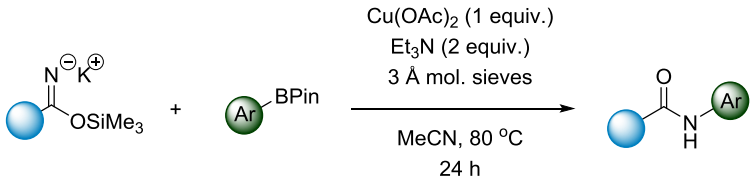


Figure 3.12: 18-crown-6

Additionally, if demonstrated to be an effective nucleophile in alkylation reactions, the applicability of the imidate as a nucleophile in S_NAr reactions could be investigated. Although shown to be chemoselective for the desired Buchwald-Hartwig reaction in the presence of aryl fluorides, further optimisation of the imidate species towards their use as nucleophiles, or the use of more activated aryl fluorides may allow the imidate species to be employed in this manner.

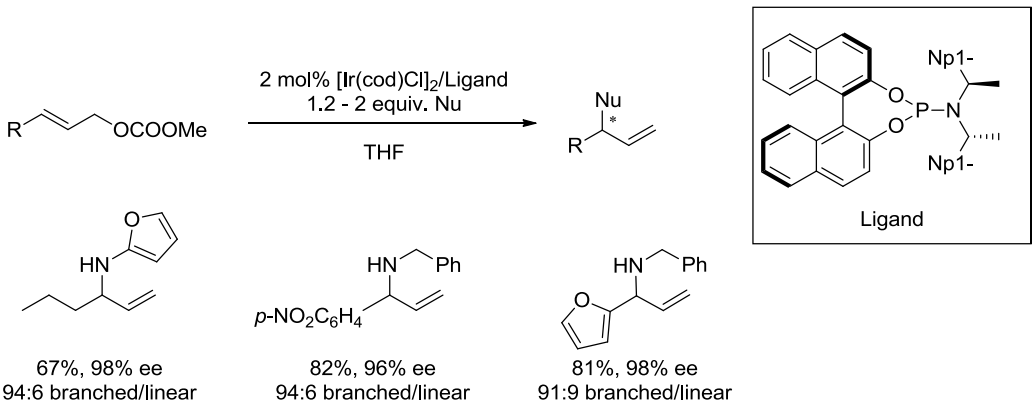
Although the use of the isolated imidate species led to inconsistencies when applied in a Chan-Evans-Lam approach to amide bond formation, the initial success of the reaction indicates that the transformation is viable. With the use of boronic acid pinacol esters recently reported as effective coupling partners with both aryl and alkyl amines in the Chan-Evans-Lam reaction,[193] the effect of these boron species in the cross-coupling with the silanoate-derived imidate species could be investigated (Scheme 3.39). Additionally, further

investigation of the nascent one-pot process, with ultimate exemplification of the scope of the reaction may allow the development of a catalytic process complimentary to the Buchwald-Hartwig amidation methodology. With the cost, toxicity and abundancy associated with the use of a copper catalyst species advantageous over the use of palladium, this would also lead to a more sustainable, cost-effective catalytic amide bond formation.[178]



Scheme 3.39: Proposed Chan-Evans-Lam process utilising the imidate species with aryl BPins.

In the Tsuji-Trost allylation process, the use of both palladium and iridium catalysis has been shown to lead to moderate formation of the desired allylated amide product. With the degradation of the desired amide **3.41** to benzamide proposed to be a potential competing pathway *via* isomerisation to the corresponding enamide, alteration of the allyl moiety could indicate whether this alternative process is viable, whilst also leading to further improvement in the desired process. Additionally, investigating the use of phosphoramidite-derived ligands in conjunction with $[Ir(cod)Cl]_2$, the use of which has led to regioselectivity in favour of the branched regioisomers, could allow the methodology to be utilised to form both linear and branched amides with judicious catalyst selection (Scheme 3.40).[192,194,195] If successful, the application of chiral variants of these ligands could also offer an approach to the development of an enantioselective allylation approach.



Scheme 3.40: Example of the regio-and enantioselectivities generated by the use of phosphoramidite-derived ligands and $[Ir(cod)Cl]_2$ in allylation reactions with amines.[192]

3.6 Experimental

3.6.1 General Techniques

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[123] When purification was carried out *via* distillation, the relevant desiccants are indicated in brackets.

3.6.1.1 Purification of Solvents

i) THF and toluene used in the formation of silanoate intermediate salts were obtained from a PureSolv SPS-400-5 solvent purification system.

ii) 2-MeTHF (CaH_2) and *tert*-butyl methyl ether ($CaSO_4$) were purified by fractional distillation.

iii) CPME (Na metal), 1,2-dimethoxyethane (CaH_2) 1,4-dioxane ($LiAlH_4$) and DMF ($MgSO_4$) were purified by vacuum distillation.

iv) DCM was purified by stirring over 4 Å molecular sieves for 24 hours.

v) Purified solvents were transferred to and stored in septum-sealed oven-dried flasks over activated 4 Å molecular sieves and purged with and stored under nitrogen.

vi) Ethyl acetate, methanol and petroleum ether 40–60 °C used for purification purposes were used as obtained from suppliers without further purification.

3.6.1.2 Purification of Reagents

i) K_3PO_4, Li_3PO_4, $Mg_3(PO_4)_2$ and Na_3PO_4 were stored in a vacuum oven at 60 °C.

ii) KO*t*Bu and NaO*t*Bu purified by sublimation.

3.6.1.3 Experimental Details

i) Alkylation, Buchwald-Hartwig and Tsuji-Trost reactions were carried out using oven-dried (150 °C) glassware, which was evacuated and purged with N_2 before use.

ii) Purging refers to a vacuum/nitrogen-refilling process.

iii) Reactions performed in Radleys Tubes using a carousel resting on a temperature-regulated hotplate/stirrer.

iv) Room-temperature was generally *ca.* 20 °C

v) Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

3.6.1.4 Purification of Products

i) Thin layer chromatography performed using Merck silica plates coated in fluorescent indicator UV254. These were then analysed under 254 nm UV light.

ii) Flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel.

iii) Strong cation exchange chromatography was carried out using Silicycle Silia*Prep*^{TM} Propylsulfonic Acid (SCX-2) cartridges.

3.6.1.5 Analysis of Products

i) Fourier Transformed Infra-Red (FTIR) spectra were obtained using a Shimadzu IRAffinity-1 machine and an A2 Technologies ATR 32 machine.

ii) ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX 500 spectrometer at 500 and 126MHz, respectively or on a Bruker AV3 400 at 400 and 101 MHz, respectively, or on a Bruker AVANCE 400 spectrometer at 400 and 101 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.16 ppm (^{13}C), DMSO-d6 referenced at 2.50 (^{1}H) and 39.52 ppm (^{13}C), and MeOD-d4 referenced at 3.31 (^{1}H) and 49.00 (^{13}C).

iii) High-resolution mass spectra were obtained on a Thermofisher LTQ Orbitrap XL instrument at the EPSRC National Mass Spectrometry Service Centre (NMSSC), Swansea

iv) Reverse phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column.

3.6.1.6 Reversed-Phase HPLC Methods

i) For *N*-Benzylbenzamide **3.6**: Reversed phase HPLC analysis was performed using a gradient method, eluting with 5 – 80% MeCN/H_2O over 5 minutes at a flow rate of 2 mL/min, with benzamide, benzonitrile, *N*-benzylbenzamide, benzyl bromide and iodobenzene internal standard eluting at 1.37, 2.27, 2.49, 3.00 and 3.30 minutes, respectively.

Time (min)	Concentration of MeCN (%)
0.0	5
2.0	60
3.7	80
4.3	5

For *N*-Phenylbenzamide **3.7**: Reversed phase HPLC analysis was performed using a gradient method, eluting with 5 – 80% MeCN/H_2O over 5 minutes at a flow rate of 2 mL/min, with benzamide, benzonitrile, *N*-phenylbenzamide, bromobenzene and 1-methylnapthalene internal standard eluting at 1.37, 2.27, 2.57, 3.14 and 3.60 minutes, respectively.

Time (min)	Concentration of MeCN (%)
0.0	5
2.0	60
3.7	80
4.3	5

For *N*-Allylbenzamide **3.41**: Reversed phase HPLC analysis was performed using a gradient method, eluting with 5 – 80% MeCN/H_2O over 6 minutes at a flow rate of 2 mL/min, with benzamide, *N*-allylamide and biphenyl internal standard eluting at 1.85, 2.80 and 4.48 minutes, respectively.

Time (min)	Concentration of MeCN (%)
0	5
4.10	60
4.3	5

ii) For *N*-Benzylbenzylamide **3.6**, *N*-phenylbenzamide **3.7** and *N*-allylamide **3.41**: For reactions using an internal standard, prior HPLC calibration was carried out using samples containing varying molarities of product and iodobenzene, 1-methylnapthalene or biphenyl respectively, allowing calculation of the response factor by substituting values into the following equation:

$$Response\ Factor = \frac{(\frac{Area}{Molarity})Product}{(\frac{Area}{Molarity})Standard}$$

Screening reactions were carried out using a known molarity of iodobenzene, 1-methylnapthalene or biphenyl internal standard as indicated in the relevant general experimental procedures.

Unknown molarities of product were calculated by rearranging the above equation, using the average value for the response factor as determined during calibration.

Conversion to product was calculated as a percentage of the theoretical molarity for the reaction.

iii) Samples for HPLC analysis were prepared by diluting a 10 μL aliquot from the reaction mixture to 1 mL with MeCN.

3.6.2 General Experimental Procedures

General Experimental Procedure A for the Isolation of the Silanoate-Derived Imidate Species

To an oven dried round-bottomed flask containing potassium trimethylsilanolate (257 mg, 2 mmol, 2 equiv.) was added anhydrous THF/toluene (5 mL) and benzonitrile (104 μL, 1 mmol, 1 equiv.). The reaction mixture was refluxed for 16 hours (THF) or for 4 hours (toluene). The solid precipitate was then filtered off, washed with the corresponding anhydrous solvent and allowed to dry *via* vacuum. The resulting imidate species was then used directly in subsequent experiments without further purification.

General Experimental Procedure B for One-Pot Alkylation Reactions Performed Using the Isolated Imidate Species

To an oven dried round-bottomed flask containing potassium trimethylsilanolate (257 mg, 2 mmol, 2 equiv.) was added solvent (5 mL) and benzonitrile (104 μL, 1 mmol, 1 equiv.). The reaction mixture was then refluxed for 16 hours. Benzyl bromide (295 μL, 1.2 mmol, 1.2 equiv.), iodobenzene (2 mmol) and an additive added (if applicable). The reaction mixture was then refluxed for 2-4 hours. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to iodobenzene as the internal standard.

Entry	Solvent	Additive	Time (h)	Conversion (%)
1	THF	-	4	8
2	THF	TBAI (10 mol%)	4	0
3	THF	BnBr (5 equiv.)	4	3
4	DMF	-	2	2

3.6.2.1 General Experimental Procedures for Buchwald-Hartwig Amidation Process

General Procedure C for One-Pot Buchwald Hartwig Process: Ligand and Base Screen

To an oven dried Radley's reaction tube containing potassium trimethylsilanolate (257 mg, 2 mmol, 2 equiv.) was added toluene (5 mL) and benzonitrile (104 μL, 1 mmol, 1 equiv.). The reaction mixture was then refluxed for 4 hours. $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 0.05 equiv.), ligand (0.1 – 0.2 mmol, 0.1 – 0.2 equiv.), and base (0 – 5 mol, 0 - 2.5 equiv.) were then added and the reaction tube purged. The reaction mixture was stirred at 80 °C for 10 min, at which point bromobenzene (188 μL, 0.8 mmol, 0.8 equiv.) and 1-methylnapthalene (71.2 μL, 0.5 mmol, 0.5 equiv.) were added and the reaction tube purged, before the reaction was stirred at 80 °C for 16 hours. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to 1-methylnapthalene as the internal standard.

Entry	Ligand	Ligand Loading (mol%)	Base	Base (equiv.)	Conversion (%)
1	JohnPhos	15	-	-	0
2	DavePhos	15	-	-	0
3	d*t*bpf	10	-	-	0
4	SPhos	15	-	-	0
5	XPhos	20	-	-	1
6	*t*BuXPhos	20	-	-	3
7	JohnPhos	15	KO*t*Bu	1.2	0
8	DavePhos	15	KO*t*Bu	1.2	0
9	d*t*bpf	10	KO*t*Bu	1.2	0
10	SPhos	15	KO*t*Bu	1.2	0
11	XPhos	20	KO*t*Bu	1.2	1
12	*t*BuXPhos	20	KO*t*Bu	1.2	4
13	JohnPhos	15	NaO*t*Bu	1.2	0
14	DavePhos	15	NaO*t*Bu	1.2	0
15	d*t*bpf	10	NaO*t*Bu	1.2	1
16	SPhos	15	NaO*t*Bu	1.2	0
17	XPhos	20	NaO*t*Bu	1.2	0
18	*t*BuXPhos	20	NaO*t*Bu	1.2	1

19	JohnPhos	15	K_3PO_4	2.5	0
20	DavePhos	15	K_3PO_4	2.5	3
21	d*t*bpf	10	K_3PO_4	2.5	2
22	SPhos	15	K_3PO_4	2.5	0
23	XPhos	20	K_3PO_4	2.5	0
24	*t*BuXPhos	20	K_3PO_4	2.5	2

General Procedure D for the Buchwald-Hartwig Amidation Process using the Isolated Imidate: Ligand, Base and Solvent Screen

To an oven dried Radley's reaction tube containing potassium (phenyl((trimethylsilyl)oxy)methylene)amide (200 mg, 0.86 mmol, 1 equiv.) was added $Pd_2(dba)_3$ (40 mg, 0.04 mmol, 0.05 equiv.), ligand (0.08 – 0.16 mmol, 0.1 – 0.2 equiv.) and base (0 – 2.5 equiv.). The reaction tube was then purged. Solvent (5 mL) was then added and the contents stirred at the required reaction temperature for 10 minutes. Bromobenzene (73 μL, 0.69 mmol, 0.8 equiv.) and 1-methylnapthalene (61 μL, 0.43 mmol, 0.5 equiv.) were then added to the reaction tube, and the reaction was then stirred at the required reaction temperature for 16 hours. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to 1-methylnapthalene as the internal standard.

Entry	**Ligand**	**Ligand Loading (mol%)**	**Base**	**Base equiv.**	**Solvent**	**Temp. (°C)**	**Conversion (%)**
1	JohnPhos	15	-	-	DME	40	0
2	DavePhos	15	-	-	Toluene	80	0
3	d*t*bpf	10	-	-	THF	80	1
4	SPhos	15	-	-	Toluene	100	2
5	XPhos	20	-	-	1,4-dioxane	100	12
6	*t*BuXPhos	20	-	-	THF	40	0
7	JohnPhos	15	KO*t*Bu	1.2	DME	40	0
8	DavePhos	15	KO*t*Bu	1.2	Toluene	80	1
9	d*t*bpf	10	KO*t*Bu	1.2	THF	80	0
10	SPhos	15	KO*t*Bu	1.2	Toluene	100	0
11	XPhos	20	KO*t*Bu	1.2	1,4-dioxane	100	3

12	*t*BuXPhos	20	KO*t*Bu	1.2	THF	40	0
13	JohnPhos	15	NaO*t*Bu	1.2	DME	40	0
14	DavePhos	15	NaO*t*Bu	1.2	Toluene	80	0
15	d*t*bpf	10	NaO*t*Bu	1.2	THF	80	0
16	SPhos	15	NaO*t*Bu	1.2	Toluene	100	1
17	XPhos	20	NaO*t*Bu	1.2	1,4-dioxane	100	0
18	*t*BuXPhos	20	NaO*t*Bu	1.2	THF	40	0
19	JohnPhos	15	K_3PO_4	2.5	DME	40	0
20	DavePhos	15	K_3PO_4	2.5	Toluene	80	0
21	d*t*bpf	10	K_3PO_4	2.5	THF	80	0
22	SPhos	15	K_3PO_4	2.5	Toluene	100	0
23	XPhos	20	K_3PO_4	2.5	1,4-dioxane	100	17
24	*t*BuXPhos	20	K_3PO_4	2.5	THF	40	0

General Experimental Procedure E for the Optimisation of the Buchwald-Hartwig Process Using the Isolated Imidate *via* a DoE Approach

To an oven dried Radley's Tube containing potassium (phenyl((trimethylsilyl)oxy)methylene) amide (200 mg, 0.86 mmol, 1 equiv.) was added $Pd_2(dba)_3$ (40 – 158 mg, 0.04 – 0.16 mmol, 0.05 – 0.2 equiv.), XPhos (21 – 82 mg, 0.04 – 0.16 mmol, 0.05 – 0.2 equiv.) and K_3PO_4 (0 – 458 mg, 0 – 2.15 mmol, 0 – 2.5 equiv.). The reaction tube was then purged and 1,4-dioxane added (4.3 – 8.6 mL). The reaction mixture was then stirred at the required temperature for 10 minutes. Bromobenzene (73 μL, 0.69 mmol, 0.8 equiv.) and 1-methylnapthalene (61 μL, 0.43 mmol, 0.5 equiv.) were then added and the reaction tube purged. The reaction mixture was then stirred at the required reaction temperature for 16 hours. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to 1-methylnapthalene as the internal standard.

Entry	K_3PO_4 Equiv.	$Pd_2(dba)_3$ Loading (mol%)	XPhos Loading (mol%)	Volume of 1,4-dioxane (mL)	Conc. (M)	Temp. (°C)	Conversion (%)
1	1.25	12.5	12.5	6.5	0.15	80	28
2	1.25	12.5	12.5	6.5	0.15	80	25
3	0	5	20	4.3	0.2	100	14
4	2.50	20	5	4.3	0.2	60	2
5	0	20	5	8.6	0.1	60	3
6	0	20	5	4.3	0.2	100	16
7	0	5	20	8.6	0.1	60	0
8	2.50	20	20	4.3	0.2	100	51
9	0	20	20	8.6	0.1	100	59 (77)[a]
10	2.50	5	5	8.6	0.1	60	0
11	2.50	20	5	8.6	0.1	100	11
12	2.50	5	5	4.3	0.2	100	1
13	2.50	20	20	8.6	0.1	60	24
14	0	20	20	4.3	0.2	60	20
15	2.50	5	20	8.6	0.1	100	7
16	0	5	5	4.3	0.2	60	0
17	2.50	5	20	4.3	0.2	60	1
18	0	5	5	8.64	0.1	100	1

[a]Isolated yield.

General Experimental Procedure F for Investigation of the Substrate Scope of the Buchwald-Hartwig Amidation Process Using the Isolated Intermediate

To an oven dried Radley's reaction tube containing desired potassium imidate species (0.86 mmol, 1 equiv.) was added $Pd_2(dba)_3$ (158 mg, 0.16 mmol, 0.2 equiv.) and XPhos (82 mg, 0.16 mmol, 0.2 equiv.). The reaction tube was then purged and 1,4-dioxane (8.6 mL) added. The reaction mixture was then heated at 100 °C for 10 min. Desired aryl halide (0.69 mmol, 0.8 equiv.) was then added and the reaction tube purged. The reaction mixture was then heated at 100 °C for 16 hours. The reaction mixture was taken up in EtOAc (30 mL) and washed with brine (3x30 mL). The organics were extracted, dried (Na_2SO_4) and then concentrated to a residue which was purified by flash column chromatography to afford the aryl amide product.

General Experimental Procedure G for Optimisation of the Buchwald-Hartwig Amidation Process towards a One-Pot Process.

To an oven dried, purged Radley's reaction tube containing potassium trimethylsilanolate (64 mg, 0.5 mmol, 2 equiv.) was added toluene or 1,4-dioxane (5 mL) and benzonitrile (26 µL, 0.25 mmol, 1 equiv.). $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 0.2 equiv.), XPhos (24 mg, 0.05 mmol, 0.2 equiv.) and bromobenzene (21 µL, 0.2 mmol, 0.8 equiv.) were added to the reaction tube at the desired time, and the tube was then re-purged and the reaction stirred at 100 °C for 16 hours. The reaction mixture was taken up in EtOAc (30 mL) and washed with brine (3 x 30 mL). The organics were extracted, dried and then concentrated to a residue which was purified by flash column chromatography (10% EtOAc/Petroleum ether (40-60 °C) to afford the amide product.

Entry	Conditions	Solvent	Yield (%)
1	Concomitant addition of reagents	1,4-dioxane	12
2	4 hour preformation of imidate at reflux	1,4-dioxane	39
3	Concomitant addition of reagents	Toluene	21
4	4 hour preformation of imidate at reflux	Toluene	67

General Experimental Procedure H for Investigating the Scope of the One-Pot Buchwald-Hartwig Amidation Process.

To an oven dried, purged Radley's reaction tube containing potassium trimethylsilanolate (64 mg, 0.5 mmol, 2 equiv.) was added toluene (5 mL) and the desired nitrile species (0.25 mmol, 1 equiv.), and the reaction heated at reflux for 4 hours. $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 0.2 equiv.) and XPhos (24 mg, 0.05 mmol, 0.2 equiv.) added to the reaction tube, which was then re-purged. Desired aryl halide (0.2 mmol, 0.8 equiv.) added to the reaction tube and the reaction stirred at 100 °C for 16 hours. The reaction mixture was taken up in EtOAc (30 mL) and washed with brine (3 x 30 mL). The organics were extracted, dried and then concentrated to a residue which was purified by flash column chromatography to afford the amide product.

3.6.2.2 General Experimental Procedures for Chan-Evans-Lam Amidation Process

General

General Experimental Procedure I for Screening the Solvent and Oxidative Conditions Used in the Chan-Evans-Lam Amidation Process

To an oven dried Radleys tube containing potassium (phenyl((trimethylsilyl)oxy)methylene) amide (100 mg, 0.43 mmol, 1 equiv.) was added phenylboronic acid (105 mg, 0.86 mmol, 2 equiv.), $Cu(OAc)_2$ (16 mg, 0.09 mmol, 0.2 equiv.) and powdered 4 Å molecular sieves. PNO (45 mg, 0.48 mmol, 1.1 equiv.), TEMPO (74 mg, 0.48 mmol, 1.1 equiv.) or myristic acid (20 µL, 0.09 mmol, 0.2 equiv.) also added if required. Solvent (5 mL) and 1-methylnapthalene (31 µL, 0.22 mmol, 0.5 equiv.) added to the reaction mixture, which was then exposed to the required atmosphere, and the reaction mixture was then stirred at 40 °C for 24 hours. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to 1-methylnapthalene as the internal standard.

Entry	Solvent	Atmosphere	Additive	Conversion (%)
1	DCM	Air	-	1
2	1,4-dioxane	Air	-	17
3	THF	Air	-	3
4	*t*BME	Air	-	16
5	CPME	Air	-	3
6	2-MeTHF	Air	-	42
7	DCM	Air	PNO	33
8	1,4-dioxane	Air	PNO	37
9	THF	Air	PNO	42
10	*t*BME	Air	PNO	13
11	CPME	Air	PNO	24
12	2-MeTHF	Air	PNO	41
13	DCM	Air	TEMPO	5
14	1,4-dioxane	Air	TEMPO	3
15	THF	Air	TEMPO	2
16	*t*BME	Air	TEMPO	16
17	CPME	Air	TEMPO	8
18	2-MeTHF	Air	TEMPO	8
19	DCM	Air	Myristic Acid	3
20	1,4-dioxane	Air	Myristic Acid	8
21	THF	Air	Myristic Acid	13
22	*t*BME	Air	Myristic Acid	4
23	CPME	Air	Myristic Acid	3
24	2-MeTHF	Air	Myristic Acid	9
25	DCM	O_2	-	4
26	1,4-dioxane	O_2	-	16
27	THF	O_2	-	22

28	*t*BME	O_2	-	19
29	CPME	O_2	-	9
30	2-MeTHF	O_2	-	22

General Experimental Procedure J for Screening the Catalyst and Oxidative Conditions Used in the Chan-Evans-Lam Amidation Process

To an oven dried Radleys tube containing potassium (phenyl((trimethylsilyl)oxy)methylene) amide (100 mg, 0.43 mmol, 1 equiv.) was added phenylboronic acid (105 mg, 0.86 mmol, 2 equiv.), the required copper catalyst (0.09 mmol, 0.2 equiv.) and powdered 4 Å molecular sieves. PNO (45 mg, 0.48 mmol, 1.1 equiv.) or TEMPO (74 mg, 0.48 mmol, 1.1 equiv.) also added if required. 2-MeTHF (5 mL) and 1-methylnapthalene (31 µL, 0.22 mmol, 0.5 equiv.) added to the reaction mixture, which was then exposed to the required atmosphere, and the reaction mixture was then stirred at 40 °C for 24 hours. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to 1-methylnapthalene as the internal standard.

Entry	**Catalyst**	**Atmosphere**	**Oxidant**	**Conversion (%)**
1	$Cu(OAc)_2$	Air	-	42
2	$Cu(OAc)_2$	O_2	-	22
3	$Cu(OAc)_2$	Air	PNO	41
4	$Cu(OAc)_2$	Air	TEMPO	8
5	CuOAc	Air	-	1
6	CuOAc	O_2	-	6
7	CuOAc	Air	PNO	2
8	CuOAc	Air	TEMPO	2
9	CuCl	Air	-	35
10	CuCl	O_2	-	44
11	CuCl	Air	PNO	40
12	CuCl	Air	TEMPO	45
13	$CuCl_2$	Air	-	27
14	$CuCl_2$	O_2	-	25
15	$CuCl_2$	Air	PNO	15
16	$CuCl_2$	Air	TEMPO	18
17	CuBr	Air	-	37
18	CuBr	O_2	-	45
19	CuBr	Air	PNO	59
20	CuBr	Air	TEMPO	27
21	$CuBr_2$	Air	-	28
22	$CuBr_2$	O_2	-	29
23	$CuBr_2$	Air	PNO	26
24	$CuBr_2$	Air	TEMPO	14
25	CuI	Air	-	0
26	CuI	O_2	-	1

27	CuI	Air	PNO	0
28	CuI	Air	TEMPO	2
29	Cu_2O	Air	-	0
30	Cu_2O	O_2	-	0
31	Cu_2O	Air	PNO	0
32	Cu_2O	Air	TEMPO	0
33	CuO	Air	-	0
34	CuO	O_2	-	4
35	CuO	Air	PNO	0
36	CuO	Air	TEMPO	0
37	$CuCO_3$	Air	-	8
38	$CuCO_3$	O_2	-	16
39	$CuCO_3$	Air	PNO	13
40	$CuCO_3$	Air	TEMPO	3
41	$Cu(OTf)_2$	Air	-	2
42	$Cu(OTf)_2$	O_2	-	3
43	$Cu(OTf)_2$	Air	PNO	2
44	$Cu(OTf)_2$	Air	TEMPO	3
45	Copper(II)tetrafluoroborate hydrate	Air	-	5
46	Copper(II)tetrafluoroborate hydrate	O_2	-	15
47	Copper(II)tetrafluoroborate hydrate	Air	PNO	8
48	Copper(II)tetrafluoroborate hydrate	Air	TEMPO	4
49	$[Cu(OH).TMEDA]_2Cl_2$	Air	-	39
50	$[Cu(OH).TMEDA]_2Cl_2$	O_2	-	64
51	$[Cu(OH).TMEDA]_2Cl_2$	Air	PNO	29
52	$[Cu(OH).TMEDA]_2Cl_2$	Air	TEMPO	28

General Experimental Procedure K for Optimisation of the Chan-Evans-Lam Amidation Process *via* a DoE Approach

To an oven dried Radleys tube containing potassium (phenyl((trimethylsilyl)oxy)methylene) amide (100 mg, 0.43 mmol, 1 equiv.) was added phenylboronic acid (53 – 158 mg, 0.43 – 1.30 mmol, 1 - 3 equiv.), CuBr (2 – 6 mg, 0.02 – 0.09 mmol, 0.05 – 0.2 equiv.), PNO (23 – 68 mg, 0.22 – 0.65 mmol, 0.5 – 1.5 equiv.), and powdered 4 Å molecular sieves. 2-MeTHF (5 mL) and 1-methylnapthalene (31 µL, 0.22 mmol, 0.5 equiv.) added, and the reaction mixture was then stirred at the required reaction temperature for 16 - 48 hours. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to 1-methylnapthalene as the internal standard.

Entry	CuBr (mol%)	Boronic acid (equiv.)	PNO (equiv.)	Temperature (°C)	Time (h)	Conversion (%)
1	5	1	1.5	80	48	2
2	20	3	0.5	80	16	1
3	12.5	2	1	50	32	16
4	20	3	0.5	20	48	2
5	20	3	1.5	80	48	3
6	5	1	0.5	80	16	5
7	5	3	1.5	80	16	0
8	20	1	0.5	80	48	53
9	5	1	1.5	20	16	0
10	20	1	1.5	20	48	90 (84)[a]
11	12.5	2	1	50	32	18
12	5	3	0.5	20	16	0
13	5	3	0.5	80	48	6
14	20	1	0.5	20	16	1
15	5	1	0.5	20	48	74 (68)[a]
16	5	3	1.5	20	48	15
17	20	1	1.5	80	16	3
18	20	3	1.5	20	16	1

[a]Isolated yield.

General Experimental Procedure L for the Time Study of the Chan-Evans-Lam Amidation Process

To an oven dried Radleys tube containing potassium (phenyl((trimethylsilyl)oxy)methylene) amide (100 mg, 0.43 mmol, 1 equiv.) was added phenylboronic acid (53 mg, 0.43 mmol, 1 equiv.), CuBr (6 mg, 0.09 mmol, 0.2 equiv.), PNO (68 mg, 0.65 mmol, 1.5 equiv.), and powdered 4 Å molecular sieves. 2-MeTHF (5 mL) and 1-methylnapthalene (31 µL, 0.22 mmol, 0.5 equiv.) added, and the reaction mixture was then stirred at 20 °C for the required reaction time. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to 1-methylnapthalene as the internal standard.

Entry	Time (h)	Yield (%)
1	1	2
2	2	4
3	3	3
4	4	3
5	5	5
6	6	0
7	7	0
8	8	91
9	24	91
10	30	84
11	48	84

3.6.2.3 General Experimental Procedures for the Tsuji-Trost Allylation Process

General Experimental Procedure M for Screening Palladium Catalysts and Solvents Using Allyl Acetate

To an oven dried, purged Radleys tube containing potassium (phenyl((trimethylsilyl)oxy)methylene) amide (50 mg, 0.22 mmol, 1 equiv.), the required catalyst (0.01 mmol, 0.05 equiv.) and biphenyl (14 mg, 0.11 mmol, 0.5 equiv.), was added solvent (2.5 mL) and allyl acetate (19 µL, 0.22 mmol, 1 equiv.). The reaction mixture was then stirred at reflux for 16 h. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to biphenyl as the internal standard.

Entry	Catalyst	Solvent	Conversion (%)[a]
1	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	CPME	0
2	$Pd_2(dba)_3$	CPME	0
3	$Pd(dba)_2$	CPME	0
4	$Pd(PPh_3)_4$	CPME	19
5	$Pd(OAc)_2$	CPME	0
6	$PdCl_2$	CPME	0
7	$Pd(t\text{-}Bu_3P)_2$	CPME	1
8	$Pd(cod)Cl_2$	CPME	0
9	$[Ir(cod)Cl]_2$	CPME	9
10	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	DCM	0
11	$Pd_2(dba)_3$	DCM	0
12	$Pd(dba)_2$	DCM	0
13	$Pd(PPh_3)_4$	DCM	5
14	$Pd(OAc)_2$	DCM	0
15	$PdCl_2$	DCM	0
16	$Pd(t\text{-}Bu_3P)_2$	DCM	0
17	$Pd(cod)Cl_2$	DCM	0
18	$[Ir(cod)Cl]_2$	DCM	1
19	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	1,4-Dioxane	0
20	$Pd_2(dba)_3$	1,4-Dioxane	0
21	$Pd(dba)_2$	1,4-Dioxane	0
22	$Pd(PPh_3)_4$	1,4-Dioxane	2
23	$Pd(OAc)_2$	1,4-Dioxane	0
24	$PdCl_2$	1,4-Dioxane	0
25	$Pd(t\text{-}Bu_3P)_2$	1,4-Dioxane	o
26	$Pd(cod)Cl_2$	1,4-Dioxane	0
27	$[Ir(cod)Cl]_2$	1,4-Dioxane	2
28	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	2-MeTHF	0
29	$Pd_2(dba)_3$	2-MeTHF	0
30	$Pd(dba)_2$	2-MeTHF	0
31	$Pd(PPh_3)_4$	2-MeTHF	0
32	$Pd(OAc)_2$	2-MeTHF	0
33	$PdCl_2$	2-MeTHF	0

34	$Pd(t\text{-}Bu_3P)_2$	2-MeTHF	0
35	$Pd(cod)Cl_2$	2-MeTHF	0
36	$[Ir(cod)Cl]_2$	2-MeTHF	4
37	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	THF	0
38	$Pd_2(dba)_3$	THF	0
39	$Pd(dba)_2$	THF	0
40	$Pd(PPh_3)_4$	THF	0
41	$Pd(OAc)_2$	THF	0
42	$PdCl_2$	THF	0
43	$Pd(t\text{-}Bu_3P)_2$	THF	1
44	$Pd(cod)Cl_2$	THF	0
45	$[Ir(cod)Cl]_2$	THF	3
46	$Pd(\eta^3\text{-}C_3H_5)Cl_2$	Toluene	0
47	$Pd_2(dba)_3$	Toluene	0
48	$Pd(dba)_2$	Toluene	0
49	$Pd(PPh_3)_4$	Toluene	12
50	$Pd(OAc)_2$	Toluene	0
51	$PdCl_2$	Toluene	0
52	$Pd(t\text{-}Bu_3P)_2$	Toluene	4
53	$Pd(cod)Cl_2$	Toluene	0
54	$[Ir(cod)Cl]_2$	Toluene	12

General Experimental Procedure N for Screening Palladium Catalysts and Solvents Using Allyl Methyl Carbonate

To an oven dried, purged Radleys tube containing potassium (phenyl((trimethylsilyl)oxy)methylene) amide (50 mg, 0.22 mmol, 1 equiv.), the required catalyst (0.01 mmol, 0.05 equiv.) and biphenyl (14 mg, 0.11 mmol, 0.5 equiv.), was added solvent (2.5 mL) and allyl methyl carbonate (21 µL, 0.22 mmol, 1 equiv.). The reaction mixture was then stirred at reflux for 16 h. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to biphenyl as the internal standard.

Entry	**Catalyst**	**Solvent**	**Allyl acetate conversion (%)**[a]	**Allyl methyl carbonate conversion (%)**[a]
1	$Pd(PPh_3)_4$	CPME	19	6
2	$Pd(t\text{-}Bu_3P)_2$	CPME	1	22
3	$[Ir(cod)Cl]_2$	CPME	9	40
4	$Pd(PPh_3)_4$	DCM	5	4
5	$[Ir(cod)Cl]_2$	DCM	1	2
6	$Pd(PPh_3)_4$	1,4-Dioxane	2	1
7	$[Ir(cod)Cl]_2$	1,4-Dioxane	2	33
8	$[Ir(cod)Cl]_2$	2-MeTHF	4	14
9	$Pd(t\text{-}Bu_3P)_2$	THF	1	8
10	$[Ir(cod)Cl]_2$	THF	3	10
11	$Pd(PPh_3)_4$	Toluene	12	13

12	Pd(*t*-$Bu_3P)_2$	Toluene	4	23
13	$[Ir(cod)Cl]_2$	Toluene	12	29

General Experimental Procedure O for Optimisation of the Pd(*t*-$Bu_3P)_2$ Catalysed Tsuji-Trost Allylation Process

To an oven dried, purged Radleys tube containing potassium (phenyl((trimethylsilyl)oxy)methylene) amide (25 – 75 mg, 0.11 – 0.33 mmol, 0.5 – 1.5 equiv.), Pd(*t*-$Bu_3P)_2$ (3 – 33 mg, 0.006 – 0.07 mmol, 0.05 – 0.2 equiv.) and biphenyl (2.4 – 18 mg, 0.06 – 0.17 mmol, 0.5 equiv.), was added toluene (0.43 – 3.24 mL) and allyl methyl carbonate (21 – 62 µL, 0.22 – 0.66 mmol, 1 - 3 equiv.). The reaction mixture was then stirred at reflux for 16 h. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to biphenyl as the internal standard.

Entry	**Pd(*t*-$Bu_3P)_2$ (mol%)**	**Allyl methyl carbonate (equiv.)**	**Imidate (equiv.)**	**Concentration (M)**	**Time (h)**	**Conversion (%)**
1	12.5	2	1	0.175	16	13
2	5	3	0.5	0.1	8	18
3	5	1	1.5	0.25	24	5
4	5	1	0.5	0.25	8	13
5	20	3	0.5	0.25	8	4
6	5	1	1.5	0.1	8	7
7	5	1	0.5	0.1	24	22
8	12.5	2	1	0.175	16	13
9	20	3	1.5	0.1	8	17
10	20	1	1.5	0.1	24	7
11	12.5	2	1	0.175	16	13
12	5	3	0.5	0.25	24	9
13	20	1	0.5	0.1	8	18
14	5	3	1.5	0.25	8	9
15	20	3	0.5	0.1	24	22
16	20	1	1.5	0.25	8	4
17	5	3	1.5	0.1	24	23
18	12.5	2	1	0.175	16	14
19	20	3	1.5	0.25	24	6
20	20	1	0.5	0.25	24	9

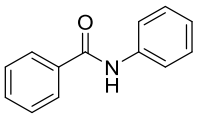
General Experimental Procedure P for Screening Ligands in the Tsuji-Trost Allylation Process

To an oven dried, purged Radleys tube containing potassium (phenyl((trimethylsilyl)oxy)methylene) amide (50 mg, 0.22 mmol, 1 equiv.), the required catalyst (0.01 mmol, 0.05 equiv.), the required ligand (0.01 mmol, 0.05 equiv.) and biphenyl (14 mg, 0.11 mmol, 0.5 equiv.), was added toluene (2.5 mL) and allyl methyl carbonate (21 µL, 0.22 mmol, 1 equiv.). The reaction mixture was then stirred at reflux for 16 h. The reaction mixture was sampled at the end of the required reaction time and the conversion determined by HPLC with reference to biphenyl as the internal standard.

Entry	Ligand	Catalyst	Conversion (%)
1	PPh_3	$[Ir(cod)Cl]_2$	42
		$Pd(t\text{-}Bu_3P)_2$	7
2	PCy_3	$[Ir(cod)Cl]_2$	42
		$Pd(t\text{-}Bu_3P)_2$	7
3	TTMPP	$[Ir(cod)Cl]_2$	20
		$Pd(t\text{-}Bu_3P)_2$	12
4	Dppe	$[Ir(cod)Cl]_2$	28
		$Pd(t\text{-}Bu_3P)_2$	8
5	Di-*tert*-butylphenylphosphine	$[Ir(cod)Cl]_2$	41
		$Pd(t\text{-}Bu_3P)_2$	14
6	$TTBP.HBF_4$	$[Ir(cod)Cl]_2$	28
		$Pd(t\text{-}Bu_3P)_2$	12
7	CyJohnPhos	$[Ir(cod)Cl]_2$	33
		$Pd(t\text{-}Bu_3P)_2$	12
8	DavePhos	$[Ir(cod)Cl]_2$	40
		$Pd(t\text{-}Bu_3P)_2$	9
9	RuPhos	$[Ir(cod)Cl]_2$	34
		$Pd(t\text{-}Bu_3P)_2$	14
10	SPhos	$[Ir(cod)Cl]_2$	38
		$Pd(t\text{-}Bu_3P)_2$	17
11	XantPhos	$[Ir(cod)Cl]_2$	38
		$Pd(t\text{-}Bu_3P)_2$	5
12	XPhos	$[Ir(cod)Cl]_2$	37
		$Pd(t\text{-}Bu_3P)_2$	9

3.6.3 Characterisation Data for Amide Products

Compound 3.7. ***N*-Phenylbenzamide**



Synthesised according to General Experimental Procedure F using potassium (phenyl((trimethylsilyl)oxy)methylene)amide (200 mg, 0.86 mmol, 1 equiv.) and bromobenzene (73 μL, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (10% EtOAc/petroleum ether 40 – 60°C) to afford the title compound as a yellow solid (105 mg, 77%).

Synthesised according to General Experimental Procedure H using potassium trimethylsilanolate (64 mg, 0.5 mmol, 2 equiv.), benzonitrile (26 μL, 0.25 mmol, 1 equiv.) and bromobenzene (21 μL, 0.2 mmol, 0.8 equiv.), and purified by flash column chromatography (10% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a yellow solid (26 mg, 67%).

Synthesised according to General Experimental Procedure K using potassium (phenyl((trimethylsilyl)oxy)methylene)amide (50 mg, 0.22 mmol, 1 equiv.) and phenylboronic acid (26 mg, 0.22 mmol, 1 equiv.), and purified by flash column chromatography (10% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a yellow solid (36 mg, 84%)

ν_{max} (neat): 3345, 3055, 1655, 1601, 1528, 750, 692 cm^{-1}

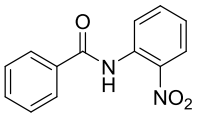
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 – 7.88 (m, 2H), 7.67 - 7.65 (m, 2H), 7.59 – 7.56 (m, 1H), 7.53 – 7.50 (m, 2H), 7.41 – 7.38 (m, 2H), 7.18 – 7.15 (m, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.9, 138.2, 135.3, 132.1, 129.3, 129.0, 127.2, 124.8, 120.4

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{12}NO$ 198.0914, found 198.0912

Consistent with previously reported data.[196]

Compound 3.8. ***N*-(2-Nitrophenyl)benzamide**



Synthesised according to General Experimental Procedure F using potassium (phenyl((trimethylsilyl)oxy)methylene)amide (200 mg, 0.86 mmol, 1 equiv.) and 1-bromo-2-nitrobenzene (140 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (5% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a brown solid (144 mg, 86%).

Synthesised according to General Experimental Procedure H using potassium trimethylsilanolate (64 mg, 0.5 mmol, 2 equiv.), benzonitrile (26 µL, 0.25 mmol, 1 equiv.) and 1-bromo-2-nitrobenzene (41 mg, 0.2 mmol, 0.8 equiv.), and purified by flash column chromatography (5% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a brown solid (37 mg, 77%).

ν_{max} (neat): 3364, 1684, 1496, 1591, 1340, 744, 698 cm^{-1}

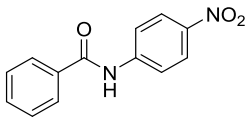
^{1}H NMR (400 MHz, MeOD-d4): δ 8.42 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.20 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.00 – 7.98 (m, 2H), 7.76 – 7.72 (m, 1H,), 7.65 – 7.61 (m, 1H), 7.58 – 7.53 (m, 2H), 7.39 – 7.35 (m, 1H) (exchangeable proton not observed)

^{13}C NMR (126 MHz, DMSO-d6): δ 165.3, 142.8, 134.0, 133.5, 132.3, 131.6, 128.7, 127.7, 125.9, 125.6, 125.0

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{11}N_2O_3$ 243.0764, found 243.0759

Consistent with previously reported data.[197]

Compound 3.9. ***N*-(4-Nitrophenyl)benzamide**



Synthesised according to General Experimental Procedure F using potassium (phenyl((trimethylsilyl)oxy)methylene)amide (200 mg, 0.86 mmol, 1 equiv.) and 1-bromo-4-nitrobenzene (140 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (5% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a yellow/orange solid (121 mg, 72%)

ν_{max} (neat): 3326, 1660, 1559, 1508, 1334, 850 cm^{-1}

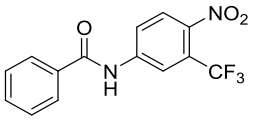
^{1}H NMR (400 MHz, DMSO-d6): δ 10.80 (s, 1H), 8.28 – 8.27 (m, 2H), 8.07 – 8.04 (m, 2H), 7.98 – 7.95 (m, 2H,), 7.66 – 7.63 (m, 1H), 7.57 – 7.53 (m, 2H)

^{13}C NMR (125 MHz, DMSO-d6): δ 166.3, 145.5, 142.5, 134.2, 132.1, 128.5, 127.9, 124.8, 119.8

HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{10}N_2O_3Na$ requires 265.0584, found 265.0583

Consistent with previously reported data.[197]

Compound 3.10. ***N*-(4-Nitro-3-(trifluoromethyl)phenyl)benzamide**



Synthesised according to General Experimental Procedure F using potassium (phenyl((trimethylsilyl)oxy)methylene)amide (200 mg, 0.86 mmol, 1 equiv.) and 5-bromo 2-nitrobenzotrifluoride (187 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (20% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a yellow solid (164 mg, 72%).

ν_{max} (neat): 3393, 3075, 2924, 1684, 1595, 1562, 1539, 1519, 1493 cm^{-1}

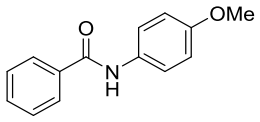
^{1}H NMR (400 MHz, DMSO-d6): δ 10.96 (s, 1H), 8.48 (d, *J* = 2.1 Hz, 1H), 8.34 (dd, *J* = 9.0, 2.1 Hz, 1H), 8.25 – 8.23 (m, 1H), 8.05 – 7.97 (m, 2H), 7.67 – 7.63 (m, 1H), 7.60 – 7.56 (m, 2H)

^{13}C NMR (101 MHz, DMSO-d6): δ 166.4, 144.0, 141.6, 133.7, 132.4, 128.6, 127.9, 127.5, 123.4, 122.7 (q, $^{2}J_{CF}$ = 33.2 Hz), 122.1 (q, $^{1}J_{CF}$ = 273.1 Hz), 118.3 (q, $^{3}J_{CF}$ = 5.8 Hz)

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{10}F_3N_2O_3$ 311.0638, found 311.0650

Consistent with previously reported data.[198]

Compound 3.15. ***N*-(4-Methoxyphenyl)benzamide**



Synthesised according to General Experimental Procedure F using potassium (phenyl((trimethylsilyl)oxy)methylene)amide (200 mg, 0.86 mmol, 1 equiv.) and 4-bromoanisole (87 μL, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (20% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a yellow solid (57 mg, 36%).

ν_{max} (neat): 3330, 3055, 2963, 2850, 1649, 1604, 1515, 1450, 1413, 1251, 826 cm^{-1}

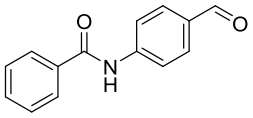
^{1}H NMR (400 MHz, DMSO-d6): δ 10.11 (s, 1H), 7.96 – 7.93 (m, 2H), 7.70 – 7.66 (m, 2H), 7.59 – 7.50 (m, 3H), 6.95 – 6.91 (m, 2H), 3.75 (s, 3H)

^{13}C NMR (126 MHz, DMSO-d6): δ 165.1, 155.5, 135.0, 132.2, 131.3, 128.3, 127.5, 122.0, 113.7, 55.2

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{14}NO_2$ 228.1020, found 228.1017

Consistent with previously reported data.[199]

Compound 3.16. ***N*-(4-Formylphenyl)benzamide**



Synthesised according to General Experimental Procedure F using potassium (phenyl((trimethylsilyl)oxy)methylene)amide (200 mg, 0.86 mmol, 1 equiv.) and 4-bromobenzyl alcohol (129 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (20% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a yellow solid (87 mg, 56%).

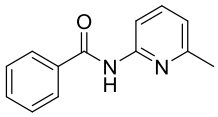
ν_{max} (neat): 3335, 1692, 1655, 1589, 1520, 1487 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 8.13 (br. s, 1H), 7.92 – 7.85 (m, 6H), 7.62 – 7.58 (m, 1H), 7.54 – 7.50 (m, 2H),

^{13}C NMR (101 MHz, $CDCl_3$): δ 191.2, 166.1, 143.7, 134.6, 132.8, 132.6, 131.4, 129.2, 127.3, 119.9

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{12}NO_2$ 226.0863, found 226.0865

Compound 3.18. ***N*-(6-Methylpyridin-2-yl)benzamide**



Synthesised according to General Experimental Procedure F using potassium (phenyl((trimethylsilyl)oxy)methylene)amide (200 mg, 0.86 mmol, 1 equiv.) and 2-bromo-6-methylpyridine (79 μL, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (20% EtOAc/petroleum ether 40-60 °C) to afford the title compound as an orange oil (83 mg, 57%).

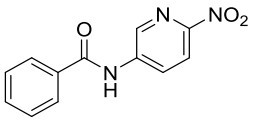
ν_{max} (neat): 3060, 2960, 2926, 1675, 1603, 1523, 1452, 1394, 700 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d6): δ 10.78 (br. s, 1H), 8.04 – 7.98 (m, 3H), 7.82 – 7.75 (m, 1H), 7.62 – 7.59 (m, 1H), 7.54 – 7.50 (m, 2H), 7.10 – 7.05 (m, 1H), 2.47 (s, 3H)

^{13}C NMR (126 MHz, DMSO-d6): δ 165.9, 156.6, 151.5, 138.3, 134.1, 131.8, 128.3, 128.0, 119.0, 111.7, 23.6

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{13}N_2O$ 213.1023 found, 213.1020

Compound 3.19. ***N*-(6-Nitropyridin-3-yl)benzamide**



Synthesised according to General Experimental Procedure F using potassium (phenyl((trimethylsilyl)oxy)methylene)amide (200 mg, 0.86 mmol, 1 equiv.) and 5-bromo-2-nitropyridine (140 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (30% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a brown solid (135 mg, 81%).

Synthesised according to General Experimental Procedure H using potassium trimethylsilanolate (64 mg, 0.5 mmol, 2 equiv.), benzonitrile (26 µL, 0.25 mmol, 1 equiv.) and 5-bromo-2-nitropyridine (41 mg, 0.2 mmol, 0.8 equiv.), and purified by flash column chromatography (30% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a brown solid (22 mg, 46%).

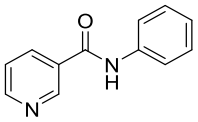
ν_{max} (neat): 3319, 1683, 1612, 1519, 1495, 1346, 703, 770 cm^{-1}

^{1}H NMR (500 MHz, DMSO-d6): δ 11.02 (s, 1H), 9.00 (d, *J* = 2.5 Hz, 1H), 8.62 (dd, *J* = 8.9, 2.5 Hz, 1H), 8.41 – 8.39 (m, 1H), 8.02 – 8.01 (m, 2H), 7.68 – 7.65 (m, 1H), 7.60 – 7.57 (m, 2H)

^{13}C NMR (126 MHz, DMSO-d6): δ 166.4, 151.3, 141.3, 139.6, 133.7, 132.5, 129.1, 128.6, 128.0, 119.3

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{10}N_3O_3$ 244.0717, found 244.0714

Compound 3.23. ***N*-Phenylnicotinamide**



Synthesised according to General Experimental Procedure F using potassium (pyridin-3-yl((trimethylsilyl)oxy)methylene)amide (201 mg, 0.86 mmol, 1 equiv.) and bromobenzene (73 μL, 0.69 mmol, 0.8 equiv.), and purified by strong cation exchange chromatography, eluting with 3 M NH_3/MeOH, to afford the title compound as a yellow oil (51 mg, 37%).

ν_{max} (neat): 3057, 1668, 1598, 1541, 1490, 754, 692 cm^{-1}

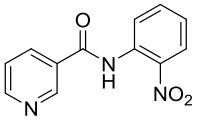
^{1}H NMR (400 MHz, DMSO-d6): δ 10.43 (s, 1H), 9.10 (app. s, 1H), 8.76 (d, *J* = 4.1 Hz, 1H), 8.31 – 8.27 (m 1H), 7.77 (d, *J* = 7.9 Hz, 2H), 7.57 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.15 – 7.11 (m, 1H)

^{13}C NMR (126 MHz, DMSO-d6): δ 164.1, 152.2, 148.7, 138.8, 135.5, 130.7, 128.7, 124.1, 123.6, 120.4

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{11}N_2O$ 199.0871, found 199.0880

Consistent with previously reported data.[200]

Compound 3.24. ***N*-(2-Nitrophenyl)nicotinamide**



Synthesised according to General Experimental Procedure F using potassium (pyridin-3-yl((trimethylsilyl)oxy)methylene)amide (201 mg, 0.86 mmol, 1 equiv.) and 1-bromo 2-nitrobenzene (139 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (30% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a brown solid (125 mg, 75%).

Synthesised according to General Experimental Procedure H using potassium trimethylsilanolate (64 mg, 0.5 mmol, 2 equiv.), 3-pyridine carbonitrile (26 mg, 0.25 mmol, 1 equiv.) and 1-bromo-2-nitrobenzene (41 mg, 0.2 mmol, 0.8 equiv.), and purified by flash

column chromatography (30% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a brown solid (19 mg, 39%).

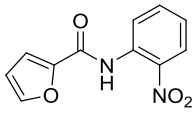
ν_{max} (neat): 3370, 1690, 1584, 1493 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.37 (s, 1H), 9.26 – 9.23 (m, 1H), 8.97 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.84 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.30 – 8.26 (m, 2H), 7.76 – 7.71 (m, 1H), 7.51 – 7.47 (m, 1H), 7.29 – 7.25 (m, 1H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.2, 153.5, 148.9, 136.8, 136.5, 135.2, 135.0, 129.9, 126.2, 124.1, 123.9, 122.4

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{10}N_3O_3$ 244.0722, found 244.0711

Compound 3.28. ***N*-(2-Nitrophenyl)furan-2-carboxamide**



Synthesised according to General Experimental Procedure F using potassium (furan-2-yl((trimethylsilyl)oxy)methylene)amide (191 mg, 0.86 mmol, 1 equiv.) and 1-bromo 2-nitrobenzene (139 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (20% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a yellow solid (74 mg, 46%).

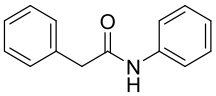
ν_{max} (neat): 3306, 3129, 1674, 1591, 1582, 1501 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d6): δ 10.85 (s, 1H), 8.07 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.04 – 7.99 (m, 2H), 7.79 – 7.75 (m, 1H), 7.43 – 7.38 (m, 1H), 7.37 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.75 (dd, *J* = 3.5, 1.7 Hz, 1H)

^{13}C NMR (101 MHz, DMSO-d6): δ 155.9, 146.8, 146.4, 141.4, 134.5, 131.5, 125.2, 124.9 (2), 116.1, 112.6

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_9N_2O_4$ 233.0562, found 233.0559

Compound 3.30. ***N*,2-Diphenylacetamide**



Synthesised according to General Experimental Procedure F using potassium (2-phenyl-1-((trimethylsilyl)oxy)ethylidene)amide (212 mg, 0.86 mmol, 1 equiv.) and bromobenzene (73 μL, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (10 % EtOAc/petroleum ether 40-60 °C) to afford the title compound as an orange solid (17 mg, 12%).

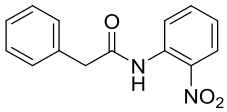
ν_{max} (neat): 3282, 3253, 1654, 1598, 1546, 1494, 1440, 754, 723, 690 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d6): δ 10.14 (s, 1H), 7.60 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.35 – 7.23 (m, 7H), 7.06 – 7.02 (m, 1H), 3.64 (s, 2H)

^{13}C NMR (101 MHz, DMSO-d6): δ 169.5, 138.1, 134.5, 129.6, 129.2, 128.8, 127.0, 123.7, 119.6, 43.8

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{14}NO$ 212.1075, found 212.1073

Compound 3.31. ***N*-(2-Nitrophenyl)-2-phenylacetamide**



Synthesised according to General Experimental Procedure F using potassium (2-phenyl-1-((trimethylsilyl)oxy)ethylidene)amide (212 mg, 0.86 mmol, 1 equiv.) and 1-bromo 2-nitrobenzene (139 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (10% EtOAc/ petroleum ether 40-60 °C) to afford the title compound as a brown solid (106 mg, 60%).

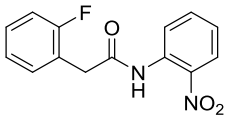
ν_{max} (neat): 3362, 2963, 1703, 1607, 1584, 1493 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d6): δ 10.42 (s, 1H), 7.95 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.76 – 7.66 (m, 2H), 7.41 – 7.31 (m, 5H), 7.29 – 7.23 (m, 1H), 3.71 (s, 2H)

^{13}C NMR (101 MHz, DMSO-d6): δ 169.3, 142.0, 135.0, 134.0, 131.3, 129.3, 128.4, 126.7, 125.1, 125.0, 124.9, 42.7

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{13}N_2O_3$ requires 257.0921, found 257.0920

Compound 3.34. **2-(2-Fluorophenyl)-*N*-(2-nitrophenyl)acetamide**



Synthesised according to General Experimental Procedure F using potassium (2-(2-fluorophenyl)-1-((trimethylsilyl)oxy)ethylidene)amide (227 mg, 0.86 mmol, 1 equiv.) and 1-bromo 2-nitrobenzene (139 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (20% EtOAc/ petroleum ether 40-60 °C) to afford the title compound as a yellow solid (82 mg, 43%).

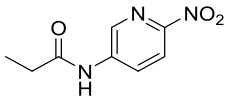
ν_{max} (neat): 3339, 2963, 1682, 1581, 1492 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d6) δ 10.46 (s, 1H), 7.97 – 7.93 (m, 1H), 7.75 – 7.67 (m, 2H), 7.43 – 7.30 (m, 3H), 7.24 – 7.13 (m, 2H), 3.78 (s, 2H)

^{13}C NMR (101 MHz, DMSO-d6) δ 168.3, 161.2 (d, $^1J_{CF}$ = 244.3 Hz), 142.1, 134.0, 132.0 (d, $^4J_{CF}$ = 4.0 Hz), 131.2, 129.1 (d, $^3J_{CF}$ = 8.1 Hz), 125.2, 125.1, 124.3 (d, $^4J_{CF}$ = 3.0 Hz), 122.2, 122.0, 115.1 (d, $^2J_{CF}$ = 21.5 Hz), 35.9

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{12}FN_2O_3$ 275.0826, found 275.0827.

Compound 3.36. ***N*-(6-Nitropyridin-3-yl)propionamide**



Synthesised according to General Experimental Procedure F using potassium (1-((trimethylsilyl)oxy)propylidene)amide (113 mg, 0.86 mmol, 1 equiv.), and 5-bromo 2-nitropyridine (110 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (50% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a brown solid (64 mg, 67%).

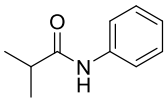
ν_{max} (neat): 3310, 3107, 2990, 1701, 1605, 1576, 1506, 1470 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 – 8.55 (m, 2H), 8.29 – 8.27 (m, 1H), 8.06 (br. s, 1H), 2.52 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0, 152.0, 140.2, 138.9, 128.7, 119.5, 30.9, 9.4

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_8H_{10}N_3O_3$ 196.0722, found 196.0724.

Compound 3.37. ***N*-Phenylisobutyramide**



Synthesised according to General Experimental Procedure F using potassium (2-methyl-1-((trimethylsilyl)oxy)propylidene)amide (171 mg, 0.86 mmol, 1 equiv.) and bromobenzene (73 μL, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (30% EtOAc/petroleum ether 40-60 °C) to afford the title compound as an orange solid (87 mg, 77%).

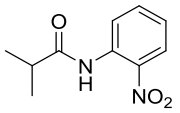
ν_{max} (neat): 3296, 3251, 3037, 2966, 2931, 1658, 1598, 1587, 1541, 754, 694 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d6): δ 9.80 (s, 1H), 7.61 – 7.59 (m, 2H), 7.30 – 7.25 (m, 2H), 7.03 – 6.99 (m, 1H), 2.58 (sept., *J* = 6.5 Hz, 1H), 1.09 (d, *J* = 6.5 Hz , 6H)

^{13}C NMR (101 MHZ, DMSO-d6): δ 175.2, 139.5, 128.6, 122.9, 119.1, 34.9, 19.5

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{14}NO$ 164.1070, found164.1065

Compound 3.38. ***N*-(2-Nitrophenyl)isobutyramide**



Synthesised according to General Experimental Procedure F using potassium (2-methyl-1-((trimethylsilyl)oxy)propylidene)amide (171 mg, 0.86 mmol, 1 equiv.) and 1-bromo 2-nitrobenzene (139 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (20% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a yellow oil (89 mg, 66%).

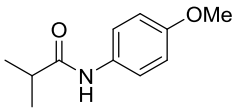
ν_{max} (neat): 3334, 2974, 2933, 2875, 1674, 1608, 1581, 1541, 1500, 1336, 740 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d6): δ 10.18 (s, 1H), 7.93 (dd, 8.2, 1.4 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.62 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.37 – 7.33 (m, 1H), 2.62 (sept., *J* = 6.8 Hz, 1H), 1.10 (d, *J* = 6.8 Hz, 6H)

^{13}C NMR (101 MHz, DMSO-d6): δ 174.9, 142.5, 133.8, 131.3, 125.3, 125.0, 124.8, 34.5, 18.9

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{13}N_2O_3$ requires 209.0926, found 209.0920.

Compound 3.39. ***N*-(4-Methoxyphenyl)isobutyramide**



Synthesised according to General Experimental Procedure F using potassium (2-methyl-1-((trimethylsilyl)oxy)propylidene)amide (171 mg, 0.86 mmol, 1 equiv.) and 4-bromoanisole (87 μL, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (20% EtOAc/Petroleum ether (40-60 °C)) to afford the title compound as a yellow solid (57 mg, 43%).

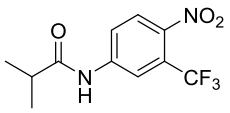
ν_{max} (neat): 3277, 2966, 2931, 1651, 1600, 1524, 1508, 825 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d6): δ 9.63 (s, 1H), 7.51 – 7.48 (m, 2H), 6.86 – 6.83 (m, 2H), 3.71 (s, 3H), 2.58 – 2.52 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 6H)

^{13}C NMR (126 MHz, DMSO-d6): δ 174.6, 155.0, 132.6, 120.6, 113.7, 55.1, 34.7, 19.5

HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{15}NO_2Na$ requires 216.1000, found 216.1001

Compound 3.40. ***N*-(4-Nitro-3-(trifluoromethyl)phenyl)isobutyramide**



Synthesised according to General Experimental Procedure F using potassium (2-methyl-1-((trimethylsilyl)oxy)propylidene)amide (171 mg, 0.86 mmol, 1 equiv.) and 5-bromo 2-nitrobenzotrifluoride (187 mg, 0.69 mmol, 0.8 equiv.), and purified by flash column chromatography (20% EtOAc/petroleum ether 40-60 °C) to afford the title compound as an orange solid (164 mg, 86%).

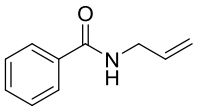
ν_{max} (neat): 3358, 3129, 3055, 2984, 1715, 1611, 1597, 1539, 1514, 1495 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 8.30 (br. s, 1H), 8.20 – 8.17 (m, 1H), 8.07 – 8.05 (m, 1H), 2.64 (sept., J = 6.9 Hz, 1H), 1.13 (d, J = 6.9 Hz, 6H)

^{13}C NMR (101 MHz, DMSO-d6): δ 176.5, 144.1, 141.1, 127.7, 123.0 (q, $^{2}J_{CF}$ = 33.3 Hz), 122.09, 122.05 (q, $^{1}J_{CF}$ = 272.9 Hz), 117.2 (q, $^{3}J_{CF}$ = 5.6 Hz), 35.3, 19.1

HRMS (ESI) *m/z*: $[M + H]^{+}$ calcd for $C_{11}H_{12}F_3N_2O_3$ 277.0800, found 277.0800

Compound 3.41. ***N*-Allylbenzamide**



Synthesised according to General Experimental Procedure N using potassium (phenyl((trimethylsilyl)oxy)methylene)amide (50 mg, 0.22 mmol, 1 equiv.), Pd(*t*-$Bu_3P)_2$ (4.6 mg, 0.01 mmol, 0.05 equiv.) and allyl methyl carbonate (20.5 µL, 0.22 mmol, 1 equiv.), and purified by flash column chromatography (40% EtOAc/petroleum ether 40-60 °C) to afford the title compound as a yellow oil (8.0 mg, 28%).

υ_{max} (neat): 3296, 3062, 1634, 1532, 1489, 1294, 693 cm^{-1}

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.80 – 7.77 (m, 2H), 7.51 – 7.46 (m, 1H), 7.44 – 7.39 (m, 2H), 6.41 (s, 1H), 5.97 – 5.88 (m, 1H), 5.28 – 5.15 (m, 2H), 4.09 – 4.05 (m, 2H)

^{13}C NMR: (101 MHz, $CDCl_3$): δ 167.6, 134.7, 134.4, 131.7, 128.8, 127.2, 116.8, 42.6

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{12}NO$ 162.0913, found 162.0910

4. References

1. A. K. Ghose, V. N. Viswanadhan, and J. J. Wendoloski, *J. Comb. Chem.*, 1999, **1**, 55–68.
2. S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451–79.
3. G. L. Patrick, *An Introduction to Medicinal Chemistry*, Oxford University Press, Oxford, UK, 4th edn., 2009.
4. T. W. J. Cooper, I. B. Campbell, and S. J. F. Macdonald, *Angew. Chem. Int. Ed.*, 2010, **49**, 8082–8091.
5. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, and A. G. Orpen, *J. Chem. Soc. Perkin Trans. II*, 1987, S1–S19.
6. J. Clayden, N. Greaves, S. Warren, and P. Wothers, *Organic Chemistry*, Oxford University Press, Oxford, 1st edn., 2001.
7. P. Y. Bruice, *Organic Chemistry*, Pearson Prentice Hall, Upper Saddle River, 5th edn., 2006.
8. B. S. Jursic and Z. Zdravkovski, *Synth. Commun.*, 1993, **23**, 2761–2770.
9. E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606–631.
10. A. El-Faham and F. Albericio, *Chem. Rev.*, 2011, **111**, 6557–6602.
11. Z. J. Kamiński, *Pept. Sci.*, 2000, **55**, 140–164.
12. H. L. Rayle and L. Fellmeth, *Org. Process Res. Dev.*, 1999, **3**, 172–176.
13. J. B. Lee, *J. Am. Chem. Soc.*, 1966, **88**, 3440–3441.
14. D. C. Lenstra, F. P. J. T. Rutjes, and J. Mecinovic, *Chem. Commun.*, 2014, **50**, 5763–5766.
15. J. P. Adams, C. M. Alder, I. Andrews, A. M. Bullion, M. Campbell-Crawford, M. G. Darcy, J. D. Hayler, R. K. Henderson, C. A. Oare, I. Pendrak, A. M. Redman, L. E. Shuster, H. F. Sneddon, and M. D. Walker, *Green Chem.*, 2013, **15**, 1542.
16. W. König and R. Geiger, *Chem. Ber.*, 1970, **103**, 788–798.
17. L. Carpino, *J. Am. Chem. Soc.*, 1993, **115**, 4397–4398.
18. A. Williams and I. T. Ibrahim, *Chem. Rev.*, 1981, **81**, 589–636.
19. K. D. Wehrstedt, P. A. Wandrey, and D. Heitkamp, *J. Hazard. Mater.*, 2005, **126**, 1–7.
20. R. Subirós-Funosas, R. Prohens, R. Barbas, A. El-Faham, and F. Albericio, *Chem. Eur. J.*, 2009, **15**, 9394–9403.
21. M. Itoh, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 2219–2221.
22. F. Albericio, J. M. Bofill, A. El-Faham, and S. A. Kates, *J. Org. Chem.*, 1998, **63**, 9678–9683.
23. L. A. Carpino, H. Imazumi, A. El-Faham, F. J. Ferrer, C. Zhang, Y. Lee, B. M. Foxman, P. Henklein, C. Hanay, C. Mügge, H. Wenschuh, J. Klose, M. Beyermann, and M. Bienert, *Angew. Chem. Int. Ed.*, 2002, **41**, 441–445.
24. B. M. Trost, *Angew. Chem. Int. Ed. English*, 1995, **34**, 259–281.
25. B. Castro, J. R. Dormoy, G. Evin, and C. Selve, *Tetrahedron Lett.*, 1975, **16**, 1219–1222.

26. J. Coste, D. Lenguyen, and B. Castro, *Tetrahedron Lett.*, 1990, **31**, 205–208.
27. F. Albericio, M. Cases, J. Alsina, S. A. Triolo, L. A. Carpino, and S. A. Kates, *Tetrahedron Lett.*, 1997, **38**, 4853–4856.
28. P. Li and J. C. Xu, *Tetrahedron*, 2000, **56**, 4437–4445.
29. P. Li and J. C. Xu, *Tetrahedron Lett.*, 1999, **40**, 3605–3608.
30. P. Li and J. C. Xu, *Tetrahedron Lett.*, 2000, **41**, 721–724.
31. P. Li and J. C. Xu, *J. Chem. Soc. Perkin Trans. 2*, 2001, 113–120.
32. L. A. Carpino and A. El-Faham, *J. Am. Chem. Soc.*, 1995, **117**, 5401–5402.
33. A. El-Faham, *Chem. Lett.*, 1998, 671–672.
34. J. Coste, M.-N. Dufour, A. Pantaloni, and B. Castro, *Tetrahedron Lett.*, 1990, **31**, 669–672.
35. J. Coste, E. Frérot, P. Jouin, and B. Castro, *Tetrahedron Lett.*, 1991, **32**, 1967–1970.
36. B. Castro and J. R. Dormoy, *Tetrahedron Lett.*, 1972, **13**, 4747–4750.
37. A. El-Faham, R. S. Funosas, R. Prohens, and F. Albericio, *Chem. Eur. J.*, 2009, **15**, 9404–9416.
38. B. Belleau and G. Malek, *J. Am. Chem. Soc.*, 1968, **90**, 1651–1652.
39. Y. Kiso and H. Yajima, *J. Chem. Soc., Chem. Commun.*, 1972, 942–943.
40. E. Valeur and M. Bradley, *Tetrahedron*, 2007, **63**, 8855–8871.
41. H. Wissmann and H.-J. Kleiner, *Angew. Chem. Int. Ed. English*, 1980, **19**, 133–134.
42. J. Klose, M. Bienert, C. Mollenkopf, D. Wehle, C. Zhang, L. A. Carpino, and P. Henklein, *Chem. Commun.*, 1999, 1847–1848.
43. D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411–420.
44. J. D. Wilson and H. Weingarten, *Can. J. Chem.*, 1970, **48**, 983–986.
45. Å. Nordahl and R. Carlson, *Acta Chem. Scand.*, 1988, **42b**, 28–34.
46. C. L. Allen, A. R. Chhatwal, and J. M. J. Williams, *Chem. Commun.*, 2012, **48**, 666–668.
47. H. Lundberg, F. Tinnis, and H. Adolfsson, *Chem. Eur. J.*, 2012, **18**, 3822–3826.
48. H. Lundberg, F. Tinnis, and H. Adolfsson, *Synlett*, 2012, **23**, 2201–2204.
49. A. C. Shekhar, A. R. Kumar, G. Sathaiah, V. L. Paul, M. Sridhar, and P. S. Rao, *Tetrahedron Lett.*, 2009, **50**, 7099–7101.
50. R. M. Lanigan and T. D. Sheppard, *Eur. J. Org. Chem.*, 2013, 7453–7465.
51. A. Basha, M. Lipton, and S. M. Weinreb, *Tetrahedron Lett.*, 1977, **18**, 4171–4172.
52. A. Novak, L. D. Humphreys, M. D. Walker, and S. Woodward, *Tetrahedron Lett.*, 2006, **47**, 5767–5769.
53. B. C. Ranu and P. Dutta, *Synth. Commun.*, 2003, **33**, 297–301.
54. R. Arora, S. Paul, and R. Gupta, *Can. J. Chem.*, 2005, **83**, 1137–1140.
55. C. Han, J. P. Lee, E. Lobkovsky, and J. A. Porco, *J. Am. Chem. Soc.*, 2005, **127**, 10039–10044.
56. L. Hie, N. F. Fine Nathel, X. Hong, Y. F. Yang, K. N. Houk, and N. K. Garg, *Angew.*

Chem. Int. Ed., 2016, **55**, 2810–2814.

57. C. Chen and S. H. Hong, *Org. Biomol. Chem.*, 2011, **9**, 20–26.
58. G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681–703.
59. R. M. De Figueiredo, J. S. Suppo, and J. M. Campagne, *Chem. Rev.*, 2016, **116**, 12029–12122.
60. C. Gunanathan, Y. Ben-David, and D. Milstein, *Science (80-.).*, 2007, **317**, 790–792.
61. A. J. A. Watson, A. C. Maxwell, and J. M. J. Williams, *Org. Lett.*, 2009, 2667–2670.
62. A. J. A. Watson, R. J. Wakeham, A. C. Maxwell, and J. M. J. Williams, *Tetrahedron*, 2014, **70**, 3683–3690.
63. T. Zweifel, J.-V. Naubron, and H. Grützmacher, *Angew. Chem. Int. Ed.*, 2009, **48**, 559–563.
64. L. U. Nordstrøm, H. Vogt, and R. Madsen, *J. Am. Chem. Soc.*, 2008, **130**, 17672–17673.
65. Y. Tamaru, Y. Yamada, and Z. Yoshida, *Synthesis (Stuttg).*, 1983, **6**, 474–476.
66. K. Ekoue-Kovi and C. Wolf, *Chem. Eur. J.*, 2008, **14**, 6302–6315.
67. Y. Suto, N. Yamagiwa, and Y. Torisawa, *Tetrahedron Lett.*, 2008, **49**, 5732–5735.
68. W. J. Yoo and C. J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 13064–13065.
69. S. Seo and T. J. Marks, *Org. Lett.*, 2008, **10**, 317–319.
70. T. Mukaiyama, K. Kamio, S. Kobayashi, and H. Takei, *Chem. Lett.*, 1973, **2**, 357–358.
71. F. Fagalde, N. Lis de Katz, and N. Katz, *J. Coord. Chem.*, 2002, **55**, 587–593.
72. R. Breslow, R. Fairweather, and J. Keana, *J. Am. Chem. Soc.*, 1967, **89**, 2135–2138.
73. W. Schibler and T. A. Kaden, *J.C.S. Chem. Comm.*, 1981, 603–604.
74. A. Goto, K. Endo, and S. Saito, *Angew. Chem. Int. Ed.*, 2008, **47**, 3607–3609.
75. S. I. Murahashi, T. Naota, and E. Saito, *J. Am. Chem. Soc.*, 1986, **108**, 7846–7847.
76. C. J. Cobley, M. van den Heuvel, A. Abbadi, and J. G. de Vries, *Tetrahedron Lett.*, 2000, **41**, 2467–2470.
77. C. L. Allen, A. A. Lapkin, and J. M. J. Williams, *Tetrahedron Lett.*, 2009, **50**, 4262–4264.
78. E. Callens, A. J. Burton, and A. G. M. Barrett, *Tetrahedron Lett.*, 2006, **47**, 8699–8701.
79. B. Anxionnat, A. Guérinot, S. Reymond, and J. Cossy, *Tetrahedron Lett.*, 2009, **50**, 3470–3473.
80. A. Pelter, T. E. Levitt, and P. Nelsoni, *Tetrahedron*, 1970, **26**, 1539–1544.
81. K. Ishihara, S. Ohara, and H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4196–4197.
82. R. M. Al-Zoubi, O. Marion, and D. G. Hall, *Angew. Chem. Int. Ed.*, 2008, **47**, 2876–2879.
83. N. Gernigon, R. M. Al-Zoubi, and D. G. Hall, *J. Org. Chem.*, 2012, **77**, 8386–400.
84. P. Starkov and T. D. Sheppard, *Org. Biomol. Chem.*, 2011, **9**, 1320.
85. R. M. Lanigan, P. Starkov, and T. D. Sheppard, *J. Org. Chem.*, 2013, **78**, 4512–4523.
86. M. T. Sabatini, L. T. Boulton, and T. D. Sheppard, *Sci. Adv.*, 2017, **3**.

87. M. Movassaghi and M. A. Schmidt, *Org. Lett.*, 2005, **7**, 2453–2456.

88. C. Sabot, K. A. Kumar, S. Meunier, and C. Mioskowski, *Tetrahedron Lett.*, 2007, **48**, 3863–3866.

89. F. J. Weiberth, Y. Yu, W. Subotkowski, and C. Pemberton, *Org. Process Res. Dev.*, 2012, **16**, 1967–1969.

90. K. E. Price, C. Larrivee-Aboussafy, B. M. Lillie, R. W. McLaughlin, J. Mustakis, K. W. Hettenbach, J. M. Hawkins, and R. Vaidyanathan, *Org. Lett.*, 2009, **11**, 2003–2006.

91. X. Yang and V. B. Birman, *Org. Lett.*, 2009, **11**, 1499–1502.

92. D. D. Sanz Sharley and J. M. J. Williams, *Chem. Commun.*, 2017, **53**, 2020–2023.

93. H. U. Vora and T. Rovis, *J. Am. Chem. Soc.*, 2007, **129**, 13796–13797.

94. P.-C. Chiang, Y. Kim, and J. W. Bode, *Chem. Commun.*, 2009, 4566.

95. G. N. Papadopoulos and C. G. Kokotos, *J. Org. Chem.*, 2016, **81**, 7023–7028.

96. M. Passerini and L. Simone, *Gazz, Chim. Ital.*, 1921, **51**, 126.

97. I. Ugi and R. Meyr, *Chem. Ber.*, 1961, **94**, 2229–2233.

98. R. H. Baker and D. Stanonis, *J. Am. Chem. Soc.*, 1951, **73**, 699–702.

99. T. Saegusa, N. Taka-ishi, and H. Fujii, *Tetrahedron*, 1968, **24**, 3795–3798.

100. I. Ugi, R. Meyr, U. Fetzer, and C. Steinbrückner, *Angew. Chem.*, 1959, **71**, 373–388.

101. M. C. Pirrung and K. Das Sarma, *J. Am. Chem. Soc.*, 2004, **126**, 444–445.

102. O. Mumm, *Ber. Dtsch. Chem. Ges.*, 1910, **43**, 886–893.

103. J. L. Davis, R. Dhawan, and B. A. Arndtsen, *Angew. Chem. Int. Ed.*, 2004, **43**, 590–594.

104. D. A. Black and B. A. Arndtsen, *Org. Lett.*, 2004, **6**, 1107–1110.

105. S. Wan, M. E. Green, J. H. Park, and P. E. Floreancig, *Org. Lett.*, 2007, **9**, 5385–5388.

106. M. V Debenedetto, M. E. Green, S. Wan, J. Park, and P. E. Floreancig, *Org. Lett.*, 2009, **11**, 835–838.

107. N. Caldwell, C. Jamieson, I. Simpson, and T. Tuttle, *Org. Lett.*, 2013, **15**, 2506–9.

108. N. Caldwell, P. S. Campbell, C. Jamieson, F. Potjewyd, I. Simpson, and A. J. B. Watson, *J. Org. Chem.*, 2014, **79**, 9347–9354.

109. N. Caldwell, C. Jamieson, I. Simpson, and A. J. B. Watson, *ACS Sustain. Chem. Eng.*, 2013, **1**, 1339–1344.

110. N. Caldwell, C. Jamieson, I. Simpson, and A. J. B. Watson, *Chem. Commun.*, 2015, **51**, 9495–9498.

111. W. P. Jencks and J. Regenstein, *Handbook of Biochemistry*, Chemical Rubber Company, Cleveland, OH, 1968.

112. R. Schwesinger and H. Schlemper, *Angew. Chem. Int. Ed. English*, 1987, **26**, 1167–1169.

113. M. J. O'Donnell, F. Delgado, C. Hostettler, and R. Schwesinger, *Tetrahedron Lett.*, 1998, **39**, 8775–8778.

114. R. S. Varma and K. P. Naicker, *Tetrahedron Lett.*, 1999, **40**, 6177–6180.

115. B. R. Kim, H. G. Lee, S. B. Kang, G. H. Sung, J. J. Kim, J. K. Park, S. G. Lee, and Y. J. Yoon, *Synthesis (Stuttg).*, 2012, **44**, 42–50.

116. N. Caldwell, PhD Thesis, University of Strathclyde, 2015.

117. L. Jiang, A. Davison, G. Tennant, and R. Ramage, *Tetrahedron*, 1998, **54**, 14233–14254.

118. Q. Wang, Y. Wang, and M. Kurosu, *Org. Lett.*, 2012, **14**, 3372–3375.

119. A. K. Cooper, MChem Thesis, University of Strathclyde, 2016.

120. Y. Toda, S. Gomyou, S. Tanaka, Y. Komiyama, A. Kikuchi, and H. Suga, *Org. Lett.*, 2017, acs.orglett.7b02722.

121. N. J. Rattray, P. A. Botham, P. M. Hext, D. R. Woodcock, I. Fielding, R. J. Dearman, and I. Kimber, *Toxicology*, 1994, **88**, 15–30.

122. A. Bubliauskas, MChem Thesis, University of Strathclyde, 2017.

123. W. L. F. Armarego and C. L. L. Chai, *Purification of Laboratory Chemicals*, Elsevier Inc., Oxford, 6th ed., 2009.

124. H. Morimoto, R. Fujiwara, Y. Shimizu, K. Morisaki, and T. Ohshima, *Org. Lett.*, 2014, **16**, 2018–2021.

125. Y. Liu, S. Shi, M. Achtenhagen, R. Liu, and M. Szostak, *Org. Lett.*, 2017, **19**, 1614–1617.

126. L. Ren, X. Li, and N. Jiao, *Org. Lett.*, 2016, **18**, 5852–5855.

127. J. Li, F. Xu, Y. Zhang, and Q. Shen, *J. Org. Chem.*, **74**, 2009, 2575–2577.

128. K. Ekoue-Kovi and C. Wolf, *Org. Lett.*, 2007, **9**, 3429–3432.

129. R. Silvestri, G. La Regina, G. De Martino, M. Artico, O. Befani, M. Palumbo, E. Agostinelli, and P. Turini, *J. Med. Chem.*, 2003, **46**, 917–920.

130. J. F. Soulé, H. Miyamura, and S. Kobayashi, *J. Am. Chem. Soc.*, 2011, **133**, 18550–18553.

131. J. Frelek, A. Fryszkowska, M. Kwit, and R. Ostaszewski, *Tetrahedron Asymmetry*, 2006, **17**, 2469–2478.

132. J. Bai, B. K. Zambron, and P. Vogel, *Org. Lett.*, 2014, **16**, 604–607.

133. R. Yamashita, A. Sakakura, and K. Ishihara, *Org. Lett.*, 2013, **15**, 3654–3657.

134. A. Dumoulin, C. Lalli, P. Retailleau, and G. Masson, *Chem. Commun.*, 2015, **51**, 5383–5386.

135. E. Richmond, K. B. Ling, N. Duguet, L. B. Manton, N. Çelebi-Ölc¸üm, Y.-H. Lam, S. Alsancak, A. M. Z. Slawin, K. N. Houk, and A. D. Smith, *Org. Biomol. Chem.*, 2015, **13**, 1807–1817.

136. R. Samanta, J. O. Bauer, C. Strohmann, and A. P. Antonchick, *Org. Lett.*, 2012, **14**, 5518–5521.

137. C. Audubert, O. J. Gamboa Marin, and H. Lebel, *Angew. Chem. Int. Ed.*, 2017, **56**, 6294–6297.

138. M. Kosugi, M. Kameyama, and T. Migita, *Chem. Lett.*, 1983, **12**, 927–928.

139. A. S. Guram and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 7901–7902.

140. A. S. Guram, R. A. Rennels, and S. L. Buchwald, *Angew. Chem. Int. Ed. English*, 1995, **34**, 1348–1350.

141. J. Louie and J. F. Hartwig, *Tetrahedron Lett.*, 1995, **36**, 3609–3612.

142. J. P. Wolfe, S. Wagaw, and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 7215–7216.

143. M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 7217–7218.

144. D. W. Old, J. P. Wolfe, and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722–9723.

145. T. E. Barder and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 5096–5101.

146. M. D. Charles, P. Schultz, and S. L. Buchwald, *Org. Lett.*, 2005, **7**, 3965–3968.

147. B. P. Fors, D. A. Watson, M. R. Biscoe, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 13552–13554.

148. D. S. Surry and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2008, **47**, 6338–6361.

149. U. Christmann and R. Vilar, *Angew. Chem. Int. Ed.*, 2005, **44**, 366–374.

150. E. R. Strieter, D. G. Blackmond, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 13978–13980.

151. T. E. Barder, M. R. Biscoe, and S. L. Buchwald, *Organometallics*, 2007, **26**, 2183–2192.

152. T. E. Barder and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 12003–12010.

153. B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, 1998, **120**, 7369–7370.

154. N. Kataoka, Q. Shelby, J. P. Stambuli, and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 5553–5566.

155. Q. Shen, T. Ogata, and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 6586–6596.

156. J. P. Wolfe, J. Åhman, J. P. Sadighi, R. A. Singer, and S. L. Buchwald, *Tetrahedron Lett.*, 1997, **38**, 6367–6370.

157. D. R. M. Walton and F. D. King, *J. Chem. Soc. Chem. Commun.*, 1974, 256–257.

158. J. Brüning, *Tetrahedron Lett.*, 1997, **38**, 3187–3188.

159. S. Lee, M. Jørgensen, and J. F. Hartwig, *Org. Lett.*, 2001, **3**, 2729–2732.

160. D. Y. Lee and J. F. Hartwig, *Org. Lett.*, 2005, **7**, 1169–1172.

161. X. Huang and S. L. Buchwald, *Org. Lett.*, 2001, **3**, 3417–3419.

162. Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 10028–10029.

163. E. D. Laganis and B. L. Chenard, *Tetrahedron Lett.*, 1984, **25**, 5831–5834.

164. A. P. Krapcho and D. Waterhouse, *Synth. Commun.*, 1998, **28**, 3415–3422.

165. J. Dziemidowicz, D. Witt, M. Sliwka-Kaszynska, and J. Rachon, *Synthesis (Stuttg).*, 2005, 569–574.

166. R. T. Boere, R. T. Oakley, and R. W. Reed, *J. Organomet. Chem.*, 1987, **331**, 161–167.

167. K. J. Merchant, *Tetrahedron Lett.*, 2000, **41**, 3747–3749.

168. J. Yin and S. L. Buchwald, *Org. Lett.*, 2000, **2**, 1101–1104.

169. S. Sharif, J. Day, H. N. Hunter, Y. Lu, D. Mitchell, M. J. Rodriguez, and M. G. Organ, *J. Am. Chem. Soc.*, 2017, **139**, 18436 – 18439

170. A. Klapars, X. Huang, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 7421–7428.

171. R. Carlson and J. E. Carlson, *Design and Optimization in Organic Synthesis*, Elsevier, Amsterdam, 2nd edn., 2005.

172. Stat-Ease Design Expert® Software v8, http://statease.com (accessed November 2017)

173. Y. Tamaru, Y. Yamada, K. Inoue, Y. Yamamoto, and Z. Yoshida, *J. Org. Chem.*, 1983, **48**, 1286–1292.

174. J. W. Baker, G. L. Bachman, I. Schumacher, D. P. Roman, and A. L. Tharp, *J. Med. Chem.*, 1967, **10**, 93–95.

175. P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, and A. Combs, *Tetrahedron Lett.*, 1998, **39**, 2941–2944.

176. D. A. Evans, J. L. Katz, and T. R. West, *Tetrahedron Lett.*, 1998, **39**, 2937–2940.

177. D. M. T. Chan, K. L. Monaco, R. P. Wang, and M. P. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933–2936.

178. K. S. Egorova and V. P. Ananikov, *Angew. Chemie. Int. Ed.*, 2016, **55**, 12150–12162.

179. J. C. Vantourout, H. N. Miras, A. Isidro-Llobet, S. Sproules, and A. J. B. Watson, *J. Am. Chem. Soc.*, 2017, **139**, 4769–4779.

180. P. Y. S. Lam, G. Vincent, C. G. Clark, S. Deudon, and P. K. Jadhav, *Tetrahedron Lett.*, 2001, **42**, 3415–3418.

181. J. C. Antilla and S. L. Buchwald, *Org. Lett.*, 2001, **3**, 2077–2079.

182. H. E. Hoydonckx, W. M. Van Rhijn, W. Van Rhijn, D. E. De Vos, and P. A. Jacobs, *Ullmann's Encyclopedia of Industrial Chemistry*, Weinhem, 2007.

183. K. Wilson, MChem Thesis, University of Strathclyde, 2015.

184. J. Tsuji, H. Takahashi, and M. Morikawa, *Tetrahedron Lett.*, 1965, **6**, 4387–4388.

185. B. M. Trost and T. J. Fullerton, *J. Am. Chem. Soc.*, 1973, **95**, 292–294.

186. B. M. Trost, T. Zhang, and J. D. Sieber, *Chem. Sci.*, 2010, **1**, 427.

187. B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395–422.

188. B. M. Trost, T. R. Verhoeven, and J. M. Fortunak, *Tetrahedron Lett.*, 1979, **20**, 2301–2304.

189. F. G. Bordwell and G. Z. Ji, *J. Am. Chem. Soc.*, 1991, **113**, 8398–8401.

190. Z. Lu and S. Ma, *Angew. Chem. Int. Ed.*, 2008, **47**, 258–297.

191. T. Ohmura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 15164–15165.

192. A. Leitner, C. Shu, and J. F. Hartwig, *Org. Lett.*, 2005, **7**, 1093–1096.

193. J. C. Vantourout, R. P. Law, A. Isidro-Llobet, S. J. Atkinson, and A. J. B. Watson, *J. Org. Chem.*, 2016, **81**, 3942–3950.

194. K. Tissot-Croset, D. Polet, and A. Alexakis, *Angew. Chemie. Int. Ed.*, 2004, **43**, 2426–2428.

195. D. Polet and A. Alexakis, *Org. Lett.*, 2005, **7**, 1621–1624.

196. T. Van Dijk, S. Burck, M. K. Rong, A. J. Rosenthal, M. Nieger, J. C. Slootweg, and K. Lammertsma, *Angew. Chem. Int. Ed.*, 2014, **53**, 9068–9071.

197. B. Vinayak and M. Chandrasekharam, *Org. Lett.*, 2017, **19**, 3528–3531.

198. G. Carbone, J. Burnley, and J. E. Moses, *Chem. Commun.*, 2013, **49**, 2759–61.

199. S. M. Crawford, C. B. Lavery, and M. Stradiotto, *Chem. Eur. J.*, 2013, **19**, 16760–

16771.

200. M. Rovira, M. Soler, I. Güell, M. Z. Wang, L. Gómez, and X. Ribas, *J. Org. Chem.*, 2016, **81**, 7315–7325.