

## Durham E-Theses

---

# *Direct Amide Formation Between Carboxylic Acids and Amines: Mechanism and Development of Novel Catalytic Solutions*

CHARVILLE, HAYLEY

### How to cite:

---

CHARVILLE, HAYLEY (2012) *Direct Amide Formation Between Carboxylic Acids and Amines: Mechanism and Development of Novel Catalytic Solutions*, Durham theses, Durham University. Available at Durham E-Theses Online: <http://etheses.dur.ac.uk/3416/>

### Use policy

---

The full-text may be used and/or reproduced, and given to third parties in any format or medium, without prior permission or charge, for personal research or study, educational, or not-for-profit purposes provided that:

- a full bibliographic reference is made to the original source
- a [link](#) is made to the metadata record in Durham E-Theses
- the full-text is not changed in any way

The full-text must not be sold in any format or medium without the formal permission of the copyright holders.

Please consult the [full Durham E-Theses policy](#) for further details.

**Direct Amide Formation Between Carboxylic Acids  
and Amines: Mechanism and Development of  
Novel Catalytic Solutions**

Hayley Charville



A thesis submitted for the degree of Doctor of Philosophy

2012

## **Declaration**

The work described in this thesis was carried out in the Department of Chemistry, University of Durham or at Syngenta, Jealott's Hill Research Centre, Bracknell between October 2008 and November 2011. All of this work is my own unless specifically stated otherwise. No part of this work has previously been submitted for a degree at this or any other university.

## **Statement of Copyright**

The copyright of this thesis rests with the author. No quotation from it should be published without their prior written consent and information derived from it should be acknowledged.

## Abstract

Despite the amide formation reaction being a key reaction in organic chemistry, the direct amide formation reaction is both little used and little explored. Acceptance of the feasibility and general applicability of this reaction depends upon the development of both an understanding of the mechanism of the reaction, and the design of catalysts, which can promote the reaction on a wide range of substrates and under ambient conditions.

Investigations into uncatalysed direct amide formation began with calorimetric studies of the mixing of a series of carboxylic acids and amines in order to measure heat output, which has been compared with their ability to react to form carboxylate ammonium salts and amides. In order to identify which species (salt or H-bonded species) were formed,  $^1\text{H}$  NMR studies were also carried out by mixing the substrates in  $d^8$ -toluene and monitoring the resulting reactions. These experiments were also compared to DFT computational studies, from which the relative merits of different mechanistic schemes for direct amide formation could be assessed. A neutral intermediate pathway, involving carboxylic acid dimerisation *via* mutual hydrogen bonding was found to be accessible and may explain how the direct amide formation reaction occurs.

The synthesis of novel boronic acid compounds, which display the potential to act as catalysts for direct amide formation, has been attempted. Although the formation and purification of a reasonable amount of material for catalytic screening proved to be extremely difficult, progress towards the synthesis of these potential catalysts has been made.

The application of direct amide formation to the synthesis of key intermediates for some economically important, commercial syntheses has been assessed. The results of these reactions display a varying degree of success and largely depend on the properties of the substrates used. Further investigations are therefore required to ensure that direct amide formation becomes a general tool for a wide range of carboxylic acid and amine partners.

## Acknowledgements

Firstly, I would like to offer my thanks to my supervisor Prof. Andy Whiting for his guidance, support and ideas throughout this project and also for his unwavering enthusiasm and encouragement over the last few years.

Secondly, thanks must go to my industrial supervisors Dr David Jackson and Dr George Hodges for the many ideas and discussions. Thanks also for allowing me to experience research outside of a university environment during an enjoyable two-month placement. I am also grateful to Dr Jon Lidster for answering my endless list of questions during this time with such patience.

Thanks to Prof. Mark Wilson for all of the computational work that has been carried out for this project and thanks also to Dr Tommaso Marcelli for his contribution.

I would like to thank the NMR spectroscopy service and staff, the mass spectrometry service and also the elemental analysis service at Durham for all of their advice and assistance. Thanks also to the NMSSC in Swansea.

All of the Whiting group members past and present have made the lab an entertaining place to work, thanks to: Jon, Fathia, Andy, Ricardo, Alex, Garr-Layy, Nim, Farhana and Adam. It has been great working with you! Special thanks must go to Ben, Irene and Vicki who have become true friends and who I miss seeing everyday.

Thank you Tom for your support, especially during the writing of this thesis, and thanks for opening my eyes to new opportunities and adventures.

Finally, I would not be where I am today and this thesis would not have been possible without the unconditional support I have from my family, for which I am truly grateful.

Thank you.

*For  
Yvonne, Michael  
and Joseph*

# Contents

<b>List of Abbreviations</b>	<b>1</b>
<b>1.0 Introduction</b>	<b>3</b>
<i>1.1 Direct Amide Formation Between Carboxylic Acids and Amines</i>	<i>4</i>
<i>1.2 Amide Formation via Pyrolysis of Amines and Carboxylic Acids and their Ammonium Carboxylate Salts</i>	<i>5</i>
<i>1.3 The Use of Stoichiometric Boron Reagents: Acyloxyboron Intermediates</i>	<i>10</i>
<i>1.4 The Use of Stoichiometric Boron Reagents: Borane and catecholborane</i>	<i>15</i>
<i>1.5 Catalytic Direct Amide Formation</i>	<i>16</i>
<i>1.5 Conclusions</i>	<i>29</i>
<b>2.0 Aims</b>	<b>31</b>
<b>3.0 The Non-Catalysed Direct Amide Formation Reaction</b>	<b>33</b>
<i>3.1 Introduction</i>	<i>33</i>
<i>3.2 Calorimetry</i>	<i>34</i>
<i>3.3 Ammonium Carboxylate Salt Formation and Solution NMR Studies</i>	<i>43</i>
<i>3.4 Computationally Calculated Proton Affinities</i>	<i>49</i>
<i>3.5 Kinetic Evidence for Acid or Base Catalysis in Direct Amide Formation</i>	<i>51</i>
<i>3.6 Computational Studies on Possible Direct Amide Formation Mechanisms (Collaboration with Prof. Mark Wilson, Durham University)</i>	<i>54</i>
<i>3.7 Conclusions</i>	<i>63</i>
<b>4.0 Towards the Synthesis of Potential Catalysts for Direct Amide Formation</b>	<b>65</b>
<i>4.1 Introduction</i>	<i>65</i>
<i>4.2 Synthesis of Current Catalysts for Direct Amide Formation</i>	<i>66</i>
4.2.1 N,N-Diisopropylbenzylaminoboronic acid 25	66
4.2.2 o-Iodophenylboronic acid 31	67
<i>4.3 Synthesis of Novel Potential Catalysts for Direct Amide Formation</i>	<i>68</i>
4.3.1 Naphthalene Based Boronic Acids	68
4.3.2 Benzimidazole Based Boronic Acids	75
4.3.4 Imidazoline and Oxazoline Based Boronic Acids	85
<i>4.4 Conclusions</i>	<i>94</i>
<b>5.0 Applications for Direct Amide Formation</b>	<b>96</b>
<i>5.1 Mandipropamid Analogues</i>	<i>96</i>
<i>5.2 Synthesis of Sildenafil Precursor</i>	<i>112</i>
<i>5.3 Attempted Synthesis of 3-Substituted Isoxazolinecarboxamides</i>	<i>115</i>
<i>5.4 Conclusions</i>	<i>116</i>
<b>6.0 Conclusions and Future Work</b>	<b>118</b>
<b>7.0 Experimental</b>	<b>122</b>
<i>7.1 General Experimental</i>	<i>122</i>

<i>7.2 General Procedure for the Preparation of Amides at 120 °C</i>	<i>123</i>
<i>7.3 General Procedure for the Preparation of Amides at 55 °C</i>	<i>123</i>
<i>7.4 General Procedure for Following Reactions Over Time</i>	<i>123</i>
<i>7.5 General Procedure for Following Direct Amide Formation Over Time Using the Gilson 215 Synthesis Workstation</i>	<i>124</i>
<i>7.6 Calorimetry Studies</i>	<i>124</i>
<i>7.7 Quantum Chemical Calculations (carried out by Prof. Mark Wilson)</i>	<i>125</i>
<i>7.8 Synthetic Procedures</i>	<i>125</i>
<b>8.0 References</b>	<b>150</b>
<b>8.0 Appendix</b>	<b>154</b>
<i>8.1 NMR data</i>	<i>154</i>
<i>8.2 Computational Chemistry Data (Prof. Mark Wilson)</i>	<i>161</i>

## List of Abbreviations

Ac - acetyl  
aq - aqueous  
Ar - aromatic  
Bn - benzyl  
b.p. - boiling point  
br - broad  
Bu - butyl  
B<sub>2</sub>Pin<sub>2</sub> - bis(pinacolato)diboron  
B3LYP - Becke, three parameter, Lee-Yang-Parr  
calc - calculated  
CDI - carbonyldiimidazole  
d - doublet  
dd - doublet of doublets  
dba - dibenzylideneacetone  
DCM - dichloromethane  
DFT - density functional theory  
DMAP - 4-dimethylaminopyridine  
DMF - dimethylformamide  
DoE - design of experiments  
dppf - 1,1'-bis(diphenylphosphino)ferrocene  
dtbpy - 4,4'-di-*tert*-butyl-2-2'-dipyridyl  
EI - electron ionization  
ES - electrospray  
Et - ethyl  
Et<sub>2</sub>O - diethyl ether  
EtOAc - ethyl acetate  
exp - experimental  
GCMS - gas chromatography mass spectrometry  
HPLC - high performance liquid chromatography  
HRMS - high resolution mass spectrometry  
IPA - isopropyl alcohol

IR - infrared  
k - rate constant  
M - molar  
m - multiplet  
Me - methyl  
MeCN - acetonitrile  
 $M_n$  - number-average molecular weight  
m.p. - melting point  
MS - mass spectrometry  
MTBE - methyl *tert*-butyl ether  
 $M_w$  - weight-average molecular weight  
NMP - N-methylpyrrolidinone  
NMR - nuclear magnetic resonance  
PCC - pyridinium chlorochromate  
PCM - polarisable continuum model  
Ph - phenyl  
PHPB - pyridinium hydrobromide perbromide  
PPA - polyphosphoric acid  
Pr - propyl  
q - quartet  
rt - room temperature  
s - singlet  
t - triplet  
TBAI - tetrabutylammonium iodide  
td - triplet of doublets  
TFA - trifluoroacetic acid  
THF - tetrahydrofuran  
TLC - thin layer chromatography  
TMEDA - tetramethylethylenediamine  
TMSCl - trimethylsilyl chloride  
TosMIC - tosylmethylisocyanide

## 1.0 Introduction

Environmentally benign alternatives to standard chemical processes are increasingly sought after for a wide range of important chemical conversions.<sup>1</sup> Therefore, there has become a significant demand for catalytic solutions for many reactions, especially if the desired product can be obtained in high yield, with high atom efficiency<sup>2</sup> and hence, a reduced E-factor<sup>3</sup> (defined as the mass ratio of waste to desired product). In particular, the use of stoichiometric reagents such as condensing and activating agents should ideally be avoided if possible and replaced by catalytic processes. This would result in lower costs and a reduced environmental impact. Condensation reactions in general are prime candidates for the development of environmentally benign solutions, and amide bond formation in particular is a key chemical transformation that needs a general environmentally benign solution. The importance of improving standard amide formation methods was highlighted in an article published in 2007<sup>1</sup> in which several pharmaceutical companies considered reaction types they would strongly prefer alternative reagents for. Amide formation avoiding the use of poor atom economy reagents received nominations from all of the pharmaceutical companies in the study and has been presented as a priority area (Table 1).

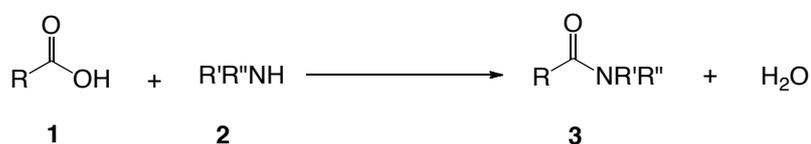
**Table 1:** Reactions companies would now use but would strongly prefer better reagents

Research Area	Number of Votes
Amide formation avoiding poor atom economy reagents	6
OH activation for nucleophilic substitution	5
Reduction of amides without hydride reagents	4
Safer and more environmentally friendly Mitsunobu reactions	3

## 1.1 Direct Amide Formation Between Carboxylic Acids and Amines

Amide bonds are typically formed from amines and pre-activated carboxylic acid derivatives such as acid chlorides (prepared from thionyl or oxalyl chloride, for example), anhydrides, or by using the carboxylic acid directly with stoichiometric amounts of coupling reagents such as carbodiimides.<sup>4-7</sup> All of these methods possess considerable drawbacks; firstly, they represent poor atom economy, secondly they all involve the use of toxic reactive reagents and, thirdly, product purification can be complicated.<sup>5</sup> The prevalence of the amide bond in natural product structures and materials, combined with its importance in industrial and pharmaceutical chemistry means there is a major drive to develop clean, catalytic, ambient and efficient processes for amide bond formation. The most desirable solution to this problem of amide formation is the direct condensation, *i.e.* by direct reaction between an amine and a carboxylic acid. However, this is generally thought to be difficult due to the formation of unreactive carboxylate-ammonium salts. Despite this, direct condensation has been known since 1858 when acetamide was produced from heating ammonium acetate.<sup>8</sup> Unfortunately, as a result of the forcing conditions employed for these early reactions, it is still generally assumed that this type of procedure is severely limited mainly due to the thermal stability of the reaction components and products under the reaction conditions, which often include high temperatures and pressures.

### Equation 1



In order to develop catalytic processes that work at lower temperature and are generally applicable to a range of substrates, it is clearly necessary to have a comprehensive understanding of how the substrates interact with each other and with the catalyst, and also the mechanistic details of the reaction and structure of

any intermediates involved is important. However, even something as apparently simple as the formation of a salt can be more complex than commonly assumed.

In the case of direct amide formation, full mechanistic details have yet to be elucidated, although some proposals have been made. This work provides a contribution to the mechanistic aspects of direct amide formation and looks at the synthesis and evolution of novel boronic acids as potential catalysts for this reaction.

## ***1.2 Amide Formation via Pyrolysis of Amines and Carboxylic Acids and their Ammonium Carboxylate Salts***

Carboxylic acids and amines can react together to form salts, strong heating of these salts can lead to amide formation, which is the case for the conversion of ammonium acetate to acetamide.<sup>9</sup> This reaction is carried out in hot acetic acid with continuous distillation to remove excess acetic acid and water, therefore ensuring that the reaction is driven towards the amide. Other examples of this method of amide formation include the preparation of benzanilide<sup>10</sup> by heating benzoic acid with an excess of aniline and also the preparation of succinimide from heating ammonium succinate.<sup>11</sup>

Mitchell and Reid<sup>8</sup> found that aliphatic amides could be synthesised by passing ammonia gas through a number of carboxylic acids at a temperature that allowed the removal of water to be continuous. Dimethyl amides were produced by the same method, with ammonia being replaced by dimethylamine. A drawback of this method became evident during the examination of carboxylic acids with a longer alkyl chain length than butyric acid; the rate of the reaction decreased considerably and the temperature at which the acid was heated to was sufficient to dehydrate the longer chain amides to nitriles. No amide was produced from either hexadecanoic acid or octadecanoic acid when heated to 125 °C or 190 °C for considerable lengths of time.<sup>8</sup> This particular approach has been used as the basis of a commercial synthesis<sup>12, 13</sup> of dimethylacetamide from the reaction of acetic acid and dimethylamine with the product being removed as an azeotrope (84% amide, 16% acetic acid, b.p. 170.8–170.9 °C). Interestingly, if a

substantial excess of dimethylamine is reacted with acetic acid under conditions of elevated temperature and pressure, a reduced amount of azeotrope is formed; optimum temperatures are 250-325 °C and pressures in excess of 6200 kPa are required.

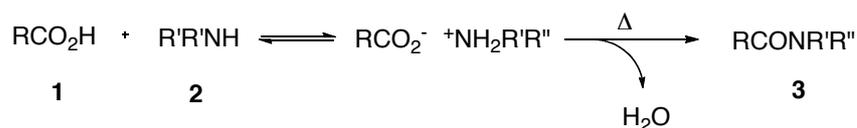
It has been reported that the pyrolysis of monocarboxylic acids in the absence of any other reagent leads to the formation of the anhydride.<sup>14</sup> Several carboxylic acids were shown to undergo dehydration when refluxed at temperatures between 250-350 °C to afford the corresponding anhydride. It is, therefore, not surprising that upon the addition of an amine to the heated carboxylic acid, amides can be formed since a conventional synthesis of amides is *via* the anhydrides,<sup>4</sup> however, the intervention of an anhydride in these pyrolysis reactions has not been reported.

In 1993, the preparation of a range of amides by heating a mixture of different amines and carboxylic acids in the absence of any catalyst or coupling agent was reported.<sup>15</sup> The optimum conditions for the heating of carboxylic acid-amine mixtures was found to be between 160-180 °C for 10-30 minutes. There are many advantages to preparing amides in this way: the procedure is simple; no catalysts or solvents are required; and the reaction times are short. Despite these advantages, there are several drawbacks to the method: both the amines and carboxylic acids used need to be thermally stable; have a melting point below 200 °C; be non-volatile; and have a high boiling point. Extreme heating can lead to tar formation, whereas not heating to a high enough temperature means that the reaction does not go to completion. For these reasons, this particular method has not developed into a widely used general method for direct amide formation and may not be amenable for small scale reactions and high value reactants. A recent communication<sup>16</sup> has shown that neat mixtures of amines and carboxylic acid are combined in the presence of 3 Å molecular sieves at between 120 and 160 °C, to give generally good to high yields of amide, with the odd exception of *N*-methylbenzylamine reacting with benzoic acid, which provides only traces of amide after 24 hours at 160 °C (compared with 75 % using benzylamine).

The use of microwave irradiation has been reported to simplify and improve a number of organic reactions, often leading to higher conversions and shorter reaction times.<sup>17, 18</sup> Preparation of amides by the heating of carboxylate-

ammonium salts obtained from the mixture of an amine and carboxylic acid has been examined under microwave irradiation conditions in the absence of a catalyst and of solvent (Scheme 1).<sup>19</sup>

**Scheme 1:** Preparation of amides from amines and carboxylic acids under microwave irradiation.



Heating the acid-amine mixture to 150 °C using microwave irradiation resulted in increased yields of the amides in comparison to conventional heating for the majority of combinations tested. For example, benzylamine reacted with benzoic acid affording the corresponding amide in high yield (80%) after 30 minutes and using 1.5 equivalents of amine. However, when the same reaction was heated using an oil bath, only 8% yield of the amide was isolated. The reaction of *n*-octylamine with phenylacetic acid (1:1 molar ratio) provided the amide in 54% yield; an improvement on the conventionally heated reaction (23%). Significant differences in reactivity were observed according to the structure of the amine and carboxylic acid reagents. The following sequence was established for the reactivities of the carboxylic acids used: *n*-C<sub>9</sub>H<sub>19</sub>CO<sub>2</sub>H ≥ C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>CO<sub>2</sub>H >> C<sub>6</sub>H<sub>5</sub>CO<sub>2</sub>H, and for the amines used, the reactivities were in the order: C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>NH<sub>2</sub> > *n*-C<sub>8</sub>H<sub>17</sub>NH<sub>2</sub> > *p*-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub> > C<sub>6</sub>H<sub>5</sub>NH<sub>2</sub>. Different factors were considered to try and explain the relative reactivities, including the relationship between reactivity and p*K*<sub>a</sub> of each substrate. Similar behavior between carboxylic acids with similar p*K*<sub>a</sub> values would be expected along with there being a large influence depending on the amine structure, the aliphatic amines have p*K*<sub>b</sub> values between 3-5 and the aromatic amines have p*K*<sub>b</sub> values between 8-10. The three carboxylic acids used in this study had similar p*K*<sub>a</sub> values (4.89, 4.31 and 4.21 for *n*-C<sub>9</sub>H<sub>19</sub>CO<sub>2</sub>H, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>CO<sub>2</sub>H, C<sub>6</sub>H<sub>5</sub>CO<sub>2</sub>H respectively). The experimental results from this study seemed to show that there was not a simple relationship between reactivity and p*K* values and, therefore,

the influence of the position of acid-base equilibrium upon reactivity was rejected as being an important factor.<sup>19</sup>

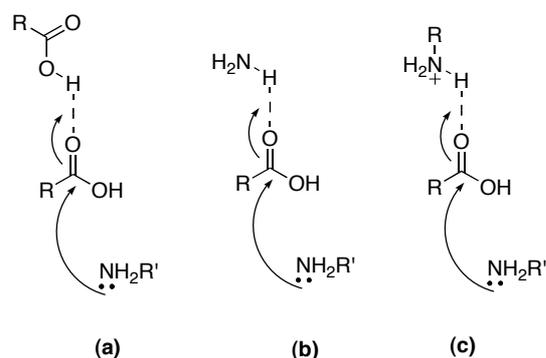
For several of the substrate combinations, it was claimed that having either the amine or carboxylic acid in excess was favourable. This was particularly evident in the case of benzylamine reacting with benzoic acid (see Table 2).

**Table 2:** Reaction of benzylamine with benzoic acid at 150 °C under microwave activation.

<b>Reaction time (min)</b>	<b>Relative ratio (acid:amine)</b>	<b>Yield (%)</b>
30	1:1	10
30	1:1.5	80
30	1.5:1	75

The simplest explanation claimed for the above observations was that the excess carboxylic acid or amine complexed to the carboxylic acid by hydrogen bonding to the carbonyl group. This results in electronic assistance to nucleophilic attack by the amine nitrogen atom [Figure 1(a) and (b)]. If this is indeed likely to occur, then another possibility is that the protonated amine could also provide assistance [as in Figure 1(c)]. It is generally assumed that the mixing of an amine and carboxylic acid results in the formation of an ammonium carboxylate salt, which could have a role in assisting the attack of the nucleophile, *i.e.* by protic acid catalysis. However, this explanation fails to take into account that the  $pK_{as}$  between (a), (b) and (c) (Figure 1) would be quite different. Perhaps another plausible theory is that the addition of an excess of either the carboxylic acid or amine starting material would help to drive the reaction towards product formation, according to Le Chatelier's Principle (assuming the reaction is not effectively irreversible under the reaction conditions).

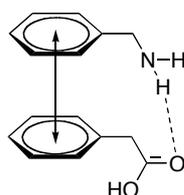
**Figure 1:** Electrophilic assistance to nucleophilic attack.



It has also been claimed that the addition of one equivalent of imidazole to a mixture of benzylamine and benzoic acid facilitates the amide formation reaction and leads to increased yields (from 13 to 61 %) under microwave conditions.<sup>20</sup> The imidazole is claimed to act by assisting the carbonyl group in a similar manner to the excess carboxylic acid or amine as portrayed in Figure 1.

It was also suggested that in the absence of solvent interactions (non-polar reaction conditions),  $\pi$ - $\pi$  interactions might be expected play an important role when both the carboxylic acid and amine possess an aromatic ring (Figure 2). It has been speculated that  $\pi$ - $\pi$  interactions might stabilise an amide formation transition state, leading to a decrease in activation energy and, therefore, a higher conversion of starting materials into product.<sup>19</sup> However, there is no direct evidence to date that such  $\pi$ - $\pi$  interactions do directly affect direct amide formations.

**Figure 2:** Optimal  $\pi$ - $\pi$  interactions



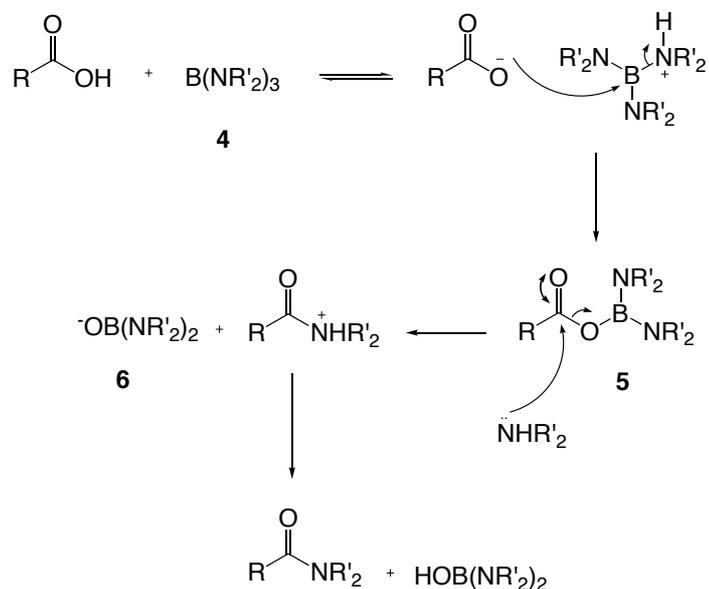
If  $\pi$ - $\pi$  interactions are important in some direct amide formation reactions, it is also possible that edge-to-face arrangements<sup>21, 22</sup> may seem more likely than that suggested in Figure 2, however, it was reported that MP3 molecular modeling

studies (where a method is adapted to describe hydrogen bonding and the interactions between non-bonding atoms) using the Hyperchem program predicted that the most stable arrangement of *N*-benzyl-2-phenylacetamide involves the overlapping of the  $\pi$ -systems. This has yet to be confirmed by more detailed modeling studies.

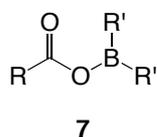
### ***1.3 The Use of Stoichiometric Boron Reagents: Acyloxyboron Intermediates***

As early as 1965, it was reported that boron containing compounds could be used as reactive entities with certain functional groups, in particular for converting carboxylic acids to amides.<sup>23</sup> The mixing of carboxylic acids with trisdialkylaminoborane compounds  $[B(NR'_2)_3]$  **4** in an inert solvent produced a considerable exotherm. Depending on the carboxylic acid used, either cooling or refluxing of the reaction mixture afforded the amide products. It was found that only one of the dialkylamino groups was employed for the conversion of the carboxylic acid to the amide. Hence, for the reaction to go to completion, one equivalent of the boron reagent was required without any additional catalyst present. A suggested mechanism for this transformation is shown in Scheme 2, *i.e.* that the reaction proceeds *via* initial salt formation followed by the production of mixed anhydrides. Mixed anhydride **5** is formed following nucleophilic attack by the carboxylate group on the protonated trisdialkylaminoborane.

**Scheme 2:** Postulated mechanism for amide formation from the mixing of carboxylic acids with trisdialkylaminoboranes.<sup>23</sup>

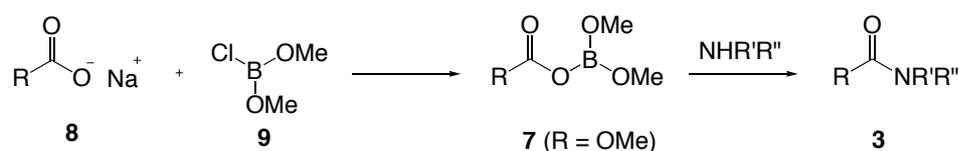


This method is just one example, which demonstrates that activated carboxylic acids, such as acyl chlorides, do not need to be prepared and are not essential for direct amide formation. The conditions for this transformation are mild and the desired amide can be produced in high yield and selectivity.<sup>23, 24</sup> However, a disadvantage of this process is that only one of the amino groups is utilised during the reaction. Further studies demonstrated that other boron containing compounds containing the general structure **7** could facilitate amide formation.<sup>24</sup> Notably, acyloxydialkylboranes [(RCO<sub>2</sub>B(OR')<sub>2</sub>)] were suggested to be good candidates for direct amide formation which fit the general structure **7**.



One possible route to acyloxydialkylboranes of type **7** is outlined in Scheme 3, *i.e.* from the addition of dimethoxyboron chloride **9** to the sodium salt of a carboxylic acid **8**. This reaction proceeded rapidly and there was infrared evidence for formation of the corresponding acyloxydialkylborane species **7**.<sup>24, 25</sup>

**Scheme 3:** Formation of acyloxydialkylborane **7** and the corresponding amide.

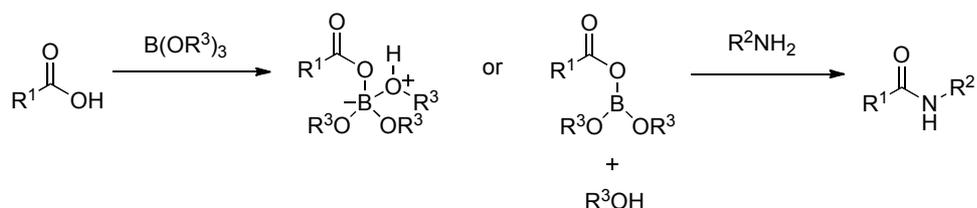


Upon the addition of amine at room temperature to the acyloxyborate derivative **7** (Scheme 3), the corresponding amide **3** was generated. Several combinations of amine and alkyloxyborane species were tested and yields were consistently below 50%. This was increased to approximately 70% by heating the reaction mixture.<sup>24</sup> The reaction conditions were mild, and when applied to peptide synthesis, racemisation was low. For these reasons, further investigations were carried out to establish why low conversions were obtained at room temperature. Possible reasons were proposed as follows: firstly, the dialkyloxyborane species was not being formed efficiently or was undergoing further reaction before the addition of the carboxylic acid; secondly, the mixed anhydride of type **7** was susceptible to decomposition or reduction; thirdly, the reaction of the mixed anhydride with an amine occurred at the boron atom or resulted in products that could not participate further in the reaction.<sup>25</sup> Investigations into each of these options showed that the third possibility was most likely. One mole of alcohol can be liberated in the attack of an amine upon the mixed anhydride species **7** [Scheme 4(a)]. This can also go on to compete with the amine for the mixed anhydride and result in the formation of an unreactive salt **10**, *i.e.* as outlined in Scheme 4(b).



More recently, the use of borate esters as convenient reagents for direct amidation and transamidation has been reported.<sup>26</sup> Having examined a range of mediators for amide formation reactions it was found that simple borate esters such as trimethyl borate (B(OMe)<sub>3</sub>) in stoichiometric quantities can act as effective reagents for direct amide formation. It is suggested that the reaction occurs *via* the generation of a three or four coordinate boron species as shown in Scheme 6. An optimisation study indicated that conventional heating was preferred over microwave conditions and the optimal solvent was found to be acetonitrile. Heating of the reaction mixture to 80 °C in acetonitrile minimised the amount of amide generated by the thermal background reaction (Table 3).

**Scheme 6:** Borate-mediated direct amidation



**Table 3:** Borate-promoted direct amide formations

Entry	Product	Isolated Yield (%)		
		B(OCH <sub>2</sub> CF <sub>3</sub> ) <sub>3</sub> <sup>a</sup>	B(OMe) <sub>3</sub> <sup>a</sup>	Thermal <sup>b</sup>
1		91	92	18
2		70	51	7
3		14	2	0
4		92	45	9
5		66	66	6
6		70	Quant.	9

<sup>a</sup>Acid (1 equiv.), amine (1 equiv.), borate (2 equiv.), 0.5M MeCN, 80 °C, 15 h

<sup>b</sup>Acid (1 equiv.), amine (1 equiv.), 0.5M MeCN, 80 °C, 15 h

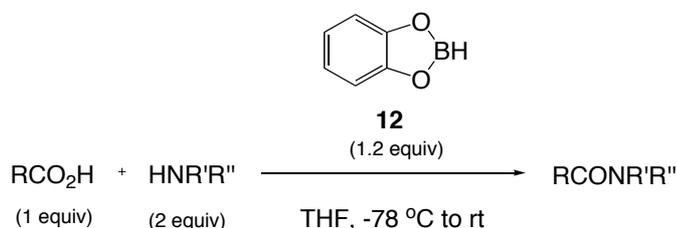
Although trimethyl borate was found promote direct amide formation and provides the amide product with high yield, tris (2,2,2-trifluoroethyl) borate was also used in this study and in fact can be used to convert primary amides to secondary amides *via* transamidation. This boron mediated transamidation reaction provided secondary amides in good yields (62-82%) and the procedure is experimentally simple, requiring equimolar quantities of amine/amide.

#### ***1.4 The Use of Stoichiometric Boron Reagents: Borane and catecholborane***

Trapani *et al.*<sup>27</sup> employed borane trimethylamine complex in a 1:1:3 molar ratio for the amine:borane:carboxylic acid, resulting in good to high amide yields under refluxing xylene conditions. It is claimed that triacyloxyborane species are the activated acylating species involved in the reaction.

Closely related to this work, Ganem *et al.*<sup>28</sup> reported that carboxylic acids and amines condense readily to form amides in the presence of stoichiometric amounts of catecholborane **12**, but under much milder conditions, *i.e.* THF, -78 °C to room temperature as outlined in Scheme 7.<sup>28</sup> The condensation is claimed to occur *via* the intermediate 2-acyloxy-1,2,3-benzodioxaborolane, for which there is some infrared evidence (1740 cm<sup>-1</sup> C=O absorption).

**Scheme 7:** Ganem's amide formation using catecholborane as condensing reagent.

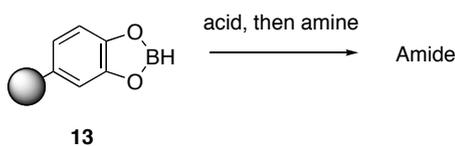


Ganem's method for direct amide formation requires the addition stoichiometric amounts of catecholborane, however, in 2006 Yamamoto proposed a possible catalytic scheme<sup>29</sup> based on this work (*vide infra*).

As mentioned previously, mixed anhydride intermediates of type **7** can be destroyed by the one equivalent of alcohol formed during the reaction (Scheme 4). For the intermediate, formed when using catecholborane this does not occur. The aromatic ring in this system enhances the reactivity of the active ester and can reduce side reactions. Following the addition of an amine, the corresponding amide can be produced with high yields. The reaction between nonanoic acid and benzylamine in the presence of catecholborane afforded the amide with a yield of 92%.<sup>28</sup>

Resin-bound catecholborane **13** can also be used for direct amide formation, as a solid phase reagent (Equation 2).<sup>30</sup> When shaken with the carboxylic acid it is claimed that the activated mixed anhydride acyloxyborane is formed. Upon addition of an amine under ambient conditions, the amide is formed in modest yields. For example, the reaction of octanoic acid with benzylamine gives the amide in a yield of 54%.

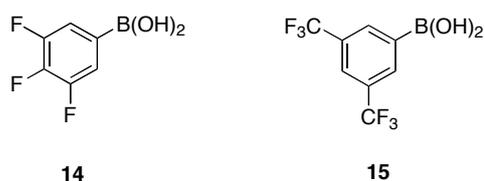
### Equation 2



### 1.5 Catalytic Direct Amide Formation

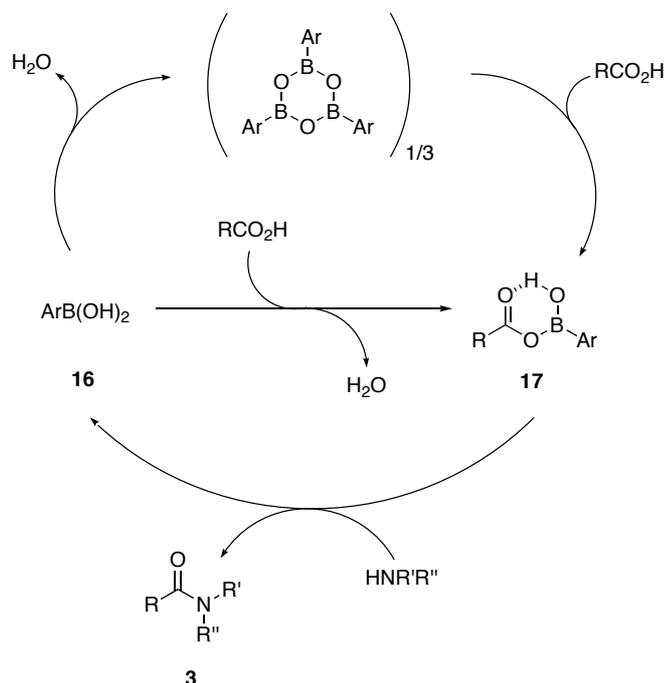
Possibly the most desirable way to make amides is to perform direct amide condensation reactions between equimolar amounts of carboxylic acids and amines under mild, catalytic conditions. Examples of amidation catalysts in the literature are largely based around boric acid or arylboronic acids possessing electron withdrawing substituents.

In 1996, Yamamoto found that benzenboronic acids bearing electron-withdrawing groups at the *meta*- or *para*-position are highly efficient catalysts for direct amide formation in less polar solvents.<sup>31</sup> Unlike the boron-mediated amidation mentioned previously, arylboronic acids with electron-withdrawing groups can overcome the problem of transformation into an inactive species or it is possible that they are in equilibrium with these species. Arylboronic acid catalysts are water-, acid- and base-tolerant Lewis acids that can generate acyloxyboron species, enhanced by the Lewis acidity and resulting in an increased reactivity with amines. 3,4,5-Trifluorobenzeneboronic acid **14** and 3,5-bis(trifluoromethyl)benzeneboronic acid **15** catalyze direct amide formation in toluene at reflux temperature with the azeotropic removal of water by 4 Å molecular sieves in a Soxhlet thimble.



Catalyst **14** (1 mol%) was found to be the most active and for the reaction of benzylamine with 4-phenylbutyric acid, produced the amide in 96% yield in 18 hours. For more demanding substrates, more forcing conditions were employed. Replacing benzylamine with aniline required refluxing mesitylene (b.p. 163-166 °C) and the yield of amide was 99% after 4 hours. A proposed mechanism is shown in Scheme 8.<sup>31</sup>

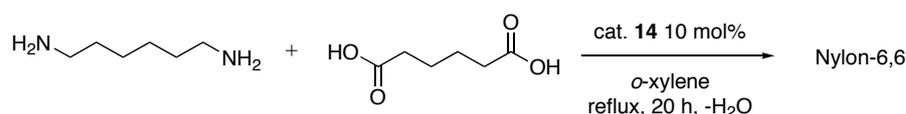
**Scheme 8:** Proposed catalytic cycle for direct amide formation.<sup>31</sup>



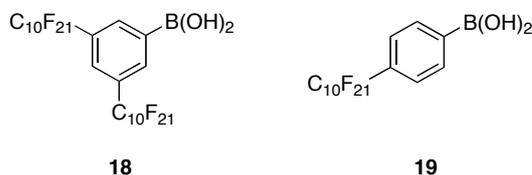
Arylboronic acids contain varying amounts of cyclic trimeric anhydrides (boroxines). On heating 4-phenylbutyric acid with **16** (2:1 mixture) in toluene- $d_8$  with removal of water for 2 hours, the mono-acyloxyboronic acid **17** was claimed to be produced. Further investigations are required to determine whether monoacyloxyboronate species are the active acylating species, since the reported  $^1\text{H}$  NMR and IR data is inconclusive without corroboration from  $^{11}\text{B}$  NMR. In addition, a much more activated carbonyl stretching frequency than the  $1586\text{ cm}^{-1}$  absorption claimed to be an monoacyloxyboronate reported (compare with the Ganem *et al.*<sup>28</sup> monoacyl species at  $1740\text{ cm}^{-1}$  *vide supra*) might be expected, since the unactivated starting carboxylic acid is reported to have an IR absorption at  $1709\text{ cm}^{-1}$ . No evidence for the detection of diacyloxyboronate derivatives was reported. However, upon addition of benzylamine to a toluene solution of **17**, the corresponding amide was produced at room temperature, with up to 50% conversion achieved. It was suggested that the reaction stopped because the intermediate **17** can be decomposed by hydrolysis with water. The results presented suggested that the rate-determining step for this catalysed reaction was the formation of monoacyloxyboronate intermediate **17**,<sup>31,32</sup> though the intervention and requirement for more activated species can not be ruled out.

3,4,5-Trifluorobenzeneboronic acid **14** is also an effective catalyst for the polycondensation of carboxylic acids and amines.<sup>33</sup> Direct polycondensation is desirable both environmentally and industrially. The direct polycondensation of adipic acid and hexamethylenediamine (Equation 3) was examined for the formation of nylon-6,6. With 10 mol% of catalyst **14** at reflux in *o*-xylene and removal of water by 4 Å molecular sieves, the desired product was formed with a yield of 89% after 20 hours. The number-average molecular weight ( $M_n$ ) and the weight-average molecular weight ( $M_w$ ) of the nylon obtained were estimated to be 2680 and 8330 respectively. These values were increased to 4690 and 22400 respectively on changing the solvent to a 1:3 mixture of *m*-cresol and *o*-xylene.

### Equation 3



The synthesis of other arylboronic acids bearing electron-withdrawing substituents and their activity towards direct amide formation has also been examined. The activity of 3,5-bis(perfluorodecyl)phenylboronic acid **18** was greater than 4-(perfluorodecyl)phenylboronic acid **19** when compared in the model reaction between 4-phenylbutyric acid (1 equiv.) and 3,5-dimethylpiperidine (1 equiv.) in toluene with removal of water (4 Å molecular sieves in a Soxhlet thimble) for 1 hour at catalyst loading of 5 mol%.<sup>34</sup>

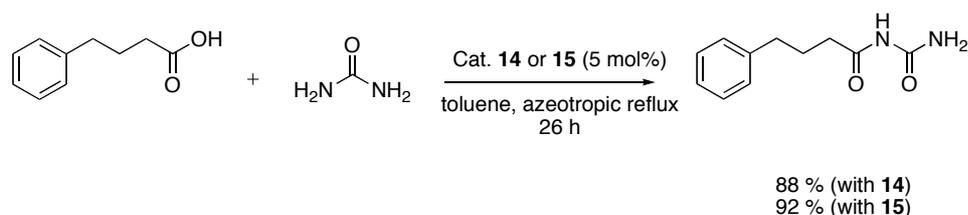


Although arylboronic acids **14** and **15** were more active than **18**, catalyst **18** can be fully recovered by extraction with fluoruous solvents. In a 1:1:1 mixture of *o*-xylene, xylene and perfluorodecalin under azeotropic reflux, amide formation reactions can be carried out with 3 mol % of catalyst **18**. Upon cooling, the two heterogenous phases can be separated and the amide can be

isolated in a quantitative yield. The catalyst can be recovered from the fluoruous phase and reused with no loss of activity.<sup>34</sup>

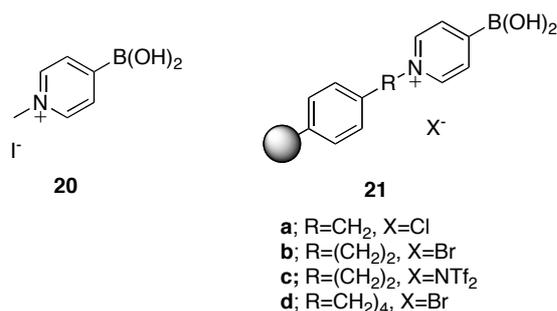
Yamamoto *et al.* have also found that the compounds **14** and **15** will catalyse the condensation of carboxylic acids with ureas (Equation 4).<sup>35</sup> *N*-acylcarbmates play an important role in medicinal chemistry, and the direct condensation of carboxylic acids and ureas can occur in the presence of excess strong acids such as chlorosulfonic acid as an example. This method is environmentally undesirable and the use of excess reagents is preferably avoided. The addition of 5 mol% of **14** or **15** to an equimolar mixture of carboxylic acid and urea derivatives (which are less nucleophilic than the amines previously screened) results in the formation of *N*-acylureas in high yields.

#### Equation 4



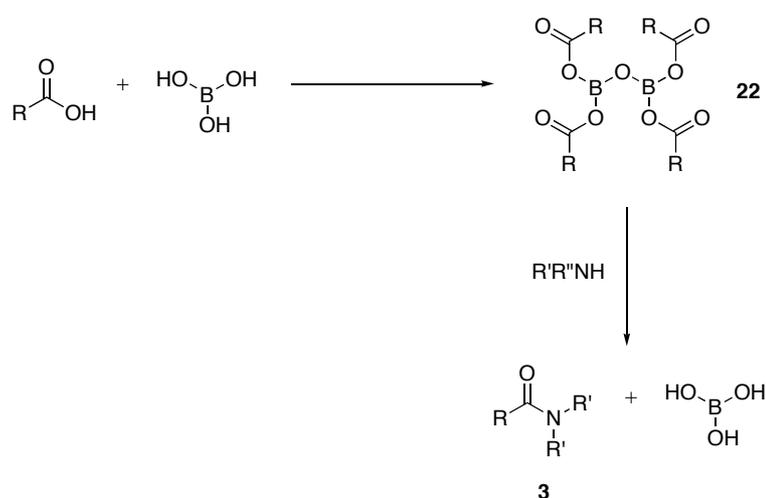
The proposed mechanism for this catalysed transformation is the same as that shown previously in Scheme 7, with the reaction perhaps proceeding *via* a monoacylated intermediate species.

A disadvantage of these arylboronic acid catalysts is that their activity is greatly reduced in polar solvents, which has restricted the scope of substrates that can be used. A polar solvent tolerant catalyst that has been demonstrated to be successful for direct amide formation is *N*-alkyl-4-boronopyridinium iodide **20**. This compound is much more active than the other arylboronic acid catalysts when direct amidation is carried out in solvents such as anisole, acetonitrile and *N*-methylpyrrolidinone (NMP).<sup>36-38</sup> Catalyst **20** can be reused through the use of ionic liquid-toluene biphasic solvents. A resin bound version of the catalyst has also been developed. *N*-polystyrene resin-bound 4-boronopyridinium salts **21a-d** have been produced as heterogenous catalysts for direct amidation without the need for ionic liquids.



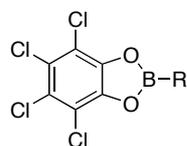
In 2005, Tang reported that cheap and readily available boric acid alone, was an efficient catalyst for direct amide formation.<sup>39</sup> Benzylamines and cyclic aliphatic amines such as piperidines reacted smoothly with a B(OH)<sub>3</sub> loading of 5 mol % leading to excellent yields. It was proposed that boric acid reacts with the carboxylic acid to form a mixed anhydride as the actual acylating agent.<sup>39</sup> Upon the addition of the amine, the desired amide is formed and boric acid is regenerated (Scheme 9). However, the intervention of tetraacyldiborate species such as **22**<sup>40-42</sup> cannot be ruled out in these types of reactions.

**Scheme 9:** Proposed scheme for direct amide formation using catalytic boric acid.



This amidation procedure has been employed in the synthesis of several active pharmaceutical ingredients.<sup>43, 44</sup>

In 2006, it was reported that 4,5,6,7-tetrachlorbenzo[*d*][1,2,3]dioxaborol-2-ol **23b** was effective as a catalyst for the amide condensation of sterically demanding carboxylic acids.<sup>29</sup>

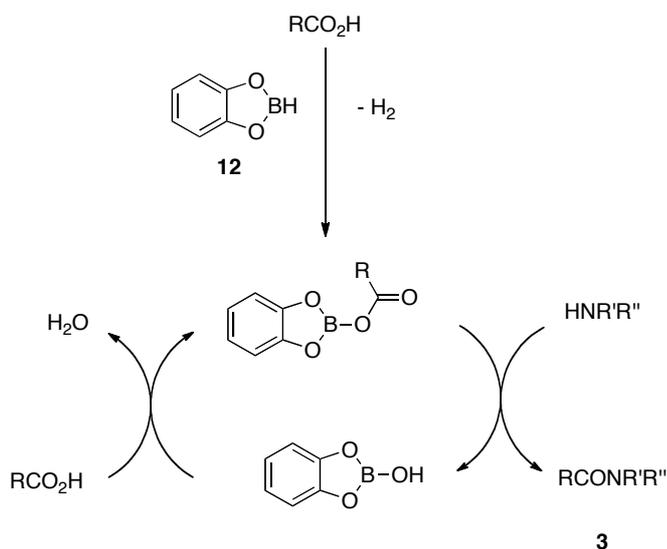


**23**

**a**; R = H  
**b**; R = OH

Taking into account the work by Ganem discussed previously,<sup>28</sup> it was found that compounds **23a-b** could be used to catalyse direct amidation with 5 mol% catalyst loading in toluene or *o*-xylene, with water removal achieved by azeotropic reflux. The proposed catalytic pathway for this transformation is shown in Scheme 10.

**Scheme 10:** Proposed catalytic scheme by which the Ganem procedure<sup>28</sup> might be transformed into a catalytic process.<sup>29</sup>

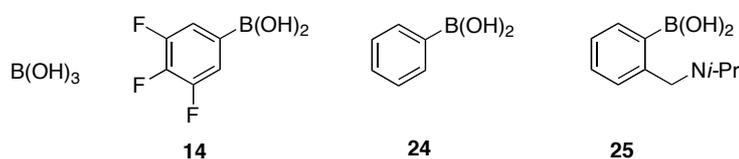


For the reaction between 4-phenylbutyric acid and benzylamine in toluene with azeotropic water removal, catalyst **23b** yielded the desired amide in 93% yield. Under the same conditions, when boric acid was used as the catalyst, the amide

yield was reduced to 31%. For a more sterically demanding combination of substrates, the direct condensation of cyclohexanecarboxylic acid with benzylamine was carried out using catalyst **24b** and boric acid. This afforded the amide in 62% and 2% respectively.

4,5,6,7-Tetrachlorbenzo[*a*][1,2,3]dioxaborol-2-ol **23b** displays a similar catalytic activity to 3,5-bis(trifluoromethyl)benzeneboronic acid **15**. Since boric acid is readily available at a low price, **23b** can be prepared relatively cheaply.<sup>29,</sup>  
43

Kinetic studies published in 2006<sup>44</sup> demonstrated that direct formation of amides from amines and carboxylic acids does occur in the absence of a catalyst under relatively low temperature conditions and is highly substrate dependant. For less reactive carboxylic acids, the presence of a boronic acid (such as **14**, **24** or **25**) or boric acid catalyst greatly improves the yield of amide produced.<sup>45</sup> Experiments combining different carboxylic acids and amines were carried out in refluxing toluene or fluorobenzene with water removal in the presence of 3 Å molecular sieves (Soxhlet). Importantly the thermal reaction was also compared with the addition of 1 mol% of several catalysts.



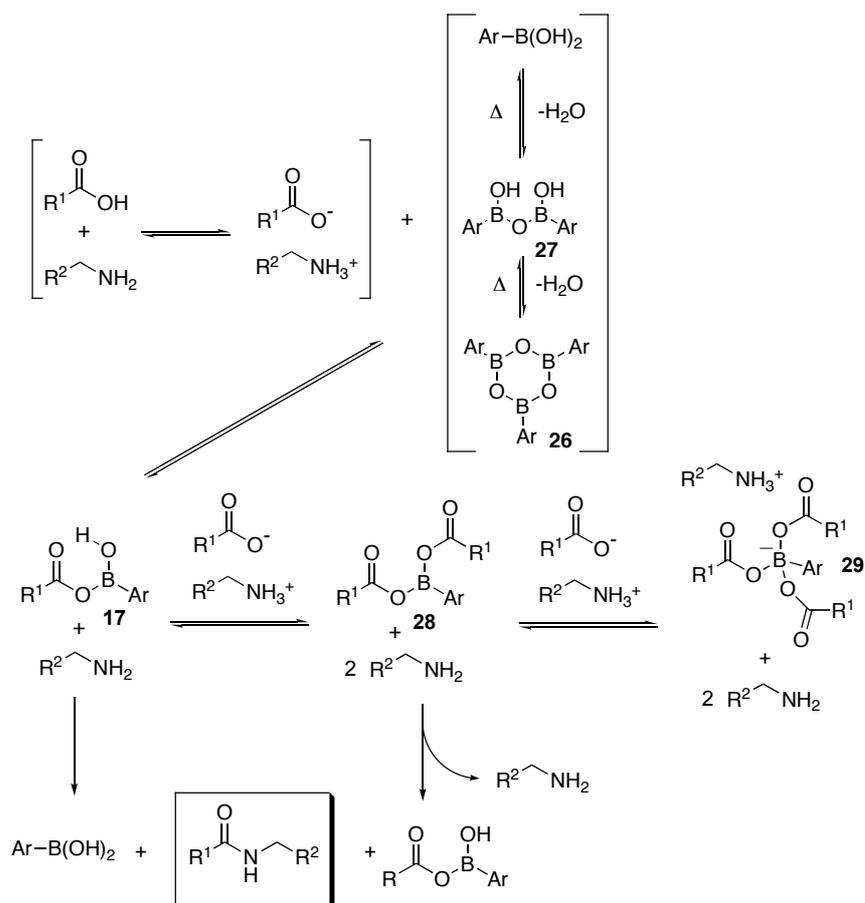
After 22 hours, the uncatalysed reaction between 4-phenylbutyric acid and benzylamine produced the corresponding amide with a yield of 60%. The performance of the catalysed reactions showed only a slight improvement, with boric acid, **14** and **25** being close to identical. In order to study only the catalytic effects, conditions that minimised the thermal reaction were employed. The reactions were carried out in refluxing fluorobenzene (85 °C) with an increased catalyst loading (10 mol %) and showed significant improvement over the thermal reaction.

For the more reactive combinations of amines and carboxylic acids, catalyst choice was not the most important factor. However, for less reactive substrates the bifunctional catalyst **25** was advantageous.<sup>46</sup> For example, the

reaction between benzoic acid and benzylamine in the presence of **25** gave the desired amide in a yield of *ca.* 80% over 48 hours. Clear evidence of bifunctional activity assisting substrate dependent reactions, particularly at low temperatures, was demonstrated.

Studies to identify the intermediate species in the catalytic pathway were also carried out and mass spectrometry provided evidence for existence of boroxine **26**, diboronate **27** and diacyloxyboronate **28** species, amongst others. On the basis of these observations, the following mechanism was proposed (Scheme 11).<sup>45</sup>

**Scheme 11:** Proposed mechanism for amide formation involving boric or arylboronic acid catalysis.



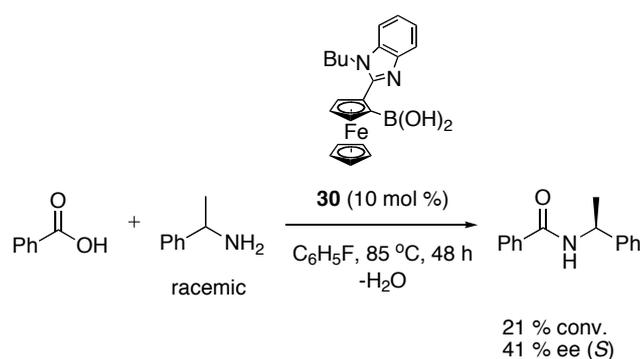
It is thought that the reaction proceeds through an intermediate, which is likely to be the mono- or di-acylated species, *i.e.* **17** or **28** respectively. For the

uncatalysed, thermal reactions it was suggested that the likely intermediate is the anhydride formed by thermolysis, which could explain the subsequent formation of the amide, however there is no direct evidence that this is the case. It is suggested that the formation of this anhydride could be rate-limiting and, therefore, by comparison with the catalysed reactions the carboxylate activation (formation of the acyloxyboronate species, whether mono- or di-acylated) is rate determining. In addition, design of experiment (DoE) studies undertaken by Whiting *et al.*<sup>46</sup> examined four factors to identify the ideal reaction conditions for catalysed direct amide formation. The results of these reactions (carried out in refluxing fluorobenzene) showed that the most important factors were catalyst loading, time and a two-factor interaction between time and catalyst loading. Concentration and excess acid or amine had no significant effect; this is in direct contrast to the work carried out by Loupy *et al.*<sup>19</sup> who reported that amide yield is significantly increased in the presence of excess carboxylic acid or amine (*vide supra*). In addition, Whiting *et al.*<sup>46</sup> reported that upon changing the experimental design to use toluene, catalyst loading was still the most important factor, followed by time. However, catalyst loading was involved in an interaction with concentration so that at higher catalyst loadings and lower concentration, an increased amide yield resulted. Carboxylic acid stoichiometry was still insignificant. The conclusions from the concentration effects suggested that the reaction rate was limited by the rate at which water can be azeotroped from the reaction mixture. The effect of not drying the reaction mixture led to zero order kinetics and a slower reaction, further corroborating the need to remove water and that the dehydration process is significantly rate limiting. This reinforces the idea that the acylation step is likely to be fast relative to the rate of physical water removal and that the amide formation is irreversible under the reaction conditions.

The first report of an asymmetric direct amide formation *via* kinetic amine resolution appeared in 2008.<sup>47</sup> Previously there had been no reports of direct amide formation involving asymmetric induction. This is because the process is generally regarded as one that requires high temperatures, which would lead to reactant or product degradation. Also, asymmetric induction processes are generally more efficient at lower temperatures as the effects of small differences in energy between diastereoisomeric transition states are

amplified. However, it is reported that asymmetric processes with respect to direct amide formation are possible under elevated temperatures (refluxing fluorobenzene) in the presence of a planar, chiral ferrocene based bifunctional amino-boronic acid catalyst **30**. This catalyst can induce the kinetic resolution of racemic  $\alpha$ -substituted benzylamines through direct amide condensation with achiral carboxylic acids (Equation 5).

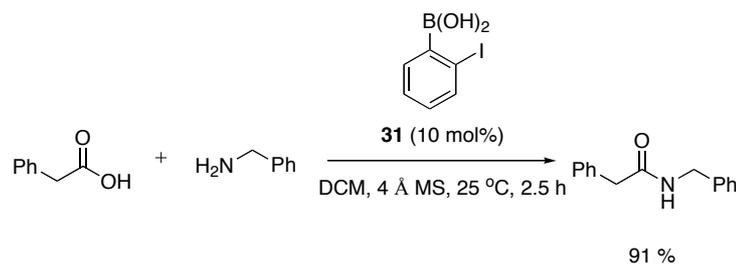
### Equation 5



Catalyst **30** is able to select one enantiomer of  $\alpha$ -chiral benzylamine with low to moderate selectivity and couple it to a moderately activated acylating agent to generate the required amide.<sup>47</sup>

In 2008, Hall and co-workers reported direct amide formation reactions carried out at 50 °C and at room temperature in the presence of a 2-halo-benzeneboronic acid catalyst.<sup>48</sup> These catalysts are significantly more active than 3,4,5-trifluorophenylboronic acid **14**, which requires temperatures of 120 °C. For the reaction of phenylacetic acid and benzylamine with water removal by 4 Å molecular sieves and a reaction temperature of 25 °C, the presence of catalyst **14** (10 mol %) resulted in the amide being formed with a yield of 42 % in dichloromethane. When the catalyst was changed to 2-iodobenzeneboronic acid **31** the amide yield increased impressively to 91%.

## Equation 6



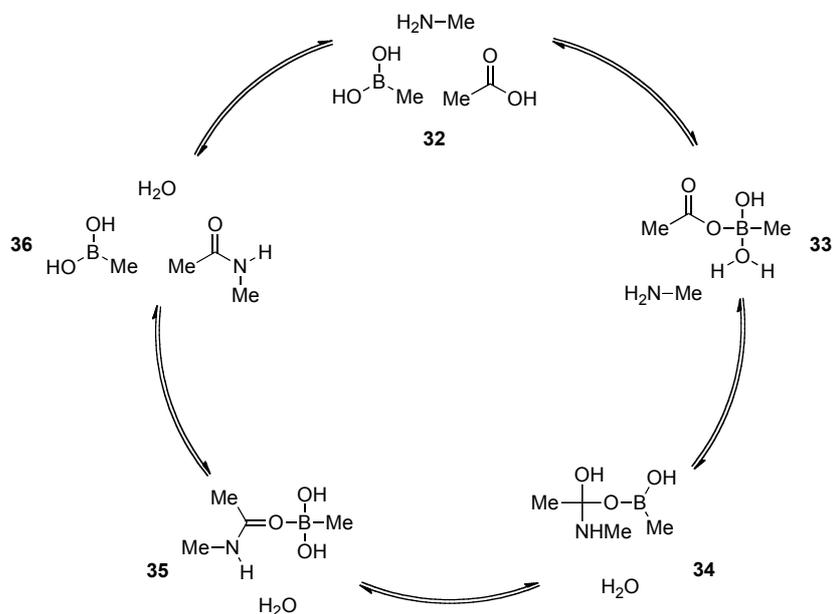
The possibility of a monoacyloxyboronate intermediate was discussed, as this would provide electrophilic activation of the carboxylic acid through boron conjugation and internal H-bonding. However, the possibility of a diacyloxyboronate intermediate was not ruled out.

2-Iodobenzeneboronic acid is the most active of the 2-halo-benzeneboronic acids. The importance of the *ortho*-substituent is confirmed by the poor activity of the *para*-isomer. When both *ortho*-positions are occupied the effectiveness of the catalyst is reduced and so confirms the importance of one unsubstituted *ortho*-position. Inductive effects do not account for the activity of **31** because of the reverse trend observed in the *o*-halide series (I > Br > Cl > F). The size and electron density of the iodo-substituent results in the distortion of the B-C-C bonds of the boronic acid. Therefore, it is possible that electronic or structural effects are important to the trend in activity observed here.<sup>48</sup>

A contribution in 2010 to the mechanism of direct amide formation catalysed by boronic acids was carried out using density functional theory.<sup>49</sup> Several mechanistic possibilities for the formation of amides from carboxylic acids and amines in the presence of boronic acid catalysts were investigated computationally. Unsurprisingly, it was found that pathways involving carboxylate-ammonium species were more energetically demanding than pathways involving neutral species. Also, reaction sequences that involved diacylboronate derivatives were found to have significantly higher overall energy barriers than sequences involving monoacylboronate derivatives. The calculations suggest that lowest energy pathway for catalysed amide formation involves the generation of a tetracoordinate monoacyl boronate. This supports previous work by Yamamoto *et. al.*<sup>31, 32</sup> who first suggested that these reactions

proceed *via* a monoacyl boron intermediate. The lowest energy catalytic cycle for direct amide formation is shown in Scheme 12.

**Scheme 12:** Lowest energy calculated catalytic cycle



Firstly, the reaction between the carboxylic acid and the catalyst occurs *via* concerted proton transfer and B-O bond formation. The calculated barrier suggests that this is a fast process, which is in contrast to previous theories.<sup>31, 45</sup> The newly generated water molecule is not expelled in this reaction step and in fact it was found that it is the tetracoordinate acyloxyboronate species which reacts with the amine. Although in principle the tricoordinate acyloxyboronate species could react with the amine, this process was found to be considerably more energetically demanding. The mechanism for C-N bond formation is suggested (Scheme 13) and begins with proton transfer from HO-B to the carbonyl oxygen (a), followed by C-N bond formation (b) and subsequent proton transfer from the amino group to an oxygen atom (c), finally water is dissociated from the boron (d) to provide hemiaminal **34**.



suggests to the chemical community that detailed studies are urgently needed. A thorough and fundamental understanding of the basic kinetics and thermodynamics of direct amide formation will be beneficial and there remains the need for the development of clean, sustainable processes for direct amidation, which will work under ambient conditions.

Clear steps have been taken in this direction, especially with the ongoing development of boron-based catalysts. However, an understanding of their mode of action is likely to be a prerequisite to developing systems which are effective on a wide range of substrates and at low temperatures and low catalyst loadings. A better understanding of the impact of amine and carboxylic acid *versus* ammonium carboxylate and exactly which of these species are reactive with precisely which activating species in the reaction is required. The uncovering of these mechanistic details will inevitably lead to major advances in catalyst design, new applications including larger scale industrial process application, and more importantly, universal acceptance that direct amide formation is a viable and important, general reaction.

## 2.0 Aims

There is an urgent need to develop clean, green processes for direct amide formation, which will proceed under ambient conditions. Current procedures, which employ the use of carboxylic acid derivatives such as acyl chlorides, anhydrides or involve coupling agents, are increasingly becoming undesirable as they represent poor atom economy and can result in the formation of toxic by-products. Partial solutions to this problem have been demonstrated by the use of boronic acids and boric acid as catalysts for the direct condensation of carboxylic acids and amines as discussed in Chapter one.<sup>31, 39, 45, 46, 48, 50</sup>

The objectives of this research are firstly, to perform thorough mechanism studies on the thermal, uncatalysed direct amide formation reaction using different combinations of carboxylic acids and amines. These studies include the examination of reaction rates and  $pK_a$  values as a starting point and also make use of calorimetry and computational DFT calculations to observe how the carboxylic acid and amine interact during the reaction. Secondly, the design and synthesis of new catalysts for direct amide formation, which will operate under ambient conditions is an aim of this research and will follow from a better understanding of the mechanism. The screening of new catalysts in comparison with the current successful catalysts under the same reaction conditions is also important.

The major challenge of this work is to provide the scientific community with a long overdue comprehensive understanding of the direct amide formation reaction (thermal and catalysed). Currently it is unclear how and why the thermal reaction occurs and why some boronic acid catalysts are more successful than others. Once this is understood, catalyst design can be optimised and novel catalysts can be developed.

Direct amide formation reactions will be applied to a range of commercial syntheses in order to establish whether a viable alternative to current procedures can be found. There is substantial industrial interest in direct amide formation as it provides an alternative to the current, costly and environmentally unfriendly processes used. The development of efficient and general catalytic

processes has the potential to have considerable impact within the chemical community.

## 3.0 The Non-Catalysed Direct Amide Formation Reaction

### 3.1 Introduction

The prevalence of the amide bond in nature and amongst industrial and pharmaceutical chemistry combined with the disadvantages of conventional methods of amide synthesis promotes amide formation as an excellent candidate for the development of a clean, sustainable, catalytic process.

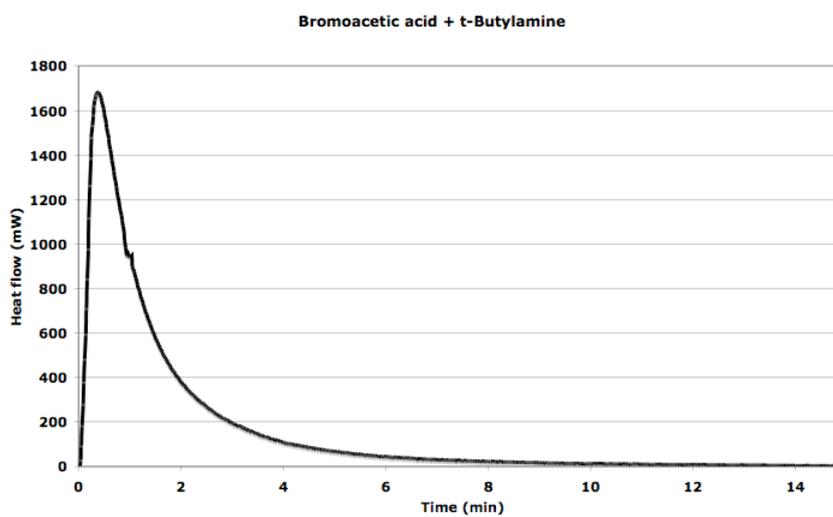
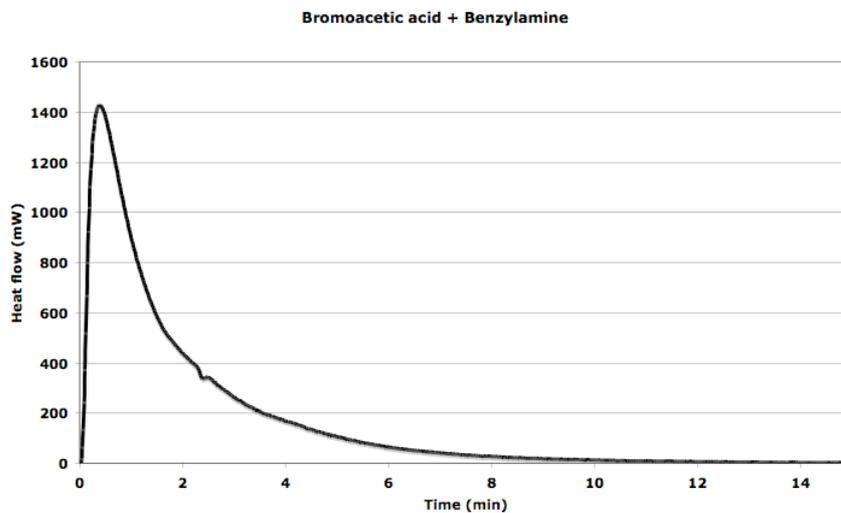
Despite the long history of direct amide formation and the more recent developments of catalysts to improve this process, it is a process that has remained relatively unexplored and relatively little is understood regarding the kinetics and mechanistic details of the reaction. A recent review of the published literature reveals how incomplete our understanding of the mechanisms are for both the uncatalysed and catalysed direct amide formation reactions.<sup>50</sup> In order to advance the development of catalyst design a comprehensive understanding of the mechanism of the catalysed and uncatalysed (thermal) direct amide formation reactions is essential.

As a starting point for investigations into the mechanistic aspects of direct amide formation and hence, the development of novel catalytic solutions, a calorimetric study of mixing carboxylic acids and amines was carried out in order to examine the relationship between heat output, salt formation and the ability of direct amide formation. Calorimetry was used to investigate whether a reaction occurs when carboxylic acids and amines are mixed in toluene. Mixing carboxylic acids and amines in water results in the formation of the carboxylate-ammonium salt but, since toluene has been shown to be an excellent solvent for direct amide formation, our investigations were directed towards identifying which species (salt or H-bonded species) are present when the mixing is carried out in toluene. Further to this, investigations including NMR studies of mixing carboxylic acids and amines in *d*<sup>8</sup>-toluene and also some interesting computational work, which has resulted in the determination of several important factors that should be considered for thermal direct amide formation and has provided insight into the mechanism of this reaction.

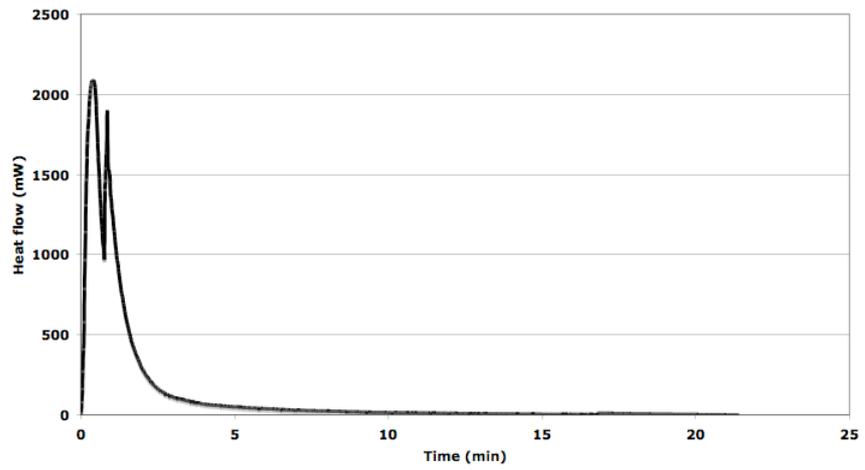
### 3.2 Calorimetry

In order to establish whether carboxylate-ammonium salt formation occurs on mixing carboxylic acids and amines in a non-polar, aprotic solvent the heat output of several combinations of amines and carboxylic acids has been measured in toluene. The selection of amines and carboxylic acids used in the study include a range of different structures, electron withdrawing or electron donating properties and a range of  $pK_a$  values in water. However, it has been previously reported that there is not a direct relationship between the  $pK_a$  values of amines and carboxylic acids in water and their ability to undergo direct amide formation.<sup>19, 51</sup> Hence, this required a more comprehensive study. To do this, stock solutions (1 M) in toluene were prepared for the amines and carboxylic acids that were to be used in this study. Due to the solubility of benzoic acid in toluene, a 0.5 M solution was made and all amines used in combination with benzoic acid had to be diluted to achieve 0.5 M solutions in order to keep the combination equimolar. The appropriate carboxylic acid was taken from the stock solution (2 mL) and injected into a calorimetry vial equipped with a stirrer bar. This was then placed into the calorimeter, which was set at 30 °C. Once the heat flow had stabilised, the appropriate amine solution (2 mL) was added and the heat output measured. The results for heat flow *versus* time for each combination is shown in Figure 3.

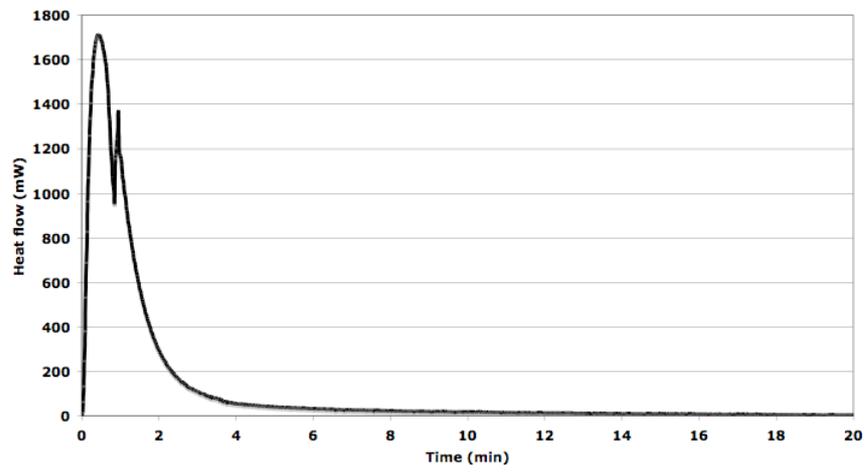
**Figure 3:** Heat output (mW) obtained from the mixing of carboxylic acids with amines.



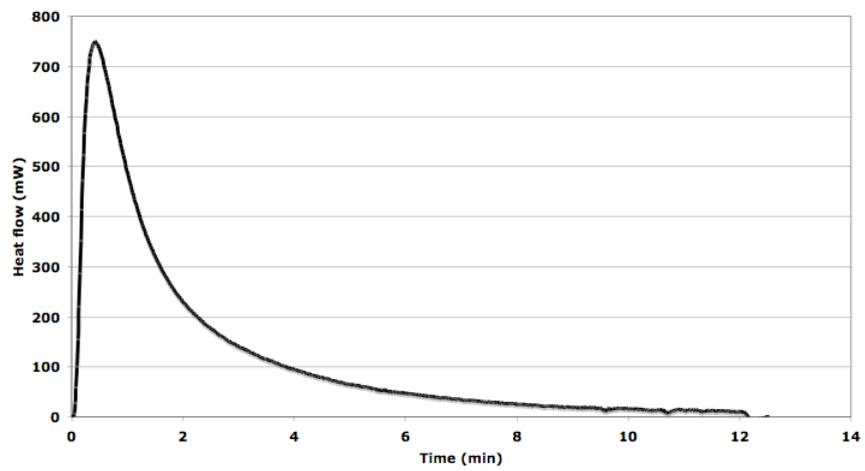
Bromoacetic acid + 2-Methoxyethylamine



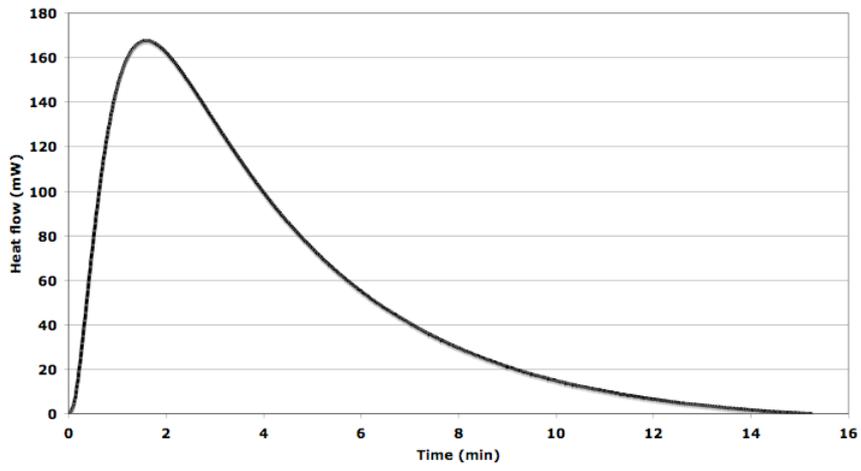
Bromoacetic acid + Piperidine



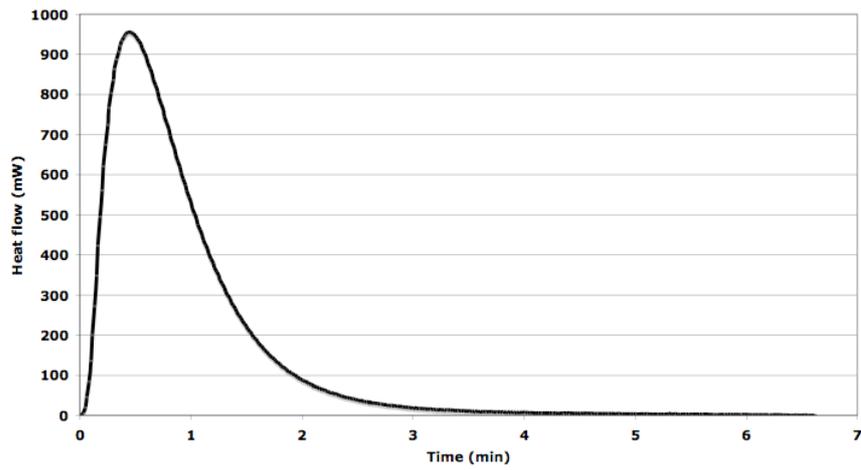
Bromoacetic acid + Aniline



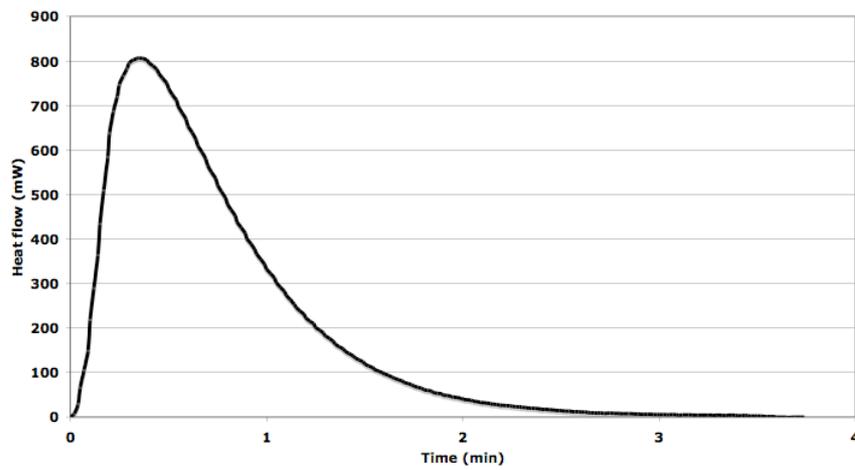
Phenylbutyric acid + Benzylamine



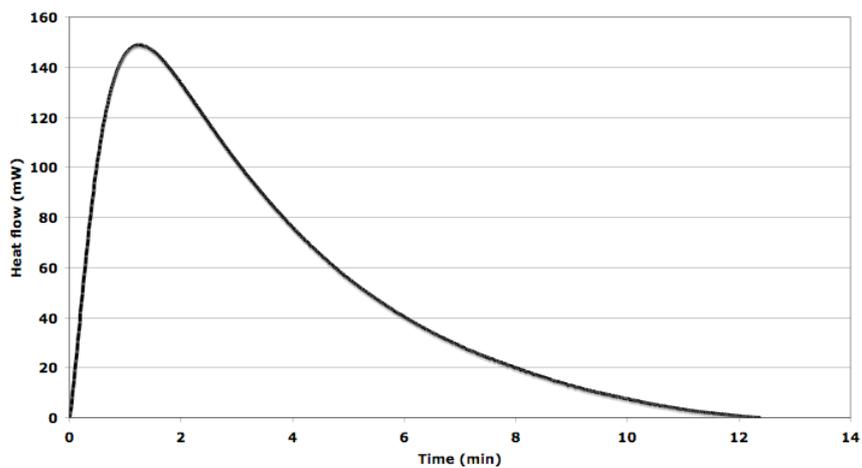
Phenylbutyric acid + t-Butylamine



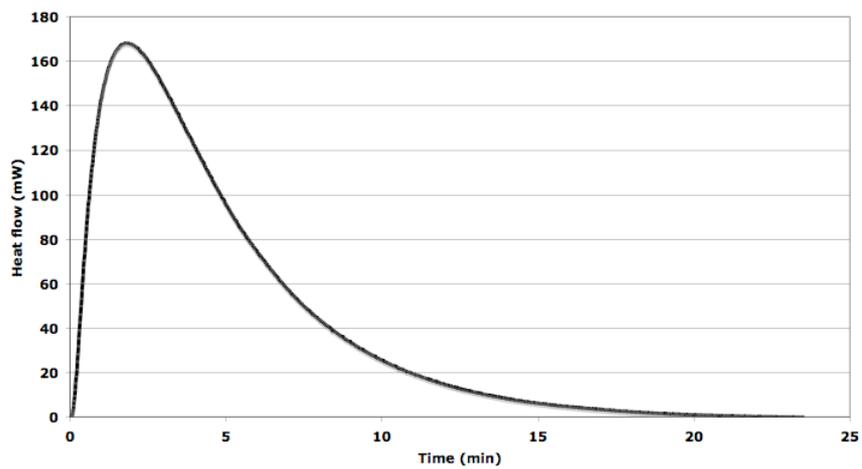
Phenylbutyric acid + 2-Methoxyethylamine



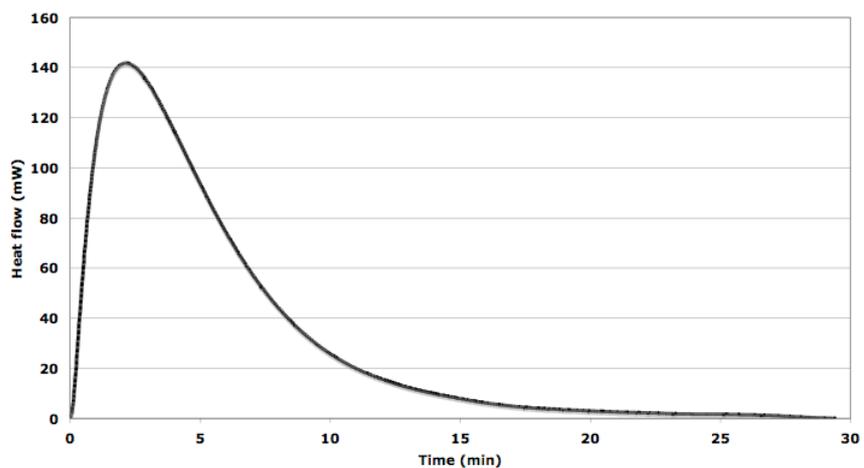
Phenylbutyric acid + Piperidine

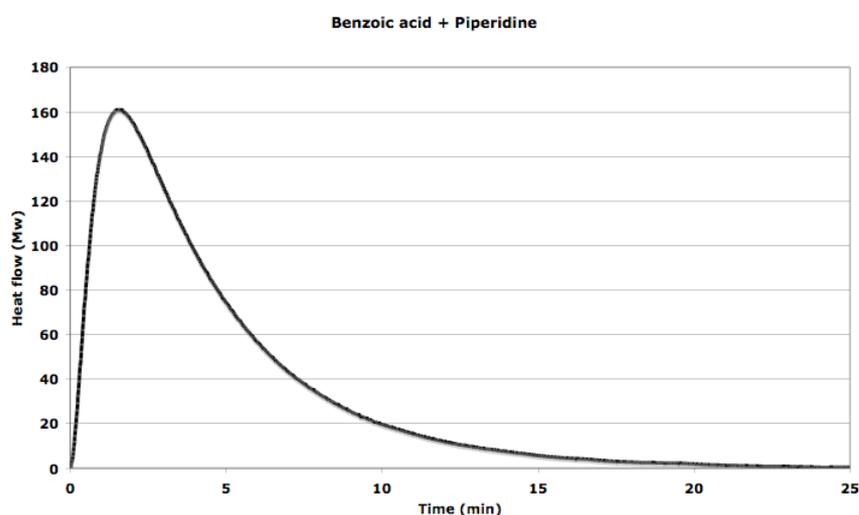
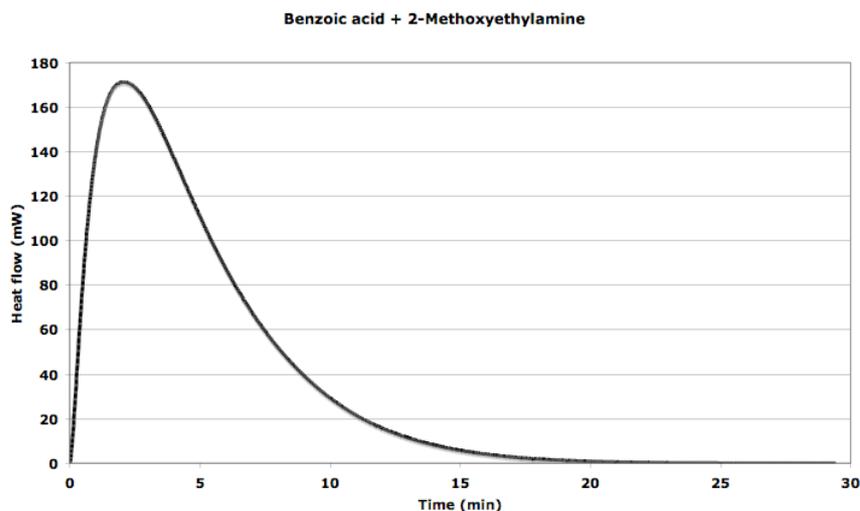


Benzoic acid + Benzylamine



Benzoic acid + t-Butylamine

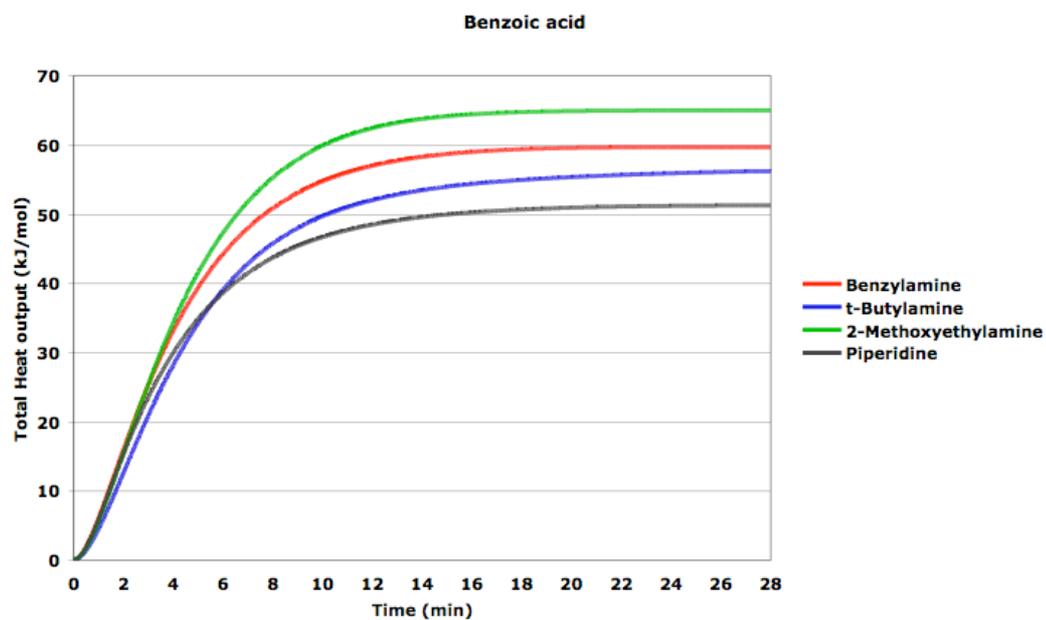
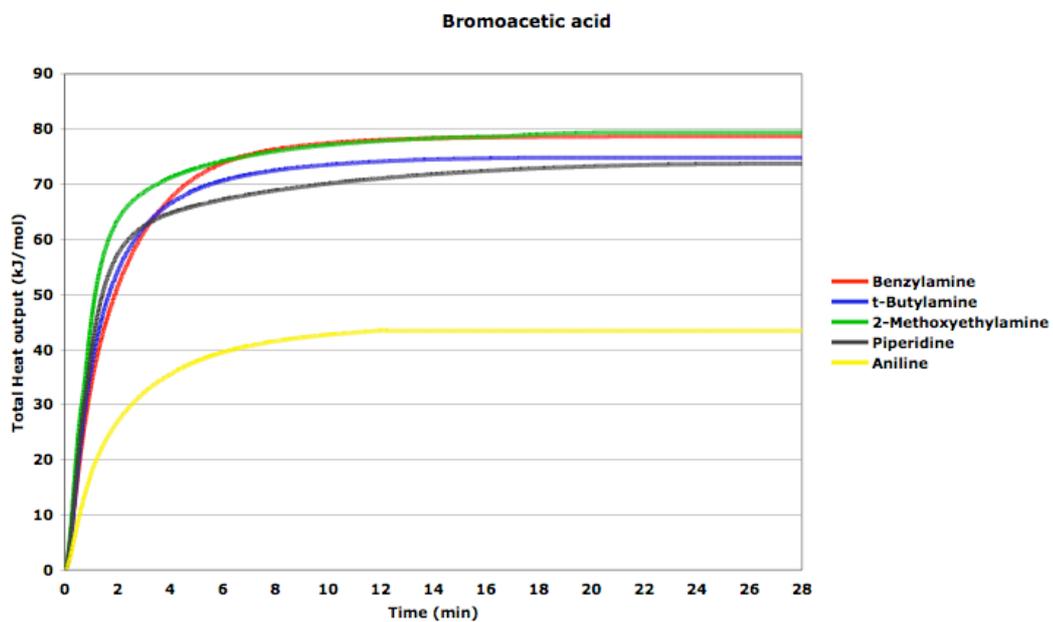


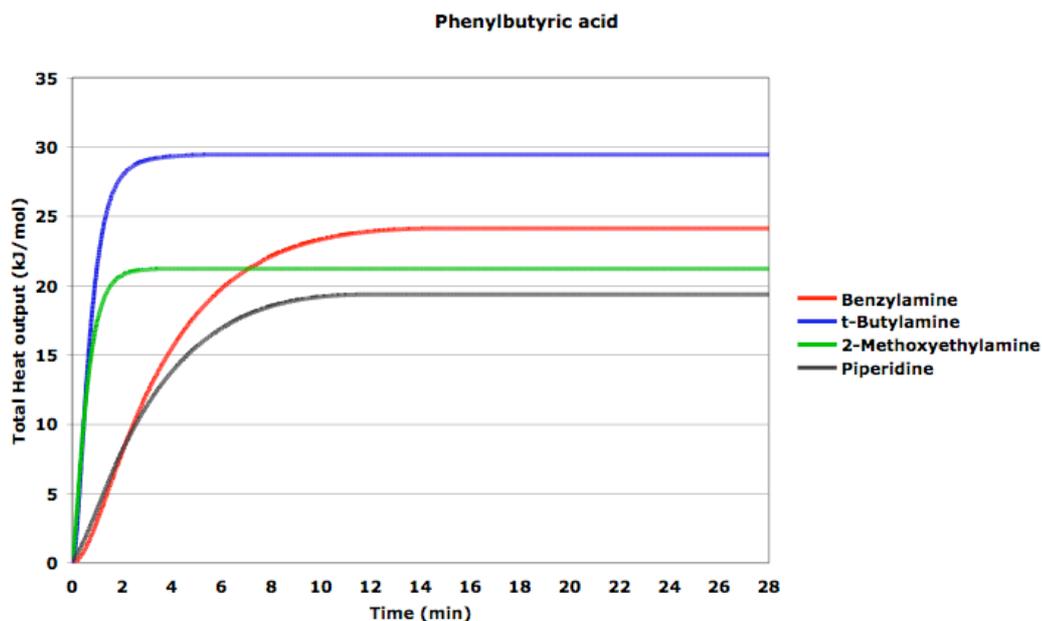


The heat flow data shows that there is a wide range of heat output values produced from the combinations of carboxylic acids and amines screened. Also for some combinations of carboxylic acid and amines the reaction that occurs on mixing is relatively fast whereas for other combinations it is much slower (bromoacetic acid with benzylamine *versus* phenylbutyric acid with benzylamine for example).

In order to make the direct comparison more obvious for the mixing of each carboxylic acid with each of the amines, the heat flow data shown in Figure 3 can be manipulated in order to achieve a plot representing the cumulative total heat output (Figure 4). For example, when bromoacetic acid was mixed with benzylamine a total heat output of 79 kJ/mol occurred in the first 9 minutes, after which time there was no further heat output.

**Figure 4:** Cumulative total heat output (kJ) obtained from the mixing of carboxylic acids with amines.





**Table 3:** Results from calorimetry and yields for direct amide formation.

Carboxylic acid	Amine	Total heat output (kJ/mol)	Direct amide formation Yield (%)		
			Uncat. <sup>a</sup>	Cat. <sup>b</sup>	Cat. <sup>c</sup>
Bromoacetic acid	Benzylamine	79 <sup>d</sup>	0	0	0
	t-Butylamine	75 <sup>d</sup>	0	0	0
	2-Methoxyethylamine	79	0	0	0
	Piperidine	74 <sup>d</sup>	0	0	0
	Aniline	43 <sup>d</sup>	0	0	0
Phenylbutyric acid	Benzylamine	24	64	89	76
	t-Butylamine	30 <sup>d</sup>	< 1	3	< 1
	2-Methoxyethylamine	21	54	70	49
	Piperidine	19	24	80	1
	Aniline	0	4	74	16
Benzoic acid	Benzylamine	60 <sup>d</sup>	14	86	2
	t-Butylamine	56 <sup>d</sup>	0	0	0
	2-Methoxyethylamine	65 <sup>d</sup>	5	24	5
	Piperidine	51	10	49	0
	Aniline	0	0	35	20

<sup>a</sup>Uncatalysed in toluene at 120 °C with Dean-Stark water removal over 48 h. <sup>b</sup>Boric acid catalyzed in toluene at 120 °C with Dean-Stark water removal over 48 h. <sup>c</sup>*o*-Iodophenylboronic acid catalyzed in toluene at 50 °C using 3Å molecular sieves over 48 h. <sup>d</sup>Crystallisation of salt occurred on mixing carboxylic acid and amine.

The results shown in Figure 4 and Table 3 demonstrate that the highest heat outputs were derived from mixing bromoacetic acid ( $pK_a$  2.69) with the different amines and the rate of heat output was also similarly rapid for each amine reaction. In contrast, phenylbutyric acid ( $pK_a$  4.76) gave much reduced heat output with benzoic acid ( $pK_a$  4.19) giving intermediate reactivity with the different amines together with much more variable rates of heat output. It seems clear that heat output is strongly  $pK_a$  related, which is demonstrated by the relative order of reactivity of the three carboxylic acids. Bromoacetic acid reacts with all the amines examined in an exothermic manner and interestingly fails to react under thermal or either of the standard boronic or boric acid catalysed reaction conditions. Phenylbutyric acid in contrast is more reactive and amide formation occurs to some extent with all the amines examined, again, with benzoic acid showing intermediate reactivity. This shows some level of correlation between carboxylic acid  $pK_a$  and ability to undergo direct amide formation, *i.e.* higher  $pK_a$  equates to higher reactivity which contrasts with previous claims.<sup>19, 51</sup>

Examining amine reactivity shows that there is no major difference in heat output between the amines, with the exception of aniline (ammonium  $pK_a$  4.63), which was considerably less reactive with all three carboxylic acids. This lower reactivity is likely to result from the lower basicity of aniline in comparison to the other amines, resulting in diminished susceptibility towards protonation. However, unlike with the carboxylic acids, lower basicity does not extrapolate to lower reactivity towards direct amide formation. In fact, the least reactive amine was *tert*-butylamine (ammonium  $pK_a$  10.83) which essentially fails to react with any of the carboxylic acids under any of the reaction conditions. These results clearly show that the amine reactivity contribution to amide formation is not a simple function of amine basicity; steric effects as well as electronic effects must be playing a part. This conclusion is reinforced by examining the reactivity of benzylamine (ammonium  $pK_a$  9.33) compared with other amines; it is the most reactive amine under all conditions with the two reactive carboxylic acids, despite being neither the most basic nor least sterically hindered amine. This enhanced reactivity of benzylamine has been reported previously<sup>45, 51</sup> and understanding the “benzylic” effect of amine reactivity is essential in order to understand how direct amide formation proceeds.

### 3.3 Ammonium Carboxylate Salt Formation and Solution NMR Studies

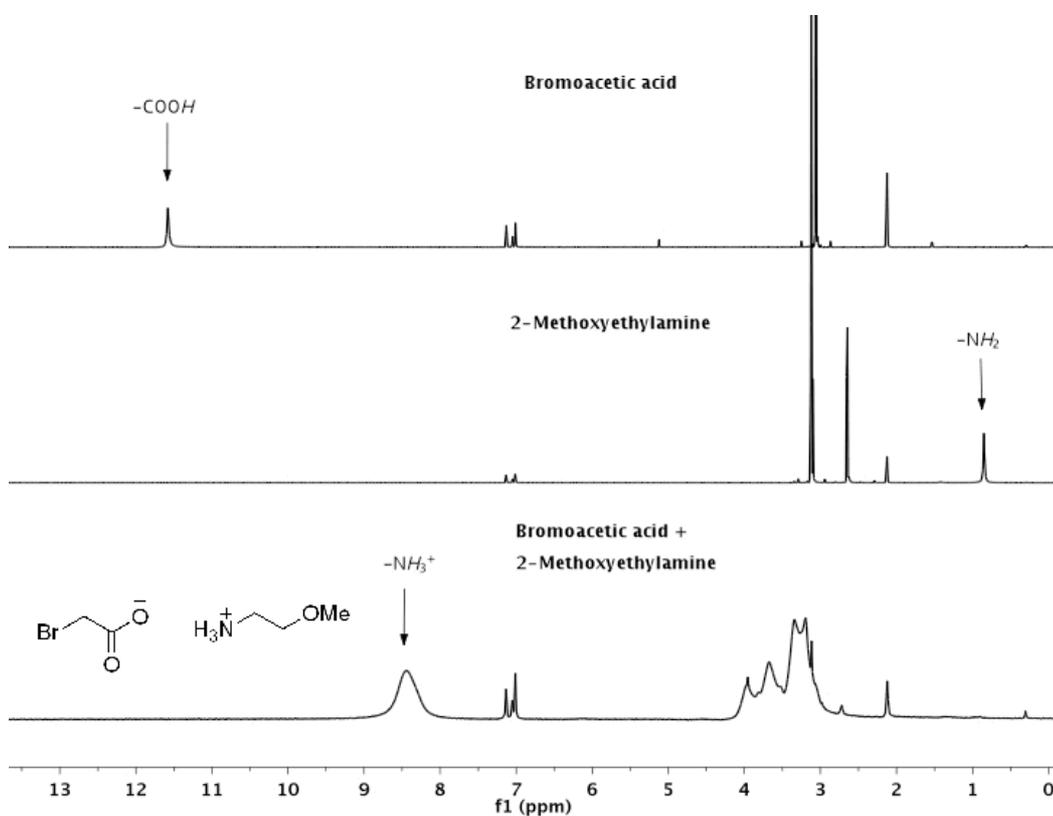
It is assumed that the high heat output from certain carboxylic acid-amine combinations (Figure 4 and Table 3) results from exothermic salt formation. However, solid products were not always produced, and in cases where the heat output was lower it was necessary to establish exactly what species were being produced upon mixing the carboxylic acids and amines.

Each carboxylic acid and amine was mixed at room temperature in toluene, and for those combinations which produced a precipitate (Table 4), this was removed by filtration and analysed (CHN analysis) to confirm that carboxylate ammonium salt formation had taken place. The combinations of carboxylic acid and amine that failed to precipitate (Table 4), were examined by NMR (in  $d^8$ -toluene) up to 24 h after mixing in order to identify which species were present in solution and how they had changed.

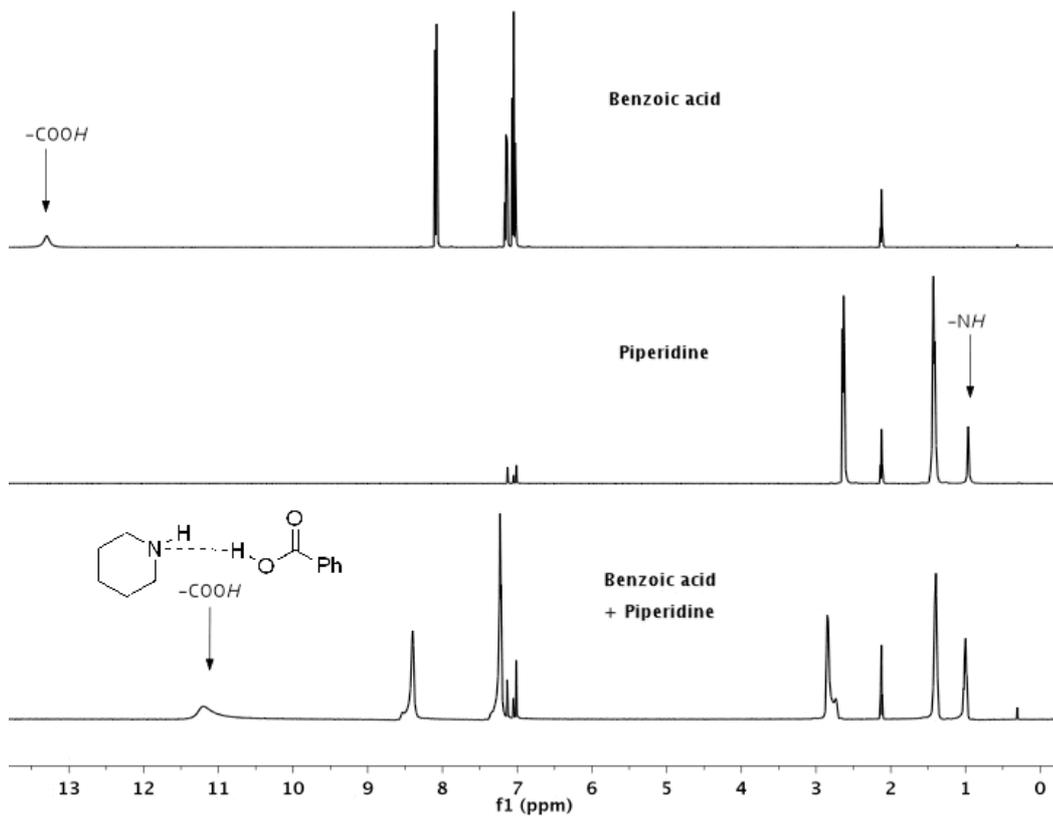
**Table 4:** Yields of ammonium salt (all of which were within microanalysis limits, *versus* salts which stayed in solution)

Carboxylic acid	Amine	Analysis	Precipitate Yield (%)
Bromoacetic acid	Benzylamine	CHN	50
	t-Butylamine	CHN	48
	2-Methoxyethylamine	NMR	-
	Piperidine	CHN	13
	Aniline	CHN	46
Phenylbutyric acid	Benzylamine	NMR	-
	t-Butylamine	CHN	100
	2-Methoxyethylamine	NMR	-
	Piperidine	NMR	-
	Aniline	NMR	-
Benzoic acid	Benzylamine	CHN	64
	t-Butylamine	CHN	100
	2-Methoxyethylamine	CHN	72
	Piperidine	NMR	-
	Aniline	NMR	-

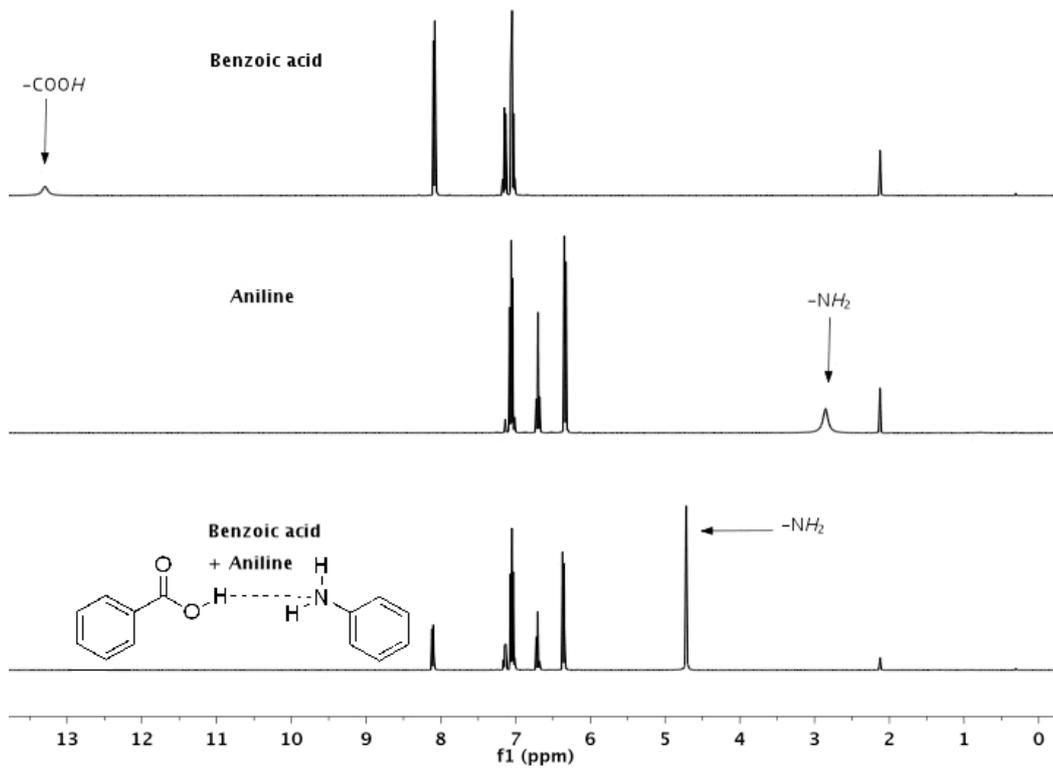
**Figure 5:**  $^1\text{H}$  NMR spectra obtained from mixing selected carboxylic acids and amines.



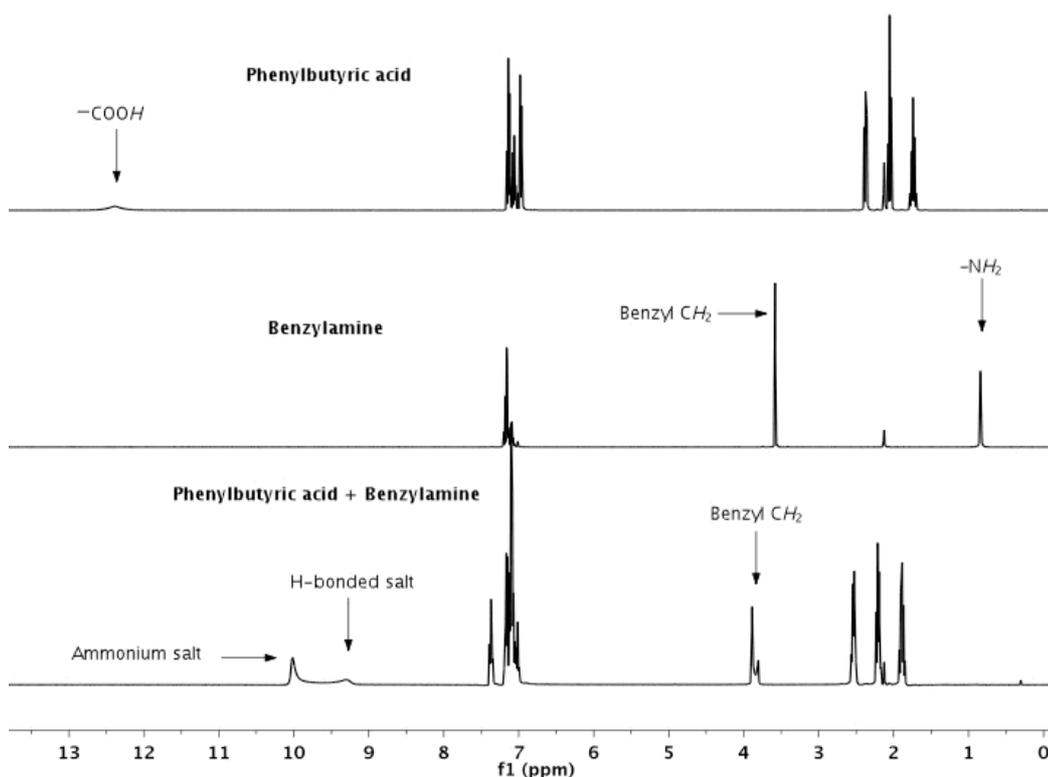
a) Bromoacetic acid + 2-Methoxyethylamine



b) Benzoic acid + Piperidine



c) Benzoic acid + Aniline



d) Phenylbutyric acid + Benzylamine

For the combinations of amines and carboxylic acid that stayed in solution upon mixing, the solutions remained homogeneous and it was reasonably straightforward to follow the reactions over time.  $^1\text{H}$  NMR suggested the presence of three different types of species being formed: 1) complete salt formation (for example Figure 5a); 2) H-bonding between ammonium and carboxylate (for example Figure 5b); 3) and H-bonding between amine and carboxylic acid (for example Figure 5c). In contrast, for the case of phenylbutyric acid with benzylamine (Figure 5d), the spectrum collected just after mixing showed the presence of an ammonium salt, however, H-bonding between the ammonium and carboxylate was also observed in a 2:1 ratio. The benzyl  $\text{CH}_2$  peak was also split (2:1) suggesting the presence of two different species. It is noteworthy that this combination of carboxylic acid and amine seems to be one of the most active for direct amide formation with or without a catalyst (see Table 3) and perhaps this NMR observed association between the ammonium and carboxylate and association between the free amine and

carboxylic acid are important for assisting direct amide formation in some way and this has been further investigated using DFT calculations (*vide infra*). Figure 5 exemplifies the 3 types of species that can be observed by  $^1\text{H}$  NMR on mixing carboxylic acids and amines; a complete summary for all of the combinations of carboxylic acid and amine that have been investigated is shown in Table 5 (see appendix for spectra).

**Table 5:** Summary of  $^1\text{H}$  NMR spectra obtained from mixing selected carboxylic acids and amines.

<b>Carboxylic Acid</b>	<b>Amine</b>	<b>Species observable by NMR</b>
Bromoacetic acid	2-Methoxyethylamine	- Complete salt formation. - Ammonium peak present at 8.4 ppm, integrates as 3H.
Phenylbutyric acid	Benzylamine	- Salt formation and H-bonding between ammonium and carboxylate (2:1). - Ammonium peak at 10 ppm, H-bonded peak at 9.3 ppm. Benzyl $\text{CH}_2$ split 2:1 and shifted from 3.5 to 3.9 ppm.
Phenylbutyric acid	2-Methoxyethylamine	- H-bonding only. No evidence of salt formation. - $\text{NH}_2$ shifted, $\text{OH}$ not present or too broad to be seen.
Phenylbutyric acid	Piperidine	- All H-bonded salt. - $\text{OH}$ shifted from 12.4 to 11.4 ppm. - $\text{NH}$ shifted from 0.9 to 1.1 ppm.
Phenylbutyric acid	Aniline	- H-bonding only. No evidence of salt formation. - $\text{NH}_2$ shifted from 2.8 to 4.9 ppm, $\text{OH}$ not present or too broad to be seen.
Benzoic acid	Piperidine	- All H-bonded salt. - $\text{OH}$ shifted from 13.3 to 11.2 ppm.
Benzoic acid	Aniline	- H-bonding only. No evidence of salt formation. - $\text{NH}_2$ shifted from 2.8 to 4.7 ppm, $\text{OH}$ not present or too broad to be seen.

Looking at the calorimetry plots (Figure 4) it is clear that the rates of some reactions were significantly faster than others, for example the reaction between phenylbutyric acid and *tert*-butylamine produced no further heat output after approximately 3 minutes. However, for the reaction of phenylbutyric acid with benzylamine, the reaction occurred over approximately 13 minutes, after which time there was no further heat output. In order to ensure that all of the reactions carried out in the NMR tube had finished, each sample was re-examined after 24 h. This second set of NMR spectra showed that for three combinations of different amines reacting with phenylbutyric acid (*i.e.* benzylamine, 2-methoxyethylamine and piperidine), the presence of ammonium salt, H-bonded salt or just H-bonding became less clear. These samples were therefore heated to 50 °C and 85 °C to see if this would result in simplification the spectra, which indeed it did and in all three cases the ammonium salt was the only species present. It should also be noted that for all three cases, increasing the temperature from 50 °C to 85 °C resulted in a higher field ammonium shift though notably at different rates depending the amine-carboxylic combination. Re-running the same NMR samples again after cooling to room temperature showed the presence of ammonium salt in all three cases, with broad ammonium N-H peaks being observed at  $\delta$  7.58 (3H) for phenylbutyric acid + benzylamine,  $\delta$  8.32 (3H) for phenylbutyric acid with 2-methoxyethylamine and  $\delta$  9.72 (2H) for phenylbutyric acid with piperidine.

Therefore, from the evidence obtained from the calorimetry, NMR studies, and the yields of direct amide formation, it can be concluded that several factors influence the reactivity of carboxylic acid-amine partners for direct amide formation, *i.e.*: 1) the stability of the ammonium carboxylate salt; 2) the  $pK_a$  of the carboxylic acid; 3) nucleophilicity *versus* basicity of the amine tuned by steric *versus* electronic (conjugation) effects. In order to understand exactly how the uncatalysed direct amide formation reaction actually occurs and to explore the plausibility of different possible mechanisms, a detailed computational study was carried out in collaboration with Professor Mark Wilson (Durham University).

### 3.4 Computationally Calculated Proton Affinities

In order to obtain a measure of the relative basicity or acidity of the substrates used in the calorimetry and NMR studies, proton affinities were determined in the gas phase using an approximate (PCM) solvation model for toluene *via* DFT calculations. This study was carried out in order to ascertain that calculated proton affinities reflected experimental  $pK_{\text{a}}$ s and, more importantly, to provide a better picture of the susceptibility to the different amine derivatives towards protonation by carboxylic acids in a simulated non-polar solvent. The values obtained using a B3LYP functional, 6-31G\*\* and 6-31+G\*\* basis sets are given in Table 6. Although the calculated proton affinity values are consistently slightly higher than the experimental values for the proton affinities, these results provide a useful trend showing relative basicity, which enables us to compare one compound with another. The trend for five experimentally known affinities is exactly reproduced, and a plot of experimental *versus* calculated affinities yields a straight line fit with an  $R^2$  coefficient of 0.998. Hence, the DFT results can be used to provide a reasonable estimate for unknown bases (including the conjugate bases of the three acids in this study).

The calculated proton affinities are in good agreement with the five experimentally measured affinities in Table 6 at the 6-31G\*\* level (mean error of 2%). With the further addition of diffuse functions using 6-31+G\*\* basis sets (which give a better representation of soft anions), the predicted values improve further to a mean error of 0.2%. The proton affinities were also estimated in toluene by using an approximate PCM solvation treatment. Here, as expected, proton affinities for the neutral bases in toluene are slightly higher because of the dielectric effects of the solvent stabilising the charged conjugate acid. While the trend in proton affinities does not change with solvation, the range of values is significantly reduced by the presence of the solvent. However, the dielectric effect of the solvent is fairly weak (compared to more polar solvents) and the basicity of the three carboxylic acid anions is such that we do not expect salt formation in toluene for any of the combinations in Table 3, at least not without an additional contribution from the lattice energy assisting precipitation, and/or interactions with water (or water molecules) stabilising an ion pair. These results

are intriguing especially in contrast to the results shown in Tables 3 and 4. From the  $pK_a$  values and from the energy differences calculated, we do not expect proton transfer to form salts to be enthalpically favoured. It is, therefore, likely that the heat output measured (Table 3) in many of the amine-carboxylic acid reactions results from precipitation of the ammonium carboxylate salt rather than proton transfer from acid to amine. In solution, where there is no precipitation, but where NMR studies indicated formation of the carboxylate ammonium salt, we expect the formation of solvent stabilised ion pairs to occur. However, this is difficult to model without the use of explicit solvent molecules.

**Table 6:** Proton affinities in the gas phase and with toluene solvation model.

Compound	Exp. affinity (kJ / mol) <sup>a</sup>	Gas Phase		Toluene Solvation Model	
		Calc. Affinity 6-31G** (kJ / mol)	Calc. Affinity 6-31+G** (kJ / mol)	Calc. Affinity 6-31G** (kJ / mol)	Calc. Affinity 6-31+G** (kJ / mol)
Ammonia	854	873	849	1050	1019
Aniline		900	879	1043	1006
Methylamine	896	916	896	1076	1049
2-Methoxyethyl-amine		923	901	1072	1040
Ethylamine		931	910	1084	1057
Dimethylamine	923	941	925	1085	1065
Benzylamine		946	924	1085	1052
t-Butylamine		955	934	1089	- <sup>b</sup>
Trimethylamine	942	957	942	1086	1072
Diethylamine		967	942	1099	1074
Piperidine		969	951	1106	1077
Triethylamine	972	991	976	1110	1090
Bromoacetic acid ion		1439	1386	1313	1263
Benzoic acid ion		1469	1412	1344	1283
Phenylbutyric acid ion		1495	1428	1359	1298
Bromoacetic acid		803	777	947	891
Benzoic acid		854	828	977	937
Phenylbutyric acid		830	807	958	- <sup>b</sup>

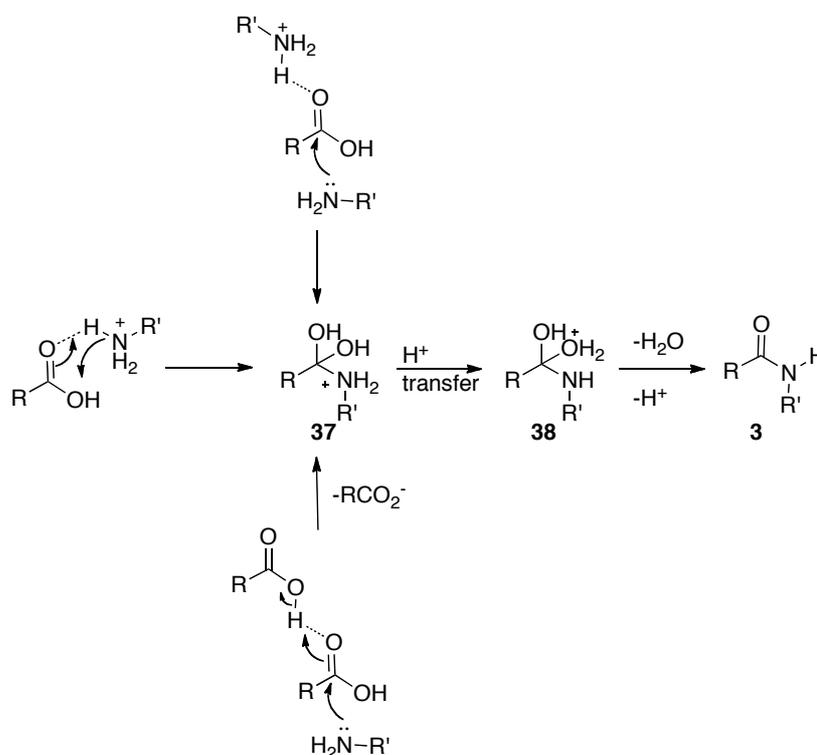
<sup>a</sup>For experimental proton affinities, see ref.<sup>32</sup>

<sup>b</sup>Convergence not obtained for 6-31+G\*\* basis set with PCM.

### 3.5 Kinetic Evidence for Acid or Base Catalysis in Direct Amide Formation

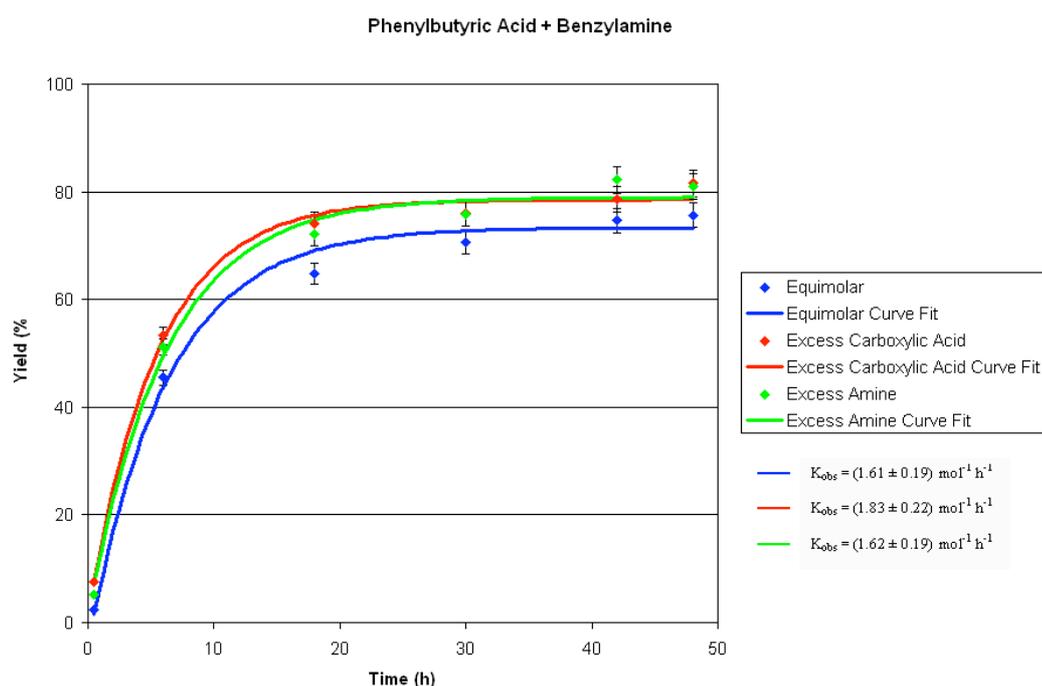
Having examined proton affinities and how these are reflected in the observed interactions and reactions between carboxylic acids and amines, the next stage was to investigate the viability of possible mechanisms for uncatalysed direct amide formation with the aim of establishing the viability of different intermediates and transition states along different reaction pathways. Initially, a mechanism analogous to the acid-catalysed esterification reaction was investigated, *i.e.* where the electrophilicity of the carboxylic acid is increased by protonation of the carbonyl oxygen, which will facilitate the attack of an amine. If a general acid can catalyse direct amide formation then it follows that the acid source could derive from an ammonium salt  $\text{NH}^+$  or from excess carboxylic acid, as shown in Scheme 14.

**Scheme 14:** Initial proposed mechanism for direct amide formation based on acid-catalysed esterification.



In order to investigate this possibility, direct amide formation reactions between phenylbutyric acid and benzylamine in the presence of either a 20% excess carboxylic acid or a 20% excess amine were followed over a 48 h time period. The results are shown in Figure 6.

**Figure 6:** Results from following the reaction between phenylbutyric acid and benzylamine over time in refluxing toluene.

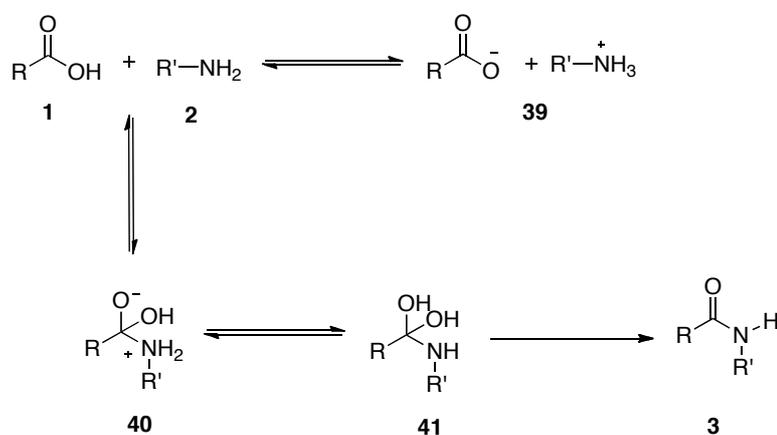


The presence of excess carboxylic acid or amine produced very similar results (Figure 6) and indeed, both show only a slight rate and yield enhancement in comparison to the equimolar reaction (for further experiments see below). It has been previously reported that an excess of either carboxylic acid or amine can enhance the direct amide formation reaction<sup>19</sup> and although the difference may be a real effect, in this case it is clearly not significant, and therefore, it seems unlikely that direct amide formation is particularly amenable to either acid or base catalysis. If the reaction were amenable to such general catalysis, a more significant increase in rate would have been expected.

A second reaction mechanism requiring consideration could involve attack of an amine directly on the carboxylic acid, *i.e.* as outlined in Scheme 15. Such a mechanism appears to be plausible when looking at the yields of direct

amide formation (Table 3), since carboxylic acids attached to electron-withdrawing groups are likely to be largely in the form of the ammonium salt due to their lower  $pK_a$ . Considering the amine; electron-donating groups stabilise ammonium salt formation, and this would explain why the combination of bromoacetic acid with *t*-butylamine shows a complete inability to undergo direct amide formation because the only species present in solution is the carboxylate salt.

**Scheme 15:** Alternative proposed mechanism for direct amide formation *via* zwitterionic species.



If direct amide formation was to proceed *via* the direct attack of the amine on the carboxylic acid (Scheme 15), then an amine that is a good nucleophile is required, followed by the formation of a stable zwitterionic intermediate species, *i.e.* **40**. If this is the case then carboxylic acid-amine combinations which form stable carboxylate ions, where the ammonium salt cannot reprotonate the carboxylate back to the neutral acid form, are predicted to be unreactive. This mechanism looks to be plausible when taking the results for direct amide formation in Table 3 into account, especially considering that there is no amide produced when complete salt formation occurs (*i.e.* with bromoacetic acid). This would suggest that the mechanism for uncatalysed direct amide formation starts from the free amine and free carboxylic acid. In order to probe this mechanistic theory further, additional computational studies were carried out.

### ***3.6 Computational Studies on Possible Direct Amide Formation Mechanisms (Collaboration with Prof. Mark Wilson, Durham University)***

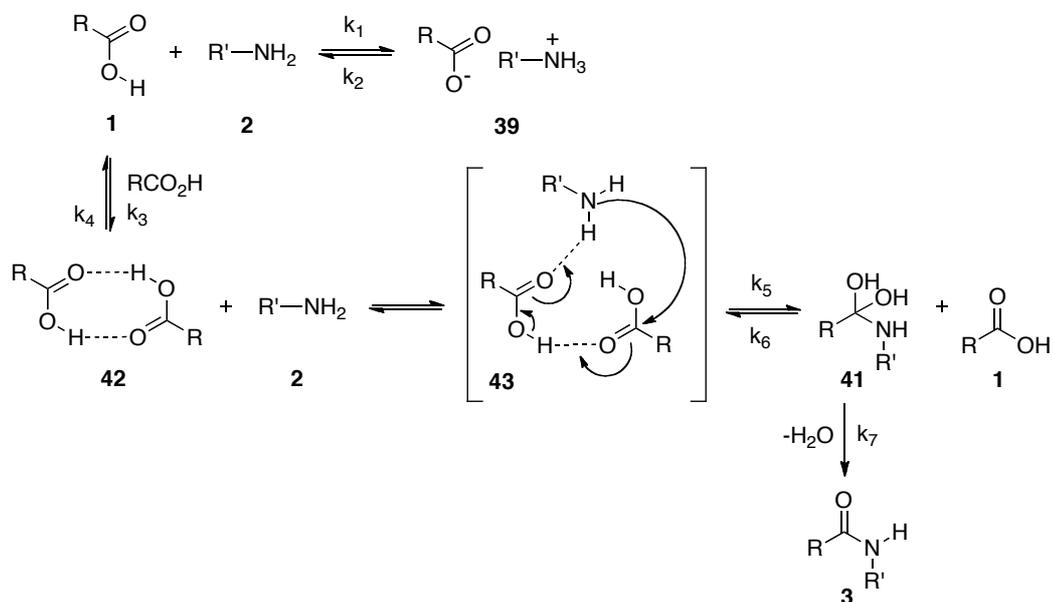
Initially, DFT calculations were used to investigate the structure and energies of possible intermediate compounds as outlined in Scheme 15. Calculations were carried out for all combinations of carboxylic acids and amines that were used in the calorimetry and NMR studies (see above). DFT calculations investigated the possibility of various species being either stable intermediates (energy minima) or transition states on the reaction surface in a simulated toluene solvent. The results clearly showed that the zwitterionic compound **40**, formed from attack of the free amine onto a free carboxylic acid, was unstable in all cases and would rapidly dissociate to give back the starting amine and carboxylic acid. From this we can, therefore, conclude that species **40** (Scheme 15) is not involved as a transition state or intermediate for uncatalysed direct amide formation and can be discounted from Scheme 15.

During the process of investigating plausible intermediates the neutral compound **41** was found to be stable in all cases. Considering all of the computational and experimental data collected, a mechanism for direct amide formation is not likely to originate directly from the ammonium-carboxylate salt. However, it is possible that the mechanism proceeds through an intermediate of type **41**, though this intermediate cannot be generated from zwitterion **40**.

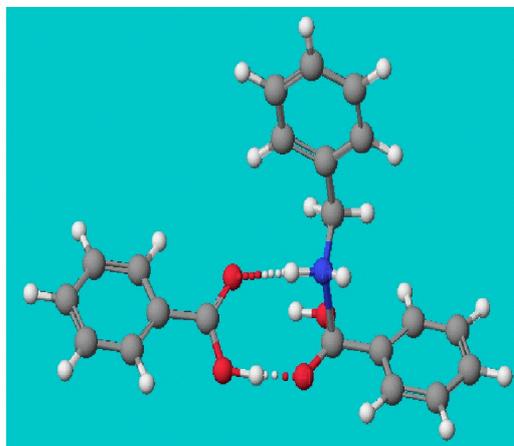
Mutual dimerisation of carboxylic acids through intermolecular hydrogen-bonding (to give **42**, Scheme 16) is well documented.<sup>53-58</sup> Not only are these dimerisations particularly efficient in non-polar solvents (such as toluene), but these carboxylic acid dimers are observable at elevated temperatures and even persist into the gas phase, where they compete with linear hydrogen-bonded dimers. Therefore, the viability of the mechanism for direct amide formation proceeding from the carboxylic acid dimer was examined. This species might be important as the potentially reactive form of the carboxylic acid and could be sufficiently activated to enable a nucleophilic attack by an amine. DFT calculations were carried out and showed that indeed, the mechanism for direct

amide formation could proceed *via* a carboxylic acid dimer **42** and this dimer could form readily in toluene. Subsequent attack on this species by the amine results in the formation of a transition state **43** as shown by Figure 7, in which the amine is able to attack one carboxylic acid of the carboxylic acid dimer **42**, and the second carboxylic acid acts as the proton acceptor. The result of a concerted proton transfer from amine to acid and release of the second carboxylic acid, is the neutral intermediate **41**, from which water is readily lost (see Scheme 16). Importantly, a mechanism that proceeds in this manner avoids the formation of the zwitterionic species **40**, which had been shown to collapse back to the starting materials from previous calculations (*vide supra*). An overall calculated energy profile using benzoic acid and benzylamine is shown in Figure 8.

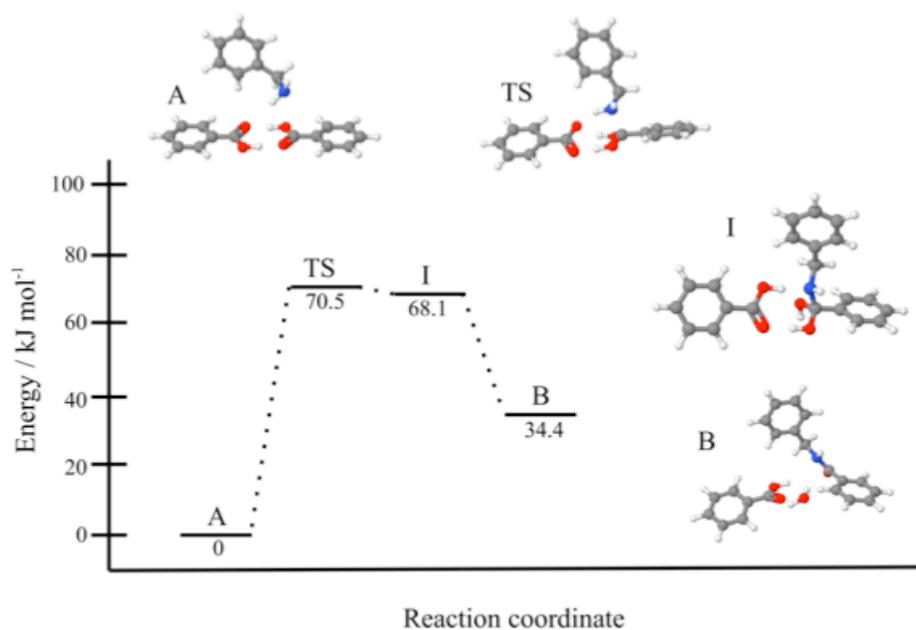
**Scheme 16:** New proposed mechanism for direct amide formation supported by DFT calculations.



**Figure 7:** Structure of proposed transition state supported by DFT calculations in simulated toluene. The transition state shown is formed from the attack of benzylamine on a carboxylic acid dimer.



**Figure 8:** Calculated energy profile for species contributing to direct amide formation *via* a hydrogen bonded acid dimer, for the reaction of benzoic acid with benzylamine.

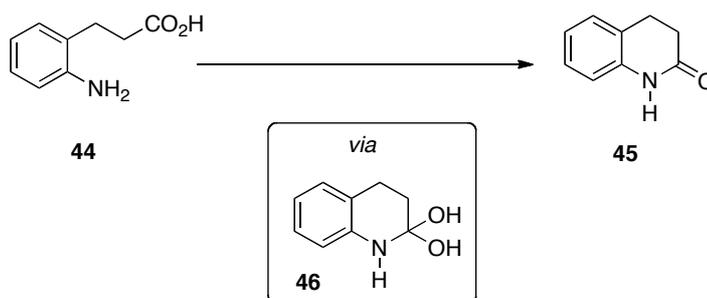


(Relative energies obtained from gas-phase DFT calculations [B3LYP/6-31g\*\*]. Calculated relative energies are shown as an approximate guide to the suggested reaction pathway; and are quoted as the sum of uncorrected electronic and zero point energies in the absence of solvent. A – amine **2** + carboxylic acid dimer **42**, TS – transition state **43**, I – dihydroxy intermediate **41** hydrogen bonded to acid **1**, B – amide **3** + acid **1** + water.)

For efficient direct amide formation to take place, the removal of water from the reaction is essential and this is usually achieved by azeotropic distillation at higher temperature,<sup>46</sup> or by the presence of activated molecular sieves under more ambient conditions.<sup>48</sup> If efficient water removal is not carried out then direct amide formation is much slower but does not stop.<sup>46</sup> If direct amide formation does indeed proceed *via* cyclic carboxylic acid dimers of type **42**, then the importance of removing the water generated during the reaction can be explained by observations that the addition of even small amounts of water which can result in hydration of the mutually H-bonded, cyclic carboxylic acid dimer. This results in the incorporation of the water molecules into the dimer structure and leads to water separated structures. Quantum chemical calculations<sup>58</sup> carried out on acetic acid, for example, show that with the addition of even one molecule of water to the carboxylic acid dimer causes the hydrogen bonds to break. Addition of a second water molecule will break the second hydrogen bond of the dimer and as more water molecules are added, more water separated complexes of the acetic acid dimer are formed.<sup>58</sup> Therefore, active water removal becomes fundamental in order to maintain a sufficient dimer **42** concentration to enable carboxylic acid activation and hence, amine nucleophilic addition.

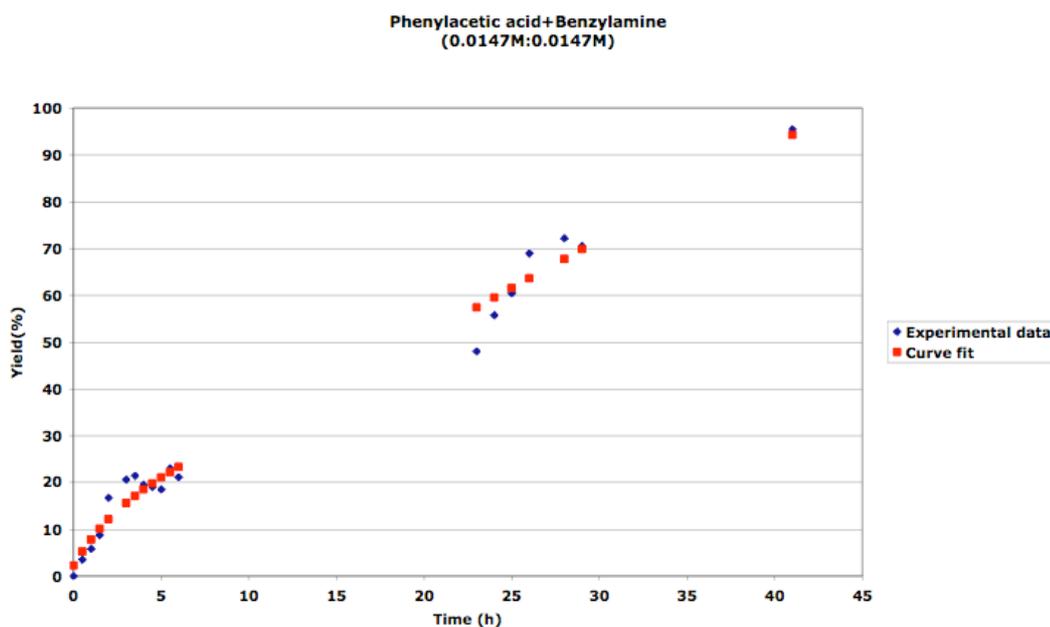
Additional support of the new mechanistic proposal outlined in Scheme 16, can be drawn from investigations carried out by Kirby *et al.* in 1979<sup>59, 60</sup> (see Equation 7). This work discusses the kinetics and mechanism of intramolecular direct amide formation and includes the importance of the formation of a similar neutral intermediate of type **41**.

### Equation 7

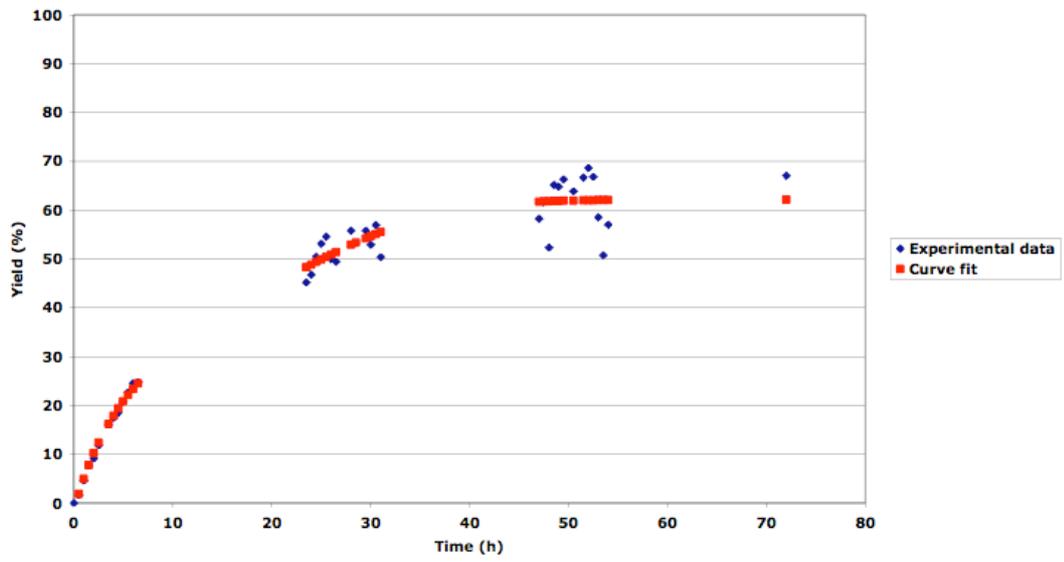


Micromath Scientist<sup>®</sup> software was employed to model the mechanism represented in Scheme 16, which allowed the observed data to be reproduced for the reaction between phenylacetic acid and benzylamine. Varying concentrations of carboxylic acid and amine were used and the results of the modeling did not contradict the potential viability of the mechanism as represented in Scheme 16. The comparison of the observed data and the data produced using a model for the proposed mechanism is shown in Figure 9. Due to the high number of parameters (rate constant,  $k$ ) involved in the proposed mechanism, it is possible for the software to alter the values for  $k$  (if the values are not fixed) until a curve is produced that will always fit the experimental data. To overcome this problem the first set of data was processed without fixing any parameters at all, the values for  $k$  that were found were then used and fixed in order to model all of the other experimental data. Although the values for the individual rate constants are, therefore, not meaningful, the fact that the same set of parameters can reproduce the experimental data for a range of experiments suggests that the mechanism shown in Scheme 16 is feasible.

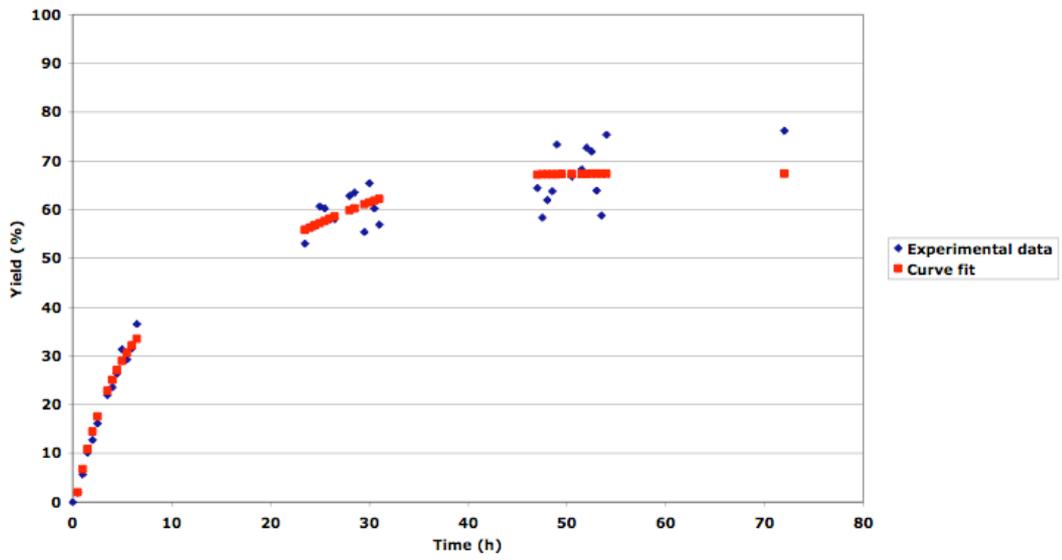
**Figure 9:** Results from following the reaction between phenylacetic acid and benzylamine over time with varying concentrations of carboxylic acid and amine.



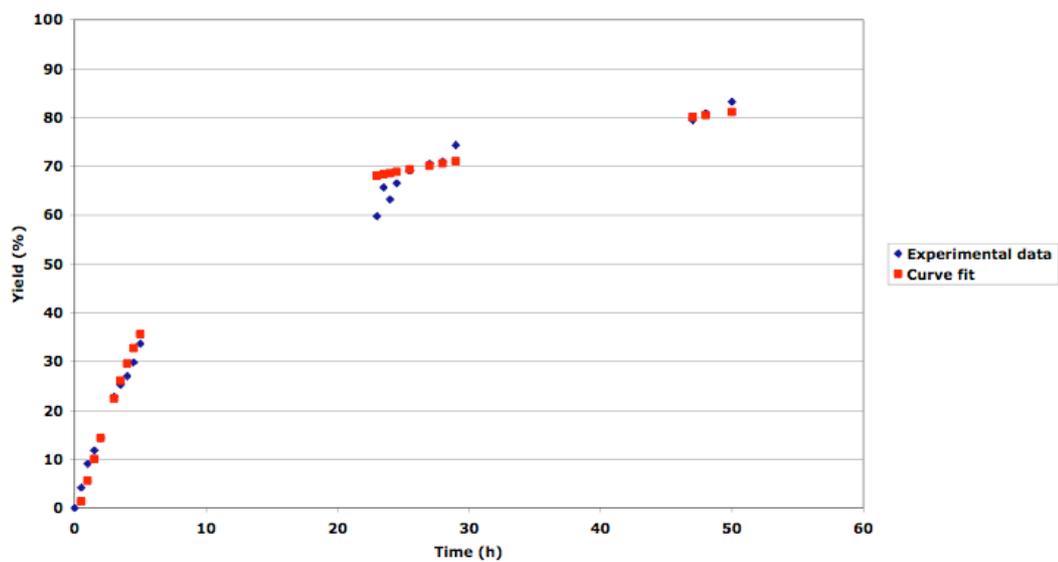
Phenylacetic Acid+Benzylamine  
(0.0735M:0.0735M)



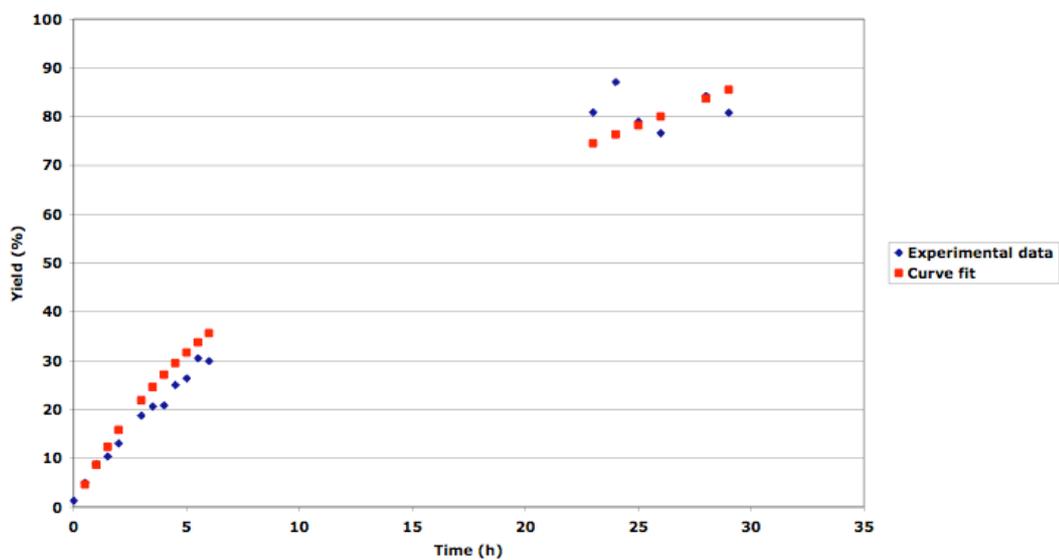
Phenylacetic acid+Benzylamine  
(0.147M:0.147M)

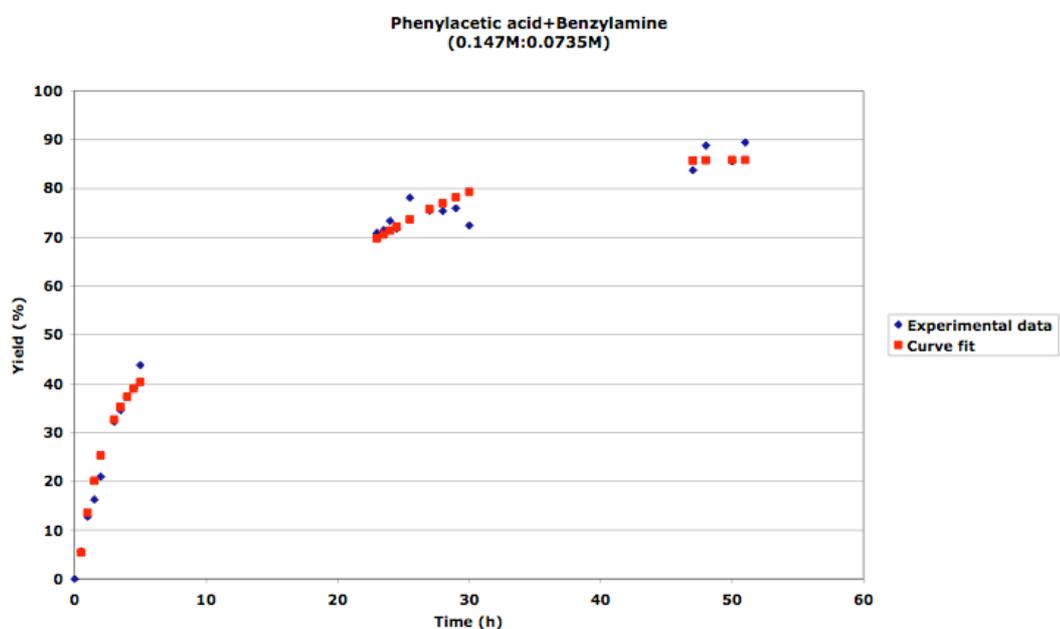
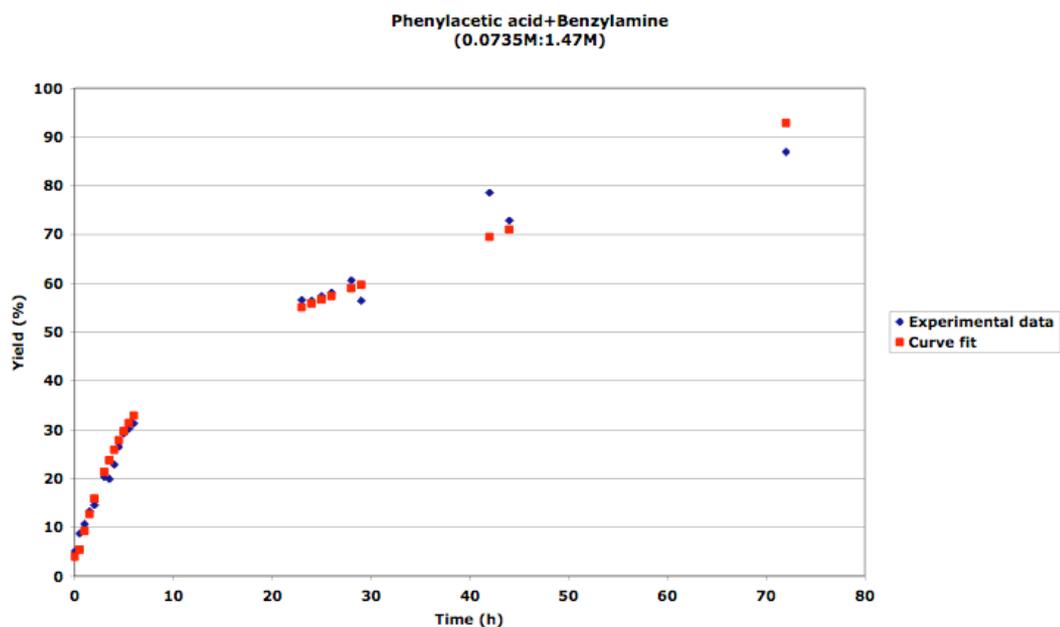


Phenylacetic acid+Benzylamine  
(0.0735M:0.147M)



Phenylacetic acid+Benzylamine  
(0.0735M:0.294M)



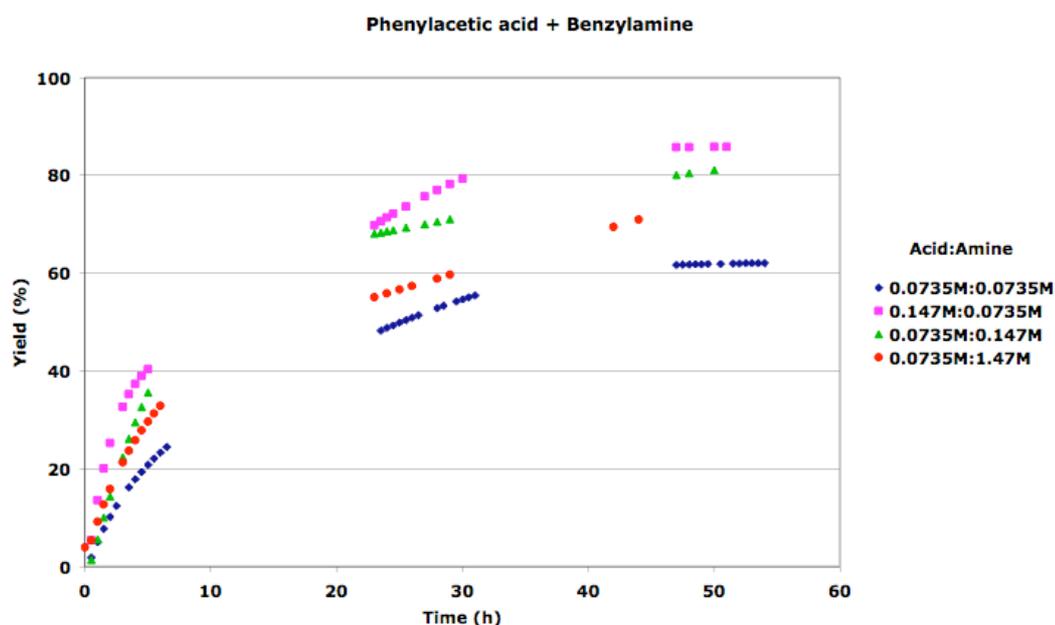


The reactions were all carried out in refluxing toluene with drying achieved by the use of molecular sieves held in a micro-Soxhlet apparatus. The increasing amount of scattering that can be seen in the experimental data as the reaction proceeds is because the amide product reaches its solubility limit in toluene and precipitates out of solution under the lower temperature sampling conditions,

therefore, reducing the accuracy of the sampling and resulting in a less reliable curve fit.

Taking the equimolar (0.0735 M for carboxylic acid and amine) reaction between phenylacetic acid and benzylamine as the standard equimolar reaction, the results shown in Figure 9 can be compared to observe the effects of varying the amount of carboxylic acid and amine. The results are shown in Figure 10, where for clarity the curve-fitted data has been used rather than the experimental data.

**Figure 10:** Results from following the reaction between phenylacetic acid and benzylamine over time with excess carboxylic acid or excess amine.



As also shown in Figure 6, one can observe that the rate and yield of amide formation is increased by the addition of either excess carboxylic acid or excess amine. Within error, this increase seems to be relatively independent of which species, either the carboxylic acid or amine, is in excess. Upon addition of a large excess of amine ( $\times 20$ ), the rate of the reaction is reduced in comparison with a smaller excess of amine or acid ( $\times 2$ ), however, the rate and yield is still improved over that of the equimolar reaction. As mentioned above, it has been previously reported that an excess of either carboxylic acid or amine can enhance

the direct amide formation reaction,<sup>19</sup> although it is still not clear exactly how this occurs.

### 3.7 Conclusions

The intervention of anhydrides has been previously postulated<sup>45</sup> as a possible mechanism by which direct amide formation might occur. However, there is no direct evidence that this process occurs in the presence of amines to result in amide formation.

The calorimetry work that has been carried out clearly shows that amines and carboxylic acids generally do react to some extent to give carboxylate ammonium salts. However, this reaction only seems to proceed to completion with combinations involving lower  $pK_a$  acids and basic amines, and completion of the reaction is likely to be driven by the formation of a salt precipitate.

<sup>1</sup>H NMR studies clearly show that a number of species can be formed in solution upon mixing carboxylic acids and amines, ranging from hydrogen bonded amine-acid species, through to hydrogen bonded ammonium-carboxylate species, and essentially non-interacting ammonium-carboxylate ions. These types of species most likely act to diminish (to varying extents) the potential for direct amide formation and in fact, the process of amide formation is likely to proceed through another equilibrium species, *i.e.* the carboxylic acid hydrogen-bonded cyclic dimer **42**.

There is little evidence for general acid or base catalysed direct amide formation under these conditions, though since hydrogen-bonding and proton transfer processes are key to this reaction, it not surprising that there is a minor effect from the addition of excess acid or amine (though it not clear at this point exactly how this occurs).

More importantly, it is clear that highly charged zwitterionic species are not involved in the direct amide formation reaction, and indeed, this seems to extrapolate to the boronic acid catalysed reaction variants.<sup>49</sup>

DFT calculations suggest that a plausible mechanism for intermolecular direct amide formation proceeds through the existence of carboxylic acid hydrogen-bonded dimers which are not only known to persist even at elevated

temperatures but are likely to be highly favourable in non-polar solvents. The role of such hydrogen-bonded dimers, as demonstrated in Scheme 16, is to enable both carboxylic acid activation towards nucleophilic attack by the amine, and to allow the reaction to proceed through to a neutral intermediate such as **41**, which according to the calculations is energetically accessible. This new mechanistic proposal has important similarities with kinetic and mechanistic studies carried out in the intramolecular amide formation reaction,<sup>59, 60</sup> in that the formation of a similar neutral intermediate is required for the direct amide formation reaction in aqueous conditions, from which water loss is rapid to give the amide. In our newly proposed mechanism, the reaction in organic solvents of course differs considerably, and especially with respect to the likelihood that carboxylate ammonium salt formation may well have the greatest effect upon the rate of direct amide formation.

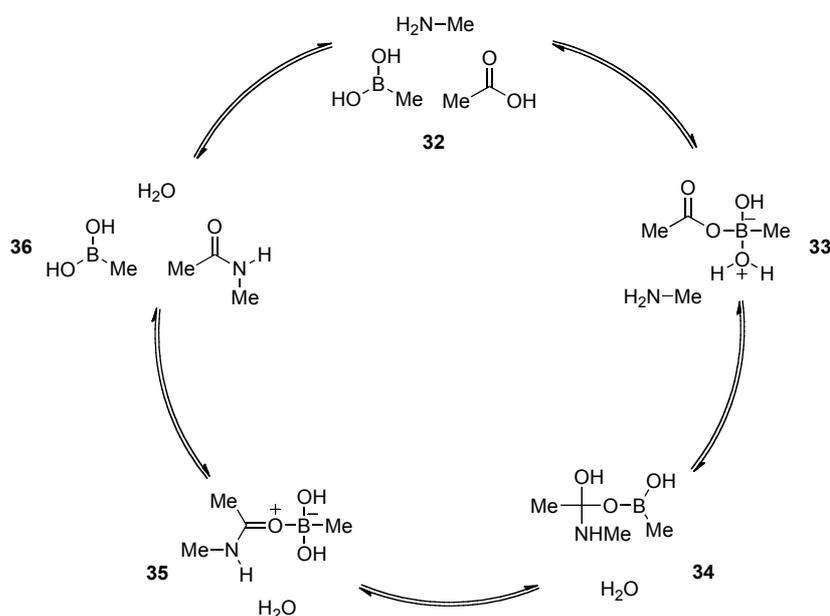
## 4.0 Towards the Synthesis of Potential Catalysts for Direct Amide Formation

### 4.1 Introduction

Although the uncatalysed, thermal direct amide formation reaction works well for a range of carboxylic acid and amine substrates there are still many cases in which catalysts are required to produce a desirable yield of amide over a shorter reaction time. Therefore, having thoroughly examined the mechanism and scope of the uncatalysed direct amide formation reaction, attention was turned to the catalysed reaction, with a particular focus on the use of boron-based catalysts for direct amide formation.

As discussed in Chapter one, work by Marcelli<sup>49</sup> investigated several mechanistic possibilities for the formation of amides from carboxylic acids and amines in the presence of boronic acid catalysts. This computational study suggests that the lowest energy pathway for catalysed amide formation involves the generation of a tetracoordinate monoacyl boronate **33** as shown in Scheme 12.

**Scheme 12:** Lowest energy calculated catalytic cycle



There are several boron-based compounds that are active direct amide formation catalysts and potentially they function in the way described in Scheme 12. Of these catalysts, some are commercially available (boric acid and phenylboronic acid **24** for example) whereas others need to be synthesised (*N,N*-diisopropylbenzylaminoboronic acid **25** and *o*-iodophenylboronic acid **31**).

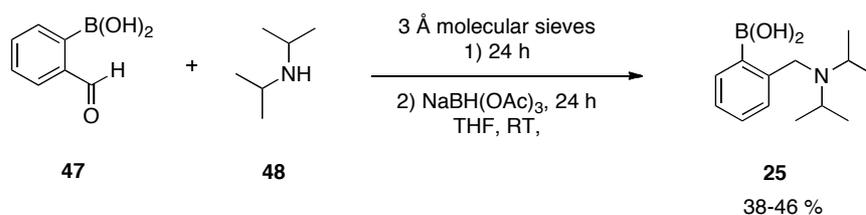
Taking into consideration the structural features of the current successful catalysts for direct amide formation and also using the computational study carried out by Marcelli as guidance, several novel potential catalysts for this reaction have been designed and attempts to synthesise them have been carried out.

## 4.2 Synthesis of Current Catalysts for Direct Amide Formation

### 4.2.1 *N,N*-Diisopropylbenzylaminoboronic acid **25**

A procedure (Equation 8), previously developed in the group for the synthesis of *N,N*-diisopropylbenzylaminoboronic acid<sup>61</sup> **25**, has been followed several times on both small and large scales resulting in yields from 38-46%. Initially, 4 equivalents of NaBH(OAc)<sub>3</sub> were used, which gave the desired product in a very poor yield of 9%. However, by increasing the number of equivalents of sodium triacetoxyborohydride to six, and by stirring the reaction for 24 h before adding 5% (w/v) HCl slowly followed by an aqueous work up and slow crystallisation, the product yield was increased typically to around 45%.

#### Equation 8

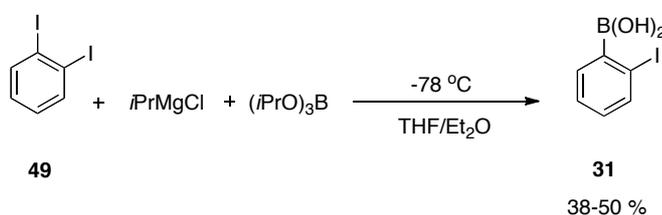


### 4.2.2 *o*-Iodophenylboronic acid **31**

As the most recent, and the most active catalyst for direct amide formation at ambient temperatures, it was important to synthesise *o*-iodophenylboronic acid **31** in order to compare the activity with the new potential catalysts.

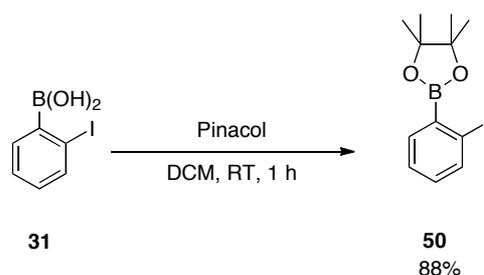
The literature procedure for the synthesis of *o*-iodophenylboronic acid **31** contained several inconsistencies and seemed to merge large and small-scale procedures.<sup>48</sup> However, the general procedure was followed, but with the number of moles recalculated (Equation 9). At -78 °C, *isopropylmagnesium chloride* (2 M in THF) was added dropwise to a solution of 1,2-diiodobenzene **49** in a mixture of THF and Et<sub>2</sub>O (1:1). After 2 hours stirring under argon, *triisopropylborate* was added and the reaction mixture warmed slowly to room temperature and left to stir overnight. The boronic acid **31** was produced with yields of 38-50% after work up and purification by SiO<sub>2</sub> column chromatography.

#### Equation 9



Catalyst **31**, in the form of the pinacol ester **50**, can be recovered from the direct amide formation reaction mixture at the end of the reaction by the addition of pinacol (1 equivalent w.r.t catalyst). This has been carried out for the reaction between phenylbutyric acid and benzylamine (at 50 °C), to provide the corresponding amide and the pinacol ester of the catalyst. Both of which remained in the organic layer during the reaction work up and therefore **50** could be recovered more easily than the boronic acid **31**. Silica gel column chromatography was used to separate the ester (75% w.r.t **31**) from the amide (70%). The pinacol ester **50** was also synthesised directly from compound **31** as shown in Equation 10.

### Equation 10

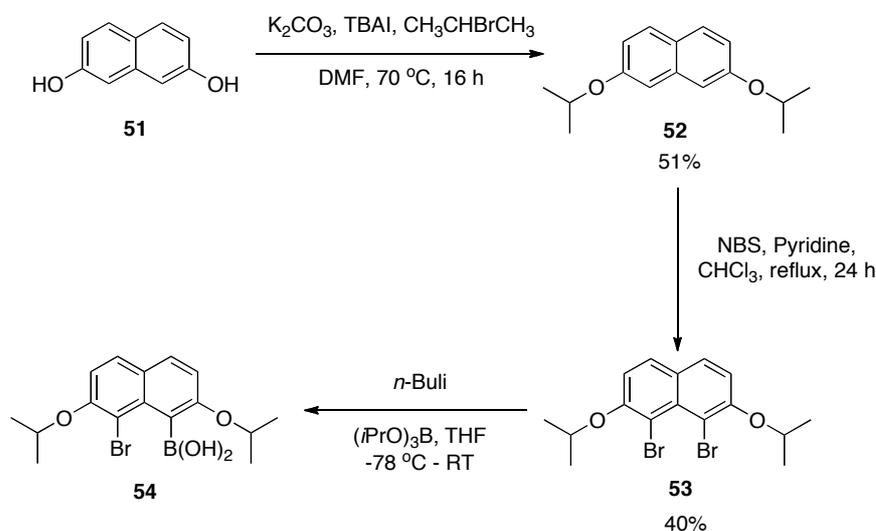


## 4.3 Synthesis of Novel Potential Catalysts for Direct Amide Formation

### 4.3.1 Naphthalene Based Boronic Acids

Compound **53** has been previously synthesised in the group<sup>62</sup> and given that *o*-bromophenylboronic acid is just as effective (in some cases better) than *o*-iodophenylboronic acid **31** as a catalyst for direct amide formation,<sup>48</sup> it was thought that boronic acid **54** could also be an active catalyst and hence, would be a good target catalyst which could be prepared from the known compound **53**. The aim of synthesising halogenated naphthalene boronic acids of this type was to begin to investigate the importance of the distance between the halogen atom and boronic acid functionality.

**Scheme 17:** Synthesis of (8-bromo-2,7-diisopropoxynaphthalen-1-yl)boronic acid **54**



Following the literature procedure,<sup>62</sup> 2,7-diisopropoxynaphthalene **52** was prepared from 2,7-dihydroxynaphthalene **51** with a yield of 51% after purification. This product was then brominated using *N*-bromosuccinimide to form 1,8-dibromo-2,7-diisopropoxynaphthalene **53** (40%) as shown in Scheme 17.

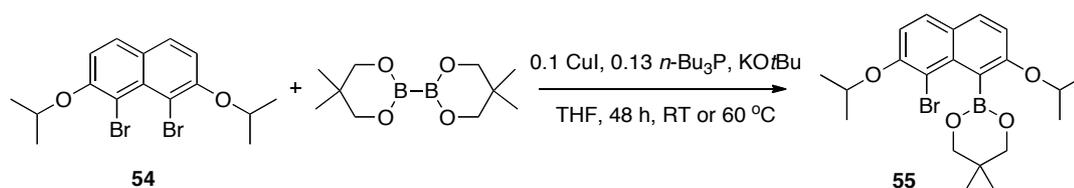
The final stage in the synthesis involved exchanging one of the bromine atoms for the boronic acid functionality. Initially the reaction shown in Scheme 17 was attempted to convert the dibromo compound **53** into the boronic acid **54**. *n*-BuLi was added dropwise to the starting material at  $-78\text{ }^\circ\text{C}$  and the mixture was stirred for 1 h before the addition of triisopropylborate and warming slowly to room temperature. The reaction was left overnight but unfortunately only starting material was recovered. Replacing the *n*-BuLi with *i*PrMgCl was also attempted, as this reaction had worked well with diiodobenzene (Equation 9). However, none of the desired boronic acid product was formed.

A further attempt at the lithium/halogen exchange using *n*-BuLi was carried out but this time the reaction was quenched with trimethylborate, rather than the sterically larger triisopropylborate, which was shown in Scheme 17. *n*-BuLi was added to the dibromo- substrate dropwise at  $-78\text{ }^\circ\text{C}$  and the reaction mixture left to stir at that temperature for 2 h, after which time trimethylborate was added and the reaction mixture allowed to slowly warm to room

temperature. The reaction mixture was worked up and purified after 48 h. TLC analysis showed that the reaction had gone to completion, however, characterisation data showed that the product obtained was the mono-brominated compound (98% yield). This proved that the lithium/halogen exchange reaction worked but suggested that trimethylborate was still too sterically hindered as an electrophile for this system.

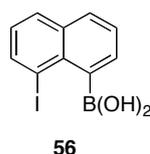
In a slightly different approach, copper-catalysed direct borylation<sup>63</sup> was also attempted (Equation 11). These types of copper-catalysed borylation reactions have been shown to work well for relatively hindered halide substrates and they are also successful with aryl bromide substrates as well as aryl iodides. Despite there being no examples of this reaction working well for substrates as hindered as **54**, the following reaction was attempted (Equation 11).

#### Equation 11



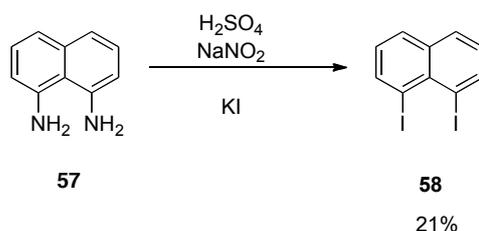
The reaction was carried out both at room temperature and then at 60 °C, however, in both cases no product was formed and only starting material was present by TLC analysis.

The large *isopropoxy* substituents were thought to be the cause of the problem. Hence, attempts at the synthesis of the less sterically demanding boronic acid **56** were carried out.



The first step was to synthesise 1,8-diiodonaphthalene **58**, following a literature procedure<sup>64</sup> starting from 1,8-diaminonaphthalene **57** (Equation 12)

### Equation 12



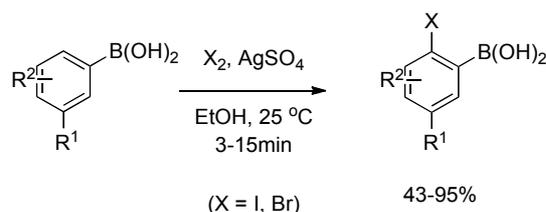
Unfortunately, the yields achieved for this reaction, although consistent, were poor. Nevertheless, enough material was acquired to try out the subsequent step. Several attempts to synthesise boronic acid **56** from 1,8-diiodonaphthalene **58** were carried out. Regrettably, however, the desired compound was not produced. Lithium/halogen exchange reactions followed by quenching with a boron electrophile were attempted, as well as some palladium-catalysed borylation conditions that had been used previously within the group, all of which proved to be unsuccessful, resulting in either the mono-iodinated compound (*i.e.* protodehalogenation) or no reaction. The conditions tested and the results obtained are summarised in Table 7.

**Table 7:** Attempts to synthesise boronic acid **56** from 1,8-diiodonaphthalene **58**

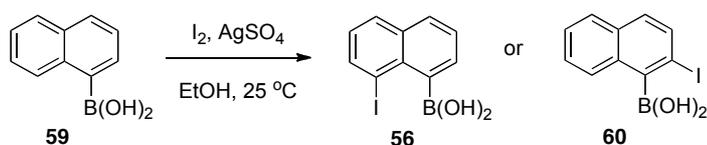
Entry	Conditions	Result
1	1) Isopropylmagnesium chloride -78 °C, 1 h 2) Triisopropylborate -78 °C to room temp, overnight	Mixture of diiodonaphthalene and iodonaphthalene (2:1 from NMR)
2	1) <i>n</i> -BuLi -78 °C, 1 h 2) Triisopropylborate -78 °C to room temp, overnight	Mixture of diiodonaphthalene and Iodonaphthalene. (1:1.5 from NMR)
3	Same as entry 2 but with titrated <i>n</i> -BuLi	Iodonaphthalene with trace diiodonaphthalene
4	1) Trimethylborate, <i>n</i> -BuLi -78 °C, 1 h 2) Warm to room temp, overnight	Mixture of diiodonaphthalene and iodonaphthalene. (2:1 from NMR)
5	3% Pd <sub>2</sub> (dba) <sub>3</sub> , PCy <sub>3</sub> , B <sub>2</sub> Pin <sub>2</sub> , Potassium acetate, dioxane, 80 °C, 24h	Mixture. Diiodonaphthalene as major component
6	10% Pd <sub>2</sub> (dba) <sub>3</sub> , PCy <sub>3</sub> , B <sub>2</sub> Pin <sub>2</sub> , Potassium acetate, dioxane, 80 °C, 24 h	Mixture. No desired product

A further attempt to synthesise **56** was made starting from 1-naphthaleneboronic acid **59** using an iodination procedure published in the literature recently.<sup>65</sup> This work describes a regioselective silver(I)-mediated electrophilic iodination and bromination reaction of arylboronic acids (Equation 13). Although this procedure has not been applied to naphthalene compounds, it was thought that perhaps by using 1-naphthaleneboronic acid as the starting material the desired iodo-naphthaleneboronic acid **56** could be formed. It was expected that as well as the desired 1,8-substitution pattern the 1,2-iodoboronic acid **60** might also be produced, and in fact, this reaction could be more favorable and both products could be screened as potential catalysts and might be of considerable catalytic interest.

#### Equation 13



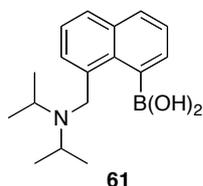
#### Equation 14



According to the literature procedure<sup>65</sup>, the reaction was complete when the iodine colour had completely disappeared (3-15 min). However, in this case, the iodine colour did not disappear after 4 hours and so the reaction was left stirring overnight. The following day, the reaction was worked up, however, only starting material was present by <sup>1</sup>H NMR.

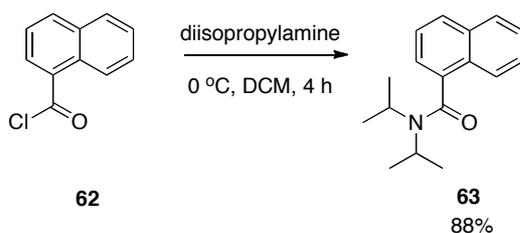
In the interests of time the decision was made not to pursue this route any further and move on to synthesise naphthaleneboronic acid **61** instead, which

possessed the diisopropylamino functionality as in compound **25**, which is already known to be a successful catalyst for direct amide formation. At the beginning of this synthesis, it was unknown whether the synthetic route planned would provide the 1,8-substitution pattern **61** or the 1,2-substitution pattern **65**.



Starting from naphthoyl chloride **62**, *N,N*-diisopropyl-1-naphthamide **63** was synthesised with a yield of 88% (Equation 15).

#### Equation 15



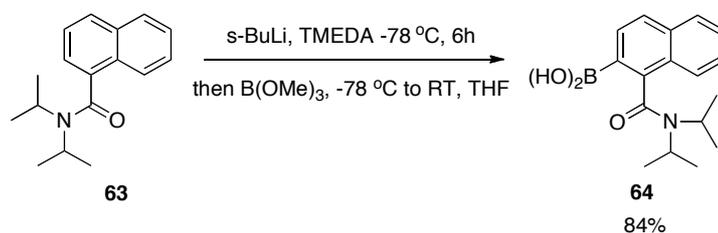
Several attempts to introduce the boronic acid group to either the 2 or 8 position were carried out. The addition of *s*-BuLi/TMEDA to **63** and stirring for 1 h at -78 °C followed by quenching with trimethylborate resulted in a mixture of starting material and a product which was substituted at the 2 position **64**. In order to achieve separation of the product and the starting material by chromatography, the pinacol ester of the boronic acid was synthesised. However, despite testing several solvent systems, the two compounds always co-eluted and so separation of the product from the starting material was not possible.

Repetition of the *s*-BuLi/TMEDA/B(OMe)<sub>3</sub> reaction but with the metallation step allowed to stir at -78 °C for a longer time of 4 h also resulted in a mixture of starting material and product, as shown by <sup>1</sup>H NMR. Diethanolamine (2 M in IPA) was added to the crude mixture and was stirred at room temperature overnight. The diethanolamine boronate ester produced could

easily be separated from the starting amide **63** by silica gel column chromatography (hexane:ethyl acetate, 2:1) and in fact, the silica was sufficiently acidic to result in diethanolamine ester cleavage to provide the free boronic acid (40%).

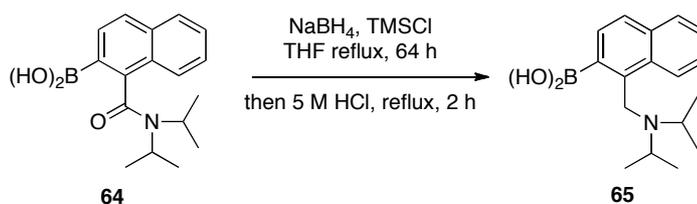
Following this, it was found that by simply leaving the metallation step for 6 h before the addition of trimethylborate, the starting material was completely consumed and the boronic acid **64** was produced as a white solid with a yield of 84% (Equation 16).

### Equation 16

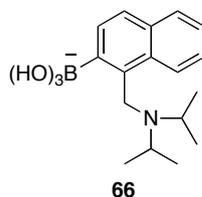


A literature procedure<sup>66</sup> to reduce the amide to the amine was followed in which **64** was added to a mixture of sodium borohydride and chlorotrimethylsilane in THF and heated to reflux for 64 h (Equation 17). The reaction did not go to completion (23% yield was obtained) and the  $^{11}\text{B}$  NMR shift for the product of this reaction was unexpected, *i.e.*  $\delta -5$  ppm, which is indicative of a boron ‘ate’-complex. Refluxing the product in 5 M HCl for 2 h resulted in formation of a white solid in a yield of 89%. The  $^{11}\text{B}$  NMR shift of this compound was  $\delta 29$  ppm, which is much more consistent with the expected boronic acid product.

### Equation 17



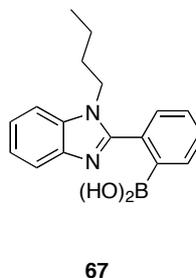
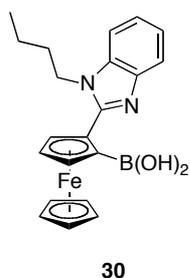
It is likely that the initial product of this reaction was the complex **66**. This complex could be the result of the borohydride reacting with water to give hydroxide, which in turn could go on to form the amino boronate ate-complex **66** which would explain the  $^{11}\text{B}$  NMR shift at  $\delta$  -5 ppm.



Unfortunately, the final stage of this synthesis, the reduction step, could not be repeated to produce a reasonable amount of **65** for full characterisation and catalyst screening.

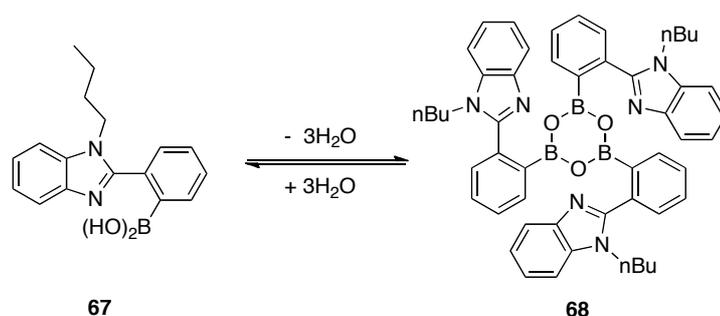
#### 4.3.2 Benzimidazole Based Boronic Acids

As mentioned in chapter one, the chiral ferrocene based bifunctional amino-boronic acid catalyst **30** can induce the kinetic resolution of racemic  $\alpha$ -substituted benzylamines through direct amide condensation with achiral carboxylic acids<sup>47</sup> (Equation 5). The phenyl based version of this catalyst **67**, which features both the benzimidazole and boronic acid functionality, has been previously synthesised within the group<sup>67</sup> though the boronic acid could never be isolated. Rather, it existed entirely as the boroxine and the activity as a catalyst for direct amide formation has been tested.



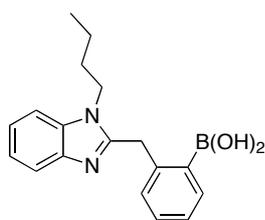
However, compound **67** (or rather its boroxine derivative **68**) did not show any activity whatsoever as a catalyst for direct amide formation and this is thought to be due to the particularly stable boroxine that this system forms (Equation 18).

### Equation 18



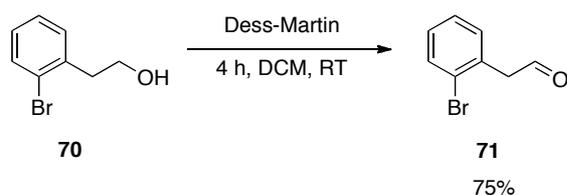
As part of a collaboration with Tommaso Marcelli, who carried out the computational study into catalysed direct amide formation (*vide supra*),<sup>49</sup> several compound structures that could act as potential catalysts have had their suitability computationally assessed. The calculations carried out were based on the mechanistic framework previously published<sup>49</sup> and they predicted that compound **67** (as the free boronic acid) should be a rather good catalyst and in fact, comparable to *o*-iodophenylboronic acid **31**. Although experimentally this was not the case, due to boroxine formation (the ease of which cannot be predicted using these calculations), the calculations provided an excellent starting point to begin to understand the kind of structures that should be synthesised as a priority.

By introducing a methylene spacer between the phenyl group and the benzimidazole in compound **67**, it was hoped that the catalytic activity for direct amide formation would be ‘switched on’. The aim of this was to disrupt any B-N chelation and, hopefully, avoid the formation of the stable boroxine. The first step in the synthesis of **69** was to make aldehyde **71** from 2-bromophenethyl alcohol **70** (Equation 19).



69

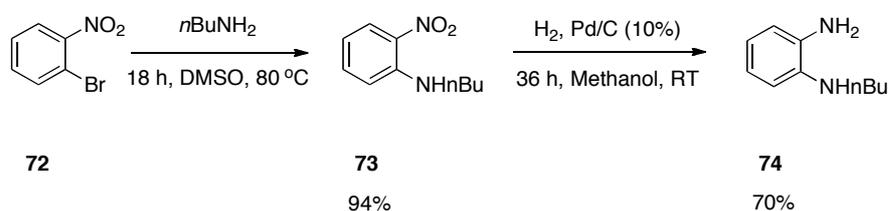
### Equation 19



Initially, the oxidation of **70** was attempted using pyridinium chlorochromate (PCC) which resulted in a mixture of compounds; oxidation using Dess-Martin periodinane proved to be a much cleaner reaction and produced the aldehyde **71** in a yield of 75% after separation from the starting material by silica gel column chromatography.

Literature procedures<sup>67</sup> were then followed to synthesise the diamine **74** from 2-bromonitrobenzene **72** (Scheme 18).

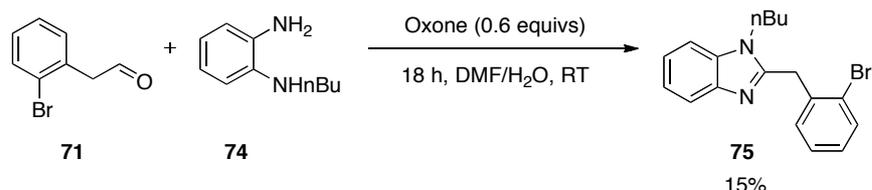
### Scheme 18: Synthesis of diamine **74**



The nucleophilic aromatic substitution reaction to afford amine **73** proceeded smoothly and the product was used in the next step without further purification. The hydrogenation reaction to reduce the nitro group to the aniline, although fairly slow, resulted in consistently good yields of the diamine **74**.

With aldehyde **71** and diamine **74** in hand the next stage of the synthesis of benzimidazole **69** was carried out under oxidising conditions in the presence of 0.6 equivalents of Oxone™ (Equation 20). The same procedure had been carried out towards the synthesis of **67** and resulted in a yield of 69%.<sup>67</sup>

### Equation 20



Initially, it seemed that the products of the reaction could not be separated by silica gel column chromatography because although there was only one new spot by TLC, when sampling from the reaction mixture, the <sup>1</sup>H NMR spectra after chromatography showed that an unidentified impurity was present, and therefore, it must have been co-eluting with the desired compound. Using hexane:ethyl acetate (1:1), some of the desired product could be isolated cleanly, however, there was still some contamination of the desired compound in the further fractions that were collected. Only 130 mg (15%) of compound **75** was isolated in a sufficiently clean form.

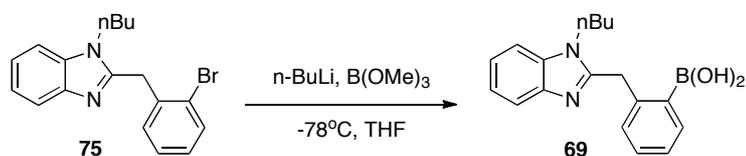
Several further attempts at the synthesis of **75** in the presence of Oxone™ were carried out but, unfortunately, these only provided the desired compound in consistently low yields (10-15%). In an attempt to purify the remaining contaminated fractions left after SiO<sub>2</sub> chromatography, the material from several attempts at this reaction were combined and dissolved in hot hexane. This solution was then washed with HCl (5%) and the pH of the aqueous layer increased to pH 8 before extracting with DCM. Following drying (MgSO<sub>4</sub>), filtration and evaporation a further 60 mg of **75** was isolated cleanly.

The mechanism by which Oxone™ operates in this reaction is as yet unclear, however, it is possible that the reaction begins with initial imine formation between the aldehyde and the amine, which then undergoes oxidation to a nitrilium species which cyclises. Whatever the mechanism, because imine formation is likely as the first step in the reaction, imine formation was

performed before the addition of Oxone™ in order to try and improve the reaction. However, this did not improve on the previous yields achieved (8% of compound **75** was isolated).

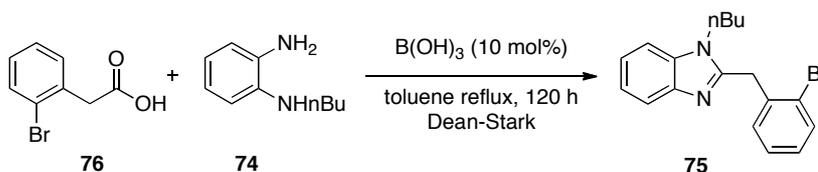
The small amount of benzimidazole **75** that had been acquired was used in the final step towards the synthesis of boronic acid **69** (Equation 21). This involved the halogen/lithium exchange reaction on compound **75**, followed by quenching with trimethylborate. The literature procedure<sup>67</sup> for the synthesis of the similar compound **67** was followed except that the boron electrophile was added to the reaction mixture before the *n*-BuLi was added in order to trap out the aryl lithium generated as the boron ‘ate’-complex. After stirring the reaction mixture for 4 h at -78 °C, it was allowed to warm to room temperature and left overnight. The following day, the solution was quenched with NaOH (10% w/v) and stirred for 30 minutes before the pH of the solution was adjusted to pH 7 with HCl (10% w/v). According to the literature procedure, the product should precipitate from the solution, however, in this case no precipitate was observed and hence, the solution was extracted with DCM, separated, dried and the solvent evaporated. This reaction did provide some of the desired compound as evidenced by <sup>11</sup>B NMR which showed a peak at δ 33 ppm, however, most of the material was found to be unreacted starting material according to TLC and <sup>1</sup>H NMR. In order to separate the small amount of **69** from the bromide starting material **75** the synthesis of the pinacol ester was attempted. Unfortunately however, this was unsuccessful and the small amount of desired material was lost during work up or purification by column chromatography. The bromide starting material **75** was recovered with a yield of 75%. Unfortunately, further attempts to repeat and improve this reaction, in order to produce a reasonable amount of **69**, were seriously hampered due to the lack of availability of the starting benzimidazole **75** from the previous benzimidazole formation reactions.

### Equation 21





### Equation 23

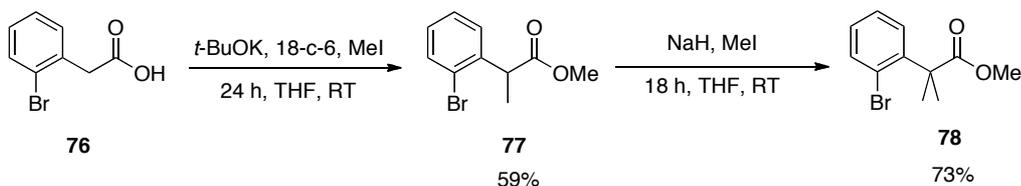


The reaction between carboxylic acid **76** and diamine **74** in the presence of Oxone™ was also attempted in case the mechanism of the reaction shown above (Equation 20) involved initial aldehyde to carboxylic acid oxidation under these conditions. Perhaps unsurprisingly, this did not result in the formation of compound **75** as determined from the crude  $^1\text{H}$  NMR from the reaction which showed that only starting material was present.

One of the major differences between the Oxone™ reaction shown in Equation 20 and the synthesis of the known compound **67** was clearly the use of an enolisable aldehyde **71** as one of the starting materials. It was thought that it was very likely that the aldehyde **71** could be responsible for such low yields from this reaction due to being susceptible to enolisation. This reaction using a non-enolisable aldehyde<sup>67</sup> in comparison, worked well. Hence, the synthesis of a non-enolisable equivalent of aldehyde **71** was examined in order to replace aldehyde **71** in the Oxone™ reaction.

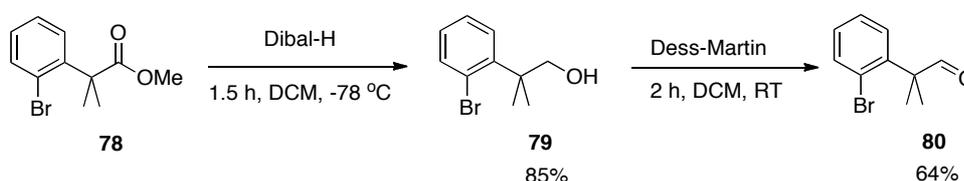
Therefore, the synthesis of aldehyde **80** began with *gem*-dimethylation of carboxylic acid **76**. A one-pot method described in the literature<sup>68</sup> was followed initially, however, the major product of this reaction was found to be the mono-methylated compound **77** (59%) rather than the *gem*-dimethylated product **78**. This was solved by carrying out the synthesis of **78** in two stages, as outlined in Scheme 19, resulting in a suitable scalable route.

### Scheme 19: Two-step synthesis of *gem*-dimethylated product **78**



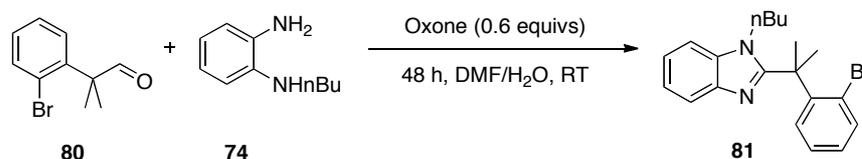
Having isolated ester **78**, the reduction of the ester function directly to the aldehyde **80** was attempted using both Red-Al and Dibal-H. No reaction occurred with Red-Al in this case, however, with Dibal-H at  $-78\text{ }^{\circ}\text{C}$  over 2 h, the reaction gave a 2:1 mixture of the alcohol **79** and the starting ester **78**. Therefore, the decision was made to simply reduce the ester **78** to the corresponding alcohol **79** and then oxidize this back to the aldehyde **80**, which was readily achieved as shown in Scheme 20.

**Scheme 20:** Synthesis of aldehyde **80**



Both of these steps (Scheme 20) worked well and the *gem*-dimethylated, non-enolisable aldehyde **80** was then used in the Oxone™ reaction along with the diamine **74**. This reaction was attempted several times (Equation 24) but unfortunately TLC analysis and  $^1\text{H}$  NMR showed a mixture of starting materials and the desired compound **81** was not produced.

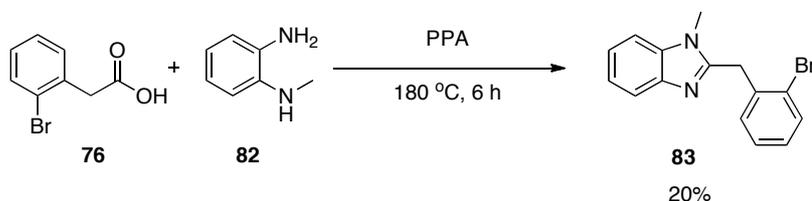
**Equation 24**



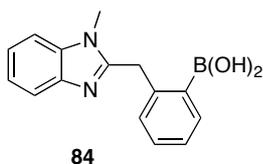
Returning back to the original benzimidazole **75**, without the *gem*-dimethyl group, it was necessary to synthesise more of compound **75** to test further borylation reactions with a view to reaching the final compound **69**. Since both of the starting materials required to make benzimidazole **75** had to be synthesised first, it was decided that a slightly different compound should be made where all of the starting materials were commercially available, *i.e.* as shown in Equation 25. Hence, compound **83** could be synthesised more quickly

than the *N*-butyl analogue **75** and used to test out the effect of the smaller *N*-methyl substituent upon the cyclisation reactions.

### Equation 25

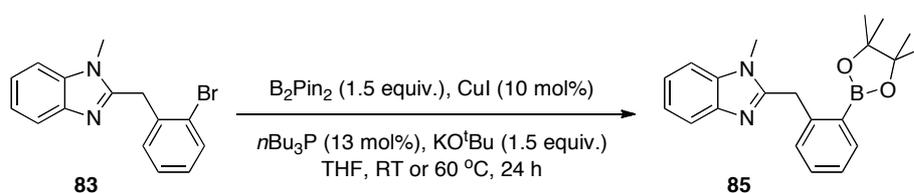


Compound **83** was obtained using the PPA conditions in a yield of 20%, and although the yield of this reaction was poor, it provided enough material for several further attempts at the synthesis of the boronic acid **84**



Various attempts were made to introduce the boronic acid functionality to compound **83** consisting of: 1) lithium/halogen exchange followed by quenching with triisopropylborate which resulted in a mixture of starting material and protodebromination; 2) recently published CuI borylation reactions<sup>63</sup> described below which also failed to produce the desired product **85**.

### Equation 26

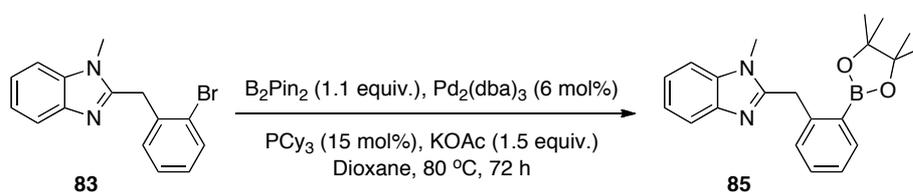


In the first of the copper-catalysed reactions, the reaction was carried out at both room temperature and at 60 °C, which according to the literature significantly

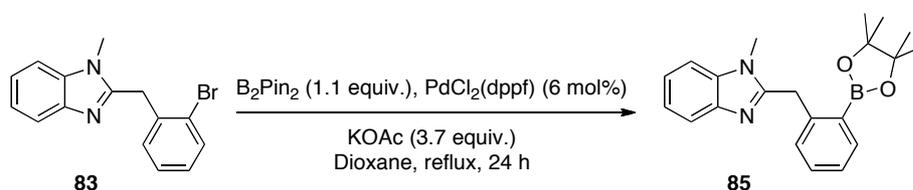
increases the yield for more difficult substrates. However, in this case none of the desired product was formed and only starting material was observed by TLC and  $^1\text{H}$  NMR of the crude reaction mixture.

The synthesis of compound **85** was also attempted using two sets of palladium-catalysed borylation conditions (Equations 27 and 28) but again, none of the desired product was produced. These reactions were followed by TLC and also by samples taken from each reaction mixture. These samples were worked up and the  $^1\text{H}$  NMR spectra collected. This showed that only the unreacted starting material was present.

#### Equation 27

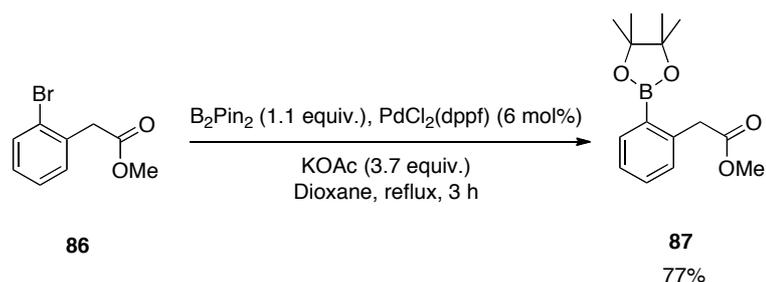


#### Equation 28



Because of the lack of reaction in these types of borylation reaction and in order to validate the experimental technique being carried out and the chemical method being used, a further test-case reaction was carried out alongside the reaction shown in Equation 28, as shown in Equation 29. This involved a reactive substrate **86** that is known in the literature<sup>69</sup> to react under the same conditions as for Equation 28.

### Equation 29

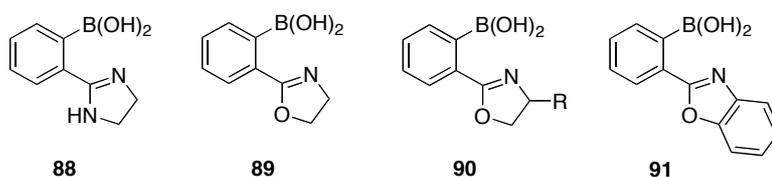


When this known reaction<sup>69</sup> was repeated under the same set of conditions as Equation 28, the yield of the reaction was a pleasing 77% of the desired product after 3 h. When using the benzimidazole substrate **83**, the reaction did not proceed and only starting material was observed by TLC. A possible explanation as to why compound **83** appears to be such a poor substrate for these reactions could be the benzimidazole functionality binding to the catalyst, although no work has been carried out to investigate this possibility and this is clearly an area which is worthy of further study.

As there had been little success towards the synthesis of the new boron containing potential catalyst structures, the synthesis of the benzimidazole based boronic acids **69** and **84** was postponed and attention was turned to other novel target structures and their screening in direct amide formation reactions.

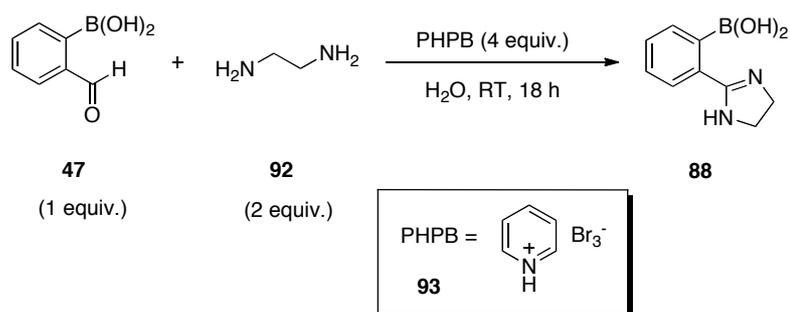
#### 4.3.4 Imidazoline and Oxazoline Based Boronic Acids

Computational calculations carried out by Tomasso Marcelli (*vide supra*) suggested that, as well as the benzimidazole compounds discussed above, oxazoline and imidazoline compounds bearing a boronic acid functionality could potentially be useful direct amidation catalysts. Hence, the synthesis of the target compounds **88-91** was planned.



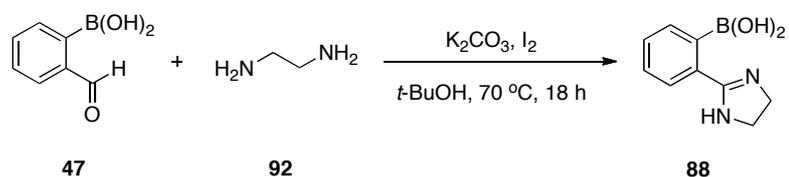
Using conditions found in the literature,<sup>70</sup> which describe the synthesis of several oxazolines and imidazolines from aromatic aldehydes using pyridinium hydrobromide perbromide (PHPB) **93** in water, the synthesis of imidazoline **88** was attempted with the boronic acid functionality already in place (Equation 30).

### Equation 30



Aldehyde **47** was reacted as outlined in Equation 30 for 18 h at room temperature; however, this resulted in a complex mixture of products from which a single compound could not be isolated. A second set of reaction conditions, which described direct oxidative conversion of aldehydes and alcohols to 2-imidazolines and 2-oxazolines using diiodine<sup>71</sup> were also tested, as outlined in Equation 31, however, these conditions also resulted in a complex mixture of products from which no single compound was isolated.

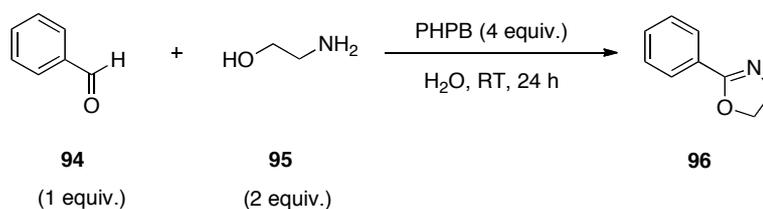
### Equation 31



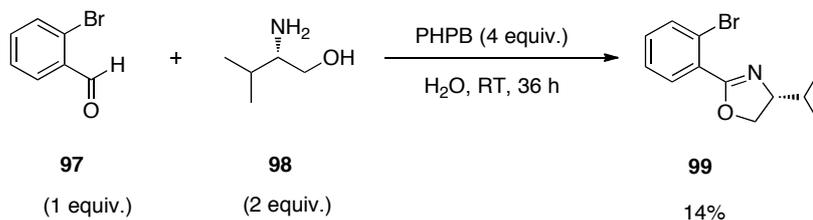
Imidazoline phenylboronic acid compounds proved to be particularly difficult to synthesise, isolate and purify, resulting in decomposition of starting material and complex mixtures of products. Hence, attention was turned to the synthesis of oxazoline and oxazole compounds.

It was thought that introducing the boronic acid at a later stage might simplify the synthesis of the imidazolines and oxazolines. In the literature, these reactions work well using more simple aldehyde starting materials.<sup>70</sup> The PHPB reaction conditions previously described were, therefore, also tested for the synthesis of oxazolines **92** and **95** which then could be used as precursors to boronic acids with the general structure **86** (See Equations 32 and 33).

### Equation 32



### Equation 33



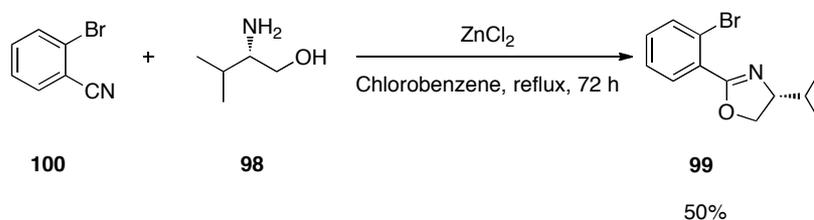
For the reaction to synthesise oxazoline **96** (Equation 32) from the condensation of aldehyde **94** with amino alcohol **95** gave a crude <sup>1</sup>H NMR which showed only trace amounts of product. Hence, rather than purification, this particular oxazoline was found to be commercially available and was purchased instead.

The attraction of oxazoline **99** is that it contains a bromine which can potentially be converted to the boronic acid *via* lithium/halogen exchange followed by quenching with a boron electrophile. Hence, it was accessed *via* Equation 33, and in this case, more success was achieved with its synthesis, which resulted in a yield of 14% from the reaction of aldehyde **97** with amino alcohol **98**.

In an effort to increase the yield of this reaction the temperature was increased to reflux temperature. Unfortunately, this had a detrimental affect on the yield and none of the desired product was formed.

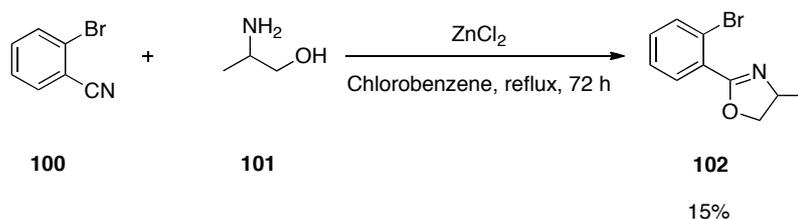
Further literature searching found that **99** could also be synthesised from 2-bromobenzonitrile **100** and valinol **98** in the presence of zinc(II) chloride<sup>72</sup> (Equation 34). The reaction was carried out in refluxing chlorobenzene and after 3 days provided the desired product after purification by silica column chromatography in 50% yield, which was only slightly lower than that quoted in the literature.

#### Equation 34



Using the same reaction conditions with (*DL*)-2-amino-1-propanol **101**, resulted in the formation of oxazoline **102**, albeit in a much lower yield of 15% (Equation 35).

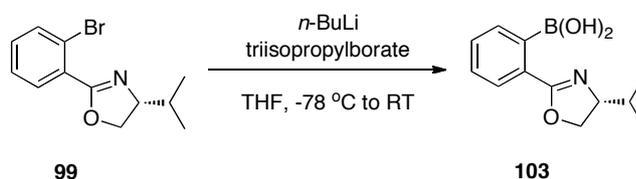
#### Equation 35



With the oxazoline compounds **99** and **102** prepared and purified, the next step was to introduce the boronic acid to synthesise compounds of type **90**. In order to introduce the boronic acid to compound **99**, the reaction shown in Equation 36 was carried out. Initially the reaction was carried out on a small scale and left for 3 hours at -78 °C with triisopropylborate already present in the reaction mixture before being left to warm to room temperature. The following day the solution was quenched with NaOH (aq. 10%) and allowed to stir for 15 minutes before

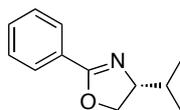
adjusting the pH to 7-8 with HCl (aq. 10%) and extracting with DCM. Evaporation of the solvent after drying resulted in a colourless oil.  $^1\text{H}$  NMR revealed this to be largely starting material, however, there was also some of a minor component present. The  $^{11}\text{B}$  NMR showed a single peak at  $\delta$  33 ppm indicating that some of the desired product had probably been formed, although in a very low yield. This result was sufficiently encouraging, due to the  $^{11}\text{B}$  NMR suggesting that the boronic acid **103** could be present and was not in the form of a boroxine, which had prevented catalysis previously (see the discussion regarding compound **67** previously).

### Equation 36



This reaction was repeated on a slightly larger scale with increased equivalents of *n*-BuLi (1.2 equiv.) and the metallation step left to stir at  $-78\text{ }^\circ\text{C}$  for 4 hours before the addition of triisopropylborate. The reaction was worked up in the same way as previously described. Evaporation of the solvent resulted in a pale yellow glassy solid. On trying to dissolve this glassy solid in  $\text{CDCl}_3$  to prepare an NMR sample, a white precipitate was produced.  $\text{CHCl}_3$  was then added to the remaining glassy solid in order to produce more of the white solid precipitate (80 mg), some of which dissolved in MeOD to obtain  $^1\text{H}$  and  $^{11}\text{B}$  NMR spectra. The  $^1\text{H}$  NMR spectrum showed that the white precipitate was seemingly one compound with the correct number of protons for **103** and the peaks shifted compared to that of the starting material in MeOD. However, there were two peaks in the  $^{11}\text{B}$  NMR spectrum ( $\delta$  13 and 18 ppm). This result was unexpected and these peaks in the  $^{11}\text{B}$  NMR spectrum were difficult to explain. Mass spectrometry ( $\text{ES}^+$  and  $\text{ES}^-$  in MeOH) did not seem to provide any insight as to what the structure of this product might be and efforts to crystallise this white powdery solid in order to obtain a crystal structure were unsuccessful.

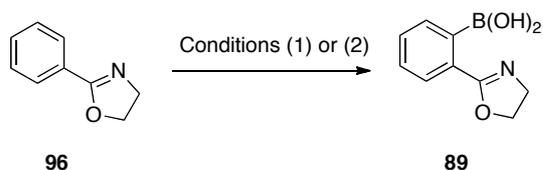
Based on conditions found in the literature<sup>63</sup> and armed with the knowledge gained from attempts to synthesise benzimidazole **85** (Equation 26), the desired compound was produced in a yield of 10% (11 mg) with a <sup>11</sup>B NMR shift at  $\delta$  30 ppm. Starting material **95** was also recovered from this reaction with a yield of 70%. As mentioned previously, according to the literature the yield of this reaction can be improved by increasing the temperature to 60 °C. The reaction was, therefore, repeated at this higher temperature and followed by TLC. After 18 h, a new spot appeared and there was some remaining starting material. After a further 48 h, with no further change in the reaction by TLC and hence, the reaction was worked up. The reaction mixture was diluted with diethyl ether and filtered through celite before the solvent was evaporated and the crude residue purified by silica gel chromatography. Unfortunately, in this case, none of the desired product was isolated, instead starting material (60%) and the de-brominated compound **104** (32%) were recovered.



**104**

An alternative approach to *ortho*-substituted systems such as **89**, **90**, and **91** is *via* directed *ortho*-metallation, in which an aryl compound bearing a directed metallation group will result in an *ortho* metallated intermediate on reaction with an alkyllithium such as BuLi. This intermediate can then be quenched with a range of electrophiles. It was decided to examine directed *ortho*-metallation with respect to the synthesis of compounds **89** and **91**. Hence, commercially available 2-phenyl-2-oxazoline **96** and 2-phenylbenzoxazole **105** were subjected to directed *ortho*-metallation conditions, as shown in Equations 37 and 38, respectively. From these attempts none of the desired boronic acids were obtained. These reactions resulted in a complex mixture of products which were not purified.

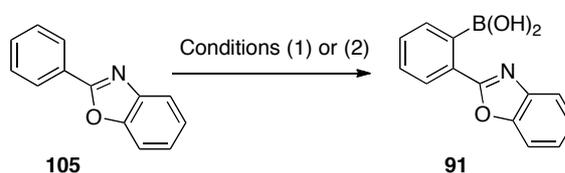
### Equation 37



Conditions: (1) *s*-BuLi, TMEDA, -78 °C, 5h  
then triisopropylborate, THF

(2) *n*-BuLi, TMEDA, 0 °C, 3h  
then triisopropylborate, THF

### Equation 38

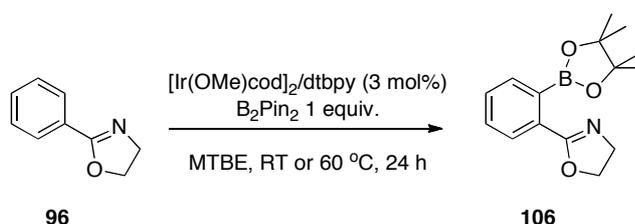


Conditions: (1) *s*-BuLi, TMEDA, -78 °C, 5h  
then triisopropylborate, THF

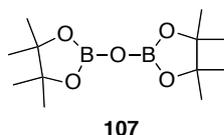
(2) *n*-BuLi, TMEDA, 0 °C, 3h  
then triisopropylborate, THF

Following further literature searching and since there was little success achieved using the directed metallation approach it was decided that the iridium catalysed borylation of oxazoline **96** should be investigated. Using reaction conditions found in the literature<sup>73</sup> and a catalyst stock solution (kindly provided by the Dr Steel/Prof. Marder research group) the following reaction was followed by TLC.

### Equation 39



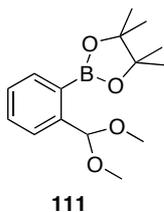
After 24 h at room temperature, TLC analysis showed that only starting material was present and so the reaction temperature was increased to 60 °C and left for a further 24 h. After work up only starting material was isolated. Performing these types of reactions in a microwave can accelerate these types of catalytic process<sup>73</sup> (although it should be noted that the substrates used in the literature are not comparable to **96**). Therefore, the reaction shown in Equation 39 was repeated with a fresh batch of catalyst stock solution under microwave conditions at 80 °C in a Personal Chemistry Emrys™ Optimiser microwave synthesiser and followed by GCMS. After 1 h, there was still starting material **96** present, however, all of the B<sub>2</sub>Pin<sub>2</sub> seemed to have been consumed according to GCMS. <sup>11</sup>B NMR analysis of the crude reaction mixture showed a peak at δ 22 ppm and GCMS analysis showed a mass of 271 both of which could correspond to the B-O-B compound **107**.<sup>74</sup> No other boronate containing component was evidenced and starting material **96** was the only other compound present.



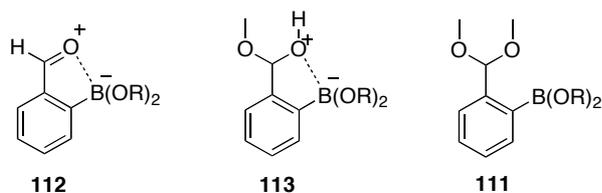
No further attempts towards the synthesis of oxazoline compounds, such as **89**, **90**, and **91**, were made. Instead, the synthesis of oxazole-containing structures, such as **110** were attempted, for example, as shown in Equation 41.

The reagent tosylmethylisocyanide (TosMIC) **109** is known to react with aldehydes to form oxazoles.<sup>75, 76</sup> It was therefore thought that starting with a boronate already present would make the synthesis of a structure such as **110** more direct through the reaction outlined in Equation 41. Such an approach avoids the Li/halogen exchange and direct borylation techniques that had so far been unsuccessful. First of all, the pinacol protected boronate ester **108** was synthesised from formylphenylboronic acid **47** (Equation 40).





This result was quite unexpected, and interesting, as there was no added acid or Lewis acid to help assist acetal formation by protonation or other form of activation of the aldehyde carbonyl group. One explanation as to why this reaction occurred so readily could be that the intramolecular boron atom facilitated this reaction and by performing the role of a Lewis acid (**112**), activated the aldehyde towards acetal formation *via* hemi-acetal **113**, as shown below.



Since the acetal **111** was so sensitive to silica gel-mediated hydrolysis, clearly the boronate must catalyse both the forward and back reactions of the acetal formation, and there was sufficient water present on the silica for hydrolysis to occur. Unfortunately, formation of the acetal explained why the desired oxazole **110** was not produced.

#### **4.4 Conclusions**

The synthesis of previously employed and successful catalysts (**25** and **31**) for direct amide formation was carried out repeatedly and with consistency with regard to reaction yields, assisted by some optimisation. However, in order to advance catalyst design and application, computational calculations (based on the mechanistic framework previously published<sup>49</sup>) were carried out by Tomasso

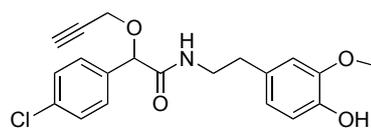
Marcelli to help us to prioritise the synthesis of potential new catalysts for direct amide formation. Of particular interest were benzimidazole compounds, such as **69** and **84**, which possessed the boronic acid functionality and would potentially not be as susceptible to boroxine formation, as with **67/68**. Disappointingly, the synthesis of these boronic acid compounds proved to be extremely difficult and no more than trace amounts were produced. Furthermore, attempts to synthesise compounds **69** and **84** were hindered due to the difficulty of the formation and purification of a reasonable amount of the benzimidazole precursors **75** and **83**. The calculations that were carried out also seemed to suggest that boronic acid compounds containing other heterocycles could be also be successful direct amide formation catalysts. The synthesis of imidazoline, oxazoline and oxazole compounds (**88**, **89**, **90**, **91** and **110**) that had the boronic acid functionality was attempted but unfortunately, with little success, and again, no more than trace amounts of the boronic acid being apparent, though not isolated.

Although the synthesis of the final boronic acid compounds in all of the cases above has proven to be problematic, steps towards their synthesis have been made, and if this chemistry is developed further in the future, these compounds still look to be prime candidates for application as potential direct amide formation catalysts.

## 5.0 Applications for Direct Amide Formation

### 5.1 Mandipropamid Analogues

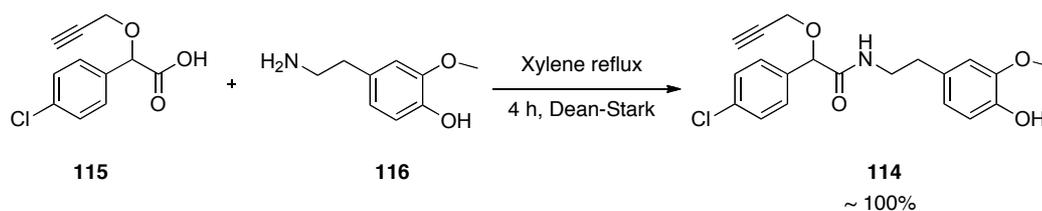
Mandipropamid **114** is a highly efficient fungicide and is the active ingredient of the commercial fungicides Revus<sup>®</sup> and Pergado<sup>®77</sup>. Mandipropamid is active against most water mould pathogens such as the economically important diseases *Phytophthora infestans* (potato and tomato late blight), *Plasmopara viticola* (grapevine downy mildew) and *Pseudoperonospora cubensis* (cucumber downy mildew). Mandipropamid also displays high levels of activity and is rapidly adsorbed to the wax layer of the plant surface. It provides a rainfast and long-lasting barrier to fungal diseases; it also has the advantage of being easy to use and has a low environmental impact.<sup>77</sup>



**114**

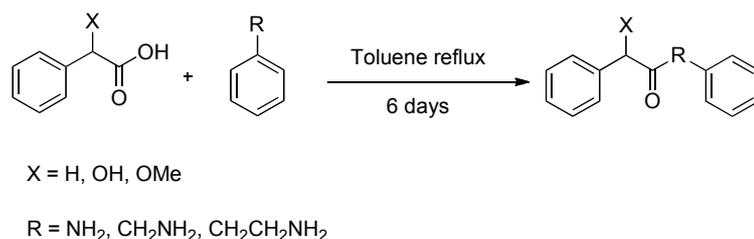
Since Mandipropamid **114** is an important target for the agrochemical industry it is, therefore, fortunate that the synthesis of **114** can be achieved in excellent yields *via* catalysed and uncatalysed direct amide formation (Equation 42). This means that the synthesis of **114** has the potential to be atom efficient and could result in a process with a favorable E-factor.

#### Equation 42



In order to begin to understand why this particular direct amide formation works so well the effect of the  $\alpha$ -activating group on the carboxylic acid was investigated using structural analogues of **114** along with a range of different amine substrates (Equation 43).

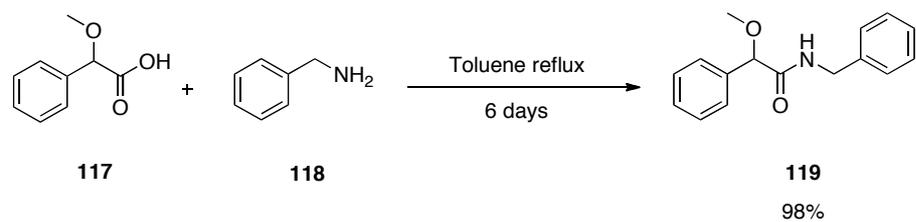
### Equation 43



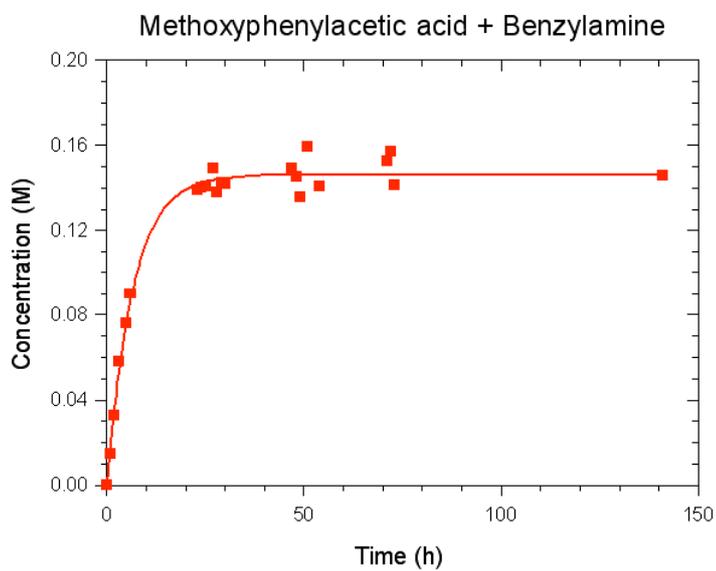
These direct amide formation reactions were carried out in refluxing toluene, in the absence of a catalyst, and followed by HPLC for six days with each reaction vessel sampled and diluted manually every hour during the working day. The response factors for each carboxylic acid, amine and amide were calculated previously to ensure that accurate concentrations of each species could be identified by HPLC. The data collected was processed using Micromath Scientist<sup>®</sup> software and fitted to a first order model, which fitted the experimental data well. After following the reactions for six days the reaction mixture was worked up to obtain an isolated yield of amide (it should be noted that due to availability of glassware, these reactions were carried out without drying.)

Initially, methoxyphenylacetic acid, a simplified analogue of **115** was investigated to probe the effect of a methoxy group in the  $\alpha$ -position of the carboxylic acid. Methoxyphenylacetic acid **117** was reacted with three different amines: benzylamine, phenylethylamine and aniline in order to determine which combinations of substrates were favourable for direct amide formation. The results are shown below.

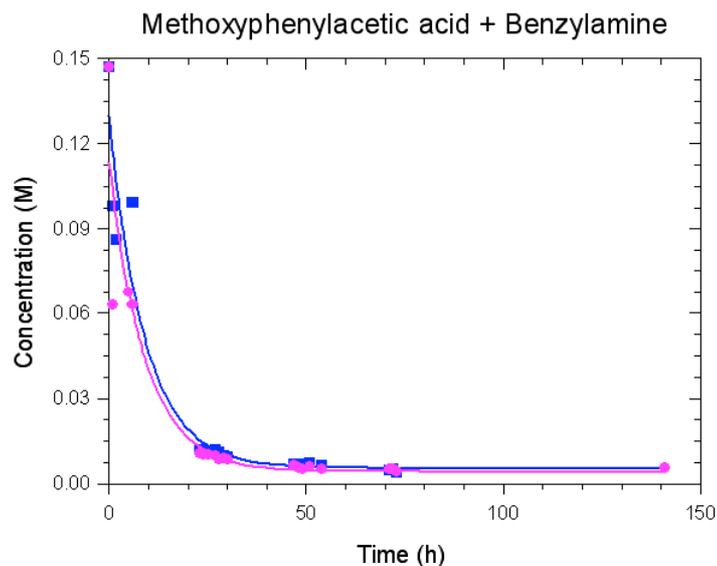
### Equation 44



**Figure 11:** Results from following the reaction between methoxyphenylacetic acid and benzylamine over time.



**Amide 119:** Final HPLC yield 98%  
Isolated yield 85%

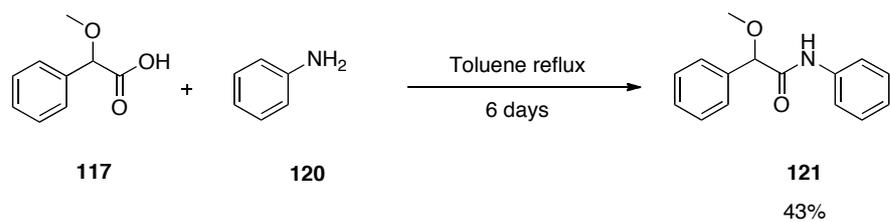


Benzylamine  
Methoxyphenylacetic acid  
 $k = 0.110 \text{ h}^{-1}$

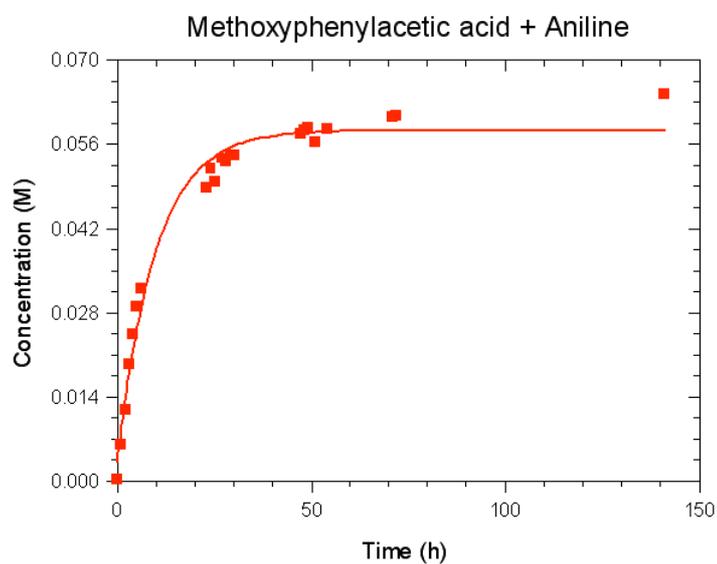
The reaction between methoxyphenylacetic acid and benzylamine was very high yielding with 98% of the corresponding amide being produced after approximately 24 hours, as shown in Figure 11. As previously discussed in Chapter Three, the increasing concentration of amide as the reaction proceeds results in inaccuracies when following the amide formation by HPLC; this can be seen in Figure 11 as the increase in scattering of the amide concentration. This is due to the amide product precipitating out of solution under the room temperature sampling conditions, having reached the saturation limit. Hence, the rate constant,  $k$ , for this reaction and all subsequent direct amide formation reactions was calculated using the data collected for following the starting material carboxylic acid and amine over time.

The reaction between methoxyphenylacetic acid and aniline (Equation 45) was also carried out under the same conditions. As expected, this reaction proved to be much slower than the reaction using benzylamine and this trend in amine reactivity has been observed previously<sup>19, 50</sup> (see Chapter One).

### Equation 45



**Figure 12:** Results from following the reaction between methoxyphenylacetic acid and aniline over time.

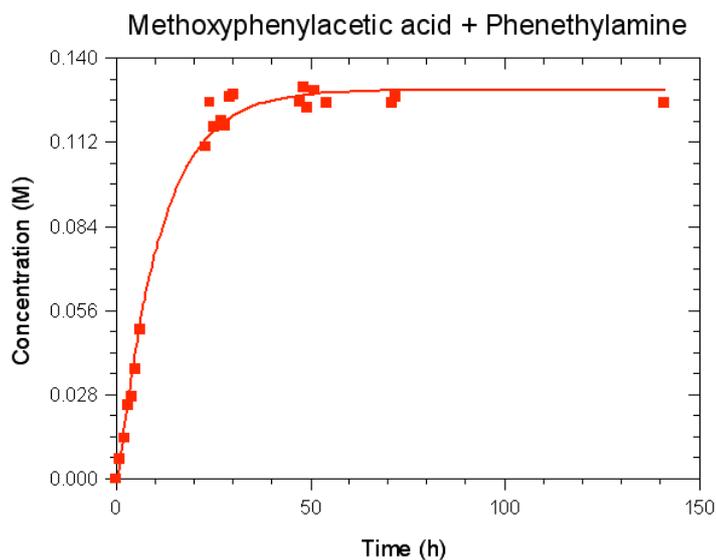


**Amide 121:** Final HPLC yield 43%

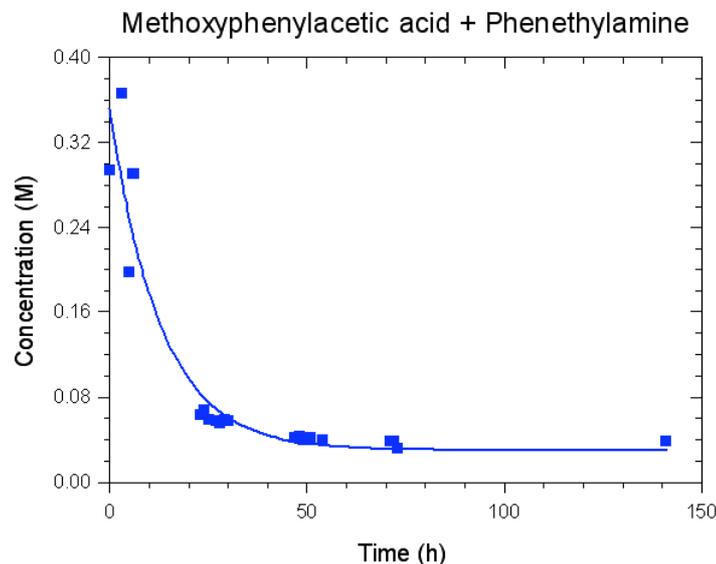
Isolated yield 40%



**Figure 13:** Results from following the reaction between methoxyphenylacetic acid and phenethylamine over time.



**Amide 123:** Final HPLC yield 85%  
Isolated yield 80%



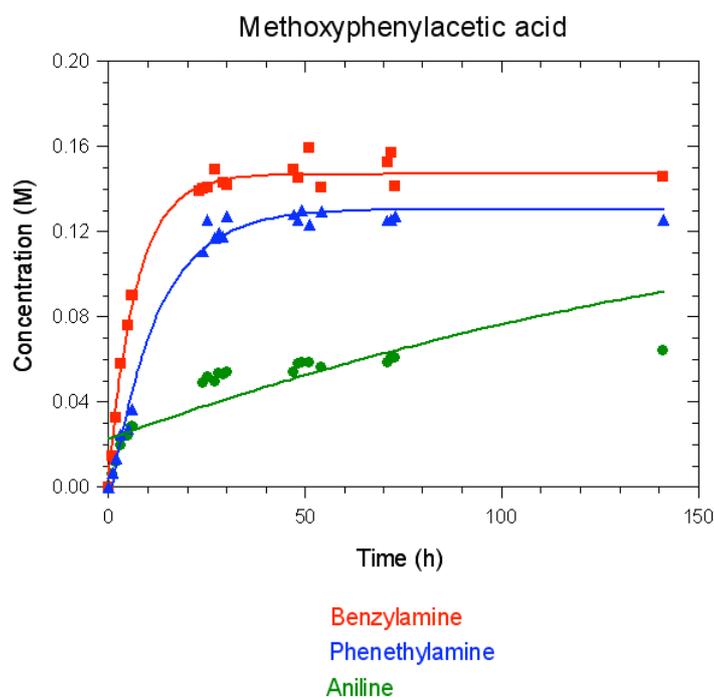
**Starting Materials**  
 $k = 0.0782 \text{ h}^{-1}$

Phenethylamine proved to be more reactive than aniline but slightly less reactive than benzylamine, again this was expected given the trend in amine reactivity seen previously.<sup>19, 50</sup> The value for the rate constant,  $k$ , was calculated using

Micromath Scientist<sup>®</sup> software with the data collected from following the loss of the starting materials. The HPLC retention times for methoxyphenylacetic acid and phenethylamine were almost identical and resulted in the overlapping of peaks in the HPLC chromatograph. Therefore, the area under the overlapping peaks was used as the combined starting materials for the reaction, which can be seen in Figure 13.

The plot shown in Figure 14 summarises these three experiments and shows the reactivity trend for the amines used in combination with methoxyphenylacetic acid. However, when the results of the three experiments were plotted simultaneously by Micromath Scientist<sup>®</sup> software (Figure 14), the curve fit for the methoxyphenylacetic acid and aniline reaction was not as smooth as when the data for this reaction was plotted individually. It is not clear what exactly the reason for this was.

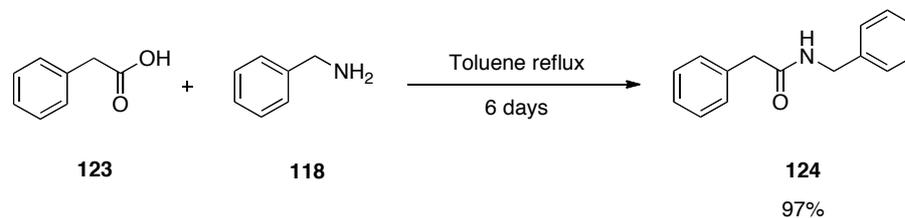
**Figure 14:** Results from following the reactions between methoxyphenylacetic acid and three different amines over time.



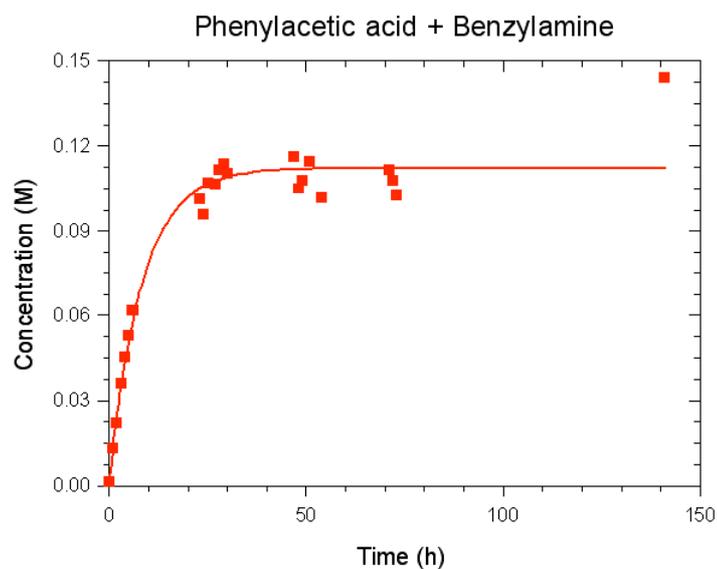
The same set of experiments was carried out with phenylacetic acid in order to compare the effect of the unsubstituted  $\alpha$ -position of the carboxylic acid with

that of the methoxy substituted  $\alpha$ -position. The uncatalysed reaction between phenylacetic acid and benzylamine is shown in Equation 47 and Figure 15.

**Equation 47**



**Figure 15:** Results from following the reaction between phenylacetic acid and benzylamine over time.

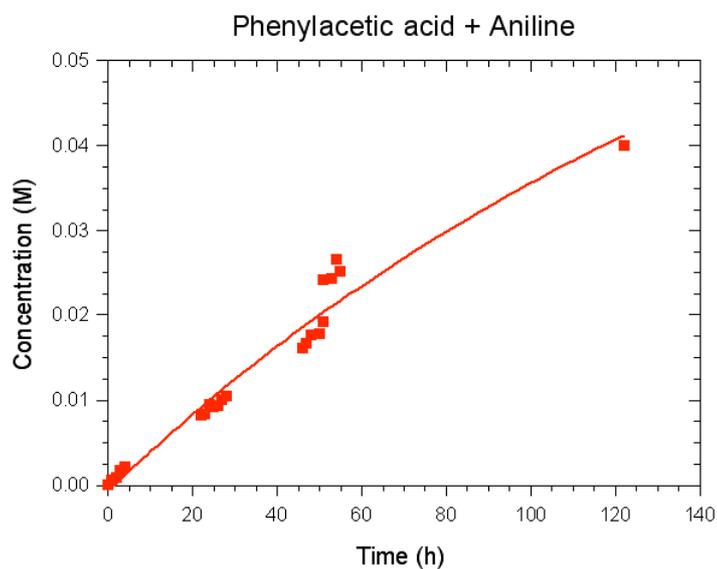


**Amide 124:** Final HPLC yield 97%

Isolated yield 82%

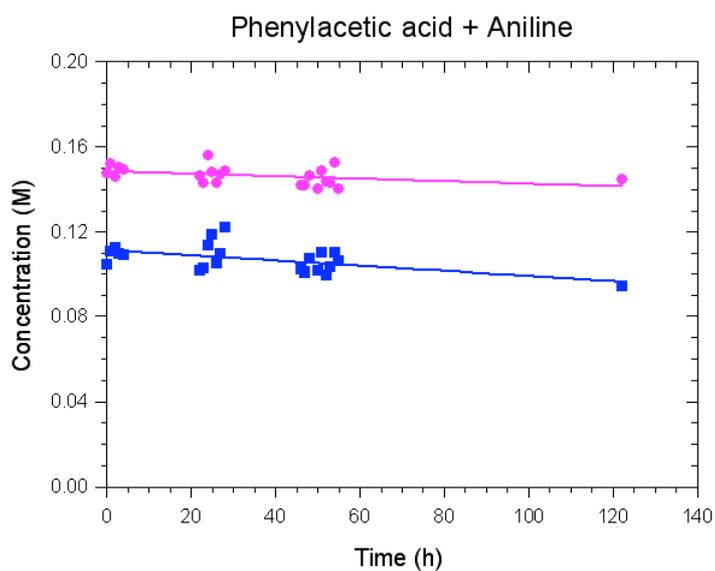


**Figure 16:** Results from following the reaction between phenylacetic acid and aniline over time.



**Amide 125:** Final HPLC yield 27%

Isolated yield 17%



Aniline

Phenylacetic acid

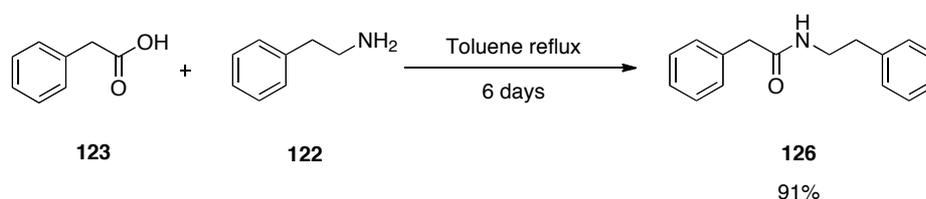
$$k = 1.83 \times 10^{-5} \text{ h}^{-1}$$

As expected, the rate and yield of direct amide formation was greatly reduced on using aniline rather than benzylamine as the amine substrate. Also, similarly to

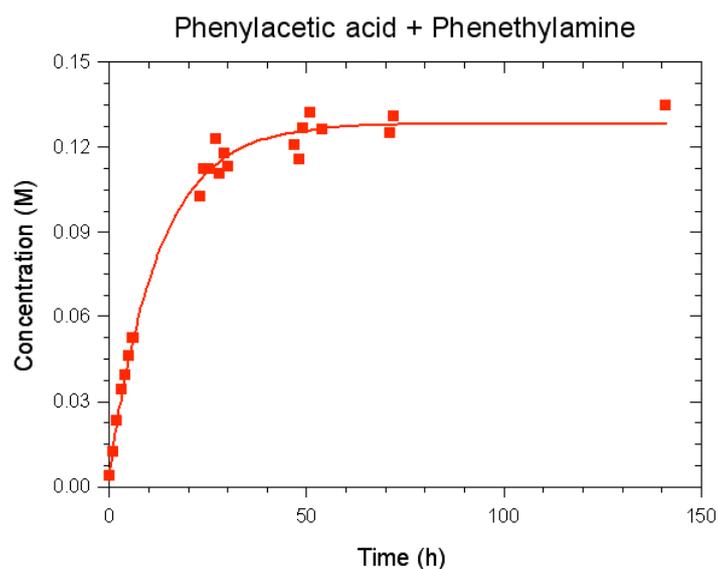
the benzylamine reactions, the reaction between phenylacetic acid and aniline is much slower than the reaction between methoxyphenylacetic acid and aniline. Following the loss of starting materials over time for the reactions using aniline proved to be difficult as the concentration of aniline in the reaction mixture could not be followed accurately. This resulted in an observed concentration of the amine that differed greatly to the concentration of carboxylic acid. This can clearly be seen in Figure 16.

The final reaction in the phenylacetic acid series was the reaction with phenethylamine as shown in Equation 49 and Figure 17.

#### Equation 49

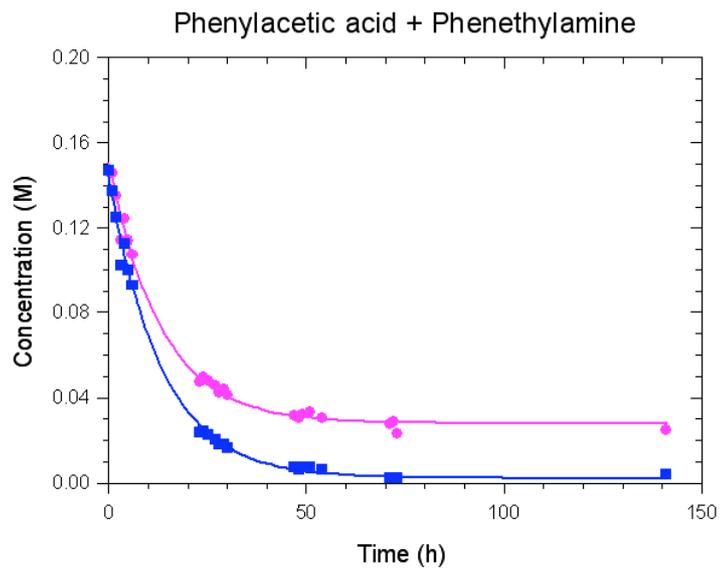


**Figure 17:** Results from following the reaction between phenylacetic acid and phenethylamine over time.



**Amide 126:** Final HPLC yield 91%

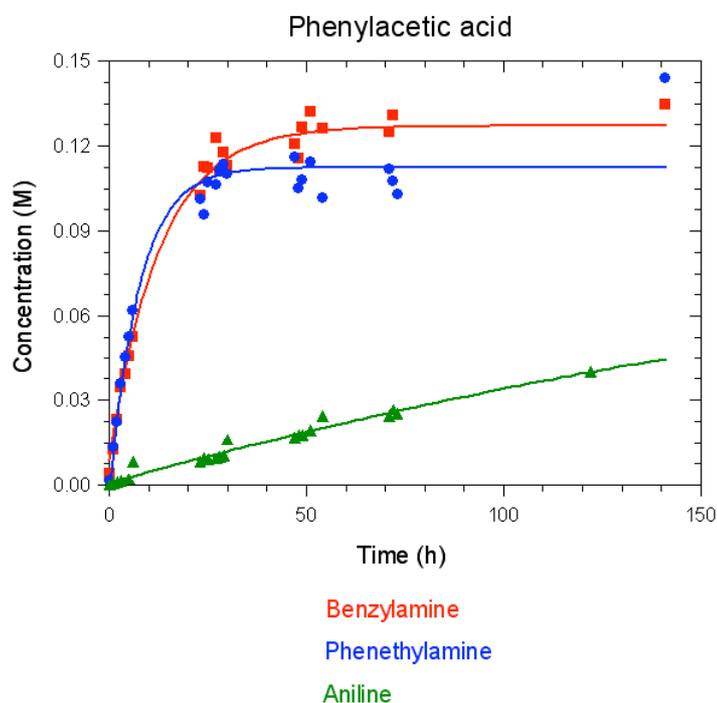
Isolated yield 79%



Phenethylamine  
Phenylacetic acid  
 $k = 0.0758 \text{ h}^{-1}$

As with Figure 14, the plot shown below in Figure 18 summarises the three experiments and shows the reactivity trend for the amines used in combination with phenylacetic acid.

**Figure 18:** Results from following the reactions between phenylacetic acid and three different amines over time.



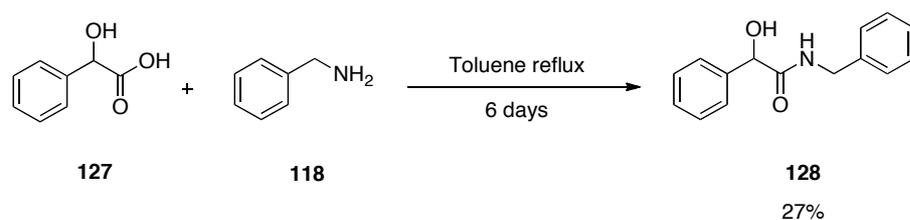
To summarise the reactions discussed so far, both methoxyphenylacetic acid and phenylacetic acid undergo uncatalysed direct amide formation with either benzylamine or phenethylamine favourably, with these reactions resulting in high yields of amide. However, in combination with aniline, the rate of amide formation with both carboxylic acids is, as expected, considerably reduced.

Direct amide formation reactions between mandelic acid **127** and benzylamine, aniline and phenethylamine were also carried out under the same conditions (Equations 50, 51 and 52). Mandelic acid **127** was used in order to compare the effect of the carboxylic acid possessing a hydroxy group in the  $\alpha$ -position and to establish whether this would improve or hinder the reactions in comparison to phenylacetic acid and methoxyphenylacetic acid.

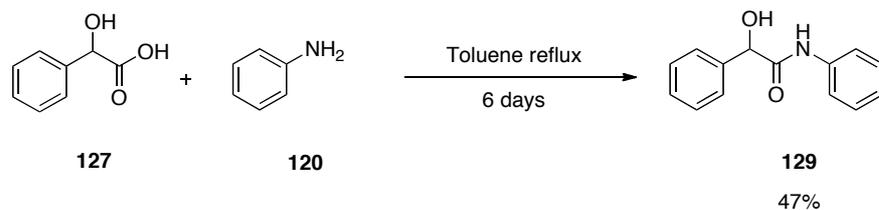
Unfortunately, following the reaction of mandelic acid with the three different amines proved to be problematic. This was due to the formation of an insoluble salt on mixing the carboxylic acid and amine. Although this had also occurred with some of the other reactions, the salt had always redissolved on heating; this was not the case with the mandelic acid reactions and the material

remained insoluble. The final yield by HPLC was measured, although this cannot be relied upon due to the issues surrounding sampling a heterogeneous reaction mixture. As with the other direct amide formation reactions the reaction mixture was also worked up to obtain an isolated yield of amide. The results for these experiments are shown in Table 8.

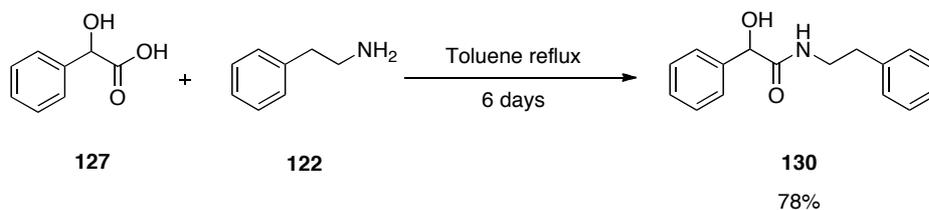
### Equation 50



### Equation 51



### Equation 51



**Table 8:** Direct Amide Formation Between Mandelic Acid and Three Different Amines.

<b>Amine</b>	<b>Solubility</b>	<b>Final HPLC yield (%)</b>	<b>Isolated yield (%)</b>
Benzylamine	Insoluble	34	27
Aniline	Insoluble up to 48 h	98	78
Phenethylamine	Insoluble up to 24 h	51	47

From these results a trend in reactivity of the carboxylic acids and amines is apparent and is shown below.

Carboxylic acid trend:

Methoxyphenylacetic acid > Phenylacetic acid > Mandelic acid (solubility problems)

Amine trend:

Benzylamine > Phenethylamine > Aniline

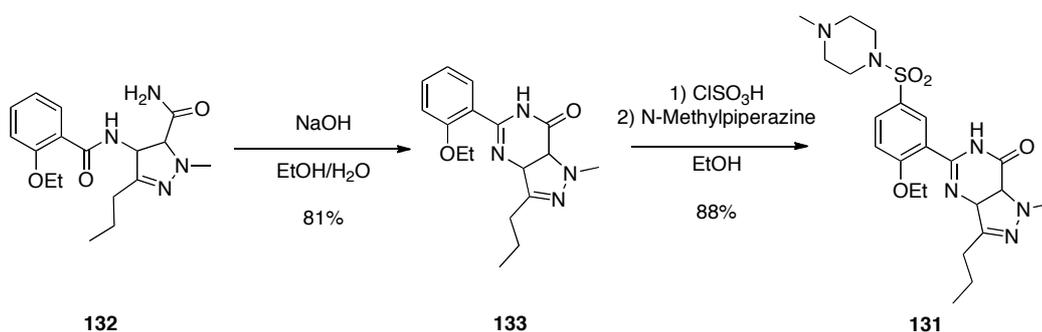
The trend that is observed for the amine substrates could be predicted and a similar trend has been seen previously (see Chapters one and three)<sup>19, 50</sup>. The carboxylic acid trend implies that an electron-donating group at the  $\alpha$ -position is slightly beneficial for uncatalysed direct amide formation. It is unfortunate that solubility problems arose when using mandelic acid as this obviously altered the ability to follow the reaction over time.

In order to fully understand the effect of varying the substituents on the carboxylic acid and amine and to appreciate why direct amide formation works so well for the synthesis of mandipropamid **114**, further experiments need to be carried out to cover a wider range of substrates. Unfortunately, time constraints meant that this was not possible during this project.

## 5.2 Synthesis of Sildenafil Precursor

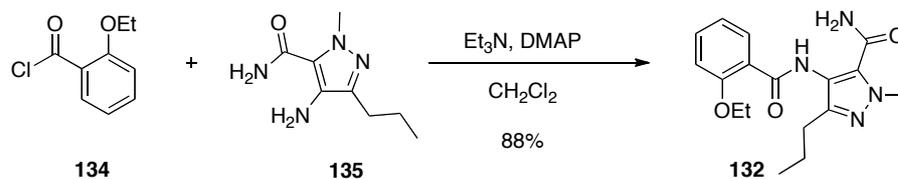
Sildenafil **131**, marketed as Viagra<sup>®</sup>, can be synthesised from the cyclisation of the precursor **132**, this is followed by sulfonation to provide the chlorosulfonyl derivative, which is finally condensed with 1-methylpiperazine to provide sildenafil **131**<sup>78-81</sup> (Scheme 21).

**Scheme 21:** One Route Towards the Synthesis of Sildenafil **131**.



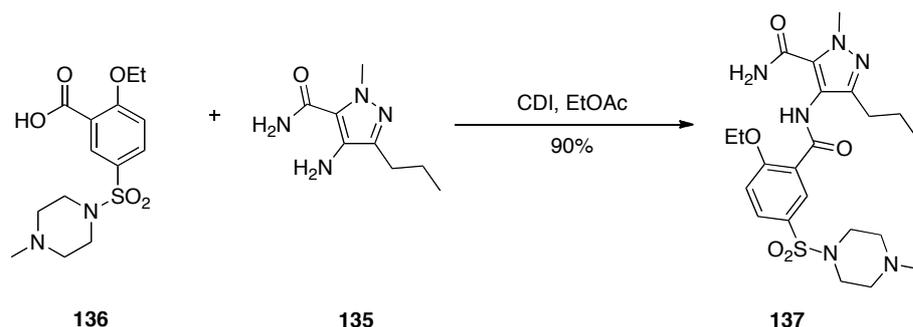
The synthesis of the amide precursor **132** typically follows standard amide formation techniques involving the use of the acid chloride **134** as demonstrated in Equation 53.<sup>78, 81</sup>

**Equation 53**



Part of a second route towards the synthesis of **131** is also shown in Equation 54 in which the chlorosulfonation reaction is carried out earlier in the synthesis. Again, the synthesis of the key intermediate involves an amide formation reaction, this time carried out using the coupling agent carbonyldiimidazole (CDI). The amide **137** can then undergo cyclisation in order to produce sildenafil **131**.

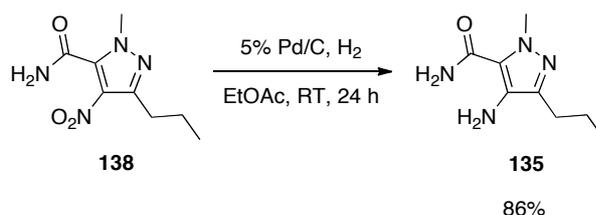
### Equation 54



The aim of this part of the project was to establish whether the reaction step described in Equation 53 could be carried out successfully by direct amide formation, and hence improve the atom efficiency of this stage of the process.

2-Ethoxybenzoic acid **138** is commercially available, but in order to screen some direct amide formation reactions to synthesise the key intermediate **132**, the amine **135** had to be synthesised. This was achieved starting from the nitropyrazole **138**, which was kindly provided by Pfizer. The hydrogenation reaction shown in Equation 55 proceeded smoothly to provide the amine as a pale orange solid with a yield of 86% after 24 h.

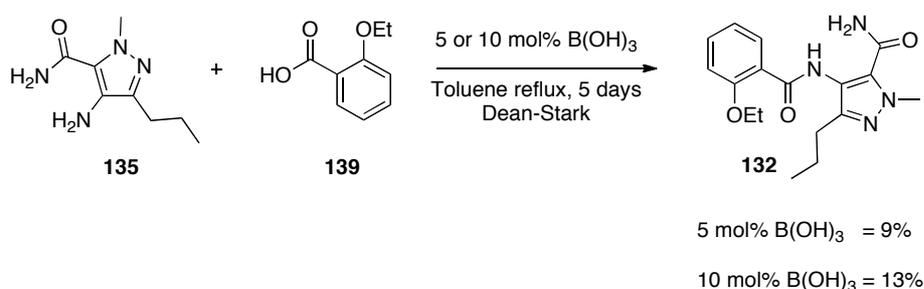
### Equation 55



With the amine in hand the direct amide formation reactions were attempted. Initially the carboxylic acid **139** and amine **135** were refluxed in toluene in the presence of 5 mol% boric acid. Drying was carried out by the use of a Dean-Stark condenser and the reaction was carried out under argon (Equation 56). Following the reaction by TLC showed that even after 5 days the reaction mixture consisted largely of starting materials. Therefore, the reaction was worked up and the amide product isolated as a white solid. The yield of amide

produced was a poor 9%. Increasing the boric acid loading to 10 mol% increased the yield of amide produced, under the same reaction conditions, slightly to 13% (Equation 56).

### Equation 56



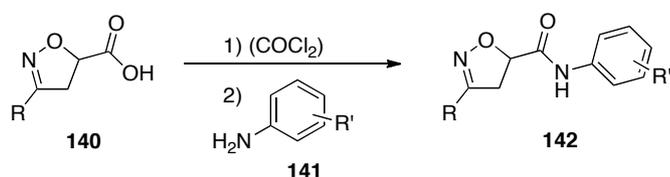
Although the direct amide formation reactions worked they were obviously sluggish and did not provide reasonable yields. Therefore, in an attempt to improve the yield of amide produced, the reaction solvent was changed to xylene in order to achieve a higher reflux temperature. With 10 mol% boric acid after 5 days the yield of amide was a disappointing 9%, which obviously shows no improvement over the reactions carried out in the lower boiling solvent toluene. It should be noted that there was no decomposition of starting materials during any of these reactions, and so the poor yields seem to be due to a genuine reactivity issue rather than the stability of the starting materials under the reaction conditions.

Since the yields achieved were poor it was decided not to investigate this reaction any further. It was thought that even changing the catalyst to the more active *N,N*-diisopropylbenzylaminoboronic acid **25** or *o*-iodophenylboronic acid **31** would not improve the yield of the reaction; at reaction temperatures as high as refluxing toluene and xylene the activity of these catalysts is comparable to boric acid.

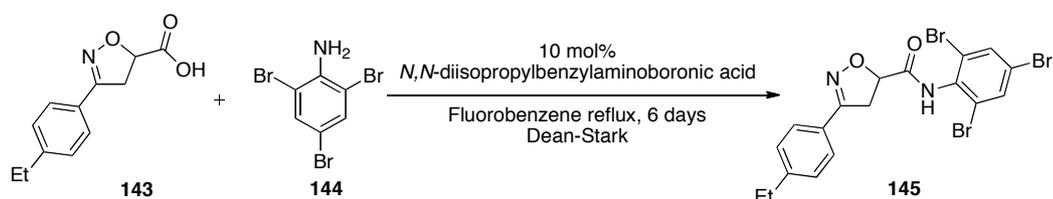
### 5.3 Attempted Synthesis of 3-Substituted Isoxazolinecarboxamides

Many amides display biological activity and in particular isoxazolinecarboxamides and isoxazolinecarboxamides, such as **142** show biological activity as fungicides.<sup>82</sup> Standard amide formation techniques, such as the use of pre-activated carboxylic acids are employed during the synthesis of such compounds (Equation 57). In an effort to improve on this method and employ direct amide formation as a useful technique in the synthesis of isoxazolinecarboxamides the reactions shown in Equations 58 and 59 were attempted.

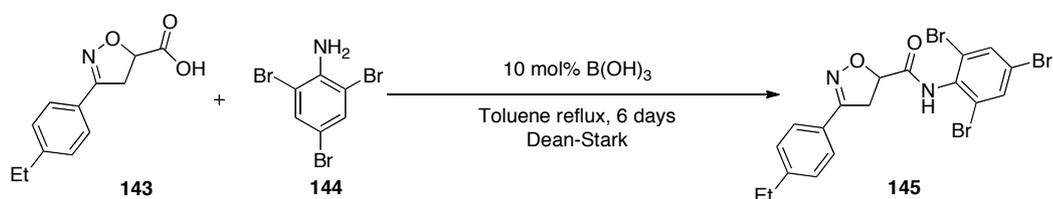
Equation 57



Equation 58



Equation 59



Unfortunately, these attempts to perform direct amide bond formation from the carboxylic acid **143** and amine **144** with boronic acid-based catalysts were unsuccessful. Indeed, even high catalyst loadings were ineffective for the

conversions shown in Equations 58 and 59. Presumably this was due to lack of reactivity of both the carboxylic acid and amine and also the hindrance of the aniline functionality. Hence, investigations into the synthesis of compounds such as **145** were suspended.

## 5.4 Conclusions

Investigations into the use of direct amide formation for economically important and commercial synthesis have begun and have shown varying levels of success. The synthesis of simplified analogues of the fungicide Mandipropamid **114** works well in the absence of a catalyst for many of the combinations screened. As expected the reactions involving aniline were the only exceptions, providing the corresponding amide in poor to moderate yields. The reactivity of phenylacetic acid **123** versus methoxyphenylacetic acid **117** was found to be similar, with perhaps the methoxy group in the  $\alpha$ -position lending a slight advantage to the reactivity of **117**. Unfortunately the insolubility of the salt formed during the reactions involving mandelic acid **127** meant that these reactions could not be followed accurately by HPLC. However, the isolated yields of amides showed that for the reactions with phenethylamine and aniline the yields of amide were good to moderate respectively. Surprisingly, a poor yield was achieved for the reaction between mandelic acid and benzylamine, presumably because the salt formed on mixing remained insoluble for the duration of the experiment. In order to fully appreciate why the uncatalysed direct amide formation reaction works so well for mandipropamid further experiments need to be carried out to include a wider range of substrates.

Catalysed direct amide formation reactions have been carried out in order to synthesise a key intermediate **132** for the synthesis of Sildenafil **131**. Although some success was achieved, the poor yields over an extended reaction time meant that this route was not a viable one.

Regrettably, the synthesis of isoxazolinecarboxamide **145** via direct amide formation was unsuccessful. This could be largely due to this choice of substrates being particularly unreactive, further investigations which include a range of substrates with different substitution patterns may be more successful.

Overall, direct amide formation, catalysed or uncatalysed, does display some potential to replace typical amide formation techniques for commercially important syntheses. However, the choice of substrates is crucial for the reactivity of these systems and further investigations are still required to ensure that direct amide formation becomes a general tool for a wide range of carboxylic acid and amine partners.

## 6.0 Conclusions and Future Work

Considering the long history of the direct amide formation reaction, and its importance to the chemical industry, it is remarkable how little of the process is understood. A review of the published literature revealed how incomplete our understandings of the mechanisms were for both the uncatalysed and catalysed direct amide formation reactions.

Investigations into the uncatalysed, thermal reaction found that the process of direct amide formation is likely to proceed through the carboxylic acid hydrogen-bonded cyclic dimer **42** (Scheme 16, page 55). The role of such hydrogen-bonded dimers is to enable carboxylic acid activation towards nucleophilic attack by the amine, and to allow the reaction to proceed through to a neutral intermediate. DFT calculations were carried out and showed that the mechanism for direct amide formation could proceed *via* this carboxylic acid dimer, which could form readily in toluene. Attack on this cyclic dimer species by the amine would then result in the formation of a transition state **43** as shown by Figure 7 (page 56). The result of a concerted proton transfer from amine to acid and release of the second carboxylic acid is the neutral intermediate **41**, from which water is readily lost to provide the amide product (see Scheme 16, page 55).

An area that is worthy of further study would be to investigate the extent to which different carboxylic acids exist as the corresponding cyclic dimer and to establish whether this reflects the observed reactivity trends. For example, does phenylbutyric acid possess more cyclic dimer character than the less reactive benzoic acid? Of course the reason for the reactivity of particular direct amide formation reactions cannot be as simple as this and there are many other factors to consider, such as the extent of salt formation and the steric *versus* electronic properties of the substrates.

Having proposed a new mechanism for the uncatalysed direct amide formation reaction, attention was turned to the synthesis of novel boronic acid compounds which had the potential to act as catalysts for this reaction.

In order to advance catalyst design and application, computational calculations (based on the mechanistic framework previously published<sup>49</sup>) were

carried out by Tommaso Marcelli to help us to prioritise the synthesis of potential new catalysts for direct amide formation. Benzimidazole compounds were of particular interest as calculations showed that the previously synthesised<sup>62</sup> **67** (Equation 18, page 76) should theoretically possess catalytic activity to rival *o*-iodophenylboronic acid **31**. However, **67** exists as the unreactive boroxine **68** and therefore is not an active catalyst for direct amide formation. Hence, the synthesis of several compounds, which hopefully would not be as susceptible to stable boroxine formation, was planned and attempted. Unfortunately the synthesis of these boronic acids proved to be extremely difficult and no more than trace amounts were observed. Also, the synthesis of the final boronic acid compounds **69** and **84** was hindered due to the difficulties in synthesising the precursors **75** and **83**.

The synthesis of several imidazoline, oxazoline and oxazole compounds containing the boronic acid functionality was also attempted based on the promising results from Tommaso Marcelli's calculations. As with the benzimidazole compounds little success was achieved and the final boronic acid compounds were only observed in trace quantities.

Despite the difficulties found in trying to produce the types of boronic acid compounds discussed above, progress towards their synthesis has been made. The synthesis of these compounds is worthy of further investigation due to the potential activity displayed in the results from the computational calculations. Different synthetic routes to the benzimidazole precursors **75** and **83** need to be examined in order to be able to apply a variety of borylation techniques to the synthesis of the final boronic acids. This will hopefully mean that the synthesis of a reasonable quantity of the final compounds **69** and **84** is achievable. This would allow for a full catalytic activity screen to be carried out, which should include all of the current successful catalysts as well as novel compounds. These compounds need to be compared under the same reaction conditions which, surprisingly, has not already been carried out thoroughly for the catalysts already in the literature.

All of the novel boronic acid compounds that have been discussed still remain prime candidates for application as potential direct amide formation catalysts.

Finally, the application of direct amide formation towards amide containing compounds that are of economic importance was investigated.

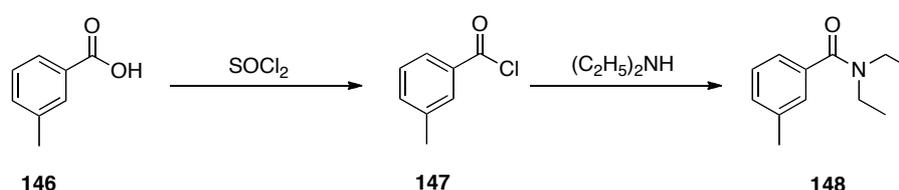
Simplified analogues of the fungicide Mandipropamid **114** (page 96) can be synthesised successfully in the absence of a catalyst. Impressive yields were achieved with substrates such as phenylacetic acid and methoxyphenylacetic acid with benzylamine or phenethylamine. As expected, reactions involving the use of aniline were much slower and resulted in a poorer yield of amide in comparison. When mandelic acid was employed the production of an insoluble salt occurred on mixing with each amine. This greatly reduced the ability to accurately follow these reactions over time and so only isolated yields of product were obtained.

Further research is required in order to fully appreciate why the uncatalysed direct amide formation reaction works so well for mandipropamid. Experiments could be carried out to include a wider range of substrates in order to understand which substitution patterns and functional groups enhance or hinder direct amide formation in this particular case.

Catalysed direct amide formation reactions have been carried out in order to synthesise a key intermediate **132** for the synthesis of Sildenafil **131** (page 112). Although some success was achieved, the poor yields over an extended reaction time and high temperatures meant that this route was not a viable one. Similarly, the synthesis of the potential fungicide isoxazolinecarboxamide **145** (page 115) *via* direct amide formation was unsuccessful.

One other area of research that could potentially be important regarding commercial synthesis and direct amide formation is the synthesis of *N,N*-diethyl-*meta*-toluamide (DEET) **148**, which is one of the most common active ingredients found in insect repellents.<sup>83, 84</sup> Currently, the synthesis of DEET involves the conversion of *m*-toluic acid **146** into the acyl chloride **147** followed by a reaction with diethylamine (Scheme 22).

**Scheme 22:** Typical Synthesis of DEET



Direct amide formation could offer a more sustainable and environmentally friendly alternative to the typical synthesis of DEET. Investigations into this possibility have already started within the group with some success. Continuation of this research and further optimisation of this process potentially could result in the synthesis of DEET *via* direct amide formation in high yields.

Overall, direct amide formation, catalysed or uncatalysed, does display some potential to replace typical amide formation techniques for commercially important syntheses. However, the choice of substrates is crucial for the reactivity of these systems and further investigations are still required to ensure that direct amide formation becomes a general tool for a wide range of carboxylic acid and amine partners. It is important that research in this area continues, and that there becomes a universal acceptance that direct amide formation is a viable and important, general reaction.

## 7.0 Experimental

### 7.1 General Experimental

All  $^1\text{H}$  NMR spectra were recorded on either Varian Mercury-400, Varian-Mercury 500 or Varian VNMRS 700 MHz spectrometers.  $^{13}\text{C}$  NMR spectra were recorded on Varian Mercury-400, Varian Mercury-500 or Varian VNMRS 700 instruments at frequencies of 100, 125 or 175 MHz.  $^{11}\text{B}$  NMR spectra were recorded on a Bruker Avance-400 instrument at a frequency of 128 MHz. All peaks are reported using the residual protic solvent peak as an internal reference.  $^1\text{H}$  NMR spectra are reported as chemical shift  $\delta$  (ppm) (number of protons, multiplicity, coupling constant  $J$  (Hz), assignment). Mass spectra were obtained using a Waters LCT or a Waters TQD spectrometer, and accurate mass obtained on a Thermo LTQ-FT spectrometer. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Elemental analysis was performed using an Exeter Analytical E-440 Elemental Analyser. Column chromatography was performed on Davisil Silica gel, 60 mesh. TLC was performed on Polygram SIL G/UV254 plastic backed silica gel plates with visualisation achieved using a UV lamp or staining with basic  $\text{KMnO}_4$ .

Glassware was oven dried (130 °C) as required and cooled under a positive pressure of argon. Dry solvents were dried by distillation (sodium-benzophenone ketyl for THF) or through the use of the Innovative Technology Inc. solvent purification system. Melting points were determined using an electrothermal melting point apparatus and are reported uncorrected. All other reagents were purchased from Acros, Aldrich, Alfa Aesar, Fluka and used without further purification unless otherwise stated. Molecular sieves were activated by heating to 200 °C. Data for reactions followed over time was obtained using a Gilson 215 Synthesis Workstation equipped with ReactArray racks and heating block, carried out using ReactArray Control Software (version 3,0,0,3048) and HPLC data analysed using ReactArray DataManager (version 1,1,33,0). HPLC conditions were under Clarity (version 2.6.05.517) with control and injections carried out in conjunction with ReactArray DataManager. The HPLC system consisted of Gilson 322 Pump, Gilson 402 Syringe Pump, Agilent 1100 Series UV Diode Array Detector and Phenomenex Luna C18 3  $\mu\text{m}$ , 150

mm × 4.60 mm column. Data for reactions followed by IR was obtained using Mettler Toledo ReactIR4000 equipment using ReactIR (version 3.0) software. Microcalorimetry was carried out at Syngenta using an Omnical reaction calorimeter and Omnical WinCRC 2000 for MS Windows software.

### ***7.2 General Procedure for the Preparation of Amides at 120 °C***

The appropriate carboxylic acid (3.05 mmol) was dissolved in toluene (30 mL) and amine (1 equivalent) was added, followed by the addition of catalyst (5 mol%). The reaction mixture was heated to 120 °C and azeotropic removal of water was performed using a Dean-Stark condenser. The mixture was allowed to stir at reflux for 48 h before being concentrated in *vacuo*. The residue was then redissolved in ethyl acetate (25 mL), washed with brine (25 mL), 5% (w/v) HCl (25 mL), brine (25 mL), 5% (w/v) NaOH (25 mL), brine (25 mL), dried (MgSO<sub>4</sub>), and the solvent evaporated in *vacuo*.

### ***7.3 General Procedure for the Preparation of Amides at 55 °C***

The appropriate carboxylic acid (3.05 mmol) was dissolved in toluene (30 mL) and amine (1 equivalent) was added, followed by the addition of catalyst (5 mol%) and activated 3 Å molecular sieves. The reaction mixture was heated to 55 °C and allowed to stir at this temperature for 48 h before being filtered through Celite and concentrated in *vacuo*. The residue was then redissolved in ethyl acetate (25 mL), washed with brine (25 mL), 5% (w/v) HCl (25 mL), brine (25 mL), 5% (w/v) NaOH (25 mL), brine (25 mL), dried (MgSO<sub>4</sub>), and the solvent evaporated in *vacuo*.

### ***7.4 General Procedure for Following Reactions Over Time***

Carboxylic acid (1.47 mmol) was weighed into each reaction vessel, followed by assembly of a micro-Soxhlet apparatus loaded with activated 3 Å molecular

sieves under argon. Dry toluene (10 mL) and amine (1.47 mmol) was then added to each reaction vessel and the reaction heated to 120 °C. The mixture was allowed to stir at reflux for 6 days before being concentrated in *vacuo*. The residue was then redissolved in ethyl acetate (15 mL), washed with brine (15 mL), 5% (w/v) HCl (15 mL), brine (15 mL), 5% (w/v) NaOH (15 mL), brine (15 mL), dried (MgSO<sub>4</sub>), and the solvent evaporated in *vacuo*. Reactions were sampled (50 µL) at 1 h intervals. Samples were diluted once (50 µL in 950 µL MeCN) and analysed by HPLC (gradient MeCN (0.05% TFA) / water (0.05% TFA) 50:50 – 90:10 – 50:50 over 7 minutes; 1 mL min<sup>-1</sup>). Column temperature 30 °C.

### ***7.5 General Procedure for Following Direct Amide Formation Over Time Using the Gilson 215 Synthesis Workstation***

The appropriate catalyst (0.233 mmol, 10 mol %) was weighed into each reaction vessel, followed by assembly of a micro-Soxhlet apparatus loaded with activated 3 Å molecular sieves under argon. Solid reagents were added using the ReactArray as standard solutions (0.5 M in toluene). Naphthalene (0.35 mmol, 15 mol %) and amine (2.33 mmol) were added to the reaction vessels at ambient temperature. The appropriate amount of toluene was then added to each reaction vessel in order to give a final reaction volume of 10 mL. After heating to reflux, carboxylic acid (2.33 mmol) was added to the stirred solution. Reactions were sampled (50 µL) at 4 h intervals (48 h reaction time). Samples were quenched with MeCN (950 µL), diluted once (50 µL in 950 µL MeCN), mixed and analysed by HPLC (gradient MeCN (0.05% TFA) / water (0.05% TFA) 60:40 to 20:80 to 60:40 over 30 minutes; 1 mL min<sup>-1</sup>). Naphthalene was used as an internal standard.

### ***7.6 Calorimetry Studies***

Microcalorimetry was carried out at using an Omnical reaction calorimeter and Omnical WinCRC 2000 for MS Windows software. The appropriate

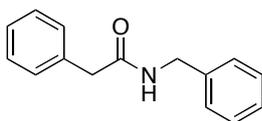
carboxylic acid (2 mL of a 1 M solution in toluene) was added to a calorimetry vial equipped with a stirrer bar. This was placed inside the calorimeter, which was set at 30 °C and once the heat flow had stabilised the appropriate amine was added (2 mL of a 1 M solution in toluene). Once the heat flow had stabilised following an exotherm the vial was removed from the calorimeter and the heat output recorded. The data was processed using Excel. Due to the solubility of benzoic acid in toluene, a 0.5 M solution was made and all amines used in combination with benzoic acid had to be diluted to achieve 0.5 M solutions keeping the combination equimolar.

### ***7.7 Quantum Chemical Calculations (carried out by Prof. Mark Wilson)***

The quantum chemical calculations used density functional theory (DFT), employing Becke's three-parameter hybrid exchange functional (B3)<sup>85</sup> combined with the correlation functional of Lee, Yang, and Parr (LYP),<sup>86</sup> together with 6-31G\*\* or 6-31+G\*\* basis sets for all atoms within the Gaussian 03 program.<sup>87</sup> Single-molecule calculations were fully optimized at this level of theory, with stationary points confirmed by vibrational analysis. Some calculations employed an implicit solvation model for toluene provided by a polarizable continuum model (PCM).<sup>88</sup>

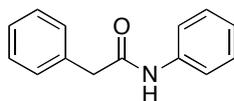
### ***7.8 Synthetic Procedures***

#### ***N-Benzyl-2-phenylacetamide***



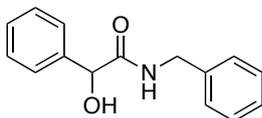
The general procedure for following reactions over time was followed to provide the title compound as a white solid (0.27 g, 82%). Spectroscopic details were the same as those reported in the literature.<sup>26</sup>

### ***N*-2-Diphenylacetamide**



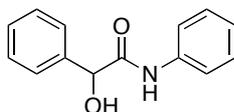
The general procedure for following reactions over time was followed to provide the title compound as a white solid (0.05 g, 17%). Spectroscopic details were the same as those reported in the literature.<sup>89</sup>

### ***N*-Benzyl-2-hydroxy-2-phenylacetamide**



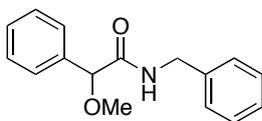
The general procedure for following reactions over time was followed to provide the title compound as a white solid (0.09 g, 27%). Spectroscopic details were the same as those reported in the literature.<sup>90</sup>

### **2-Hydroxy-*N*-2-diphenylacetamide**



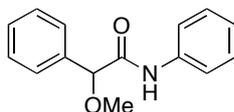
The general procedure for following reactions over time was followed to provide the title compound as a white solid (0.16 g, 47%). Spectroscopic details were the same as those reported in the literature.<sup>91</sup>

### ***N*-Benzyl-2-methoxy-2-phenylacetamide**



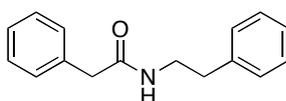
The general procedure for following reactions over time was followed to provide the title compound as a white solid (0.32 g, 85%). Spectroscopic details were the same as those reported in the literature.<sup>92</sup>

### **2-Methoxy-*N*-2-diphenylacetamide**



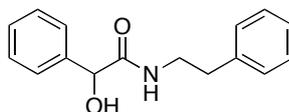
The general procedure for following reactions over time was followed to provide the title compound as a white solid (0.14 g, 40%). Spectroscopic details were the same as those reported in the literature.<sup>36, 93</sup>

### ***N*-Phenethyl-2-phenylacetamide**



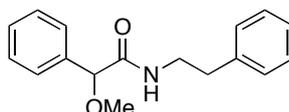
The general procedure for following reactions over time was followed to provide the title compound as a white solid (0.28 g, 79%). Spectroscopic details were the same as those reported in the literature.<sup>94</sup>

## 2-Hydroxy-*N*-phenethyl-2-phenylacetamide



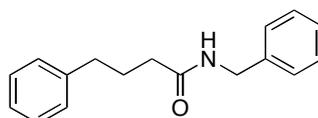
The general procedure for following reactions over time was followed to provide the title compound as a white solid (0.29 g, 78%). Spectroscopic details were the same as those reported in the literature.<sup>95</sup>

## 2-Methoxy-*N*-phenethyl-2-phenylacetamide



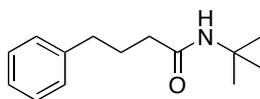
The general procedure for following reactions over time was followed to provide the title compound as a white solid (0.32 g, 80%). M.p. 40-43 °C.  $\nu_{\max}$  (ATR): 698s, 1098, 1194, 1450, 1537, 1646s, 3292  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.74 (t, 2H,  $J = 7.0$ ,  $\text{CH}_2$ ), 3.23 (s, 3H,  $\text{CH}_3$ ), 3.42 (sextet, 1H,  $J = 6.2$ ,  $\text{CH}_2$ ), 3.48 (sextet, 1H,  $J = 6.9$ ,  $\text{CH}_2$ ), 4.51 (s, 1H,  $\text{CHOMe}$ ), 6.67 (s, (br),  $\text{NH}$ ), 7.07-7.09 (m, 2H,  $\text{ArH}$ ), 7.12-7.27 (m, 8H,  $\text{ArH}$ ).  $^{13}\text{C}$  NMR (176 MHz,  $\text{CDCl}_3$ ):  $\delta$  35.6 ( $\text{CH}_2$ ), 40.1 ( $\text{NCH}_2$ ), 57.2 ( $\text{CH}_3$ ), 83.86 ( $\text{CH}$ ), 126.4 ( $\text{ArC}$ ), 126.9 ( $\text{ArC}$ ), 128.3 ( $\text{ArC}$ ), 128.4 ( $\text{ArC}$ ), 128.5 ( $\text{ArC}$ ), 128.7 ( $\text{ArC}$ ), 137.0 ( $\text{ArC}$ ), 138.7 ( $\text{ArC}$ ), 170.5 ( $\text{C=O}$ ).  $m/z$  ( $\text{ES}^+$ ): 292.3 [ $\text{M}+\text{Na}$ ], 561.4 [ $2\text{M}+\text{Na}$ ]. HRMS ( $\text{ES}^+$ ):  $\text{C}_{17}\text{H}_{19}\text{NO}_2$  requires 292.1313 [ $\text{M}+\text{Na}$ ] found 292.1313 [ $\text{M}+\text{Na}$ ].

## *N*-Benzyl-4-phenylbutyramide



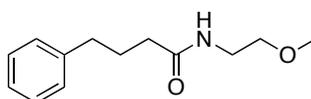
The general procedure for the preparation of amides was followed. Yield in the presence of boric acid: (0.69 g, 89 %), yield in the presence of *o*-iodophenylboronic acid: (0.59, 76 %), yield in the absence of catalyst: (0.49 g, 64 %) as a white solid. M.p. 79-80 °C.  $\nu_{\max}$  (ATR): 740, 1000, 1077, 1213, 1267, 1411, 1451, 1494, 1540, 1639s, 3283  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.97-2.05 (m, 2H,  $\text{CH}_2$ ), 2.22 (t, 2H,  $J = 6.8$ ,  $\text{ArCH}_2$ ), 2.67 (t, 2H,  $J = 7.6$ ,  $\text{CH}_2$ ), 4.43 (d, 2H,  $J = 6$ ,  $\text{CH}_2\text{N}$ ), 5.63 (s, (br), 1H,  $\text{NH}$ ), 7.15-7.35 (m, 10H,  $\text{ArH}$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  27.1 ( $\text{CH}_2$ ), 35.2 ( $\text{CH}_2$ ), 35.9 ( $\text{CH}_2$ ), 43.7 ( $\text{CH}_2$ ), 126.0 ( $\text{ArC}$ ), 127.6 ( $\text{ArC}$ ), 127.9 ( $\text{ArC}$ ), 128.4 ( $\text{ArC}$ ), 128.5 ( $\text{ArC}$ ), 128.7 ( $\text{ArC}$ ), 138.2 ( $\text{ArC}$ ), 141.4 ( $\text{ArC}$ ), 172.4 ( $\text{C}=\text{O}$ ).  $m/z$  ( $\text{ES}^+$ ): 254.2 [ $\text{M}+\text{H}^+$ ]. Spectroscopic details were the same as those reported in the literature.<sup>29, 31</sup>

#### ***N*-(*tert*-Butyl)-4-phenylbutanamide**



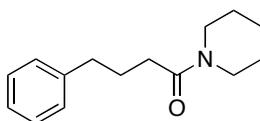
The general procedure for the preparation of amides was followed. Yield in the presence of boric acid: (0.017 g, 3 %) as a yellow oil.  $\nu_{\max}$  (ATR): 696vs, 741, 1221, 1543s, 1644vs, 2927, 3301  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.3 (s, 9H, 3( $\text{CH}_3$ )), 1.93-1.99 (m, 2H,  $\text{CH}_2$ ), 2.09 (dd, 2H,  $J = 14$  and 7.2,  $\text{CH}_2$ ), 2.63-2.68 (m, 2H,  $\text{CH}_2$ ), 5.19 (s, 1H,  $\text{NH}$ ), 7.17-7.21 (m, 3H, 3( $\text{ArH}$ )), 7.26-7.30 (m, 2H, 2( $\text{ArH}$ )).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.6 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_2$ ), 21.4 ( $\text{CH}_2$ ), 28.8 ( $\text{CH}_2$ ), 60.3 ( $\text{C}(\text{CH}_3)_3$ ), 125.3 ( $\text{ArC}$ ), 128.2 ( $\text{ArC}$ ), 128.3 ( $\text{ArC}$ ), 128.5 ( $\text{ArC}$ ), 129 ( $\text{ArC}$ ), 137.8( $\text{ArC}$ ), 171.1 ( $\text{C}=\text{O}$ ).  $m/z$  ( $\text{ES}^+$ ): 220.1 [ $\text{M}+\text{H}^+$ ]. HRMS ( $\text{ES}^+$ ):  $\text{C}_{14}\text{H}_{24}\text{NO}$  requires 220.1701 [ $\text{M}+\text{H}^+$ ] found 220.1704 [ $\text{M}+\text{H}^+$ ].

#### ***N*-(2-Methoxyethyl)-4-phenylbutanamide**



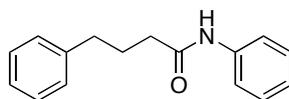
The general procedure for the preparation of amides was followed. Yield in the presence of boric acid: (0.47 g, 70 %), yield in the presence of *o*-iodophenylboronic acid: (0.33, 49 %), yield in the absence of catalyst: (0.36 g, 54 %) as a pale yellow oil.  $\nu_{\max}$  (ATR): 700s, 1010, 1251, 1433, 1542s, 1650vs, 2852, 2929  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.94-1.98 (m, 2H,  $\text{CH}_2$ ), 2.17 (t, 2H,  $J = 7.7$ ,  $\text{CH}_2$ ), 2.64 (t, 2H,  $J = 7.7$ ,  $\text{CH}_2$ ), 3.33 (s, 3H,  $\text{CH}_3$ ), 3.43 (m, 4H, 2( $\text{CH}_2$ )), 5.82 (s, 1H,  $\text{NH}$ ), 7.16-7.18 (m, 3H, 3( $\text{ArH}$ )), 7.25-7.72 (m, 2H, 2( $\text{ArH}$ )).  $^{13}\text{C}$  NMR (175 MHz,  $\text{CDCl}_3$ ):  $\delta$  27.1 ( $\text{CH}_2$ ), 35.1 ( $\text{CH}_2$ ), 35.8 ( $\text{CH}_2$ ), 39.1 ( $\text{OCH}_3$ ), 58.7 ( $\text{CH}_2$ ), 71.2( $\text{CH}_2$ ), 126.9 (2  $\text{ArC}$ ), 128.3 (3  $\text{ArC}$ ), 141.5, 172.7 ( $\text{C}=\text{O}$ ).  $m/z$  ( $\text{ES}^+$ ): 222.4 [ $\text{M}+\text{H}^+$ ], 244.8 [ $\text{M}+\text{H}^++\text{Na}$ ]. HRMS ( $\text{ES}^+$ ):  $\text{C}_{13}\text{H}_{20}\text{NO}_2$  requires 222.1489 [ $\text{M}+\text{H}^+$ ] found 222.1490 [ $\text{M}+\text{H}^+$ ].

### 1-(4-Phenylbutanoyl)piperidine



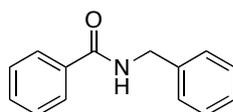
The general procedure for the preparation of amides was followed. Yield in the presence of boric acid: (0.56 g, 80 %), yield in the presence of *o*-iodophenylboronic acid: (0.008 g, 1 %), yield in the absence of catalyst: (0.17 g, 24 %) as a colourless oil.  $\nu_{\max}$  (ATR): 698s, 1225, 1251, 1433s, 1634vs, 2852, 2929  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.5-1.7 (m, 6H, 3( $\text{CH}_2$ )), 1.9-2.1 (m, 2H,  $\text{CH}_2$ ), 2.32 (t, 2H,  $J = 7.7$ ,  $\text{CH}_2$ ), 2.68 (t, 2H,  $J = 7.7$ ,  $\text{CH}_2$ ), 3.31 (t, 2H,  $J = 0.7$ ,  $\text{CH}_2$ ), 3.54 (t, 2H,  $J = 0.7$ ,  $\text{CH}_2$ ), 7.1-7.4 (m, 5H,  $\text{ArH}$ ).  $^{13}\text{C}$  NMR (175 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.5 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ), 26.8 ( $\text{CH}_2$ ), 32.5 ( $\text{CH}_2$ ), 36.4 ( $\text{CH}_2$ ), 42.6 ( $\text{CH}_2$ ), 46.6 ( $\text{CH}_2$ ), 125.8 (2  $\text{ArC}$ ), 128.5 (3  $\text{ArC}$ ), 141.8, 170.9 ( $\text{C}=\text{O}$ ).  $m/z$  ( $\text{ES}^+$ ): 232.3 [ $\text{M}+\text{H}^+$ ]. Spectroscopic and analytical details were consistent with those reported in the literature.<sup>96</sup>

#### 4-Phenylbutyranilide



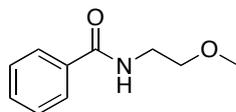
The general procedure for the preparation of amides was followed. Yield in the presence of boric acid: (0.54 g, 74 %), yield in the presence of *o*-iodophenylboronic acid: (0.12, 16 %), yield in the absence of catalyst: (0.030 g, 4 %) as a white solid. M.p. 84-86 °C.  $\nu_{\max}$  (ATR): 731, 1443, 1529s, 1660s, 3314  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.08 (m, 2H,  $\text{ArCH}_2$ ), 2.35 (t, 2H,  $J = 7.2$ ,  $\text{CH}_2$ ), 2.73 (t, 2H,  $J = 7.6$ ,  $\text{CH}_2$ ), 7.03 (s (br), 1H,  $\text{NH}$ ), 7.10 (t, 1H,  $J = 7.2$ ,  $\text{ArH}$ ), 7.20-7.22 (m, 3H,  $\text{ArH}$ ), 7.28-7.33 (m, 4H,  $\text{ArH}$ ), 7.49 (d, 2H,  $J = 7.6$ ,  $\text{ArH}$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  26.8 ( $\text{CH}_2$ ), 35.0 ( $\text{CH}_2$ ), 36.8 ( $\text{CH}_2$ ), 119.7 ( $\text{ArC}$ ), 124.2 ( $\text{ArC}$ ), 126.1 ( $\text{ArC}$ ), 128.4 ( $\text{ArC}$ ), 128.5 ( $\text{ArC}$ ), 129.0 ( $\text{ArC}$ ), 138.0 ( $\text{ArC}$ ), 141.3 ( $\text{ArC}$ ), 171.0 ( $\text{C=O}$ ).  $m/z$  ( $\text{ES}^+$ ): 240.2 [ $\text{M}+\text{H}^+$ ]. Spectroscopic details were the same as those reported in the literature.<sup>97</sup>

#### *N*-Benzylbenzamide



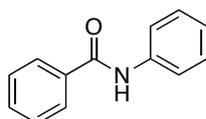
The general procedure for the preparation of amides was followed. Yield in the presence of boric acid: (0.56 g, 86 %), yield in the presence of *o*-iodophenylboronic acid: (0.011 g, 2 %), yield in the absence of catalyst: (0.092 g, 14 %) as a white solid. M.p. 86-87 °C.  $\nu_{\max}$  (ATR): 692s, 1416, 1545s, 1635s, 3080, 3296  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.56 (d, 2H,  $J = 6.0$ ,  $\text{CH}_2$ ), 6.30 (s (br), 1H,  $\text{NH}$ ), 7.19-7.42 (m, 8H,  $\text{ArH}$ ), 7.67 (d, 2H,  $J = 6.0$ ,  $\text{ArH}$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  44.2 ( $\text{CH}_2$ ), 126.9 ( $\text{ArC}$ ), 127.7 ( $\text{ArC}$ ), 127.9 ( $\text{ArC}$ ), 128.6 ( $\text{ArC}$ ), 128.8 ( $\text{ArC}$ ), 131.6 ( $\text{ArC}$ ), 134.4 ( $\text{ArC}$ ), 138.1 ( $\text{ArC}$ ), 167.3 ( $\text{CONH}$ ).  $m/z$  ( $\text{ES}^+$ ): 212.2 [ $\text{M}+\text{H}^+$ ]. Spectroscopic details were the same as those reported in the literature.<sup>29</sup>

### ***N*-(2-Methoxyethyl)benzamide**



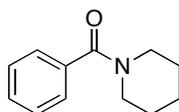
The general procedure for the preparation of amides was followed. Yield in the presence of boric acid: (0.13 g, 24 %), yield in the presence of *o*-iodophenylboronic acid: (0.027 g, 5 %), yield in the absence of catalyst: (0.028 g, 5 %) as a pale yellow oil.  $\nu_{\max}$  (ATR): 694vs, 1018, 1115, 1299, 1533vs, 1638vs, 2927, 3309  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.39 (s, 3H,  $\text{CH}_3$ ), 3.56 (t, 2H,  $J = 5.6$ ,  $\text{CH}_2$ ), 3.65 (dd, 2H,  $J = 5.6$  and 4.9,  $\text{CH}_2$ ), 6.54 (s, 1H,  $\text{NH}$ ), 7.43 (t, 2H,  $J = 7.7$ , 2(ArH)), 7.49 (t, 1H,  $J = 7.7$ , ArH), 7.79 (d, 2H,  $J = 7$ , 2(ArH)).  $^{13}\text{C}$  NMR (175MHz,  $\text{CDCl}_3$ ):  $\delta$  39.7 ( $\text{CH}_2$ ), 59.8 ( $\text{OCH}_3$ ), 71.2 ( $\text{CH}_2$ ), 126.9 (2 ArC), 128.5 (2 ArC), 131.4 (ArC), 134.5, 167.4 ( $\text{C}=\text{O}$ ).  $m/z$  ( $\text{ES}^+$ ): 180 [ $\text{M}+\text{H}^+$ ]. HRMS ( $\text{ES}^+$ ):  $\text{C}_{10}\text{H}_{14}\text{NO}_2$  requires 180.1019 [ $\text{M}+\text{H}^+$ ] found 180.1020 [ $\text{M}+\text{H}^+$ ].

### **Benzanilide**



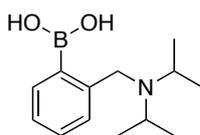
The general procedure for the preparation of amides was followed. Yield in the presence of boric acid: (0.21 g, 35%), yield in the presence of *o*-iodophenylboronic acid: (0.12 g, 20%) as a white solid. M.p. 123-124  $^{\circ}\text{C}$ .  $\nu_{\max}$  (ATR): 689s, 746s, 1080, 1318, 1516, 1642s, 3336  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.14–7.19 (m, 1H, ArH), 7.35-7.40 (m, 2H, ArH), 7.46-7.52 (m, 2H, ArH), 7.54-7.58 (m, 1H, ArH), 7.64 (dd, 2H,  $J = 8.4$  and 1.2, ArH), 7.82 (s (br), 1H,  $\text{NH}$ ), 7.86-7.89 (m, 2H, ArH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  120.2 (ArC), 124.6 (ArC), 127.0 (ArC), 128.8 (ArC), 129.1 (ArC), 131.9 (ArC), 135.1 (ArC), 137.9 (ArC), 165.7 ( $\text{C}=\text{O}$ ).  $m/z$  (EI): 198.9 [ $\text{M}^+$ ]. Spectroscopic details were the same as those reported in the literature.<sup>97</sup>

## ***N*-Benzoylpiperidine**



The general procedure for the preparation of amides was followed. Yield in the presence of boric acid: (0.28 g, 49%), yield in the presence of *o*-iodophenylboronic acid: (0.058 g, 10%) as a white solid. M.p. 48-50 °C.  $\nu_{\max}$  (ATR): 786, 1260, 1275, 1434, 1623, 2859, 2947  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: (700 MHz,  $\text{CDCl}_3$ )  $\delta$  1.50-1.67 (m, 6H, 3( $\text{CH}_2$ )), 3.34-3.71 (d (br), 4H, 2( $\text{NCH}_2$ )), 7.36–7.19 (m, 5H,  $\text{ArH}$ )  $^{13}\text{C}$  NMR (175 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.6 ( $\text{CH}_2$ ), 25.6 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 43.1 ( $\text{CH}_2$ ), 48.8 ( $\text{CH}_2$ ), 126.8 ( $\text{ArCH}$ ), 128.4 ( $\text{ArCH}$ ), 129.3 ( $\text{ArCH}$ ), 136.5 ( $\text{ArC}$ ), 170.3 ( $\text{C=O}$ ).  $m/z$  ( $\text{ES}^+$ ): 190.0 [ $\text{M}+\text{H}^+$ ], 253 [ $\text{M}^++\text{Na}+\text{MeCN}$ ]. Spectroscopic details were the same as those reported in the literature.<sup>98</sup>

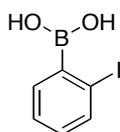
## ***N,N*-Diisopropylbenzylamine-2-boronic acid**



To THF (20 mL) and 3 Å activated molecular sieves (4.0 g) was added 2-formylbenzeneboronic acid (0.91 g, 6 mmol) and diisopropylamine (0.85 mL, 6 mmol). After stirring for 24 h sodium triacetoxyborohydride (8.0 g, 36 mmol) was added, the reaction was then stirred for a further 24 h. Then 5% (w/v) HCl (10 mL) was added slowly and after 20 minutes the resulting suspension was filtered through a sinter and washed with water (50 mL). The filtrate THF was removed in *vacuo* and the aqueous mixture was then neutralised by slow addition of sat.  $\text{NaHCO}_3$  (aq). The filtrate mixture was allowed to stand for 72 h, during which time the product crystallised. The product was extracted into DCM (50 mL) and washed with brine (50 mL), the organic layer was dried ( $\text{MgSO}_4$ ) and

solvents evaporated to afford a white solid. This was dissolved in 5% (w/v) HCl (5 mL) and washed with DCM (5 mL). To the aqueous phase was added 20% (w/v) NaOH (2 mL) and the precipitated product extracted with DCM (5 × 20 mL). The solvent was removed in *vacuo* and the resulting white solid dried in *vacuo* to give (0.63 g, 45%). M.p. 150-152 °C.  $\nu_{\max}$  (ATR): 572, 1376, 1974, 2190, 2372  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.12 (d, 12H,  $J = 6.8$ ,  $\text{CH}_3$ ), 3.13 (septet, 2H,  $J = 6.8$ , 2(CH)), 3.84 (s, 2H,  $\text{CH}_2$ ), 7.22-7.26 (m, 1H, ArH), 7.30-7.38 (m, 2H, ArH), 7.96-7.99 (m, 1H, ArH).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  19.7, 47.5, 51.9 ( $\text{CH}_2$ ), 127.1 (ArC), 130.3 (ArC), 130.8 (ArC), 136.6 (ArC), 142.2 (ArC).  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  29.67.  $m/z$  ( $\text{ES}^+$ ): 236 [ $\text{M}+\text{H}^+$ ]. CHN analysis, calculated: C 66.41, H 9.43, N 5.96, found: C 66.28, H 9.41, N 5.96. Spectroscopic details were consistent with those previously reported.<sup>61</sup>

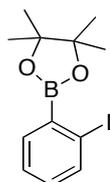
### ***o*-Iodophenylboronic acid**



To a solution of 1,2-diiodobenzene (0.65 mL, 5 mmol) in a mixture (1:1) of THF and  $\text{Et}_2\text{O}$  (120 mL) at -78 °C was added *isopropylmagnesium chloride* (2 M in THF, 2.5 mL, 5 mmol) dropwise. The mixture was stirred for 2 h, and then triisopropyl borate (2.3 mL, 10 mmol) was added. The solution was slowly warmed up to room temperature and stirred overnight. 10% (w/v) HCl (150 mL) was added and the mixture stirred for 30 minutes at room temperature. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 × 150 mL), the organic phase dried ( $\text{MgSO}_4$ ) and solvents evaporated to afford a light brown solid, which was purified by silica gel chromatography (hexane:EtOAc, 4:1) to yield a white solid (0.47 g, 38 %). M.p. 155-156 °C.  $\nu_{\max}$  (ATR): 748s, 997s, 1350s, 1580, 3226  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.22 (s, 2H,  $\text{B}(\text{OH})_2$ ), 7.14 (td, 1H,  $J = 7.6$  and 1.8 Hz, ArH), 7.41 (td, 1H,  $J = 7.6$  and 1.2 Hz, ArH), 7.86 (dd, 2H,  $J = 7.6$  and 1.2, ArH).  $^{13}\text{C}$  NMR: (175 MHz,  $\text{CDCl}_3$ ):

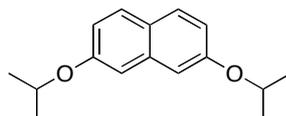
$\delta$  100.7 (ArC), 128.0 (ArC), 132.5 (ArC), 137.0 (ArC), 139.8 (ArC).  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.16. Spectroscopic details were consistent with those in the literature (see reference supporting information).<sup>48</sup>

### 2-(2-Iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To a stirring solution of *o*-iodophenylboronic acid (20 mg, 0.081 mmol) in DCM (20 mL) was added pinacol (9.57 mg, 0.081 mmol). After 1 h the reaction mixture was dried ( $\text{MgSO}_4$ ) and DCM evaporated to give the title compound as a pale yellow oil (23 mg, 88%).  $\nu_{\text{max}}$  (ATR): 756, 850, 1080, 1100, 1215, 1301, 1352, 1380, 1400, 1470, 1586, 2931, 3436  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.38 (s, 12H,  $\text{CH}_3$ ), 7.07 (ddd, 1H,  $J = 8$  and 8 and 2, ArH), 7.31 (ddd, 1H,  $J = 7$  and 7 and 1, ArH), 7.52 (dd, 1H,  $J = 7$  and 2, ArH) 7.83, (dd, 1H,  $J = 7$  and 1, ArH).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  24.8 ( $\text{CH}_3$ ), 84.5 ( $\text{C}(\text{CH}_3)_2$ ), 100.9 (ArC), 127.0 (ArC), 131.7 (ArC), 136.0 (ArC), 139.8 (ArC).  $m/z$  (EI) 330 [ $\text{M}^+$ ]. Spectroscopic details were consistent with those in the literature.<sup>99</sup>

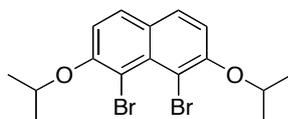
### 2,7-Diisopropoxynaphthalene



A solution of 2,7-dihydroxynaphthalene (5 g, 31 mmol), potassium carbonate (12.9 g, 93.6 mmol), tetrabutylammonium iodide (1.15 g, 3.12 mmol) and DMF (75 mL) under argon was stirred for 2 h. 2-Bromopropane (17.6 mL, 0.187 mol) was added and the solution heated at 70  $^\circ\text{C}$  for 9 h. After cooling to room

temperature, Et<sub>2</sub>O (75 mL) was added followed by washing with 5% (w/v) NaOH solution (75 mL), water (5 × 75 mL), drying (MgSO<sub>4</sub>) and evaporation. The resulting crude product was purified by silica gel chromatography (petroleum ether:ethyl acetate, 50:1 as the eluent) to give a pale green oil that solidified on cooling and was recrystallised from petroleum ether to give the desired product as a white solid (3.9 g, 51%): M.p. 59-60 °C;  $\nu_{\max}$  (ATR): 827s, 1112s, 1207s, 1330, 1388, 1507, 1627 cm<sup>-1</sup>; <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>):  $\delta$  1.41 and 1.43 (s, each 6H, 2(CH<sub>3</sub>)), 4.69 (sept, 2H, *J* = 6.3, 2(CH)), 6.98 (dd, 2H, *J* = 8.5 and 2.1, 2(ArH)), 7.05 (d, 2H, *J* = 2.3, 2(ArH)) and 7.65 (d, 2H, *J* = 8.5, 2(ArH)); <sup>13</sup>C NMR (175 MHz, CDCl<sub>3</sub>)  $\delta$  22.3 (CH<sub>3</sub>), 70.0 (OCH(CH<sub>3</sub>)<sub>2</sub>), 108.0, 117.3 and 129.3 (ArCH), 124.4, 136.2 and 156.5 (ArC); *m/z* (ES<sup>+</sup>): 245 [M+H<sup>+</sup>]. CHN analysis: C<sub>16</sub>H<sub>20</sub>O<sub>2</sub> requires C, 78.8; H, 8.3%. Found C, 79.2; H, 8.3%. Spectroscopic details were consistent with those in the literature.<sup>62</sup>

### 1,8-Dibromo-2,7-diisopropoxynaphthalene



A solution of NBS (4.96 g, 27.9 mmol) in CHCl<sub>3</sub> (68 mL) under argon was treated with pyridine (2.21 g, 27.9 mmol). The mixture was heated at reflux for 1 h (all NBS had dissolved and the solution turned from colourless to orange). A solution of 2,7-diisopropoxynaphthalene (1.70 g, 6.97 mmol) in CHCl<sub>3</sub> (~5 mL) was added dropwise, followed by heating at reflux for 9 h. After cooling to room temperature and evaporation, the crude reaction mixture was purified by silica gel chromatography (petroleum ether:ethyl acetate, 9:1 as eluent) to provide a solid which was recrystallised from DCM – petroleum ether to yield the product (1.09 g, 40%) as an off white solid: M.p. 129-131 °C;  $\nu_{\max}$  (ATR): 615, 828, 946s, 1101s, 1257s, 1371, 1380, 1505, 1607 cm<sup>-1</sup>; <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>):  $\delta$  1.43 and 1.44 (s, each 6H, 2(CH<sub>3</sub>)), 4.68 (sept, 2H, *J* = 6.3, 2(CH)), 7.12 and 7.67 (d, each 2H, *J* = 8.4, 2(ArH)); <sup>13</sup>C NMR (175 MHz, CDCl<sub>3</sub>):  $\delta$  22.6 (CH<sub>3</sub>), 74.0 (OCH(CH<sub>3</sub>)<sub>2</sub>), 109.3, 128.1 and 155.6 (ArC), 116.0 and 129.7 (ArCH); *m/z*

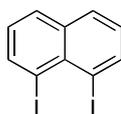
(ES<sup>+</sup>): 403 [M+H<sup>+</sup>]. CHN analysis: C<sub>16</sub>H<sub>18</sub>Br<sub>2</sub>O<sub>2</sub> requires C, 47.8; H, 4.5%. Found C, 48.3; H 4.6%. Spectroscopic details were consistent with those in the literature.<sup>62</sup>

### 1-Bromo-2,7-diisopropoxynaphthalene



*n*-BuLi (0.16 mL, 0.44 mmol, 2.5 M in THF) was added dropwise to a stirred solution of 1,8-dibromo-2,7-diisopropoxynaphthalene (0.15 g, 0.37 mmol) in THF (10 mL) under argon at -78 °C. The mixture was allowed to stir for 2 h. Trimethylborate (0.083 mL, 0.74 mmol) was then added quickly and the reaction mixture slowly warmed to room temperature and left for 48 h. 20% (w/v) HCl (5 mL) was added and the mixture left to stir for 30 minutes. The products were extracted with EtOAc (3 × 10 mL) and washed with brine (3 × 10 mL), dried (MgSO<sub>4</sub>) and organics evaporated in *vacuo*. The resulting crude product was purified by silica gel chromatography (petroleum ether:ethyl acetate, 6:1) to provide a yellow oil (0.13 g, 98 %).  $\nu_{\max}$  (ATR): 655, 827, 950, 981s, 1106vs, 1212s, 1260, 1382, 1506s, 1624s, 2976 cm<sup>-1</sup>; <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>):  $\delta$  1.43 (m, 12H, 4(CH<sub>3</sub>)), 4.67 (sept, 1H, *J* = 7.0, CH), 4.78 (sept, 1H, *J* = 7, CH), 7.02 (dd, 1H, *J* = 7, ArH) 7.07 (d, 1H, *J* = 7, ArH), 7.55 (d, 1H, *J* = 7, ArH), 7.65 (m, 2H, 2(ArH)); <sup>13</sup>C NMR (175 MHz, CDCl<sub>3</sub>):  $\delta$  21.9 (CH<sub>3</sub>), 22.4 (CH<sub>3</sub>), 69.9 (OCH(CH<sub>3</sub>)<sub>2</sub>), 73.3 (OCH(CH<sub>3</sub>)<sub>2</sub>), 107.4, 110.3, 114.9, 118.2, 125.3, 128.2, 129.6 and 134.7 (ArC), 153.1 and 157.4 (ArCH); *m/z* (ES<sup>+</sup>): 323.2.

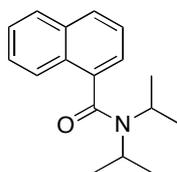
### Diiodonaphthalene



1,8-diaminonaphthalene (recrystallised from hexane) (2 g, 12.6 mmol) was suspended in 25 mL of aqueous 6.9 M H<sub>2</sub>SO<sub>4</sub> and cooled to -20 °C (ice/ethanol bath). A solution of NaNO<sub>2</sub> (2.62 g, 37.9 mmol) in water (10 mL) was added dropwise while the temperature was maintained at -15 to -20 °C. When the addition was complete a solution of KI (12.8 g) in water (10 mL) was added dropwise at -15 to -20 °C. The resulting mixture was heated to 80 °C for 1 hour then cooled to room temperature and made alkaline by the addition of solid NaOH. The mixture was filtered and the black solid residue was extracted with Et<sub>2</sub>O in a Soxhlet apparatus overnight. The extract was successively washed with 20 mL 20% (w/v) HCl solution, sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and 20% (w/v) NaOH solution. Drying (MgSO<sub>4</sub>) and concentrating in *vacuo* afforded the desired compound as a light brown solid, which was recrystallised from hexane (1 g, 21%). M.p. 110-112 °C.  $\nu_{\text{max}}$  (ATR): 514, 648, 736, 802, 946, 1130, 1524, 1810, 2594 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.08 (t, 2H, *J* = 8.0, ArH), 7.84 (dd, 2H, *J* = 1.1 and 8.0, ArH), 8.42 (dd, 2H, *J* = 1.1 and 7.4, ArH). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  96.0 (ArC), 126.9 (ArC), 131.0 (ArC), 132.2 (ArC), 135.8 (ArC), 144.1 (ArC). *m/z* (ES<sup>-</sup>): 380.7 (M<sup>+</sup>), 126.9 (I<sup>-</sup>). All analytical and spectroscopic properties were consistent with those reported in the literature.<sup>64</sup>

100

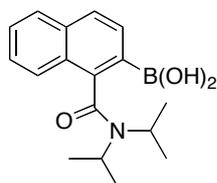
### ***N,N*-Diisopropyl-1-naphthamide**



Diisopropylamine (11.2 mL, 80 mmol) was added dropwise to a stirred solution of naphthoyl chloride (3 mL, 20 mmol) in dry DCM (100 mL) under argon at 0 °C. After 4 h the reaction mixture was washed with 5% (w/v) HCl (aq) (3 × 50 mL), dried (MgSO<sub>4</sub>) and concentrated to yield the amide as a white solid (4.51 g, 88%). M.p. 185-187 °C;  $\nu_{\text{max}}$  (ATR): 784s, 1045, 1120, 1206, 1332, 1373, 1443, 1620s, 2964 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.04 (d, 3H, *J* = 10 CH<sub>3</sub>), 1.09

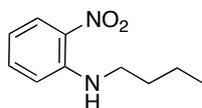
(d, 3H,  $J = 5$ ,  $CH_3$ ), 1.65 (d, 3H,  $J = 5$ ,  $CH_3$ ), 1.72 (d, 3H,  $J = 5$ ,  $CH_3$ ), 3.62 (sept, 2H,  $J = 10$ , 2( $CH$ )) 7.33 (dd, 1H,  $J = 10$  and 1.2,  $ArH$ ), 7.51 (m, 3H,  $ArH$ ), 7.85 (m, 3H,  $ArH$ );  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  20.9, 20.9, 21.0, 21.1 ( $CH_3$ ), 46.2, 51.3 ( $CH$ ), 122.3, 125.2, 125.5, 126.5, 126.9, 128.4, 128.5, 129.8, 133.8, 136.9 ( $ArC$ ), 170.3 ( $C=O$ );  $m/z$  ( $ES^+$ ): 256.3 [ $M+H^+$ ]. HRMS ( $ES^+$ ):  $C_{17}H_{21}NO$  requires 256.1701 [ $M+H^+$ ] found 256.1719 [ $M+H^+$ ].

### ***N,N*-Diisopropyl-1-naphthamide-2-boronic acid**



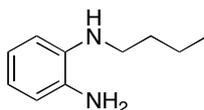
To a stirred solution of *N,N*-diisopropyl-1-naphthamide (0.8 g, 3.12 mmol) and TMEDA (0.7 mL, 4.7 mmol) in dry THF (60 mL) was added *s*-BuLi (3.4 mL, 1.4 M, 4.7 mmol) dropwise at  $-78$  °C. The reaction mixture was allowed to stir at this temperature for 6 h and then  $B(OMe)_3$  (0.69 mL, 6.26 mmol) was added in one portion. The mixture was allowed to warm to room temperature overnight. Saturated  $NH_4Cl$  (aq) (6 mL) and  $H_2O$  (15 mL) were added and the mixture acidified to pH 6 with 20% (w/v) HCl (aq). THF was removed by evaporation and the residue was extracted with DCM (3  $\times$  50 mL) the organic extracts were combined, washed with brine (100 mL), dried ( $MgSO_4$ ) and evaporated to afford a white solid (0.78 g, 84%). M.p. 281-282 °C;  $\nu_{max}$  (ATR): 611, 745vs, 913vs, 1371, 1593s, 2853  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  1.00 (dd, 6H,  $J = 6.7$  and 3.4, 2( $CH_3$ )), 1.69 (d, 3H,  $J = 6.8$ ,  $CH_3$ ), 1.75 (d, 3H,  $J = 6.8$ ,  $CH_3$ ), 3.39-3.44 (m, 1H,  $CH$ ), 3.60-3.65 (m, 1H,  $CH$ ) 5.82 (s (br), 2H,  $B(OH)_2$ ) 7.50-7.55 (m, 2H,  $ArH$ ), 7.81-7.91 (m, 4H,  $ArH$ );  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  20.2, 20.6, 20.7, 20.8 ( $CH_3$ ), 46.7, 51.9 ( $CH$ ), 125.0, 126.9, 127.5, 127.8, 128.5, 128.9, 130.9, 134.6, 141.9 ( $ArC$ ), 173.3 ( $C=O$ );  $^{11}B$  NMR (128 MHz,  $CDCl_3$ )  $\delta$  29.47;  $m/z$  HRMS (ASAP):  $C_{17}H_{22}BNO_3$  requires 300.1766 [ $M+H^+$ ] found 300.1771 [ $M+H^+$ ].

## 1-Butylamine-2-nitrobenzene



2-Bromonitrobenzene (5 g, 24.75 mol) and *n*-butylamine (9 mL, 91.5 mmol) were dissolved in DMSO (25 mL) and heated to 80 °C and stirred overnight. After cooling to room temperature water was added (75 mL). The resulting solution was then extracted with DCM (3 × 50 mL). The combined extracts were then washed with brine (3 × 50 mL) and dried over MgSO<sub>4</sub>. Filtration and evaporation gave the title compound as a yellow oil (4.49 g, 94%), which was used for the following step without further purification.  $\nu_{\max}$  (ATR): 738vs, 862, 1037, 1155s, 1258s, 1353, 1418, 1509vs, 1572, 1617s, 2932, 3379 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.97 (t, 3H,  $J = 8.0$  CH<sub>3</sub>), 1.48 (sextet, 2H,  $J = 8.0$ , CH<sub>2</sub>), 1.72 (quintet, 2H,  $J = 8.0$ , CH<sub>2</sub>), 3.29 (m, 2H, -NHCH<sub>2</sub>), 6.62 (m, 1H, ArH) 6.84 (dd, 1H,  $J = 8.0$  and 0.8, ArH), 7.42 (m, 1H, ArH), 8.05 (s (br), 1H, NH) 8.16 (dd, 1H,  $J = 8.6$  and 1.6, ArH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  13.7 (CH<sub>3</sub>), 20.2, 30.9, 42.7 (CH<sub>2</sub>), 113.7, 114.9, 126.9, 131.8, 136.1, 145.6 (ArC);  $m/z$  (ES<sup>+</sup>): 195.2 [M+H<sup>+</sup>]. HRMS (ES<sup>+</sup>): C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> requires 195.1134 [M+H<sup>+</sup>] found 195.1145 [M+H<sup>+</sup>]. All analytical and spectroscopic properties were consistent with those reported in the literature.<sup>67</sup>

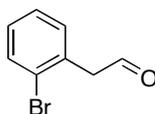
## *N*-*n*-Butyl-1,2-phenylenediamine



1-*N*-butylamine-2-nitrobenzene (2 g, 10 mmol) and Pd/C catalyst (0.2 g, 10%) were placed in methanol (25 mL) and stirred under hydrogen for 36 h. The resulting solution was filtered through Celite and evaporation of the solvent gave the diamine as a viscous brown liquid (1.13 g, 70%), which was used for the

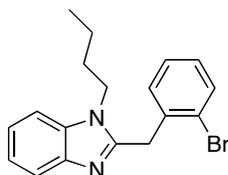
following step without further purification.  $\nu_{\max}$  (ATR): 733vs, 1144, 1272, 1453, 1507s, 1600, 2956, 3317  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.98 (t, 3H,  $J = 7.4$   $\text{CH}_3$ ), 1.48 (hexet, 2H,  $J = 7.4$ ,  $\text{CH}_2$ ), 1.67 (quintet, 2H,  $J = 7.4$ ,  $\text{CH}_2$ ), 3.11 (d, 2H,  $J = 7.2$ ,  $-\text{NHCH}_2$ ), 3.30 (s (br), 3H,  $\text{NH}$ ), 6.66-6.68 (m, 2H,  $\text{ArH}$ ), 6.71-6.73 (m, 1H,  $\text{ArH}$ ), 6.83 (td, 1H,  $J = 7.4$  and 1.6,  $\text{ArH}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.2 ( $\text{CH}_3$ ), 20.7, 32.1, 44.1 ( $\text{CH}_2$ ), 111.8, 116.7, 118.5, 121.0, 134.2, 138.4 ( $\text{ArC}$ );  $m/z$  ( $\text{ES}^+$ ): 165.2 [ $\text{M}+\text{H}^+$ ]. HRMS ( $\text{ES}^+$ ):  $\text{C}_{10}\text{H}_{16}\text{N}_2$  requires 165.1392 [ $\text{M}+\text{H}^+$ ] found 165.1396 [ $\text{M}+\text{H}^+$ ]. All analytical and spectroscopic properties were consistent with those reported in the literature.<sup>67</sup>

### 2-(2-Bromophenyl)acetaldehyde



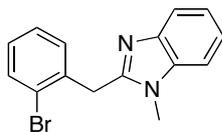
2-bromophenethyl alcohol (0.8 mL, 5.8 mmol) was added to dry DCM (25 mL) under argon and Dess-Martin periodinane (3.47 g, 8.2 mmol) in DCM (20 mL) was added dropwise. After 4 h the reaction mixture was added to 1 M NaOH (55 mL) and left to stir for 30 minutes.  $\text{Et}_2\text{O}$  was added and the layers separated. The aqueous layer was washed with  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL) and the organic extracts combined, dried ( $\text{MgSO}_4$ ) and evaporated to afford the aldehyde as a colourless oil (0.87 g, 75%).  $\nu_{\max}$  (ATR): 749s, 1027s, 1132, 1439, 1471, 1723s, 2828  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.87 (d, 2H,  $J = 1.75$   $\text{CH}_2$ ), 7.19 (td, 1H,  $J = 7.7$  and 1.7,  $\text{ArH}$ ), 7.24-7.27 (m, 1H,  $\text{ArH}$ ), 7.33 (td, 1H,  $J = 7.5$  and 1.2,  $\text{ArH}$ ), 7.63 (dd, 1H,  $J = 8.0$  and 1.1,  $\text{ArH}$ ) 9.77 (t, 1H,  $J = 1.75$ ,  $\text{CHO}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  50.8 ( $\text{CH}_2$ ), 125.2, 128.1, 129.5, 131.9, 132.9, 133.2 ( $\text{ArC}$ ), 198.5 ( $\text{CHO}$ );  $m/z$  ( $\text{ES}^-$ ): 220.8 [ $\text{M}-\text{H}^++\text{Na}$  for  $^{79}\text{Br}$ ] and 222.5 [ $\text{M}-\text{H}^++\text{Na}$  for  $^{81}\text{Br}$ ]. HRMS ( $\text{ES}^-$ ):  $\text{C}_8\text{H}_7\text{OBr}$  requires 196.9602 [ $\text{M}-\text{H}^+$ ] and 198.9580 [ $\text{M}-\text{H}^+$ ] found 196.9612 [ $\text{M}+\text{H}^+$ ] and 198.9597 [ $\text{M}-\text{H}^+$ ].

## 2-(2-Bromobenzyl)*N*-*n*-butyl-benzimidazole



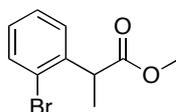
A solution of aldehyde 2-(2-bromophenyl)acetaldehyde (0.5 g, 2.51 mmol) in DMF (10 mL) and H<sub>2</sub>O (0.32 mL) was treated with amine *N*-*n*-butyl-1,2-phenylenediamine (0.41 g, 2.51 mmol) and Oxone™ (0.93 g, 1.51 mmol). After stirring at room temperature overnight the reaction was carefully quenched by the addition of an aqueous solution of K<sub>2</sub>CO<sub>3</sub> (0.04 M, 31 mL). The resulting suspension was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts dried (MgSO<sub>4</sub>) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate:hexane, 1:1) to provide a viscous pale brown oil (0.13 g, 15%).  $\nu_{\max}$  (ATR): 741vs, 913vs, 1457, 1970, 2032, 2954 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  0.87 (t, 3H, *J* = 7.4, CH<sub>3</sub>), 1.33 (hextet, 2H, *J* = 7.5, CH<sub>2</sub>), 1.57 (quintet, 2H, *J* = 7.7, CH<sub>2</sub>), 4.00 (t, 2H, *J* = 7.7, -NCH<sub>2</sub>), 4.45 (s, 2H, CH<sub>2</sub>) 7.09-7.13 (m, 2H, ArH), 7.17-7.20 (m, 1H, ArH), 7.24-7.27 (m, 2H, ArH), 7.31-7.32 (m, 1H, ArH), 7.59-7.60 (m, 1H, ArH), 7.76-7.78 (m, 1H, ArH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  13.9 (CH<sub>3</sub>), 20.4, 32.0, 34.3, 44.1 (CH<sub>2</sub>), 109.8, 119.9, 122.1, 122.6, 124.2, 128.1, 128.9, 130.7, 133.0, 135.6, 136.3, 142.9, 152.5 (ArC); *m/z* (ES<sup>+</sup>): 343.1 [M+H<sup>+</sup> for <sup>79</sup>Br], 345.2 [M+H<sup>+</sup> for <sup>81</sup>Br]; HRMS: C<sub>18</sub>H<sub>19</sub>BrN<sub>2</sub> requires 343.0810 [M+H<sup>+</sup>] and 344.0711 [M+H<sup>+</sup>], found 343.0804 and 345.0788.

## 2-(2-Bromobenzyl)*N*-*n*-methyl-benzimidazole



2-Bromophenylacetic acid (5 g, 23.25 mmol) and N-methyl-benzene-1,2-diamine (2.64 mL, 23.25 mmol) were mixed into polyphosphoric acid (15 g) and vigorously stirred at 180 °C for 6 h. This resulted in a black solution, which was poured into ice-water (200 mL) whilst hot. The resulting water-tar mixture was adjusted to alkaline pH by addition of dilute ammonium hydroxide and further ice. The aqueous phase was then extracted with DCM (2 × 200 mL), NaOH was added to the remaining aqueous phase which was then extracted again with DCM (2 × 200 mL). The combined organic extracts were washed with dilute ammonium hydroxide (10% v/v) and dried over MgSO<sub>4</sub>. The solvent was removed in *vacuo* to provide the product as a brown/grey solid, which was purified by silica gel chromatography (1:1 hexane:ethyl acetate). (1.32 g, 20%) M.p. 127-128 °C;  $\nu_{\max}$  (ATR): 739s, 1118, 1428, 1758, 1914, 1990, 2068, 2159, 2340, 3112, 3560 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  3.64 (s, 3H, CH<sub>3</sub>), 4.48 (s, 2H, CH<sub>2</sub>), 7.07-7.08 (m, 1H, ArH), 7.12-7.14 (m, 1H, ArH), 7.19-7.22 (m, 1H, ArH), 7.28-7.33 (m, 3H, ArH), 7.59-7.61 (m, 3H, ArH), 7.78-7.79 (m, 1H, ArH); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  30.1 (CH<sub>3</sub>), 33.9 (CH<sub>2</sub>), 109.2, 119.4, 122.3, 122.6, 123.9, 127.9, 128.7, 130.2, 132.9, 135.6, 135.7, 152.4 (ArC); *m/z* (ES<sup>+</sup>): 301.1 [M+H<sup>+</sup> for <sup>79</sup>Br], 303.2 [M+H<sup>+</sup> for <sup>81</sup>Br]; HRMS: C<sub>15</sub>H<sub>13</sub>BrN<sub>2</sub> requires 301.0339 [M+H<sup>+</sup>] found 301.0340.

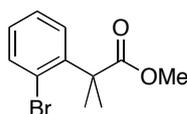
### Methyl 2-(2-bromophenyl)propanoate



A solution of 2-bromophenylacetic acid (1.87 g, 8.70 mmol), methyl iodide (2.17 mL, 34.80 mmol) and 18-crown-6 (0.57 g, 2.18 mmol) in THF 100 mL was treated with potassium *tert*-butoxide (3.90 g, 34.80 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with water (80 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. The crude product was purified by SiO<sub>2</sub> column chromatography (4:1 hexane:ethyl

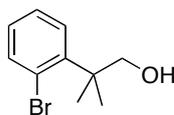
acetate) to afford a colourless oil. (1.24 g, 59%).  $\nu_{\max}$  (ATR): 669, 749s, 1020, 1081, 1167s, 1206s, 1433, 1732vs, 2982  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.48 (d, 3H,  $J = 7.1$ ,  $\text{CH}_3$ ), 3.68 (s, 3H,  $\text{CH}_3$ ), 4.23 (q, 1H,  $J = 7.1$  CH), 7.10-7.12 (m, 1H, ArH), 7.29-7.31 (m, 2H, ArH), 7.57 (d, 1H,  $J = 8.1$  ArH);  $^{13}\text{C}$  NMR (175 MHz,  $\text{CDCl}_3$ ):  $\delta$  17.8 ( $\text{CH}_3$ ), 44.6 (CH), 52.1 ( $\text{OCH}_3$ ), 124.3, 127.8, 128.3, 128.5 (ArC), 140.1 (CBr), 174.4 ( $\text{C}=\text{O}$ );  $m/z$  HRMS:  $\text{C}_{10}\text{H}_{11}\text{BrO}_2$  requires 243.0015 [ $\text{M}+\text{H}^+$ ] found 243.0020 [ $\text{M}+\text{H}^+$  for  $^{79}\text{Br}$ ], 244.9999 [ $\text{M}+\text{H}^+$  for  $^{81}\text{Br}$ ]. All spectroscopic and analytical data is consistent with that found in the literature.<sup>101</sup>

### Methyl 2-(2-bromophenyl)-2-methylpropanoate



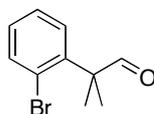
Methyl 2-(2-bromophenyl)propanoate (1.24 g, 5.14 mmol) and methyl iodide (0.96 mL, 15.42 mmol) were dissolved in dry THF (50 mL) under argon at room temperature. To this, NaH (60% dispersion in mineral oil) (0.33 g, 8.22 mmol) was added with caution. After 18 h the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3  $\times$  50 mL). The combined organic extracts were washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated. The crude product was purified by silica gel chromatography (6:1 hexane:ethyl acetate) to afford a colourless oil. (0.96 g, 73%).  $\nu_{\max}$  (ATR): 754, 1008, 1148, 1241s, 1428, 1464, 1735s, 1990, 2251, 2958  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.64 (s, 6H, 2( $\text{CH}_3$ )), 3.68 (s, 3H,  $\text{CH}_3$ ), 7.10-7.14 (td, 1H,  $J = 1.6$  and 7.7 ArH), 7.30-7.34 (td, 1H,  $J = 1.2$  and 7.7, ArH), 7.41-7.43 (dd, 1H,  $J = 1.6$  and 7.7, ArH), 7.55-7.57 (dd, 1H,  $J = 1.4$  and 7.8, ArH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  26.6 2( $\text{CH}_3$ ), 48.3 ( $\text{C}(\text{CH}_3)_2$ ), 52.7 ( $\text{OCH}_3$ ), 124.0, 127.4, 127.7, 128.5, 134.5 (ArC), 143.9 (CBr), 177.6 ( $\text{C}=\text{O}$ );  $m/z$  HRMS:  $\text{C}_{11}\text{H}_{13}\text{BrO}_2$  requires 257.0172 [ $\text{M}+\text{H}^+$ ] found 257.0178 [ $\text{M}+\text{H}^+$  for  $^{79}\text{Br}$ ], 259.0155 [ $\text{M}+\text{H}^+$  for  $^{81}\text{Br}$ ] All spectroscopic and analytical data is consistent with that found in the literature.<sup>68</sup>

## 2-(2-Bromophenyl)-2-methylpropanol



Methyl 2-(2-bromophenyl)-2-methylpropanoate (1 g, 3.89 mmol) was dissolved in dry DCM (100 mL) under argon at  $-78\text{ }^{\circ}\text{C}$  and Dibal-H (1 M in cyclohexane, 11.7 mL, 11.7 mmol) was added dropwise. After 1.5 h at this temperature MeOH (50 mL) was added slowly followed by brine (50 mL). The organic layer was separated and dried ( $\text{MgSO}_4$ ) and the solvent evaporated in *vacuo* to provide the crude product, which was purified by silica gel chromatography (2:1 hexane:ethyl acetate as eluent) to provide the alcohol as a colourless liquid (0.76 g, 85%)  $\nu_{\text{max}}$  (ATR): 640, 748, 1012s, 1036s, 1420, 1468, 1955, 2961, 3336  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.51 (s, 6H, 2( $\text{CH}_3$ )), 4.04 (s, 2H,  $\text{CH}_2$ ), 7.06-7.09 (m, 1H, ArH), 7.27-7.29 (m, 1H, ArH), 7.46-7.48 (dd, 1H,  $J = 1.7$  and 7.9, ArH), 7.59-7.61 (dd, 1H,  $J = 1.5$  and 7.9, ArH);  $^{13}\text{C}$  NMR (175 MHz,  $\text{CDCl}_3$ ):  $\delta$  25.2 ( $\text{CH}_3$ ), 42.3 ( $\text{C}(\text{CH}_3)_2$ ), 69.6 ( $\text{CH}_2$ ), 122.2, 127.3, 128.1, 130.1, 135.8, 143.6 (ArC);  $m/z$  ( $\text{ES}^+$ ): 190.3 [ $[\text{C}_6\text{H}_4\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}]^+ + \text{MeCN}$ ], 352.4 [ $2 \times [\text{C}_6\text{H}_4\text{Br}]^+ + \text{MeCN}$  for  $^{79}\text{Br}$ ] and 354.4 [ $2 \times [\text{C}_6\text{H}_4\text{Br}]^+ + \text{MeCN}$  for  $^{81}\text{Br}$ ]. All spectroscopic and analytical data is consistent with that found in the literature.<sup>68</sup>

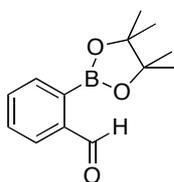
## 2-(2-Bromophenyl)-2-methylpropanal



2-(2-Bromophenyl)-2-methylpropanol (0.34 g, 1.45 mmol) was added to dry DCM (15 mL) under argon and Dess-Martin periodinane (1.00 g, 2.36 mmol) in DCM (15 mL) was added dropwise. After 2 h the reaction mixture was added to 1 M NaOH (30 mL) and left to stir for 30 minutes.  $\text{Et}_2\text{O}$  was added and the layers separated. The aqueous layer was washed with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL) and the organic extracts combined, dried ( $\text{MgSO}_4$ ) and evaporated to afford the aldehyde

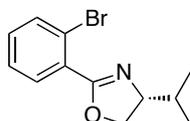
as a colourless oil (0.21 g, 64%).  $\nu_{\max}$  (ATR): 753s, 1020, 1464, 1720vs, 2974  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.52 (s, 6H, 2( $\text{CH}_3$ )), 7.17-7.20 (m, 1H,  $\text{ArH}$ ), 7.36-7.39 (m, 1H,  $\text{ArH}$ ), 7.42 (dd, 1H,  $J = 6.6$  and 1.4,  $\text{ArH}$ ), 7.60 (dd, 1H,  $J = 6.6$  and 1.1,  $\text{ArH}$ ) 9.79 (s, 1H,  $\text{CHO}$ );  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  23.2 2( $\text{CH}_3$ ), 51.8 ( $\text{C}(\text{CH}_3)_2$ ), 123.4, 127.8, 128.5, 129.1, 134.4, 142.3 ( $\text{ArC}$ ), 203.1 ( $\text{CHO}$ ). All spectroscopic and analytical data is consistent with that found in the literature.<sup>102</sup>

### (2-Formylphenyl)boronic acid pinacol ester



To a stirring solution of formylbenzene boronic acid (3.00 g, 20.01 mmol) in DCM (150 mL), in the presence of 3 Å molecular sieves, was added pinacol (2.6 g, 22.01 mmol). After 24 h the reaction mixture was filtered through Celite and DCM evaporated to give an oil, which was purified by silica gel column chromatography (ethyl acetate:hexane, 1:4 as eluent) to afford a pale yellow oil (3.74 g, 81%).  $\nu_{\max}$  (ATR): 768, 860, 1151, 1379, 1463, 1600, 1700, 2853  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.35 (s, 12H,  $\text{CH}_3$ ), 7.54-7.59 (m, 2H,  $\text{ArH}$ ), 7.86 (d, 1H,  $J = 6$ ,  $\text{ArH}$ ), 7.96 (d, 1H,  $J = 6$ ,  $\text{ArH}$ ) 10.54, (s, 1H,  $\text{CHO}$ ).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.8 4( $\text{CH}_3$ ), 84.4 2( $\text{C}(\text{CH}_3)_2$ ), 127.9 ( $\text{ArC}$ ), 130.7 ( $\text{ArC}$ ), 132.9 ( $\text{ArC}$ ), 135.4 ( $\text{ArC}$ ), 141.2 ( $\text{ArC}$ ), 194.6 ( $\text{CHO}$ ).  $m/z$  ( $\text{ES}^+$ ): 255.3 [ $\text{M}+\text{H}^++\text{Na}$ ]. Spectroscopic details were consistent with those in the literature.<sup>103</sup>

### (S)-2-(2-Bromophenyl)-4-isopropyl-2-oxazoline



A mixture of (L)-valinol (1.13 g, 10.99 mmol), 2-bromobenzonitrile (2.00 g, 10.99 mmol) and zinc (II) chloride (1 M in Et<sub>2</sub>O, 0.8 mL) in chlorobenzene (20 mL) was heated to reflux temperature for 3 days. The solvent was then evaporated and the residue purified by SiO<sub>2</sub> column chromatography (2:1 hexane:ethyl acetate) to provide the desired compound as a colourless oil (1.49 g, 50%).  $\nu_{\max}$  (ATR): 955s, 1024vs, 1089s, 1241, 1307, 1351, 1431, 1469, 1589, 1654s, 2957 cm<sup>-1</sup>; <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>):  $\delta$  0.98 (d, 3H, *J* = 6.7, CH<sub>3</sub>), 1.05 (d, 3H, *J* = 6.7, CH<sub>3</sub>), 1.89-1.92 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 4.15-4.19 (m, 2H, CH<sub>2</sub>), 4.41-4.45 (m, 1H, CH CH(CH<sub>3</sub>)<sub>2</sub>) 7.26 (td, 1H, *J* = 7.5 and 1.8, ArH), 7.33 (td, 1H, *J* = 7.5 and 1.2, ArH), 7.63 (dd, 1H, *J* = 7.9 and 1.1, ArH), 7.65 (dd, 1H, *J* = 7.6 and 1.8, ArH); <sup>13</sup>C NMR (175 MHz, CDCl<sub>3</sub>):  $\delta$  18.2, 18.8 (CH<sub>3</sub>), 32.7 (CHCH<sub>3</sub>), 70.3 (CHCHCH<sub>3</sub>), 72.9 (CH<sub>2</sub>), 121.8 (CBr), 127.0, 130.1, 131.3, 131.5, 133.7 (ArC), 162.8 (CNO); *m/z* (ES<sup>+</sup>): 268.2 [M+H<sup>+</sup>]. HRMS (ES<sup>+</sup>): C<sub>12</sub>H<sub>14</sub>NOBr requires 268.0322 [M+H<sup>+</sup>] found 268.0337 [M+H<sup>+</sup>]. All spectroscopic data is consistent with that found in the literature.<sup>104</sup>

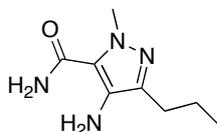
### (S)-2-(2-Bromophenyl)-4-methyl-2-oxazoline



A mixture of (DL)-2-amino-1-propanol (0.21 mL, 2.75 mmol), 2-bromobenzonitrile (0.5 g, 2.75 mmol) and zinc (II) chloride (1 M in Et<sub>2</sub>O, 0.15 mL) in chlorobenzene (10 mL) was heated to reflux temperature for 3 days. The solvent was then evaporated and the residue purified by SiO<sub>2</sub> column chromatography (3:1 hexane:ethyl acetate) to provide the desired compound as a colourless oil (0.09 g, 15%).  $\nu_{\max}$  (ATR): 730s, 763s, 960, 1022vs, 1077, 1241, 1303, 1345, 1430, 1472, 1588, 1650s, 2966 cm<sup>-1</sup>; <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>):  $\delta$  1.37 (d, 3H, *J* = 6.7, CH<sub>3</sub>), 3.99 (t, 1H, *J* = 8.0, CH), 4.41-4.42 (m, 1H, CH(CH<sub>3</sub>)), 4.52 (t, 1H, *J* = 8.0, CH), 7.26 (td, 1H, *J* = 8.0 and 1.8, ArH), 7.33 (td, 1H, *J* = 7.5 and 1.2, ArH), 7.62 (dd, 1H, *J* = 8.0 and 1.2, ArH), 7.66 (dd, 1H,

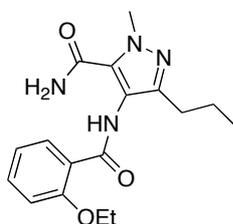
$J = 7.7$  and  $1.8$ ,  $ArH$ );  $^{13}C$  NMR (175 MHz,  $CDCl_3$ ):  $\delta$  21.4 ( $CH_3$ ), 62.4 ( $CHCH_3$ ), 74.2 ( $CH_2$ ), 121.8 ( $CBr$ ), 127.0, 129.9, 131.2, 131.5, 133.7 ( $ArC$ ), 162.9 ( $CNO$ );  $m/z$  ( $ES^+$ ): 240.1 [ $M+H^+$ ]. HRMS ( $ES^+$ ):  $C_{10}H_{10}NOBr$  requires 240.0027 [ $M+H^+$ ] found 240.0024 [ $M+H^+$ ]. All spectroscopic data is consistent with that found in the literature.<sup>104</sup>

#### 4-Amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide



1-Methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxamide (2 g, 9.40 mmol), Pd/C catalyst (0.2 g, 5%) and ethyl acetate (25 mL) and stirred under hydrogen for 24 h at room temperature. The reaction mixture was then diluted with ethyl acetate (30 mL) and filtered through Celite. The filtrate was washed with brine ( $2 \times 30$  mL), the organic layer separated and dried over  $MgSO_4$  before being concentrated in *vacuo* to afford a pale orange solid which was used without purification for the next step (1.48 g, 86%). Spectroscopic details were consistent with those in the literature.<sup>79</sup>

#### 4-(2-Ethoxybenzamido)-1-methyl-3-propyl-1H-pyrazole-5-carboxamide



2-Ethoxybenzoic acid (0.2 mL, 1.37 mmol) and 4-Amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide (0.25 g, 1.37 mmol) were dissolved in toluene (50 mL) and 5 mol% boric acid (0.008 g, 0.137 mmol) was added. The reaction mixture

was heated to reflux temperature under argon for 5 days. Water removal was achieved by the use of a Dean-Stark condenser. After 5 days the toluene was evaporated and the residue re-dissolved in ethyl acetate (25 mL). This was washed with 5% (w/v) HCl (20 mL), brine (20 mL), 5% (w/v) NaOH (20 mL), brine (20 mL), dried (MgSO<sub>4</sub>) and the solvent removed in *vacuo* to yield the title compound as a white solid (0.03 g, 13%). Spectroscopic details were consistent with those in the literature.<sup>80</sup>

## 8.0 References

1. 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.
2. B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695-705.
3. R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273-1283.
4. J. March and M. B. Smith, *Advanced Organic Chemistry*, 6th edn., John Wiley & Sons, New Jersey, 2007.
5. C. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827-10852.
6. E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606-631.
7. S. Y. Han and Y. A. Kim, *Tetrahedron*, 2004, **60**, 2447-2467.
8. J. A. Mitchell and E. E. and Reid, *J. Am. Chem. Soc.*, 1931, **53**, 1879-1883.
9. G. H. Coleman and A. M. Alvarado, *Org. Synth.*, 1923, **3**, 3-5.
10. C. N. Webb, *Org. Synth.*, 1927, **7**, 6-7.
11. H. T. Clarke and L. D. Behr, *Org. Synth.*, 1936, **16**, 75-76.
12. C. Downing (Chemstrand Corp.), *U.S Patent*, 2667511, 1954.
13. A. W. Campbell (Commercial Solvents Corp.), *U.S Patent*, 3006956, 1961.
14. D. Davidson and P. Newman, *J. Am. Chem. Soc.*, 1952, **74**, 1515-1516.
15. B. S. Jursic and Z. Zdravkovski, *Synth. Commun.*, 1993, **23**, 2761-2770.
16. L. J. Goossen, D. M. Ohlmann and P. P. Lange, *Synthesis*, 2009, 160-164.
17. S. Caddick, *Tetrahedron*, 1995, **51**, 10403-10432.
18. R. S. Varma, *Green Chem.*, 1999, **1**, 43-55.
19. L. Perreux, A. Loupy and F. Volatron, *Tetrahedron*, 2002, **58**, 2155-2162.
20. B. W. Baldwin, T. Hirose and Z. H. Wang, *Chem. Commun.*, 1996, 2669-2670.
21. S. L. Cockroft and C. A. Hunter, *Chem. Commun.*, 2009, 3961-3963.
22. S. E. Wheeler and K. N. Houk, *Mol. Phys.*, 2009, **107**, 749-760.
23. P. Nelson and A. Pelter, *J. Chem. Soc.*, 1965, 5142-5144.
24. A. Pelter, T. E. Levitt and P. Nelson, *Tetrahedron*, 1970, **26**, 1539-1544.
25. A. Pelter and T. E. Levitt, *Tetrahedron*, 1970, **26**, 1545-1553.
26. P. Starkov and T. D. Sheppard, *Org. Biomol. Chem.*, 2011, **9**, 1320-1323.
27. G. Trapani, A. Reho and A. Latrofa, *Synthesis*, 1983, 1013-1014.
28. D. B. Collum, S. C. Chen and B. Ganem, *J. Org. Chem.*, 1978, **43**, 4393-4394.
29. T. Maki, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2006, **8**, 1431-1434.
30. W. Q. Yang, X. M. Gao, G. Springsteen and B. H. Wang, *Tet. Lett.*, 2002, **43**, 6339-6342.
31. K. Ishihara, S. Ohara and H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4196-4197.
32. K. Ishihara, S. Ohara and H. Yamamoto, *Organic Syntheses*, 2002, **79**, 176-185.
33. K. Ishihara, S. Ohara and H. Yamamoto, *Macromol.*, 2000, **33**, 3511-3513.
34. K. Ishihara, S. Kondo and H. Yamamoto, *Synlett*, 2001, 1371-1374.
35. T. Maki, K. Ishihara and H. Yamamoto, *Synlett*, 2004, 1355-1358.

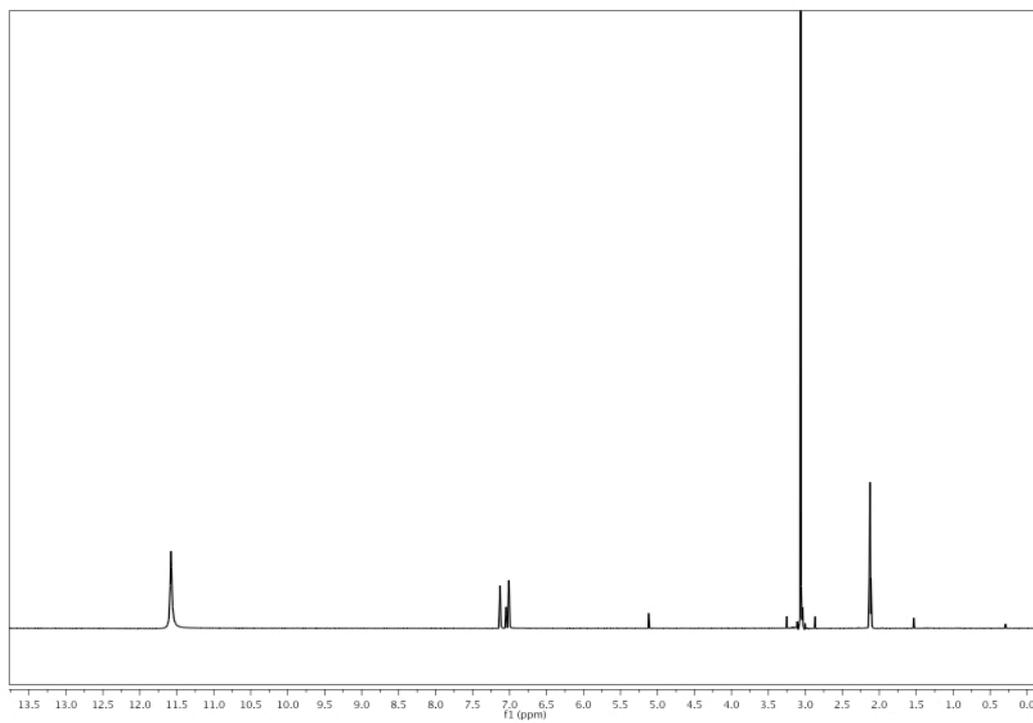
36. T. Maki, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2005, **7**, 5043-5046.
37. T. Maki, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2005, **7**, 5047-5050.
38. T. Maki, K. Ishihara and H. Yamamoto, *Tetrahedron*, 2007, **63**, 8645-8657.
39. P. Tang, *Organic Syntheses*, 2005, **81**, 262-267.
40. R. G. Hayter, A. W. Laubengayer and P. G. Thompson, *J. Am. Chem. Soc.*, 1957, **79**, 4243-4244.
41. A. D. Negro, L. Ungaretti, A. Perotti, *J. Chem. Soc. Dalton Trans.*, 1972, **15**, 1639-1643.
42. L. A. Duncanson, W. Gerrard, M. F. Lappert, H. Pyszora and R. Shafferman, *J. Chem. Soc.*, 1958, 3652-3656.
43. K. Ishihara, *Tetrahedron*, 2009, **65**, 1085-1109.
44. R. K. Mylavaram, G. C. M. Kondaiah, N. Kolla, R. Veeramalla, P. Koilkonda, A. Bhattacharya and R. Bandichhor, *Org. Process Res. Dev.*, 2007, **11**, 1065-1068.
45. K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith and A. Whiting, *Adv. Synth. Catal.*, 2006, **348**, 813-820.
46. K. Arnold, A. S. Batsanov, B. Davies and A. Whiting, *Green Chem.*, 2008, **10**, 124-134.
47. K. Arnold, B. Davies, D. Herault and A. Whiting, *Angew. Chem. Int. Ed.*, 2008, **47**, 2673-2676.
48. R. M. Al-Zoubi, O. Marion and D. G. Hall, *Angew. Chem. Int. Ed.*, 2008, **47**, 2876-2879.
49. T. Marcelli, *Angew. Chem. Int. Ed.*, 2010, **49**, 6840-6843.
50. H. Charville, D. Jackson, G. Hodges and A. Whiting, *Chem. Commun.*, 2010, **46**, 1813-1823.
51. A. Loupy, L. Perreux, M. Liagre, K. Burle and M. Moneuse, *Pure App. Chem.*, 2000, **73**, 161-166.
52. W. Jolly, *Modern Inorganic Chemistry*, 2nd edn., McGraw-Hill, New York, 1991.
53. M. L. Huggins, *J. Org. Chem.*, 1936, **1**, 407-456.
54. J. Semmler and D. E. Irish, *J. Solution Chem.*, 1988, **17**, 805-824.
55. R. W. Gora, S. J. Grabowski and J. Leszczynski, *J. Phys. Chem. A*, 2005, **109**, 6397-6405.
56. R. M. Balabin, *J. Phys. Chem. A*, 2009, **113**, 4910-4918.
57. H. Pasalic, A. J. A. Aquino, D. Tunega, G. Haberhauer, M. H. Gerzabek, H. C. Georg, T. F. Moraes, K. Coutinho, S. Canuto and H. Lischka, *J. Comput. Chem.*, 2010, **31**, 2046-2055.
58. J. Chocholousova, J. Vacek, P. Hobza, *J. Phys. Chem. A*, 2003, **107**, 3086-3092.
59. A. J. Kirby, T. G. Mujahid and P. Camilleri, *J. Chem. Soc. Perkin Trans. 2*, 1979, 1610-1616.
60. P. Camilleri, R. Ellul, A. J. Kirby and T. G. Mujahid, *J. Chem. Soc. Perkin Trans. 2*, 1979, 1617-1620.
61. R. L. Giles, PhD Thesis, Durham University, 2006.
62. C. Thirsk, G. E. Hawkes, R. T. Kroemer, K. R. Liedl, T. Loerting, R. Nasser, R. G. Pritchard, M. Steele, J. E. Warren and A. Whiting, *J. Chem. Soc. Perkin Trans. 2*, 2002, 1510-1519.
63. C. Kleeberg, L. Dang, Z. Y. Lin and T. B. Marder, *Angew. Chem. Int. Ed.*, 2009, **48**, 5350-5354.

64. H. O. House, W. J. Campbell and D. G. Koepsell, *J. Org. Chem.*, 1972, **37**, 1003-1011.
65. R. M. Al-Zoubi and D. G. Hall, *Org. Lett.*, 2010, **12**, 2480-2483.
66. S. W. Coghlan, R. L. Giles, J. A. K. Howard, L. G. F. Patrick, M. R. Probert, G. E. Smith and A. Whiting, *J. Organomet. Chem.*, 2006, **691**, 538-538.
67. A. J. Blatch, O. V. Chetina, J. A. K. Howard, L. G. F. Patrick, C. A. Smethurst and A. Whiting, *Org. Biomol. Chem.*, 2006, **4**, 3297-3302.
68. D. Crich and Q. W. Yao, *J. Org. Chem.*, 1996, **61**, 3566-3570.
69. R. Yougnia, C. Rochais, J. S. D. Santos, P. Dallemagne, S. Rault, *Tetrahedron*, 2010, **66**, 2803-2808.
70. S. Sayama, *Synlett*, 2006, 1479-1484.
71. M. Ishihara and H. Togo, *Tetrahedron*, 2007, **63**, 1474-1480.
72. J. Sedelmeier, T. Hammerer and C. Bolm, *Org. Lett.*, 2008, **10**, 917-920.
73. P. Harrisson, J. Morris, T. B. Marder and P. G. Steel, *Org. Lett.*, 2009, **11**, 3586-3589.
74. V. Montiel-Palma, M. Lumbierres, B. Donnadiou, S. Sabo-Etienne and B. Chaudret, *J. Am. Chem. Soc.*, 2002, **124**, 5624-5625.
75. A. M. Van Leusen, H. Siderius, B. E. Hoogenboom, *Tetrahedron. Lett.*, 1972, **23**, 2369-2372.
76. H. Hiemstra, H. A. Houwing, O. Possel and A. M. Vanleusen, *Can. J. Chem.*, 1979, **57**, 3168-3170.
77. C. Lamberth, A. Jeanguenat, F. Cederbaum, A. De Mesmaeker, M. Zeller, H.-J. Kempf and R. Zeun, *Bioorg. Med. Chem.*, 2008, **16**, 1531-1545.
78. N. K. Terrett, A. S. Bell, D. Brown and P. Ellis, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1819-1824.
79. T. G. Gant, S. Sarshar, *USA Patent*, 0194529, 2008.
80. G. Tian, Y. Zhu, Z. Liu, Z. Wang, J. Shen, *USA Patent*, 0048897, 2010.
81. D. J. Dale, P. J. Dunn, C. Golightly, M. L. Hughes, P. C. Levett, A. K. Pearce, P. M. Searle, G. Ward and A. S. Wood, *Org. Process Res. Dev.*, 2000, **4**, 17-22.
82. M. Gucma, W. M. Golebiewski, B. Morytz, H. Charville and A. Whiting, *Lett. Org. Chem.*, 2010, **7**, 502-507.
83. A. R. Katritzky, Z. Q. Wang, S. Slavov, M. Tsikolia, D. Dobchev, N. G. Akhmedov, C. D. Hall, U. R. Bernier, G. G. Clark and K. J. Linthicum, *PNAS*, 2008, **105**, 7359-7364.
84. J. C. Habeck, L. Diop and M. Dickman, *J. Chem. Educ.*, 2010, **87**, 528-529.
85. A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648-5652.
86. C. T. Lee, W. T. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785-789.
87. M. J. Frisch, Gaussian 0.3, Revision C.02 ed., 2004, Gaussian inc., Wallingford, CT.
88. J. Tomasi, B. Mennucci and R. Cammi, *Chem. Rev.*, 2005, **105**, 2999-3093.
89. J. H. Dam, G. Osztrovszky, L. U. Nordstrom and R. Madsen, *Chem. Eur. J.*, 2010, **16**, 6820-6827.
90. C.-T. Chen, S. Bettigeri, S.-S. Weng, V. D. Pawar, Y.-H. Lin, C.-Y. Liu, W.-Z. Lee, *J. Org. Chem.*, 2007, **72**, 8175-8185.

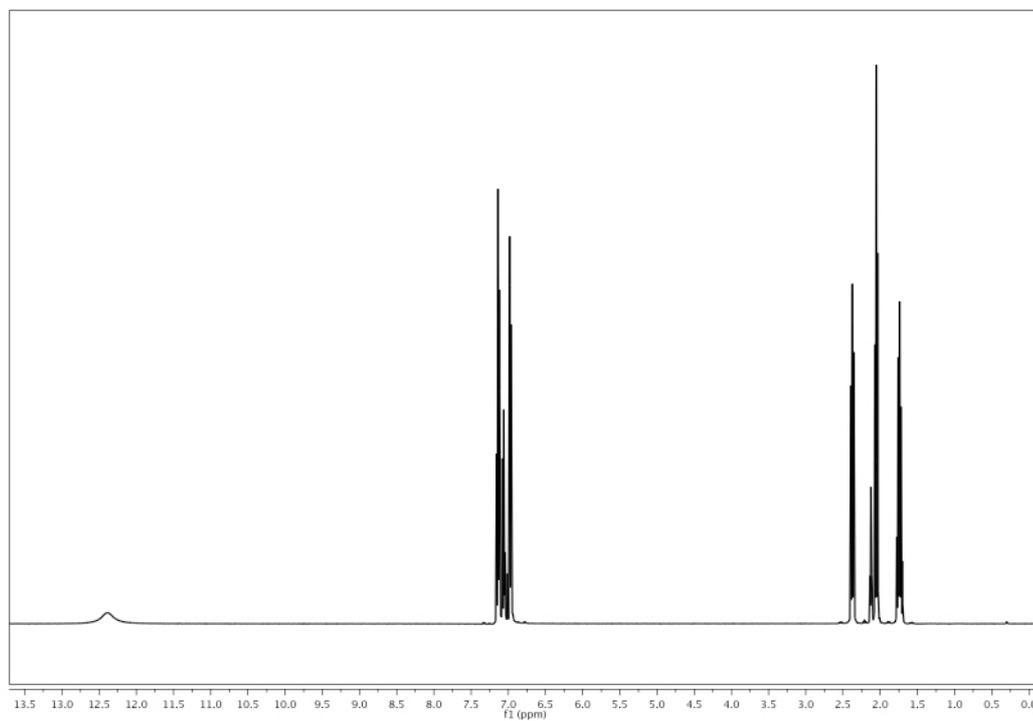
91. N. Kambe, T. Inoue, T. Takeda, S.-i. Fujiwara and N. Sonoda, *J. Am. Chem. Soc.*, 2006, **128**, 12650-12651.
92. R. V. Hoffman and N. K. Nayyar, *J. Org. Chem.*, 1995, **60**, 7043-7046.
93. R. H. Prager and J. A. Smith, *Aust. J. Chem.*, 1995, **48**, 217-226.
94. J. W. Bode, R. M. Fox and K. D. Baucom, *Angew. Chem. Int. Ed.*, 2006, **45**, 1248-1252.
95. A. R. Katritzky, S. K. Singh, C. M. Cai and S. Bobrov, *J. Org. Chem.*, 2006, **71**, 3364-3374.
96. T. Satoh, H. Unno, Y. Mizu and Y. Hayashi, *Tetrahedron*, 1997, **53**, 7843-7854.
97. J. W. Comerford, J. H. Clark, D. J. Macquarrie and S. W. Breeden, *Chem. Commun.*, 2009, 2562-2564.
98. T. Ohshima, T. Iwasaki, Y. Maegawa, A. Yoshiyama and K. Mashima, *J. Am. Chem. Soc.*, 2008, **130**, 2944-2945.
99. O. Baron and P. Knochel, *Angew. Chem. Int. Ed.*, 2005, **44**, 3133-3135.
100. M. Weimar, G. Duerner, J. W. Bats and M. W. Goebel, *J. Org. Chem.*, 2010, **75**, 2718-2721.
101. M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J. L. Peglion, E. Clot, O. Baudoin, *J. Am. Chem. Soc.*, 2008, **130**, 15157-15166.
102. C. Pascal, J. Dubois, D. Guenard and F. Gueritte, *J. Org. Chem.*, 1998, **63**, 6414-6420.
103. C. M. Vogels, L. G. Nikolcheva, D. W. Norman, H. A. Spinney, A. Decken, M. O. Baerlocher, F. J. Baerlocher and S. A. Westcott, *Can. J. Chem.*, 2001, **79**, 1115-1123.
104. Q. L. Zhou and A. Pfaltz, *Tetrahedron*, 1994, **50**, 4467-4478.

## 8.0 Appendix

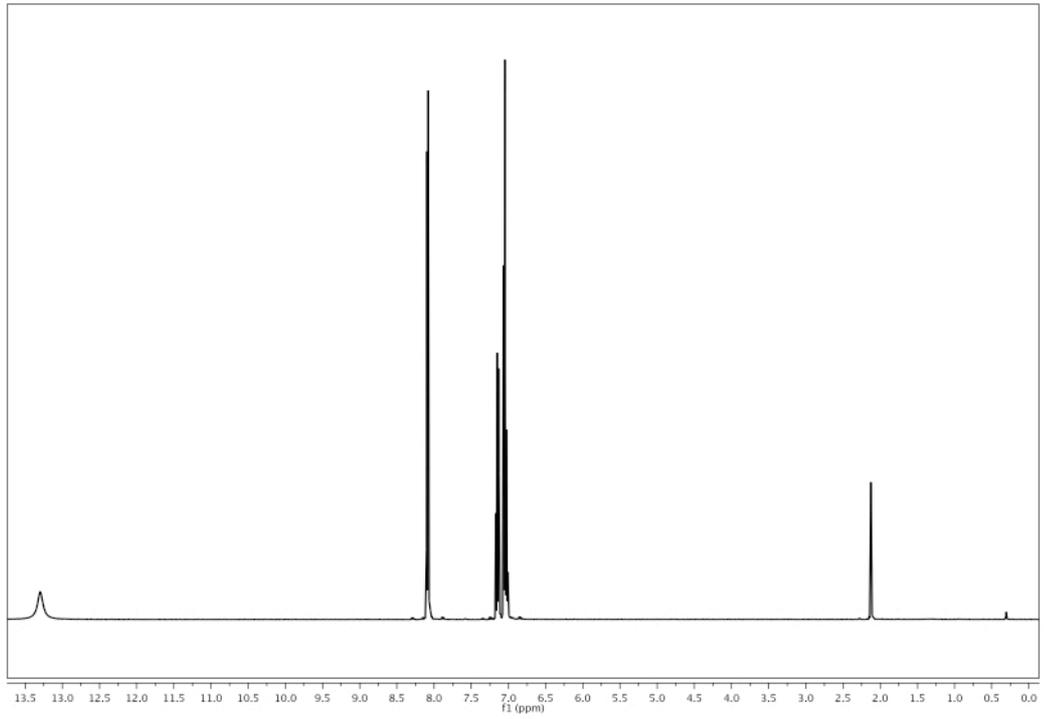
### 8.1 NMR data



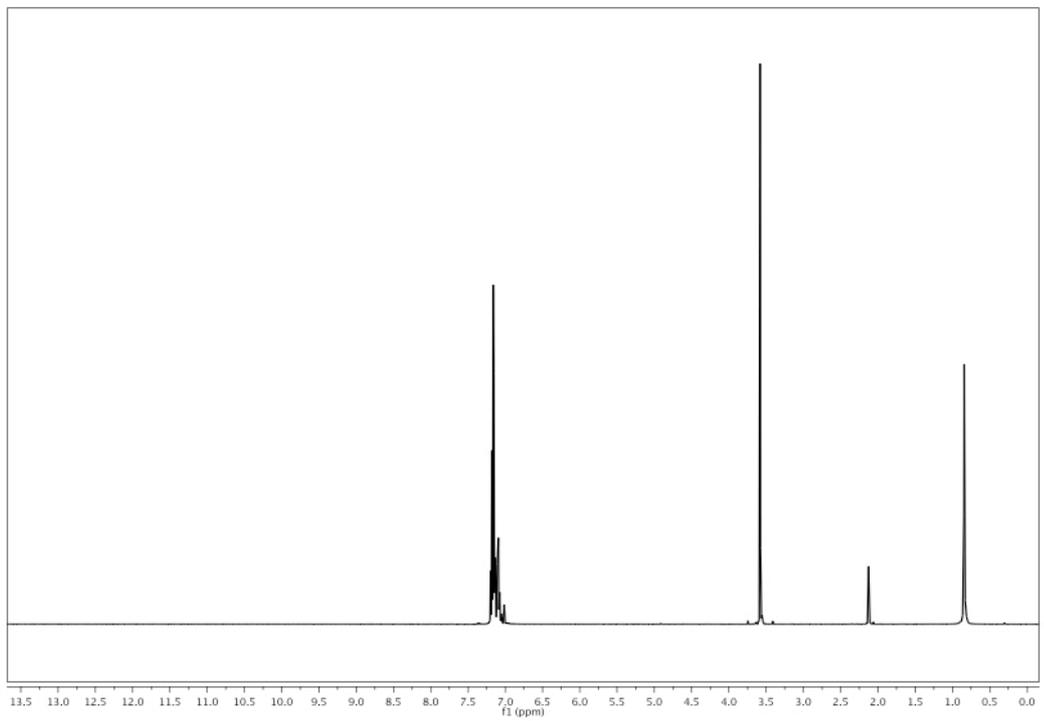
Bromoacetic acid



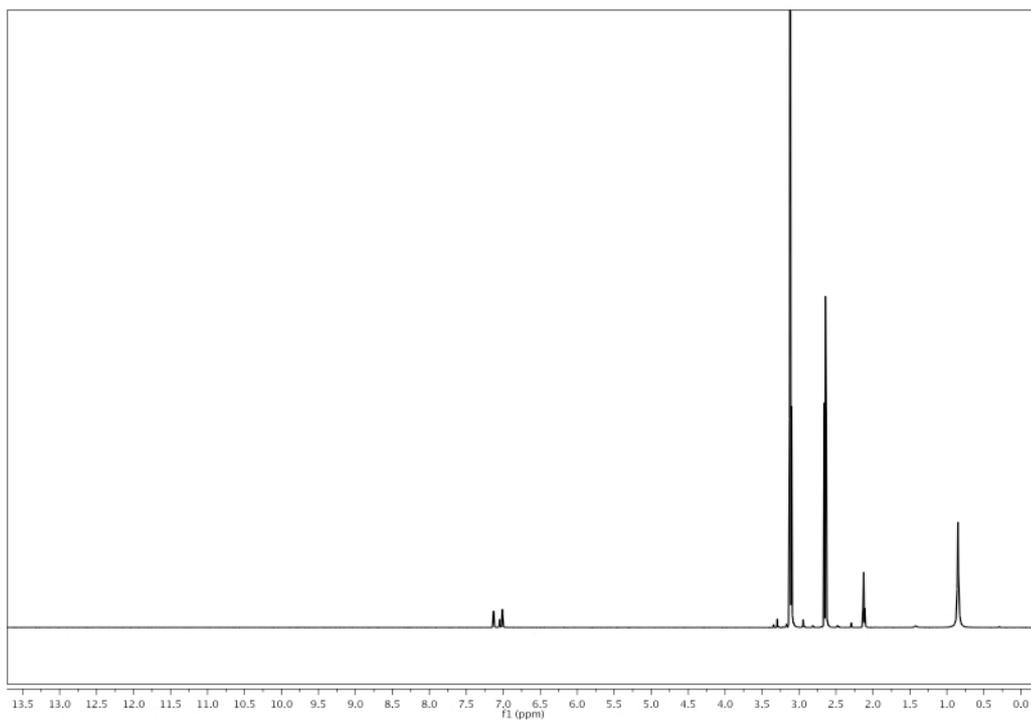
Phenylbutyric acid



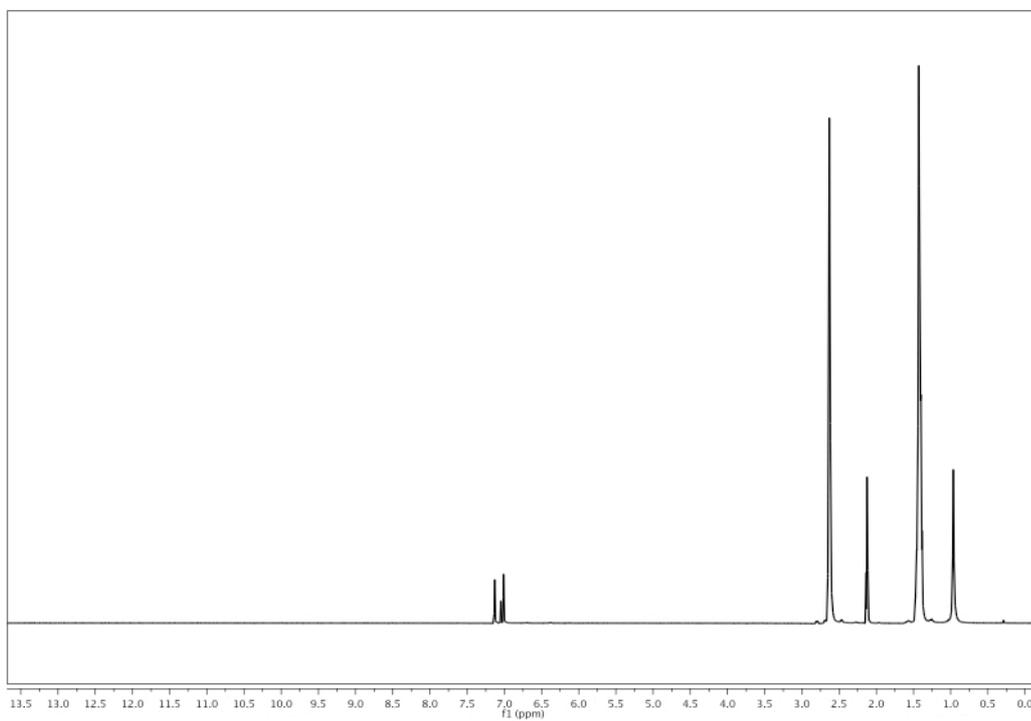
Benzoic acid



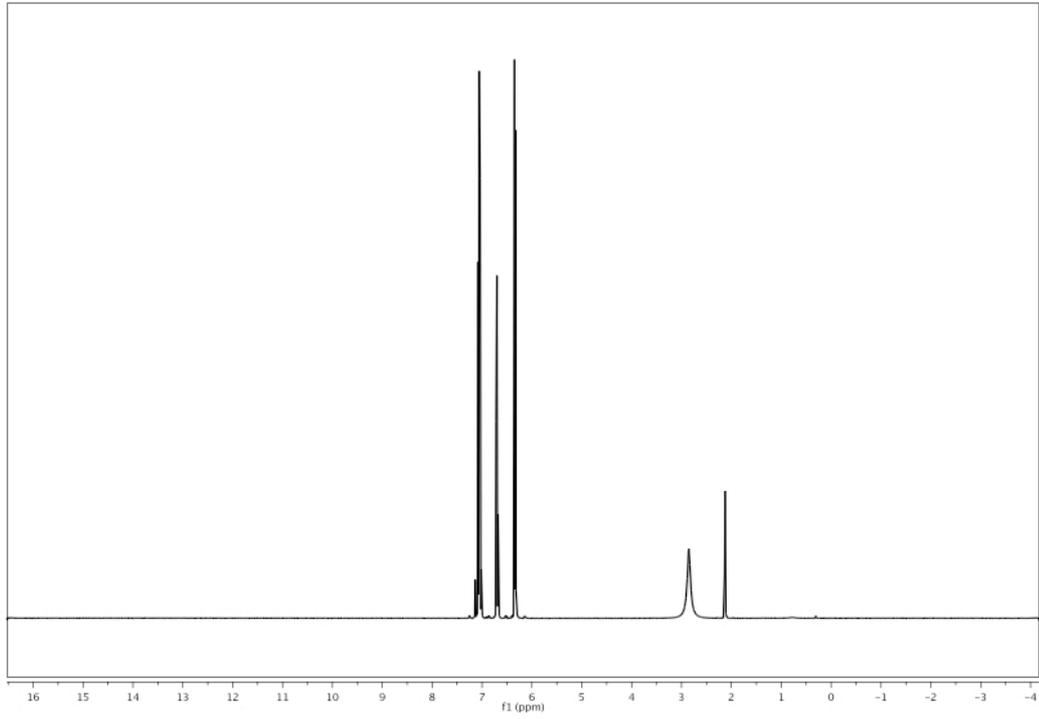
Benzylamine



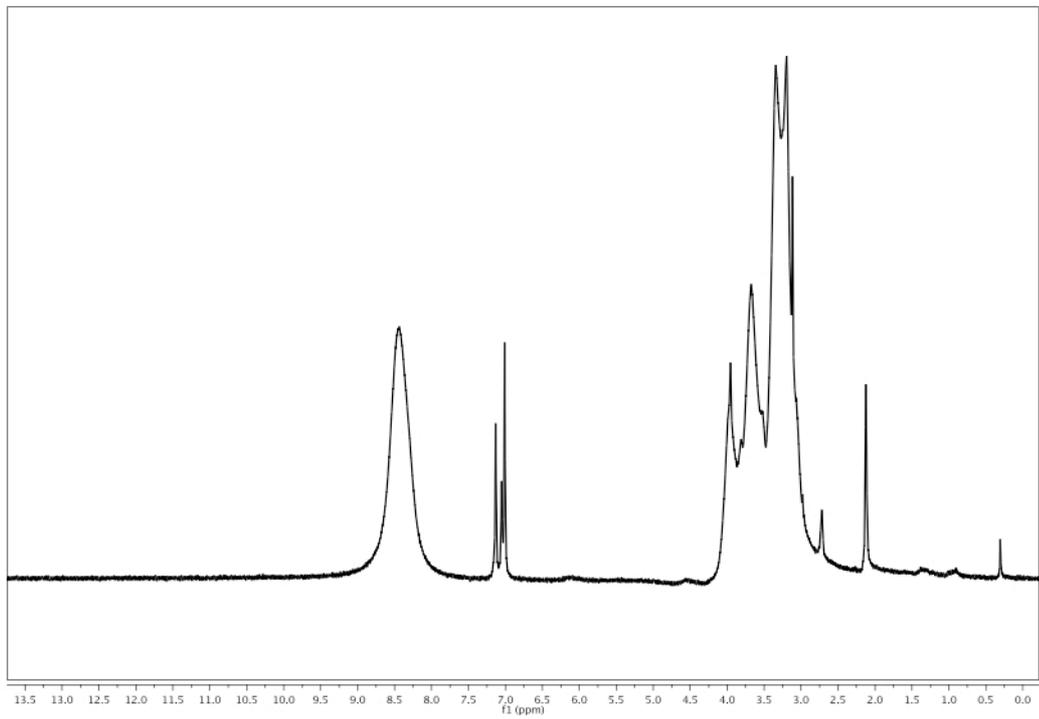
2-Methoxyethylamine



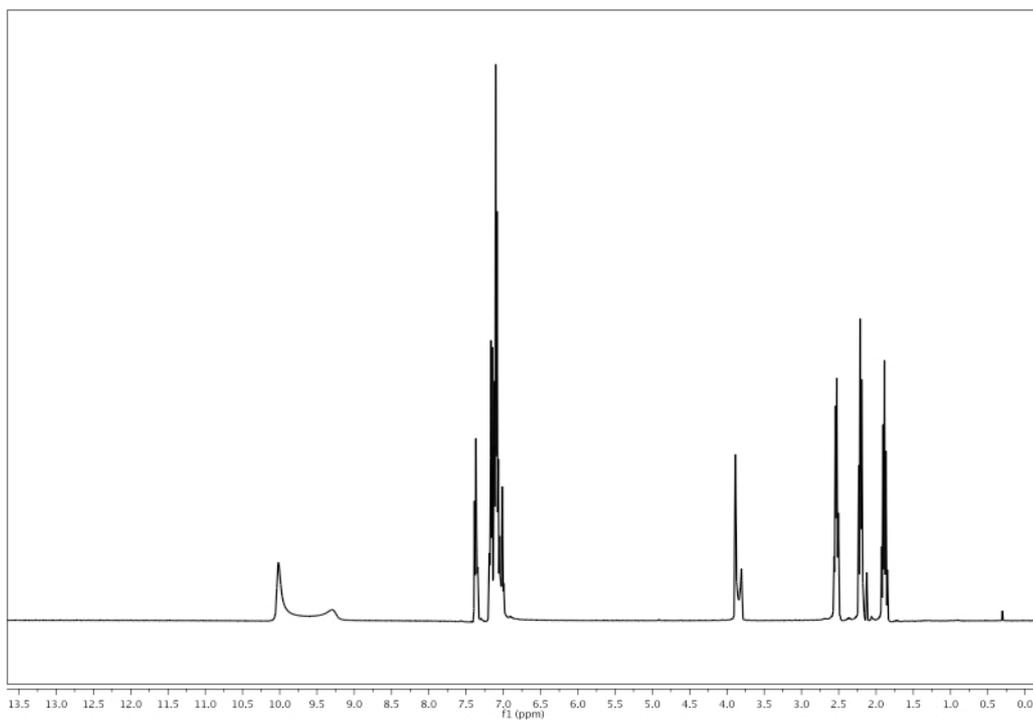
Piperidine



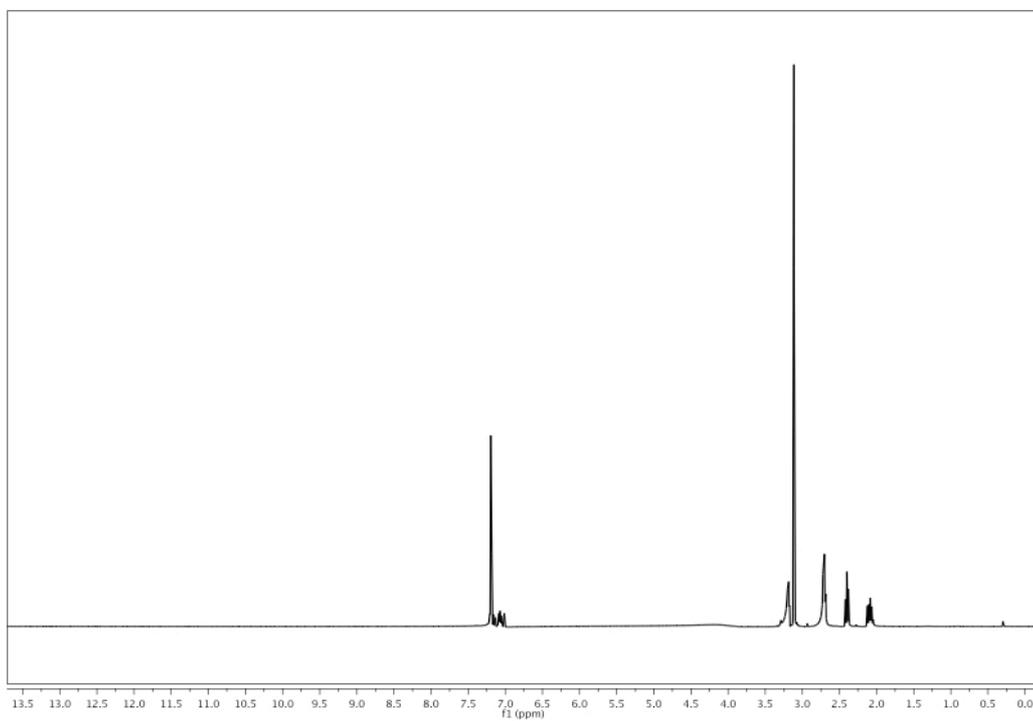
Aniline



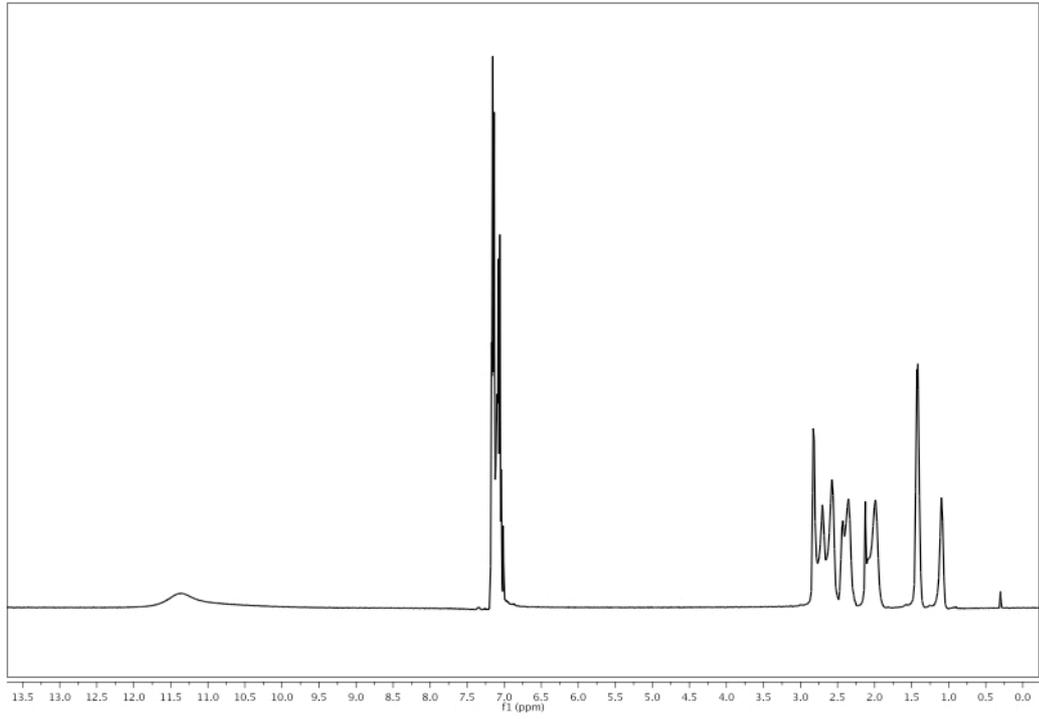
Bromoacetic acid + 2-Methoxyethylamine



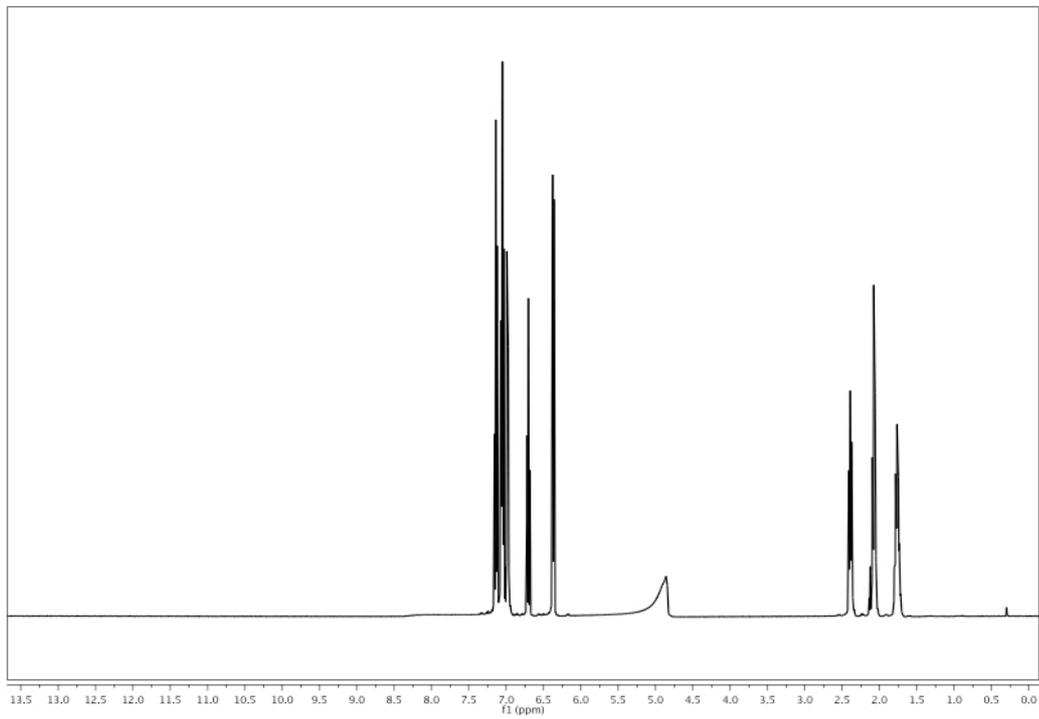
Phenylbutyric acid + Benzylamine



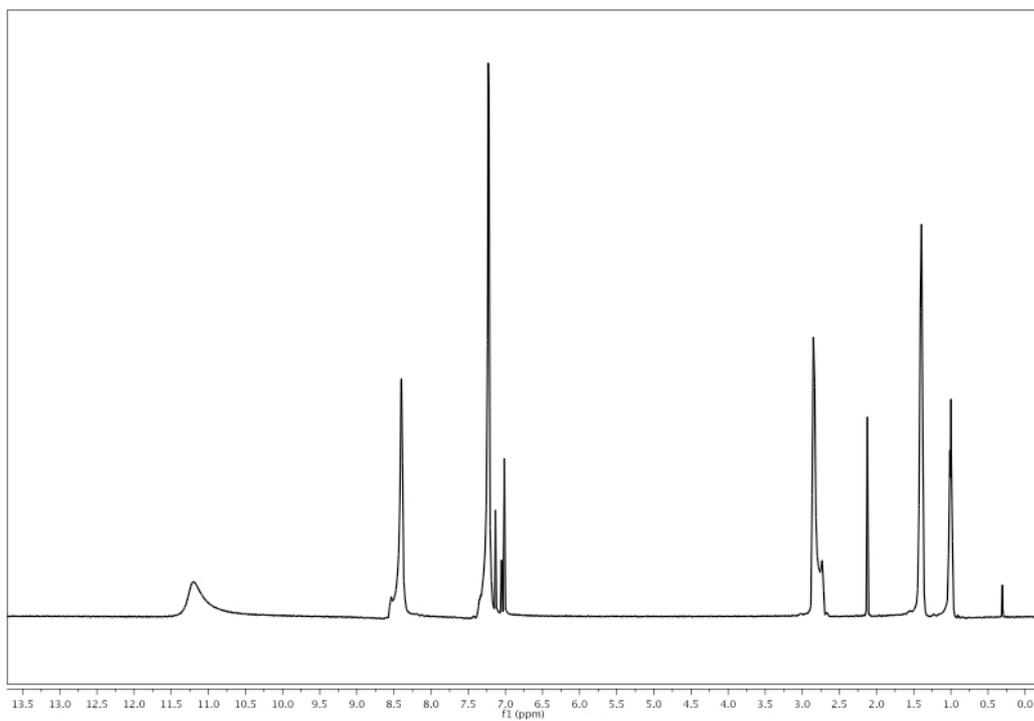
Phenylbutyric acid + 2-Methoxyethylamine



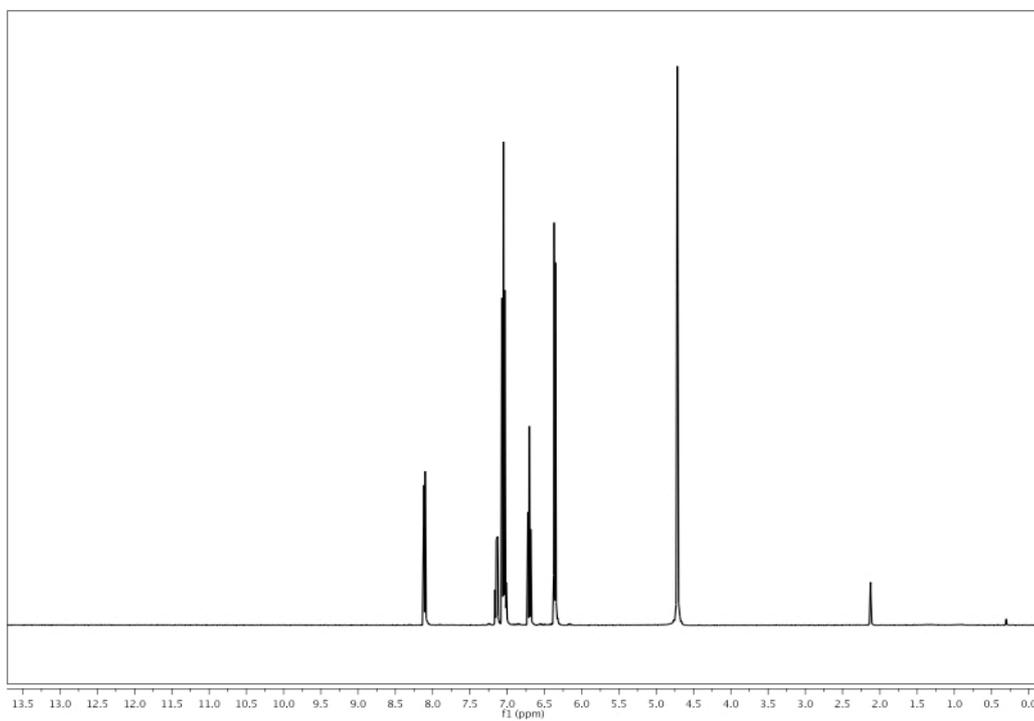
Phenylbutyric acid + Piperidine



Phenylbutyric acid + Aniline



Benzoic acid + Piperidine



Benzoic acid + Aniline

## 8.2 Computational Chemistry Data (Prof. Mark Wilson)

Jmol: an open-source Java viewer for chemical structures in 3D was used to produce molecular structure figures. <<http://www.jmol.org/>><http://www.jmol.org/>

**Table 9:** Energies of acids, amines, dihydroxy intermediates and amides calculated at B3LYP/6-31G\*\* level with PCM solvation treatment for toluene solvent. (Energies are tabulated as the sum of electronic and thermal energies.)

	Carboxylic acid	Amine	E (acid) / Ha	E (amine) / Ha	E(int.) / Ha	E(amide) / Ha
1a	Bromoacetic	Benzylamine	-2800.1349	-326.7745	-3126.9003	-3050.5095
1b	"	t-Butylamine	-2800.1349	-2.6693	-3013.7874	-2937.4013
1c	"	2-Methoxyethylamine	-2800.1349	-249.5697	-3049.6995	-2973.3102
1d	"	Piperidine	-2800.1349	-251.7587	-3051.8820	-2975.4907
1e	"	Aniline	-2800.1349	-287.4990	-3087.6228	-3011.2301
2a	Phenylbutyric	Benzylamine	-538.5782	-326.7745	-865.3329	-788.9488
2b	"	t-Butylamine	-538.5782	-213.6693	-752.2194	-675.8413
2c	"	2-Methoxyethylamine	-538.5782	-249.5697	-788.1259	-711.7451
2d	"	Piperidine	-538.5782	-251.7587	-790.3131	-713.9316
2e	"	Aniline	-538.5782	-287.4990	-826.0554	-749.6654
3a	Benzoic	Benzylamine	-420.7206	-326.7745	-747.4708	-671.0894
3b	"	t-Butylamine	-420.7206	-213.6693	-634.3590	-557.9821
3c	"	2-Methoxyethylamine	-420.7206	-249.5697	-670.2640	-593.8857
3d	"	Piperidine	-420.7206	-251.7587	-672.4564	-596.0694
3e	"	Aniline	-420.7206	-287.4990	-708.1938	-631.8060

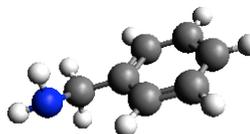
**Table 10:** Energies of dihydroxy intermediate compounds and amide plus water (products) relative to acid + amide reactants calculated at B3LYP/6-31G\*\* level with PCM solvation treatment for toluene solvent. (Energies are tabulated as energy differences calculated from a sum of electronic and thermal Energies.)

	Carboxylic acid	Amine	$\Delta E$ intermediate / $\text{kJ mol}^{-1}$	$\Delta E$ Amide + water / $\text{kJ mol}^{-1}$
1a	Bromoacetic	Benzylamine	24.19	-3.33
1b	“	t-Butylamine	44.12	4.55
1c	“	2-Methoxyethylamine	13.82	-17.71
1d	“	Piperidine	30.70	4.45
1e	“	Aniline	29.19	6.93
2a	Phenylbutyric	Benzylamine	52.24	7.14
2b	“	t-Butylamine	73.87	13.12
2c	“	2-Methoxyethylamine	57.90	4.30
2d	“	Piperidine	62.76	10.84
2e	“	Aniline	57.34	27.83
3a	Benzoic	Benzylamine	64.01	11.76
3b	“	t-Butylamine	81.24	17.22
3c	“	2-Methoxyethylamine	69.39	8.97
3d	“	Piperidine	60.38	23.01
3e	“	Aniline	67.91	32.61

**Table 11:** B3LYP/6-31G\*\* energy minimised structures of bases and protonated bases used in table 9.

### Benzylamine

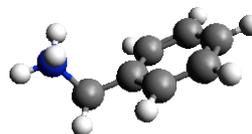
C	-1.40548	-1.33724	0.05675
C	-2.31951	-0.29198	-0.09267
C	-1.85876	1.02448	-0.13039
C	-0.49293	1.29004	-0.01984
C	0.42995	0.24972	0.13859
C	-0.04160	-1.06910	0.17259
C	1.90823	0.55164	0.30158
N	2.74704	-0.47598	-0.32372
H	-3.38134	-0.50224	-0.18372
H	-2.56035	1.84481	-0.25386
H	-0.13856	2.31776	-0.05902
H	0.67620	-1.87578	0.27994
H	-1.75634	-2.36533	0.08335
H	2.09837	1.57653	-0.06188
H	2.15610	0.56036	1.37228



H	2.62963	-0.44651	-1.33409
H	3.72761	-0.28315	-0.13665

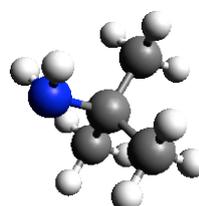
### Protonated benzylamine

C	-1.65905	-1.21171	0.10111
C	-2.33660	-0.00007	0.25683
C	-1.65905	1.21167	0.10146
C	-0.29970	1.21416	-0.20556
C	0.38757	0.00004	-0.35677
C	-0.29951	-1.21409	-0.20523
C	1.85661	0.00002	-0.64431
N	2.64949	-0.00001	0.68928
H	-3.39690	-0.00017	0.48787
H	-2.19067	2.15140	0.20768
H	0.21925	2.15938	-0.34892
H	0.21967	-2.15925	-0.34827
H	-2.19079	-2.15143	0.20686
H	2.19335	0.89111	-1.17711
H	2.19329	-0.89109	-1.17718
H	2.39972	0.82456	1.24589
H	2.39894	-0.82405	1.24633
H	3.66606	-0.00052	0.54674



### t-Butylamine

C	0.00000	-0.00497	0.01635
C	1.25868	-0.79930	-0.36538
H	2.16672	-0.25318	-0.08271
H	1.27070	-1.76361	0.15017
H	1.30039	-0.97642	-1.44492
C	-1.25866	-0.79934	-0.36534
H	-1.30038	-0.97650	-1.44488
H	-1.27067	-1.76363	0.15024
H	-2.16672	-0.25323	-0.08269
C	-0.00003	1.35826	-0.70770
H	-0.00006	1.24207	-1.79781
H	-0.88620	1.94356	-0.43510
H	0.88614	1.94357	-0.43515
N	0.00002	0.13749	1.48731
H	-0.81238	0.68354	1.77208
H	0.81242	0.68354	1.77206



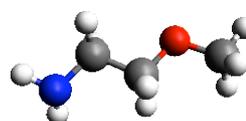
### Protonated t-butylamine

C	-0.00137	-0.00173	-0.09518
C	1.13269	-0.93625	-0.51945
H	2.11003	-0.57213	-0.18617
H	0.98515	-1.95538	-0.14747
H	1.15861	-0.98777	-1.61048

C	-1.37967	-0.53164	-0.49393
H	-1.44104	-0.57134	-1.58400
H	-1.55329	-1.54583	-0.11965
H	-2.18622	0.12127	-0.14478
C	0.22654	1.44120	-0.54793
H	0.22128	1.47400	-1.63994
H	-0.56564	2.11017	-0.19642
H	1.19518	1.82706	-0.21393
N	0.01923	0.02512	1.46748
H	-0.71614	0.63773	1.83575
H	0.91902	0.36942	1.81886
H	-0.13069	-0.91249	1.85487

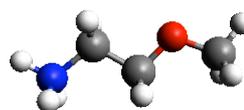
### 2-Methoxyethylamine

C	2.39124	-0.19547	0.01063
H	3.19330	0.54027	-0.08752
H	2.50768	-0.72143	0.97162
H	2.49010	-0.93736	-0.79828
O	1.16778	0.50217	-0.06244
C	0.04284	-0.34794	0.05367
H	0.03641	-1.09475	-0.76156
H	0.05894	-0.90632	1.00307
C	-1.21432	0.51089	-0.01362
H	-1.21186	1.19460	0.84196
H	-1.16117	1.13519	-0.92112
N	-2.40164	-0.34454	0.07833
H	-2.53077	-0.85061	-0.79536
H	-3.23198	0.22993	0.19432



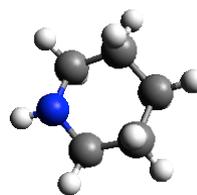
### Protonated 2-methoxyethylamine

C	2.47104	-0.18613	0.00003
H	3.23048	0.59521	-0.00009
H	2.58808	-0.80902	0.89611
H	2.58810	-0.80929	-0.89586
O	1.20670	0.48279	-0.00008
C	0.11284	-0.38123	-0.00000
H	0.09609	-1.03569	-0.89112
H	0.09620	-1.03566	0.89113
C	-1.09955	0.55012	0.00005
H	-1.10821	1.18043	0.89044
H	-1.10818	1.18054	-0.89025
N	-2.39847	-0.24377	-0.00002
H	-2.46855	-0.84742	-0.82739
H	-3.21586	0.37615	0.00010
H	-2.46850	-0.84765	0.82720



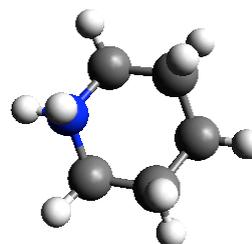
### Piperidine

C	-0.75780	1.21234	0.20695
N	-1.37987	-0.00506	-0.31850
C	-0.74888	-1.21795	0.20679
C	0.72078	-1.26193	-0.22616
C	1.45915	0.00545	0.23185
C	0.71130	1.26719	-0.22632
H	-0.80457	1.26933	1.31357
H	-1.30314	2.07869	-0.18403
H	-0.79552	-1.27555	1.31338
H	-1.28771	-2.08822	-0.18450
H	1.20217	-2.15874	0.18154
H	0.76000	-1.33554	-1.31996
H	1.52730	0.00577	1.32927
H	2.48856	0.00929	-0.14523
H	0.74970	1.34088	-1.32014
H	1.18607	2.16767	0.18109
H	-2.37108	-0.00876	-0.09416



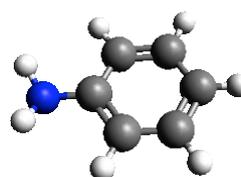
### Protonated piperidine

C	0.70037	-1.27177	0.24300
N	1.39780	0.00001	-0.22536
C	0.70035	1.27178	0.24300
C	-0.75134	1.26742	-0.22759
C	-1.49286	-0.00001	0.22515
C	-0.75132	-1.26744	-0.22760
H	0.77828	-1.26876	1.33352
H	1.27475	-2.11297	-0.15088
H	0.77827	1.26878	1.33351
H	1.27472	2.11299	-0.15088
H	-1.23130	2.16672	0.16974
H	-0.78149	1.35927	-1.32142
H	-1.59176	-0.00002	1.31784
H	-2.50741	-0.00002	-0.18117
H	-0.78146	-1.35928	-1.32142
H	-1.23126	-2.16674	0.16973
H	2.37138	0.00002	0.09415
H	1.43147	0.00001	-1.25099



### Aniline

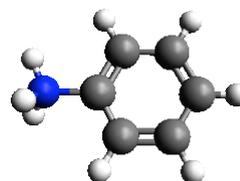
C	-0.93915	-0.00000	-0.00971
C	-0.22129	-1.20820	-0.00501
C	1.17144	-1.20231	0.00334
C	1.88129	0.00000	0.00797
C	1.17144	1.20232	0.00334
C	-0.22129	1.20820	-0.00501
H	-0.76296	-2.15112	-0.01244
H	1.70518	-2.14881	0.00872
H	2.96651	0.00000	0.01578



H	1.70518	2.14881	0.00872
H	-0.76296	2.15112	-0.01244
N	-2.33562	-0.00000	-0.07706
H	-2.77816	0.83565	0.28080
H	-2.77817	-0.83564	0.28081

**Protonated aniline**

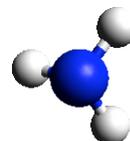
C	0.82680	0.00060	0.00003
C	0.16923	-1.22477	-0.00001
C	-1.22558	-1.21307	0.00001
C	-1.91994	-0.00025	0.00000
C	-1.22892	1.21194	-0.00003
C	0.16765	1.22302	0.00005
H	0.71467	-2.16446	0.00002
H	-1.76578	-2.15339	-0.00001
H	-3.00460	-0.00152	-0.00004
H	-1.76891	2.15232	-0.00005
H	0.71159	2.16411	0.00001
N	2.32455	0.00047	-0.00002
H	2.69004	0.95921	-0.00072
H	2.70785	-0.47279	-0.82793
H	2.70789	-0.47157	0.82856



**Table 12:** B3LYP/6-31G\*\* energy minimised structures of additional bases and protonated bases used in Table 10.

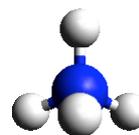
**Ammonia**

N	0.00000	0.11925	0.00000
H	-0.93718	-0.27817	0.00000
H	0.46859	-0.27831	0.81155
H	0.46859	-0.27831	-0.81155



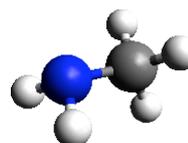
**Ammonium ion**

N	0.00000	0.00000	0.00000
H	0.00000	0.00000	1.02732
H	0.00000	0.96856	-0.34244
H	0.83880	-0.48428	-0.34244
H	-0.83880	-0.48428	-0.34244



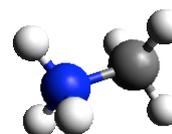
**Methylamine**

N	0.75228	0.00000	-0.12566
C	-0.70522	0.00000	0.01756
H	1.14336	0.81153	0.34704
H	1.14336	-0.81154	0.34704
H	-1.11723	-0.88031	-0.48641
H	-1.08686	-0.00001	1.05296
H	-1.11723	0.88032	-0.48640



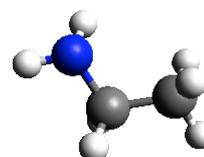
**Protonated methylamine**

N	-0.71300	-0.00001	0.00000
H	-1.08899	0.23363	-0.92598
C	0.80401	0.00001	-0.00001
H	-1.08901	0.68513	0.66529
H	-1.08896	-0.91875	0.26065
H	1.14461	-0.25331	1.00294
H	1.14466	-0.74195	-0.72080
H	1.14464	0.99523	-0.28208



**Ethylamine**

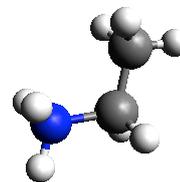
N	-1.20821	-0.32507	-0.12004
C	-0.05044	0.56032	0.05386
H	-1.25677	-0.97533	0.66254
H	-2.06807	0.21814	-0.08466
C	1.24808	-0.23809	-0.02748
H	-0.07367	1.29845	-0.75719
H	-0.06312	1.13569	0.99746
H	1.30532	-0.77851	-0.97667
H	1.30806	-0.97490	0.78269



H	2.11987	0.41858	0.05786
---	---------	---------	---------

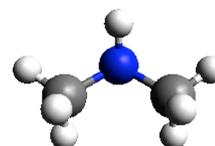
**Protonated ethylamine**

N	1.20991	-0.24501	0.00000
C	-0.06057	0.60997	0.00000
H	1.24523	-0.85336	0.82608
H	1.24523	-0.85336	-0.82608
H	2.06009	0.32963	0.00000
C	-1.29761	-0.27032	0.00000
H	0.00694	1.24116	0.88826
H	0.00694	1.24116	-0.88826
H	-1.35233	-0.90127	0.89245
H	-1.35232	-0.90127	-0.89245
H	-2.18007	0.37454	-0.00000



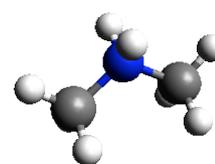
**Dimethylamine**

N	0.00000	0.56500	-0.14956
C	1.21391	-0.22236	0.02050
C	-1.21391	-0.22236	0.02050
H	0.00000	1.32801	0.52206
H	1.27597	-0.76833	0.98092
H	1.27960	-0.96666	-0.78175
H	2.09060	0.42765	-0.05974
H	-1.27960	-0.96666	-0.78175
H	-1.27597	-0.76833	0.98092
H	-2.09060	0.42765	-0.05974



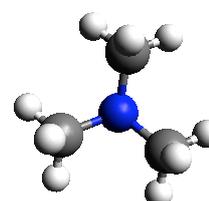
**Protonated dimethylamine**

N	0.00000	0.54163	0.00000
C	1.26857	-0.27658	0.00000
C	-1.26857	-0.27658	0.00000
H	0.00000	1.16097	0.81761
H	-0.00000	1.16097	-0.81761
H	-1.27596	-0.89883	-0.89457
H	-1.27596	-0.89884	0.89457
H	-2.12284	0.40045	0.00001
H	1.27596	-0.89883	0.89457
H	1.27596	-0.89884	-0.89457
H	2.12284	0.40045	-0.00001



**Trimethylamine**

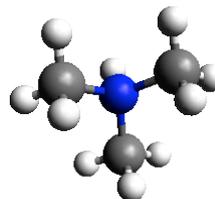
N	0.00001	-0.00007	-0.37155
C	-0.33404	1.34842	0.06094
C	1.33500	-0.38497	0.06097
C	-1.00100	-0.96341	0.06098
H	-1.31441	1.63290	-0.33490



H	-0.36670	1.46094	1.16312
H	0.40562	2.05630	-0.32703
H	1.44826	-0.41552	1.16314
H	1.57925	-1.37831	-0.32927
H	2.07127	0.32335	-0.33266
H	-1.08897	-1.04105	1.16312
H	-0.75204	-1.95649	-0.32692
H	-1.98215	-0.68188	-0.33509

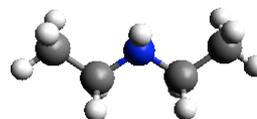
### Protonated trimethylamine

N	-0.00004	-0.00010	-0.33907
C	1.18617	-0.81828	0.10347
C	-1.30189	-0.61790	0.10346
C	0.11574	1.43621	0.10342
H	-0.00010	-0.00001	-1.36410
H	-1.32453	-0.62843	1.19358
H	-2.12630	-0.01937	-0.28428
H	-1.35975	-1.63508	-0.28406
H	2.09595	-0.35792	-0.28200
H	1.20515	-0.83451	1.19358
H	1.08207	-1.83093	-0.28633
H	0.12068	1.46114	1.19356
H	-0.73790	1.99394	-0.28183
H	1.04492	1.85172	-0.28671



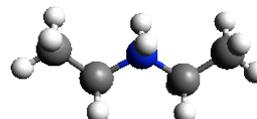
### Diethylamine

N	0.00000	-0.27514	-0.07024
C	-1.22273	0.51880	0.02211
C	1.22273	0.51880	0.02212
H	-0.00000	-0.96421	0.68084
C	-2.46147	-0.37145	-0.03339
H	-1.25728	1.14737	0.93394
H	-1.23284	1.21532	-0.82678
H	-2.49014	-1.06147	0.81846
H	-2.46471	-0.96855	-0.94983
H	-3.37641	0.22832	-0.00273
H	1.23283	1.21533	-0.82677
H	1.25728	1.14736	0.93395
C	2.46147	-0.37145	-0.03340
H	2.49013	-1.06150	0.81844
H	2.46473	-0.96852	-0.94985
H	3.37641	0.22832	-0.00270



### Protonated diethylamine

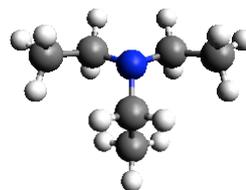
N	0.00000	-0.26158	0.00000
C	-1.28598	0.54885	0.00001
C	1.28598	0.54885	-0.00001



H	0.00000	-0.88448	0.81577
H	-0.00001	-0.88448	-0.81577
C	-2.50716	-0.35757	-0.00001
H	-1.24287	1.18521	0.88675
H	-1.24286	1.18524	-0.88671
H	-2.54687	-0.99140	0.89135
H	-2.54687	-0.99137	-0.89138
H	-3.40546	0.26469	0.00001
C	2.50716	-0.35757	0.00001
H	1.24287	1.18521	-0.88675
H	1.24287	1.18524	0.88670
H	2.54687	-0.99137	0.89138
H	2.54687	-0.99140	-0.89135
H	3.40546	0.26469	-0.00001

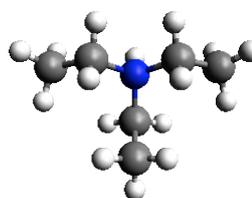
### Triethylamine

N	0.00002	-0.38319	-0.22024
C	-0.00003	1.01919	-0.65330
C	1.20995	-0.79587	0.49606
C	-1.20989	-0.79596	0.49605
C	-0.00010	2.09807	0.44528
H	0.87086	1.16798	-1.29946
H	-0.87090	1.16791	-1.29950
H	0.88391	2.03093	1.08766
H	-0.88415	2.03090	1.08759
H	-0.00009	3.09376	-0.01114
H	1.33813	-0.26526	1.45977
H	1.07666	-1.85342	0.75390
C	2.49078	-0.66014	-0.32877
H	2.37337	-1.14915	-1.30078
H	2.77035	0.38330	-0.50285
H	3.32435	-1.13499	0.19864
H	-1.33808	-0.26540	1.45979
H	-1.07656	-1.85352	0.75382
C	-2.49073	-0.66023	-0.32877
H	-2.77033	0.38321	-0.50279
H	-2.37331	-1.14919	-1.30080
H	-3.32428	-1.13513	0.19862



### Protonated triethylamine

N	-0.00006	-0.38849	0.24624
C	0.00007	1.07789	0.67449
C	-1.25386	-0.81349	-0.50919
C	1.25365	-0.81359	-0.50927
H	-0.00002	-0.92375	1.12087
C	0.00044	2.06993	-0.47846
H	-0.87974	1.20362	1.30672
H	0.87964	1.20337	1.30712

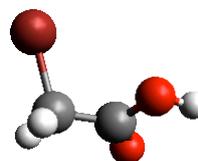


H	-0.88896	1.98878	-1.10805
H	0.89009	1.98859	-1.10765
H	0.00046	3.07585	-0.05006
C	-2.53908	-0.60476	0.27832
H	-1.25270	-0.26161	-1.45056
H	-1.10879	-1.87142	-0.73980
H	-2.50528	-1.09609	1.25653
H	-2.78830	0.44931	0.41790
H	-3.35890	-1.06016	-0.28334
C	2.53883	-0.60524	0.27841
H	1.25264	-0.26144	-1.45047
H	1.10838	-1.87142	-0.74018
H	2.50482	-1.09666	1.25656
H	2.78823	0.44878	0.41815
H	3.35863	-1.06073	-0.28320

**Table 13:** B3LYP/6-31G\*\* energy minimised structures of acids, deprotonated acid anions, and protonated acids used in Table 9 and 10.

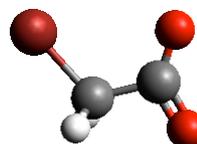
#### Bromoacetic acid

C	0.30848	-0.59819	0.77880
C	1.54466	-0.11246	0.05672
O	1.69901	1.22295	0.16636
O	2.31775	-0.83422	-0.52931
Br	-1.32275	0.04567	-0.12376
H	0.27573	-1.68336	0.75626
H	0.26384	-0.21034	1.79555
H	2.50368	1.44948	-0.32979



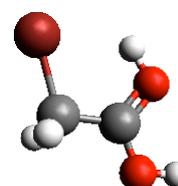
#### Bromoacetic acid anion

C	-0.47100	-0.82217	0.00033
C	-1.71465	0.12914	-0.00005
O	-1.57646	1.36033	0.00013
O	-2.73353	-0.61088	-0.00026
Br	1.38598	0.03039	-0.00005
H	-0.45801	-1.45017	0.89056
H	-0.45750	-1.45090	-0.88944



#### Protonated bromoacetic acid

C	0.32711	-0.93983	0.00041
Br	-1.36136	0.02623	-0.00009
C	1.48729	0.00877	0.00002
O	1.36817	1.27913	0.00022
O	2.65736	-0.51267	-0.00032
H	0.38380	-1.57387	-0.88904



H	0.38366	-1.57290	0.89062
H	3.38296	0.14690	-0.00046
H	0.40664	1.53652	0.00036

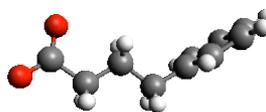
### Phenylbutyric acid

C	-4.07365	-0.07194	0.63878
C	-3.44268	1.16084	0.46579
C	-2.17573	1.22328	-0.11516
C	-1.51605	0.06005	-0.53312
C	-2.16216	-1.17060	-0.35509
C	-3.42882	-1.23881	0.22565
C	-0.12513	0.12818	-1.12704
C	0.98523	-0.00117	-0.06712
C	2.38420	0.07884	-0.67872
C	3.49041	-0.03858	0.34636
O	3.34625	-0.18473	1.53983
O	4.71502	0.04063	-0.23422
H	-5.06116	-0.12266	1.08798
H	-3.93836	2.07521	0.77954
H	-1.69231	2.18810	-0.25037
H	-1.66853	-2.08403	-0.67896
H	-3.91371	-2.20281	0.35143
H	-0.00485	-0.66722	-1.87397
H	-0.00168	1.07765	-1.66362
H	0.87077	0.78520	0.68667
H	0.87468	-0.94867	0.47104
H	2.54024	-0.70924	-1.42696
H	2.53145	1.02343	-1.21845
H	5.35958	-0.04262	0.48882



### Phenylbutyric acid anion

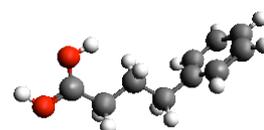
C	-4.02138	-0.05131	0.63586
C	-3.38415	1.17359	0.42846
C	-2.11642	1.21612	-0.15246
C	-1.45176	0.04309	-0.54124
C	-2.10661	-1.17881	-0.32316
C	-3.37406	-1.22925	0.25758
C	-0.06266	0.09174	-1.13452
C	1.07032	0.00123	-0.08543
C	2.47074	0.05904	-0.69383
C	3.64704	-0.02748	0.35907
O	3.29499	-0.12994	1.56153
O	4.79358	0.01827	-0.14752
H	-5.00975	-0.08758	1.08681
H	-3.87632	2.09891	0.71866
H	-1.62643	2.17436	-0.30892
H	-1.60913	-2.10128	-0.61367
H	-3.85835	-2.19037	0.41374



H	0.05245	-0.72865	-1.85597
H	0.05427	1.02229	-1.70628
H	0.96282	0.80859	0.64794
H	0.96643	-0.92337	0.49386
H	2.60799	-0.75562	-1.42104
H	2.60107	0.98825	-1.26915

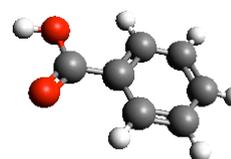
### Protonated phenylbutyric acid

C	3.42206	1.25302	0.26466
C	4.06977	0.08449	0.66898
C	3.46155	-1.15431	0.45984
C	2.20803	-1.22311	-0.14856
C	1.54850	-0.05611	-0.55475
C	2.16852	1.18222	-0.34337
C	0.17090	-0.13009	-1.17878
C	-0.94450	-0.03956	-0.11267
C	-2.34671	-0.06991	-0.73834
C	-3.46423	0.02302	0.23525
O	-4.67032	0.03533	-0.20505
O	-3.30967	0.09293	1.51282
H	5.04803	0.13849	1.13603
H	3.96640	-2.06694	0.76084
H	1.74749	-2.19309	-0.32286
H	1.67749	2.09611	-0.67067
H	3.89612	2.21817	0.41361
H	0.03707	0.68479	-1.90007
H	0.05545	-1.06954	-1.73199
H	-0.82220	-0.88245	0.58172
H	-0.80266	0.89181	0.45242
H	-2.49642	0.74611	-1.45982
H	-2.51998	-0.99010	-1.31569
H	-5.34311	0.09813	0.50412
H	-2.36716	0.08437	1.77657



### Benzoic acid

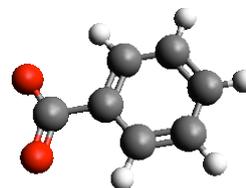
C	-2.57004	-0.04132	0.00012
C	-1.90361	1.18677	0.00017
C	-0.51218	1.22232	-0.00012
C	0.21992	0.02729	-0.00015
C	-0.45017	-1.20390	-0.00014
C	-1.84335	-1.23409	-0.00006
C	1.70362	0.12113	-0.00003
O	2.31474	-1.09146	0.00016
O	2.33579	1.15900	-0.00006
H	-3.65589	-0.06880	0.00009
H	-2.46942	2.11344	0.00028
H	0.12161	-2.12470	-0.00003
H	-2.36286	-2.18756	-0.00018



H	0.02939	2.16203	-0.00016
H	3.26780	-0.90384	0.00046

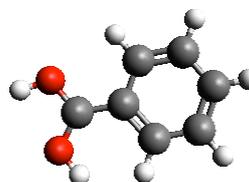
### Benzoic acid anion

C	2.53827	0.00000	0.00002
C	1.83290	1.20785	-0.00001
C	0.43687	1.20277	-0.00003
C	-0.28003	0.00000	-0.00002
C	0.43688	-1.20276	-0.00002
C	1.83290	-1.20786	0.00000
C	-1.83519	-0.00000	0.00004
O	-2.36630	-1.13883	-0.00001
O	-2.36632	1.13882	0.00002
H	3.62691	-0.00000	0.00006
H	2.37689	2.15181	-0.00001
H	-0.14769	-2.11858	-0.00003
H	2.37689	-2.15181	0.00004
H	-0.14770	2.11859	-0.00004



### Protonated benzoic acid

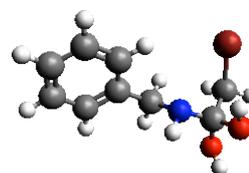
C	-1.89226	-1.22798	0.00001
C	-2.59463	-0.01734	0.00002
C	-1.91504	1.20898	-0.00000
C	-0.53042	1.22845	-0.00006
C	0.18872	0.00939	-0.00004
C	-0.50569	-1.22422	-0.00001
C	1.62233	-0.00192	-0.00001
O	2.39659	1.04764	0.00005
O	2.25153	-1.13621	-0.00002
H	-3.68006	-0.02600	0.00009
H	-2.47010	2.14028	0.00002
H	0.04756	-2.15604	0.00003
H	-2.42937	-2.16989	0.00009
H	-0.02928	2.19365	-0.00006
H	3.22083	-1.01888	0.00003
H	1.91738	1.89330	0.00008



**Table 14:** B3LYP/6-31G\*\* (PCM toluene solvent) energy minimised structures of intermediate compounds from Table 9.

### Intermediate 1a

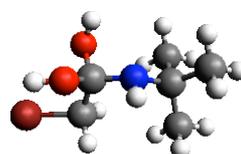
C	-2.34194	0.39134	-0.68581
H	-1.99398	0.48138	-1.71279
Br	-2.14526	-1.50941	-0.18896
H	-3.40409	0.61575	-0.62435
C	-1.59070	1.32295	0.27944



O	-1.78703	2.60675	-0.28723
H	-1.91828	3.22233	0.45558
O	-2.20791	1.35035	1.54551
H	-1.93963	0.53851	2.01084
N	-0.21333	0.94666	0.47419
H	0.19562	1.59305	1.15074
C	0.64522	0.84763	-0.71220
H	0.17571	0.13974	-1.40440
H	0.74638	1.80482	-1.24569
C	4.52935	-0.71652	0.36307
C	4.43164	0.51526	-0.28391
C	3.17697	1.02752	-0.62785
C	2.01136	0.31435	-0.33267
C	2.11859	-0.92285	0.31958
C	3.36772	-1.43524	0.66408
H	5.50379	-1.11673	0.63203
H	5.32978	1.08089	-0.51983
H	3.10391	1.98958	-1.13135
H	1.21016	-1.47256	0.54906
H	3.43820	-2.39743	1.16581

**Intermediate 1b**

C	0.70998	-0.57554	-0.27674
Br	2.66731	-0.37167	0.02779
H	0.39887	-1.33464	0.43593
H	0.61673	-0.92846	-1.30122
C	-0.04348	0.75361	-0.08457
O	0.48207	1.73986	-0.94839
H	1.43702	1.79269	-0.77194
O	0.12414	1.10085	1.26429
H	-0.40292	1.91008	1.39273
N	-1.44410	0.72313	-0.45356
H	-1.51883	0.90089	-1.45287
C	-2.45314	-0.27121	-0.01645
C	-3.81245	0.36284	-0.37640
H	-3.93645	1.32069	0.13605
H	-3.88738	0.54322	-1.45523
H	-4.63636	-0.29882	-0.09148
C	-2.34096	-1.62552	-0.75577
H	-2.32991	-1.47514	-1.84124
H	-1.43740	-2.17523	-0.48006
H	-3.19756	-2.26531	-0.51766
C	-2.39692	-0.49555	1.50287
H	-3.21199	-1.16351	1.79866
H	-1.45546	-0.94620	1.82417
H	-2.51318	0.44860	2.04154



**Intermediate 1c**

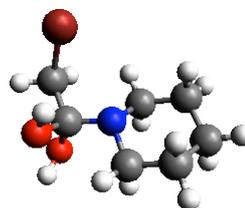
C	1.05748	-0.68354	-0.04510
H	0.82967	-1.25408	-0.94381

H	0.84986	-1.26144	0.85276
Br	3.02961	-0.43877	-0.06319
C	0.30614	0.65841	-0.05539
O	0.63422	1.30653	1.14574
H	0.11745	2.13338	1.14660
O	0.64714	1.42011	-1.18538
H	1.61726	1.50058	-1.19623
N	-1.12764	0.49347	-0.15647
H	-1.39199	0.22506	-1.10187
C	-1.79668	-0.32917	0.84939
H	-1.42372	-0.03161	1.83423
H	-1.61295	-1.41030	0.73546
C	-3.29732	-0.09854	0.79850
H	-3.51370	0.97601	0.90922
H	-3.78811	-0.63486	1.62788
O	-3.77335	-0.57421	-0.45116
C	-5.15512	-0.33512	-0.63656
H	-5.42707	-0.73511	-1.61625
H	-5.76151	-0.83698	0.13328
H	-5.38903	0.74018	-0.61286



**Intermediate 1d**

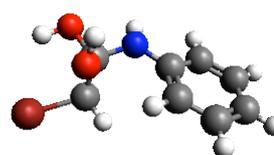
C	-1.55408	0.62587	0.80607
H	-1.40447	0.25635	1.81788
Br	-2.24822	-0.88411	-0.26128
H	-2.33226	1.38499	0.79260
C	-0.28679	1.24348	0.19234
O	-0.60989	1.88645	-1.02280
H	-0.72612	1.18904	-1.69181
O	0.04189	2.27804	1.10594
H	0.30084	3.05173	0.57627
C	1.07218	-0.64131	1.05634
N	0.78292	0.29164	-0.04376
C	2.01752	0.94163	-0.52081
C	3.00801	-0.09628	-1.05285
C	3.33922	-1.13355	0.02679
C	2.04641	-1.73120	0.59329
H	0.14484	-1.12414	1.36942
H	1.49073	-0.11008	1.93064
H	1.74901	1.64905	-1.30853
H	2.49396	1.51763	0.29298
H	2.56675	-0.59595	-1.92478
H	3.91631	0.41431	-1.39484
H	3.98561	-1.92253	-0.37513
H	3.90080	-0.64593	0.83649
H	2.26218	-2.39854	1.43621
H	1.54813	-2.33146	-0.17841



**Intermediate 1e**

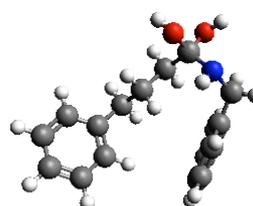
C	-1.04758	-0.21164	-0.59672
---	----------	----------	----------

H	-0.98657	0.12444	-1.62978
Br	-2.94739	-0.69828	-0.30632
H	-0.47658	-1.12460	-0.44639
C	-0.59371	0.91070	0.34989
O	-0.70972	0.41857	1.65549
H	-0.37060	1.11963	2.24317
O	-1.35051	2.07937	0.15695
H	-2.28818	1.83427	0.25140
N	0.76041	1.33961	0.05421
H	0.76245	2.07647	-0.64498
C	4.23189	-1.06649	-0.11629
C	4.10973	0.08819	-0.89272
C	2.94915	0.85580	-0.84320
C	1.88192	0.49292	-0.00102
C	2.01059	-0.66428	0.78885
C	3.17408	-1.43120	0.71761
H	5.13554	-1.66784	-0.15878
H	4.91994	0.39343	-1.55064
H	2.86154	1.74934	-1.45859
H	1.21154	-0.94690	1.46350
H	3.25193	-2.32324	1.33485



#### Intermediate **2a**

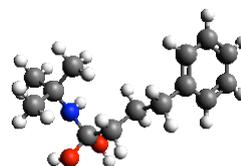
C	-2.86864	0.70795	-0.00360
C	-2.61630	-0.55179	0.55937
C	-3.62150	-1.52547	0.48500
C	-4.84345	-1.25252	-0.13322
C	-5.08087	0.00528	-0.69012
C	-4.08798	0.98555	-0.62282
H	-2.10010	1.47584	0.04603
H	-3.44605	-2.50713	0.92137
H	-5.61107	-2.02167	-0.17604
H	-6.03252	0.22151	-1.16922
H	-4.26548	1.96996	-1.04975
C	-1.27878	-0.85847	1.19911
H	-0.92945	0.01773	1.75958
H	-1.39932	-1.66997	1.92812
C	-0.19717	-1.25302	0.17390
H	-0.54010	-2.11591	-0.40841
H	-0.06870	-0.42933	-0.53730
C	1.14399	-1.57783	0.83575
H	1.47670	-0.73719	1.45272
H	1.02941	-2.43027	1.51932
C	2.27349	-1.93551	-0.15229
O	1.86896	-2.97956	-1.02456
H	1.57495	-3.71759	-0.46448
O	3.35665	-2.34374	0.65567
H	4.08908	-2.51731	0.03553
N	2.73495	-0.91019	-1.07205
H	2.07216	-0.78554	-1.83282



C	3.24182	0.35265	-0.52777
H	3.96671	0.74485	-1.25421
H	3.80939	0.10660	0.37392
C	0.42783	3.54837	0.32330
C	1.23664	3.03772	1.33953
C	2.13442	2.00232	1.06661
C	2.23790	1.45801	-0.21965
C	1.42757	1.98889	-1.23425
C	0.52766	3.02114	-0.96773
H	-0.26914	4.35616	0.53184
H	1.17117	3.44506	2.34558
H	2.76624	1.61384	1.86322
H	1.50667	1.59788	-2.24759
H	-0.08985	3.42052	-1.76869

**Intermediate 2b**

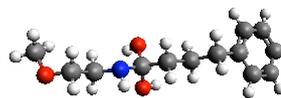
C	-3.75389	-1.05684	0.02809
C	-2.89745	-0.10800	-0.54892
C	-3.27532	1.24070	-0.50287
C	-4.47106	1.63256	0.10225
C	-5.31310	0.67706	0.67379
C	-4.95021	-0.67114	0.63405
H	-3.48156	-2.11032	-0.00336
H	-2.62829	1.99165	-0.95148
H	-4.74652	2.68438	0.12288
H	-6.24636	0.97942	1.14224
H	-5.60176	-1.42402	1.07140
C	-1.58399	-0.52937	-1.17285
H	-1.71649	-1.48309	-1.70036
H	-1.28639	0.20527	-1.93184
C	-0.44700	-0.68108	-0.14224
H	-0.74781	-1.39549	0.63158
H	-0.30048	0.27596	0.37064
C	0.86302	-1.14793	-0.78299
H	0.71693	-2.13771	-1.23603
H	1.15058	-0.48651	-1.60682
C	2.05279	-1.27633	0.19410
O	3.05379	-1.94672	-0.54281
O	1.67040	-2.05780	1.32347
H	1.43329	-2.93601	0.98079
H	3.84017	-1.93949	0.03197
N	2.60243	-0.08844	0.82091
H	2.08176	0.11003	1.67123
C	2.99884	1.16196	0.13365
C	3.83081	1.93931	1.17458
H	3.23157	2.16687	2.06429
H	4.69500	1.34895	1.49160
H	4.18489	2.88872	0.76030
C	1.80996	2.05601	-0.29288
H	1.16032	2.27110	0.56270



H	2.17294	3.01372	-0.68207
H	1.20397	1.59296	-1.07484
C	3.88874	0.86814	-1.08596
H	4.23184	1.81301	-1.51968
H	4.76824	0.28621	-0.79641
H	3.36070	0.30944	-1.86115

**Intermediate 2c**

C	-5.67831	-0.95207	0.57164
C	-4.42636	-1.14662	-0.01437
C	-3.71300	-0.07298	-0.56559
C	-4.29003	1.20370	-0.51560
C	-5.54167	1.40377	0.06894
C	-6.24038	0.32542	0.61578
H	-6.21707	-1.79942	0.98916
H	-3.99788	-2.14668	-0.05045
H	-3.75363	2.04860	-0.94370
H	-5.97328	2.40161	0.09326
H	-7.21701	0.47854	1.06812
C	-2.33780	-0.27928	-1.16412
H	-2.17671	0.44203	-1.97500
H	-2.27837	-1.27739	-1.61653
C	-1.20494	-0.12735	-0.12947
H	-1.37631	-0.84976	0.68033
H	-1.25411	0.87133	0.31900
C	0.18191	-0.34242	-0.74114
H	0.33221	0.34163	-1.58294
H	0.26065	-1.36259	-1.13718
C	1.35327	-0.12200	0.22922
O	1.33106	1.23718	0.61283
O	1.25146	-0.93991	1.39712
H	0.44557	-0.68738	1.87630
N	2.58711	-0.45394	-0.45128
C	3.83010	-0.21041	0.28229
H	3.82535	0.83446	0.60938
H	3.94939	-0.83915	1.17756
C	5.02051	-0.44384	-0.65437
H	5.00061	-1.47742	-1.02164
H	4.93864	0.22144	-1.52749
O	6.27541	-0.28829	-0.00845
C	6.67393	1.06056	0.15754
H	7.68041	1.04619	0.58315
H	6.70267	1.59419	-0.80480
H	6.01652	1.61776	0.84018
H	2.53831	-1.43561	-0.72520
H	1.81740	1.30451	1.45103



**Intermediate 2d**

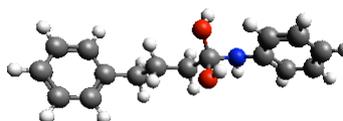
C	5.51859	0.58127	-1.17738
C	4.21748	0.09405	-1.31252



C	3.57791	-0.56059	-0.25047
C	4.27997	-0.71606	0.95304
C	5.58127	-0.23118	1.09347
C	6.20533	0.42073	0.02781
H	5.99765	1.08199	-2.01544
H	3.69096	0.21719	-2.25724
H	3.80240	-1.22822	1.78635
H	6.10959	-0.36665	2.03428
H	7.22006	0.79602	0.13414
C	2.15218	-1.05116	-0.38605
H	2.01080	-1.94710	0.23155
H	1.96346	-1.35250	-1.42424
C	1.11160	0.01039	0.02416
H	1.26232	0.90499	-0.59176
H	1.28782	0.30283	1.06620
C	-0.32679	-0.49517	-0.13158
H	-0.43520	-1.41971	0.44285
H	-0.53454	-0.72573	-1.18195
C	-1.39589	0.51491	0.33132
O	-1.26515	0.58886	1.75418
O	-1.15475	1.79617	-0.22548
H	-0.41595	2.17749	0.27365
C	-3.18098	-1.18819	0.29679
N	-2.72923	0.14540	-0.12734
C	-3.76758	1.15156	0.15132
C	-5.04687	0.83439	-0.62889
C	-5.56546	-0.56727	-0.28769
C	-4.44547	-1.59859	-0.46745
H	-3.37990	-1.21143	1.38450
H	-2.39519	-1.91925	0.10162
H	-4.01534	1.18624	1.23285
H	-3.38257	2.13083	-0.13156
H	-5.80385	1.59578	-0.40527
H	-4.82474	0.89828	-1.70142
H	-5.90680	-0.58213	0.75736
H	-6.43343	-0.82345	-0.90649
H	-4.19503	-1.68899	-1.53197
H	-4.76823	-2.58824	-0.12236
H	-1.88211	1.26919	2.07086

**Intermediate 2e**

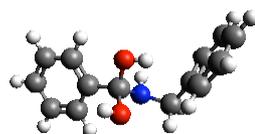
C	-5.77832	0.00301	1.40262
C	-4.55997	-0.61189	1.11040
C	-3.98286	-0.50092	-0.16250
C	-4.66187	0.24351	-1.13684
C	-5.88104	0.86014	-0.85025
C	-6.44366	0.74208	0.42216
H	-6.21031	-0.09858	2.39546
H	-4.04974	-1.18969	1.87893
H	-4.23169	0.33676	-2.13240



H	-6.39320	1.42973	-1.62221
H	-7.39448	1.21886	0.64700
C	-2.64287	-1.13773	-0.46471
H	-2.59385	-1.39789	-1.53011
H	-2.55096	-2.08021	0.09058
C	-1.45057	-0.22653	-0.11110
H	-1.47596	0.01550	0.95655
H	-1.54134	0.72425	-0.64740
C	-0.10548	-0.87248	-0.45165
H	-0.05914	-1.11369	-1.52124
H	0.00505	-1.81730	0.09672
C	1.10685	0.01360	-0.11990
O	0.99669	1.30406	-0.70244
O	1.10750	0.20250	1.26786
H	1.74913	0.89998	1.47723
H	1.21257	1.20956	-1.64649
N	2.31015	-0.64359	-0.64083
H	2.21202	-1.65414	-0.60296
C	6.25690	0.45289	0.43729
C	5.26875	1.43075	0.32358
C	3.95903	1.09700	-0.02635
C	3.60678	-0.24697	-0.25298
C	4.60858	-1.22795	-0.13487
C	5.91500	-0.88044	0.19781
H	7.27483	0.72285	0.70410
H	5.51521	2.47560	0.49838
H	3.21488	1.87527	-0.14894
H	4.35269	-2.27210	-0.30661
H	6.66822	-1.66058	0.27970

**Intermediate 3a**

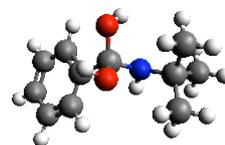
C	-4.05764	1.10382	1.00945
C	-4.58807	1.00642	-0.28036
C	-4.02781	0.10960	-1.19069
C	-2.94142	-0.68558	-0.81271
C	-2.39659	-0.59367	0.47737
C	-2.97316	0.31036	1.38259
C	-1.20309	-1.45034	0.88494
N	0.12173	-0.80884	0.90524
C	0.65772	-0.27593	-0.33122
O	0.02646	0.90761	-0.80152
C	2.13791	0.06352	-0.12935
C	2.62512	1.36969	-0.22721
C	3.98578	1.62959	-0.03639
C	4.86692	0.58793	0.25268
C	4.38254	-0.72015	0.35312
C	3.02651	-0.97938	0.16533
O	0.49030	-1.31247	-1.28240
H	5.92481	0.79127	0.40054
H	4.35428	2.64966	-0.11490



H	1.93906	2.17803	-0.45362
H	2.64077	-1.99117	0.24479
H	5.06308	-1.53750	0.57946
H	0.81316	-0.95906	-2.12917
H	-0.91897	0.70701	-0.87865
H	0.18027	-0.08984	1.62372
H	-1.36871	-1.82715	1.90048
H	-1.13748	-2.31852	0.22592
H	-5.43477	1.62331	-0.57069
H	-4.43816	0.02249	-2.19391
H	-2.50679	-1.38592	-1.52237
H	-2.57131	0.38700	2.39176
H	-4.49378	1.79584	1.72590

**Intermediate 3b**

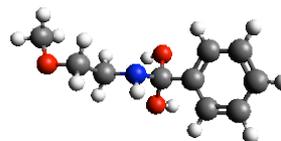
C	3.11954	-1.43654	-0.24491
C	3.95810	-0.55557	0.44246
C	3.47749	0.69720	0.82678
C	2.16346	1.06609	0.53041
C	1.31702	0.18752	-0.15141
C	1.80735	-1.06622	-0.54072
C	-0.14703	0.55741	-0.45479
N	-0.98821	-0.02921	0.55878
C	-2.43627	-0.32029	0.36113
C	-2.66599	-1.57386	-0.51162
O	-0.49429	0.10919	-1.75505
O	-0.31771	1.97113	-0.47088
C	-3.16380	0.88636	-0.25134
C	-2.99191	-0.58522	1.77341
H	4.98152	-0.84230	0.67153
H	4.12655	1.39157	1.35489
H	1.79650	2.04729	0.81349
H	1.15906	-1.74016	-1.09300
H	3.48944	-2.41046	-0.55645
H	-0.02565	0.68318	-2.38692
H	-0.57669	2.21912	0.43038
H	-0.53148	-0.83891	0.96497
H	-4.23213	0.66102	-0.33335
H	-3.05394	1.77527	0.37778
H	-2.77834	1.11857	-1.24467
H	-4.06052	-0.81936	1.72991
H	-2.48461	-1.43632	2.24351
H	-2.85055	0.28901	2.41568
H	-3.73258	-1.82263	-0.55563
H	-2.29871	-1.41551	-1.52600
H	-2.14218	-2.43866	-0.08665



**Intermediate 3c**

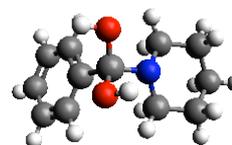
C	4.19645	-0.93191	-0.41207
C	3.40523	-1.47533	0.60428

C	2.14843	-0.93811	0.87877
C	1.67387	0.15533	0.14438
C	2.46623	0.69473	-0.87336
C	3.72392	0.15243	-1.15128
H	5.17595	-1.35308	-0.62513
H	3.76870	-2.32055	1.18379
H	1.52972	-1.35744	1.66540
H	2.09607	1.54274	-1.44206
H	4.33290	0.58053	-1.94383
C	0.27999	0.72031	0.42123
O	0.16270	2.07878	0.00247
H	0.82879	2.59282	0.49320
O	0.06216	0.65496	1.81627
N	-0.69257	-0.07563	-0.29668
C	-2.09360	0.33586	-0.18582
H	-2.34315	0.39299	0.87926
H	-2.30507	1.32008	-0.62891
C	-2.98009	-0.71951	-0.85655
H	-2.71674	-0.79667	-1.91875
H	-2.79613	-1.70189	-0.39564
O	-4.36040	-0.38813	-0.82379
C	-4.99073	-0.66907	0.41272
H	-6.05406	-0.45081	0.28581
H	-4.87619	-1.72741	0.69295
H	-4.60603	-0.05146	1.23711
H	-0.41286	-0.11768	-1.27642
H	-0.66780	1.26404	2.01652



**Intermediate 3d**

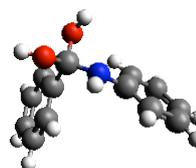
C	-1.36122	-0.50901	-1.12044
C	-2.83197	-0.93312	-1.19114
C	-3.32436	-1.43726	0.17122
C	-3.02045	-0.40148	1.26071
C	-1.54351	0.00879	1.24109
N	-1.18002	0.52239	-0.08811
H	-1.03883	-0.09927	-2.07992
H	-0.73571	-1.39771	-0.91565
H	-2.94720	-1.70933	-1.95732
H	-3.43435	-0.07143	-1.50669
H	-4.39706	-1.66163	0.13727
H	-2.81199	-2.37923	0.41397
H	-3.63574	0.49355	1.10264
H	-3.27038	-0.79699	2.25267
H	-1.36085	0.79171	1.97700
H	-0.92065	-0.86345	1.51643
C	0.09552	1.24302	-0.17395
C	3.56964	-1.33983	0.22159
C	3.06174	-1.04186	-1.04453
C	1.95827	-0.19812	-1.18042
C	1.34768	0.36381	-0.05075



C	1.86510	0.06060	1.21664
C	2.96775	-0.78464	1.35201
H	4.43040	-1.99574	0.32589
H	3.52874	-1.46288	-1.93173
H	1.57700	0.04333	-2.16659
H	1.41037	0.50454	2.09655
H	3.35884	-1.00466	2.34246
O	0.04158	2.20235	0.86309
H	0.86626	2.71444	0.80440
O	0.16187	1.88556	-1.42441
H	-0.69155	2.34929	-1.51623

**Intermediate 3e**

C	3.03039	-2.10085	-0.29648
C	2.92045	-1.47913	0.94686
C	2.14879	-0.32302	1.09099
C	1.47749	0.21968	-0.00934
C	1.59545	-0.40792	-1.25681
C	2.36471	-1.56048	-1.40040
H	3.62902	-3.00170	-0.40714
H	3.43396	-1.89328	1.81128
H	2.06258	0.15744	2.05884
H	1.08062	0.00937	-2.11799
H	2.44399	-2.03905	-2.37344
C	0.66483	1.51648	0.08972
O	1.27222	2.53427	-0.69171
H	2.20734	2.57516	-0.42875
O	0.61715	1.88584	1.44460
N	-0.67045	1.46252	-0.47510
H	-0.69052	1.80589	-1.42924
H	0.02981	2.66179	1.48894
C	-3.64273	-1.42248	0.34047
C	-2.64895	-1.15827	1.28461
C	-1.65010	-0.21660	1.03884
C	-1.62198	0.47754	-0.18427
C	-2.62401	0.20701	-1.13445
C	-3.62264	-0.72663	-0.87050
H	-4.41876	-2.15520	0.54410
H	-2.64950	-1.68687	2.23531
H	-0.90160	-0.00623	1.79255
H	-2.61330	0.73770	-2.08499
H	-4.38559	-0.91540	-1.62239



**Table 15:** B3LYP/6-31G\*\* (PCM toluene solvent) energy minimised structures of water and amides from Table 9 and 10.

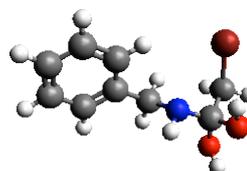
**Water**

O	0.00000	0.12019	0.00000
H	0.75964	-0.48074	0.00000
H	-0.75964	-0.48074	0.00000



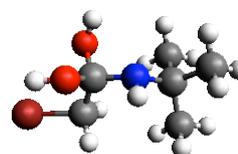
**Amide\_final 1a**

C	4.22712	-0.59054	-0.79369
C	4.27759	-1.12035	0.49512
C	3.24694	-0.84380	1.39713
C	2.17509	-0.04091	1.01179
C	2.11542	0.49606	-0.28153
C	3.14954	0.20993	-1.17854
C	0.96472	1.39113	-0.69737
N	-0.33930	0.79498	-0.43278
C	-1.31632	1.45647	0.22776
O	-1.22329	2.59894	0.66376
C	-2.65133	0.74700	0.45367
Br	-2.80235	-1.12630	-0.17499
H	5.11245	-1.74627	0.79616
H	3.28029	-1.25252	2.40293
H	1.37545	0.17196	1.71581
H	3.11194	0.61690	-2.18612
H	5.02168	-0.80349	-1.50292
H	0.97598	2.33588	-0.14504
H	1.05438	1.63719	-1.76276
H	-0.52270	-0.15030	-0.74207
H	-2.86149	0.72550	1.52145
H	-3.43702	1.29924	-0.05963



**Amide\_final 1b**

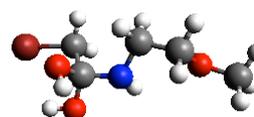
C	-2.78681	-0.80946	1.26715
C	-2.59672	0.04390	0.00037
N	-1.23998	0.65132	-0.00043
C	-0.06291	-0.02971	-0.00162
O	0.03930	-1.24902	-0.00152
C	-2.78821	-0.80963	-1.26607
C	-3.59100	1.21450	0.00085
C	1.14823	0.92287	-0.00187
Br	2.85487	-0.02659	0.00062
H	-1.19826	1.66105	-0.00014
H	1.14602	1.55384	-0.89154
H	1.14475	1.55628	0.88606
H	-2.05652	-1.61967	1.29784
H	-2.66778	-0.19628	2.16623
H	-3.79193	-1.24311	1.27893



H	-2.67012	-0.19659	-2.16537
H	-2.05799	-1.61989	-1.29744
H	-3.79336	-1.24324	-1.27672
H	-3.46410	1.84097	0.89070
H	-3.46509	1.84088	-0.88920
H	-4.61593	0.83463	0.00144

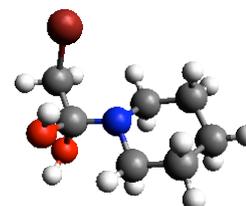
Amide\_final 1c

C	-4.86619	-0.69495	-0.63421
O	-3.90036	-0.32850	0.33272
C	-2.58279	-0.33405	-0.17919
C	-1.65549	0.12543	0.94661
N	-0.25514	0.10108	0.55187
C	0.35950	1.17856	0.01949
O	-0.17840	2.26590	-0.17488
C	1.83356	1.06701	-0.36604
Br	2.71868	-0.68086	-0.06029
H	1.94017	1.27292	-1.42960
H	2.40527	1.79574	0.20596
H	-1.91120	1.14776	1.23233
H	-1.78931	-0.52108	1.81834
H	0.27587	-0.75346	0.64894
H	-4.69481	-1.71340	-1.01537
H	-4.86885	-0.00218	-1.48920
H	-5.84307	-0.65965	-0.14682
H	-2.48637	0.34816	-1.03855
H	-2.29709	-1.34333	-0.52164



Amide\_final 1d

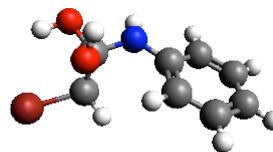
C	1.67909	-1.15561	0.66431
N	1.13987	0.18793	0.43445
C	2.14651	1.25738	0.45981
C	3.25596	0.98680	-0.56311
C	3.87096	-0.40489	-0.35726
C	2.78126	-1.48649	-0.35287
C	-0.17060	0.50837	0.20564
O	-0.55314	1.65807	0.02298
C	-1.14481	-0.68284	0.19101
Br	-2.98842	-0.12237	-0.15009
H	-0.90020	-1.39497	-0.59691
H	-1.16317	-1.20130	1.14961
H	1.63061	2.19583	0.26260
H	2.57518	1.30684	1.47170
H	4.02200	1.76561	-0.47590
H	2.83285	1.06115	-1.57275
H	4.40557	-0.42698	0.60284
H	4.61315	-0.61639	-1.13462
H	3.20680	-2.46725	-0.11195
H	2.33066	-1.56368	-1.35059
H	2.09455	-1.19495	1.68235



H	0.88261	-1.89723	0.61660
---	---------	----------	---------

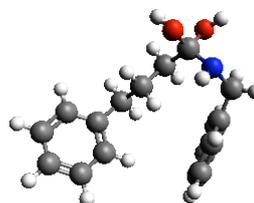
Amide\_final 1e

C	-3.39751	-1.62919	0.00012
C	-4.30501	-0.56779	-0.00007
C	-3.82290	0.74146	-0.00021
C	-2.45313	1.00807	-0.00015
C	-1.54722	-0.06279	0.00007
C	-2.02789	-1.38137	0.00019
N	-0.14377	0.10609	0.00005
C	0.57316	1.25863	0.00011
O	0.11827	2.39791	0.00015
C	2.09921	1.14625	0.00011
Br	2.88643	-0.67169	-0.00008
H	-5.37335	-0.75979	-0.00013
H	-4.51881	1.57536	-0.00038
H	-2.08134	2.02256	-0.00025
H	-1.32512	-2.21101	0.00032
H	-3.75366	-2.65497	0.00023
H	0.40085	-0.74814	0.00012
H	2.48721	1.63984	-0.88932
H	2.48723	1.63962	0.88965



Amide\_final 2a

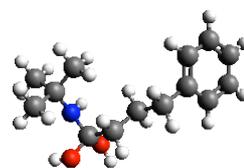
C	-4.66456	-0.43087	0.70694
C	-3.91195	-0.15462	-0.44348
C	-4.17989	1.02940	-1.14336
C	-5.16859	1.91371	-0.70798
C	-5.90917	1.62642	0.43973
C	-5.65369	0.44936	1.14650
C	-2.81457	-1.09589	-0.89294
C	-1.48121	-0.85172	-0.16175
C	-0.37266	-1.80852	-0.61882
C	0.88544	-1.67533	0.23460
O	0.83173	-1.59567	1.46180
N	2.06404	-1.68550	-0.45133
C	3.36155	-1.56171	0.20894
C	3.94933	-0.16427	0.13657
C	5.11764	0.08727	-0.58972
C	5.65320	1.37641	-0.65590
C	5.02009	2.42897	0.00462
C	3.85160	2.18674	0.73357
C	3.32049	0.89992	0.80027
H	5.43398	3.43194	-0.04445
H	6.56206	1.55570	-1.22320
H	5.61483	-0.73108	-1.10546
H	2.41670	0.70726	1.37158
H	3.35772	3.00186	1.25486
H	4.05323	-2.28280	-0.23867
H	3.19569	-1.85186	1.24919



H	2.03854	-1.64542	-1.45961
H	-0.14686	-1.66133	-1.68185
H	-0.71981	-2.84523	-0.51229
H	-1.61906	-0.96988	0.91734
H	-1.16284	0.18579	-0.32237
H	-2.66133	-0.99039	-1.97426
H	-3.12727	-2.13414	-0.72218
H	-3.61036	1.25862	-2.04111
H	-5.36228	2.82460	-1.26756
H	-6.68079	2.31147	0.77875
H	-6.22762	0.21441	2.03852
H	-4.47496	-1.34728	1.26098

Amide\_final **2b**

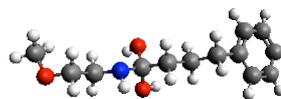
C	5.08632	-1.12417	0.47306
C	5.64268	0.06636	0.94517
C	5.00035	1.27751	0.68187
C	3.81065	1.29491	-0.04802
C	3.24034	0.10777	-0.52734
C	3.89659	-1.10096	-0.25580
C	1.93058	0.12491	-1.28657
C	0.70638	-0.06152	-0.37047
C	-0.61901	-0.04322	-1.14131
C	-1.80779	-0.39647	-0.24451
O	-1.73901	-1.31441	0.57433
N	-2.92327	0.35819	-0.44010
C	-4.22333	0.19517	0.25445
C	-5.15906	1.26998	-0.31956
C	-4.79791	-1.20550	-0.02658
C	-4.03949	0.41244	1.76769
H	-2.87055	1.08624	-1.13727
H	-0.58637	-0.79830	-1.93872
H	-0.76602	0.92598	-1.63359
H	-4.11918	-1.97622	0.34182
H	-4.94466	-1.35254	-1.10163
H	-5.76659	-1.32222	0.47029
H	-3.34324	-0.32179	2.17557
H	-3.64745	1.41509	1.96709
H	-5.00078	0.31173	2.28223
H	-4.76402	2.27595	-0.13871
H	-5.29749	1.13879	-1.39872
H	-6.14185	1.20483	0.15496
H	0.70050	0.72693	0.39241
H	0.78192	-1.01133	0.16748
H	1.83555	1.07279	-1.83138
H	1.93304	-0.67052	-2.04273
H	6.57011	0.05037	1.51022
H	5.42716	2.20982	1.04109
H	3.31875	2.24300	-0.25312
H	3.47178	-2.03230	-0.62290



H	5.58063	-2.07155	0.66919
---	---------	----------	---------

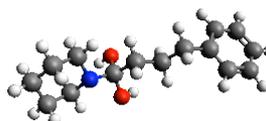
Amide\_final 2c

C	-5.06094	0.57954	1.29360
C	-4.02267	-0.30289	0.99408
C	-3.41003	-0.29461	-0.26719
C	-3.86850	0.62305	-1.22177
C	-4.90730	1.50807	-0.92749
C	-5.50710	1.48953	0.33268
C	-2.25995	-1.23003	-0.57439
C	-0.90341	-0.69313	-0.08064
C	0.26056	-1.63922	-0.40379
C	1.56405	-1.18043	0.24373
O	1.61754	-0.82345	1.41897
N	2.66707	-1.21757	-0.55915
C	3.98915	-0.84092	-0.08407
C	4.26598	0.65336	-0.25362
O	5.59085	0.89321	0.18084
C	5.94801	2.26032	0.12033
H	0.37514	-1.75567	-1.48834
H	0.04037	-2.63713	-0.00144
H	4.74226	-1.41640	-0.63019
H	4.05743	-1.10072	0.97434
H	2.55767	-1.48163	-1.52639
H	-0.93369	-0.53734	1.00211
H	-0.71592	0.28982	-0.53071
H	-3.68418	-1.01120	1.74667
H	-3.40929	0.64060	-2.20750
H	-5.24991	2.20880	-1.68379
H	-6.31744	2.17499	0.56310
H	5.29781	2.87958	0.75660
H	5.89626	2.65034	-0.90812
H	6.97685	2.34415	0.47793
H	4.14004	0.94805	-1.30985
H	3.54175	1.23054	0.34175
H	-5.52430	0.55412	2.27590
H	-2.44471	-2.20682	-0.10884
H	-2.20986	-1.40488	-1.65644



Amide\_final 2d

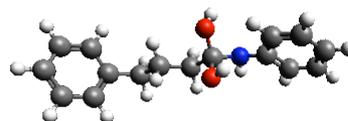
C	-5.30401	-0.14609	1.39119
C	-4.01685	-0.63158	1.15561
C	-3.42684	-0.52733	-0.11145
C	-4.16422	0.07676	-1.13925
C	-5.45144	0.56420	-0.90941
C	-6.02620	0.45449	0.35834
C	-2.01565	-1.01910	-0.35474
C	-0.95292	0.07262	-0.12369
C	0.46718	-0.43904	-0.37607
C	1.52443	0.64811	-0.15975



O	1.19556	1.78457	0.18469
N	2.83817	0.30804	-0.36418
C	3.33248	-1.00495	-0.77935
C	4.37479	-1.53912	0.21464
C	5.50651	-0.52365	0.42784
C	4.93935	0.84810	0.82230
C	3.88379	1.31992	-0.18543
H	0.54804	-0.82479	-1.40106
H	0.67962	-1.29124	0.28317
H	3.79238	-0.91064	-1.77548
H	-1.02866	0.45291	0.90002
H	-1.15390	0.92908	-0.77524
H	-3.46191	-1.10110	1.96454
H	-3.72481	0.16272	-2.13037
H	-6.00677	1.02612	-1.72097
H	-7.02913	0.83035	0.53871
H	2.50374	-1.70442	-0.87452
H	4.77142	-2.49102	-0.15723
H	3.87682	-1.74545	1.17069
H	6.08131	-0.42361	-0.50388
H	6.20544	-0.88561	1.19008
H	-5.74385	-0.24008	2.38017
H	-1.80696	-1.87202	0.30383
H	-1.93047	-1.39278	-1.38337
H	5.73986	1.59442	0.88328
H	4.47829	0.78712	1.81632
H	4.36016	1.50916	-1.15952
H	3.39530	2.23805	0.13786

Amide\_final 2e

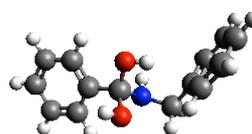
C	-5.61192	-0.39609	1.45077
C	-4.44319	-0.94145	0.91656
C	-3.86696	-0.41326	-0.24650
C	-4.49558	0.67775	-0.86309
C	-5.66386	1.22669	-0.33338
C	-6.22624	0.69117	0.82720
C	-2.57829	-0.97962	-0.80417
C	-1.33034	-0.22992	-0.30110
C	-0.02894	-0.80676	-0.86890
C	1.18796	0.04205	-0.50257
O	1.12730	1.26478	-0.43085
N	2.33785	-0.68324	-0.29405
C	3.64176	-0.22827	-0.00079
C	3.96807	1.12644	0.16893
C	5.28564	1.48110	0.46117
C	6.28521	0.51602	0.58858
C	5.95578	-0.83032	0.41886
C	4.64655	-1.20142	0.12637
H	7.30577	0.80707	0.81677
H	5.52776	2.53210	0.59072



H	3.19467	1.87410	0.07093
H	4.39751	-2.25194	-0.00541
H	6.71860	-1.59752	0.51360
H	2.24850	-1.68587	-0.37990
H	-1.30126	-0.26423	0.79475
H	-1.39258	0.82769	-0.57393
H	0.10583	-1.84624	-0.54554
H	-0.08525	-0.82812	-1.96649
H	-3.97325	-1.79115	1.40641
H	-4.06608	1.09817	-1.76943
H	-6.13689	2.06985	-0.82893
H	-7.13714	1.11532	1.23947
H	-6.04413	-0.82285	2.35154
H	-2.49788	-2.04067	-0.53624
H	-2.60139	-0.93585	-1.90067

Amide\_final **3a**

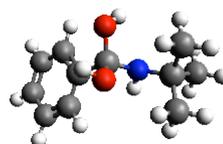
C	3.43020	1.90519	-0.39957
C	4.67321	1.28555	-0.25838
C	4.74132	-0.07805	0.03894
C	3.57133	-0.81864	0.18989
C	2.31982	-0.20892	0.03025
C	2.25807	1.16229	-0.25713
C	1.10089	-1.07211	0.20844
O	1.14146	-2.11631	0.86024
N	-0.04332	-0.62767	-0.39263
C	-1.29734	-1.36653	-0.32586
C	-2.49606	-0.45921	-0.13047
C	-2.50528	0.51142	0.88124
C	-3.62131	1.32430	1.07465
C	-4.74736	1.17768	0.25981
C	-4.74748	0.21500	-0.74972
C	-3.62612	-0.59489	-0.94407
H	-5.61647	1.81117	0.41078
H	-3.61457	2.07108	1.86349
H	-1.63082	0.62776	1.51531
H	-3.62869	-1.34045	-1.73545
H	-5.61634	0.09653	-1.39068
H	-1.18846	-2.06545	0.50856
H	-1.43709	-1.97216	-1.23084
H	0.01540	0.13477	-1.05097
H	5.58495	1.86454	-0.37193
H	5.70636	-0.56201	0.15593
H	3.60264	-1.87497	0.43332
H	1.29936	1.66647	-0.33676
H	3.37189	2.96840	-0.61227



Amide\_final **3b**

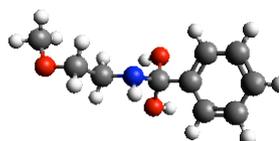
C	3.58673	-0.84934	-0.28866
C	4.01417	0.47063	-0.12271

C	3.08285	1.47263	0.15535
C	1.72666	1.15971	0.25364
C	1.28965	-0.16082	0.07573
C	2.23392	-1.16354	-0.18172
C	-0.15594	-0.57894	0.17741
O	-0.45821	-1.73705	0.47601
N	-1.07222	0.39665	-0.08252
C	-2.54503	0.22326	-0.08609
C	-3.13967	1.59882	-0.42537
C	-3.01983	-0.22029	1.30899
C	-2.95687	-0.80837	-1.15347
H	5.06928	0.71571	-0.20104
H	3.41205	2.49657	0.30506
H	1.01864	1.94440	0.50439
H	1.88354	-2.18396	-0.29267
H	-0.72381	1.24937	-0.49482
H	4.30887	-1.63289	-0.49818
H	-2.57656	-1.18024	1.57620
H	-2.73602	0.51968	2.06404
H	-4.11003	-0.31964	1.31728
H	-2.63540	-0.48330	-2.14851
H	-2.50316	-1.77732	-0.93893
H	-4.04561	-0.92426	-1.16682
H	-2.84773	2.34886	0.31757
H	-2.81139	1.94144	-1.41372
H	-4.23147	1.54295	-0.43887



Amide\_final 3c

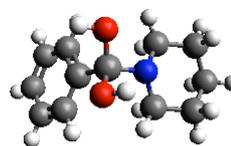
C	3.40327	-1.50795	-0.21369
C	4.35680	-0.49102	-0.28820
C	3.95561	0.84562	-0.21745
C	2.60769	1.16273	-0.06773
C	1.64645	0.14785	0.02987
C	2.05395	-1.19124	-0.05459
C	0.21172	0.56705	0.19482
O	-0.18117	1.67971	-0.15771
N	-0.62633	-0.34805	0.76635
C	-2.02648	-0.04414	1.02441
C	-2.91326	-0.33465	-0.18653
O	-4.24794	-0.05176	0.18865
C	-5.16389	-0.22554	-0.87481
H	-2.11628	1.01313	1.28654
H	-2.36393	-0.64112	1.87574
H	-0.23494	-1.18554	1.16758
H	5.40713	-0.73886	-0.40952
H	4.69374	1.63945	-0.28210
H	2.27463	2.19393	-0.02353
H	1.32159	-1.99324	-0.03341
H	3.70785	-2.54758	-0.28765
H	-5.16884	-1.26306	-1.24355



H	-4.93570	0.43966	-1.72131
H	-6.15766	0.01751	-0.49155
H	-2.59630	0.29498	-1.03181
H	-2.80531	-1.38865	-0.49398

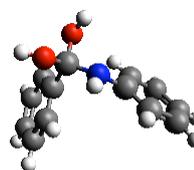
Amide\_final 3d

C	2.78653	-1.50491	-0.70934
C	3.87741	-0.90099	-0.08155
C	3.72089	0.33887	0.54343
C	2.47917	0.97113	0.53996
C	1.37225	0.35779	-0.06175
C	1.53804	-0.88150	-0.69586
C	0.07899	1.12999	-0.11090
O	0.10356	2.32356	-0.42130
N	-1.09631	0.46530	0.14372
C	-1.21806	-0.75710	0.94779
C	-2.24067	-1.71835	0.33137
C	-3.59281	-1.01970	0.12784
C	-3.41688	0.28356	-0.66507
C	-2.36052	1.19155	-0.02454
H	-1.55147	-0.47584	1.95982
H	-0.24200	-1.22800	1.04956
H	-2.34946	-2.59241	0.98355
H	-1.85919	-2.07795	-0.63300
H	-4.02952	-0.78961	1.10989
H	-4.29711	-1.68723	-0.38076
H	-4.36575	0.82835	-0.72853
H	-3.10818	0.05292	-1.69260
H	-2.71237	1.54103	0.95895
H	-2.15778	2.07235	-0.63242
H	4.84729	-1.38960	-0.08701
H	4.56905	0.81682	1.02466
H	2.35335	1.94746	0.99616
H	0.69540	-1.34693	-1.19835
H	2.90724	-2.45900	-1.21388



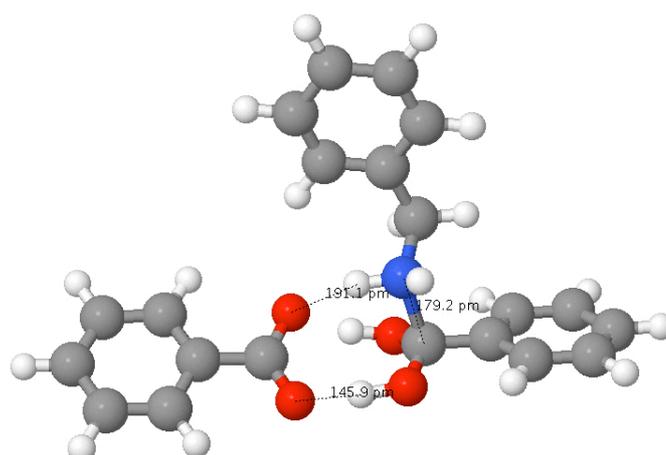
Amide\_final 3e

C	4.22396	-0.71719	0.41619
C	4.59996	0.57802	0.05058
C	3.63152	1.48904	-0.37439
C	2.28912	1.11245	-0.42023
C	1.90335	-0.18200	-0.04149
C	2.88542	-1.09721	0.36216
C	0.48112	-0.67008	-0.07743
O	0.21931	-1.86399	-0.20575
N	-0.47282	0.31203	0.06030
C	-1.87863	0.19514	0.04443
C	-2.55386	-1.00536	-0.22680
C	-3.94910	-1.01896	-0.23205
C	-4.68674	0.13659	0.02731



C	-4.01077	1.32854	0.29651
C	-2.61950	1.36005	0.30487
H	-5.77188	0.11017	0.02073
H	-4.46196	-1.95312	-0.44242
H	-1.98475	-1.90234	-0.42137
H	-2.09994	2.29232	0.51429
H	-4.56557	2.23949	0.50090
H	-0.12829	1.23375	0.28638
H	5.64428	0.87321	0.08816
H	3.92057	2.48995	-0.68006
H	1.55543	1.82273	-0.79101
H	2.57694	-2.10179	0.62979
H	4.97529	-1.43082	0.74058

**Table 16:** B3LYP/6-31G\*\* transition state structure for reaction (one imaginary frequency)



C	-1.42146	-1.46582	0.06848
H	-3.11169	-1.22713	2.18393
H	-5.59424	-1.39160	2.17388
O	-0.84193	-2.11803	-0.93196
O	-0.87771	-1.52727	1.30232
H	0.08810	-1.25254	1.21821
N	-1.08986	0.23834	-0.37517
C	-1.63222	1.31005	0.49824
C	-1.07594	2.67421	0.15217
C	-1.90577	3.66930	-0.37534
C	-1.38929	4.92520	-0.70016
C	-0.03487	5.19361	-0.50425
C	0.80115	4.20367	0.01888
C	0.28554	2.95157	0.34880

H	-0.05828	0.22008	-0.29433
H	-1.35129	0.36704	-1.35219
H	-1.36718	1.01798	1.51798
H	-2.72117	1.29307	0.41585
H	-2.96255	3.46337	-0.52761
H	-2.04463	5.69037	-1.10567
H	0.36911	6.16939	-0.75712
H	1.85632	4.40858	0.17334
H	0.94011	2.18042	0.74910
C	6.41575	-0.77777	0.09568
C	5.60723	-0.02374	0.94963
C	4.22144	-0.16557	0.90254
C	3.63542	-1.06403	0.00229
C	4.45074	-1.82111	-0.84912
C	5.83579	-1.67650	-0.80341
H	7.49599	-0.66680	0.13206
H	6.05820	0.67195	1.65164
H	3.57541	0.40610	1.55952
C	2.14319	-1.22079	-0.05132
H	3.97876	-2.51518	-1.53566
H	6.46457	-2.26416	-1.46619
O	1.43028	-0.45850	0.69429
O	1.66594	-2.09323	-0.82998
H	0.20795	-2.14210	-0.85550
C	-5.71314	-1.78301	0.05714
C	-4.99185	-1.95876	-1.12605
C	-3.60129	-1.86340	-1.11861
C	-2.92361	-1.58500	0.07439
C	-3.64665	-1.41537	1.26012
C	-5.03837	-1.51579	1.24927
H	-6.79635	-1.86206	0.05076
H	-5.51208	-2.17973	-2.05334
H	-3.02934	-2.02488	-2.02586