$B(OCH_2CF_3)_3$-mediated amidation reactions

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Declaration

I, Rachel Margaret Lanigan confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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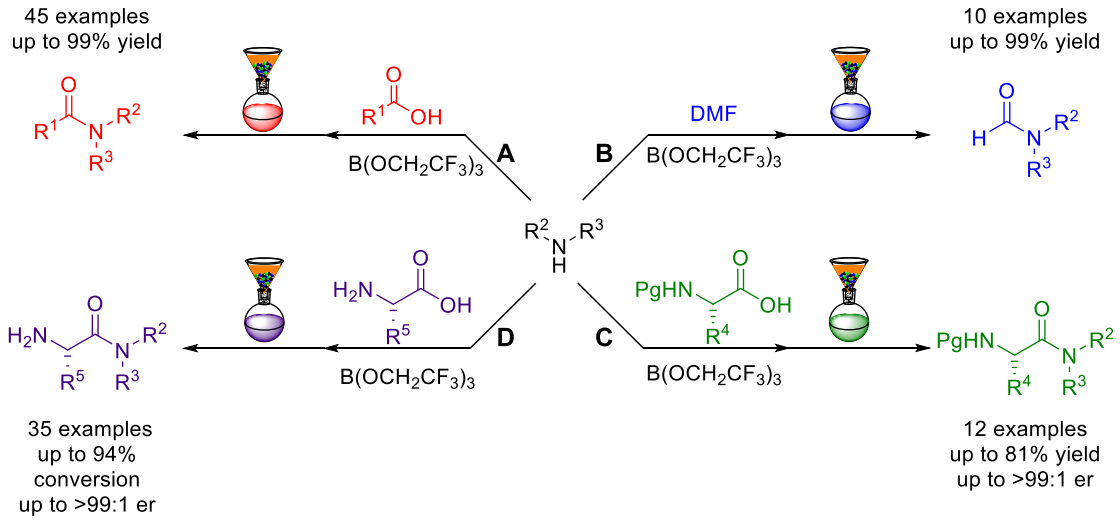
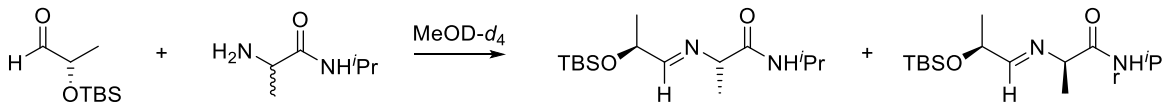
Abstract

This thesis describes the further development of a borate ester, $B(OCH_2CF_3)_3$, as a reagent for amidation with a focus on carboxylic acids, including *N*-protected amino acids, and on the amidation of unprotected amino acids. In addition, a novel methodology for the determination of enantiomeric ratio in chiral amines is reported.



The $B(OCH_2CF_3)_3$-mediated direct amidation of carboxylic acids furnishes the amide product in generally excellent yield (**A**). A formylation method using DMF as the formyl donor was also developed (**B**). The $B(OCH_2CF_3)_3$-mediated amidation method allows the amidation of α-chiral acids (for example, *N*-protected amino acids) in good yield with excellent retention of enantiopurity (**C**). Importantly, a solid-phase work-up procedure was developed which enables the purification of all of these amide products without the need for column chromatography or aqueous work-up. The application of $B(OCH_2CF_3)_3$ to the amidation of unprotected amino acids is described (**D**). This covers an optimisation study and an investigation into the scope of the reaction. As a result of this study a new method for the determination of enantiomeric purity of chiral amines was developed. Using an aldehyde derived from lactic acid the enantiopurity of chiral amines can be determined by NMR, circumventing the need for chiral HPLC.



Additionally, a mechanistic study of the direct amidation reaction is discussed. A reaction intermediate as well as a tentative mechanism are proposed based on the results of this mechanistic study and preliminary experimental evidence.

Contents

Abbreviations

Ac	Acetyl
AcOH	Acetic acid
MeCN	Acetonitrile
Ac	Acetyl
API	Active Pharmaceutical Ingredients
ACS	American Chemical Society
Bz	Benzoyl
Bn	Benzyl
bp	Boiling point
9-BBN	9-Borabicyclo(3.3.1)nonane
Bu	Butyl
Cbz	Carboxybenzyl
CI	Chemical ionisation
Cy	Cyclohexyl
CPME	Cyclopentyl methyl ether
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM-d_2	Deuterated DCM
DMSO-d_6	Deuterated DMSO
DCM	Dichloromethane
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EI	Electron impact

ES	Electrospray ionisation
ee	Enantiomeric excess
er	Enantiomeric ratio
Et	Ethyl
Eq. or equiv.	Equivalents
GSK	GlaxoSmithKline
g	Grams
GCI	Green Chemistry Institute
h	Hour(s)
IR	Infrared spectroscopy
i-	Iso
mp	Melting point
m-	Meta
Me	Methyl
MW	Microwave
mg	Milligram
mL	Millilitre
mmol	Millimole
min	Minute(s)
MS	Molecular sieves
NMR	Nuclear magnetic resonance spectroscopy
Nu	Nucleophile
o-	Ortho
o/n	Overnight

p-	Para
ppm	Parts per million
Ph	Phenyl
Pr	Propyl
rds	Rate determining step
rt	Room temperature
s	Seconds
Temp	Temperature
t or *tert*	Tertiary
Boc	*tert*-Butoxycarbonyl
TBS	*tert*-Butyldimethylsilyl
TBME	*tert*-Butylmethyl ether
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TFA	Trifluoroacetic acid
UV	Ultraviolet
UCL	University College London
υ	Wavenumber cm^{-1}

Acknowledgements

Firstly, I would like to thank my supervisor, Dr Tom Sheppard, for giving me the opportunity to work on this project. His constant support and seemingly limitless knowledge of chemistry have provided great inspiration and encouragement to me throughout my PhD. Tom's enthusiastic leadership is definitely evident throughout the Sheppard group. I would also like to thank Jon, Jamie, Mark and Richard for their help over the last few years.

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A massive thank you goes to Dr Abil Aliev for his extensive knowledge of NMR and all of his help, even with some possibly stupid questions. Following on from this, I would also like to thank Dr Lisa Haigh and, of course, Vincent, for their incredibly efficient mass spec service. Going further back, my chemistry teachers from school – Dr Vevers and Mr Dixon – who, without a doubt, piqued my interest in chemistry from a young age and deserve a huge thank you for encouraging me down this route.

My parents and all of my family have been a constant emotional (and often financial) support. They are always incredibly proud of any achievement, no matter how small, and without their love and encouragement I would definitely not have been able to come this far. Last, and by no means least, I would like to thank my girlfriend, Natalie, for supporting and encouraging me throughout my PhD. Without her by my side in the last few years, particularly in the last couple of months, I could never have completed this.

To my granny, Alison Waugh, and
to the memory of my grandparents
Lily and George Lanigan

1. Introduction

The amide bond is incredibly important in organic chemistry, particularly in pharmaceutical chemistry, as it is present in over 25% of top-selling drugs.[1] The moiety is found in natural products such as vitamin B_5 **1** and β-lactam antibiotics, penicillin **2** and cephalexin **3** as well as drugs such as lidocaine **4** and paracetamol **5** (Figure 1). As a result amidation reactions are amongst the most commonly used reactions in medicinal and pharmaceutical chemistry. In fact, representatives of GSK, AstraZeneca and Pfizer carried out a small survey of 128 drug candidate molecules, from this survey set they found that around 10% of the reactions used in their synthesis involved an amidation reaction (*N*-acylation or amino protection).[2] A more recent survey of the literature from GSK, AstraZeneca and Pfizer of 3566 medicinal compounds found that amidations accounted for 16% of all reaction carried out in the synthesis of these compounds.[3] The amide bond was found in over half of these molecules. Even though there is increasing interest directed towards the development of new amidation methods, many of the methods currently used for the synthesis of the amide bond tend to have large quantities of potentially hazardous by-products that can result in purification difficulties as well as more serious environmental impacts.

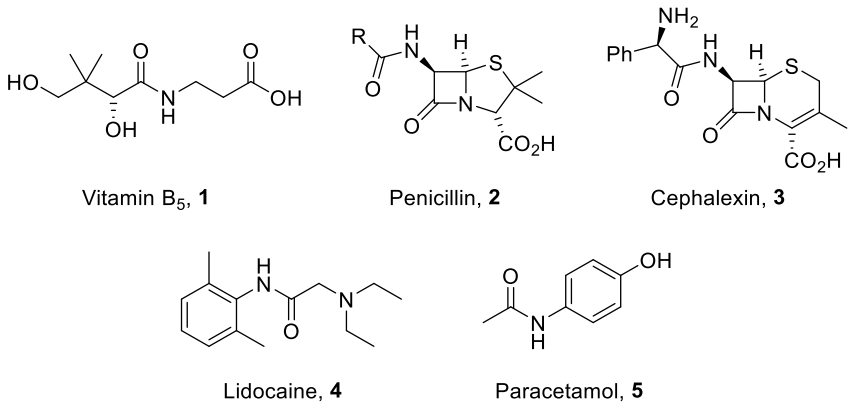


Figure 1 Structure of a selection of amide containing natural products and drugs

In 2005, the ACS Green Chemistry Institute (ACS GCI) alongside several large pharmaceutical companies set up the ACS GCI Pharmaceutical Roundtable to develop the use of green chemistry in the pharmaceutical industry (and in academic research as an extension).[4] The result of this Roundtable was a list of reactions that required improved reagents as a matter of urgency, as well as a list of reactions that are desirable for use in industry but require further development, and a list of improvements to the

use of solvents and the way they are used. Following a vote by representatives of the pharmaceutical companies involved '*Amide formation avoiding poor atom economy reagents*' came top of the list for reactions that companies would strongly prefer better reagents for (Table 1).

Table 1 Reactions in use for which better reagents are required

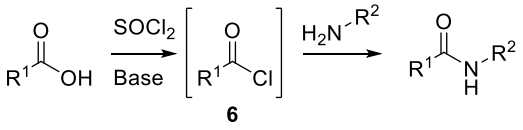
Research area	Number of votes
Amide formation avoiding poor atom economy reagents	6
OH activation for nucleophilic substitution	5
Reduction of amides without hydride reagents	4
Oxidation/epoxidation methods without the use of chlorinated solvents	4
Safer and more environmentally friendly Mitsunobu reactions	3

As a consequence, these industrially important reactions have driven many advancements in amidation, which have been reported in recent years and highlighted by the pharmaceutical industry.[5] As there is such focus on developing these amidation reactions to have a lower environmental impact, i.e. reducing waste by-products and solvents used, there have been several articles from the pharmaceutical industry that evaluate these 'green' goals.[6]

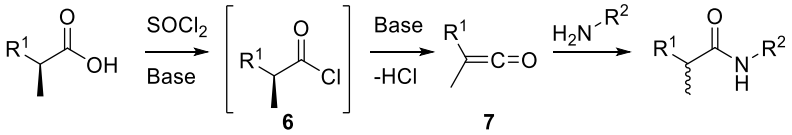
There are numerous reviews on methods of amidation with a focus on traditional methods of amide bond formation,[7-8] metal-catalysed amide bond formation,[9-10] and new catalytic methodology,[11] as well as native peptide ligation strategies,[12] and ribosomal protein synthesis.[13] Given the incredibly vast area of the literature that is devoted to the synthesis of amide bonds and the development of reagents and catalysts for amidation, this introductory review will focus on more recent advances in the area as well as a more general overview of the development of boron based reagents and catalysts for amidation.[14]

By far the most widely used method for activation of carboxylic acids for amidation is as an acid chloride **6** by, for example, thionyl chloride.[2,15] The first reports of this method were in the 1880s by Schotten[16] and Baumann.[17] The acid chloride formation is generally performed *in situ*, although the acid chloride can be isolated in some cases, and then reacted with amine in the presence of a base (Scheme 1). While this can be an

efficient route to amides, the main problem associated with acid chlorides is racemisation of α-chiral acids *via* ketene **7** formation (Scheme 2).



Scheme 1 Amidation by formation of an acid chloride



Scheme 2 Racemisation by ketene **7** formation from acid chloride **6**

Coupling reagents such as carbodiimides are widely used in the synthesis of amides.[2] Examples of these carbodiimides include dicyclohexylcarbodiimide (DCC, **8**) and diisopropyl carbodiimide (DIC, **9**) (Figure 2).[7] This proceeds *via* an *O*-acylurea **12** formed by reaction of carboxylic acid and DIC, **12** can then react by a number of routes (Scheme 3). Firstly, formation of the amide by reaction of **12** with amine, or formation of an unreactive *N*-acylurea by-product **13**. Finally, formation of the acid anhydride **14** by reaction of another molecule of acid with **12**, which is not detrimental to the reaction as this anhydride **14** can react with the amine to form the amide product.

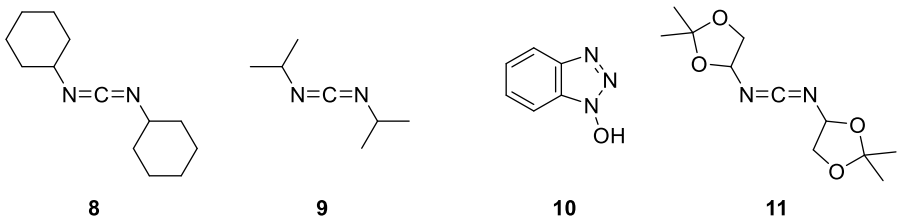
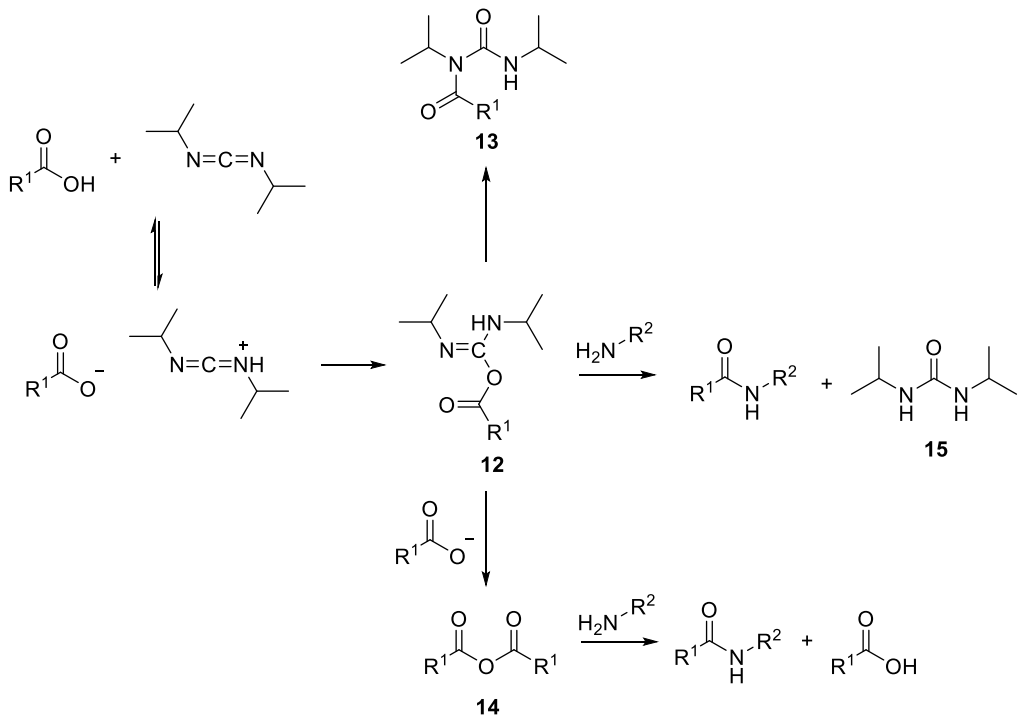
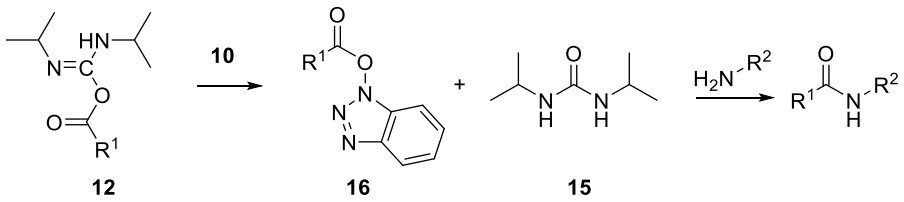


Figure 2 Examples of carbodiimide reagents and HOBt



Scheme 3 DIC-mediated amidation

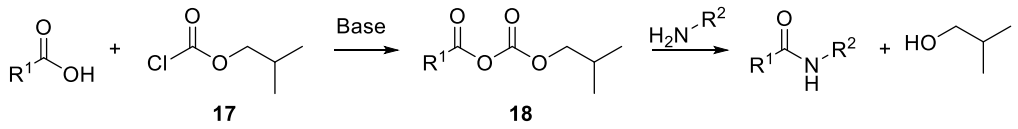
Epimerisation can be a problem in carbodiimide-mediated amidations *via* oxazolone formation from **12**. In order to reduce epimerisation these carbodiimides are generally used in conjunction with an additive, e.g. *N*-hydroxybenzotriazole (HOBt, **10**) which is thought to increase the reactivity of the active ester **16** through hydrogen bonding to the amine (Scheme 4). However, these benzotriazoles must be handled with care as they can be shock-sensitive as well as sensitive to heat and pressure.[18] The main issue with the use of carbodiimides is the urea by-product **15** formed during the reaction that can impede purification of the amide product as it is difficult to remove. However, improvements in the purification of carbodiimide-mediated amidation have been made with the synthesis of water-soluble bis[[4-(2,2-dimethyl-l,3-dioxolyl)]methyl]carbodiimide (BDDC, **11**) which can be more easily removed.[19]



Scheme 4 HOBt additive in carbodiimide-mediated amidation

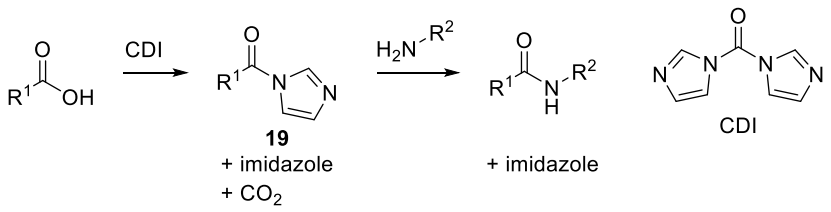
In addition, active ester formation by *iso*-butylchloroformate **17**, for example, is classed as a 'green' reaction.[15] This can activate the carboxylic acid as a mixed anhydride **18**, in

the presence of a base to sequester the HCl generated, which can then react with an amine to give the amide product (Scheme 5).



Scheme 5 *iso*-Butylchloroformate active ester formation and amidation

Carbonyldiimidazole (CDI) has also found wide use as an amidation reagent,[2] including in the synthesis of a number of drug molecules, for example, sildenafil citrate.[20] The active acylating agent is an *N*-acylimidazole **19** which can react with the amine (Scheme 6). Although the by-products of CDI-mediated amidation are relatively innocuous – imidazole and CO_2 – the synthesis of CDI is not ideal as it is formed from phosgene and imidazole.



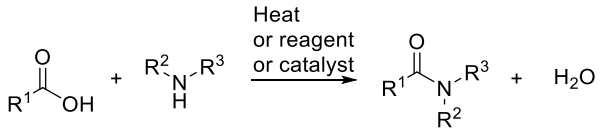
Scheme 6 CDI-mediated amidation

Despite their prevalence, these routes to the amide bond are not ideal as they can generate hazardous and corrosive by-products, which can result in purification as a well as environmental issues. As a result there is still a considerable effort from the research community in the development of new amidation methods. With these issues in mind it is clear that a widely applicable amidation reagent or catalyst is still required.

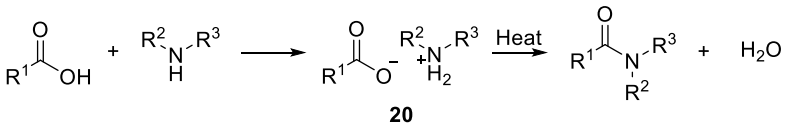
1.1. Recent developments in amide bond formation

The thermal synthesis of amides is obviously a very desirable route as this would provide a direct route to amides without the need for any coupling reagents or catalysts (i.e. minimising waste by-products). However, the formation of an amide by the reaction of a carboxylic acid and an amine with the expulsion of a molecule of water is not necessarily as simple as it would appear in theory (Scheme 7). Traditionally, the synthesis of amides from the thermal reaction of an amine and a carboxylic acid had been thought to be an unviable approach due to the favourable formation of an ammonium carboxylate salt **20** that will not undergo condensation to form an amide

(Scheme 8). However, this is not necessarily the case as the ammonium carboxylate salt formation is dependent on the reaction conditions (i.e. solvent) and the reactants employed. A thermal synthesis of amides has previously been reported that required high temperatures to proceed with the requisite elimination of water from the ammonium carboxylate salt that can form in the absence of solvent.[21] Under these conditions, the reaction can be carried out neat, only heating the amine and acid mixture in an open flask. This method is not ideal as these are obviously harsh conditions and require the reactants to be non-volatile and thermally stable at high temperatures.

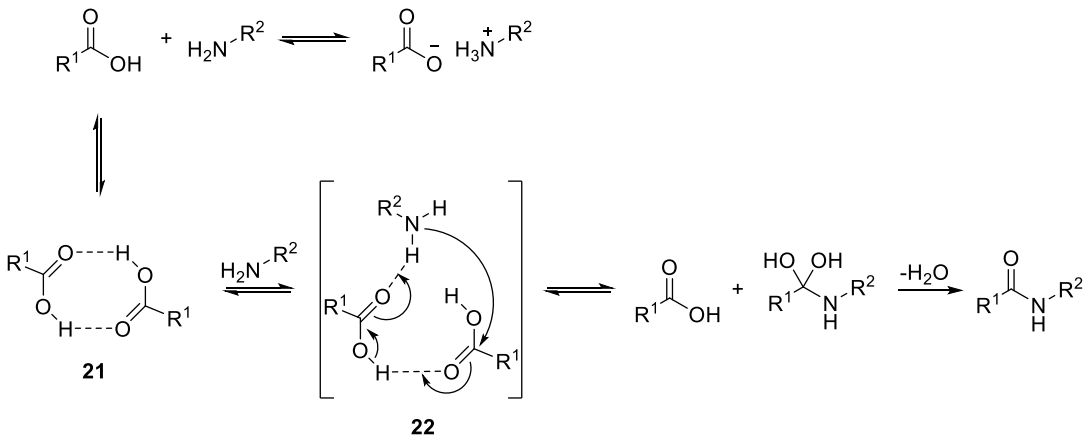


Scheme 7 Simplified amidation reaction



Scheme 8 Ammonium carboxylate salt formation

A computational and experimental study carried out by Whiting *et al.*, in 2011, has provided some insight into the mechanism of the thermal amidation reaction.[22] The activated carboxylic acid species was proposed as a hydrogen bonded carboxylic acid dimer **21** which can then be attacked by the amine along with a concerted proton transfer in transition state **22** which can then undergo the requisite elimination of water to form the amide product (Scheme 9). The ammonium carboxylate salt formation can still occur, especially with strong acids as well as in the presence of excess acid or amine. Active water removal is required to ensure the stability of the dimer **21**, if any water generated in the reaction is not removed from the reaction mixture then the hydrogen bonds of dimer **21** are broken, deactivating this species. The acidity of the carboxylic acid strongly influences the reactivity of the acid under these conditions with acids with lower pKas being unreactive. This is thought to be due to the increased ammonium carboxylate salt formation from stronger acids. The effect of the amine partner, on the other hand, is not quite as clear cut and appears to be the result of a combination of electronic and steric effects.

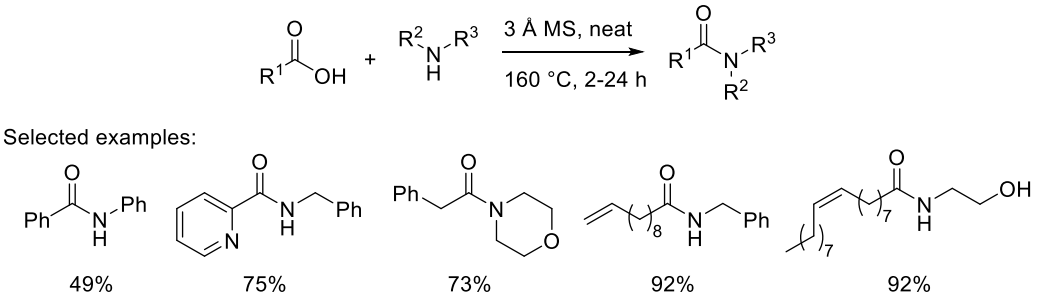


Scheme 9 Proposed mechanism of thermal amidation

This potential reagent and catalyst free thermal amidation was recently exploited by Gooßen *et al.* in 2009.[23] They showed that the direct thermal condensation of carboxylic acids and amines to furnish amides can achieved at 160 °C. This route requires neat conditions as well as 3Å molecular sieves (MS) to remove the water generated in the reaction (Scheme 3). Initially the reaction was carried out at 120 °C and during optimisation of this method it was observed that MS did not have a noticeable effect on the yield of the reaction, in fact, the reaction yield was the same in the absence of MS (Table 2, entries 1 and 2). The reaction yield could be improved, however, by increasing the reaction temperature to 160 °C but the same effect with MS was observed (Table 2, entries 3 and 4). To prevent any pressure build up in the reaction flask MS were used to remove the water by-product from the reaction. The explored scope of this reaction is somewhat limited, however, alcohols and phenols were tolerated (Scheme 10).

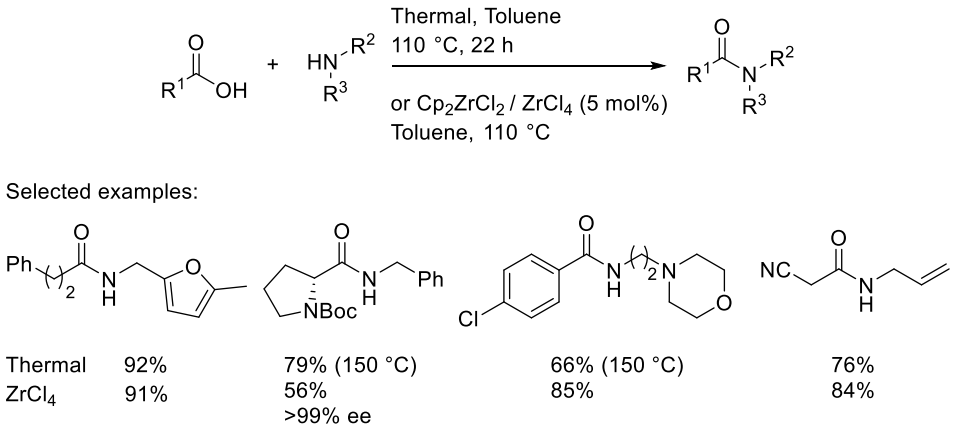
Table 2 Comparison of temperature and the use of MS in thermal amidation

Entry	MS	Temperature (°C)	Yield (%)
1	Yes	120	49
2	No	120	49
3	Yes	160	89
4	No	160	95



Scheme 10 Direct thermal amidation examples

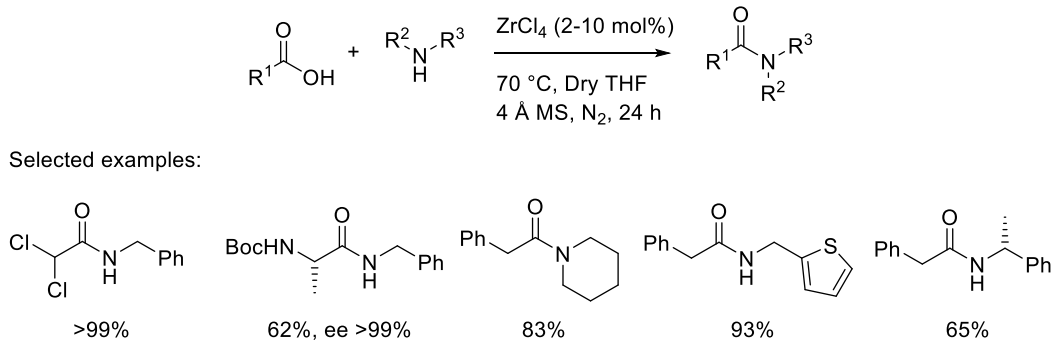
Recently, in 2012, the Williams group published on the direct amide formation from amines and carboxylic acids using toluene as the reaction solvent.[24] Due to the non-polar nature of toluene, ammonium carboxylate salt formation is disfavoured allowing direct attack of the amine on the carboxylic acid. This method also requires high temperatures although the reaction is carried out at a lower temperature than the Gooßen procedure (110 °C) and does not require water removal (MS, Dean-Stark, etc.) but anhydrous reaction conditions are used. This procedure has a broad substrate scope and a wide functional group tolerance (Scheme 11). Enantiopure α-chiral acids are tolerated under the reaction conditions with no observable racemisation. Less reactive substrates, such as anilines and benzoic acids, gave lower yields under the standard conditions, however, these could be improved by using refluxing xylenes as the solvent (150 °C) or by the addition of a zirconium catalyst ($ZrCl_4$ or Cp_2ZrCl_2).



Scheme 11 Direct thermal and Zr catalysed amidation in toluene

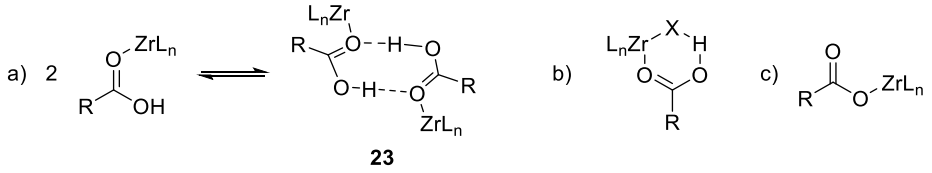
At the same time as the report by Williams *et al.*, Adolfsson *et al.* also reported the $ZrCl_4$-catalysed direct amidation.[25] This report required active water removal through the use of 4 Å MS but the reaction could be carried out at the lower temperature of 70 °C, although the less active acids, such as benzoic acids, and amines, such as secondary

amines, required a higher reaction temperature (100 °C). A range of aliphatic, aromatic and heteroaromatic acids and amines were tolerated under the reaction conditions in generally good yield (Scheme 12). α-Chiral acids underwent amidation without any observable racemisation. The reaction is amenable to scale-up as a large scale synthesis can be carried out without a detrimental effect on the yield (>5g).



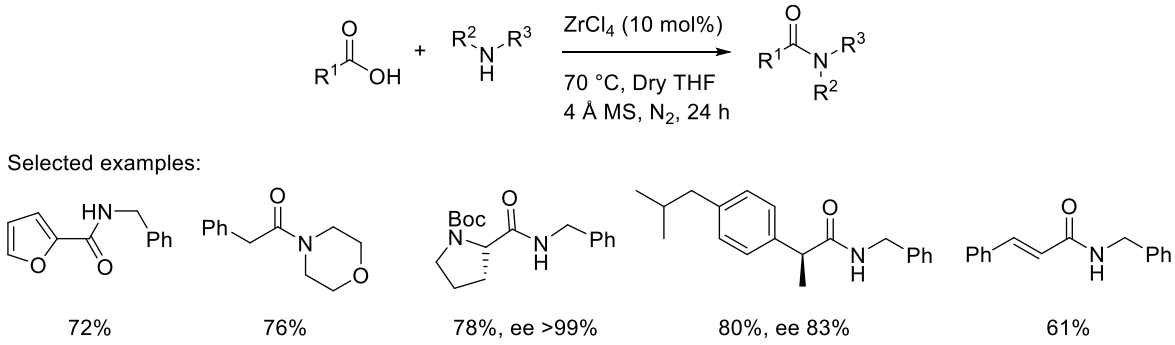
Scheme 12 $ZrCl_4$-catalysed amidation examples

The Zr-catalysed amidation has been proposed to activate the carboxylic acid in a number of different ways (Scheme 13).[25] In an analogous fashion to the dimer **21** proposed by Whiting for thermal amidation, Zr may act as a Lewis acid to activate the carbonyl of the dimer **23** or alternatively the carboxylic acid monomer (Scheme 13a).[22] Alternatively, Zr can activate the carboxylic acid carbonyl as a Lewis acid in addition to activation of the leaving group by hydrogen bonding (Scheme 13b). Activation of the leaving group by Zr provides the final possible mode of activation (Scheme 13c).



Scheme 13 Possible mechanisms of activation in Zr-catalysed amidation

Soon after, Adolfsson *et al.* also reported the use of $Ti(O^iPr)_4$ as a catalyst for the direct amidation of carboxylic acids using similar reaction conditions to that reported for $ZrCl_4$.[26] Aliphatic, (hetero)aromatic and unsaturated acids undergo amidation with both primary and secondary amines (Scheme 14). The amidation of three α-chiral acids is reported, while no racemisation is observed for the amidation of Boc-L-proline or Boc-L-alanine, some racemisation was observed in the case of (*S*)-ibuprofen (83% ee). Due to the Lewis acidity of $Ti(O^iPr)_4$, this catalyst can presumably activate carboxylic acids to amidation in a similar fashion to that reported for $ZrCl_4$ (Scheme 13).



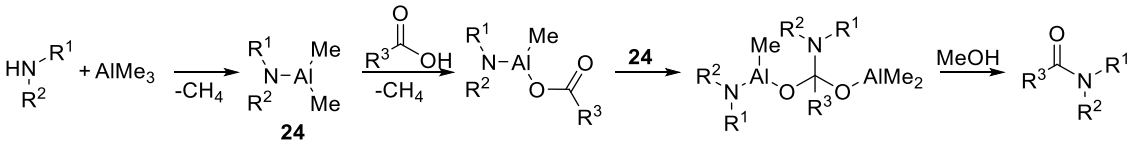
Scheme 14 Ti(O^iPr)$_4$-catalysed amidation examples

Additionally, during the reaction optimisation, several other transition-metal salts were found to catalyse the amidation reactions (Table 3).[26] Due to the low price and commercial availability of Ti(O^iPr)$_4$, this was deemed the most suitable catalyst for further study.

Table 3 Catalyst screen for transition metal-catalysed amidation of phenylacetic acid with benzylamine

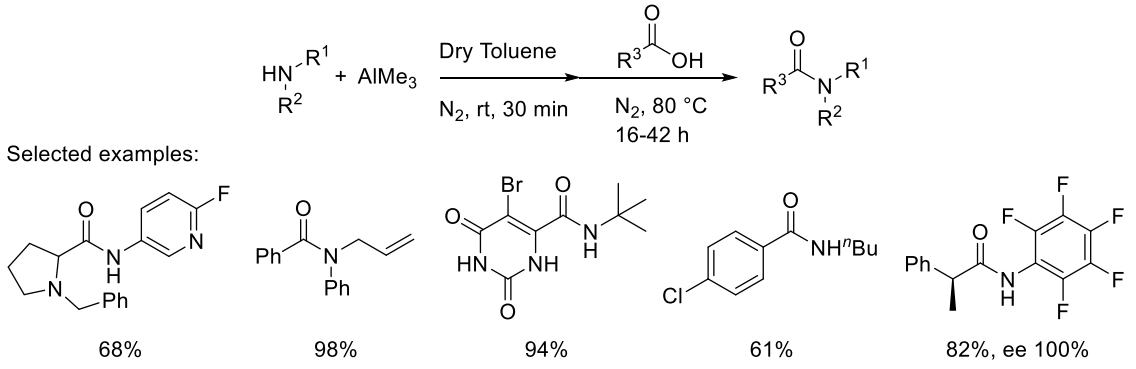
Catalyst	**Amide yield (%)**
Ti(O^iPr)$_4$	91
Ti(OBu)$_4$	89
$ZrCl_4$	>99
Zr(OEt)$_4$	93
Zr(O^tBu)$_4$	93
Hf(O^tBu)$_4$	89
Nb(OEt)$_5$	88

Li *et al.* (2012) have reported that $AlMe_3$ can mediate amidation reactions although stoichiometric quantities are required.[27] In addition, dry reaction conditions are required as well as a three-fold excess of the amine and $AlMe_3$. Preformation of the dimethylaluminium amide **24** is required before reaction with the carboxylic acid (Scheme 15).



Scheme 15 $AlMe_3$-mediated amidation mechanism

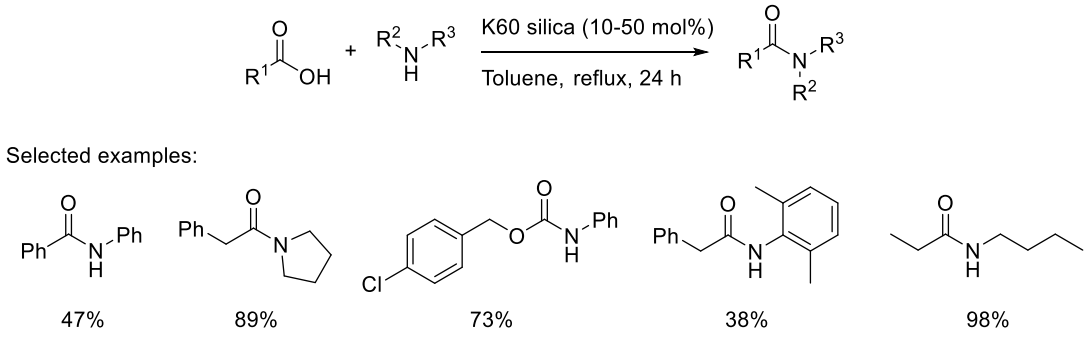
A range of examples were reported, however, the method displays limited functional group tolerance as ester, nitro and cyano groups are not stable under the reaction conditions. Aliphatic and aromatic as well as secondary amines provide the corresponding amides in good to excellent yield when coupled with aromatic and aliphatic acids (Scheme 16). More sterically encumbered examples, such as those derived from *tert*-butylamine are also reported. Excellent retention of enantiopurity was observed in the amidation of (*R*)-2-phenylpropanoic acid (100% ee), however, the low basicity of pentafluoroaniline may contribute to this observation. Again, considering the high temperatures and the solvent (toluene), the background reaction may be significant, however, it is not reported.[24]



Scheme 16 Examples of $AlMe_3$-mediated amidation

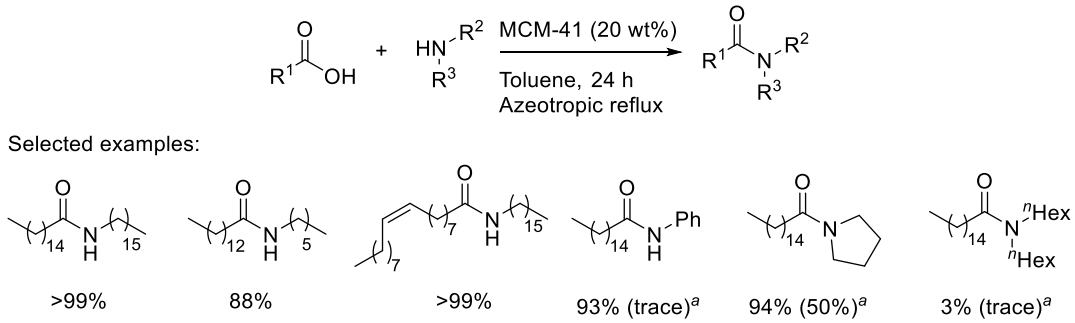
In 2009, Clark *et al.* reported on the use of 'off-the-shelf' Kieselgel 60 (K60) silica as an efficient catalyst for amidation following activation at 700 °C.[28] This method does not require active water removal or an inert atmosphere, in fact, it tolerates addition of water into the toluene solvent. The catalyst can be removed by filtration and reused up

to four times following reactivation at 700 °C. The functional group tolerance was not explored, however, a range of aliphatic and aromatic acids and amines were investigated (Scheme 17). For less reactive substrates higher catalyst loadings are required (50 mol%). They also demonstrate the applicability of this catalyst in flow.



Scheme 17 K60 silica-catalysed amidation examples

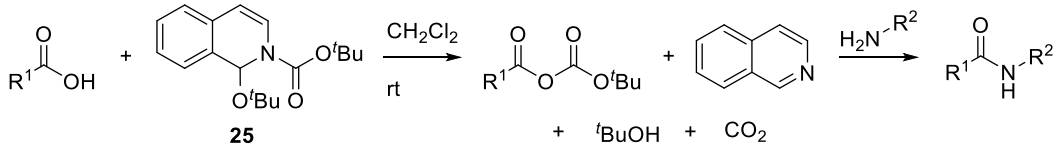
Komura *et al.* (2011) describe the use of mesoporous silica MCM-41 as a catalyst for the amidation of fatty acids by long chain amines.[29] MCM-41 is composed of amorphous silica with a mesoporous framework that is utilised widely as a catalyst. In their search for a catalyst that is suitable for long-chain aliphatic acids and amines MCM-41 was identified as a suitable candidate as it displayed high catalytic activity in a catalyst screen. MCM-41 catalyses the amidation at relatively high catalyst loadings (20 wt%) at azeotropic reflux in toluene (Scheme 18). In addition to the long-chain aliphatic amines MCM-41 also displays activity with smaller aliphatic and aromatic amines but is not active with bulky amines such as *tert*-butylamine. There is a significant background reaction in some cases as can be expected due to the high temperatures involved in the reaction (see thermal amidation, *vide supra*).



Scheme 18 MCM-41 catalysed amidation of fatty acids. [a]Thermal amidation in the absence of MCM-41.

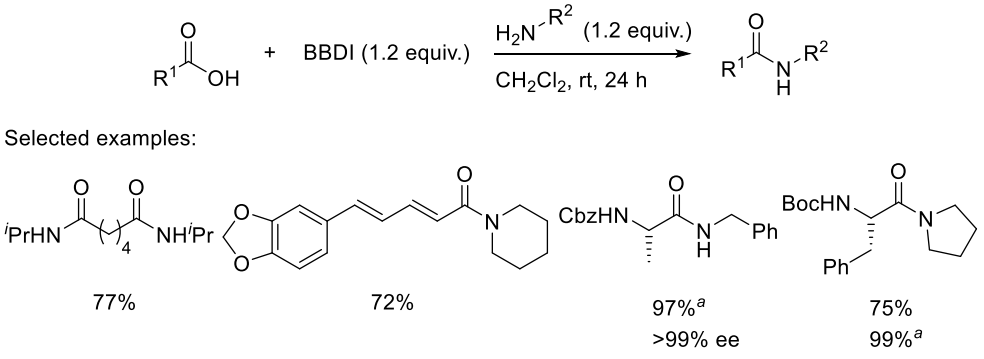
Flow chemistry has very recently (2014) been applied to the synthesis of dipeptides by Fuse *et al*.[30] Using triphosgene as the carboxylic acid activating agent (residence time 0.5 s) and then reacting this active species with an amine (residence time 4.3 s) in flow resulted in excellent yields of the dipeptides and very low levels of epimerisation as compared to the batch reactions. Boc and Fmoc protecting groups are untouched under these conditions.

1-*tert*-Butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline **25** (BBDI) has been described as a novel coupling reagent which can mediate amidation reactions effectively at room temperature.[31] The carboxylic acid is activated as a mixed anhydride by reaction with BBDI. The large isoquinoline is produced as a by-product in the formation of the mixed anhydride as well as *tert*-butanol and CO_2 so in terms of atom-economy this procedure is not ideal (Scheme 19). An excess of both BBDI and the amine are required for this reaction to proceed in good yield.



Scheme 19 BBDI-mediated amidation

Aliphatic amines, anilines and secondary amines could be coupled with aliphatic, benzoic, heteroaromatic and unsaturated acids effectively under the reaction conditions (Scheme 20). More sterically hindered acids and amines resulted in lower yields but these could be improved by increasing the reaction temperature from rt to reflux. The amidation of protected amino acids was explored, although enantiopurities were not reported for all examples, low levels of racemisation were observed for some of these α-chiral acids.

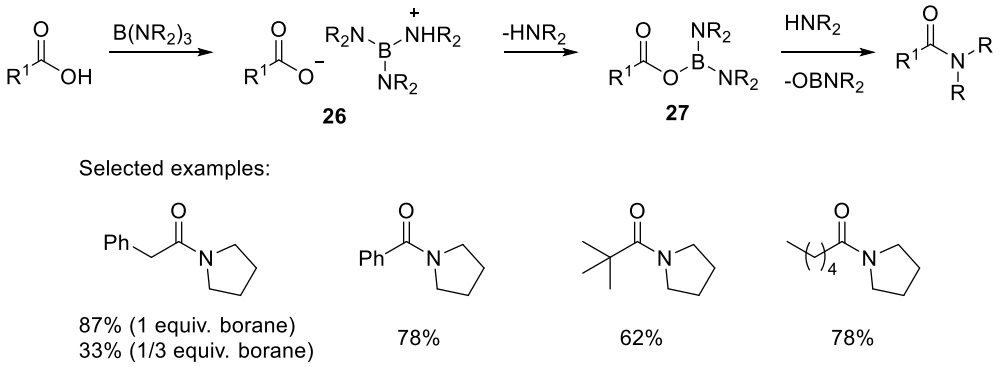


Scheme 20 Examples of BBDI-mediated amidation. [a]Reaction time of 5 h.

1.2. Boron in amide bond formation

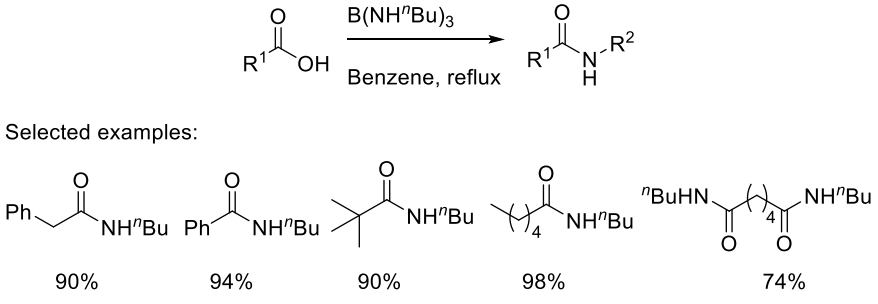
1.2.1. Stoichiometric boron amidation reagents

One of the first examples of a stoichiometric boron-based amidation reagent was reported by Pelter *et al.* in 1965.[32] Formation of the ionic species **26**, followed by attack of the carboxylic acid to form bisdialkylaminoacyloxyboron species **27**, was postulated as the reaction mechanism. This intermediate **27** can then react with liberated molecule of amine to yield the amide product (Scheme 21). The amine investigated in this case was pyrrolidine in tripyrrolidinylborane, which acts as the amidation reagent as well as the amine donor. A small selection of examples are reported (aromatic and aliphatic carboxylic acids) with good yields. Only one of the three amine groups is involved in the amidation as using 1/3 equivalent only gives 1/3 of the yield. Carboxylic acids with lower reactivity (benzoic and pivalic acid) require reflux in benzene while phenylacetic acid and hexanoic acid react at room temperature.



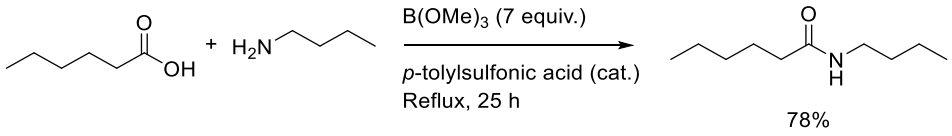
Scheme 21 Trisdialkylaminoborane mediated amidation

Soon after, in 1966, Pelter *et al.* also described the use of trismonoalkylaminoboranes to form secondary amides in a similar fashion to that described for trisdialkylaminoboranes (Scheme 22).[33] Again, these reactions proceed in good yield in refluxing benzene, however, limited scope was explored.



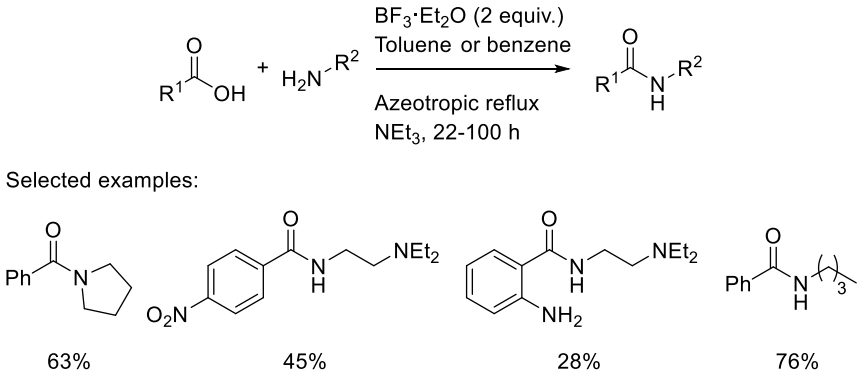
Scheme 22 Trismonoalkylaminoborane mediated amidation

In 1970, Pelter *et al.* then described the use of trimethylborate alongside a catalytic amount of *p*-toluenesulfonic acid as an amidation reagent.[34] One example is reported, formation of *N*-butylhexanamide, which proceeds in good yield at 65 °C with a seven-fold excess of $B(OMe)_3$ (78%). The utility of $B(OMe)_3$ was not explored further as the conditions did not prove suitable for the peptide synthesis they wished to carry out.



Scheme 23 Formation of *N*-butylhexanamide mediated by $B(OMe)_3$

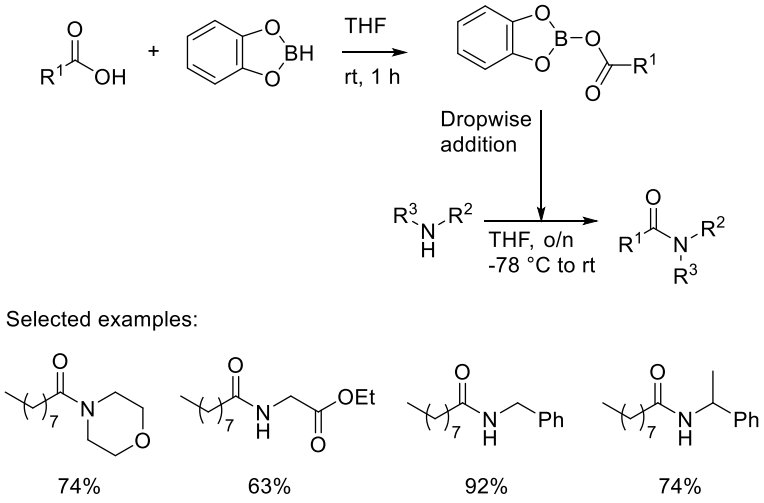
Inoue *et al.* reported the first use of boron trifluoride etherate as a reagent for amidation, in 1975.[35] This procedure requires an inert solvent, such as toluene or benzene, under azeotropic reflux conditions as well as an excess of amine and $BF_3{\cdot}Et_2O$ and long reaction times (Scheme 24).



Scheme 24 $BF_3{\cdot}Et_2O$-mediated amidation examples

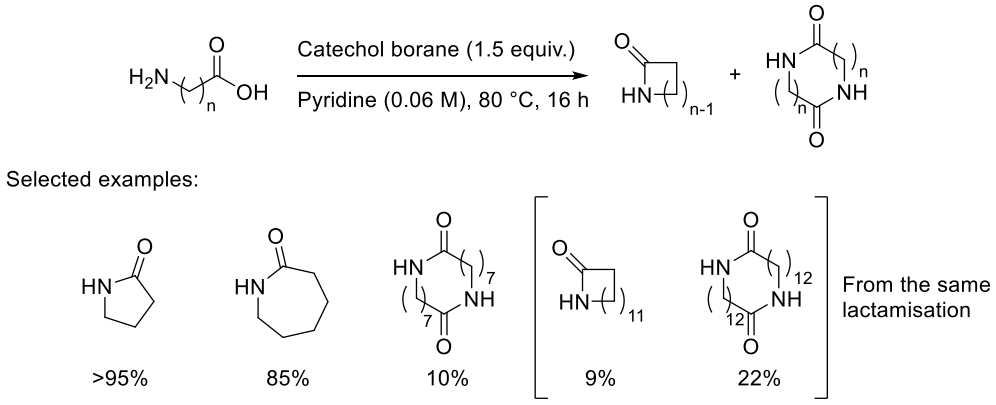
They observed that aliphatic primary amines react in refluxing benzene but aniline derivatives and aliphatic secondary amines do not. As these unreactive amines reacted in refluxing toluene the choice of solvent allowed for amidation of amino-substituted benzoic acids without protection of the amine group. Again, there is likely to be a significant background reaction in some cases (*vide supra*).[24] The substrate scope investigated is rather limited. The acid partner is generally benzoic acid or a derivative (NO_2, NH_2 or Cl) with only one aliphatic and one unsaturated example. And the amine component is generally aliphatic or aromatic with no additional functionality aside from a tertiary amine.

Catechol borane has been described as a reagent for the amidation of carboxylic acids with an excess of amine by Ganem *et al.*, in 1978.[36] A small sample of amines were coupled with nonanoic acid in good to excellent yield, although very little functionality was explored (Scheme 25). This method has also been applied to optically active acids with good retention of enantiopurity (*N*-benzoyl-L-leucine, >98% ee). Additionally, 3-methoxy and 4-nitrocatechol borane were both shown to act as amidation reagents.



Scheme 25 Catechol borane-mediated amidation examples

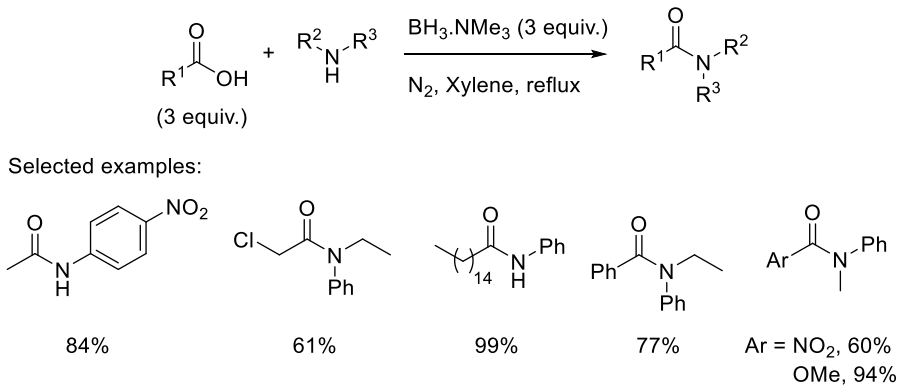
In the same paper Ganem *et al.* also reported a method for the lactamisation of amino acids using catechol borane.[36] This procedure was not as efficient as the amidation method; lactamisation to small rings gave excellent yields but medium and large rings were synthesised in low yields. Some dimerisation was observed for the ω-amino acids that would produce large or medium rings by lactamisation (Scheme 26).



Scheme 26 Catechol borane-mediated lactamisation examples

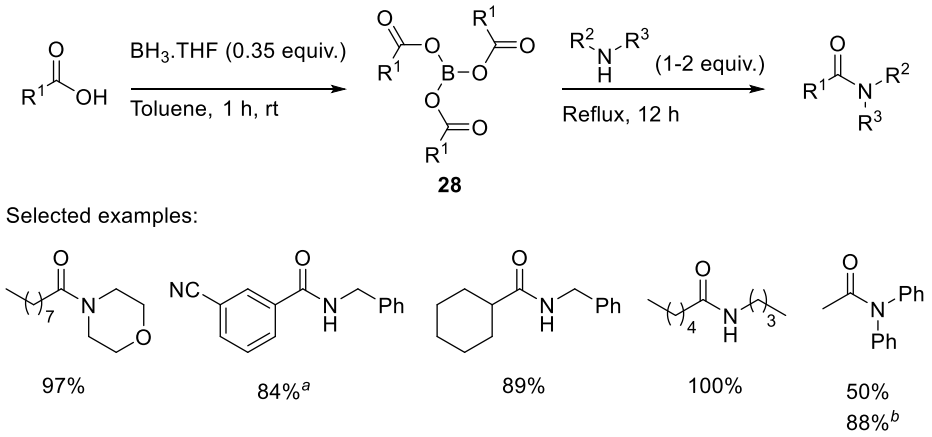
In 1983, Trapani *et al.* described the use of trimethylamine borane complex as an amidation reagent that is effective for the formation of both secondary and tertiary

amides (Scheme 27).[37] This reaction requires anhydrous conditions and high temperatures to give a range of aromatic and aliphatic amides.



Scheme 27 $BH_3 \cdot NMe_3$ mediated amidation

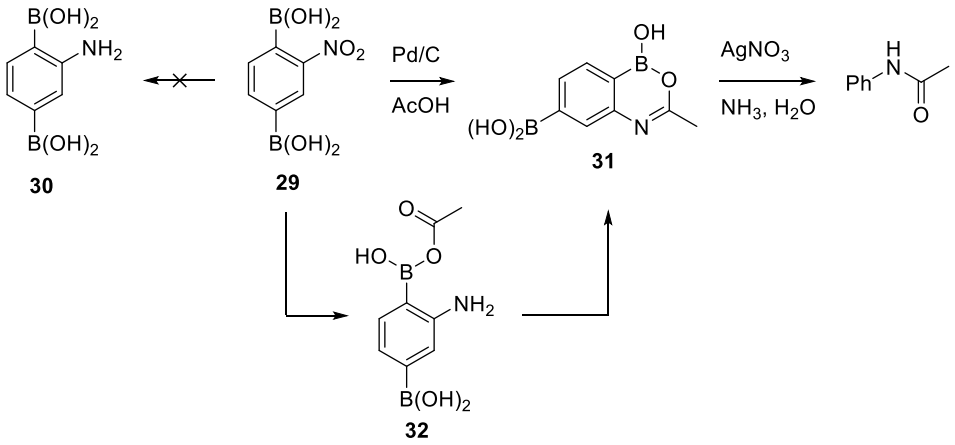
Huang *et al.*, in 2007, reported on the synthesis of amides by the proposed formation of triacyloxyboranes **28** from the reaction of $BH_3 \cdot THF$ complex with the carboxylic acid (Scheme 28).[38] No evidence of **28** is reported so it is possible that mono- and diacyloxyboranes are involved in the reaction. This acyloxyborane is then reacted with an excess of amine to afford amides in generally high yields. This method tolerates aromatic and aliphatic acids and amines as well as more sterically hindered reactants and secondary amines. Functional groups that are prone to reduction such as the cyano group are also tolerated during the reaction. Presumably a similar mechanism is at play for Trapani's report of the trimethylamine borane complex (*vide supra*).



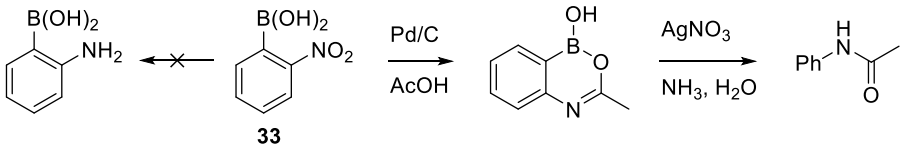
Scheme 28 $BH_3 \cdot THF$-mediated amidation. [a]Toluene : THF (5:1 used as solvent), [b]$BH_3 \cdot THF$ (1.1 equiv.), acid (3 equiv.), amine (1 equiv.)

1.2.2. Boronic acids as catalysts for amidation

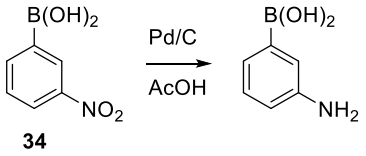
The first example of the use of a boronic acid for amidation was reported in 1959 by Soloway.[39] This was a fortuitous discovery as reduction of 2-nitrobenzene-1,4-diboronic acid **29** was expected to yield 2-amino-1,4-diboronic acid **30**; instead 2-acetamidobenzene-1,4-diboronic acid monoanhydride **31** was thought to have formed *via* the mixed anhydride **32** (Scheme 29). Deboronation of this compound gave acetanilide which lent evidence to the proposed structure **31**. This was also the case for the reduction of *o*-nitrobenzeneboronic acid **33**, which also formed acetanilide following deboronation (Scheme 30) but not for *m*-nitrobenzeneboronic acid **34** which exclusively formed the reduced *m*-aminobenzeneboronic acid (Scheme 31). This suggests that a mixed anhydride is formed between acetic acid and the boronic acid which can then be attacked by the *o*-amino group but not the *m*-amino group. This indicated, for the first time, that boronic acids can promote the acylation of amines.



Scheme 29 Boronic acid-mediated acylation following reduction of 2-nitrobenzene-1,4-diboronic acid

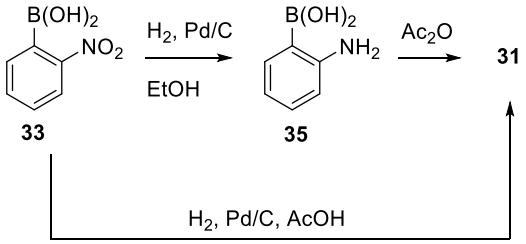


Scheme 30 Boronic acid-mediated acylation following reduction of *o*-nitrobenzeneboronic acid



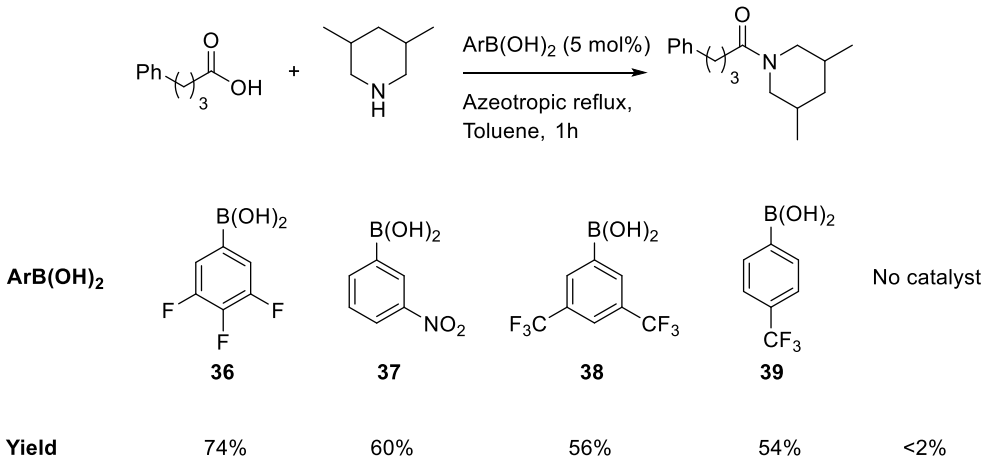
Scheme 31 Reduction of *m*-nitrobenzeneboronic acid to *m*-aminobenzeneboronic acid

Groziak *et al.* later published a report, in 1994, confirming the structure of **31** by synthesising it from **33** as reported by Soloway, as well as reducing the nitro group in the absence of acetic acid then reacting the resultant *o*-aminobenzeneboronic acid **35** with acetic anhydride (Scheme 32).[40] Both of these routes produced **31** as proposed by Soloway.



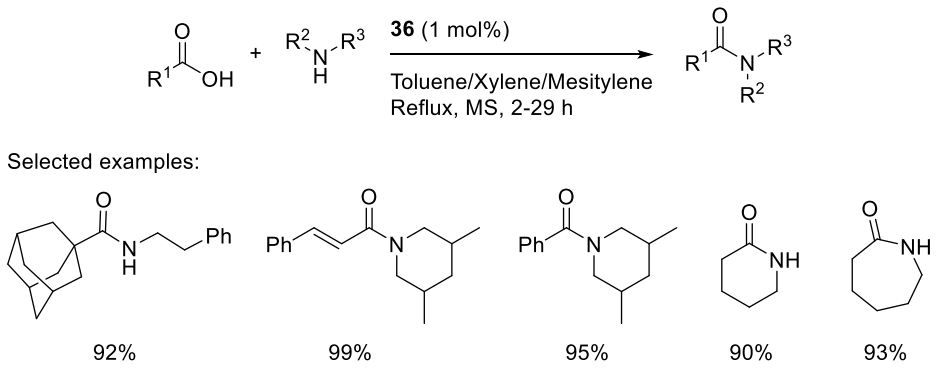
Scheme 32 Structure of **31** confirmed by Groziak

The first report of the use of a boronic acid catalyst developed specifically for amidation was reported by Yamamoto *et al.* in 1996.[41] 3,4,5-Trifluorobenzene boronic acid **36** showed the highest catalytic activity in the study of a small selection of boronic acids (Scheme 33). Trace quantities of the amide product were observed in the absence of a boronic acid catalyst.



Scheme 33 Yamamoto *et al.* screen of boronic acids for amidation

Although limited examples were explored, bulky and unsaturated acids as well as aliphatic, aromatic and secondary amines underwent amidation catalysed by **36** (Scheme 34). The examples reported proceed in good yield although very high temperatures and long reaction times are required. **36** also catalysed the lactamisation of amino acids in excellent yield. For some of the more reactive combinations the background reaction might be expected to be significant when considering the thermal amidations that can be achieved in toluene.[24]

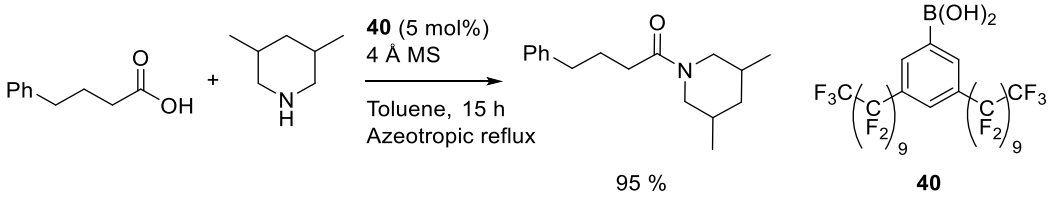


Scheme 34 Examples of **36**-catalysed amidation

Subsequently, in 2000, Yamamoto *et al.* successfully applied catalyst **36** to the polycondensation of dicarboxylic acids and diamines, although the reaction required very high temperatures to give good yield (300 °C), which would presumably result in a significant background reaction.[42]

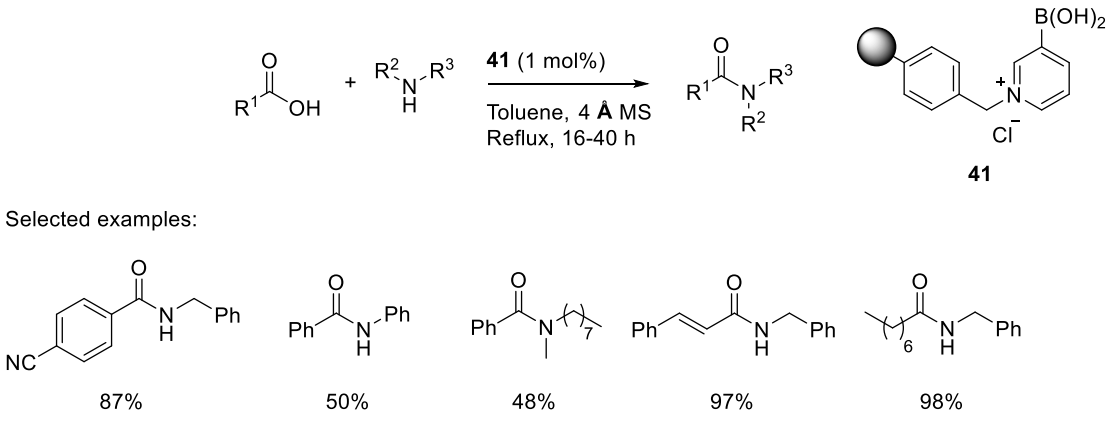
In a development of their 3,4,5-trifluorobenzeneboronic acid catalyst **36**, in 2001, Yamamoto *et al.* reported the catalytic ability of a perfluoroboronic acid, 3,5-bis(perfluorodecyl)phenylboronic acid **40**, in amidation reactions.[43] In the model

reaction, the catalyst gives excellent yield over 15 h in refluxing toluene with active water removal (Scheme 35). The key advantage of **40** as a catalyst is its potential for recyclability into a fluorous phase. The catalyst **40** can be fully recovered from the reaction mixture and reused in further amidations up to ten times without the need for purification. The catalyst **40** can either be extracted into perfluorodecalin from toluene and *o*-xylene at room temperature (1:1:1 solvent ratio) or, due to the insolubility of **40** in toluene/*o*-xylene, the catalyst can be isolated by decanting the reaction mixture and leaving the catalyst residue in the flask for reuse. The scope of this reaction was not fully assessed.



Scheme 35 40-catalysed amidation

In a further advance on the recyclability of boronic acid catalysts, and the first report of a polystyrene-bound boronic acid catalyst in 2001, Wang *et al.* reported polystyrene-bound pyridinium boronic acid **41**.[44] A relatively small substrate scope was explored but aliphatic and aromatic amines are tolerated in addition to unsaturated acids and secondary amines (Scheme 36). This catalyst **41** is unsuitable for the synthesis of dipeptides and presumably the amidation of α-chiral acids as the synthesis of Cbz-Phe-Ala-O^{t}Bu resulted in total racemisation. **41** can be recycled without a detrimental effect on the yield of amide product; however, even longer reaction times are required when using recycled catalyst.



Scheme 36 Polystyrene-bound catalyst **41** amidation examples

The use of *N*-alkyl-4-boronopyridinium salts **42** and **43** as amidation catalysts was later described by Yamamoto *et al.*, in 2005 (Figure 3).[45] By carrying out the reaction in a biphasic mixture of toluene or *o*-xylene with [emim][OTf] (an ionic liquid) at azeotropic reflux, the catalyst **42** can be recycled in the ionic liquid and used up to three times with no effect on the amide yield on the second and third run (Scheme 37). This procedure has a reasonable substrate scope with conjugated acids, α-substituted acids and benzoic acids as well as aliphatic amines, anilines and secondary amines all tolerated under the reaction conditions.

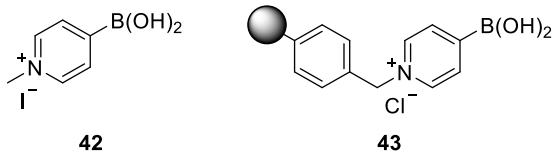
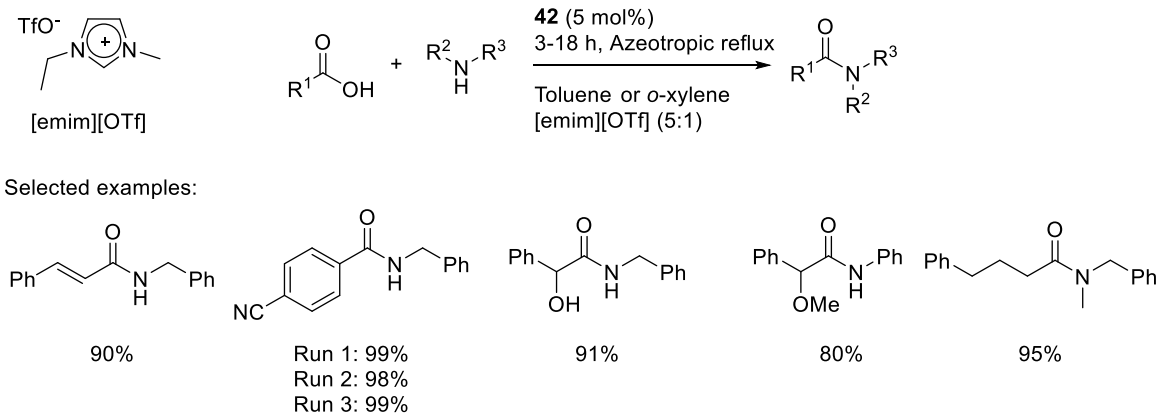
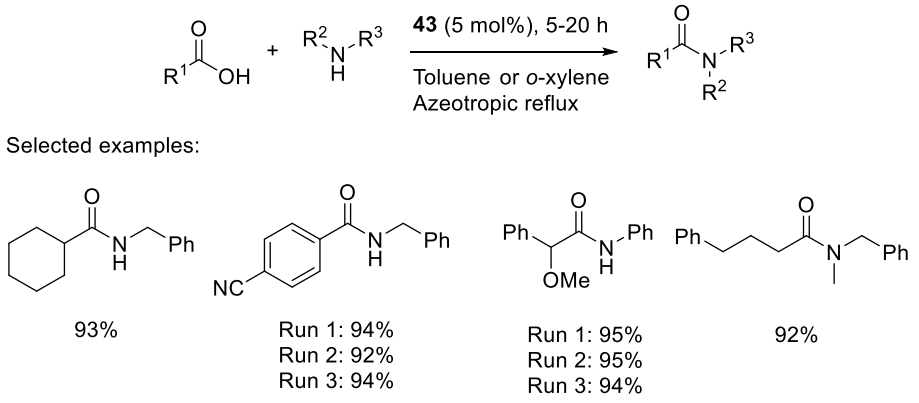


Figure 3 Boronopyridinium salt catalysts



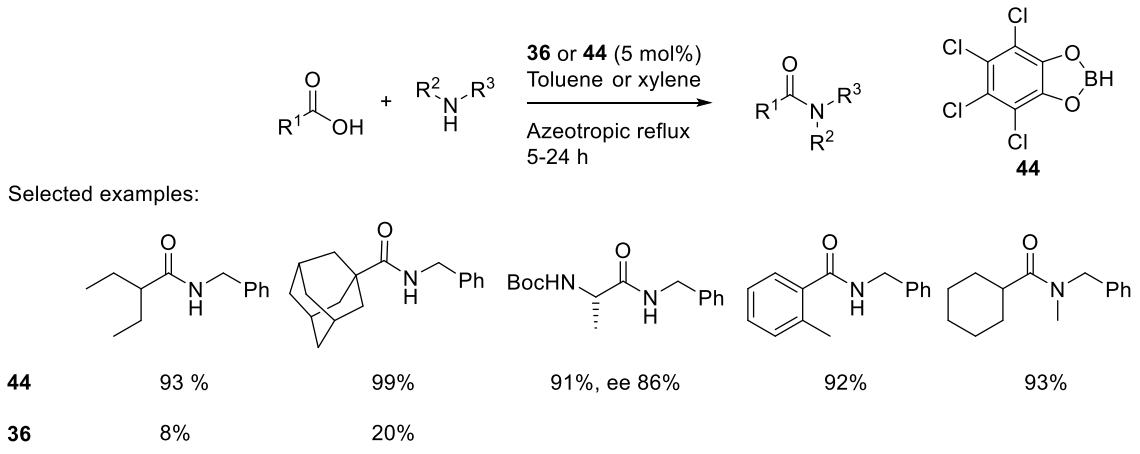
Scheme 37 Examples of **42**-catalysed amidation

As an extension to this methodology to aid in the recyclability of the catalyst and remove the need for the use of an ionic liquid, Yamamoto *et al.* developed a related *N*-polystyrene-bound boronic acid catalyst **43** (Figure 3).[45] This displayed similar utility to **42**, although a smaller substrate scope was trialled in the amidation (Scheme 38). In this case the catalyst can be removed from the reaction mixture by filtration and reused up to three times.



Scheme 38 Examples of **43**-catalysed amidation

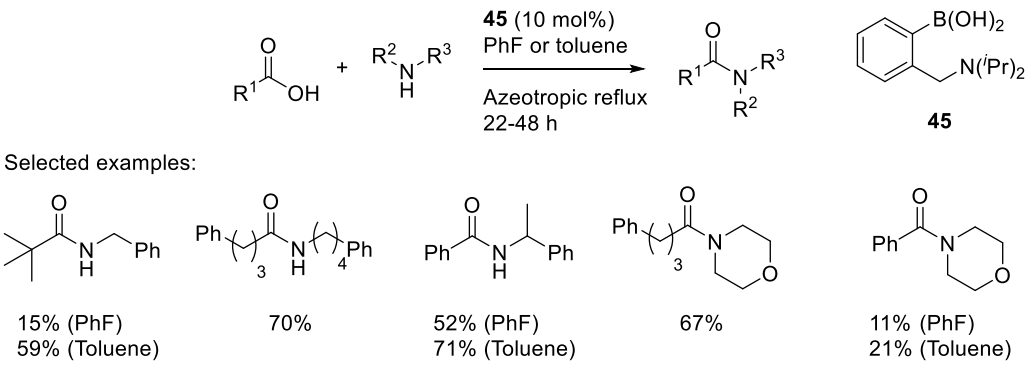
Additionally, Yamamoto *et al.* reported a catalyst, 4,5,6,7-tetrachlorobenzo[*d*]-[1,3,2]dioxaborole **44**, which can catalyse the formation of amides from more sterically demanding carboxylic acids in excellent yield.[46] Compared with the original Yamamoto catalyst **36**, **44** displays superior activity in the case of more sterically demanding carboxylic acids but lower activity for non-sterically demanding acids (Scheme 39). This catalyst shows excellent activity for bulky carboxylic acids including adamantane carboxylic acid as well as Boc-L-alanine, which displays some erosion of enantiopurity.



Scheme 39 Synthesis of more sterically demanding amides catalysed by **44**

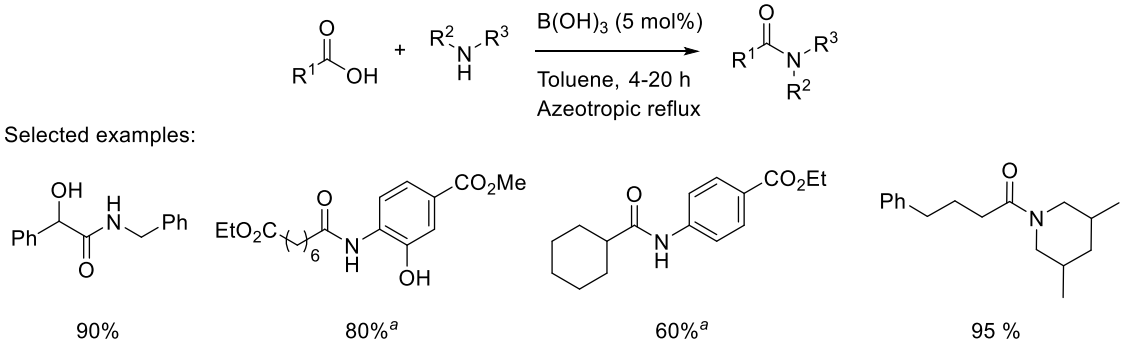
The use of bifunctional catalyst, *o*-*N*,*N*-di-isopropylbenzylaminoboronic acid **45**, as an amidation catalyst was explored by Whiting *et al* in 2008.[47] This commercially available boronic acid can catalyse amide bond formation in refluxing fluorobenzene, or toluene if higher reaction temperatures are required (Scheme 40). This methodology made advances in boronic acid-catalysed amidation by allowing the use of a lower boiling azeotropic solvent, fluorobenzene; although this temperature was not suitable in

all cases. Generally moderate to good yields were achieved, although some combinations could not be improved by increasing the reaction temperature.



Scheme 40 45-catalysed amidation examples

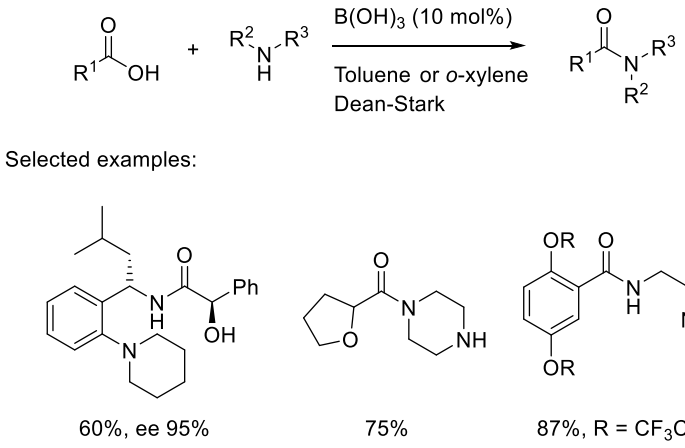
Interestingly, Tang reported the use of cheap, commercially available boric acid as an amidation catalyst in 2005.[48] This had previously been trialled as an amidation catalyst by Yamamoto *et al.* under similar conditions, although over shorter reaction times, in a catalyst screen but it was found to give very low amide yields.[46] The reaction is carried out in toluene at azeotropic reflux for up to 20 h (Scheme 41). This method tolerates free hydroxyl groups and phenols and the corresponding ester product is not observed. Aliphatic and aromatic acids are tolerated under the reaction conditions, even in the presence of α-substituents. Additionally aromatic, aliphatic and secondary amines all undergo amidation including electron-poor anilines.



Scheme 41 $B(OH)_3$-catalysed amidation examples. [a]$B(OH)_3$ (25 mol%).

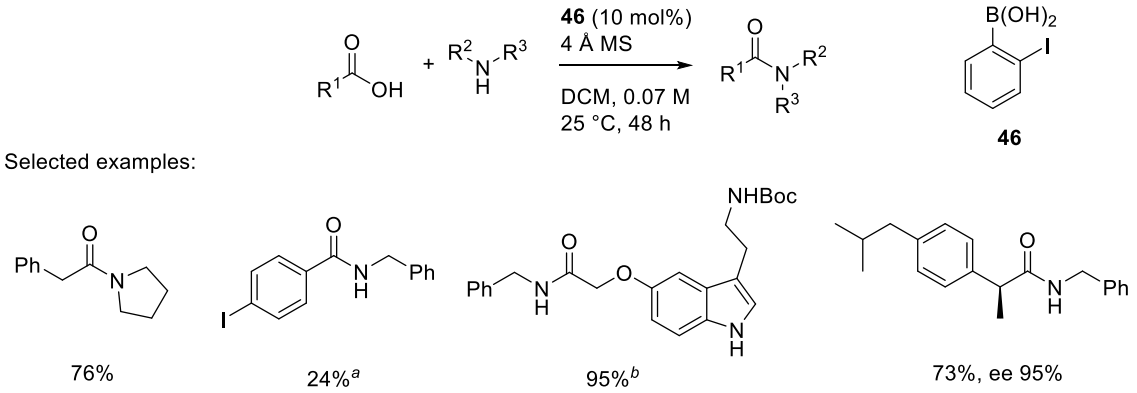
Bandichhor *et al.* have subsequently displayed the utility of $B(OH)_3$ as an amidation catalyst for the synthesis of some Active Pharmaceutical Ingredients (API).[49] A range of functionalised amides were prepared by this methodology (Scheme 42). Monoacylation of piperazine was possible using this methodology, although a small quantity of the

diacylated product was observed. This procedure results in minimal racemisation of α-chiral acids.



Scheme 42 $B(OH)_3$-catalysed amidation of APIs

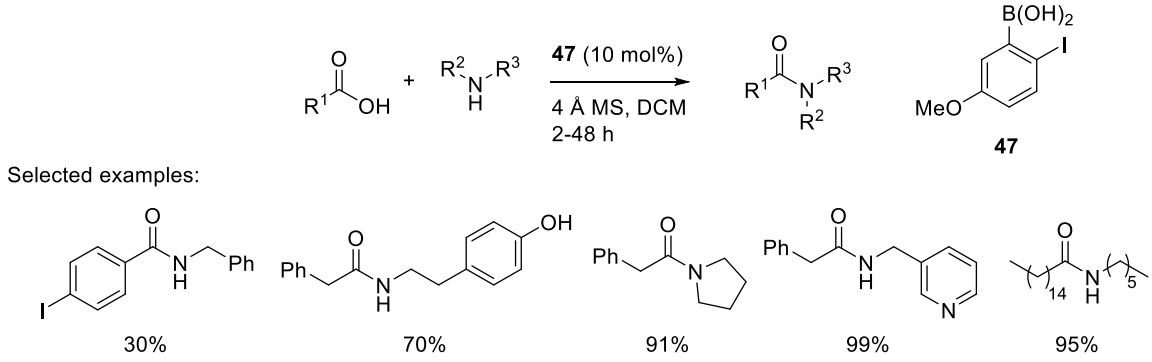
Until 2008, the state-of-the-art boronic acid amidation catalyst required high reaction temperatures, generally in refluxing toluene. To improve the applicability of boronic acid catalysts Hall *et al.* identified a range of *o*-substituted benzeneboronic acids which catalysed amide bond formation at room temperature.[50] The most promising of these was *o*-iodobenzeneboronic acid **46** (Scheme 43). Aromatic and aliphatic acids and amines, including secondary amines, are tolerated in good yield. Benzoic acids require increased reaction temperatures, however even at these higher temperatures comparatively low conversion was observed.



Scheme 43 Examples of **46**-catalysed amidation. [a]**46** (20 mol%), 50 °C; [b]**46** (20 mol%)

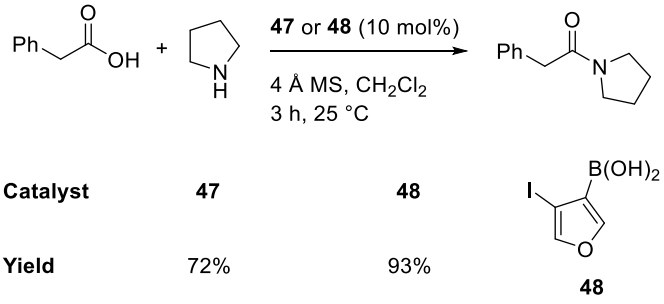
Four years later, Hall *et al.* reported an improvement on catalyst **46** with 2-iodo-5-methoxybenzeneboronic acid **47**, the presence of an electron-donating group on the ring significantly improved the catalyst activity.[51] This is in contrast to the previously

reported boronic acid catalysts which contain electron-poor aromatic rings. The electron-donating methoxy group is thought to improve the activity of the catalyst by increasing the electron density on iodine, which in turn may stabilise the transition state of the reaction. This methodology is suitable for the amidation of aliphatic, (hetero)aromatic and α-branched acids, although benzoic acids are still challenging substrates for this catalyst; however, some improvements compared to catalyst **46** are observed. Aliphatic and cyclic secondary amines are tolerated under the reaction conditions, but acyclic secondary amines are unreactive (Scheme 44).



Scheme 44 47-catalysed amidation examples

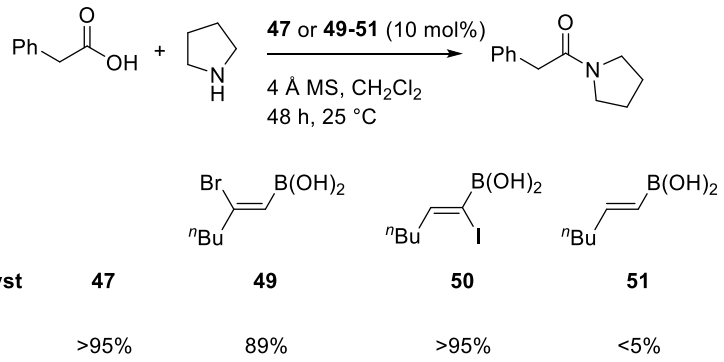
Additionally, Hall *et al.* have patented a number of boronic acid amidation catalysts, some of which show excellent activity at room temperature.[52] Firstly, (4-iodofuran-3-yl)boronic acid **48** has been shown to have superior activity to **47** over a 3 h reaction time at rt (Scheme 45).



Scheme 45 Comparison of catalysts **47** and **48** in amidation

Further boronic acids reported for the amidation of carboxylic acids include alkenylboronic acids (Scheme 46).[52] Alkenylboronic acids containing halogen atoms display excellent activity in the amidation reagent (**49** and **50**). On the other hand, the

absence of a halogen atom on the alkene significantly affects the activity of the catalyst resulting in negligible amide formation (**51**).



Scheme 46 Amidation catalysed by alkenylboronic acids **47** and **49**-**51**

The boronic acid catalyst **47** reported by Hall *et al.* has been derivatised as a solid supported catalyst **52** to further improve the 'greenness' of this catalyst.[53] To reduce any impact on the electronic properties of **47** the linker was introduced on the *m*-methoxy substituent (Figure 4).

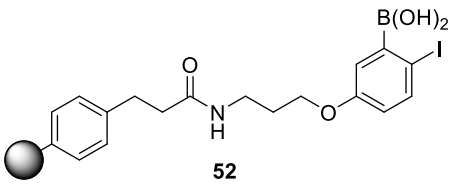
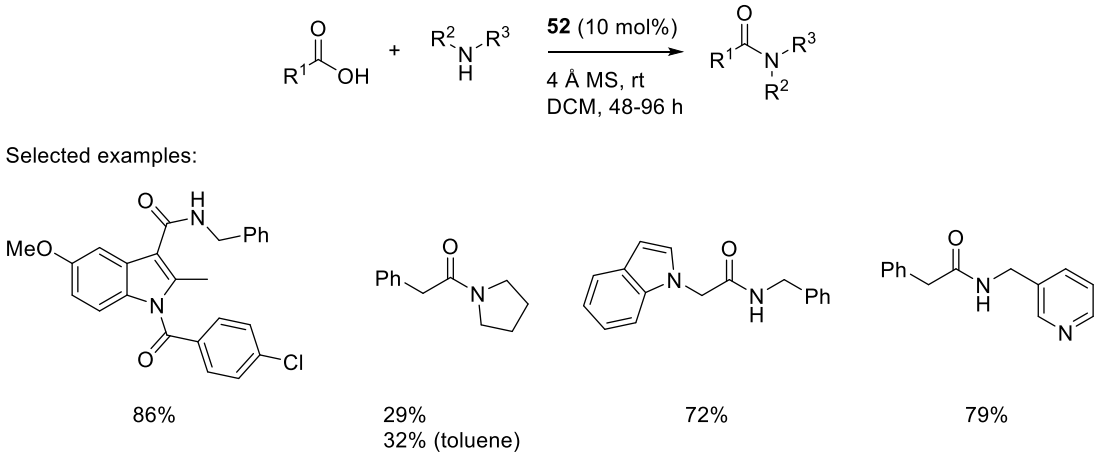


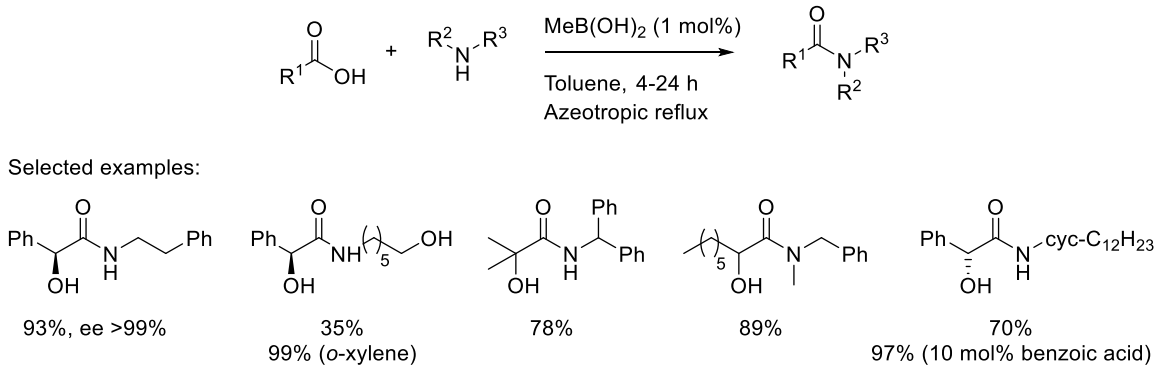
Figure 4 Solid-supported derivative of boronic acid catalyst **52**

This catalyst was applied to a selection of the amide couplings reported for **47** (Scheme 47). The high catalyst activity is limited to primary amines, which form the secondary amide in good to excellent yield, as a comparable yield for amidation with a cyclic secondary amine was not achieved. Although a thorough study of the recyclability of the catalyst has not yet been carried out, the same batch of catalyst was used for all amidations reported in the paper so it can be reused at least five times.



Scheme 47 Examples of **52**-catalysed amidation

A primary alkyl boronic acid catalyst for amidation of α-hydroxycarboxylic acids has been reported by Ishihara *et al.*, in 2013.[54] In the model reaction – mandelic acid and 3,5-dimethylpiperidine – the previously discussed catalysts **36**, **45** and **46** gave poor yield of the amide product (8%, 8% and 6%, respectively). However, primary alkyl boronic acids (methyl **53** and butyl **54**) show good activity (73% and 89%, respectively). The amidation yields can be improved by the addition of benzoic acid (10 mol%) as an additive (96% and 99%, respectively). Under the reaction conditions aliphatic acids and amines are tolerated as well as secondary and α-branched amines. The corresponding esterification of hydroxyl groups is not observed (Scheme 48). In general, no observable racemisation occurred, with the notable exception of the combination of (*R*)-mandelic acid and 2-phenylethylamine (79% ee). This can be improved by using the lower boiling 1,2-dichloroethane as the solvent (94% ee), although at the expense of amide yield (98% reduced to 63%). Interestingly, the amidation of the benzoic acid additive is not reported to occur even in low yield.

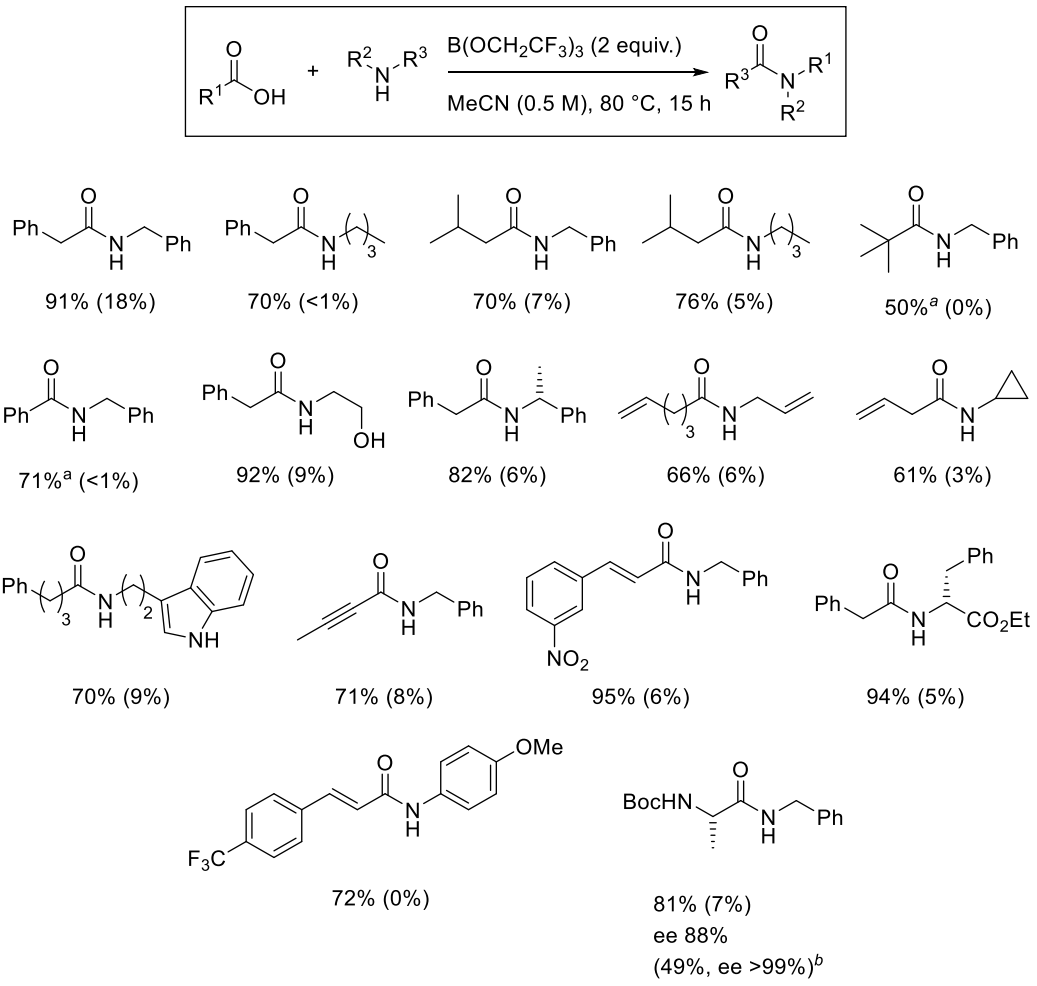


Scheme 48 Examples of methylboronic acid **53** catalysed amidation

Of course the high temperatures required for some of these boron-mediated or catalysed reactions, excluding the room temperature amidations reported by Hall,[50-53] are likely to result in a significant background reaction when the toluene thermal amidation reported by Williams is taken into consideration.[24]

1.3. Project background

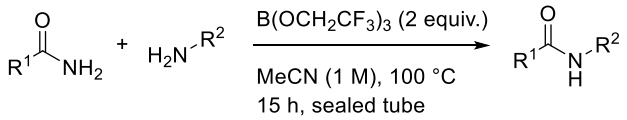
Following work by a previous PhD student, the Sheppard Group has reported on the development of stoichiometric boron reagent, tris(2,2,2-trifluoroethyl)borate **54** for direct amidation reactions after it was identified as an amidation reagent with advantages over $B(OMe)_3$.[55-56] This reagent has a number of advantages over current stoichiometric boron reagents as reactions can be carried out open to the air, without the need for active water removal and only stoichiometric quantities of carboxylic acid and amine are required to give the amide products in good to excellent yield. The scope of the reaction explored is detailed in Scheme 49. Aliphatic and aromatic acids and amines are tolerated as well as conjugated acids and α-substituted acids and amines, including Boc-L-alanine. A number of functional groups are compatible with the reaction conditions – alkenes, alkynes, hydroxyls, esters and nitro groups.

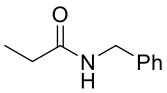
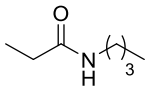
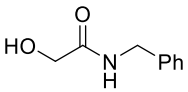
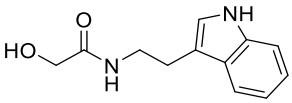


Scheme 49 Previous examples of $B(OCH_2CF_3)_3$-mediated amidation. Thermal yield in parentheses

In addition, $B(OCH_2CF_3)_3$ was shown to mediate the transamidation of primary amides in good yield (Table 4). Four examples were reported including those containing free hydroxyl as well as heteroaromatic groups.

Table 4 $B(OCH_2CF_3)_3$-mediated transamidation



Entry	Product	Yield (%)
1		73
2		63
3		82
4		62

This thesis focuses on further development of the use of $B(OCH_2CF_3)_3$ in the synthesis of amide bonds. Chapter two details further investigation into the synthesis of amides mediated by $B(OCH_2CF_3)_3$. This includes the direct amidation of carboxylic acids, *N*-protected amino acids and the formylation of amines by transamidation of DMF. The development of a solid-phase work-up procedure for these amidation reactions is also described.

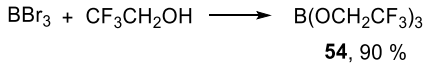
Chapter three details the application of $B(OCH_2CF_3)_3$ to the amidation of unprotected amino acids. This covers an optimisation study and the scope of the reaction, as well as the development of a new method for the determination of enantiomeric purity of chiral amines.

Chapter four describes a mechanistic study into the direct amidation reaction. A reaction intermediate as well as a tentative mechanism are proposed based on the results of this mechanistic study and preliminary experimental evidence.

2. $B(OCH_2CF_3)_3$ as a reagent for direct amidation

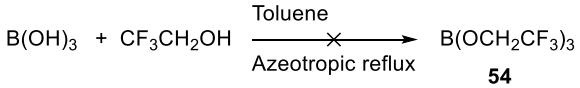
2.1. Synthesis of $B(OCH_2CF_3)_3$

As discussed in the introduction, this thesis focuses on the use of $B(OCH_2CF_3)_3$, as an amidation reagent. $B(OCH_2CF_3)_3$ has been previously prepared in the group using 2,2,2-trifluoroethanol (CF_3CH_2OH) and boron tribromide (BBr_3) in strictly anhydrous conditions (Scheme 50).[55] Despite the high yield (90%) of this reaction, a milder route avoiding highly reactive BBr_3 was sought.



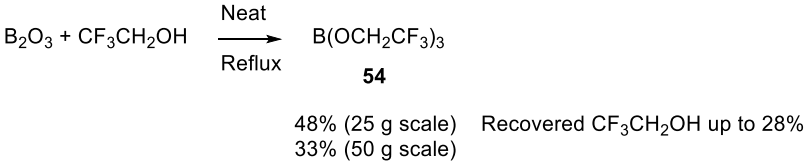
Scheme 50 Synthesis of $B(OCH_2CF_3)_3$ from BBr_3

The first alternative route attempted utilised cheap boric acid and CF_3CH_2OH under Dean-Stark conditions in toluene. However, the high temperature required led to the removal of CF_3CH_2OH from the reaction mixture and, therefore, an unsuccessful synthesis of $B(OCH_2CF_3)_3$ (Scheme 51).[57]



Scheme 51 Attempted synthesis of $B(OCH_2CF_3)_3$ from $B(OH)_3$

Another, more successful, synthesis was established using B_2O_3 and CF_3CH_2OH (Scheme 52).[58] Although synthesising $B(OCH_2CF_3)_3$ from B_2O_3 instead of BBr_3 results in a lower final yield (48% compared to 90%), this route is significantly more attractive from an operational perspective.[59] The handling and use of B_2O_3 is much safer and more convenient as it is not sensitive to moisture. An additional advantage is that B_2O_3 drastically reduces the cost of the synthesis as BBr_3 costs around £90/mol compared to 98p/mol for B_2O_3. In addition, the unreacted CF_3CH_2OH (£12/mol) can be recovered for reuse during distillation.

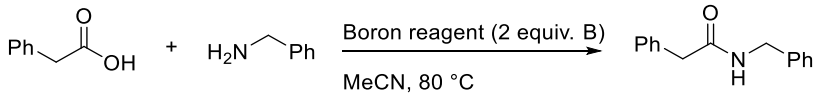


Scheme 52 Synthesis of $B(OCH_2CF_3)_3$ from B_2O_3

2.2. Comparison of different boron reagents

The efficacy of B_2O_3, $B(OMe)_3$, $B(OCH_2CF_3)_3$ as amidation reagents was tested. The amidation of phenylacetic acid with benzylamine was chosen as the model system to compare these reagents (Table 5). Previous work in the Sheppard group investigated these reactions over a reaction time of 15 h.[55] However, it was observed that this length of reaction time was not necessary in the case of $B(OCH_2CF_3)_3$ (Table 5, entries 1 and 2). $B(OMe)_3$, however, required the longer reaction time (Table 5, entries 3 and 4). B_2O_3 from which $B(OCH_2CF_3)_3$ is synthesised, is also slightly active as an amidation reagent but is significantly less efficient than $B(OMe)_3$ or $B(OCH_2CF_3)_3$ (Table 5, entry 5).

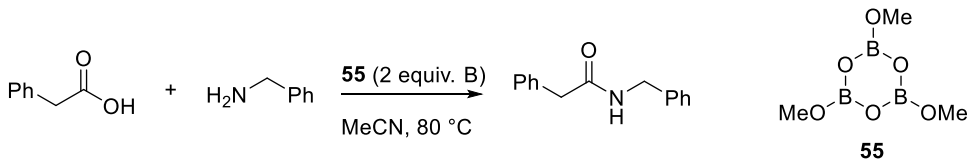
Table 5 Amidation study of boron reagents



Entry	Boron reagent	Time (h)	Yield (%)
1	$B(OCH_2CF_3)_3$	15	91
2	$B(OCH_2CF_3)_3$	5	88
3	$B(OMe)_3$	15	92
4	$B(OMe)_3$	5	69
5	B_2O_3	5	15

Boroxines have been shown to have a higher Lewis acidity than borate esters using the Acceptor Number (AN) scale.[57] $B(OCH_2CF_3)_3$ has an AN of 66.4 (higher than that of the non-halogenated parent borate ester, $B(O^nPr)_3$ with an AN of 20.3). With this in mind, trimethoxyboroxine (**55**, Table 6) was trialled in the amidation of phenylacetic acid and benzylamine. From the AN of triethoxyboroxine (80.1) and tri(*n*-propoxy)boroxine (79.1), it can be inferred that trimethoxyboroxine **55** has a similar AN and, therefore, a higher Lewis acidity than $B(OCH_2CF_3)_3$. Trimethoxyboroxine performs reasonably well as an amidation reagent but is not comparable to $B(OMe)_3$ or $B(OCH_2CF_3)_3$ even over 15 h (Table 6, entries 1 and 2).

Table 6 Amidation study of **55**

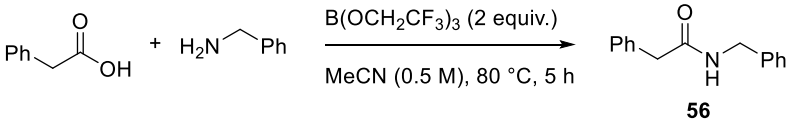


Entry	Boron reagent	Time (h)	Yield (%)
1	**55**	5	72
2	**55**	15	81

The simplicity of the use of $B(OCH_2CF_3)_3$ as well as its synthesis make it a highly attractive option for amidation reactions. Additionally, the $B(OCH_2CF_3)_3$ reagent is now commercially available from Sigma-Aldrich (product number RNI00014).

2.3. Investigation of solid phase work-up

With a view to optimising the total reaction efficiency we wanted to streamline the work up procedure. Previous work made use of aqueous work ups.[55] Due to the nature of the reaction we envisioned that the components of the reaction mixture could all be removed with appropriate solid-phase resins. To determine whether this was a suitable method for purifying the amide products, Amberlyst^{TM} 15, which was readily available in the laboratory, was trialled in the reaction mixture. The reaction of phenylacetic acid and benzylamine was chosen as the model reaction (Scheme 53).



Scheme 53 Solid-phase work-up test reaction

Amberlyst^{TM} 15 is a widely used macro reticular polystyrene resin with an acidic sulfonic acid residue (Figure 5a). The uses of Amberlyst^{TM} 15 as a heterogenous catalyst in synthesis cover a vast area and have recently been reviewed.[60] Initially Amberlyst^{TM} 15 was used in a test reaction of the amidation of phenylacetic acid by excess benzylamine, however the borate reagent remained. Ideally an acidic as well as a basic resin was required to remove both the residual carboxylic acid and residual amine.

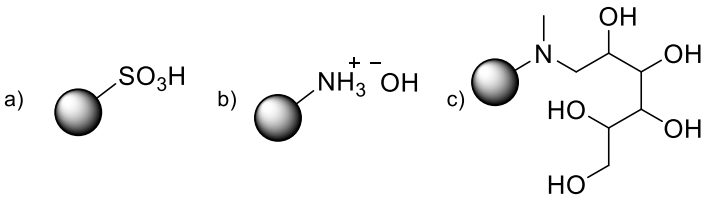
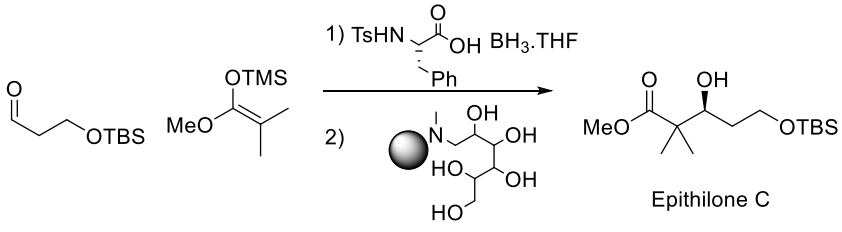


Figure 5 Resins used in $B(OCH_2CF_3)_3$-mediated amidation purification. a) Amberlyst™ 15, b) Amberlyst™ A26(OH) and c) Amberlite™ IRA743

Amberlyst™ A26(OH) is a basic resin with an ammonium hydroxide residue (Figure 5b). This resin has found use as a catalyst in a number of reactions as well as for neutralisation of reactions by removal of acid.[61] For example, Amberlyst™ A26(OH) has been used to purify a pentasaccharide by removing DDQ from the reaction mixture following its conversion to dihydroquinone by L-ascorbic acid.[62] The use of Amberlyst™ A26(OH) as a support for the hydrogen peroxide epoxidation of α,β-unsaturated ketones at room temperature has also been reported.[63] Ester hydrolysis can also be effected with Amberlyst™ A26(OH).[64]

Following the use of Amberlyst™ 15 and Amberlyst™ A26(OH), ^1H and ^{13}C-NMR spectra showed clean product **56**, however a yield of 111 % was recorded. This suggested that boron residues remained in the final product and elemental analysis indicated that the product was impure.

Therefore, a resin that could scavenge boron from the reaction mixture was required. At the time of our investigation into the possible use of a resin to scavenge any boron residues from the $B(OCH_2CF_3)_3$-mediated amidation reactions, there was only one report in the literature of Amberlite™ IRA743 used for this purpose (Figure 5c). Ley described the use of a series of immobilised reagents and scavengers in the synthesis of Epithilone C, which included an aldol reaction mediated by a borane-*N*-tosylphenylalanine complex (Scheme 54).[65] It was felt that a similar procedure could also be applied to our $B(OCH_2CF_3)_3$-mediated amidation reactions to aid in the purification of the amide products.



Scheme 54 Use of Amberlite™ IRA743 by Ley

In addition to this reference to the use of Amberlite™ IRA743 as a boron scavenger in organic synthesis, there are numerous references to this resin in the removal of boron in water treatment processes,[66] as well as its use in enzyme immobilisation[67] and removal of metals.[68] Use of Amberlite™ IRA743 as a boron scavenger was successful in removing the boron residues still present in the reaction mixture and the clean sample was confirmed by elemental analysis.

In summary, we required three different resins: an acidic resin to remove any amine residues, a basic resin to remove any carboxylic acid residues and a boron scavenger to remove any boron residues. Three resins were found to be suitable for this purpose – Amberlyst™ 15 (an acidic resin), Amberlyst™ A26(OH) (a basic resin) and Amberlite™ IRA743 (a boron scavenger).

2.3.1. Use of solid-phase resins in amidation reactions

After finding these three suitable resins we sought to establish whether the combination of these resins would prove fruitful for a solid-phase work-up to remove any residual acid and amine as well as any boron residues

After carrying out the $B(OCH_2CF_3)_3$-mediated amidation a work-up was necessary to remove residual starting materials as well as any boron residues. Using a combination of these resins in a mixture of CH_2Cl_2 and water (6:1 v/v, on a 1 mmol scale – CH_2Cl_2 3 mL and H_2O 0.5 mL) and stirring at room temperature for 30 min removes any residual starting materials and any boron residues. Following water and resin removal by $MgSO_4$ and filtration, respectively, the analytically pure amide product is directly isolated (Figure 6).[59] In place of CH_2Cl_2 in the solid-phase work-up EtOAc is also suitable as the solvent (a 'greener' option). The simplicity of this method is incredibly advantageous as only a filtration is required to yield the clean product. Therefore, this amidation method coupled with the solid-phase work-up procedure could potentially be automated.

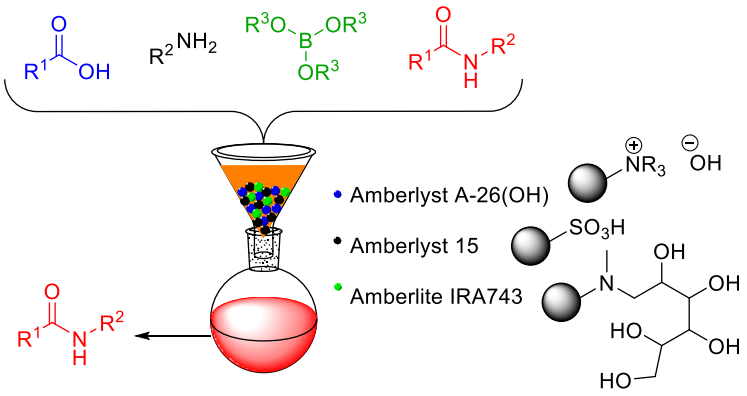


Figure 6 Solid-phase work-up method

2.4. Amidation investigation

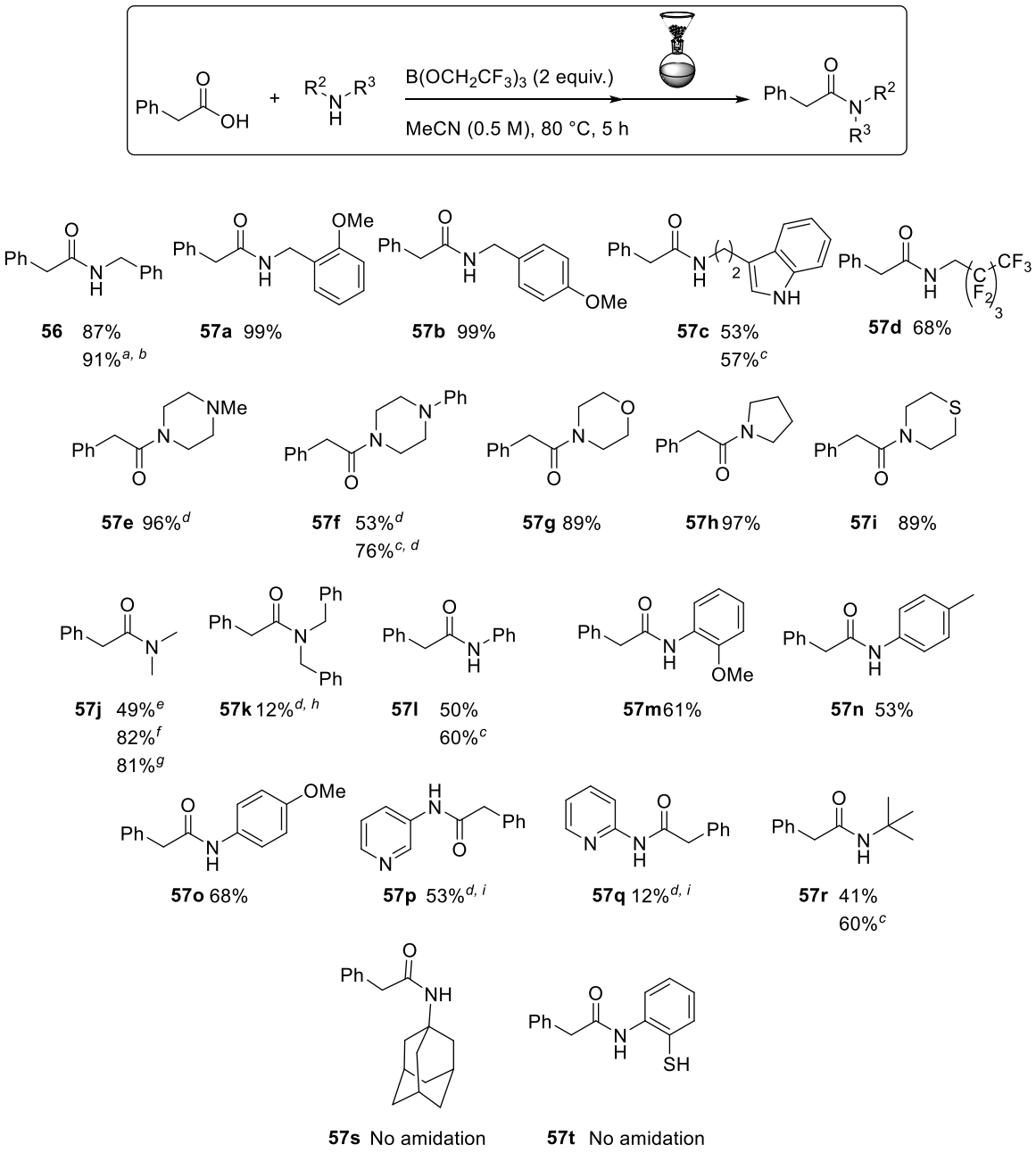
2.4.1. Scope of the $B(OCH_2CF_3)_3$-mediated amidation reaction

In order to evaluate the full scope of the reaction the amidation was carried out using a wide range of amines and carboxylic acids.[59]

The amine scope was evaluated through the synthesis of a series of phenylacetamides by reaction of phenylacetic acid with a range of different amines (Scheme 55). These were prepared using the standard reaction conditions [phenylacetic acid (1 equiv.), amine (1 equiv.), $B(OCH_2CF_3)_3$ (2 equiv.), MeCN (0.5 M), 80 °C], and any deviation from this method is noted. Benzylamines are well tolerated under the reaction conditions (**56**, **57a-b**), as well as functionalised aliphatic amines (heterocycle **57c** and perfluoro **57d**). Cyclic secondary amines generally undergo amidation in excellent yield (**57e-i**) although *N*-phenylpiperazine (**57f**) required a higher reaction temperature of 100 °C to improve the yield from 53% to 76%. In terms of amidation with acyclic secondary amines, this is less efficient than amidation with cyclic secondary amines. Dimethylamine hydrochloride can undergo amidation in good yield as long as two or more equivalents of the salt are used alongside the same number of equivalents of DIPEA to liberate the free amine (**57j**). More than two equivalents are required due to the low boiling point of the free amine (7 °C). The other acyclic secondary amine investigated, dibenzylamine gave a low yield of the amide product (**57k**), alongside a significant quantity of **56**, suggesting that debenzylation had taken place. The overall low conversion of dibenzylamine to either of the product amides (**57k** and **56**) is likely due to steric crowding by the free movement of the benzyl arms, this would not have been the case with cyclic secondary amines or dimethylamine. Less nucleophilic amines, such as aniline, its derivatives and *tert*-butylamine reacted with phenylacetic acid to give the corresponding amide product, although, higher temperatures were

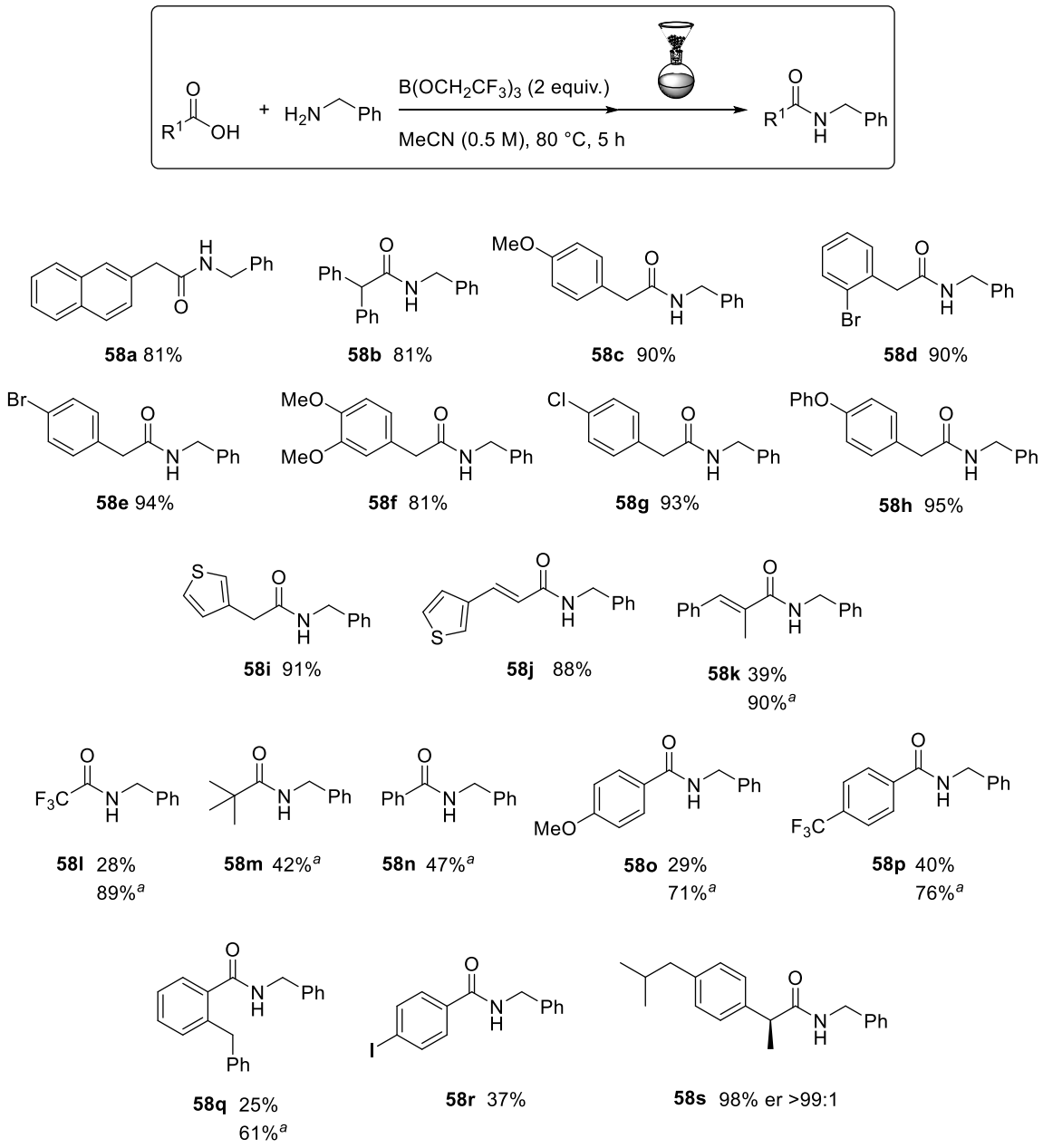
required in some cases to give good yields (**57l**-**57r**). In the case of 2-aminopyridine, high temperatures and long reaction times produced only a very low yield (**57q**, 12%). To ensure that this low yield is not an artefact of the pyridyl nitrogen deactivating $B(OCH_2CF_3)_3$ by coordination, amidation with 3-aminopyridine was carried out, and this gave a moderate yield (**57p**, 53%) indicating that the pyridyl nitrogen is not deactivating $B(OCH_2CF)_3$. Adamantylamine (**57s**) and 2-aminothiophenol (**57t**) were completely unreactive under the reaction conditions.

The purification of the amide products from dibasic amines (**57f** and **57g**) was slightly more complex than the standard resin purification. Residual acid and any boron residues were removed using Amberlyst® A-26(OH) and Amberlite® IRA743. The unreacted amine was then separated from the product by flash column chromatography.



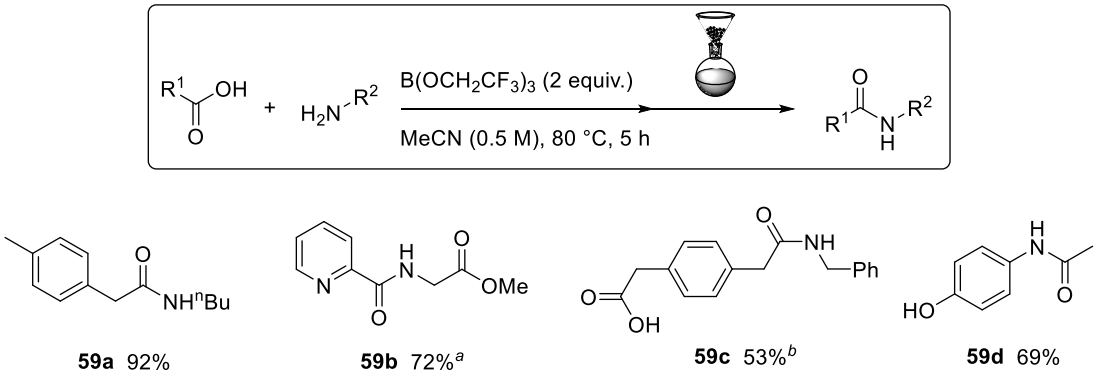
Scheme 55 Scope of amine functionality in $B(OCH_2CF_3)_3$-mediated amidation. All reactions were carried out at 80 °C for 5 h and the solid phase work-up procedure was used unless otherwise stated; [a]Aqueous work-up procedure; [b]80 °C for 15 h; [c]100 °C for 15 h in a sealed tube; [d]Purified by column chromatography; [e]From 1 equiv. $Me_2NH.HCl$, 1 equiv. DIPEA; [f]From 2 equiv. $Me_2NH.HCl$, 2 equiv. DIPEA; [g]From 3 equiv. $Me_2NH.HCl$, 3 equiv. DIPEA; [h]6% of **56** was also isolated; [i]100 °C for 24 h in a sealed tube.

To evaluate the carboxylic acid scope in the $B(OCH_2CF_3)_3$-mediated amidation reaction the synthesis of a range of *N*-benzylamides was carried out with a range of carboxylic acids (Scheme 56).[59] Phenylacetic acid (**57a**) and substituted phenylacetic acids as well as heteroaromatic acids were well tolerated under the reaction conditions to give the corresponding amide in excellent yield (**58a**-**58i**). α-Substituted acids undergo amidation to give the product in good to excellent yield (**58b**, **58k**, **58m** and **58s**). Amidation of unsaturated conjugated acids proceeds in excellent yield (**58k** and **58k**), although the more hindered α-methylcinnamic acid requires a higher reaction temperature to give reasonable yield (**58k**). The less reactive hindered aliphatic acids trifluoroacetic acid and pivalic acid (**58l** and **58m**) also required a higher reaction temperature to give the amide product in reasonable yield. Similar to anilines, benzoic acids displayed lower reactivities and required higher reaction temperatures in order to achieve reasonable conversion (**58n**-**58r**). The more sterically hindered benzoic acid, α-phenyl-*o*-toluic acid, underwent amidation in good yield with an increase in reaction temperature (**58q**). α-Chiral acids such as (*S*)-(+)-ibuprofen undergo amidation in excellent yield with total retention of enantiopurity (**58s**). This is gratifying as ibuprofen is known to racemise under basic conditions.[69]



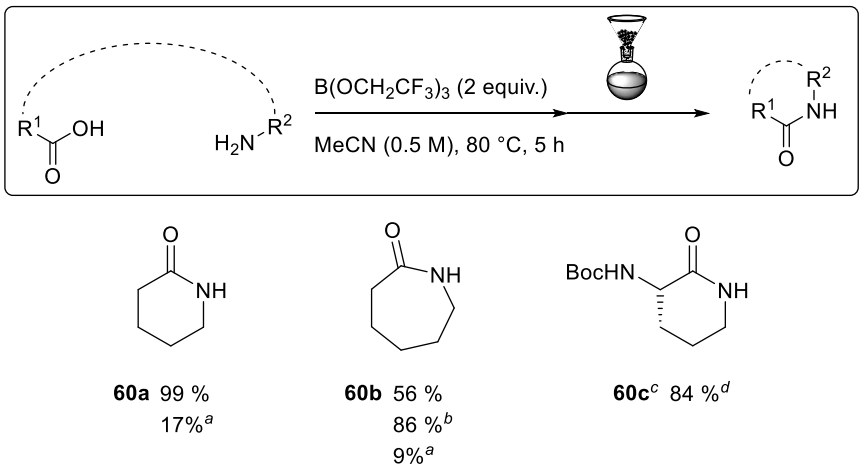
Scheme 56 Scope of acid amidation using $B(OCH_2CF_3)_3$. All reactions were carried out at 80 °C for 5 h and the solid phase work-up procedure was used unless otherwise stated; [a]100 °C for 15 h in a sealed tube.

A selection of other amidations were carried out to further demonstrate the utility of this method (Scheme 57). Amidation of *p*-tolylacetic acid with *n*-butylamine proceeded in excellent yield (**59a**). The more challenging picolinic acid underwent amidation with glycine methyl ester with purification by column chromatography to give **59b** in good yield. Pleasingly, monoamidation of a dicarboxylic acid, 1,4-phenylenediacetic acid, could be effected with 0.5 equivalents of benzylamine in moderate yield (**59c**). Due to the acid functionality present in the product this amide could not be purified by solid-phase work-up procedures, instead an aqueous work up was carried out, still avoiding column chromatography. Paracetamol (**59d**) could also be synthesised in good yield by amidation of acetic acid with *p*-aminophenol mediated by $B(OCH_2CF_3)_3$.



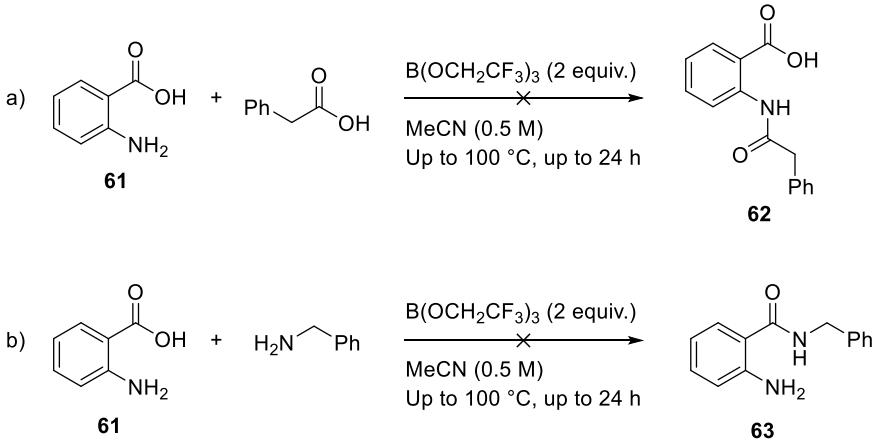
Scheme 57 Other examples of $B(OCH_2CF_3)_3$-mediated amidation. [a]Purified by column chromatography; [b]Aqueous work-up procedure.

The use of $B(OCH_2CF_3)_3$ was investigated in intramolecular amidations (lactamisations) using 5-aminovaleric acid and 6-aminocaproic acid to prepare piperidin-2-one **60a** and azepan-2-one **60b**, respectively (Scheme 58). Cyclisation to six-membered ring piperidin-2-one **60a** proceeds in excellent yield, whereas the seven-membered ring cyclisation to azepan-2-one **60b** proceeds in moderate yield at 80 °C and excellent yield at 100 °C. The background reaction of these lactamisations is low at 80 and 100 °C. The lactamisation of *N*-Boc-L-ornithine was also carried out in excellent yield (**60c**). The optical purity of lactam **60c** was confirmed by carrying out an $[\alpha]_D^{20}$ measurement as *N*-Boc-DL- or D-ornithine were not commercially available to allow measurement of the er by chiral HPLC.



Scheme 58 Examples of lactamisation by $B(OCH_2CF_3)_3$. [a]Yield without $B(OCH_2CF_3)_3$; [b]100 °C for 5 h in a sealed tube; [c]$[\alpha]_D^{25}$ −9.5 (*c* 1.22, MeOH) [Lit.[16] $[\alpha]_D^{20}$ −10.6 (*c* 1.22, MeOH)]; [d]80 °C for 15 h.

The selective amidation of anthranilic acid **61** was attempted. Anthranilic acid was used as either the carboxylic acid or the amine partner (Scheme 59). Unfortunately this was unsuccessful and did not produce either the *N*-acylated anthranilic acid **62** or benzamide **63**, even at high temperatures and extended reaction times. Presumably this lack of reactivity under these reaction conditions is due to the low nucleophilicity of the amine and the low electrophilicity of the acid.

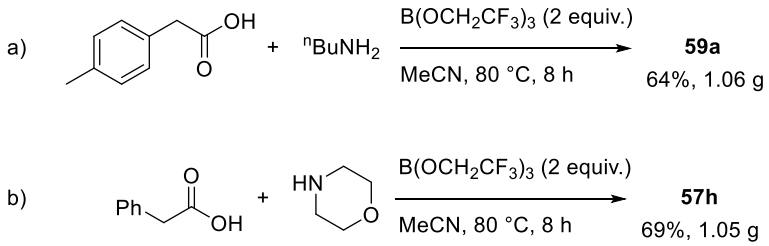


Scheme 59 a) Attempted acylation of anthranilic acid; b) Attempted benzamide formation from anthranilic acid

2.4.2. Reaction scale-up

We wished to determine whether the $B(OCH_2CF_3)_3$-mediated amidation was amenable to larger scale reactions so we attempted the synthesis of a secondary (**59a**) and a tertiary (**57h**) amide on a gram scale (Scheme 60). Pleasingly, gram-scale amidation

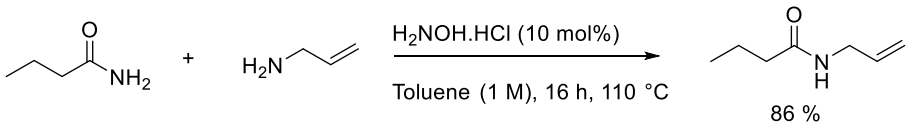
using our methodology was successful, albeit with a slight reduction in yield. In each case, more than 1 g of amide was synthesised and purified by the solid-phase work-up procedure without the need for column chromatography. This procedure required less than 15 mL of MeCN, whereas, the same reaction using a boronic acid catalyst is reported to require around 70 mL of solvent.[51]



Scheme 60 Gram-scale amidation of a) secondary amide **59a** and b) tertiary amide **57h**

2.4.1. *N*-Formylation of amines by transamidation of DMF

During the course of our further investigation into the $B(OCH_2CF_3)_3$-mediated transamidation reaction a method for the transamidation of primary amides was published by the Williams group which described transamidation of primary amides with amines using hydroxylamine hydrochloride as a catalyst.[70] This method sees excellent yields for most of the transamidation products and good reaction scope (Scheme 61).



Scheme 61 Transamidation using hydroxylamine hydrochloride as a catalyst

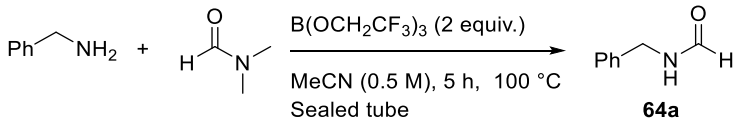
In addition to this report a number of other procedures for transamidation have recently been reported, including organic – $PhI(OAc)_2$,[71] $B(OH)_3$[72] and L-proline[73] – as well as metal – Cp_2ZrCl_2,[74] $Cu(OAc)_2$[75] and CeO_2[76] – catalysts and reagents. As a result of these and other recent methods it was felt that the utility of $B(OCH_2CF_3)_3$ as a reagent for transamidation was limited and would not be worth pursuing. However, during the initial solvent screen at the start of the direct amidation project $B(OCH_2CF_3)_3$ was shown to mediate the transamidation of DMF. As a result of this observation we sought to investigate the utility and scope of this reaction. There are number of recently reported literature methods for the formylation of amines. For example, the transamidation of formamide by NaOMe,[77] $NH_2OH{\cdot}HCl$[70] or Cp_2ZrCl_2;[74] and the amidation of formic acid catalysed by protic ionic liquids,[78] and/or sodium formate.[79]

However, these methods generally require anhydrous conditions as well as purification by column chromatography. The *N*-formylation of amines specifically by transamidation of DMF with several reagents and catalysts has recently been reported - $PhI(OAc)_2$,[71] $B(OH)_3$,[72] L-proline,[73] and imidazole.[80] Again, these methods require high temperatures, long reaction times, and/or purification by column chromatography. Compared to the conditions required for the transamidation of DMF using the catalysts and reagents detailed above, the $B(OCH_2CF_3)_3$-mediated transamidation of DMF for *N*-formylation of amines would be a comparatively straightforward procedure given that the products could easily be purified by the solid-phase work-up procedure.

To explore the efficacy of this reaction the formylation of benzylamine was used as a model system. The background reaction, neat DMF in the absence of $B(OCH_2CF_3)_3$, was negligible (Table 7, entry 1). Surprisingly, using only 1 equivalent of DMF in MeCN as solvent gave improved yields compared to using neat DMF (Table 7, entries 2 and 3). Increasing the quantity of DMF used in the formylation in MeCN increased the formylation to almost quantatitive yield (Table 7, entries 4-8). Using higher quantities of DMF than 10 equivalents decreased the final yield, perhaps due to complexation and deactiviation of $B(OCH_2CF_3)_3$ by DMF which would also explain the lower yield observed in neat DMF (Table 7, entry 9). The reaction temperature could be lowered from 100 °C to 80 °C without any impact on the yield of formamide product (Table 7, entry 10). The formamide product can be isolated pure following the solid-phase work-up and evaporation of DMF. As a result of this optimisation study the final $B(OCH_2CF_3)_3$-mediated formylation procedure is as follows: amine (1 equiv.), DMF (10 equiv.), $B(OCH_2CF_3)_3$ (2 equiv.) in MeCN (0.5 M) at 80 °C for 5 h.[59]

The formylation of benzylamine could also be carried out with two other related formyl donors – formamide (88%) and *N*-methylformamide (94%) – in similar yield to that achieved with DMF as the formyl donor. However, the use of DMF is more attractive as it has a lower boiling point than formamide and *N*-methylformamide (152 °C compared to 210 °C and 183 °C, respectively) as well as being significantly cheaper than these other formyl donors.

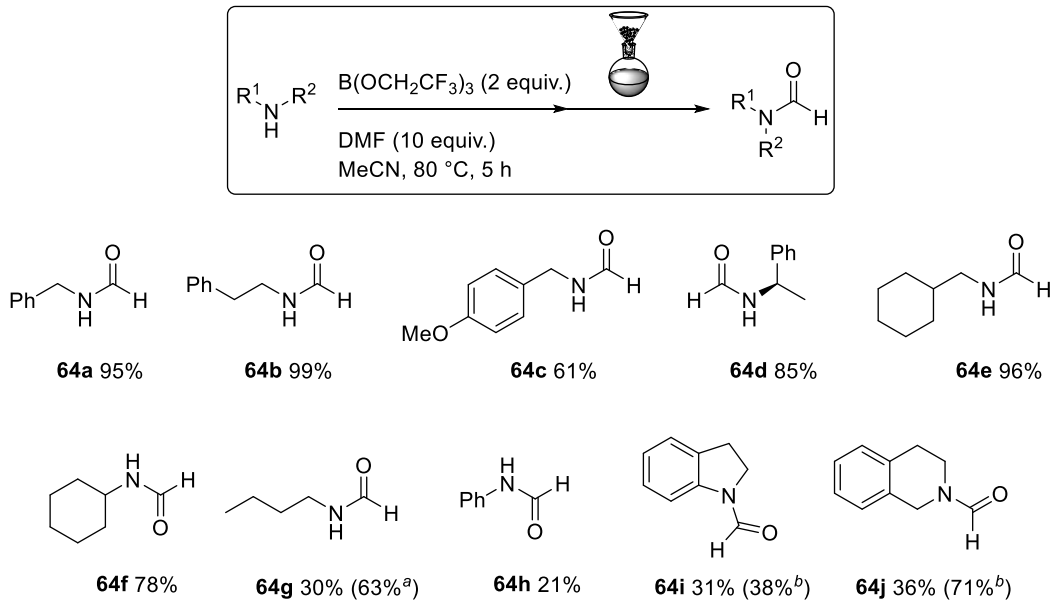
Table 7 Optimisation of $B(OCH_2CF_3)_3$-mediated formylation



Entry	DMF (equiv.)	Yield (%)[a]
1	Neat[b]	11
2	Neat[c]	41
3	1	60
4	2	62
5	3	66
6	4	72
7	5	74
8	10	98
9	15	92
10[d]	10	95

Product isolated by solid phase work-up followed by column chromatography unless otherwise stated. [a]Isolated yield; [b]DMF (0.5 M) as solvent, no $B(OCH_2CF_3)_3$; [c]DMF (0.5 M) as solvent; [d]80 °C, solid phase work-up followed by evaporation of DMF, no column chromatography required.

The scope of the $B(OCH_2CF_3)_3$-mediated *N*-formylation reaction was evaluated on a selection of amines (Scheme 62). Benzylic and aliphatic amines all underwent *N*-formylation *via* this method in good to excellent yield (**64a**-**g**). *n*-Butylamine is formylated in good yield as measured by ^{1}H-NMR, however, the product is volatile so a large proportion is lost on isolation (**64g**). α-Substituted amines, such as α-methylbenzylamine and cyclohexylamine, were well tolerated under the reaction conditions giving the formamide product in excellent yield (**64d** and **64f**). Due to low nucleophilicity of aniline and the related indoline these amines underwent formylation in lower yields (**64h** and **64i**). The procedure was also suitable for the formylation of secondary amines although these amines required higher reaction temperatures to give reasonable yield (**64i** and **64j**).



Scheme 62 Scope of $B(OCH_2CF_3)_3$-mediated *N*-formylation. [a]Yield measured by ^{1}H-NMR with naphthalene internal standard; [b]100 °C reaction temperature.

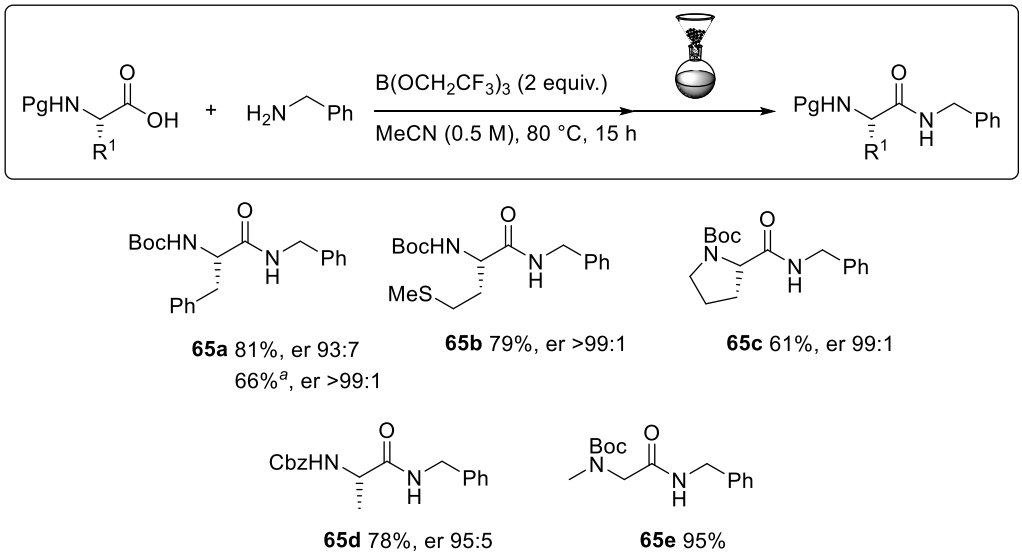
2.5. *N*-Protected amino acid coupling

Due to the success of the amidation of *S*-(+)-ibuprofen with regards to the retention of enantiopurity, the amidation of *N*-protected amino acids was investigated to determine whether a $B(OCH_2CF_3)_3$-mediated amidation would be a feasible route to *N*-protected amino acid amides. This would provide a simple route to these products, in addition to the multitude of methods available, which would require only a solid-phase work-up for purification.[59]

2.5.1. Secondary amides

A series of *N*-protected amino acids with common protecting groups was investigated under the $B(OCH_2CF_3)_3$-mediated amidation conditions; reaction times were, however, extended up to 15 h (Scheme 63). The scope of this reaction was evaluated by reaction of the *N*-protected amino acids with benzylamine. The *N*-Boc protecting group is well tolerated under the reaction conditions, with *N*-Boc-phenylalanine undergoing amidation in excellent yield, albeit with some erosion of enantiopurity (**65a**). This can be rectified by reducing the reaction time; however, the yield of the reaction is reduced. Amidation of *N*-Boc-methionine proceeds in excellent yield with complete retention of enantiopurity (**65b**). Similarly, *N*-Boc-proline retains excellent enantiopurity with good yield of the amide product (**65c**). The *N*-Cbz protecting group is also well tolerated in the $B(OCH_2CF_3)_3$-mediated amidation reaction with *N*-Cbz-alanine undergoing

amidation with benzylamine in excellent yield with good retention of enantiopurity (**65d**). *N*-Boc-sarcosine also gives the amide product in excellent yield (**65e**).



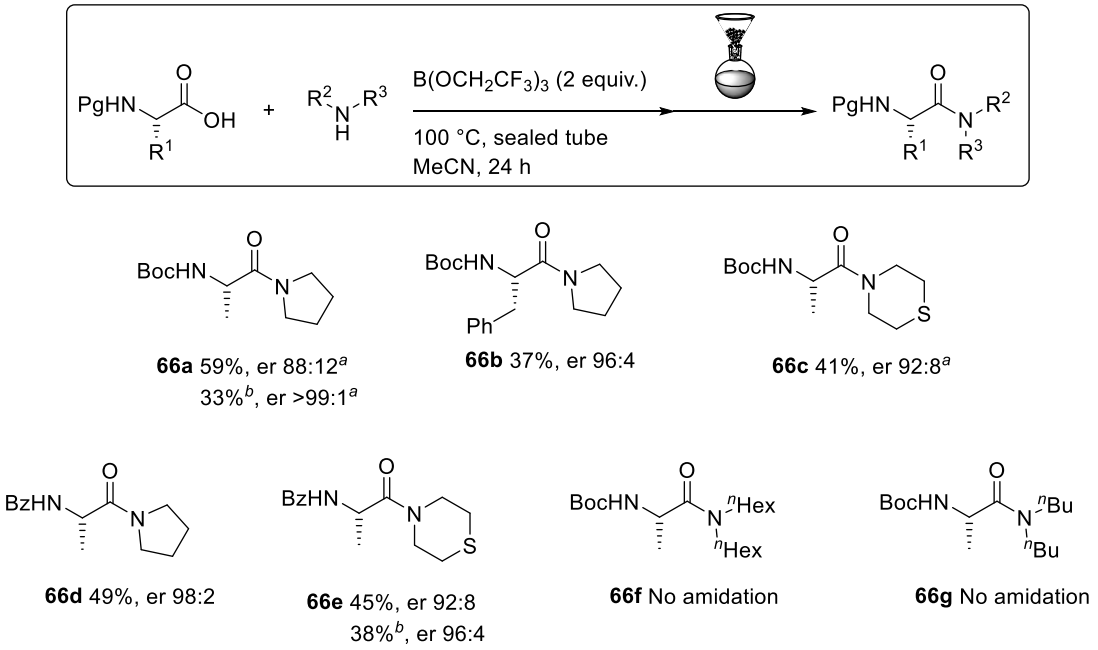
Scheme 63 Scope of $B(OCH_2CF_3)_3$-mediated amidation of *N*-protected amino acids. [a]Reaction time of 8 h.

2.5.2. Tertiary amides

Tertiary amides derived from *N*-Boc-protected amino acids can be difficult to synthesise. A number of groups have published on the amidation of *N*-Boc-protected amino acids with secondary amines using carbodiimides and additives,[81] or uronium salts.[82] The drawbacks of these methods are the large reagents required to activate the carboxylic acid and the associated by-products which are often hazardous and difficult to remove from the amide product. At present, there are no reports in the literature on the amidation of *N*-Boc-protected amino acids with secondary amines promoted by a boron reagent or catalyst.

Pleasingly, our method is a viable alternative to the established routes to these *N*-Boc-protected amino acid tertiary amides as it produces the product in reasonable yield and only requires purification by the simple solid-phase work-up. Tertiary amide preparation compared to secondary amide preparation requires longer reaction times (24 h) and higher temperatures (100 °C) for any reaction to occur (Scheme 64). At 80 °C no reaction is observed, even at prolonged reaction times. *N*-Boc-L-alanine and phenylalanine both undergo amidation with cyclic secondary amines, pyrrolidine and thiomorpholine, in moderate yield with reasonable retention of enantiopurity (**66a-c**). In the case where poor retention of enantiopurity is observed, this can be improved by

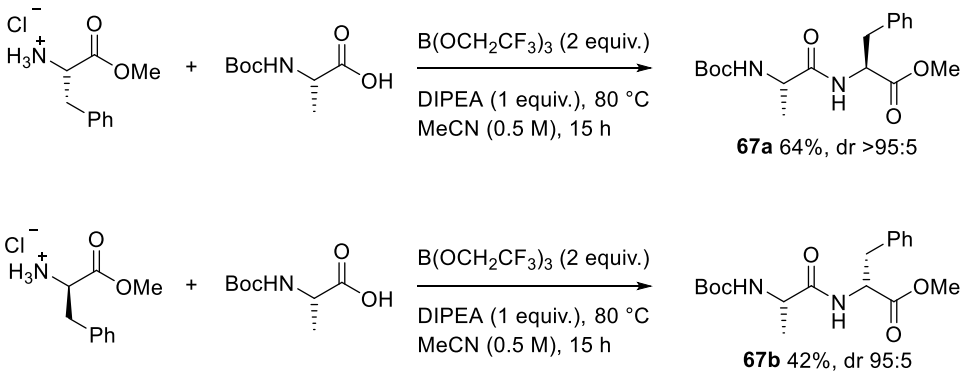
reducing the reaction time in an analogous fashion to amidation of *N*-Boc-protected amino acids with primary amines (**66a**). *N*-Bz-protected amino acids are also well tolerated under the reaction conditions to give the tertiary amide product in moderate yield with good retention of enantiopurity (**66d-e**). The amidation of *N*-Boc-amino acids with acyclic secondary amines was unsuccessful (**66f-g**).



Scheme 64 $B(OCH_2CF_3)_3$-mediated synthesis of *N*-protected amino acid tertiary amides. [a]er measured by derivatisation as *N*-benzoylamide; [b]Reaction time of 8 h.

2.5.3. Dipeptide Synthesis

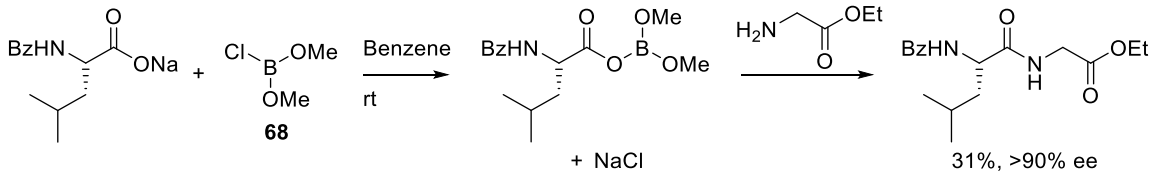
The applicability of $B(OCH_2CF_3)_3$ to dipeptide synthesis was investigated by synthesising a dipeptide from L-phenylalanine methyl ester hydrochloride and D-phenylalanine methyl ester hydrochloride with Boc-L-alanine (Scheme 65, **67a-b**). Both dipeptides were synthesised in good yield with no measurable racemisation. Although our yields are moderate, these dipeptides can be isolated pure following the simple solid-phase work-up with no measurable loss in enantiopurity. Previously, these dipeptides have been synthesised by carbodiimide coupling in good to excellent yield but purification required aqueous work-up, column chromatography or recrystallisation to remove the urea by-product and yield the pure dipeptide.[83]



Scheme 65 Synthesis of dipeptide **67a** and **67b**

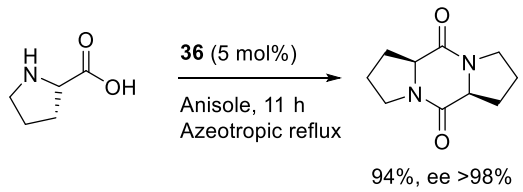
All of these *N*-Boc protected amino acid amides were purified using the solid-phase work-up procedure. Interestingly, we found the *N*-Boc protecting group to be stable to Amberlyst^{TM} 15 at room temperature in CH_2Cl_2 for 30 min, despite precedent in the literature.[84] Romo *et al.* report the use of Amberlyst^{TM} 15 to deprotect and purify *N*-Boc amines, although these reactions are carried out under similar conditions to our solid-phase work-up they require at least 4 h, and in some cases 4 days, for the deprotection to occur. The observed stability of our *N*-Boc amino acid amide products is likely due to their relatively short exposure to Amberlyst^{TM} 15 (30 min) compared to the several hours (or days) of the Romo deprotection method.

There are limited reports of boron reagents used to mediate or catalyse amidation of *N*-protected amino acids. Levitt reports on the use of chlorodimethoxyborane **68** to mediate the amidation of *N*-benzoyl-L-leucine with glycine ethyl ester.[34] Carrying out this reaction at room temperature in benzene gave a low yield but good retention of enantiopurity (>90% ee). Increasing the reaction temperature resulted in complete racemisation of the α-chiral centre and using a more polar solvent (MeCN) had a similar effect.



Scheme 66 $(MeO)_2BCl$-mediated amidation of benzoyl-L-leucine

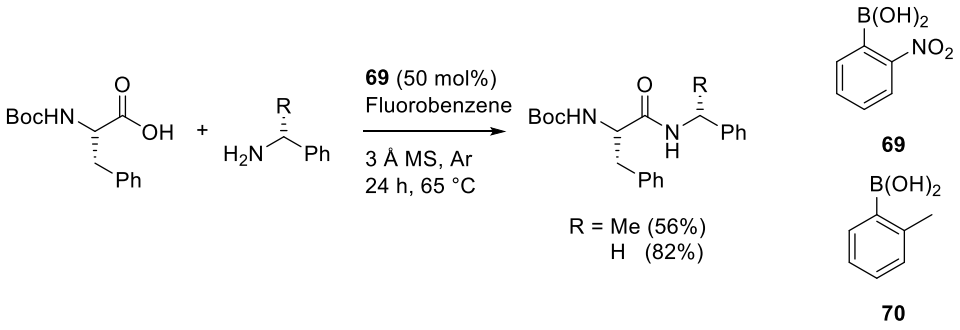
In Yamamoto's report on the use of 3,4,5-trifluorobenzeneboronic acid **36** as an amidation catalyst, there is one example of the use of an amino acid.[41] The lactamisation of L-proline was reported to proceed in excellent yield with high retention of enantiopurity (Scheme 67).



Scheme 67 36-catalysed lactamisation of L-proline

Additionally, Yamamoto reports on the use of the boron-based catalyst **44** (*vide supra*) which is effective for the amidation of more sterically demanding carboxylic acids.[46] Using this catalyst Boc-L-alanine can undergo amidation with benzylamine to give the amide product in excellent yield, however, some erosion of enantiopurity is observed (86% ee).

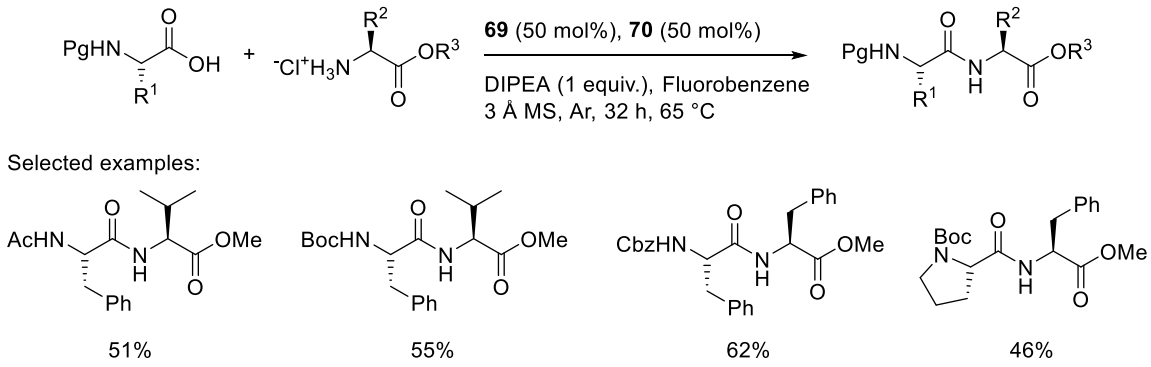
Following our report of the amidation of *N*-protected amino acids mediated by $B(OCH_2CF_3)_3$,[59] Whiting *et al*. reported the amidation of *N*-Boc-protected amino acids and the synthesis of dipeptides catalysed by *o*-nitrophenylboronic acid **69** and *o*-tolylboronic acid **70** under anhydrous conditions.[85] The amidation of amino acids proceeds in excellent yield with unhindered amines, however, more sterically encumbered amines lower the yield of the amide product (Scheme 68).



Scheme 68 Amidation of *N*-protected amino acids catalysed by **69**

In the case of dipeptide formation a 1:1 ratio (100 mol%) of **69** and **70** was required as the reagent to give the dipeptide in moderate yield (Scheme 69). Acid-labile protecting groups such as Boc are tolerated under the reaction conditions. Importantly,

enantiopurity is maintained during the reaction. In this case, limited side-chain functionality was explored.



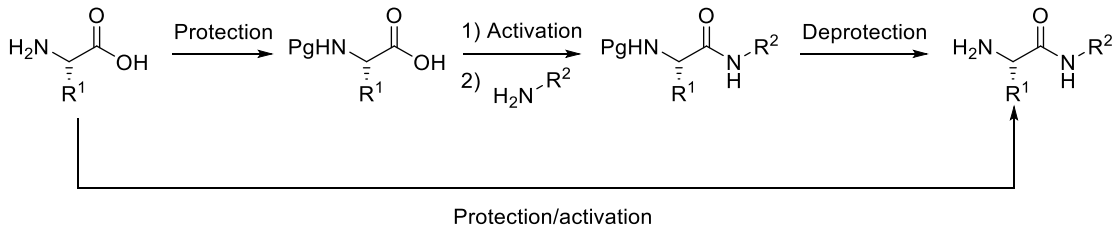
Scheme 69 Dipeptide formation catalysed by **69** and **70**

The use of $B(OCH_2CF_3)_3$ as a reagent in *N*-protected amino acid amidations is therefore of synthetic value in terms of boron-based reagents as it represents an advancement on the current state of the art. *N*-Protected amino acid secondary amides can be synthesised in good to excellent yield with low levels of racemisation. In the cases where racemisation does occur (**65a**, **66a** and **66e**), this can be reduced by shortening the reaction time, although this is at the expense of amide yield. The synthesis of *N*-protected amino acid tertiary amides is possible with $B(OCH_2CF_3)_3$ in moderate yield with excellent retention of enantiopurity when cyclic secondary amines are used, however no reaction is observed with acyclic secondary amines. All of these amide products can be isolated following the solid-phase work-up procedure which simplifies the process and avoids the need for column chromatography.

3. $B(OCH_2CF_3)_3$-mediated amidation of unprotected amino acids

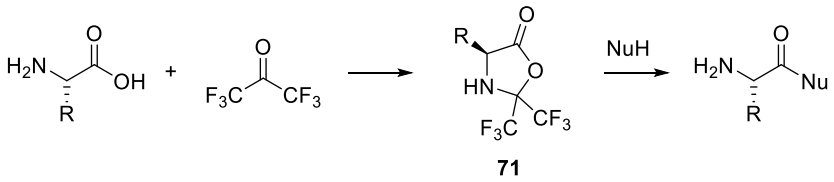
3.1. Background

The amidation of unprotected amino acids generally requires protection and deprotection of any functional groups not involved in the coupling to prevent any undesired side reactions. In addition, the preactivation of the carboxylic acid partner is required (Scheme 70). The protection and deprotection of either the amine or acid functionality as well as the protection of any sidechain functionality adds at least two extra steps to any synthetic sequence. Ideally a reagent that could accomplish both protection and activation of the unprotected amino acid is required. There are few procedures which accomplish this feat without the need for protecting groups and preactivation of the acid.



Scheme 70 Simplified route to the amidation of unprotected amino acids

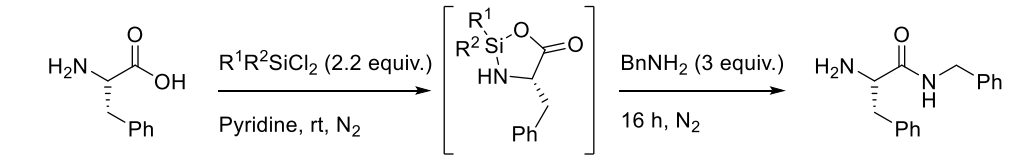
Burger *et al.* have described and reviewed the use of hexafluoroacetone for the protection/activation of unprotected amino acids to form 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones **71** (Scheme 71).[86-87] Protection with hexafluoroacetone also allows for selective functionalisation on the amino acid side-chain, particularly amine or acid functionality, as well as activation of the carboxylic acid for nucleophilic attack. Importantly, these lactone-type rings **71** are stable and can be isolated. However, despite its great utility, hexafluoroacetone is a very toxic gas so great care must be taken when handling it.



Scheme 71 Reaction of amino acid with hexafluoroacetone

In 2002, Liskamp *et al.* reported a simultaneous protection-activation method for the synthesis of amino acid amides. This procedure utilised dichlorodialkylsilanes as the

protecting group and the coupling reagent. Due to the propensity of dichlorodialkylsilanes towards hydrolysis this reaction requires anhydrous conditions.[88] The report focused on dichlorodimethylsilane, however, bulkier dichlorodialkylsilanes were also investigated (Scheme 72). They postulate that the reaction proceeds through the reactive cyclic silane intermediate **73**. Isolation of **73** was not possible but indirect evidence for its presence in the mechanism is provided by the absence of the reaction in carboxylic acids without a free α-amino group as *N*-protected amino acids do not undergo amidation. This procedure is limited to primary amine nucleophiles that lack substituents in the α-position, the presence of a substituent at this position significantly affects the yield of the reaction. For example, using L-phenylalanine methyl ester as the amine nucleophile gives a low yield (17 %) and use of even bulkier isopropylamine or *sec*-butylamine give yields of less than 5 %. In this report no er (or ee) data is given and no discussion of the retention of enantiopurity is made.



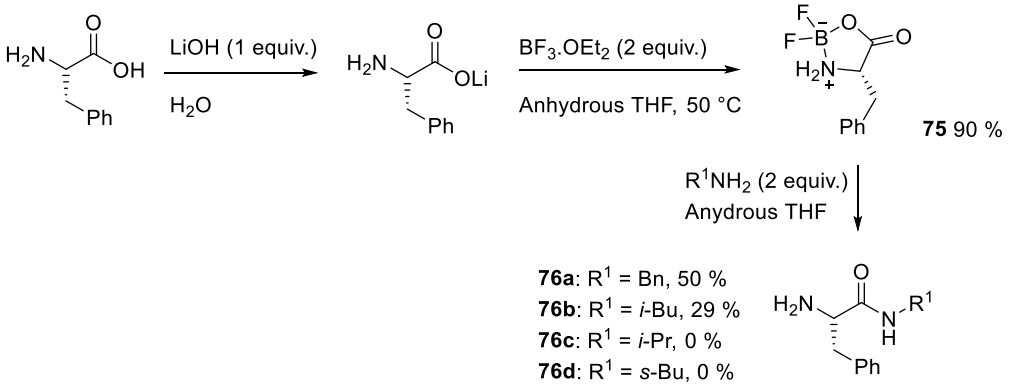
72a: R^1 = Me, R^2 = Me
72b: R^1 = *t*-Bu, R^2 = *t*-Bu
72c: R^1 = Me, R^2 = H
72d: R^1 = Me, R^2 = Ph
72e: R^1 = Et, R^2 = Et

73

74a: 98 %
74b: 0 %
74c: 90 %
74d: 75 %
74e: 25 %

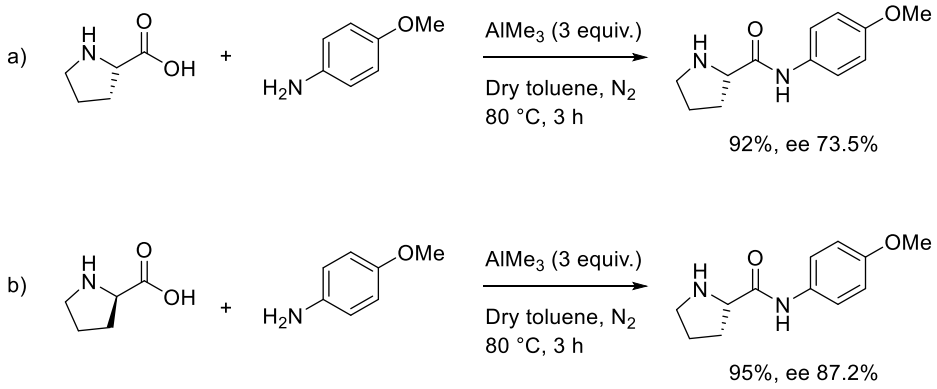
Scheme 72 Unprotected amino acid amidation using dichlorodialkylsilanes

Following this report, in 2005, Liskamp *et al.* published a related procedure using boron trifluoride diethyl etherate in a similar protection-activation strategy (Scheme 73).[89] In this case the additional step of forming the lithium salt of L-phenylalanine was required compared to the previous example. The lithium salt is then reacted with $BF_3.Et_2O$. In this case the cyclic intermediate, 2,2-difluoro-1,3,2-oxazaborolidin-5-one **75**, could be isolated in 90 % yield. Attack of an amine on **75** yields the amide products. However, the yields compared to the dichlorodialkylsilane equivalent are significantly lower. The lower yields observed for the product are thought to be due to steric hindrance around the carbonyl reaction centre. Under these reaction conditions absolutely no reaction was observed with amines containing α-substituents (**76c-d**), the reaction can only be carried out with primary amines with no α-substituents. Again, no discussion of possible racemisation of the chiral centre of the amino acids was made and ers (or ees) were not reported.



Scheme 73 Unprotected amino acid amidation using $BF_3.OEt_2$

Additionally, Li *et al.* have shown one example of unprotected amino acid amidation mediated by $AlMe_3$.[27] They describe the amidation of L- and D-proline with *p*-anisidine, which both proceed in excellent yield although significant racemisation was observed (Scheme 74). This procedure also requires anhydrous conditions.



Scheme 74 $AlMe_3$-mediated amidation of a) L- and b) D-proline with *p*-anisidine

With these reports in mind, it was worth investigating the potential of $B(OCH_2CF_3)_3$ as a reagent for the amidation of unprotected amino acids. The conditions required could provide a significantly milder procedure for the amidation of unprotected amino acids without the need for anhydrous conditions by using the air stable $B(OCH_2CF_3)_3$ reagent. We expected that $B(OCH_2CF_3)_3$ would protect and activate the unprotected amino acid in a similar fashion to that described by Liskamp (Figure 7).[89]

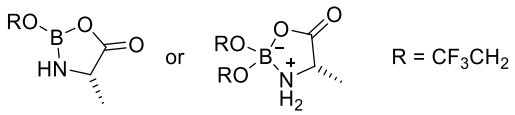


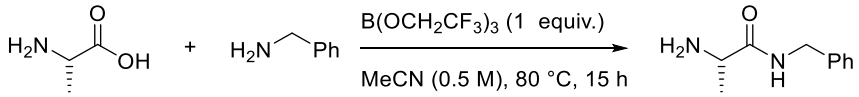
Figure 7 Proposed unprotected amino acid protection-activation by $B(OCH_2CF_3)_3$

3.2. Initial attempt at reaction optimisation

3.2.1. Previous work in the Sheppard group

Two test reactions on the amidation of unprotected amino acids carried out by a previous PhD student in the Sheppard group showed that $B(OCH_2CF_3)_3$ could be used to mediate the amidation of unprotected amino acids (Table 8).[56] In the absence of a base (DIPEA) no amidation was observed in the model system, however on addition of DIPEA (1 equiv.) a 35 % conversion was observed. The base was thought to aid the solubility of L-alanine in MeCN. No significant dipeptide formation by the amidation of L-alanine with another molecule of L-alanine was observed.

Table 8 Initial unprotected amino acid amidation work



Entry	Additive	Conversion (%)[a]
1	No additive	0
2	DIPEA	35

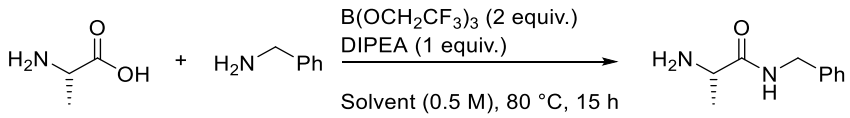
[a]By ^{1}H-NMR

3.2.2. This work

Following this initial finding a more thorough investigation of the reaction was undertaken. The preliminary optimisation studies focused on the $B(OCH_2CF_3)_3$-mediated amidation of L-alanine with benzylamine as a model system. Firstly, a solvent screen was carried out to determine whether the pre-established conditions using acetonitrile as the solvent for $B(OCH_2CF_3)_3$-mediated amide couplings were suitable for unprotected amino acid couplings (Table 9). MeCN, either anhydrous or HPLC grade, has been shown to be the best solvent of those investigated in this screen (Table 9, entries 1 and 2). Reducing the reaction time from 15 h to 5 h decreases the conversion of the reaction (Table 9, entry 3). There is no measured background reaction in MeCN (Table 9, entry 4). Low conversion was observed in 1,4-dioxane, EtOAc, toluene and chloroform although the *N*-benzylacetamide amidation product resulting from transamidation of EtOAc was observed (Table 9, entries 5-8). Negligible conversion occurred in petrol (40-60 °C) and THF (Table 9, entries 9 and 10). No reaction occurred in methyl *tert*-butyl ether, DMSO or 1,2-dichloroethane (Table 9, entries 11-13). Use of

an alcoholic solvent gave no reaction, presumably as a result of deactivation of $B(OCH_2CF_3)_3$ (Table 9, entries 14-16).

Table 9 Solvent screen for L-alanine and benzylamine coupling

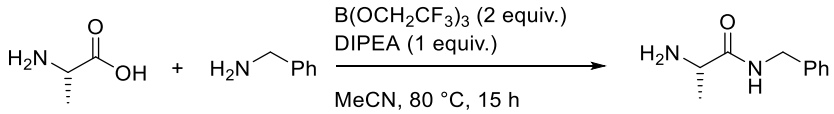


Entry	Solvent	Temperature (°C)	Conversion (%)[a]
1	MeCN	80	65
2	MeCN[b]	80	65
3	MeCN[c]	80	34
4	MeCN[d]	80	0
5	1,4-Dioxane[b]	80	12
6	EtOAc	80	14[e]
7	Toluene	80	18
8	$CHCl_3$	60	14
9	Petrol (40-60 °C)	60	5
10	THF	60	2
11	TBME	60	0
12	DMSO	80	0
13	1,2-Dichloroethane	80	0
14	MeOH	60	0
15	CF_3CH_2OH	80	0
16	EtOH	80	0

[a]Measured relative to residual benzylamine by ^{1}H-NMR; [b]Anhydrous; [c]5 h instead of 15 h reaction time; [d]No $B(OCH_2CF_3)_3$; [e]BnNHCOMe, an amidation product of EtOAc was also present.

A concentration screen of the reaction was carried out to determine the optimum concentration for the reaction (Table 10). Increasing or decreasing the concentration from the 0.5 M in MeCN used for the amidation of carboxylic acids reduces the conversion of the reaction (Table 10, entry 3). As a result the concentration used for the amidation of unprotected amino acids remains at 0.5 M.

Table 10 Concentration screen

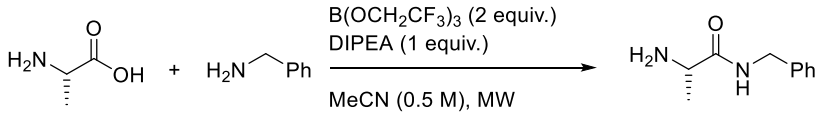


Entry	Concentration (M)	Conversion (%)[a]
1	Neat	21
2	0.1	19
3	0.5	65
4	1.0	38
5	2.0	45

[a]Measured relative to residual benzylamine by ^{1}H-NMR

As an attempt to improve the conversion of the reaction and, therefore, the isolated yield we carried out a brief investigation into the use of microwave heating to perform the unprotected amino acid amidation. Initial results suggested that this may be an efficient way to perform the reaction by giving reasonable conversion and greatly reducing the reaction time (Table 11, entries 1, 5 and 6). Increasing the reaction time at both 100 °C and 120 °C resulted in a decrease in purity of the crude product and an inability to measure the conversion by ^{1}H-NMR (Table 11, entries 2-4, 7 and 8). As a result of this reduction in purity of the reaction we decided to avoid using the microwave as we wanted the reaction to be as clean as possible to aid in purification.

Table 11 Microwave reactions of L-alanine and benzylamine

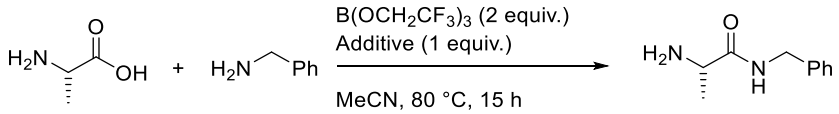


Entry	Temperature (°C)	Time (mins)	Conversion (%)[a]
1	100	10	5
2	100	20	-
3	100	40	-
4	100	60	-
5	120	10	35
6	120	20	68
7	120	40	-
8	120	60	-

[a]Measured relative to residual benzylamine by ^{1}H-NMR

An additive screen was carried out to determine whether the conversion to product could be improved with the presence of an additive other than DIPEA (Table 12). Initially varying the equivalents of the substrates as well as DIPEA was investigated. Excluding DIPEA from the reaction mixture gave a very low conversion compared to the use of DIPEA (Table 12, entries 1 and 2). Using an excess of L-alanine gave comparable yields to that observed with one equivalent of L-alanine (Table 12, entry 3). An excess of benzylamine reduced the observed conversion (Table 12, entry 4). Using an additional equivalent of $B(OCH_2CF_3)_3$ as the additive along with one equivalent of DIPEA gave the best conversion (Table 12 entry 5). Use of $MgSO_4$ as a drying agent to remove the water generated in the reaction and drive the reaction forward did quite the opposite as the reaction completely stopped (Table 12, entry 7). Several different tertiary amine bases were investigated as alternatives to DIPEA, however, none of these gave improved conversion (Table 12, entries 8-16). Use of ethanolamine based tertiary amines gave negligible conversion, this is presumably due to deactivation of $B(OCH_2CF_3)_3$ by chelation. Using trimethoxyboroxine with and without DIPEA gave very low conversion (Table 12, entries 17 and 18), which is curious given that trimethoxyboroxine displays reasonable utility in the amidation of phenylacetic acid with benzylamine.

Table 12 Additive screen



Entry	Additive	Conversion (%)[a]
1	No additive	12
2	DIPEA	65
3	DIPEA, L-Alanine[b]	63
4	Benzylamine[c]	36
5	$B(OCH_2CF_3)_3$, DIPEA	71
6	$B(OCH_2CF_3)_3$, L-Alanine, DIPEA[b]	48
7	$MgSO_4$	0
8	Imidazole	13
9	*N*-Methylimidazole	3
10	NEt_3	28
11	*n*-Bu_3N	11
12	DBU	9
13	Pyridine	49
14	*N*, *N*-Diethylaniline	53
15	Triethanolamine	1
16	*N*,*N*-Dimethylethanolamine	7
17	Trimethoxyboroxine[d]	4
18	Trimethoxyboroxine, DIPEA	4

[a]Measured relative to residual benzylamine by ^{1}H-NMR, [b]L-alanine (0.5 equiv.), DIPEA (1.5 equiv.), [c]0.5 equiv., [d]No DIPEA,

As a result of these studies the optimum conditions for the $B(OCH_2CF_3)_3$-mediated amidation of L-alanine are as follows: carboxylic acid (1 equiv.), amine (1 equiv.), DIPEA (1 equiv.) and $B(OCH_2CF_3)_3$ (3 equiv.) in MeCN (0.5 M) at 80 °C for 15 h.

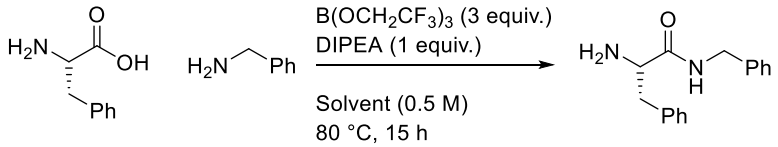
3.2.3. Further optimisation of unprotected amino acid amidation

We decided to approach the further optimisation of this reaction from a different angle, this time utilising an internal standard to directly quantify the yield of the reaction relative to the limiting reagent. For this optimisation we used the amidation of L-phenylalanine by benzylamine as the model system as some solubility issues were

observed with L-alanine. Additionally, separation of the L-alanine benzylamide product from benzylamine was proving troublesome so we sought a more lipophilic amino acid to simplify the isolation process. We initially carried out a solvent screen which investigated 'greener' solvents than the solvents investigated in the solvent screen. Suitable, readily available, solvents were chosen with reference to GSK's green solvent guide.[90]

The reaction was carried out under the optimum conditions from the previous screens [acid (1 equiv.), amine (1 equiv.), $B(OCH_2CF_3)_3$ (3 equiv.), DIPEA (1 equiv.) in MeCN (0.5 M)]. In this case alcoholic solvents were not investigated as they had previously been shown to be unsuitable. Following the selection of available solvents we found that toluene, EtOAc, 2-MeTHF and TBME all gave moderate conversions (Table 13, entries 2-5). Some of these solvents were investigated in the previous solvent screen and did not perform as well, this may be due to the relative solubilities of L-alanine and L-phenylalanine in these solvents. We were pleasantly surprised that dimethylcarbonate gave a reasonable conversion and that cyclopentyl methyl ether (CPME) was comparable in performance to MeCN (Table 13, entries 1, 6 and 7). Carrying out the reaction in CPME at 100 and 125 °C led to further improvements in the conversion (Table 13, entries 8 and 9).

Table 13 Solvent screen for unprotected amino acid amidation



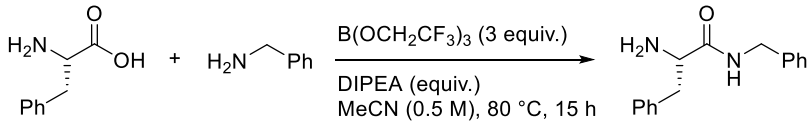
Entry	Solvent	Yield (%)[a]
1	MeCN	61
2	Toluene	39
3	EtOAc	33
4	2-MeTHF	43
5	TBME	39
6	Dimethylcarbonate	51
7	CPME	65
8	CPME[b]	69
9	CPME[c]	89

[a]Yield measured by ^{1}H-NMR using naphthalene internal standard; [b]100 °C; [c]125 °C

Due to the similar conversion observed using both MeCN and CPME we elected to optimise the reaction in both solvents. As we had seen a potential solubility difference between L-alanine and L-phenylalanine in the two solvent screens we felt that either MeCN or CPME would be suitable for the amidation depending on the amino acid used.

The optimisation of the reaction in MeCN is detailed in Table 14. Compared to the yield observed in MeCN for equimolar quantities of L-phenylalanine and benzylamine using a slight excess of L-phenylalanine does not have a detrimental effect on the yield, however a larger excess does have an impact on the yield of the reaction (Table 14, entry 1-3). However, excess benzylamine has a positive effect on the yield of the reaction, which plateaus around 2 equivalents (Table 14, entries 4 and 5). Providing the excess base as a tertiary amine (DIPEA) that does not take part in the reaction does not improve the reaction yield (Table 14, entry 6).

Table 14 Unprotected amino acid amidation optimisation in MeCN

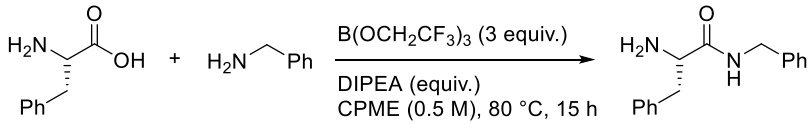


Entry	L-Phenylalanine (equiv.)	Benzylamine (equiv.)	DIPEA (equiv.)	Yield (%)[a]
1	1	1	1	61
2	1.5	1	1.5	62
3	2	1	2	40
4	1	2	1	84
5	**1**	**3**	**1**	**86**
6	1	1	2	61

[a]Yield measured by ^{1}H-NMR using naphthalene internal standard.

We also carried out a reaction optimisation in CPME as this would be the preferred solvent due its green credentials (Table 15). The observations of this optimisation are in agreement with those made in the reaction optimisation in MeCN (Table 15). However, in this case increasing the number of equivalents of L-phenylalanine to 1.5 does begin to have a positive effect on the yield of the reaction, although increasing to 2 equivalents begins to reduce the yield observed (Table 15, entries 1-3). In keeping with the observations of the MeCN optimisation, increasing the number of equivalents of benzylamine significantly improves the yield of the reaction (Table 15, entries 4 and 5). Using triethylamine as the basic additive in place of DIPEA has a detrimental effect in the yield (Table 15, entry 6). Again, using DIPEA to provide the excess base instead of excess benzylamine decreases the reaction yield (Table 15, entry 7). In the presence of excess benzylamine, the basic DIPEA additive is not required as a comparable reaction yield is observed (Table 15, entry 8). Reducing the loading of $B(OCH_2CF_3)_3$ from 3 to 2 equivalents still gives a reasonable yield but it is nowhere near the excellent yield observed in the presence of 3 equivalents of $B(OCH_2CF)_3$ (Table 15, entry 9).

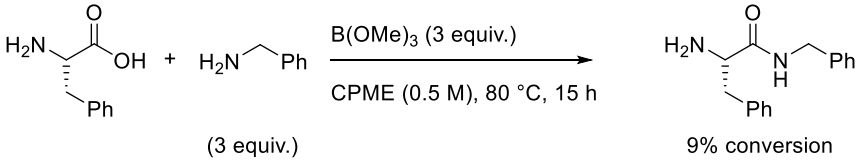
Table 15 Unprotected amino acid amidation optimisation in CPME



Entry	L-Phenylalanine (equiv.)	Benzylamine (equiv.)	DIPEA (equiv.)	Yield (%)[a]
1	1	1	1	65
2	1.5	1	1.5	74
3	2	1	2	68
4	1	2	1	86
5	1	3	1	90
6	1	3	1[b]	82
7	1	1	2	63
8	**1**	**3**	**0**	**95**
9[c]	1	3	0	72

[a]Yield measured by ^{1}H-NMR using naphthalene internal standard; [b]NEt_3 used in place of DIPEA; [c]$B(OCH_2CF_3)_3$ (2 equiv.).

The commercially available $B(OMe)_3$ was trialled in the reaction to ensure that $B(OCH_2CF_3)_3$ also conferred an advantage in the case of unprotected amino acid amidation, the yield observed using $B(OMe)_3$ was negligible (Scheme 75).

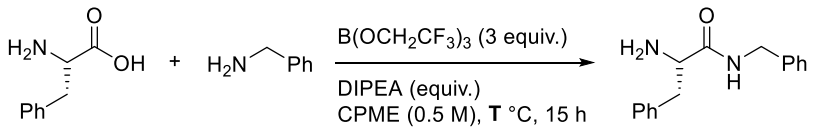


Scheme 75 $B(OMe)_3$-mediated amidation of L-phenylalanine. Conversion measured by ^{1}H-NMR using naphthalene internal standard

As the boiling point of CPME is significantly higher than MeCN (106 °C compared to 81 °C) we investigated whether a higher temperature would be advantageous to the yield in the unprotected amino acid amidation (Table 16). Increasing the reaction temperature to 100 °C does not have a significant impact on the yield whereas increasing the reaction tempertature to 125 °C results in a large increase in the yield (Table 16, entries 1 and 2). At this higher temperature increasing the equivalents of benzylamine used does not have an impact on the yield (Table 16, entries 3 and 4).

Again, removing DIPEA from the reaction mixture does not have a detrimental effect on the yield (Table 16, entry 5).

Table 16 Unprotected amino acid amidation optimisation in CPME at higher temperatures



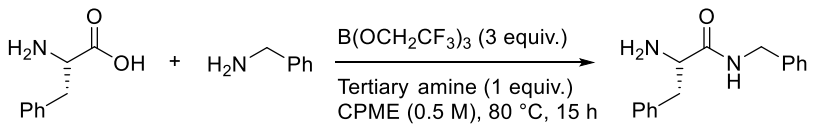
Entry	L-Phenylalanine (equiv.)	Benzylamine (equiv.)	DIPEA (equiv.)	T (°C)	Yield (%)[a]
1	1	1	1	100	69
2	1	1	1	125	89
3	1	2	1	125	82
4	1	3	1	125	92
5	**1**	**3**	**0**	**125**	**91**

[a]Yield measured by ^{1}H-NMR using naphthalene internal standard.

As a result of this series of optimisations the final procedure for $B(OCH_2CF_3)_3$-mediated amidation of unprotected amino acids is as follows: amino acid (1 equiv.), amine (3 equiv.), $B(OCH_2CF_3)_3$ (3 equiv.) in CPME at 80 °C for 15 h. If this procedure does not give sufficient yield of the amide product this may be a result of low amino acid solubility in CPME, in this case MeCN can be used as the solvent to improve amino acid solubility.

If it is the case that the amidation is being carried out with a 'valuable' amine then it is possible to perform the reaction with the amino acid in excess albeit in lower yield (Table 17). Carrying out the amidation with excess L-phenylalanine and DIPEA gives the amide product in poor yield (Table 17, entry 1). This can be improved upon by using NEt_3 as the excess base (Table 17, entry 2).

Table 17 Unprotected amino acid amidation optimisation for 'valuable' amine



Entry	L-Phenylalanine (equiv.)	Benzylamine (equiv.)	Tertiary amine	Yield (%)[a]
1	1	⅓	DIPEA	14
2	1	⅓	NEt_3	49

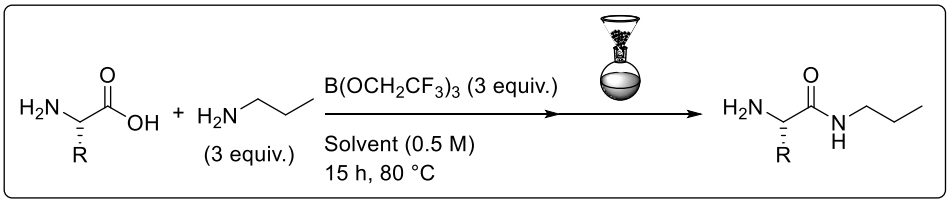
[a]Yield measured by ^{1}H-NMR using naphthalene internal standard.

3.3. Scope of the B(OCH$_2$CF$_3$)$_3$-mediated amidation of unprotected amino acids

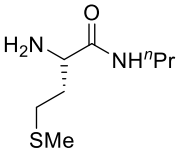
To evaluate the scope of the B(OCH$_2$CF$_3$)$_3$-mediated unprotected amino acid amidation we subjected all natural as well as some unnatural amino acids to an amidation with *n*-propylamine (Scheme 76). *n*-Propylamine was used for this study due to its low boiling point and hence the ease with which any excess amine could be removed from the reaction mixture. The conversion to amide product was measured by ^{1}H-NMR in the presence of naphthalene as an internal standard. Some of the examples in which the amide product was obtained in a synthetically useful conversion (>~70%) were isolated as either the hydrochloride salt or the free amine. These amides were purified with the solid-phase work-up, in this case only Amberlyst™ A26(OH) and Amberlite™ IRA743 were used. The excess *n*-propylamine could be removed under vacuum.

Amino acids with nonpolar side chains – L-phenylalanine, L-methionine, L-leucine, L-*p*-hydroxyphenylglycine, L-proline and sarcosine – all react well under the reaction conditions to give the amide product in excellent yield (**77a**-**77f**). Diamidation of L-aspartic acid can be carried out in good yield, although 6 equivalents of amine and 4 equivalents of B(OCH$_2$CF$_3$)$_3$ are required (**77g**). Lactamisation of the side chain of L-glutamic acid as well as amidation of the carboxylic acid proceeds in good yield (**77h**). β-Alanine undergoes amidation in moderate yield in CPME and a switch to MeCN did not improve the yield (**77i**). Interestingly, L-cysteine provides the amide product in good yield in CPME at 125 °C, but no reaction occurs in MeCN (**77j**). Similarly, increasing the reaction temperature to 125 °C in CPME gives quantitative conversion for the L-valine amidation (**77k**). Amidation proceeds in excellent yield in the case of L-alanine

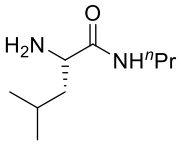
and L-phenylglycine in MeCN (**77l** and **77m**). The amidation of glycine, L-isoleucine and L-tyrosine occurs in poor yield in CPME, a solvent change to MeCN improved these to moderate yields (**77n**-**77p**). Subjecting L-lysine to the reaction conditions results in lactamisation of the amine in the amino acid side-chain (**77q**). Heteroaromatic-containing amino acids, L-tryptophan and L-histidine, undergo amidation in low to moderate yield in both CPME and MeCN (**77r** and **77s**). Amino acids with primary amide side chains, L-asparagine and L-glutamine, both give low yields for the amidation in both CPME and MeCN (**77t** and **77u**). In the case of L-glutamine a significant quantity of the cyclisation product from transamidation was also observed (**77h**). L-Serine does not undergo amidation at all either in CPME or MeCN, interestingly L-homoserine and L-threonine do undergo amidation in CPME and MeCN, respectively, however only in low yield (**77v**-**77x**). Presumably the lack of reactivity in L-serine is due to complex formation between the hydroxyl group on L-serine and $B(OCH_2CF_3)_3$, which does not form in the case of L-homoserine and L-threonine. In the case of L-serine only decomposition was observed by ^{1}H-NMR. L-Arginine did not undergo amidation at all in either CPME or MeCN, only starting material remained presumably due to a lack of solubility in either of these solvents (**77y**).



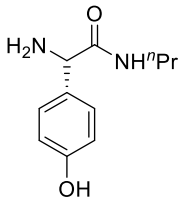
77a[a] 94% (90%)[b]



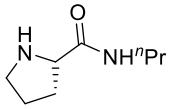
77b[a] 83% (81%)[c]



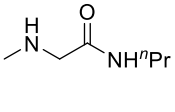
77c[a] 76% (73%)[c]



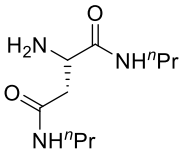
77d[a] 82%



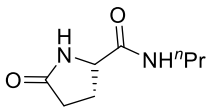
77e[a] 87% (86%)[c]



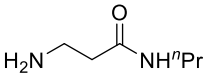
77f[a] 90% (84%)[b]



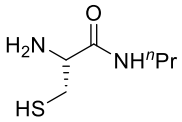
77g[a,d] 70% (68%)[b]



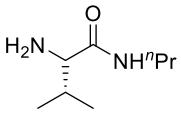
77h[a] 79%[e]



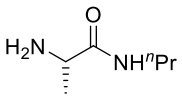
77i[a] 57%



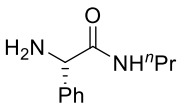
77j[a,f] 62%



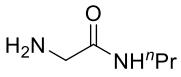
77k[a,f] Quant. (95%)



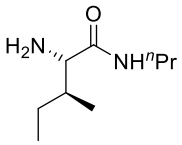
77l[g] 76% (71%)[b]



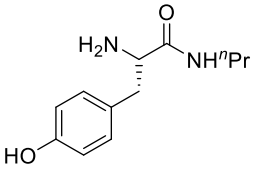
77m[g] 87%



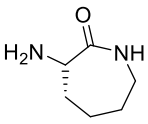
77n[g] 63%



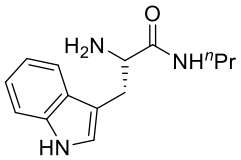
77o[g] 53%
dr>95:5



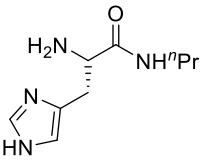
77p[g] 48%



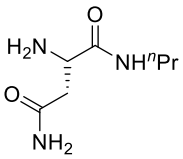
77q[h] 44%



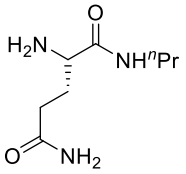
77r[a] 56%



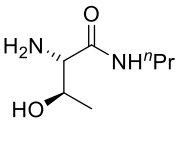
77s[g] 30%



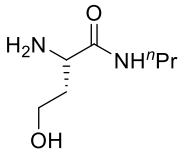
77t[g] 16%



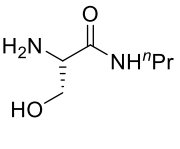
77u[g, i] 21%



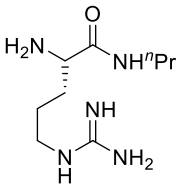
77v[g] 53%
dr >95:5



77w[a] 40%



77x nr



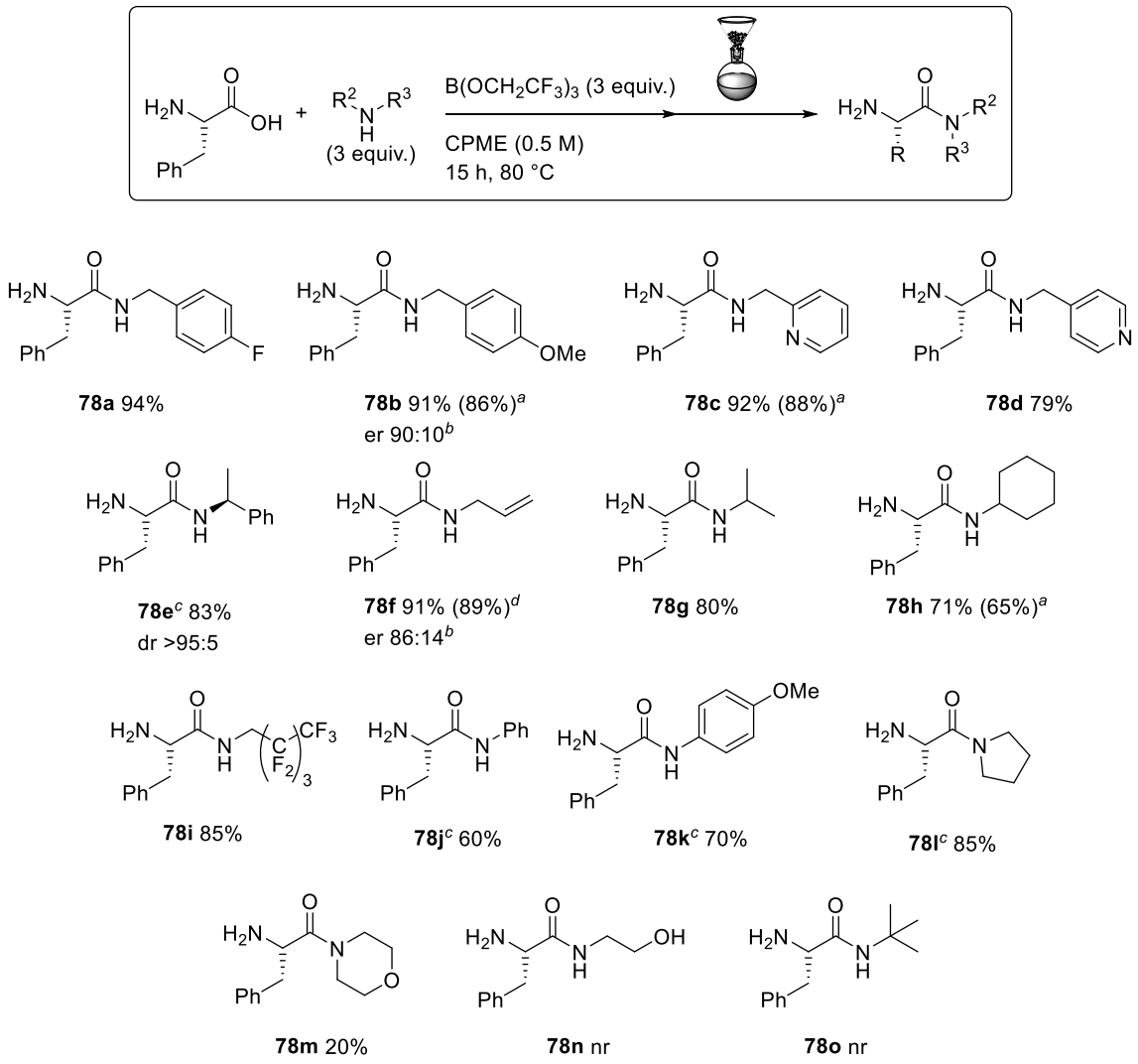
77y nr

Scheme 76 Amino acid scope in $B(OCH_2CF_3)_3$-mediated unprotected amino acid amidation. Conversion measured by ^{1}H-NMR with naphthalene internal standard, isolated yield in parentheses. [a]CPME (0.5 M); [b]Isolated as hydrochloride salt; [c]Isolated as free amine; [d]$B(OCH_2CF_3)_3$ (4 equiv.), propylamine (6 equiv.); [e]Isolated yield; [f]125 °C; [g]MeCN (0.5 M); [h]No propylamine, DIPEA (3 equiv.); [i]15% transamidation cyclisation product **77h** also observed.

Amides **77a**, **77f**, **77g** and **77l** were obtained as the hydrochloride salt. Amides **77b**, **77c**, **77e** and **77k** were isolated as the free amine as the hydrochloride salts of these amides were incredibly hygroscopic and could not be obtained as a sufficiently dry salt. The isolated yields of these amide products was in good agreement with the conversion measured by ^{1}H-NMR.

The amine scope for the $B(OCH_2CF_3)_3$-mediated amidation reaction was evaluated by preparing amides of L-phenylalanine (Scheme 77). The amidation of L-phenylalanine with benzylamine derivatives all proceed in excellent conversion, including those containing pyridine rings (**78a-e**). Although benzylamine derivatives with α-substituents require a higher reaction temperature to achieve reasonable conversion (**78e**). Aliphatic amines, including unsaturated amines, those with α-substituents and perfluoroamines, amidate L-phenylalanine in excellent conversion (**78f-i**). Amines with lower nucleophilicity such as aniline and the more electron-rich *p*-anisidine furnish the corresponding amide product under the reaction conditions, however, higher reaction temperatures are necessary to achieve a synthetically useful conversion (**78j** and **78k**). Tertiary amides can be prepared by amidation of L-phenylalanine with secondary amines, although higher temperatures are required for reasonable conversion (**78l** and **78m**). Ethanolamine and *tert*-butylamine were unreactive under the reaction conditions, even at 125 °C (**78n** and **78o**).

Amides **78b**, **78c** and **78h** were isolated as the free amine, **78f** was isolated as the hydrochloride salt. No racemisation was observed in the case of **78e**. The enantiopurities of **78b** and **78f** were measured by chiral HPLC, in these cases some racemisation was observed. The source of this racemisation is not clear but may be related to the excess amine present in the reaction mixture.



Scheme 77 Amine scope in $B(OCH_2CF_3)_3$-mediated unprotected amino acid amidation. Conversion measured by ^{1}H-NMR with naphthalene internal standard, isolated yield in parentheses. [a]Isolated as free amine; [b]er measured by chiral HPLC; [c]125 °C; [d]Isolated as hydrochloride salt.

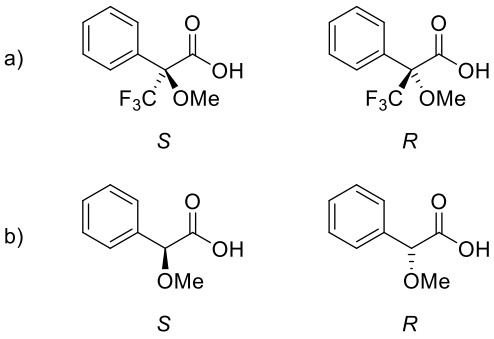
3.4. A new chiral amine enantiomeric ratio determination method

3.4.1. Background

During the course of our research into the amidation of unprotected amino acids mediated by $B(OCH_2CF_3)_3$, it became necessary to find a simple way to measure the er of the products. We initially intended to use chiral HPLC, however, due to the free amine present in the product, an additional step would be required to protect the amine. The amine would be protected with either Boc anhydride or benzoyl chloride (depending on whether the product contained a chromophore) and the products of both these protection methods require purification. Additionally, synthesising the *N*-Boc or

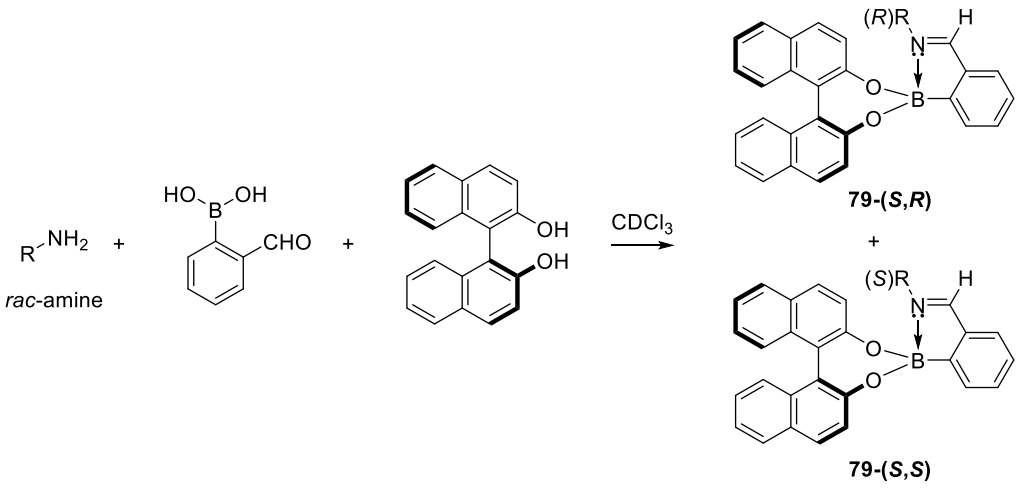
N-benzoyl derivative of the product would somewhat defeat the objective of the methodology. We felt that a less laborious method of determining the er of these unprotected amino acid amides would be preferable, ideally by use of easily accessible ^{1}H-NMR.

With this in mind, we sought a way to derivatise these chiral products as diastereomers to measure the er by ^{1}H-NMR. The use of Mosher's acid (α-methoxy-α-trifluoromethylphenylacetic acid) was a possibility (Scheme 78a).[91] However, this can require the use of the acid chloride to ensure that the amidation proceeds to completion. Additionally, the use of the similar Trost's *O*-methylmandelic acid protocol could also be considered (Scheme 78b).[92] However, the derivatisation of the amine required either a DCC-mediated amide coupling or use of pre-synthesis of the acid chloride, followed by purification by column chromatography, before the dr could be measured by NMR. Both of these derivatisation methods result in the formation of an irreversible bond and can give rotamers of the amide product, which can complicate the NMR analysis and potentially give inaccurate dr measurements. Obviously these procedures are more laborious than we had envisaged.



Scheme 78 a) *S*- and *R*- α-methoxy-α-trifluoromethylphenylacetic acid; b) *S*- and *R*-*O*-methylmandelic acid; a) *S*- and *R*- α-methoxy-α-trifluoromethylphenylacetic acid

The eventual chosen method was using a chiral aldehyde to generate diastereomeric imines which should be distinguishable by ^{1}H-NMR and allow recovery of the amino acid amide product following er determination. After searching the literature to establish if such a method has been published, we found one paper describing the use of 2-formylphenyl boronic acid and (*S*)-BINOL in combination with a racemic amine to generate diastereomeric imine complexes that are distinguishable in ^{1}H-NMR (Scheme 79, **79-(*S*,*R*)** and **79-(*S*,*S*)**).[93]



Scheme 79 Diastereomeric imine complex to determine ee of chiral amine

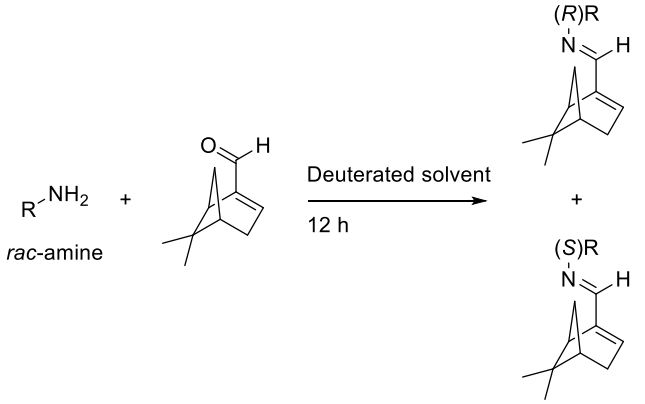
Applying this method to our unprotected amino acid amides was not entirely reliable as there were some issues with solubility of the complex so we could not be sure that all of the unprotected amino acid amide had reacted to form the complex or that the results would be reproducible. Additionally, this method has only been shown to measure the ee of an amine on one example, α-methylbenzylamine, with reasonable accuracy (Table 18).

Table 18 ee measurement using chiral BINOL imine complex

Proton	**Integration**	**%ee**
C*H*N	11.1:1	83.5
CH(CH_3)N	8.3:1	78.5

A review of the literature shows that Dufrasne *et al.* made use of 1*R*-(−)-myrtenal as a chiral derivatising agent (Scheme 80).[94] This is a simple method as it only requires the reaction of two components (the chiral amine and the chiral aldehyde), however, the reaction is left for 12 h before the ^{1}H-NMR is run which is not ideal as we sought a method that would provide an er measurement in a timely fashion. This er determination method can be used for aliphatic primary amines, β-aminoalcohols, β-diamines and α-amino-acids. Only amines with α- or β-aryl substituents could be resolved using this methodology. A complement to this method is also reported by Dufrasne *et al.*, that utilises ^{13}C-NMR integrations to measure the er of the produced imines. In this case the amines do not need to contain an aromatic moiety.[95] They measure either *C*=N-C or C=N-*C* to determine the er of the amine after shaking the two

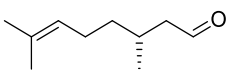
components in an NMR tube at rt for 1 h. One drawback of the use of 1*R*-(−)-myrtenal is that both enantiomers of the chiral amine are required to reliably determine the enantiopurity of the amine. This may not always be possible depending on the method used to synthesise the amine. Ideally, using 1*S*-(+)-myrtenal would avoid this and provide a check for the enantiopurity, however, 1*S*-(+)-myrtenal is not commercially available.



Scheme 80 1*R*-(−)-Myrtenal as a chiral derivatising agent

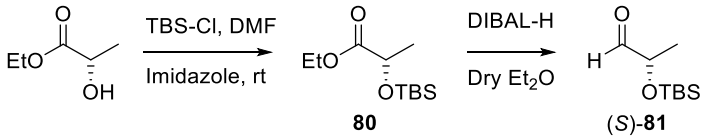
3.4.2. Our method

Due to the ready availability of both enantiomers of citronellal in our labs, initial attempts at this proposed method of er determination looked at the use of this chiral aldehyde. Our initial hope was to generate the imines of L- and DL-alanine propylamide from (+)-citronellal and to analyse these by ^{1}H-NMR. We hoped to use the ratio of the imine proton of each diastereomer to measure the ratio of enantiomers. Unfortunately this was not as simple as we had hoped as the imine peaks for each diastereomer were obviously triplets and also overlapped in the spectrum making it impossible to separately integrate the two signals. However, separation of the two imine carbon signals was observed in the ^{13}C-NMR. These signals were separate but rather close in proximity (0.05 ppm) so there is the potential for overlap when looking at different chiral amines. Ideally we wished to integrate signals in the ^{1}H-NMR to determine the er of the amine. We sought another chiral aldehyde to determine whether we could observe separation in the ^{1}H-NMR or even larger separation in the ^{13}C-NMR.



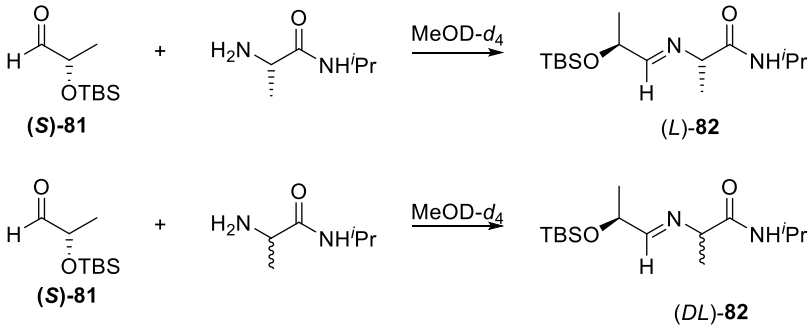
Scheme 81 (+)-Citronellal

With this in mind, we looked at the aldehyde derived from TBS-protected ethyl lactate **80**. This is synthesised by protection of *S*-ethyl lactate with TBS-Cl to give ester **80** followed by DIBAL-H reduction of ester **80** to aldehyde **81** (Scheme 82).



Scheme 82 Preparation of chiral aldehyde (*S*)-**81**

Reaction of aldehyde (*S*)-**81** with both enantiomers of a model amine (L and DL-alanine propylamide) was carried out to determine whether the imine proton, or carbon, in the diastereomeric imines L and DL-**82** were distinguishable by NMR (Scheme 83). Unfortunately, we observed overlap of the imine protons by ^{1}H-NMR (Figure 8), but the imine carbons were distinguishable by ^{13}C-NMR and could be integrated (Figure 9). As analogous diastereomeric carbons which share the same environment are being integrated it is possible to infer a dr (and therefore er) from the integral ratio.



Scheme 83 Formation of diastereomeric imines

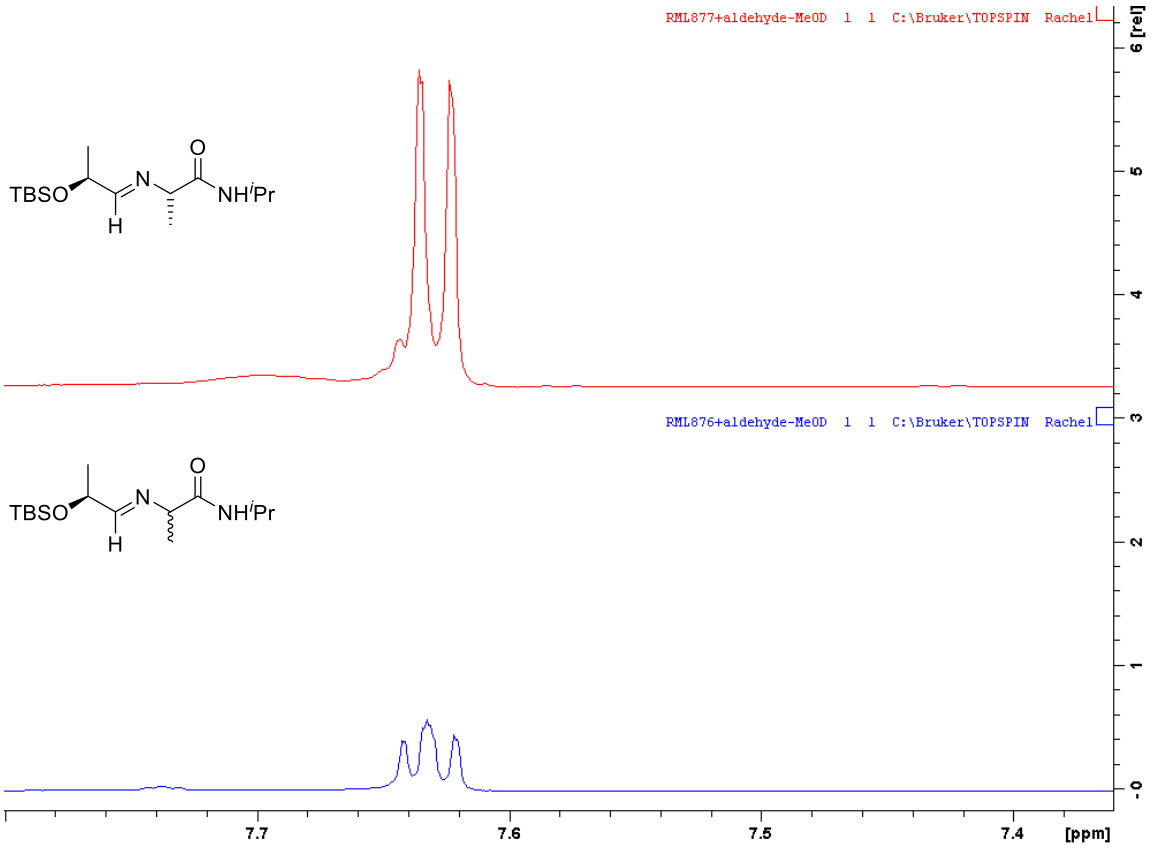


Figure 8 ^{1}H-NMR of L and DL-**82**

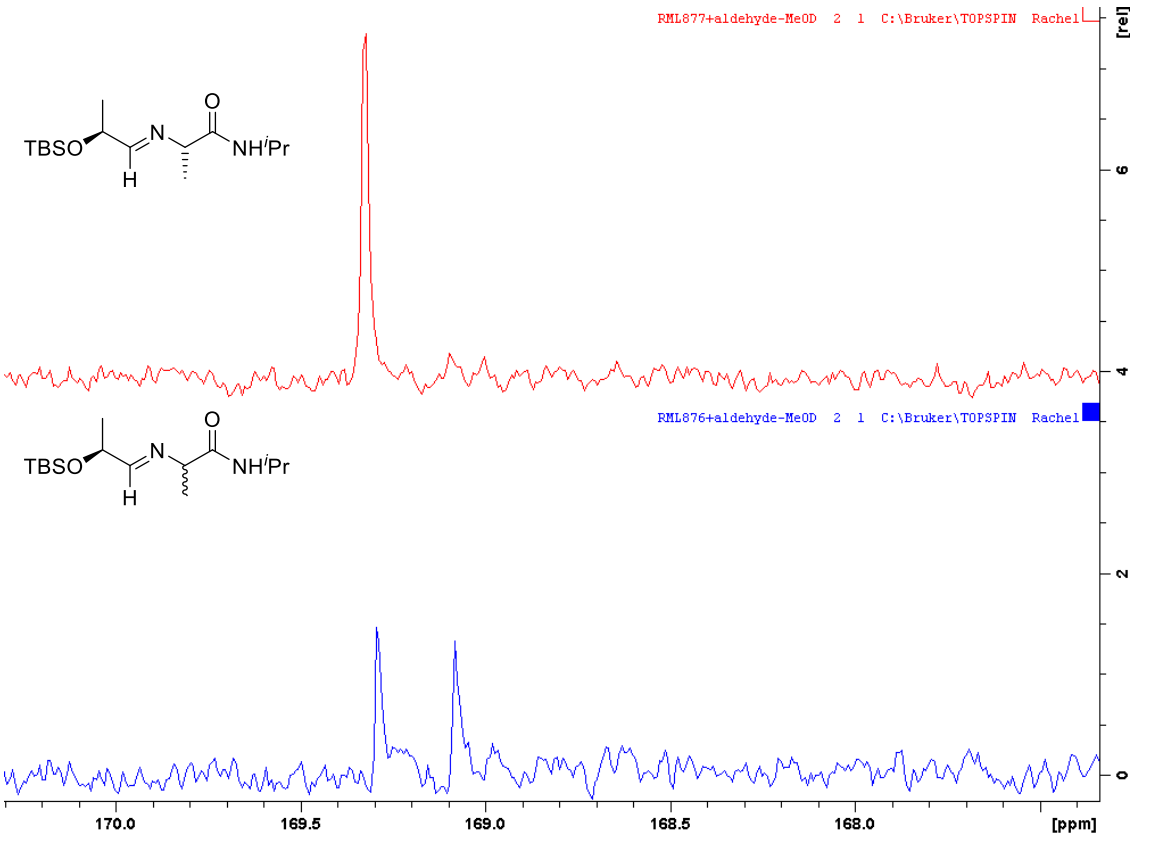


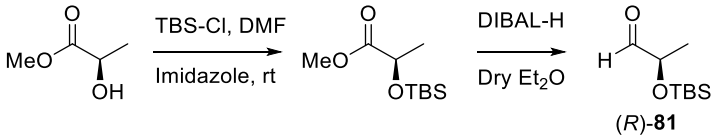
Figure 9 ^{13}C-NMR of L and DL-**82**

The initial investigation had been carried out in MeOD-d_4 so a comparison of other deuterated solvents was carried out to determine which gave the largest peak separation of the imine carbon peak. While the imine carbon signal is distinguishable in all the deuterated solvents explored, the largest peak separation was observed with MeOD-d_4 (Table 19).

Table 19 Comparison of imine carbon peak separation in different deuterated solvents

Entry	Solvent	Peak separation (ppm)
1	$CDCl_3$	0.11
2	DMSO-d_6	0.09
3	MeOD-d_4	0.21
4	C_6D_6	0.13

To develop a robust method to determine er which would not depend on having both enantiomers of the chiral amine, we synthesised the *R* enantiomer of **81** to provide a check of the enantiopurity measured by (*S*)-**81**. This was synthesised in a similar way to (*S*)-**81** starting from *R*-methyl lactate as this is significantly cheaper than *R*-ethyl lactate (Scheme 84).

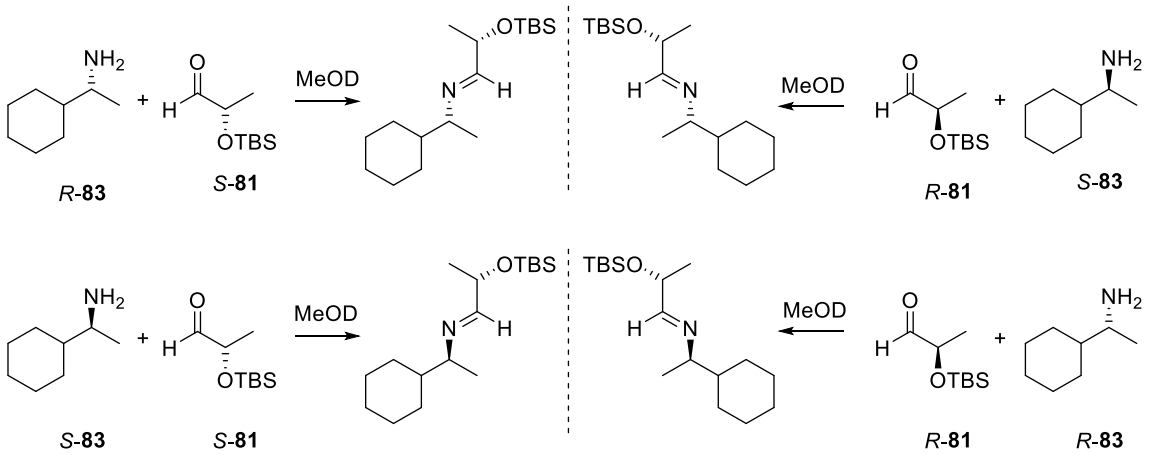


Scheme 84 Preparation of chiral aldehyde (*R*)-**81**

With this in mind, we wanted to ensure that the aldehyde was reliable as a chiral derivatising agent. This was carried out by analysis of both enantiomers of three commercially available α-chiral amines, α-methyl benzylamine, 1,2,3,4-tetrahydro-1-naphthylamine and 1-cyclohexylethylamine as well as some 'real' examples taken from earlier amidation work: *N*-Boc-L-methionine-benzylamide, *N*-Boc-L-alanine-benzylamide and *N*-Boc-L-phenylalanine-benzylamide.

Reaction of (*S*)- and (*R*)-**81** with (*S*)- and (*R*)-1-cyclohexylethylamine **83** gives 4 diastereomers and 2 enantiomers (Scheme 85). The imine carbons of these diastereomers are distinguishable by ^{13}C-NMR. With both enantiomers of aldehyde **81**, we were able to form the diastereomeric imines from each enantiomer of the amine to

measure the optical purity of these chiral amines (Table 20). In addition, a roughly 50:50 sample of both enantiomers of **83** was prepared (*R*:*S* 49:51) which displays the accuracy of this method.

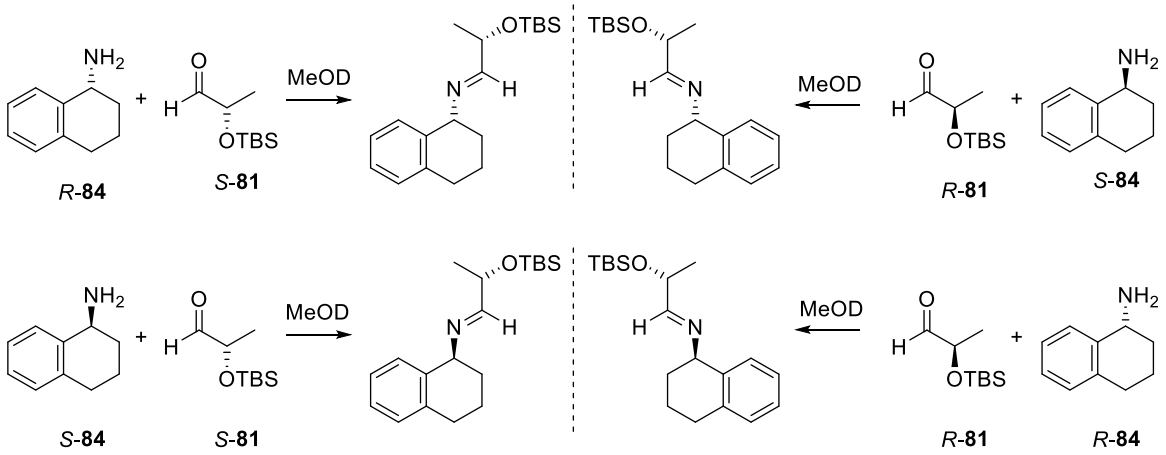


Scheme 85 Reaction of (*S*)- and (*R*)-**81** with (*S*)- and (*R*)-**83**

Table 20 er for 1-cyclohexylethylamine **83**

Amine 83	**Aldehyde 81**	*S*	*R*
R		2:98	99:1
S		98:2	1:99
R:*S* (49:51)		51:49	49:51

In parallel with the evaluation of (*S*)- and (*R*)-**83**, we also carried out the same study with (*S*)- and (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **84** (Scheme 86). Again, there is good distinction between the imine carbons by ^{13}C-NMR and good agreement with the measured er values (Table 21).

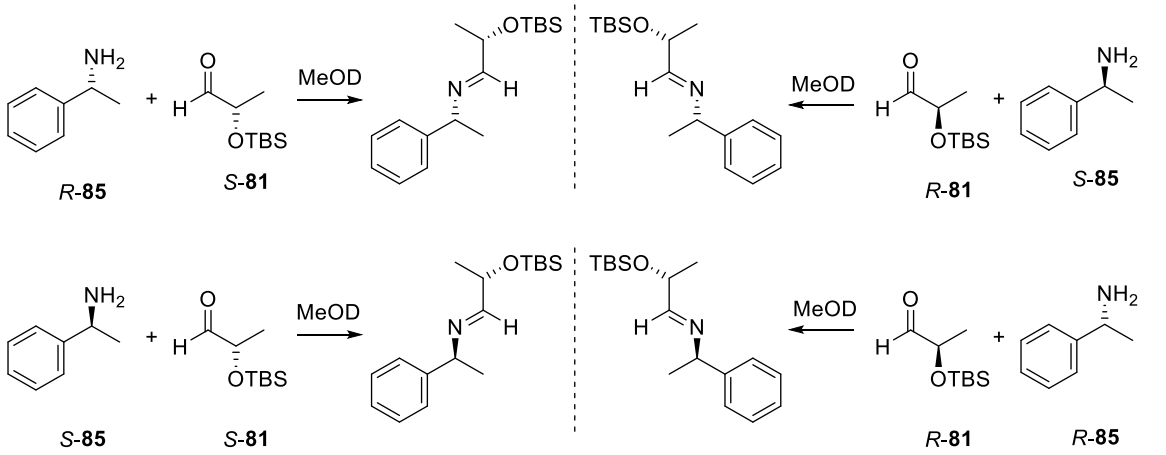


Scheme 86 Reaction of (*S*)- and (*R*)-**81** with (*S*)- and (*R*)-**84**

Table 21 er for 1,2,3,4-tetrahydro-1-naphthylamine **84**

Amine 84	**Aldehyde 81**	*S*	*R*
R		2:98	99:1
S		98:2	1:99
R:*S* (51:49)		49:51	51:49

Similarly, (*S*)- and (*R*)-α-methylbenzylamine **85** also display good agreement between each enantiomer of the chiral aldehyde **81**, as well as distinguishable carbon signals to measure ratios of the amine (Scheme 87 and Table 22).



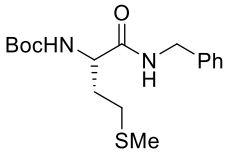
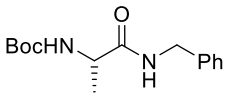
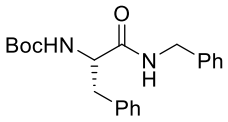
Scheme 87 Reaction of (*S*)- and (*R*)-**81** with (*S*)- and (*R*)-**85**

Table 22 er for α-methylbenzylamine **85**

Amine 85	**Aldehyde 81**	*S*	*R*
R		3:97	98:2
S		98:2	1:99
R:*S* (50:50)		52:48	49:51

The real examples were synthesised *via* our standard amidation method (*vide supra*) and then the enantiopurity analysed by chiral HPLC.[59] The enantiopurity was then measured with (*S*)- and (*R*)-**81** using our chiral aldehyde method following Boc-deprotection with TFA/DCM (Table 23). There is good agreement between the er measured by chiral HPLC and the er measured by the chiral aldehyde method in each case.

Table 23 Enantiopurity measurement of amines compared to chiral HPLC

Amide	**er by chiral HPLC**	**er by (*S*)-81[a]**	**er by (*R*)-81[a]**
	98:2	98:2	1:99
	>99:1	99:1	1:99
	99:1	98:2	3:97

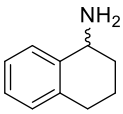
[a]er by chiral aldehyde method measured after Boc-deprotection by TFA/DCM

These results indicate that er determination using aldehyde **81** is possible and that the method is in agreement with the er measured by chiral HPLC. In order to fully verify the method 'blind tests' were carried out with three chiral amines by three experimenters – Laure Benhamou, Sam Gibson and myself. Each experimenter prepared a sample of unknown enantiopurity from all three amines (**83**-**85**). This sample was then analysed by the other two experimenters and the measured er reported and then compared to the er as measured by weight (Table 24). The results of this blind test were generally promising with excellent agreement of the measured enantiopurity with the actual enantiopurity as well as between sample testers for each sample. However, amines with high enantiopurity are underestimated by this method (Table 24, samples **85** – B, **85** – C and **83** – C). This suggests that the chiral aldehyde **81** may not be

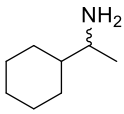
enantiopure, which would affect amines with higher enantiopurities more than those with lower enantiopurities. However, based on the results above this does not appear to be the case.

Table 24 'Blind test' of aldehyde **81** er determination

85



84



83

Sample	Actual R:S	Adjusted R:S*	Tester	(*S*)-aldehyde measurement	(*R*)-aldehyde measurement
85 – A	70:30	69:31	B	32:68	71:29
			C	31:69	68:32
84 – A	34:66	34:66	B	65:35	34:66
			C	65:35	35:65
83 – A	79:21	77:23	B	23:77	77:23
			C	23:77	79:21
85 – B	5:95	6:94	A	9:91	92:8
			C	10:90	92:8
84 – B	87:13	86:14	A	86:14	13:87
			C	85:15	15:85
83 – B	23:77	24:76	A	76:24	25:75
			C	75:25	24:76
85 – C	90:10	89:11	A	12:88	87:13
			B	14:86	87:13
84 – C	53:47	53:47	A	48:52	53:47
			B	48:52	53:47
83 – C	15:85	16:84	A	82:18	17:83
			B	81:19	17:83

* Adjusted in relation to measured enantiopurities of **83-85** (Table 20-Table 22)

It is also possible that racemisation could occur during imine formation or on standing. This was investigated by rerunning the NMR of the inaccurate samples again, 4 days later, the imines had not racemised any further on standing (Table 25). This suggests

that there is potentially an as yet unidentified problem in the case of amines of high enantiopurity.

Table 25 Check of inaccurate samples

Sample	Actual R:S	Tester	(*S*)-aldehyde rerun	(*R*)-aldehyde rerun
85 – B	5:95	A	9:91	92:8
85 – C	90:10	A	13:87	88:12
83 – C	15:85	A	82:18	17:83

It seems that this method performs well although issues were evident with amines of high enantiopurity. However, with these results in hand we wished to trial this method for the er determination of some examples of the $B(OCH_2CF_3)_3$-mediated unprotected amino acid amidation (Figure 10). Unfortunately, this method does not appear to be broadly applicable to this type of compound. In some cases the imine carbon signals from each diastereomer were distinct and could be easily integrated (**77a-c** and **77l-k**). In general, good retention of enantiopurity was observed (**77a-c** and **77l**), however in the case of L-valine a significant erosion of enantiopurity was observed (**77k**). Presumably this can be attributed to the high reaction temperature required for the amidation. In the case of amides **77g**, **78b**, **78c**, **77f** and **78h** the signals for each diastereomer were not separable so the er could not be measured by ^{13}C-NMR in those cases. It must also be noted that these measures of er are an indication of the minimum level of the enantiopurity.

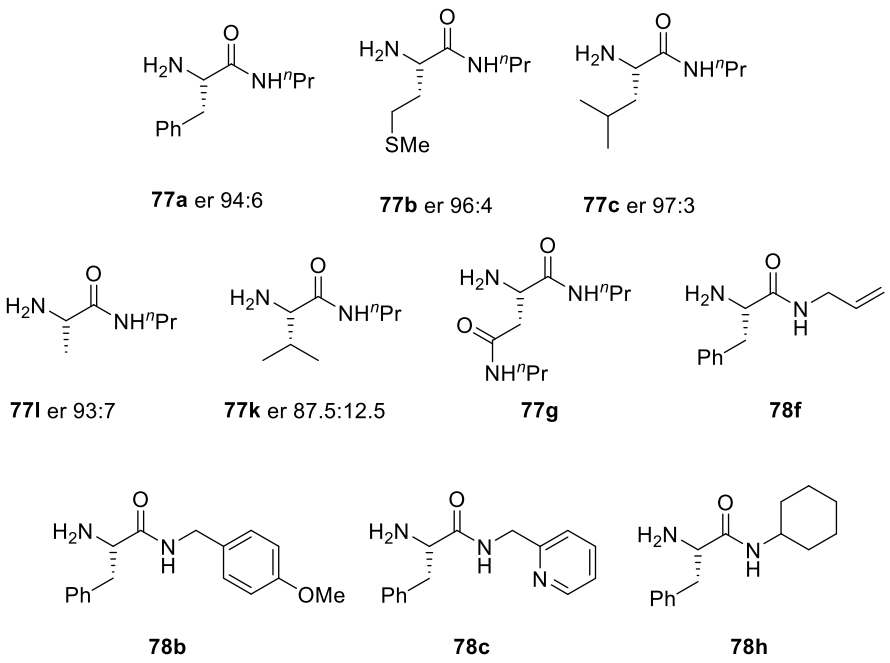


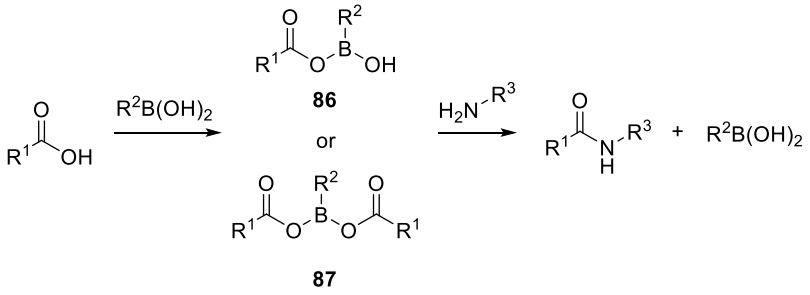
Figure 10 Attempted er measurement of unprotected amino acid amidation products with aldehyde **81**

4. $B(OCH_2CF_3)_3$-mediated amidation mechanistic study

4.1. Background

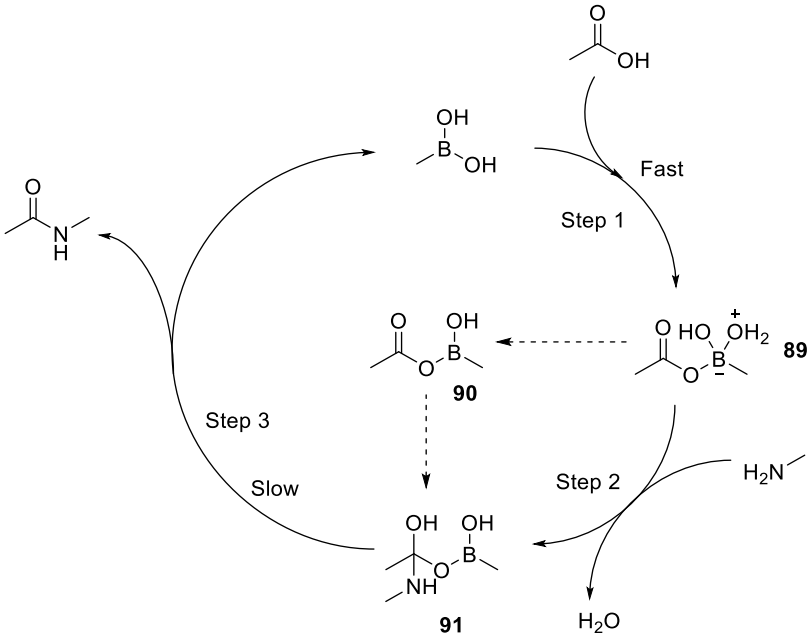
With a view to gaining a deeper understanding of the mechanism of the $B(OCH_2CF_3)_3$-mediated amidation reaction, a mechanistic study was undertaken. We expected that the $B(OCH_2CF_3)_3$-mediated amidation would proceed *via* a similar mechanism to that reported for boronic acid-catalysed amidations.

The mechanism of boronic acid-catalysed amidation has been the subject of a number of recent studies. There is general agreement in the literature that boronic acid catalysis of amidation proceeds *via* an acyloxyboron intermediate (**86** or **87**), which is the active acylating species in the reaction. The monoacyloxyboron species **86** was isolated and partially characterised (^{1}H-NMR and IR) by Yamamoto in the seminal work on boronic acid catalysis of amidation.[41] However, in the mechanistic investigation by Whiting, the monoacyloxyboron species **86** was not observed by mass spectrometry methods but, interestingly, the diacyloxyboron species **87** was.[96]



Scheme 88 Proposed formation of mono and diacyloxyboron species in boronic acid catalysed amidation

Marcelli reported a gas phase theoretical study of the methyl boronic acid-catalysed **88** amidation of acetic acid by methylamine (Scheme 89).[97] Formation of the monoacyloxyboron species **89** from acetic acid and methylboronic acid is a facile process (step 1). The barrier to formation of a diacyloxyboron species was found to be too high and therefore not a feasible reaction intermediate. Reaction of the tricoordinate acyloxyboron species **90** with methylamine to form **91** was found to be less favourable than reaction of the tetracoordinate acyloxyboron species **89** with methylamine (step 2). The rate determining step of this mechanism was proposed to be the formation of the amide from the boron bound hemiaminal (step 3).



Scheme 89 Boronic acid-catalysed amidation mechanism proposed by Marcelli

Marcelli[97] also investigated the *o*-iodophenylboronic acid catalyst reported by Hall[50] to explain the exceptional reactivity it displays compared to other phenylboronic acid catalysts. It was shown that the iodine atom can stabilise the rate determining transition state *via* an intramolecular O−H···I hydrogen bond **92** (Figure 11).

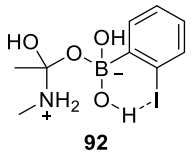
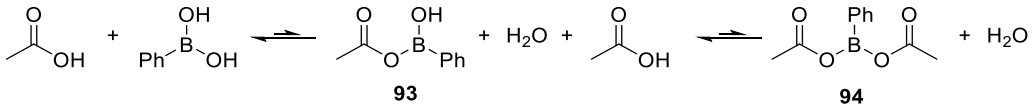


Figure 11 Proposed hydrogen-bonded transition state of *o*-iodobenzene boronic acid-catalysed amidation

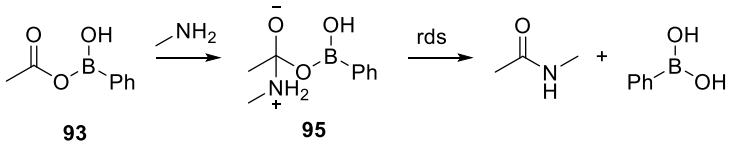
Subsequently, Fu reported on the mechanism of the phenylboronic acid-catalysed amidation of acetic acid by methylamine.[98] In contrast to Marcelli's report, in this mechanistic study the role of the solvent (dichloroethane) was taken into account. Importantly, 2-phenylacetic acid can undergo amidation with benzylamine to give the corresponding amide in 31% yield. This amidation is catalysed by phenylboronic acid (20 mol%) in dichloroethane in the presence of 4 Å mol sieves at 35–40 °C for 48 h.[50] The most stable form of acetic acid and methylamine in dichloroethane was found to be as the individual molecules. The formation of both the mono **93** and diacyloxyboronic acid intermediates **94** was found to be kinetically favourable although the equilibrium lies to the left. This equilibrium can be driven to the right by removing water from the

reaction mixture (molecular sieves). The removal of water is not required in the mechanism proposed by Marcelli.

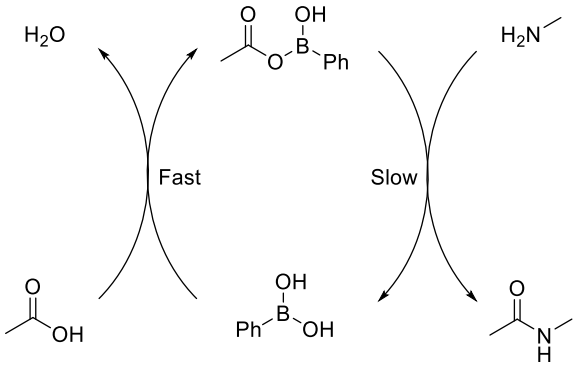


Scheme 90 Formation of mono and diacyloxyboronic acid intermediates

Fu established that the diacyloxyboronic acid intermediate **94** is unlikely to form and therefore the monoacyloxyboronic acid intermediate **93** is the most likely intermediate in the formation of the amide bond. The rate determining step was calculated to be the C-O bond cleavage to form the amide from the hemiaminal intermediate **95** (Scheme 91). The proposed mechanism is shown in **Scheme 92**.

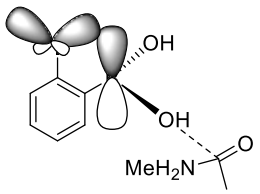


Scheme 91 Formation of amide from monoacyloxyboronic acid intermediate



Scheme 92 Mechanism for boronic acid-catalysed amidation proposed by Fu

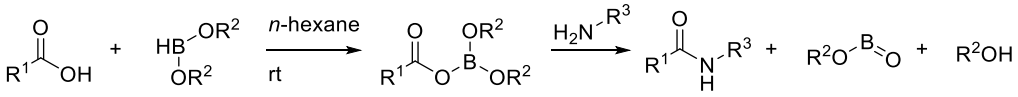
Fu also considered the *o*-iodophenylboronic acid reported by Hall.[50] The steric bulk of the *o*-iodo substituent as well as the orbital overlap of the filled sp^2 orbital of the iodine and the empty p orbital of the boron was proposed to assist in the stabilisation of the transition state **96** (Figure 12).



96

Figure 12 Proposed orbital overlap in transition state of *o*-iodobenzene boronic acid-catalysed amidation

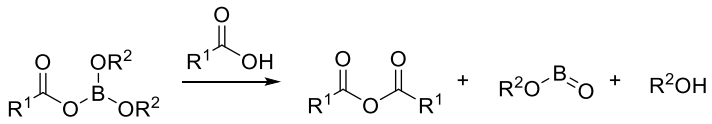
Early work by Pelter *et al.* discussed the mechanism of the reaction between acyloxyboranes and amines (Scheme 93).[99] Reaction of monoacyloxydialkyloxyboranes with amines was shown to be a viable route to amides, however, the conversion to amide product was low (30-50%).



97

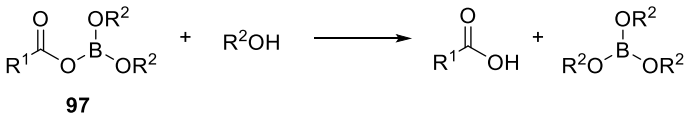
Scheme 93 *In situ* formation of **97** and subsequent amidation

Pelter *et al.* investigated this reaction to elucidate the low conversions observed.[99] A monoacyloxydialkoxyborane **97** formed from a dialkoxyborane and carboxylic was shown to be susceptible to reduction by any residual dialkoxyborane, however, in the case of $B(OCH_2CF_3)_3$-mediated amidation this is not a consideration. **97** was stable in solution but degraded to anhydride in the presence of acid, however this should not be detrimental to the yield as the anhydride can also react to form amide as long as there are sufficient quantities of acid (Scheme 94).



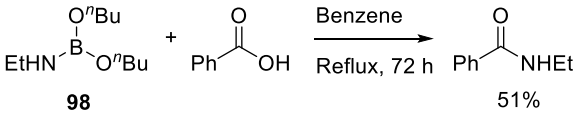
Scheme 94 Anhydride formation from **97**

Additionally, Pelter *et al.* highlighted observations that explain the lack of ester formation mediated by $B(OMe)_3$ (or $B(OCH_2CF_3)_3$).[99] Addition of *iso*-propanol to **97** (where $R^1 = C_5H_{11}$ and $R^2 = {}^{i}Pr$) exclusively led to triisopropoxyborane and hexanoic acid, and none of the corresponding ester was observed (Scheme 95).



Scheme 95 Solvolysis of **97**

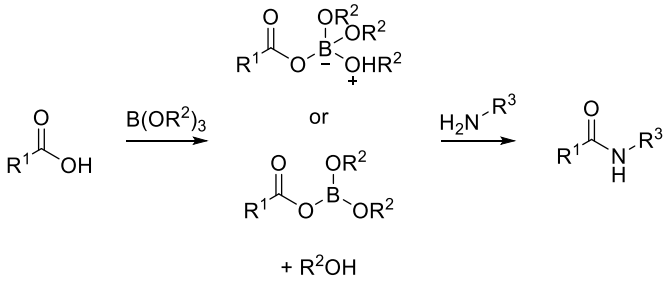
To establish whether an amine would have a detrimental effect on the reaction by acting in the same way as an alcohol the reaction of di-*n*-butoxyethylaminoborane **98** and benzoic acid was carried out (Scheme 96). Although the reaction required high temperature and a long reaction time the corresponding amide was formed in moderate yield suggesting that **98** may be a viable intermediate.



Scheme 96 Amidation of benzoic acid using **98**

4.2. NMR study

We expected that the $B(OCH_2CF_3)_3$-mediated amidation might follow a similar mechanism to that reported in the literature for boronic acid-catalysed amidations (Scheme 97, *vide supra*). However, from the observations made in our preliminary NMR study, the $B(OCH_2CF_3)_3$-mediated amidation does not seem to follow the reaction pathway shown in Scheme 89 or Scheme 91.



Scheme 97 Proposed $B(OR^2)_3$-mediated amidation mechanism

A brief NMR study was carried out to determine the different interactions in the reaction mixture over the course of the reaction (see Appendix). The model reaction investigated was the amidation of *p*-tolylacetic acid with butylamine due to the easily identifiable signals for the starting materials and product. The change in the ^{1}H, ^{13}C, ^{19}F and ^{11}B-NMR of the *p*-tolylacetic acid and $B(OCH_2CF_3)_3$ mixture (Figure 13, entry 1), *n*-butylamine and $B(OCH_2CF_3)_3$ (Figure 13, entry 2) as well as the reaction mixture

(Figure 13, entry 3) was monitored over time. Each sample was heated at 80 °C over 5 h in MeCN-d_3 and an aliquot taken before heating and then at 30 min, 3 h and 5h.

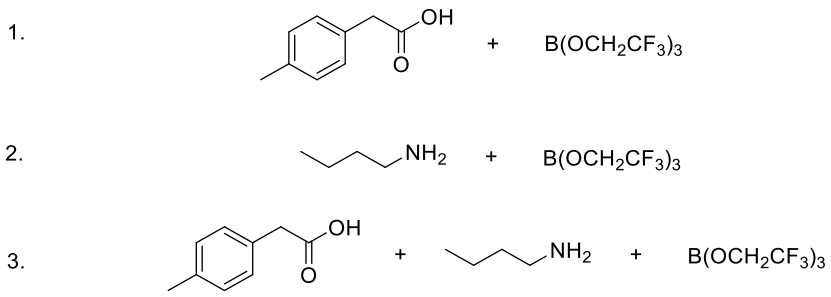


Figure 13 NMR reaction mixtures

The results of the NMR study of the reaction mixture containing *p*-tolylacetic acid and $B(OCH_2CF_3)_3$ are inconclusive. No interaction between *p*-tolylacetic acid and $B(OCH_2CF_3)_3$ was observed by ^{1}H, ^{13}C, ^{11}B and ^{19}F-NMR as both reagents appear unchanged over the reaction period (Figure 14). An acyloxyboron species analogous to that observed for boronic acid catalysed amidation is not observed by NMR following the interaction of *p*-tolylacetic acid and $B(OCH_2CF_3)_3$ at 80 °C over 5 h (Figure 13, entry 1). However, it is possible that any formation of an acyloxyboron species is too rapid on the NMR timescale. This result is broadly in agreement with observations reported by Levitt on the $B(OMe)_3$-mediated amidation reaction.[34] $B(OMe)_3$ and hexanoic acid were found to interact weakly at room temperature. However, no acyloxyboron species was formed. On addition of a catalytic amount of *p*-toluenesulfonic acid, facile formation of the acyloxyboron species was observed. Pelter found that a solution of **97** was stable in solution over night so it seems likely that if an analogous acyloxyboron species is formed in our case that it would be observable by NMR.[99]

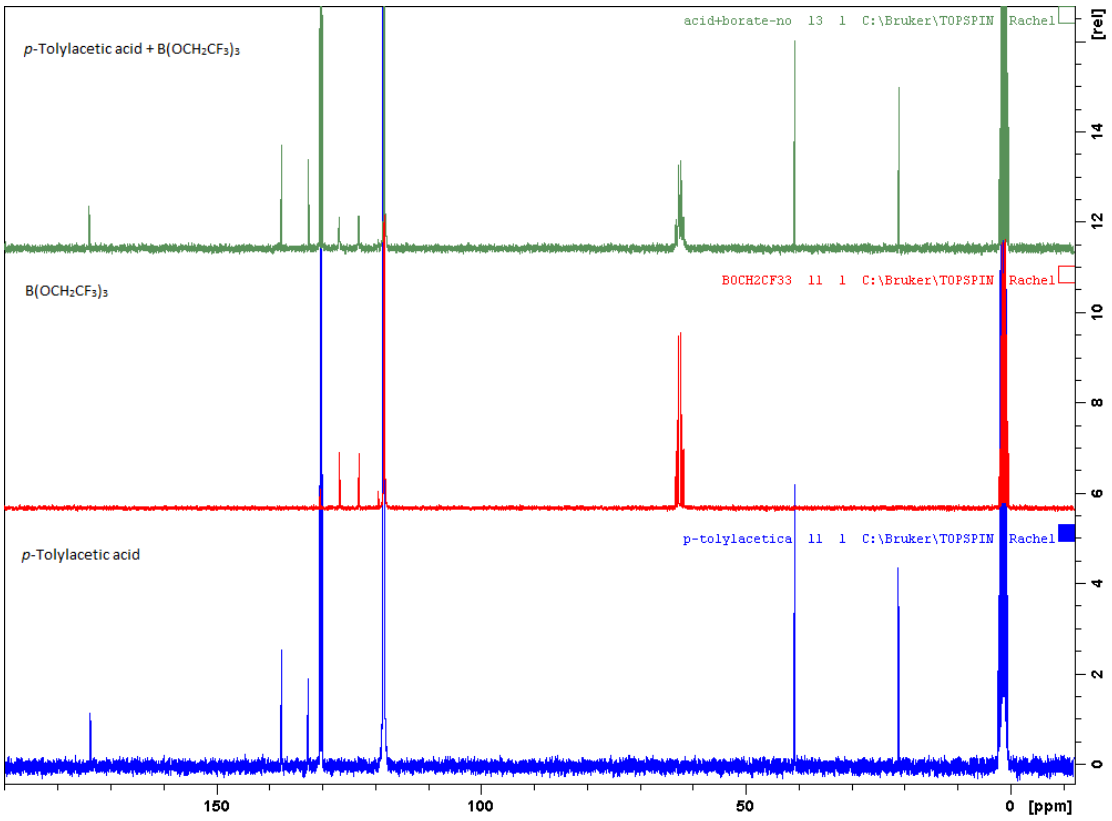
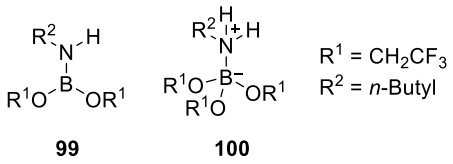


Figure 14 ^{13}C-NMR comparison of *p*-tolylacetic acid, $B(OCH_2CF_3)_3$ and *p*-tolylacetic acid-$B(OCH_2CF_3)_3$

The NMR evidence suggests that, in the case of $B(OCH_2CF_3)_3$, one of active species (or reaction intermediates) may be an amine-$B(OCH_2CF_3)_3$ complex, either trigonal **99** or tetrahedral **100** at boron (Figure 15). An intermediate of the form **99** would be in keeping with observations made by Pelter *et al.* in the case of $B(OMe)_3$.[99]



99 **100**

Figure 15 Possible amine-$B(OCH_2CF_3)_3$ complexes

Addition of $B(OCH_2CF_3)_3$ to butylamine at room temperature shows immediate disappearance of $B(OCH_2CF_3)_3$, appearance of CF_3CH_2OH, and appearance of a new amine derived species in both ^{1}H- and ^{13}C-NMR (Figure 16). The signal due to the NH_2 protons in ^{1}H-NMR is shifted downfield from ~1.1 ppm to ~5.3 ppm suggesting complexation through nitrogen to $B(OCH_2CF_3)_3$. As there are two NH protons present this indicates the complex may be a structure like **100** with a tetrahedral boron centre (Figure 15).

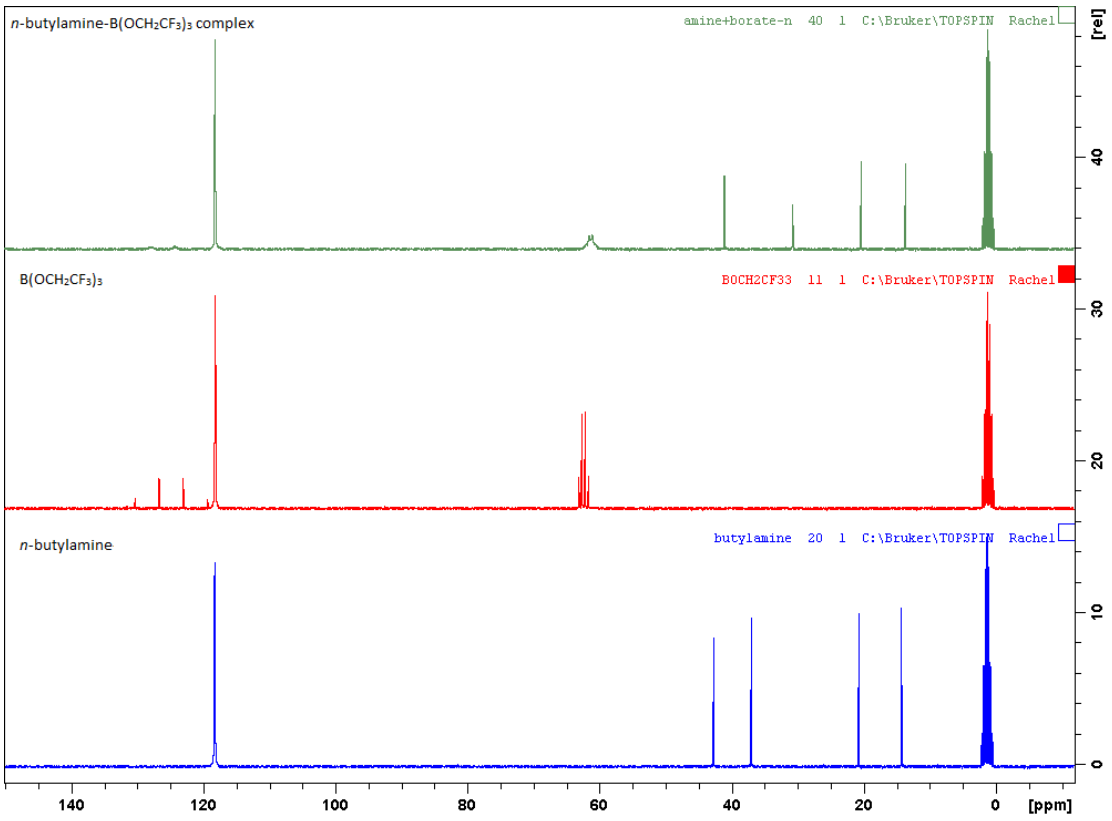


Figure 16 ^{13}C-NMR comparison of *n*-butylamine, $B(OCH_2CF_3)_3$ and *n*-butylamine-$B(OCH_2CF_3)_3$ complex

This is supported by the results of ^{11}B-NMR which shows the formation of two new peaks at 2.7 and 10.0 ppm as the signal due to $B(OCH_2CF_3)_3$ disappears (17.9 ppm), one of these new peaks could be due to the tetrahedral boron species and the other may be due to a trigonal boron species (Figure 17). An analogous example to the $B(OCH_2CF_3)_3$-*n*-butylamine complex is reported in the literature of the ethylamine complex of $B(OEt)_3$, $B(OEt)_3$-NH_2Et.[100] This pair displays a shift from 18.1 ppm for $B(OEt)_3$ to 13.7 ppm for $B(OEt)_3$-NH_2Et.

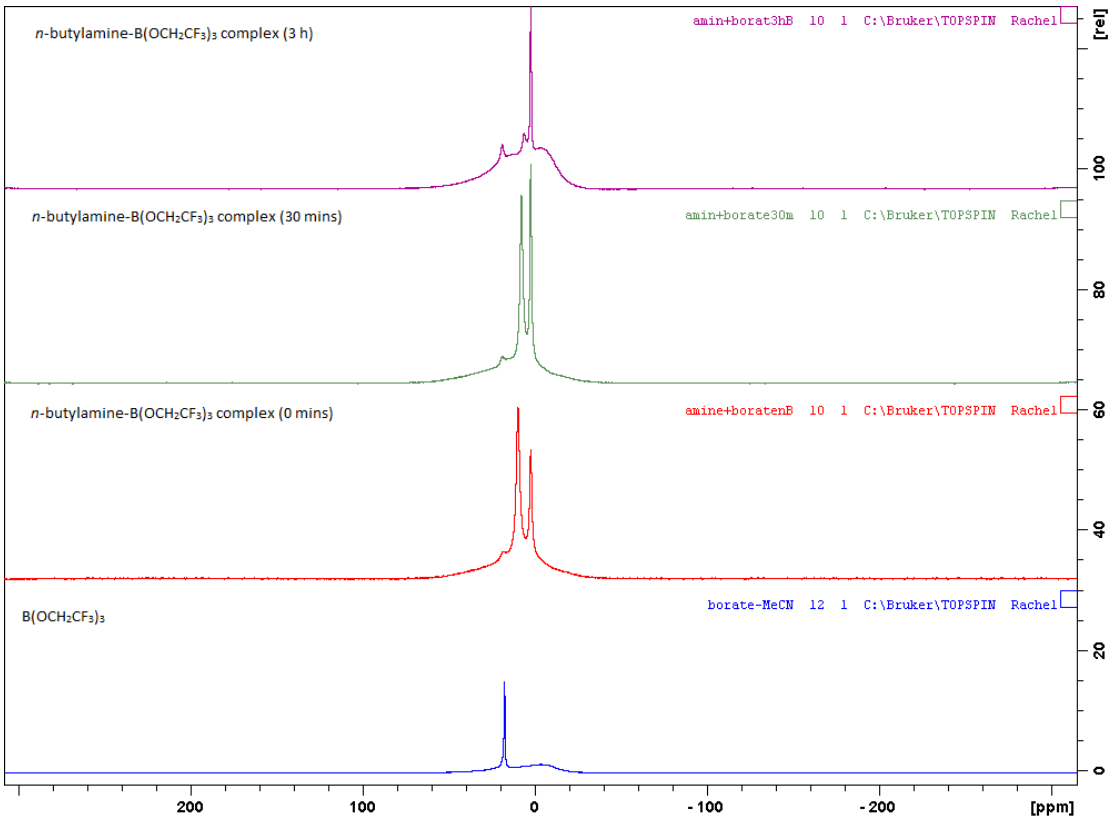


Figure 17 ^{11}B-NMR comparison of *n*-butylamine, $B(OCH_2CF_3)_3$ and *n*-butylamine-$B(OCH_2CF_3)_3$ complex

Additionally, two new peaks are also observed in the ^{19}F-NMR spectrum in the absence of a $B(OCH_2CF_3)_3$ signal. The results of the ^{19}F-NMR are in agreement with the observations of the ^{11}B-NMR spectra as both indicate the formation of two new species from the mixture of $B(OCH_2CF_3)_3$ and *n*-butylamine by the appearance of two new signals in both the ^{11}B- and ^{19}F-NMR.

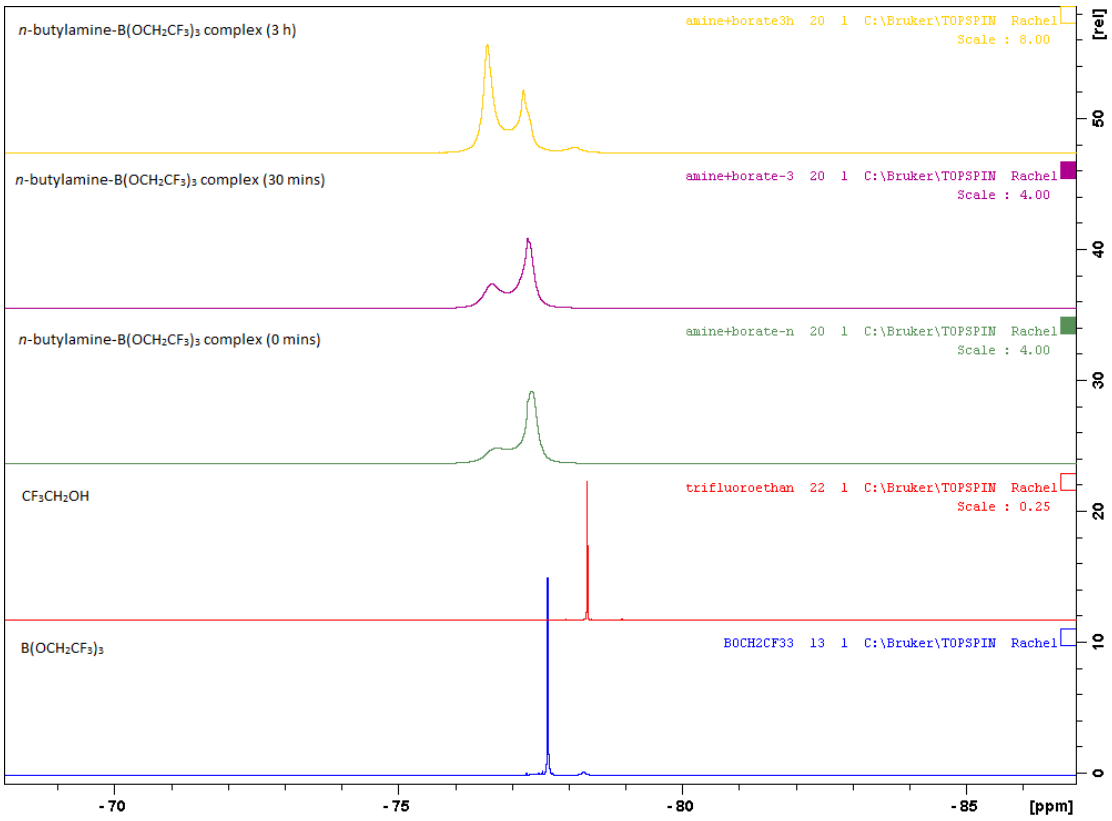


Figure 18 ^{19}F-NMR comparison of *n*-butylamine, $B(OCH_2CF_3)_3$ and *n*-butylamine-$B(OCH_2CF_3)_3$ complex

We were able to crystallise and obtain a crystal structure of one component of the *n*-butylamine-$B(OCH_2CF_3)_3$ mixture. The species observed in this crystal structure is the ammonium salt, $[(CF_3CH_3O)_4B]^-[H_3N^nBu]$ (Figure 19 and Figure 20). The origin of the additional molecule of CF_3CH_2OH in this crystal is unclear. However, if the other intermediate is the trigonal boron species **99** then the formation of that species can explain the source of the additional CF_3CH_2OH. Alternatively, hydrolysis of $B(OCH_2CF_3)_3$ by any water present in the reaction mixture would liberate CF_3CH_2OH, which could form the salt observed in the crystal structure. This may not necessarily be an intermediate in the reaction and may be an artefact of the crystallisation process in the presence of water. A similar observation was made by Pelter *et al.* as on addition of methanol to a mixture of trimethoxyborane and *tert*-butylamine they observed $[(MeO)_4B]^-[H_3N^tBu]$.[99]

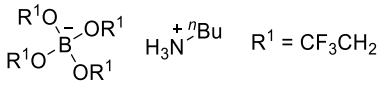


Figure 19 Chemical structure of isolated crystal

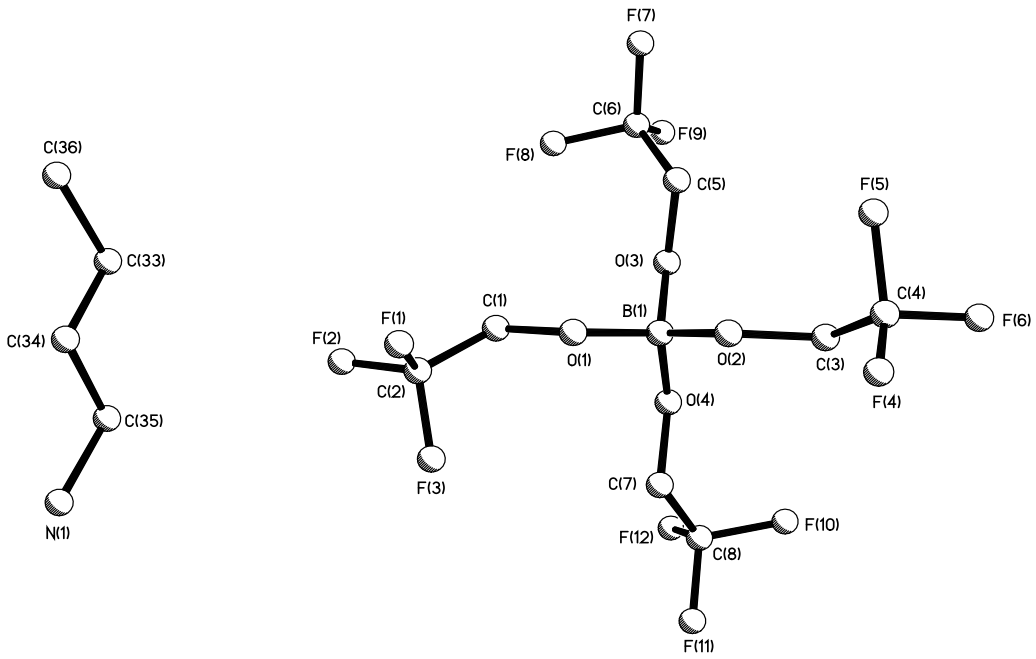


Figure 20 Crystal structure of isolated borate-amine complex

Observing the NMR spectra (^{1}H, ^{13}C, ^{19}F and ^{11}B) of the reaction mixture [*p*-tolylacetic acid, *n*-butylamine and $B(OCH_2CF_3)_3$] over the course of the reaction indicated that the initial complex seen in the reaction mixture is the same as that observed on mixing butylamine and $B(OCH_2CF_3)_3$. This suggests that this complex reacts with the carboxylic acid to form the amide product. The amide NH peak can be seen by ^{1}H-NMR before the reaction mixture is heated to 80 °C indicating that amide formation takes place to some degree at room temperature in the presence of $B(OCH_2CF_3)_3$. In ^{13}C-NMR, the amide C=O peak can be seen gradually increasing alongside the reduction of the acid C=O peak over the course of the reaction. These observations suggest that any other intermediates present in the reaction mixture may be too short-lived to be observable on the NMR timescale.

4.3. Rate study

A rate study was also undertaken with the aim of elucidating the rate law of the reaction. Using the same reaction model as that used for the NMR study (*p*-tolylacetic acid and *n*-butylamine), the reaction was monitored over time by NMR. Each reaction was carried out in an NMR tube heated at 50 °C then cooled on ice to analyse the

sample. All reactions were carried out in 1 mL MeCN-d_3 at a reaction concentration of 0.5 M, unless otherwise stated. In a preliminary rate study carried out at room temperature, the conversion was found to be negligible, even over extended reaction times, so the time lapse between cooling the NMR tube and running the NMR (<10 mins) was not significant. The conversion was measured relative to a naphthalene internal standard.

Firstly, we looked at varying the concentration of *p*-tolylacetic acid in the reaction mixture (Figure 21). On increasing the concentration of acid in the reaction mixture, no change was observed in the initial rate of conversion. However, decreasing the concentration of the acid by half results in a small increase in the rate of the reaction.

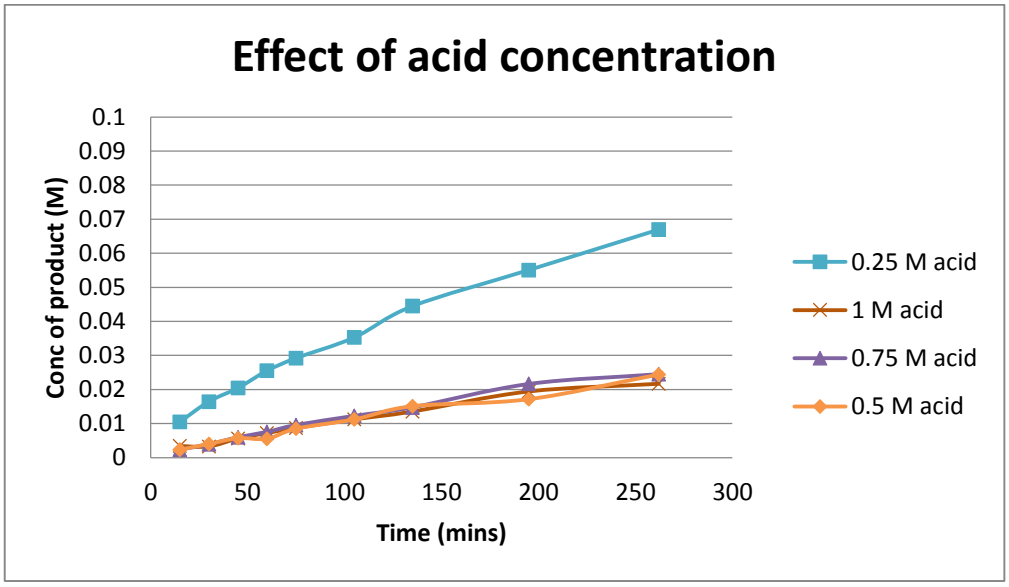


Figure 21 Graph of reaction dependence on *p*-tolylacetic acid concentration. Full conversion at 0.5 M product (0.25 M in the case of 0.25 M acid). Acid (varied), amine (0.5 M) and $B(OCH_2CF_3)_3$ (1 M) in MeCN-d_3 (1 mL).

We then examined the effect of the amine concentration on the reaction (Figure 22). There is a negligible reduction in the rate of the reaction on reducing the concentration of *n*-butylamine. Increasing the concentration of *n*-butylamine has a significant effect on the rate of the reaction. However, the effect plateaus when the concentration of *n*-butylamine is around 1.5 M. With this in mind, it appears that the improvement in rate observed on decreasing the concentration of *p*-tolylacetic acid is due to the relative excess of *n*-butylamine present in the reaction mixture and, therefore, the increase in pH of the reaction.

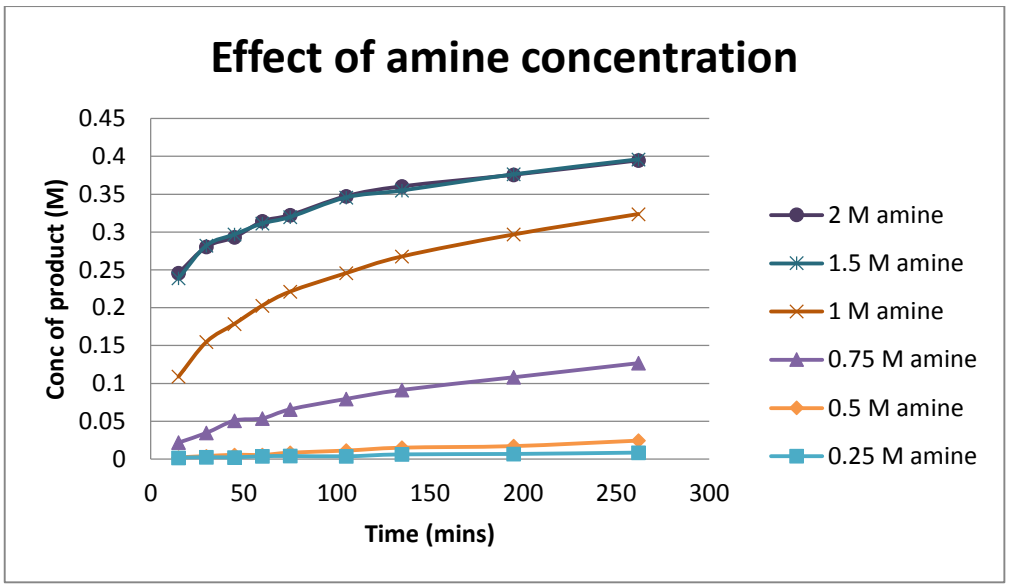


Figure 22 Graph of reaction dependence on *n*-butylamine concentration. Full conversion at 0.5 M product (0.25 M in the case of 0.25 M amine). Acid (0.5 M), amine (varied) and $B(OCH_2CF_3)_3$ (1 M) in MeCN-d_3 (1 mL).

The positive effect that an excess of amine has on the reaction can be exploited to improve the yield of amidations involving more challenging substrates. The yield of the amidation of benzoic acid with benzylamine can be improved by adding two equivalents of excess base either in the form of benzylamine or triethylamine. This improves the yield from 47% at 100 °C for 15 h to 78% and 65%, respectively, at 80°C for 15 h. Unfortunately, the same effect was not observed for amidation of phenylacetic acid with 2-aminopyridine, addition of two equivalents of triethylamine gave a yield of 15%, which is comparable to the 12% obtained without any excess base.

To investigate the reaction dependence on $B(OCH_2CF_3)_3$ we varied the $B(OCH_2CF_3)_3$ concentration and found that decreasing the concentration increases the rate of the reaction up to a point (Figure 23). At a $B(OCH_2CF_3)_3$ concentration of around 0.375 M, the rate reaches an optimum after which it begins to decrease. This suggests that there is an ideal $B(OCH_2CF_3)_3$ concentration for the reaction to proceed at the best possible rate. Adding $B(OCH_2CF_3)_3$ did appear to improve the initial rate of the reaction, however, this improvement begins to tail off.

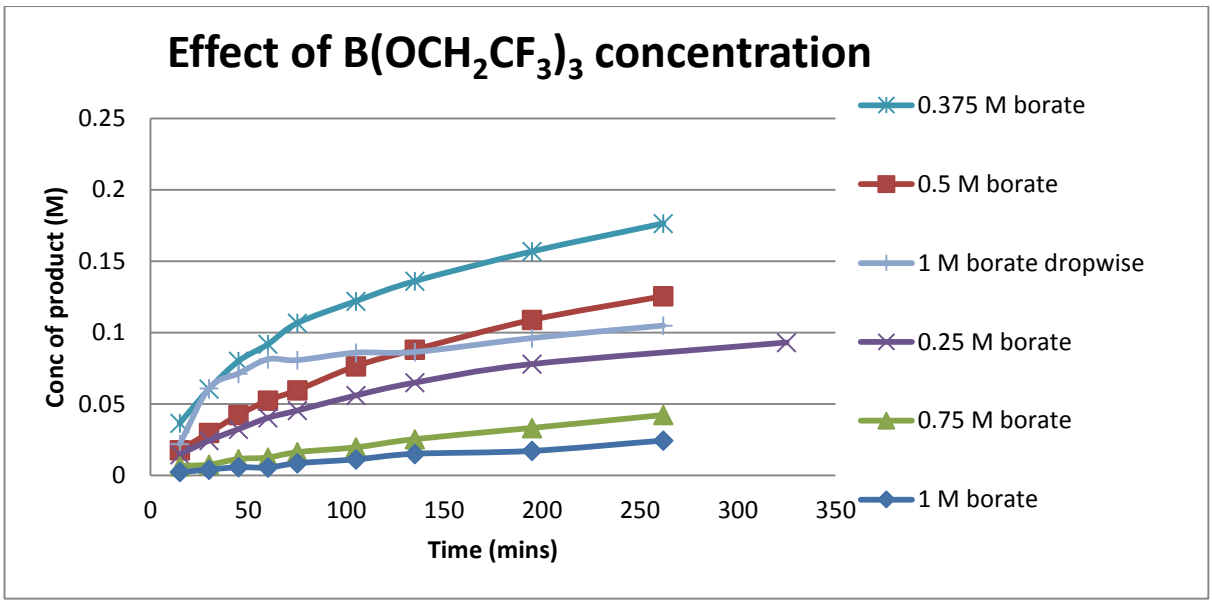


Figure 23 Graph of reaction dependence on $B(OCH_2CF_3)_3$ concentration. Full conversion at 0.5 M product. Acid (0.5 M), amine (0.5 M) and $B(OCH_2CF_3)_3$ (varied) in MeCN-d_3 (1 mL).

Finally, the overall concentration of the reaction has a negligible effect on the rate and conversion of the reaction compared to the effect seen on varying *n*-butylamine and $B(OCH_2CF_3)_3$ concentrations (Figure 24). It appears that a concentration of 0.5 M is optimal. On increasing the concentration to 0.75 M and 1 M we observed poorer solubility that would potentially impact on the results of the study so the investigation of more concentrated samples was not carried out.

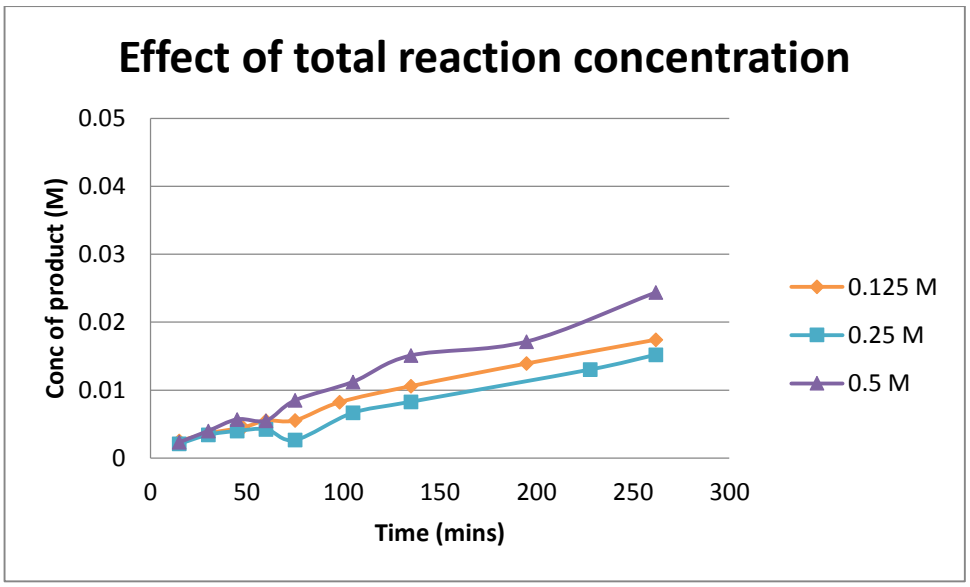
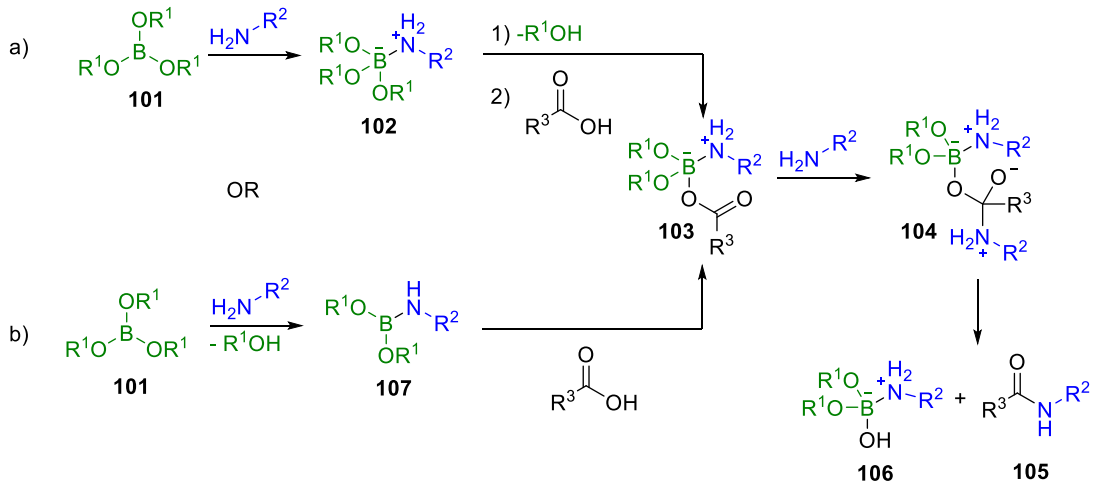


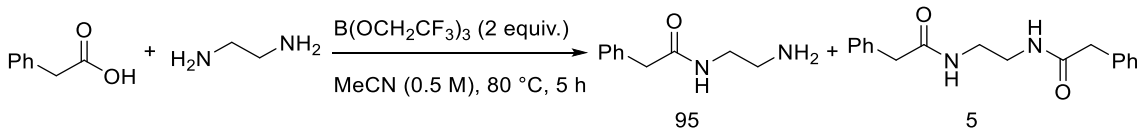
Figure 24 Graph of the reaction dependence on reaction concentration. Full conversion at 0.125, 0.25 and 0.5 M product, respectively. Concentration of reagents relative to overall reaction concentration.

Although we cannot deduce the exact dependence of the reaction on each component, we can infer that the reaction is pH dependent. In addition, it appears that the active species is an amine-$B(OCH_2CF_3)_3$ complex. From these results, we propose a tentative mechanism for the $B(OCH_2CF_3)_3$-mediated amidation reaction: reaction of borate **101** with a molecule of amine to form tetravalent boron species **102** which can then react with the carboxylic acid to form the active acylating species **103** with the concomitant elimination of a molecule of alcohol (Scheme 98a). This active species **103** can then be attacked by another molecule of amine to give heminal **104**. Collapse of **104** can form the amide product **105** and tetravalent boron species **106**, which could potentially activate a further molecule of carboxylic acid. Alternatively, reaction of the borate with a molecule of amine to displace a molecule of alcohol can form the trivalent species **107**, which can subsequently react with a molecule of the carboxylic acid to give the active tetravalent boron species **103** (Scheme 98b). The tetravalent boron species **103** can then follow the same reaction pathway as detailed before. The improved rate observed with excess amine lends support to these possible reaction mechanisms.



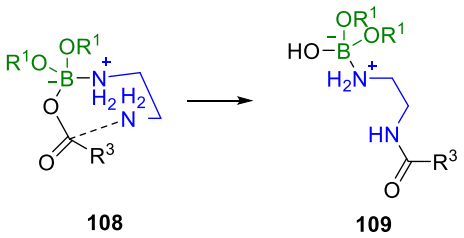
Scheme 98 Proposed mechanism for $B(OCH_2CF_3)_3$-mediated amidation

The amidation of phenylacetic acid with ethylenediamine provides some preliminary experimental support for this proposed mechanism (Scheme 99). By ^{1}H-NMR, the major product is that resulting from monoacylation of ethylene diamine and the minor product is the diamide formed by diacylation of ethylene diamine (95 mono : 5 di).



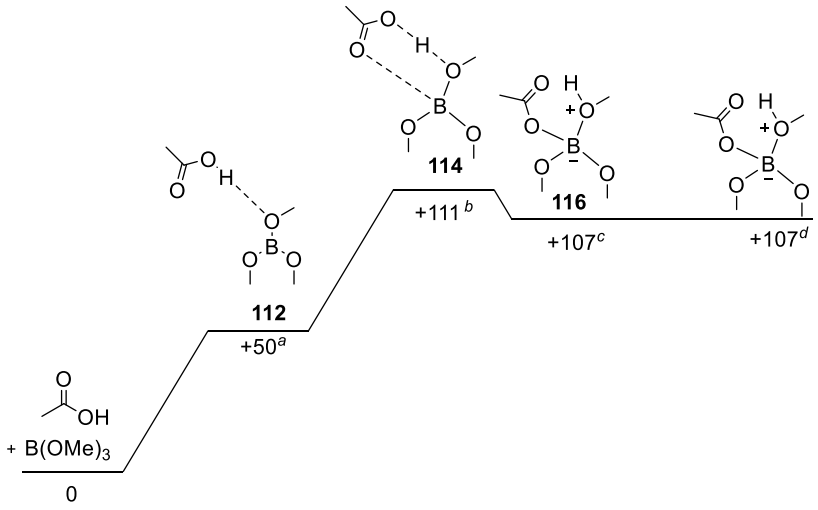
Scheme 99 Monoacylation of ethylene diamine

This experimental observation supports our proposed mechanism as it seems feasible that the incoming amine nucleophile, when tethered to the boron bound amine in **108**, could form the seven-membered ring transition state to acylate on one end of the diamine and leave the other complexed to the boron, and therefore, 'protected' from acylation **109** (Scheme 100).

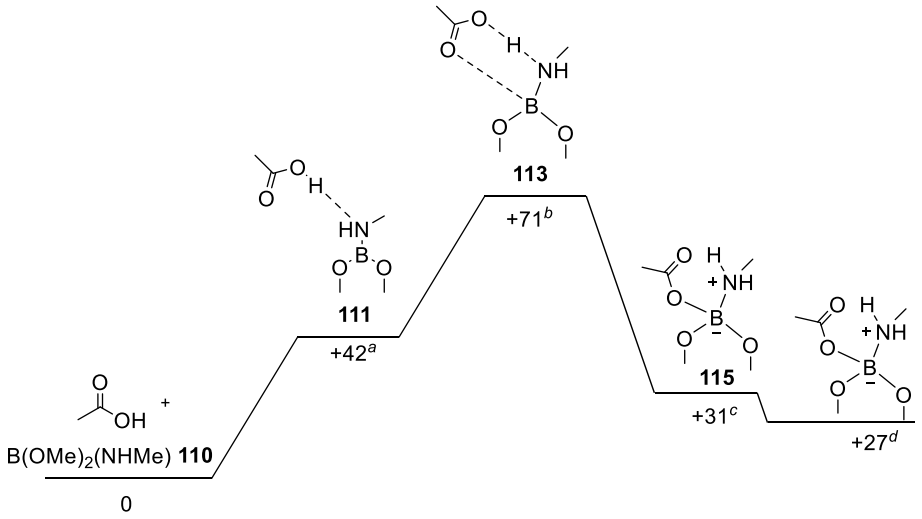


Scheme 100 Proposed transition state in the monoacylation of ethylene diamine

In addition to this experimental evidence, we also have some computational evidence for **103** acting as the active species (Scheme 98). This computational work, carried out by Dr Mike Porter at UCL Chemistry, models one possible step in the trimethylborate-mediated amidation of acetic acid by methylamine, the association of $B(OMe)_3$ and acetic acid.[101] The interactions of acetic acid and $B(OMe)_3$ as well as acetic acid and $B(OMe)_2(NHMe)$ **110** were modelled (Scheme 101 and Scheme 102). Formation of the initial hydrogen-bonded complex, in the case of $B(OMe)_2(NHMe)$ (**111**) requires less energy than that of $B(OMe)_3$ (**112**). Similarly, the transition state for the reaction of $B(OMe)_2(NHMe)$ (**113**) with acetic acid is more energetically favourable than for $B(OMe)_3$ (**114**). Also formation of **115** is significantly more favourable than formation of **116**. Although we cannot yet say how **109** forms it is clear that this is more energetically favourable as a reaction pathway for activation of the carboxylic acid. This suggests that preactivation of the borate species by the amine (**109**) may be a key step in the reaction mechanism of borate-mediated amidation reactions.



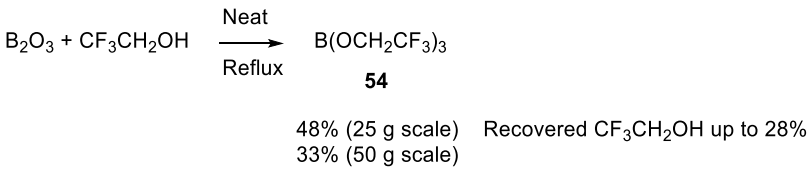
Scheme 101 DFT model for acetic acid + $B(OMe)_3$ (G_{rel}(MeCN)/kJmol^{-1}). [a]hydrogen-bonded complex; [b]Transition state; [c]Local minimum; [d]Global minimum.



Scheme 102 DFT model for acetic acid + $B(OMe)_2(NHMe)$ (G_{rel}(MeCN)/kJmol^{-1}). [a]hydrogen-bonded complex; [b]Transition state; [c]Local minimum; [d]Global minimum.

5. Conclusions and Future Work

This thesis has focused on the use of $B(OCH_2CF_3)_3$ as an amidation reagent. $B(OCH_2CF_3)_3$ was initially synthesised from extremely reactive BBr_3 so a milder synthesis of $B(OCH_2CF_3)_3$ was developed which circumvented the use of BBr_3 in favour of B_2O_3. This synthesis can be carried out on a multigram scale without the need for anhydrous conditions (Scheme 103). The $B(OCH_2CF_3)_3$ reagent is now commercially available from Sigma-Aldrich (product number RNI00014).



Scheme 103 Synthesis of $B(OCH_2CF_3)_3$

Additionally, a solid-phase work-up procedure utilising Amberlyst^{TM} 15, Amberlyst^{TM} A26(OH) and Amberlite^{TM} IRA743 resins for the purification of products from the $B(OCH_2CF_3)_3$-mediated amidation reactions has been developed. This is an operationally simple procedure that only requires stirring of the reaction mixture with the resins followed by a filtration to yield the analytically pure amide product (Figure 25). In most cases, except those containing free acid or amine functionality, this avoids the need for column chromatography. There is the potential that this work-up procedure could be automated due to the inherent simplicity of the method.

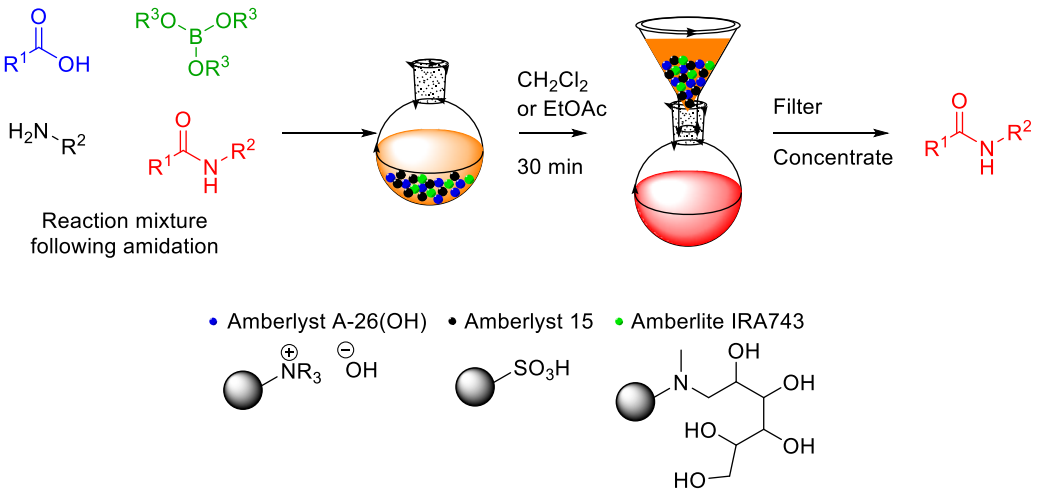
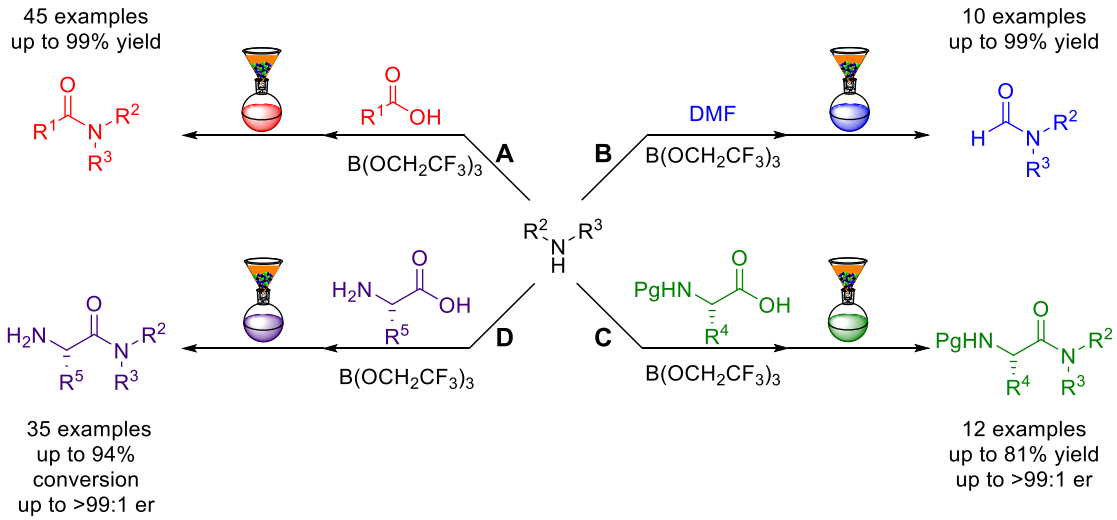


Figure 25 Solid-phase work-up of $B(OCH_2CF_3)_3$-mediated amidation

A general overview of the $B(OCH_2CF_3)_3$-mediated amidation reactions discussed in this thesis is shown in **Scheme 104**.



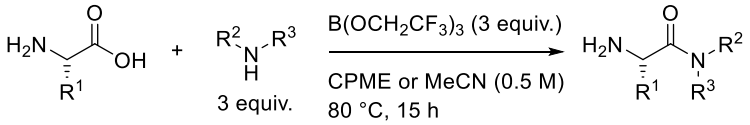
Scheme 104 Overview of the use of $B(OCH_2CF_3)_3$ in amidation

The direct amidation of carboxylic acids by amines was fully explored and the scope and limitations of the method discussed (Scheme 104, **A**). This method is incredibly simple and gives the amide product in generally excellent yield. Lactamisations can be effected in good yield and this methodology can be scaled-up to furnish over a gram of amide product. All of the amide products could be purified and isolated by the solid-phase work-up procedure. No column chromatography was necessary except in examples containing amine or acid functionality, in which an aqueous work-up or column chromatography was required.

A method for the formylation of amines *via* transamidation of DMF was developed and the scope investigated with 10 amines (Scheme 105, **B**). This can be applied to aliphatic, aromatic and secondary amines in good to excellent yield. The products of this reaction can be purified by the simple solid-phase work-up followed by evaporation of DMF. No column chromatography was necessary in the purification of these formamides.

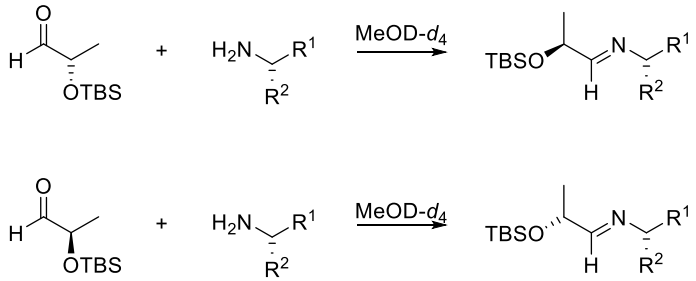
As an extension to the direct amidation methodology, the direct amidation of *N*-protected amino acids with primary and secondary amines was described (Scheme 104, **C**). Boc, Cbz and Bz protecting groups are tolerated under the reaction conditions to give the *N*-protected amino acid amide products in good to excellent yield. The retention of enantiopurity is generally good, although in cases where a significant erosion of enantiopurity is observed, this can be improved by shortening the reaction time.

$B(OCH_2CF_3)_3$ can be used as a reagent for the amidation of unprotected amino acids (Scheme 104, **D**). An optimisation study was carried out to investigate the effect of solvent, concentration and any additives. The ideal solvent was either CPME or MeCN. As CPME is a green solvent this was the first choice, however, in some cases the amino acid solubility was improved in MeCN leading to better product yields. The optimum reaction was found to be: amino acid (1 equiv.), amine (3 equiv.), $B(OCH_2CF_3)_3$ (3 equiv.) in CPME or MeCN (0.5 M) at 80 °C for 15 h (Scheme 105). This was trialled with all natural and several unnatural amino acids with generally moderate to excellent conversion although in some cases very little or no reaction was observed. In addition, the amine scope of the reaction was evaluated by the amidation of L-phenylalanine with a range of amines, including aliphatic, aromatic and secondary amines.



Scheme 105 $B(OCH_2CF_3)_3$-mediated amidation of unprotected amino acids

Due to the necessity of enantiopurity determination of the amine products a new method for the determination of enantiopurity of chiral amines was developed. Forming a diastereomeric imine from the amide product and a chiral aldehyde **81** gave a means to measure the enantiopurity by ^{13}C-NMR (Scheme 106). The initial development of this method looked very promising and the procedure was operationally simple. However, in a 'blind test' the determination of the er of amines with high enantiopurity proved to be problematic.



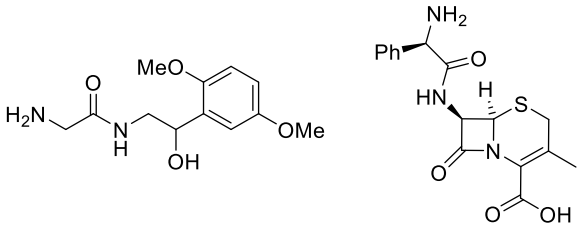
Scheme 106 Diastereomeric imine formation

Applying this method to the unprotected amino acid amide products had variable results. Although the enantiopurity could be measured in some cases, there were other examples where the imine carbon signals were not separable in ^{13}C-NMR. There remains a need to measure the er of all the amide products. Ideally a method avoiding

the use of HPLC would be used to remove the need for derivatisation of the amino functionality. The use of 1*R*-(−)-myrtenal as described previously could be investigated, although this would require the derivatisation of either the other enantiomer or the racemate in addition to the product.[94,95]

If the issues with the er determination of highly enantiopure amines can be resolved this method would provide a simple way to determine the er of chiral amines. At present only α-chiral amines have been trialled in the new chiral amine determination method. The scope of this reaction is yet to be fully explored and the limit on the position of the chirality relative to the amine group is not yet clear.

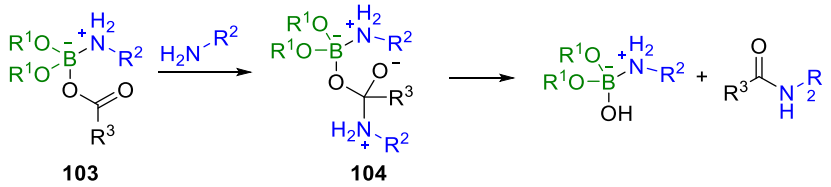
The amino acid moiety is present in a number of drug molecules. Midodrine **117**, which is a drug used to treat low blood pressure by vasoconstriction, could potentially be synthesised from reaction of glycine and 2-amino-1-(2,5-dimethoxyphenyl)ethan-1-ol.[102] Although ethanolamine was unsuccessful in our reactions the additional steric bulk and lipophilicity of this arylethanolamine could potentially improve the reaction. Additionally, Cephalexin **118**, which is an oral antibiotic could also be synthesised in one step from D-phenylglycine and 7-aminocephalosporanic acid.[103] The $B(OCH_2CF_3)_3$-mediated amidation of unprotected amino acids could potentially be applied to the synthesis of such compounds to obtain them directly without the need for *N*-protecting groups.



117 **118**

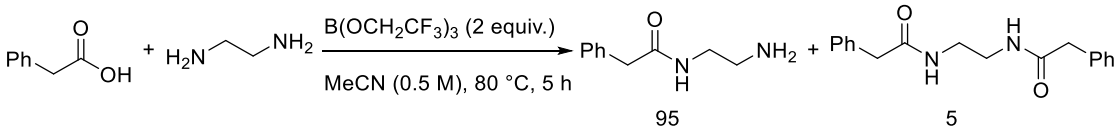
Scheme 107 Structure of Midodrine **117** and Cephalexin **118**

A mechanistic study was carried out to provide some insight into the $B(OCH_2CF_3)_3$-mediated amidation reaction. Although no firm conclusions were drawn a tentative mechanism was proposed as well as possible intermediates in the reaction. The reaction is proposed to proceed *via* reaction of the amine with active intermediate **103** to form hemiaminal **104** followed by the subsequent formation of the amide (Scheme 108). We have some preliminary computational support for **103** acting as the active acylating species.[101]



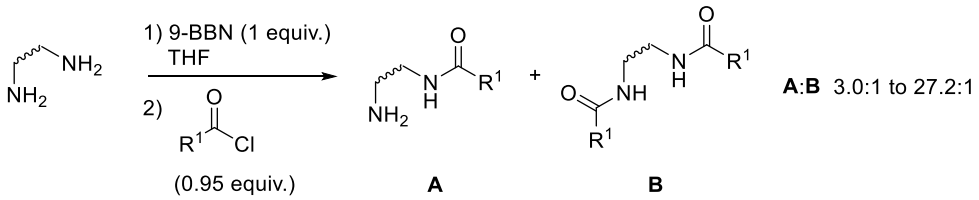
Scheme 108 Proposed key step in $B(OCH_2CF_3)_3$-mediated amidation

This obviously requires further investigation to elucidate the true mechanism of the reaction. Firstly, the amine-$B(OCH_2CF_3)_3$ complexes observed by NMR should be isolated and characterised. Following that, these complexes should be subjected to the reaction conditions to determine whether they take part in the reaction. The experimental support for this mechanism in the form of the monoacylation of ethylenediamine is worthy of further study (Scheme 109).



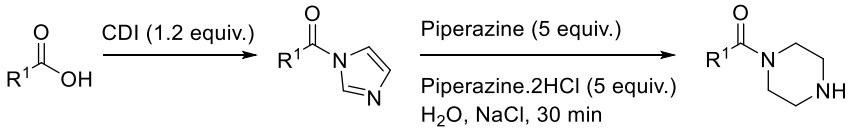
Scheme 109 Monoacylation of ethylene diamine

The use of $B(OCH_2CF_3)_3$ could provide a simple route to monoacylated diamines from equimolar quantities of acid and diamine. A number of methods for monoacylation of diamines have recently been reported. For example, Wang *et al.* describe the use of 9-BBN to complex and deactivate one nitrogen atom of the diamine, the second nitrogen atom can then react with an acyl chloride (Scheme 110).[104] This reaction requires anhydrous conditions as well as preparation of the acyl chloride.



Scheme 110 Monoacylation by protection with 9-BBN

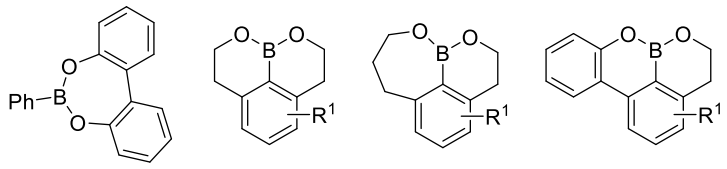
More recently, CDI has been shown to mediate monoacylation as reported by Kaushik *et al.* requires ten equivalents of diamine as both the free amine and the hydrochloride salt as well as preformation of the *N*-acylimidazole from the carboxylic acid (Scheme 111).[105]



Scheme 111 Monoacylation of diamines *via* an *N*-acylimidazole

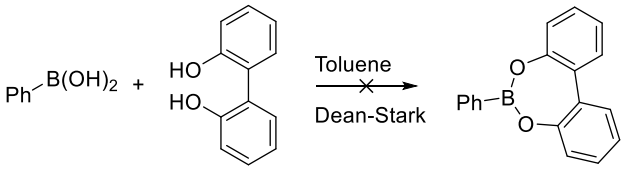
Therefore, $B(OCH_2CF_3)_3$ displays potential as a reagent to mediate the monoacylation of diamines. This reaction can be performed 'open-to-the-air' with equimolar quantities of acid and diamine to give promising selectivity in the initial example with ethylenediamine and phenylacetic acid.

Ultimately the development of a catalytic equivalent of $B(OCH_2CF_3)_3$ is highly desirable. This catalyst could combine the activities of the boronic acid catalysts reported by Hall,[50-53] as well as the stability and scope of $B(OCH_2CF_3)_3$. There are a number of possible preliminary catalyst structures that could be targeted (Scheme 112). Ideally the alkoxy substituent on the boron should be replaced during the reaction with carboxylic acid or amine but reattach following the reaction. There is likely to be a delicate balance of the electronic effects to ensure that the catalyst can reform following dissociation of one of the alkoxy substituents on boron.



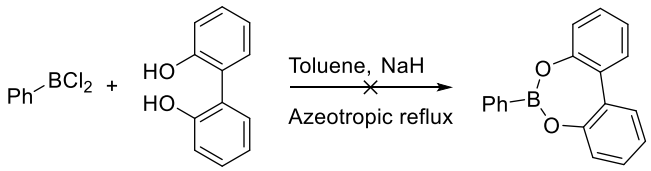
Scheme 112 Possible catalyst structures

Several attempts at the synthesis of catalyst **119** were made, all of which were unsuccessful. Firstly, the synthesis directly from phenylboronic acid using Dean-Stark conditions did not result in the desired **119** product (Scheme 113).



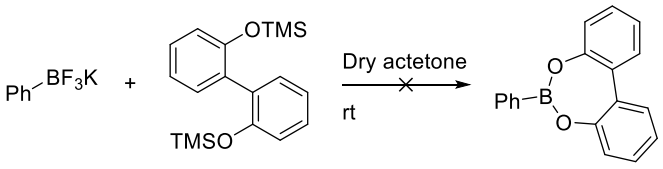
Scheme 113 Unsuccessful synthesis of **119** from phenylboronic acid

Additionally, the synthesis of **119** from dichlorophenylborane was investigated (Scheme 114). This was unsuccessful and did not provide **119**.



Scheme 114 Unsuccessful synthesis of **119** from dichlorophenylborane

A final route from the potassium trifluoroborate salt of phenylboronic acid with TMS-protected biphenol was attempted (Scheme 115).[106] Again, this was unsuccessful and did not provide catalyst **119**.



Scheme 115 Unsuccessful synthesis of **119** from potassium phenyltrifluoroborate

There may be an inherent instability in **119** as it is not reported in the literature. The synthesis of another of these proposed catalysts **120**-**122** may prove more fruitful. If the synthesis of a catalyst of this type is successful, then it can be trialled in an amidation reaction to determine whether they would provide a competitive advantage over the current boronic acid catalysts and $B(OCH_2CF_3)_3$.

6. Experimental

6.1. General methods

All solvents and chemicals were used as supplied unless otherwise indicated. Reactions in MeCN at 100 °C were performed in a sealed (screw cap) carousel tube. All resins were washed with CH_2Cl_2 and dried under vacuum prior to use. Column chromatography was carried out using silica gel and analytical thin layer chromatography was carried out using aluminium-backed silica plates. Components were visualized using combinations of UV (254 nm) and potassium permanganate. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}, concentration (*c*) in g per 100 mL. ^1H NMR spectra were recorded at 300, 400, 500 or 600 MHz in the stated solvent using residual protic solvent $CDCl_3$ (δ = 7.26 ppm, s), DMSO (δ = 2.56 ppm, qn) or MeOD (δ = 4.87, s and 3.31, quintet) as the internal standard. Chemical shifts are quoted in ppm using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad or a combination of these. The coupling constants (*J*) are measured in Hertz. ^{13}C NMR spectra were recorded at 75, 100, 125 or 150 MHz in the stated solvent using the central reference of $CDCl_3$ (δ = 77.0 ppm, t), DMSO (δ = 39.52 ppm, septet) or MeOD (δ = 49.15 ppm, septet) as the internal standard. Chemical shifts are reported to the nearest 0.1 ppm. Mass Spectrometry data were collected on either TOF or magnetic sector analysers. The ionization method is reported in the experimental data.

6.2. General Procedures

6.2.1. General Procedure for Amidation of Carboxylic acids

All reactions were performed on a 1 mmol scale. $B(OCH_2CF_3)_3$ (2.0 mmol, 2 equiv.) was added to a solution of acid (1.0 mmol, 1 equiv.) and amine (1.0 mmol, 1 equiv.) in MeCN (2 mL, 0.5 M). The reaction mixture was stirred at the indicated temperature (80 °C, or 100 °C in a sealed tube) for the indicated time (5-24 h).

Solid phase work-up

After the indicated time, the reaction mixture was diluted with CH_2Cl_2 or EtOAc (3 mL) and water (0.5 mL). Amberlyst® A-26(OH) (150 mg), Amberlyst® 15 (150 mg) and Amberlite® IRA743 (150 mg) were added to the reaction mixture and it was stirred for 30 min. $MgSO_4$ was added to the reaction mixture which was then filtered and the

solids washed three times with CH_2Cl_2 or EtOAc and the filtrate concentrated *in vacuo* to yield the amide product.

For amides **2i**, **2j**, **2t**, **2u** and **4e,** Amberlyst® 15 was not used. In these cases, the product was separated from any excess amine by column chromatography.

Aqueous work-up procedure

After the reaction was complete, the solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (15 mL) and washed with aqueous solutions of $NaHCO_3$ (15 mL, 1 M) and HCl (15 mL, 1 M), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the amide product.

6.2.2. General Procedure for the Formylation of Amines with DMF

All reactions were performed on a 1 mmol scale. $B(OCH_2CF_3)_3$ (2.0 mmol, 2 equiv.) was added to a solution of amine (1.0 mmol, 1 equiv.) and DMF (10.0 mmol, 10 equiv.) in MeCN (2 mL, 0.5 M). The reaction mixture was stirred at 80 °C for 5 h. After 5 h, the reaction mixture was diluted with CH_2Cl_2 or EtOAc (3 mL) and water (0.5 mL). Amberlyst® 15 (150 mg) and Amberlite® IRA743 (150 mg) were added to the reaction mixture and it was stirred for 30 min. The reaction mixture was dried over $MgSO_4$, then filtered, and the solids washed three times with CH_2Cl_2 or EtOAc and the filtrate diluted with toluene (10 mL) and then concentrated *in vacuo* repeatedly (5 times) to yield the formamide product.

6.2.3. General Procedure for the amidation of unprotected amino acids

All reactions were performed on a 0.5 mmol scale. $B(OCH_2CF_3)_3$ (2.0 mmol, 2 equiv.) was added to a solution of amine (0.5 mmol, 3 equiv.) and amino acid (0.5 mmol, 1 equiv.) in CPME or MeCN (1 mL, 0.5 M). The reaction mixture was stirred at 80 or 125 °C for 15 h. After 15 h, the reaction mixture was diluted with CH_2Cl_2 or EtOAc (3 mL) and water (0.5 mL). Amberlyst® A26(OH) (80 mg) and Amberlite® IRA743 (80 mg) were added to the reaction mixture and it was stirred for 30 min. The reaction mixture was dried over $MgSO_4$, then filtered, and the solids washed three times with CH_2Cl_2 or EtOAc. The filtrate was concentrated *in vacuo*. In the case of amides **77a-c**, **77e-f**, **77g**, **77l**, **77k** and **78f** the product was isolated by removing the volatile amine under vacuum. Amide **78h** was isolated by column chromatography and amides **78b-c** were isolated by triturating the amide/residual amine mixture with Et_2O. Amides **77a**, **77f**,

77g, and **77l** were isolated as the hydrochloride salts. Amides **77b-c**, **77e**, **77k**, **78b-c** and **78h** were isolated as the free amine as the hydrochloride salts were hygroscopic.

Tris-(2,2,2-trifluoroethyl) borate 54

25 g Scale

A suspension of B_2O_3 (25.6 g, 0.37 mol) in 2,2,2-trifluoroethanol (53 mL, 0.73 mol) was stirred at 80 °C for 8 h. The reaction mixture was then filtered to remove excess boric anhydride. The filtrate was purified by distillation to give $B(OCH_2CF_3)_3$ as a clear liquid (36.0 g, 117 mmol, 48%).

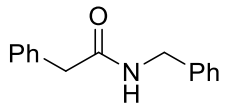
50 g Scale (with CF_3CH_2OH recovery)

A suspension of B_2O_3 (48.1 g, 0.69 mol) in 2,2,2-trifluoroethanol (100 mL, 1.37 mol) was stirred at 80 °C for 24 h. The reaction mixture was then filtered to remove excess boric anhydride. The filtrate was purified by distillation to give $B(OCH_2CF_3)_3$ as a clear liquid (46.3 g, 150 mmol, 33%). 2,2,2-Trifluoroethanol (38.4 g, 28%) was recovered during the distillation.

bp 122-125 °C (760 Torr) [Lit.[55] 120-123 °C (760 Torr)]; ν_{max} (film/cm^{-1}) 3165 (C-H), 1441 (C-F), 1376 (B-O), 1156 (C-O); δ_H (300 MHz, $CDCl_3$) 4.24 (6H, q, *J* 8.3, 3 × CH_2); δ_C (75 MHz, $CDCl_3$) 61.8 (3C, q, J_{C-F} 36.5, 3 × CH_2), 123.2 (3C, q, J_{C-F} 276, 3 × CF_3); δ_F (282 MHz, $CDCl_3$) −77.06; Found (CI): $[M+H]^+$ 309.0334 $C_6H_7O_3F_9B$, requires 309.0344.

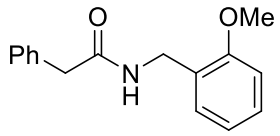
6.3. Characterisation of Amides

***N*-Benzyl-2-phenylacetamide 56**



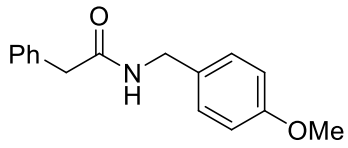
White solid; mp 113-114 °C (DCM) [Lit.[55] 118-120 °C]; ν_{max} (solid/cm^{-1}) 3003 (C-H), 1639 (C=O); δ_H (500 MHz, $CDCl_3$) 3.64 (s, 2H, CH_2CO), 4.42 (d, *J* 5.75, 2H, CH_2NH), 5.65 (1H, br, 1H, NH), 7.18 (d, *J* 7.6, 2H, ArH), 7.22-7.32 (m, 6H, ArH), 7.33-7.37 (m, 2H, ArH); δ_C (125 MHz, $CDCl_3$) 43.7, 44.0, 127.5, 127.6, 128.7, 129.2, 129.6, 134.8, 138.2, 170.9; Found (EI): $[M]^+$ 225.11514 $C_{15}H_{15}ON$, requires 225.11482.

***N*-(2-Methoxybenzyl)-2-phenylacetamide 57a**



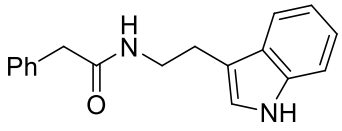
Yellow solid (256 mg, 99%); mp 94-95 ˚C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3284 (N-H), 3066, 3030, 2939, 2837 (C-H), 1646 (C=O); δ_H (600 MHz, $CDCl_3$) 3.58 (s, 2H, CH_2CO), 3.66 (s, 3H, OCH_3), 4.39 (d, *J* 5.8, 2H, C*H*$_2$NH), 6.01 (br s, 1H, NH), 6.80 (d, *J* 8.1, 1H, ArH), 6.87 (td, *J* 7.4, 0.9, 1H, ArH), 7.17 (dd, *J* 7.4, 1.6, 1H, ArH), 7.22-7.25 (m, 3H, ArH), 7.27-7.30 (m, 1H, ArH), 7.33-7.36 (m, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 40.0, 44.0, 55.1, 110.2, 120.7, 126.1, 127.4, 128.9, 129.0, 129.6, 129.7, 135.1, 157.6, 170.7; Found (EI): $[M]^+$ 255.12510 $C_{16}H_{17}O_2N$, requires 255.12538.

***N*-(4-Methoxybenzyl)-2-phenylacetamide 57b**



Yellow solid (252 mg, 99%); mp 139-141 ˚C (CH_2Cl_2) [Lit.[107] 138-139 °C]; ν_{max} (solid/cm^{-1}) 3235 (N-H), 3063, 3032, 2969, 2936 (C-H), 1623 (C=O); δ_H (600 MHz, $CDCl_3$) 3.62 (s, 2H, CH_2CO), 3.78 (s, 3H, OCH_3), 4.34 (d, *J* 5.8, 2H, C*H*$_2$NH), 5.60 (br s, 1H, NH), 6.81-6.83 (m, 2H, ArH), 7.09-7.12 (m, 2H, ArH), 7.25-7.26 (m, 1H, ArH), 7.26-7.30 (m, 2H, ArH), 7.32-7.36 (m, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 43.2, 44.0, 55.4, 114.1, 127.5, 129.0, 129.2, 129.6, 130.3, 134.9, 159.1, 170.9; Found (EI): $[M]^+$ 255.12571 $C_{16}H_{17}O_2N$, requires 255.12538.

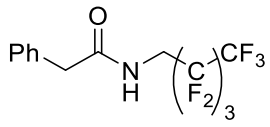
***N*-(2-(1H-Indol-3-yl)ethyl)-2-phenylacetamide 57c**



Yellow solid (158 mg, 57%); mp 145-146 ˚C (CH_2Cl_2) [Lit.[108] 151-153 °C]; ν_{max} (solid/cm^{-1}) 3391 (N-H), 3249 (N-H), 3062, 3033, 2920, 2850 (C-H), 1634 (C=O); δ_H (500 MHz, $CDCl_3$) 2.90 (t, *J* 6.7, 2H, C*H*$_2$CH$_2$NH), 3.50-3.56 (m, 4H, CH_2CO and C*H*$_2$NH), 5.44 (br s, 1H, N*H*CH_2), 6.77 (s, 1H, ArH), 7.08-7.15 (m, 3H, ArH), 7.18-7.22 (m, 1H, ArH), 7.23-7.28 (m, 1H, ArH), 7.26-7.30 (m, 2H, ArH), 7.35 (d, *J* 8.1, 1H,

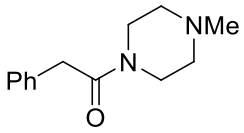
ArH), 7.54 (d, *J* 7.8, 1H, ArH), 8.00 (br s, 1H indole NH); δ_C (125 MHz, $CDCl_3$) 25.1, 39.8, 44.0, 111.3, 112.8, 118.7, 119.6, 122.0, 122.3, 127.3, 129.0 (2C), 129.5, 135.0, 136.4, 171.0; Found (ES): $[M+Na]^+$ 301.1305 $C_{18}H_{18}ON_2Na$, requires 301.1317.

_N_-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-2-phenylacetamide 57d



White solid (128 mg, 68%); mp 85-87 ˚C (CH_2Cl_2); ν_{max} 3278 (NH), 3082 (C-H), 1661 (C=O); δ_H (600 MHz, $CDCl_3$) 3.66 (s, 2H, CH_2CO), 3.97 (td, *J* 6.5, 15.6, 2H, CH_2NH), 5.64 (br s, 1H, NH), 7.25-7.25 (m, 2H, ArH), 7.31-7.34 (m, 1H, ArH), 7.39-7.40 (m, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 39.1 (t, *J* 23.3), 43.6, two signals in the range 106.2-112.6 (splitting results in multiplets), 115.3 (tt, *J* 31.8, 256.9), 117.3 (qt, *J* 33.7, 288.3), 127.9, 129.4, 129.5, 133.9, 171.3; Found (ES+): $[M+H]^+$ 368.0582 $C_{13}H_{11}F_9NO$, requires 367.0619.

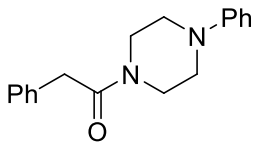
_N_-Methyl-_N'_-phenylacetylpiperazine 57e



Purified by column chromatography (89:10:1 Et_2O:MeOH:NEt_3).

Yellow oil (170 mg, 96%); ν_{max} (film/cm^{-1}) 3029, 2940, 2853, 2795 (C-H), 1627 (C=O); δ_H (500 MHz, $CDCl_3$) 2.20 (t, *J* 5.1, 2H, C*H*$_2$NHCH$_3$), 2.25 (s, 3H, CH_3), 2.34 (t, *J* 5.1, 2H, C*H*$_2$NCH$_3$), 3.45 (t, *J* 5.1, 2H, CH_2NCO), 3.66 (t, *J* 5.1, 2H, CH_2NCO), 3.72 (s, 2H, CH_2CO), 7.21-7.25 (m, 3H, ArH), 7.29-7.33 (m, 2H, ArH); δ_C (125 MHz, $CDCl_3$) 41.0, 41.7, 46.0 (2C), 54.7, 55.0, 126.9, 128.7, 128.8, 135.1, 169.5.

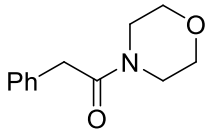
***N*-Phenyl-*N'*-phenylacetylpiperazine 57f**



Purified by column chromatography (Et_2O).

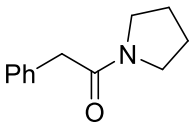
Brown solid (209 mg, 76%); mp 91-93 ˚C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 2919, 2827 (C-H), 1632 (C=O); δ_H (600 MHz, $CDCl_3$) 2.95-2.98 (m, 2H, CH_2NPh), 3.10-3.13 (m, 2H, CH_2NPh), 3.56-3.59 (m, 2H, CH_2NCO), 3.78-3.82 (m, 4H, CH_2NCO and CH_2CO), 6.87-6.93 (m, 3H, ArH), 7.25-7.31 (m, 5H, ArH), 7.33-7.37 (m, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 41.2, 41.8, 46.1, 49.3, 49.6, 116.7, 120.6, 127.1, 128.8, 129.0, 129.4, 135.2, 151.0, 169.6; Found (ES): $[M+H]^+$ 281.1656 $C_{18}H_{21}ON_2$, requires 281.1654.

***N*-Phenylacetylmorpholine 57g**



White solid (182 mg, 89%); mp 65-67 °C (CH_2Cl_2) [Lit.[109] 62-64 °C]; ν_{max} (solid/cm^{-1}) 3064, 3033, 2961, 2917, 2893, 2851 (C-H), 1640 (C=O); δ_H (400 MHz, $CDCl_3$) 3.40-3.44 (m, 2H, CH_2O), 3.44-3.48 (m, 2H, CH_2O), 3.63 (s, 4H, 2×CH_2N), 3.72 (s, 2H, CH_2CO), 7.21-7.27 (m, 3H, ArH), 7.29-7.34 (m, 2H, ArH); δ_C (100 MHz, $CDCl_3$) 40.8, 42.1, 46.5, 66.4, 66.8, 126.9, 128.5, 128.8, 134.8, 169.6.

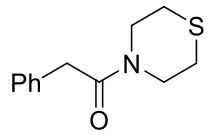
2-Phenyl-1-(pyrrolidin-1-yl)ethanone 57h



Clear oil (185 mg, 97%); ν_{max} (film/cm^{-1}) 3061, 3030, 2971, 2874 (C-H), 1623 (C=O); δ_H (500 MHz, $CDCl_3$) 1.80 (quintet, *J* 6.7, 2H, C*H*$_2$$CH_2N$), 1.88 (quintet, *J* 6.7, 2H, C*H*$_2$$CH_2N$), 3.39 (t, *J* 6.7, 2H, CH_2N), 3.46 (t, *J* 6.7, 2H, CH_2N), 3.63 (s, 2H, CH_2CO), 7.19-7.23 (m, 1H, ArH), 7.24-7.31 (m, 4H, ArH); δ_C (125 MHz, $CDCl_3$) 24.4, 26.2,

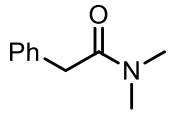
42.3, 46.0, 47.0, 126.7, 128.6, 129.0, 135.0, 169.6; Found (ES+): $[M+H]^+$ 190.12264 $C_{12}H_{16}ON$, requires 190.12319.

***N*-Phenylacetylthiomorpholine 57i**



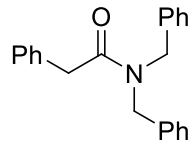
Yellow solid (194 mg, 89%); mp 73-74 °C (CH_2Cl_2) [Lit.[110] 73-75 °C]; ν_{max} (solid/cm^{-1}) 3024, 2960, 2911 (C-H), 1639 (C=O); δ_H (400 MHz, $CDCl_3$) 2.26-2.30 (m, 2H, CH_2S), 2.52-2.59 (m, 2H, CH_2S), 3.65-3.70 (m, 2H, CH_2N), 3.72 (s, 2H, CH_2CO), 3.85-3.90 (m, 2H, CH_2CO), 7.20-7.26 (m, 3H, ArH), 7.29-7.34 (m, 2H, ArH); δ_C (100 MHz, $CDCl_3$) 27.2, 27.4, 41.3, 44.4, 48.8, 126.9, 128.5, 128.9, 134.8, 169.4.

***N*,*N*-Dimethyl-2-phenylacetamide 57j**



White solid (134 mg, 82%); mp 37-39 °C (CH_2Cl_2) [Lit.[111] 38-40 °C]; ν_{max} (solid/cm^{-1}) 3062, 3029, 2931 (C-H), 1634 (C=O); δ_H (600 MHz, $CDCl_3$) 2.91 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 3.66 (s, 2H, CH_2), 7.17-7.23 (m, 3H, ArH), 7.25-7.28 (m, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 35.7, 37.8, 41.1, 126.8, 128.7, 128.9, 135.2, 171.1

***N*,*N*-Dibenzyl-2-phenylacetamide 57k**

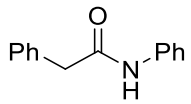


Purified by column chromatography (Et_2O:PE 3:1).

Colourless oil (37 mg, 12%); ν_{max} (film/cm^{-1}) 3062, 3029, 2925 (C-H), 1639 (C=O); δ_H (500 MHz, $CDCl_3$, 35 °C) 3.83 (s, 2H, CH_2CO), 4.47 (s, 2H, CH_2N), 4.66 (s, 2H, CH_2N), 7.11-7.17 (m, 2H, ArH), 7.19-7.25 (m, 2H, ArH), 7.25-7.42 (m, 11H, ArH); δ_C

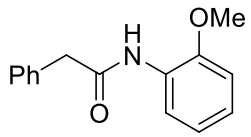
(125 MHz, $CDCl_3$, 35 °C) 41.0, 48.3, 50.3, 126.5, 126.9, 127.4, 127.6, 128.3, 128.5, 128.7, 128.8, 128.9, 135.0, 136.5, 137.3, 171.6.

_N_,2-Diphenylacetamide 57l



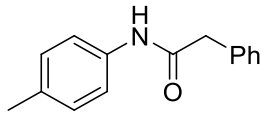
Off white solid (125 mg, 60%); mp 116-118 ˚C (CH_2Cl_2) [Lit.[112] 116-117 °C]; ν_{max} (solid/cm^{-1}) 3254 (N-H), 3135, 3061, 3025 (C-H), 1655 (C=O); δ_H (600 MHz, $CDCl_3$) 3.69 (s, 2H, CH_2), 7.09 (t, *J* 7.4, 1H, ArH), 7.27 (t, *J* 7.8, 2H, ArH), 7.33-7.34 (m, 3H, ArH), 7.36-7.39 (m, 2H, ArH), 7.45 (d, *J* 8.0, 2H, ArH), 7.61 (br s, 1H, NH); δ_C (150 MHz, $CDCl_3$) 44.8, 120.1, 124.6, 127.7, 129.1, 129.3, 129.6, 134.7, 137.9, 169.6.

_N_-(2-Methoxyphenyl)-2-phenylacetamide 57m



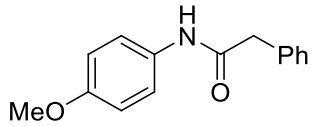
Yellow solid (143 mg, 61%); mp 82-83 ˚C (CH_2Cl_2) [Lit.[113] 80-81 °C]; ν_{max} (solid/cm^{-1}) 3284 (N-H), 3028, 3011, 2959, 2939, 2918, 2837 (C-H), 1648 (C=O), δ_H (500 MHz, $CDCl_3$) 3.72 (s, 3H, CH_3), 3.76 (s, 2H, CH_2), 6.80 (dd, *J* 8.1, 1.1, 1H, ArH), 6.93 (td, *J* 7.8, 1.1, 1H, ArH), 7.01 (td, *J* 7.8, 1.5, 1H, ArH), 7.31-7.37 (m, 3H, ArH), 7.37-7.42 (m, 2H, ArH), 7.79 (br s, 1H, NH), 8.35 (dd, *J* 8.0, 1.4, 1H, ArH); δ_C (125 MHz, $CDCl_3$) 45.3, 55.7, 110.0, 119.6, 121.2, 123.8, 127.5, 127.7, 129.1, 129.7, 134.7, 147.9, 168.9.

2-Phenyl-_N_-_p_-tolylacetamide 57n



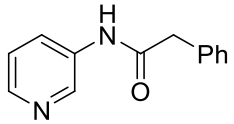
White solid (105 mg, 53%); mp 132-133 ˚C (CH_2Cl_2) [Lit.[112] 131-132 °C]; ν_{max} (solid/cm^{-1}) 3289 (N-H), 3063, 3031, 2922 (C-H), 1650 (C=O); δ_H (500 MHz, $CDCl_3$) 2.29 (s, 3H, CH_3), 3.73 (s, 2H, CH_2), 7.01 (br s, 1H, NH), 7.08 (d, *J* 8.4, 2H, ArH), 7.28 (d, *J* 8.4, 2H, ArH), 7.31-7.36 (m, 3H, ArH), 7.38-7.42 (m, 2H, ArH); δ_C (125 MHz, $CDCl_3$) 23.6, 47.4, 122.9, 130.2, 131.8, 132.2, 133.3, 136.8, 137.5, 138.0, 172.1.

***N*-(4-Methoxyphenyl)-2-phenylacetamide 57o**



White solid (164 mg, 68%); mp 122-123 ˚C (CH_2Cl_2) [Lit.[114] 124-125 °C]; ν_{max} (solid/cm^{-1}) 3315 (N-H), 3084, 3026, 3009, 2943 (C-H), 1650 (C=O); δ_H (500 MHz, $CDCl_3$) 3.73 (s, 2H, CH_2), 3.77 (s, 3H, CH_3), 6.80-6.83 (m, 2H, ArH), 6.97 (br s, 1H, NH), 7.29-7.36 (m, 5H, ArH), 7.38-7.42 (m, 2H, ArH); δ_C (125 MHz, $CDCl_3$) 44.8, 55.5, 114.1, 121.9, 127.7, 129.3, 129.6, 130.7, 134.6, 156.6, 169.0.

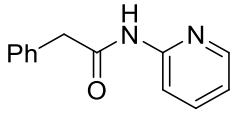
***N*-(Pyridin-3-yl)-2-phenylacetamide 57p**



Purified by column chromatography (4 % MeOH in EtOAc).

White solid (114 mg, 53%); mp 107-108 ˚C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3170 (N-H), 3032, 2971 (C-H), 1686 (C=O); δ_H (500 MHz, $CDCl_3$) 3.68 (s, 2H, CH_2), 7.20 (dd, *J* 8.3, 4.7, 1H, ArH), 7.23-7.33 (m, 5H, ArH), 8.06-8.10 (m, 1H, ArH), 8.27 (dd, *J* 4.7, 1.2, 1H, ArH), 8.57 (d, *J* 2.4, 1H, ArH), 9.05 (br s, 1H, NH); δ_C (125 MHz, $CDCl_3$) 44.3, 123.9, 127.5, 127.6, 129.0, 129.3, 134.4, 135.4, 141.3, 144.9, 170.4; Found (EI): $[M]^+$ 212.09471 $C_{13}H_{12}ON_2$, requires 212.09441.

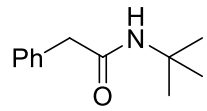
***N*-(Pyridin-2-yl)-2-phenylacetamide 57q**



Purified by column chromatography (3:1 EtOAc:Petrol, 10 % NEt_3).

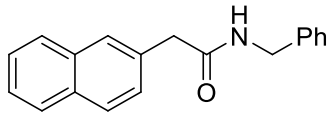
White solid (25 mg, 12%); mp 121-122 ˚C (CH_2Cl_2) [Lit.112 122-124 °C]; ν_{max} (solid/cm^{-1}) 3230 (N-H), 3046, 2959, 2921 (C-H), 1656 (C=O); δ_H (500 MHz, $CDCl_3$) 3.74 (s, 2H, CH_2), 6.98-7.03 (m, 1H, ArH), 7.27-7.33 (m, 3H, ArH), 7.33-7.38 (m, 2H, ArH), 7.66-7.71 (m, 1H, ArH), 8.19-8.27 (m, 2H, ArH), 8.52 (br s, 1H, NH); δ_C (125 MHz, $CDCl_3$) 45.1, 114.1, 120.0, 127.8, 129.3, 129.6, 134.0, 138.5, 147.7, 151.3, 169.6; Found (ES): $[M+H]^+$ 213.1035 $C_{13}H_{13}ON_2$, requires 213.1028.

***N*-*tert*-Butyl-2-phenylacetamide 57r**



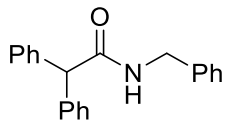
White solid (116 mg, 60%); mp 104-106 ˚C (CH_2Cl_2) [Lit.[115] 103 °C]; ν_{max} (solid/cm^{-1}) 3303 (N-H), 3063, 2962, 2872 (C-H), 1638 (C=O); δ_H (600 MHz, $CDCl_3$) 1.28 (s, 9H, 3×CH_3), 3.48 (s, 2H, CH_2CO), 5.17 (br s, 1H, NH), 7.24 (d, *J* 7.2, 2H, ArH), 7.26-7.30 (m, 1H, ArH), 7.35 (t, *J* 7.4, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 28.8, 45.0, 51.4, 127.3, 129.1, 129.4, 135.6, 170.4.

***N*-Benzyl-2-(naphthalen-2-yl)acetamide 58a**



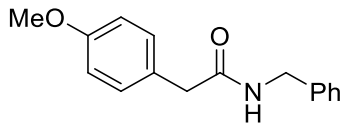
Yellow solid (225 mg, 81%); mp 168-169 ˚C (CH_2Cl_2) [Lit.[116] 170-174 °C]; ν_{max} (solid/cm^{-1}) 3225 (N-H), 3053, 3030, 2976, 2936 (C-H), 1628 (C=O); δ_H (500 MHz, $CDCl_3$) 3.79 (s, 2H, CH_2CO), 4.41 (d, *J* 5.8, 2H, C*H*$_2$NH), 5.81 (br s, 1H, NH), 7.18 (d, *J* 7.0, 2H, ArH), 7.21-7.30 (m, 3H, ArH), 7.39 (dd, *J* 8.3, 1.7, 1H, ArH), 7.46-7.52 (m, 2H, ArH), 7.72 (br s, 1H, ArH), 7.78-7.82 (m, 1H, ArH), 7.82-7.85 (m, 2H, ArH); δ_C (125 MHz, $CDCl_3$) 43.7, 44.1, 126.2, 126.5, 127.4, 127.5, 127.6, 127.7, 127.8, 128.4, 128.7, 129.0, 132.3, 132.6, 133.6, 138.2, 170.8.

***N*-Benzyl-2,2-diphenylacetamide 58b**



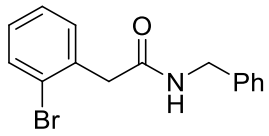
Yellow solid (247 mg, 81%); mp 127-128 ˚C (CH_2Cl_2) [Lit.[117] 126-128 °C]; ν_{max} (solid/cm^{-1}) 3311 (N-H), 3060, 3030, 2930 (C-H), 1634 (C=O); δ_H (500 MHz, $CDCl_3$) 4.48 (d, *J* 5.7, 2H, C*H*$_2$NH), 4.96 (s, 1H, CH), 5.94 (br s, 1H, NH), 7.19-7.22 (m, 2H, ArH), 7.24-7.30 (m, 8H, ArH), 7.30-7.35 (m, 5H, ArH); δ_C (125 MHz, $CDCl_3$) 43.9, 59.3, 127.4, 127.6, 127.7, 128.8, 128.9, 129.0, 138.2, 139.4, 171.8.

***N*-Benzyl-2-(4-methoxyphenyl)acetamide 58c**



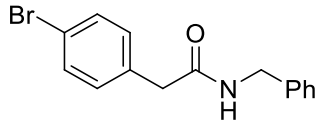
Yellow solid (232 mg, 90%); mp 134-135 ˚C (CH_2Cl_2) [Lit.[118] 136 °C]; ν_{max} (solid/cm^{-1}) 3286 (N-H), 3082, 3063, 3033, 2968, 2838 (C-H), 1635 (C=O); δ_H (600 MHz, $CDCl_3$) 3.57 (s, 2H, CH_2CO), 3.79 (s, 3H, CH_3), 4.40 (d, *J* 5.8, 2H, C*H*$_2$NH), 5.75 (br s, 1H, NH), 6.86-6.89 (m, 2H, ArH), 7.16-7.19 (m, 4H, ArH), 7.23-7.26 (m, 1H, ArH), 7.28-7.31 (m, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 43.0, 43.7, 55.4, 114.6, 126.8, 127.5, 127.6, 128.8, 130.7, 138.3, 159.0, 171.5.

***N*-Benzyl-2-(2-bromophenyl)acetamide 58d**



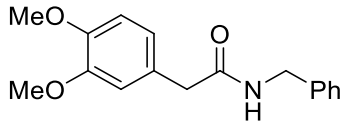
Yellow solid (276 mg, 90%); mp 143-144 ˚C (CH_2Cl_2) [Lit.[119] 144-145 °C]; ν_{max} (solid/cm^{-1}) 3272 (N-H), 3055, 3030, 2920, 2871 (C-H), 1642 (C=O); δ_H (600 MHz, $CDCl_3$) 3.77 (s, 2H, CH_2CO), 4.44 (d, *J* 5.7, 2H, C*H*$_2$NH), 5.75 (br s, 1H, NH), 7.16 (td, *J* 7.7, 1.7, 1H, ArH), 7.21-7.27 (m, 3H, ArH), 7.30 (app t, *J* 7.6, 3H, ArH), 7.37 (dd, *J* 7.5, 1.6, 1H, ArH), 7.58 (dd, *J* 8.0, 1.0, 1H, ArH); δ_C (150 MHz, $CDCl_3$) 43.8, 44.2, 125.0, 127.6, 127.7, 128.2, 128.8, 129.4, 131.9, 133.3, 134.8, 138.1, 169.5.

***N*-Benzyl-2-(4-bromophenyl)acetamide 58e**



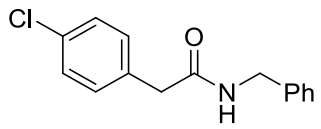
Yellow solid (289 mg, 94%); mp 165-166 ˚C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3280 (N-H), 3056, 3026, 2917, 2872 (C-H), 1642 (C=O); δ_H (600 MHz, $CDCl_3$) 3.55 (s, 2H, CH_2CO), 4.41 (d, *J* 5.6, 2H, C*H*$_2$NH), 5.72 (br s, 1H, NH), 7.15 (d, *J* 8.4, 2H, ArH), 7.19 (d, *J* 7.0, 2H, ArH), 7.25-7.28 (m, 1H, ArH), 7.29-7.33 (m, 2H, ArH), 7.45-7.48 (m, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 43.2, 43.8, 121.6, 127.7, 127.8, 128.9, 131.2, 132.2, 133.8, 138.0, 170.2; Found (EI): $[M]^+$ 303.02563 $C_{15}H_{14}ONBr$, requires 303.02533.

***N*-Benzyl-2-(3,4-dimethoxyphenyl)acetamide 58f**



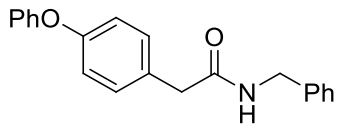
Brown solid (235 mg, 81%); mp 100-101 ˚C (CH_2Cl_2) [Lit.[120] 98-100 °C]; ν_{max} (solid/cm^{-1}) 3297 (N-H), 3065, 3033, 3000, 2936, 2835 (C-H), 1634 (C=O); δ_H (600 MHz, $CDCl_3$) 3.58 (s, 2H, CH_2CO), 3.85 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.41 (d, *J* 5.6, 2H, C*H*$_2$NH), 5.74 (br s, 1H, NH), 6.76-6.80 (m, 2H, ArH), 6.83 (d, *J* 8.0, 1H, ArH), 7.18 (d, *J* 7.0, 2H, ArH), 7.23-7.26 (m, 1H, ArH), 7.28-7.31 (m, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 43.6, 43.7, 55.98, 56.02, 111.6, 112.4, 121.8, 127.2, 127.58, 127.61, 128.8, 138.3, 148.4, 149.4, 171.3; Found (EI): $[M]^+$ 285.13532 $C_{17}H_{19}O_3N$, requires 285.13594.

***N*-Benzyl-2-(4-chlorophenyl)acetamide 58g**



Yellow solid (244 mg, 93%); mp 157-158 ˚C (CH_2Cl_2) [Lit.[121] 151-153 °C]; ν_{max} (solid/cm^{-1}) 3277 (N-H), 3056, 3027, 2918, 2874 (C-H), 1642 (C=O), 690 (C-Cl); δ_H (600 MHz, $CDCl_3$) 3.56 (s, 2H, CH_2CO), 4.41 (d, *J* 5.8, 2H, C*H*$_2$NH), 5.76 (br s, 1H, NH), 7.18-7.22 (m, 4H, ArH), 7.24-7.28 (m, 1H, ArH), 7.29-7.32 (m, 4H, ArH); δ_C (150 MHz, $CDCl_3$) 43.1, 43.8, 127.69, 127.74, 128.9, 129.2, 130.9, 133.3, 133.5, 138.1, 170.4.

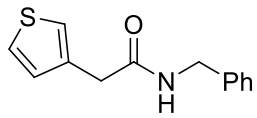
***N*-Benzyl-2-(4-phenoxyphenyl)acetamide 58h**



Yellow solid (298 mg, 95%); mp 125-126 ˚C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3285 (N-H), 3085, 3064, 3033, 2921 (C-H), 1636 (C=O); δ_H (600 MHz, $CDCl_3$) 3.60 (s, 2H, CH_2CO), 4.43 (d, *J* 5.9, 2H, C*H*$_2$NH), 5.71 (br s, 1H, NH), 6.96-7.01 (m, 4H, ArH), 7.10-7.13 (m, 1H, ArH), 7.18-7.21 (m, 2H, ArH), 7.21-7.24 (m, 2H, ArH), 7.25-7.28 (m, 1H, ArH), 7.29-7.36 (m, 4H, ArH); δ_C (150 MHz, $CDCl_3$) 43.2, 43.8, 119.2, 119.3,

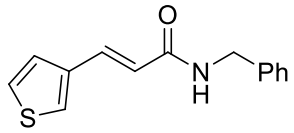
123.6, 127.6, 127.7, 128.8, 129.5, 129.9, 130.9, 138.2, 156.8, 157.0, 171.0; Found (EI): $[M]^+$ 317.14158 $C_{21}H_{19}O_2N$, requires 317.14103.

_N_-Benzyl-2-(thiophen-3-yl)acetamide 58i



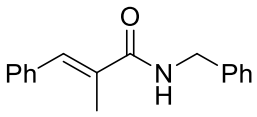
Yellow solid (212 mg, 91%); mp 96-98 ˚C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3279 (N-H), 3086, 3062, 3032, 2925 (C-H), 1635 (C=O); δ_H (600 MHz, $CDCl_3$) 3.65 (s, 2H, CH_2CO), 4.42 (d, *J* 5.8, 2H, C*H*$_2$NH), 5.85 (br s, 1H, NH), 7.01 (d, *J* 4.8, 1H, ArH), 7.14-7.15 (m, 1H, ArH), 7.19 (d, *J* 7.5, 2H, ArH), 7.23-7.34 (m, 4H, ArH); δ_C (150 MHz, $CDCl_3$) 38.3, 43.7, 123.7, 127.0, 127.61, 127.62, 128.6, 128.8, 134.8, 138.2, 170.5; Found (ES): $[M+H]^+$ 232.0789 $C_{13}H_{14}ONS$, requires 232.0796.

(*E*)-*N*-Benzyl-3-(thiophen-3-yl)acrylamide 58j



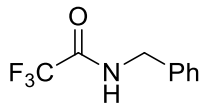
Yellow solid (217 mg, 88%); mp 107-110 ˚C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3275 (N-H), 3029, 2971 (C-H), 1639 (C=O); δ_H (600 MHz, $CDCl_3$) 4.55 (d, *J* 5.7, 2H, C*H*$_2$NH), 6.05 (br s, 1H, NH), 6.26 (d, *J* 15.5, 1H, C*H*CO), 7.22-7.24 (m, 1H, ArH), 7.26-7.36 (m, 6H, ArH), 7.42 (d, *J* 2.1, 1H, ArH), 7.65 (d, *J* 15.5, 1H, C*H*CHCO); δ_C (150 MHz, $CDCl_3$) 44.0, 120.2, 125.1, 126.9, 127.4, 127.7, 128.0, 128.9, 135.2, 137.8, 138.3, 166.1; Found (ES+): $[M+H]^+$ 244.0800 $C_{14}H_{14}NOS$, requires 244.0796.

(*E*)-*N*-Benzyl-2-methyl-3-phenylacrylamide 58k



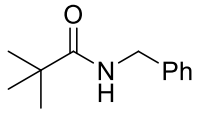
White solid (229 mg, 90%); mp 120-121 ˚C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3332 (N-H), 3079, 3059, 2921, 2852 (C-H), 1631 (C=O); δ_H (600 MHz, $CDCl_3$) 2.11 (s, 3H, CH_3), 4.56 (d, *J* 5.7, 2H, C*H*$_2$NH), 6.69 (br s, 1H, NH), 7.27-7.40 (m, 11H, ArH and CH); δ_C (150 MHz, $CDCl_3$) 14.5, 44.2, 127.7, 127.98, 128.04, 128.5, 128.9, 129.5, 131.9, 134.3, 136.2, 138.5, 169.6; Found (ES): $[M+H]^+$ 252.1394 $C_{17}H_{18}ON$, requires 252.1388.

***N*-Benzyl-2,2,2-trifluoroacetamide 58l**



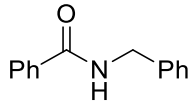
Yellow solid (183 mg, 89%); mp 72-74 ˚C (CH_2Cl_2) [Lit.[122] 70-71 °C]; ν_{max} (solid/cm^{-1}) 3300 (N-H), 3110, 3035, 2923 (C-H), 1702 (C=O); δ_H (500 MHz, $CDCl_3$) 4.54 (d, *J* 5.8, 2H, CH_2NH), 6.52 (br s, 1H, NH), 7.28-7.32 (m, 2H, ArH), 7.32-7.41 (m, 3H, ArH); δ_C (125 MHz, $CDCl_3$) 43.9, 116.0 (q, J_{C-F} 285.4), 128.0, 128.2, 129.0, 136.1, 157.5 (q, J_{C-F} 36.9); δ_F (282 MHz, $CDCl_3$) -76.2.

***N*-Benzylpivalamide 58m[55]**



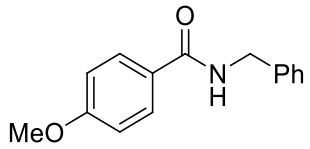
Brown solid; ν_{max} (solid/cm^{-1}) 3303 (N-H), 2963 (C-H), 1638 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, CH_3), 4.45 (2H, d, *J* 5.68, CH_2), 6.01 (1H, br s, NH), 7.26-7.32 (3H, m, ArH), 7.33-7.38 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 27.8, 38.8, 43.7, 127.6, 127.8,128.8, 138.7, 178.5.

***N*-Benzylbenzamide 58n**



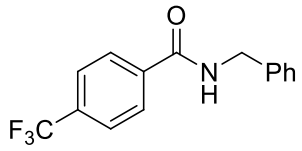
White solid; mp 99-101 °C [Lit.[55] 100-101 °C]; ν_{max} (solid/cm^{-1}) 3282 (N-H), 3062 (C-H), 1636 (C=O); δ_H (500 MHz, $CDCl_3$) 4.66 (2H, d, *J* 5.66, CH_2), 6.40 (1H, br s, NH), 7.28-7.33 (1H, m, ArH), 7.36 (4H, d, *J* 4.43, ArH), 7.41-7.45 (2H, m, ArH), 7.50 (1H, t, *J* 7.31, ArH)7.78-7.79 (1H, m, ArH), 7.79-7.81 (1H, m, ArH); δ_C (125 MHz, $CDCl_3$) 44.2, 127.0, 127.7, 128.0, 128.7, 128.9, 131.6, 134.5, 138.2, 167.4.

***N*-Benzyl-4-methoxybenzamide 58o**



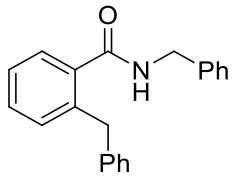
Yellow solid (172 mg, 71%); mp 129-130 ˚C (CH_2Cl_2) [Lit.[123] 129-130 °C]; ν_{max} (solid/cm^{-1}) 3256 (N-H), 3058, 2957, 2930, 2834 (C-H), 1631 (C=O); δ_H (500 MHz, $CDCl_3$) 3.85 (s, 3H, CH_3), 4.64 (d, *J* 5.7, 2H, C*H*$_2$NH), 6.28 (br s, 1H, NH), 6.90-6.94 (m, 2H, ArH), 7.28-7.32 (m, 1H, ArH), 7.36 (m, 4H, ArH), 7.74-7.77 (m, 2H, ArH); δ_C (125 MHz, $CDCl_3$) 44.1, 55.5, 113.8, 126.7, 127.6, 128.0, 128.8, 128.9, 138.5, 162.3, 167.0.

***N*-Benzyl-4-(trifluoromethyl)benzamide 58p**



Yellow solid (212 mg, 76%); mp 168-170 ˚C (CH_2Cl_2) [Lit.[114] 149-151 °C]; ν_{max} (solid/cm^{-1}) 3326 (N-H), 3091, 3071, 3036 (C-H), 1643 (C=O); δ_H (600 MHz, $CDCl_3$) 4.65 (d, *J* 5.6, 2H, C*H*$_2$NH), 6.53 (br s, 1H, NH), 7.29-7.33 (m, 1H, ArH), 7.33-7.38 (m, 4H, ArH), 7.68 (d, *J* 8.2, 2H, ArH), 7.89 (d, *J* 8.2, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 44.5, 123.7 (q, $J_{C\text{-}F}$ 272.5), 125.8 (q, $J_{C\text{-}F}$ 3.8), 127.6, 128.0, 128.1, 129.0, 133.4 (q, $J_{C\text{-}F}$ 32.7), 137.7, 137.8, 166.2; δ_F (282 MHz, $CDCl_3$) -63.4.

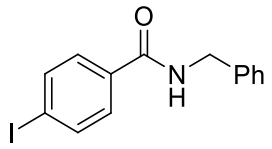
***N*,2-Dibenzylbenzamide 58q**



Yellow solid (184 mg, 61%); mp 119-120 ˚C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3296 (N-H), 3057, 3025, 3008, 2921, 2873 (C-H), 1633 (C=O), δ_H (600 MHz, $CDCl_3$) 4.22 (s, 2H, CH_2Ph), 4.49 (d, *J* 5.6, 2H, C*H*$_2$NH), 5.86 (br s, 1H, NH), 7.13 (d, *J* 7.1, 2H, ArH), 7.16-7.19 (m, 3H, ArH), 7.21-7.25 (m, 4H, ArH), 7.26-7.32 (m, 3H, ArH), 7.33-7.37 (m, 1H, ArH), 7.39-7.42 (m, 1H, ArH); δ_C (150 MHz, $CDCl_3$) 39.0, 44.1, 126.2, 126.5,

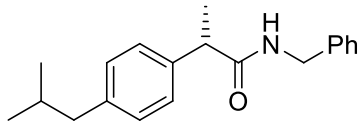
127.3, 127.7, 128.0, 128.6, 128.9, 129.0, 130.3, 131.3, 136.5, 137.9, 139.0, 140.9, 169.9; Found (ES): $[M+H]^+$ 302.1532 $C_{21}H_{20}NO$, requires 302.1545.

_N_-Benzyl-4-iodobenzamide 58r



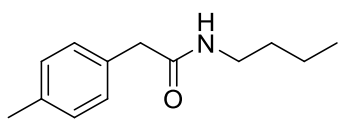
White solid (124 mg, 37%); mp 167-168 ˚C (CH_2Cl_2) [Lit.[124] 166-167 °C]; ν_{max} (solid/cm^{-1}) 3311 (N-H), 3083, 3060, 3028 (C-H), 1640 (C=O); δ_H (600 MHz, DMSO-d_6) 4.47 (d, *J* 6.0, 2H, CH_2NH), 7.22-7.26 (m, 1H, ArH), 7.29-7.35 (m, 4H, ArH), 7.66-7.69 (m, 2H, ArH), 7.84-7.88 (m, 2H, ArH), 9.10 (br t, *J* 6.0, 1H, NH); δ_C (150 MHz, DMSO-d_6) 42.7, 98.9, 126.8, 127.3, 128.3, 129.3, 133.8, 137.2, 139.5, 165.6; Found (EI): $[M]^+$ 337.99617 $C_{14}H_{12}INO$, requires 337.99581.

(*S*)-*N*-Benzyl-2-(4-isobutylphenyl)propanamide 58s



Yellow solid (294 mg, 98%); mp 77-78 ˚C (CH_2Cl_2); $[\alpha]_D^{25}$ +7.2 (*c* 0.88, CH_2Cl_2) [Lit.[51] $[\alpha]_D^{20}$ +7.1 (*c* 0.88, CH_2Cl_2)]; ν_{max} (solid/cm^{-1}) 3304 (N-H), 2949, 2866 (C-H), 1638 (C=O); δ_H (600 MHz, $CDCl_3$) 0.90 (d, *J* 6.6, 6H, (CH_3)$_2$CH), 1.55 (d, *J* 7.2, 3H, CH_3CH), 1.85 (app nonet, *J* 6.8, 1H, (CH$_3$)$_2$C*H*), 2.45 (d, *J* 7.0, 2H, CH_2CH), 3.58 (q, *J* 7.2, 1H, CHCO), 4.37 (dd, *J* 15.1, 5.7, 1H, C*H*HNH), 4.41 (dd, *J* 15.1, 5.8, 1H, CH*H*NH), 5.66 (br s, 1H, NH), 7.10-7.14 (m, 4H, ArH), 7.19-7.29 (m, 5H, ArH); δ_C (150 MHz, $CDCl_3$) 18.6, 22.5, 30.3, 43.5, 45.1, 46.6, 127.3, 127.41, 127.43, 128.6, 129.6, 138.7, 138.8, 140.6, 174.7; HPLC (hexane/*i*-PrOH 100:0, 0.5 mL/min, Chiracel Daicel AD): t_R (S) = 5.01 min (>99%), t_R (R) = 7.41 min (<1%).

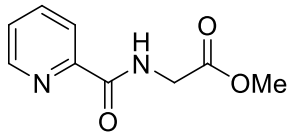
_N_-Butyl-2-*p*-tolylacetamide 59a



White solid (188 mg, 92%); mp 82-83 ˚C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3301 (N-H), 2959, 2931, 2866 (C-H), 1649 (C=O); δ_H (500 MHz, $CDCl_3$) 0.86 (t, *J* 7.3, 3H, CH_3CH$_2$), 1.24

(sextet, *J* 7.3, 2H, CH_3CH_2), 1.39 (quintet, *J* 7.3, 2H, $CH_3CH_2CH_2$), 2.34 (s, 3H, CH_3Ar), 3.18 (dt, *J* 7.3, 6.0, 2H, CH_2NH), 3.52 (s, 2H, CH_2CO), 5.43 (br s, 1H, NH), 7.11-7.17 (m, 4H, ArH); δ_C (125 MHz, $CDCl_3$) 13.8, 20.0, 21.2, 31.6, 39.5, 43.6, 129.5, 129.8, 132.0, 137.1, 171.2; Found (EI): $[M]^+$ 205.14639 $C_{13}H_{19}NO$, requires 205.14611.

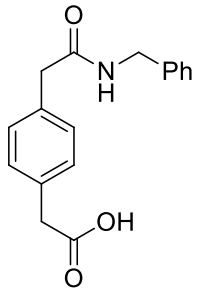
Methyl 2-(picolinamido)acetate 59b



Purified by column chromatography (PE:EtOAc 1:1).

White solid (132 mg, 72%); mp 82-84 ˚C (CH_2Cl_2) [Lit.[125] 81-82 °C]; ν_{max} (solid/cm^{-1}) 3375 (N-H), 3059, 2954, 2852 (C-H), 1746 (C=O), 1668 (C=O); δ_H (600 MHz, $CDCl_3$) 3.74 (s, 3H, CH_3), 4.23 (d, *J* 5.7, 2H, CH_2), 7.38-7.42 (m, 1H, ArH), 7.80 (t, *J* 7.6, 1H, ArH), 8.13 (d, *J* 7.6, 1H, ArH), 8.49 (br s, 1H, NH), 8.53 (br d, *J* 4.5, ArH); δ_C (150 MHz, $CDCl_3$) 41.3, 52.5, 122.4, 126.6, 137.4, 148.4, 149.3, 164.7, 170.3.

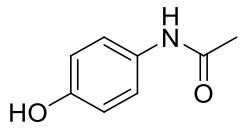
2-(4-(2-(Benzylamino)-2-oxoethyl)phenyl)acetic acid 59c



$B(OCH_2CF_3)_3$ (621.8 mg, 2.02 mmol, 2 equiv.) was added to a solution of phenylene diacetic acid (192 mg, 0.99 mmol, 1 equiv.) and benzylamine (0.11 mL, 1.01 mmol, 1 equiv.) in MeCN (2 mL, 0.5 M). The reaction mixture was stirred at 80 °C for 5 h. After 5 h the solvent was removed *in vacuo* and the residue diluted in Et_2O (20 mL) and washed with $NaHCO_3$ (20 mL, 1 M) and extracted with Et_2O (3 × 20 mL). The aqueous layer was acidifed with HCl (1 M) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the product as a white solid (146 mg, 0.52 mmol, 52%); mp 163-166 °C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3284 (N-H/O-H), 3030, 3060 (C-H), 1699 (C=O), 1632 (C=O); δ_H (600 MHz, DMSO-d_6) 3.45 (s, 2H, CH_2CO_2H), 3.53 (s, 2H, CH_2CONH), 4.26 (d, *J* 6.0, 2H, CH_2NH), 7.16-7.19 (m, 2H, ArH), 7.20-7.25 (m, 5H, ArH), 7.29-7.32 (m, 2H, ArH),

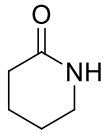
8.55 (br t, *J* 5.6, 1H, NH), 12.31 (br s, 1H, OH); δ_C (150 MHz, DMSO-d_6) 40.3, 42.0, 42,2, 126.8, 127.3, 128.3, 128.9, 129.3, 133.1, 134.7, 139.5, 170.2, 172.8; Found (EI): $[M+H]^+$ 284.12789 $C_{17}H_{18}O_3N$, requires 284.12866.

_N_-(4-Hydroxyphenyl)acetamide 59d



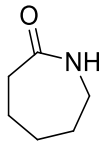
White solid (97 mg, 69%); mp 169-170 ˚C (CH_2Cl_2) [Lit.[126] 167-168 °C]; ν_{max} (solid/cm^{-1}) 3242 (N-H/O-H), 1632 (C=O); δ_H (600 MHz, MeOD) 2.07 (s, 3H, CH_3), 6.71-6.74 (m, 2H, ArH), 7.28-7.32 (m, 2H, ArH); δ_C (150 MHz, MeOD) 23.5, 116.2, 123.4, 131.7, 155.4, 171.4.

Piperidin-2-one 60a[127]



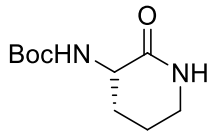
Colourless oil (95 mg, 99%); ν_{max} (film/cm^{-1}) 3245 (N-H), 2945, 2870 (C-H), 1637 (C=O); δ_H (500 MHz, $CDCl_3$) 1.69-1.82 (m, 4H, C*H*$_2$CH$_2$CO and C*H*$_2$CH$_2$NH), 2.30 (t, *J* 6.5, 2H, CH_2CO), 3.26-3.32 (m, 2H, C*H*$_2$NH), 7.03 (br s, 1H, NH); δ_C (125 MHz, $CDCl_3$) 20.8, 22.2, 31.5, 42.1, 172.9.

Azepan-2-one 60b



White solid (100 mg, 86%); mp 67-68 ˚C (CH_2Cl_2) [Lit.[128] 66-68 °C]; ν_{max} (solid/cm^{-1}) 3202 (N-H), 2927, 2855 (C-H), 1648 (C=O); δ_H (500 MHz, $CDCl_3$) 1.60-1.71 (m, 4H, C*H*$_2$C*H*$_2$CH$_2$NH), 1.72-1.78 (m, 2H, C*H*$_2$CH$_2$CO), 2.42-2.47 (m, 2H, CH_2CO), 3.17-3.22 (m, 2H, C*H*$_2$NH), 6.42 (br s, 1H, NH); δ_C (125 MHz, $CDCl_3$) 23.3, 29.8, 30.6, 36.8, 42.8, 179.5; Found (EI): $[M]^+$ 113.08274 $C_6H_{11}ON$, requires 113.08351.

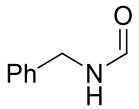
(*S*)-*tert*-Butyl 2-oxopiperidin-3-ylcarbamate 60c



White solid (180 mg, 84%); mp 100-101 ˚C (CH_2Cl_2) [Lit.[129] 101-103 °C]; $[\alpha]_D^{25}$ −9.5 (*c* 1.22, MeOH) [Lit.[129] $[\alpha]_D^{20}$ −10.6 (*c* 1.22, MeOH)]; ν_{max} (solid/cm^{-1}) 3264 (N-H), 2968 (C-H), 1715 (C=O), 1652 (C=O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.45 (s, 9H, $C(CH_3)_3$), 1.54-1.67 (m, 1H, CHC*H*H), 1.82-1.93 (m, 2H, $NHCH_2CH_2$), 2.41-2.50 (m, 1H, CHCH*H*), 3.27-3.33 (m, 2H, CH_2NH), 4.01 (dt, *J* 11.3, 5.6, 1H, CH), 5.45 (br s, 1H, N*H*CH), 6.33 (br s, 1H, N*H*CH_2); δ_C (100 MHz, $CDCl_3$, 58 °C) 21.1, 27.9, 28.3, 41.7, 51.6, 79.5, 155.8, 171.6.

6.4. Characterisation of Formamides

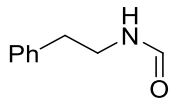
***N*-Benzylformamide 64a**



Mixture of rotamers (1:0.16). Data for major rotamer reported.

White solid (139 mg, 98%); mp 63-64 °C (CH_2Cl_2) [Lit.[130] 60-62 °C]; ν_{max} (solid/cm^{-1}) 3269 (N-H), 3089, 3056, 2925, 2886 (C-H), 1637 (C=O); δ_H (500 MHz, $CDCl_3$) 4.41 (d, *J* 6.0, 2H, CH_2), 6.41 (br s, 1H, NH), 7.20-7.28 (m, 3H, ArH) 7.29-7.37 (m, 2H, ArH), 8.17 (s, 1H, CHO); δ_C (125 MHz, $CDCl_3$) 42.3, 127.8, 127.9, 128.9, 137.6, 161.1.

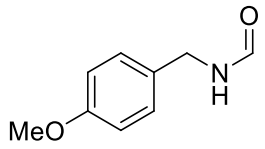
***N*-Phenethylformamide 64b**



Mixture of rotamers (1:0.22). Data for major rotamer reported.

Colourless oil (152 mg, 99%); ν_{max} (film/cm^{-1}) 3273 (N-H), 3061, 3028, 2934, 2866 (C-H), 1656 (C=O); δ_H (400 MHz, $CDCl_3$, 58 °C) 2.84 (t, *J* 7.1, 2H, $PhCH_2$), 3.55 (app q, *J* 6.7, 2H, CH_2NH), 5.96 (br s, 1H, NH), 7.14-7.26 (m, 3H, ArH), 7.27-7.34 (m, 2H, ArH), 8.09 (s, 1H, CHO); δ_C (100 MHz, $CDCl_3$, 58 °C) 35.5, 39.2, 126.5, 128.59, 128.63, 138.6, 161.1.

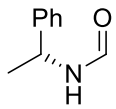
***N*-(4-Methoxybenzyl)formamide 64c**



Mixture of rotamers (1:0.17). Data for major rotamer reported.

Yellow solid (101 mg, 61%); mp 81-83 ˚C (CH_2Cl_2) [Lit.[131] 79-80 °C]; ν_{max} (solid/cm^{-1}) 3283 (N-H), 3010, 2933, 2891 (C-H), 1642 (C=O); δ_H (600 MHz, $CDCl_3$) 3.77 (s, 3H, CH_3), 4.37 (d, *J* 5.9, 2H, CH_2), 6.11 (br s, 1H, NH), 6.83-6.86 (m, 2H, ArH), 7.17-7.20 (m, 2H, ArH), 8.18 (s, 1H, CHO); δ_C (150 MHz, $CDCl_3$) 41.7, 55.4, 114.2, 129.2, 129.9, 159.1, 161.3.

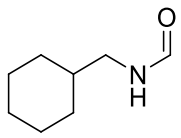
(*R*)-*N*-(1-Phenylethyl)formamide 64d



Mixture of rotamers (1:0.19). Data for major rotamer reported.

Pale yellow oil (129 mg, 85%); $[\alpha]_D^{25}$ +160.9 (*c* 0.52, $CHCl_3$) [Lit.[132] $[\alpha]_D^{20}$ +161.4 (*c* 0.50, $CHCl_3$)]; ν_{max} (film/cm^{-1}) 3270 (N-H), 3032, 2977, 2931, 2829 (C-H), 1653 (C=O); δ_H (500 MHz, $CDCl_3$) 1.45 (d, *J* 6.9, 3H, CH_3), 5.13 (app quintet, *J* 7.2, 1H, C*H*CH_3), 6.71 (br s, 1H, NH), 7.21-7.35 (m, 5H, ArH), 8.04 (s, 1H, CHO); δ_C (125 MHz, $CDCl_3$) 22.0, 47.7, 126.2, 127.4, 128.7, 143.0, 160.7; Found (EI): $[M]^+$ 149.08325 $C_9H_{11}ON$, requires 149.08351.

***N*-(Cyclohexylmethyl)formamide 64e**

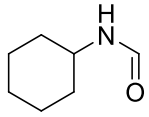


Mixture of rotamers (1:0.25). Data for major rotamer reported.

Colourless oil (135 mg, 96%); ν_{max} (film/cm^{-1}) 3280 (N-H), 3060, 2922, 2851 (C-H), 1657 (C=O); δ_H (600 MHz, $CDCl_3$) 0.77-0.88 (m, 2H, cyclohexyl), 1.00-1.18 (m, 3H, cyclohexyl), 1.34-1.42 (m, 1H, cyclohexyl), 1.53-1.68 (m, 5H, cyclohexyl), 3.01 (t, *J* 6.6, 2H, C*H*$_2$NH), 6.71 (br s, 1H, NH), 8.06 (s, 1H, CHO); δ_C (150 MHz, $CDCl_3$) 25.8,

26.4, 30.8, 37.8, 44.4, 161.8; Found (EI): $[M+H]^+$ 142.122721 $C_8H_{16}NO$, requires 142.12264.

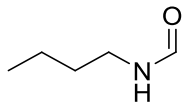
_N_-Cyclohexylformamide 64f



Mixture of rotamers (1:0.30). Data for major rotamer reported.

Brown oil (95 mg, 78%); ν_{max} (film/cm^{-1}) 3268 (N-H), 3050, 2929, 2854 (C-H), 1652 (C=O); δ_H (500 MHz, $CDCl_3$) 1.09-1.39 (m, 5H, cyclohexyl), 1.53-1.63 (m, 1H, cyclohexyl), 1.64-1.76 (m, 2H, cyclohexyl), 1.82-1.95 (m, 2H, cyclohexyl), 3.78-3.86 (m, 1H, C*H*NH), 5.78 (br s, 1H, NH), 8.07 (s, 1H, CHO); δ_C (125 MHz, $CDCl_3$) 24.8, 25.5, 33.1, 47.1, 160.5.

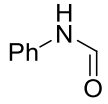
_N_-Butylformamide 64g



Mixture of rotamers (1:0.23). Data for major rotamer reported.

Yellow oil (31 mg, 30%); ν_{max} (film/cm^{-1}) 3280 (N-H), 3058, 2959, 2933, 2868 (C-H), 1655 (C=O); δ_H (500 MHz, $CDCl_3$) 0.90 (t, *J* 7.2, 3H, CH_3), 1.33 (sext, *J* 7.2, 2H, CH_3CH_2), 1.48 (quintet, *J* 7.2, 2H, $CH_3CH_2CH_2$), 3.26 (q, *J* 6.7, 2H, CH_2NH), 5.95 (br s, 1H, NH), 8.12 (s, 1H, CHO); δ_C (125 MHz, $CDCl_3$) 13.7, 20.0, 31.5, 37.9, 161.5; Found (EI): $[M]^+$ 101.08274 $C_5H_{11}ON$, requires 101.08351.

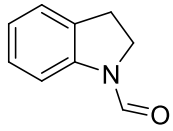
_N_-Phenylformamide 64h



Mixture of rotamers (1:0.93). Data for major rotamer reported.

Yellow oil (25 mg, 21%); ν_{max} (film/cm^{-1}) 3273 (N-H), 3066, 2923, 2854 (C-H), 1682 (C=O); δ_H (600 MHz, $CDCl_3$) 7.08-7.11 (m, 1H, ArH), 7.19 (t, *J* 7.5, 1H, ArH), 7.31-7.38 (m, 2H, ArH), 7.53-7.56 (m, 1H, ArH), 8.41 (br s, 1H, NH), 8.71 (d, *J* 11.3, 1H, CHO); δ_C (150 MHz, $CDCl_3$) 118.9, 125.4, 129.9, 136.8, 162.8.

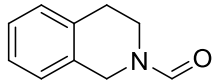
1-Indolinecarbaldehyde 64i



Mixture of rotamers (1:0.22). Data for major rotamer reported.

Brown solid (55 mg, 38%); mp 56-58 °C (CH_2Cl_2) [Lit.[133] 58-61 °C]; ν_{max} (solid/cm^{-1}) 3053, 2960, 2921, 2854 (C-H), 1656 (C=O); δ_H (600 MHz, $CDCl_3$) 3.14 (2H, t, *J* 8.6, CCH_2), 4.05 (2H, app td, *J* 8.5, 0.9, CH_2N), 7.04 (1H, td, *J* 7.2, 1.5, ArH), 7.14-7.22 (2H, m, ArH), 7.24 (1H, d, *J* 7.2, ArH) 8.92 (1H, s, CHO); δ_C (150 MHz, $CDCl_3$) 27.3, 44.8, 109.5, 124.4, 126.2, 127.7, 132.1, 141.2, 157.7.

3,4-Dihydro-2(1*H*)-isoquinolinecarbaldehyde 64j

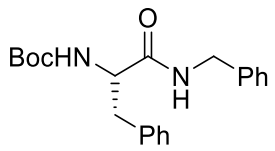


Mixture of rotamers (1:0.60). Data for major rotamer reported.

Pale yellow oil (119 mg, 71%); ν_{max} (film/cm^{-1}) 3056, 3026, 2929, 2886 (C-H), 1646 (C=O); δ_H (500 MHz, $CDCl_3$) 2.87 (t, *J* 5.9, 2H, CCH_2CH_2), 3.60 (t, *J* 5.9, 2H, CCH_2CH_2), 4.65 (s, 2H, CCH_2NH), 7.05-7.19 (m, 4H, ArH), 8.16 (s, 1H, CHO); δ_C (125 MHz, $CDCl_3$) 29.8, 42.4, 43.3, 126.70, 126.71, 126.8, 129.0, 131.8, 133.7, 161.8.

6.5. Characterisation of *N*-protected amino acid amides

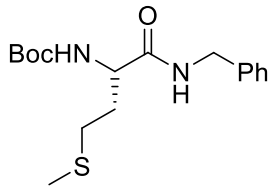
Boc-L-Phenylalanine-benzylamide 65a



Yellow solid (287 mg, 81%); mp 128-129 °C (CH_2Cl_2) [Lit.[134] 128 °C]; $[\alpha]_D^{25}$ +5.2 (*c* 1.1, CH_2Cl_2) [Lit.[135] $[\alpha]_D^{22}$ +4.9 (*c* 0.20, CH_2Cl_2)]; ν_{max} (solid/cm^{-1}) 3343 (N-H), 3312 (N-H), 3024, 2927 (C-H), 1678 (C=O), 1659 (C=O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.43 (s, 9H, $C(CH_3)_3$), 3.09 (dd, *J* 13.8, 7.2, 1H, CHC*H*H), 3.13 (dd, *J* 13.8, 6.7, 1H, CHCH*H*), 4.32-4.40 (m, 3H, $NHCH_2$ and CH), 5.00 (br s, 1H, N*H*CH), 6.03 (br s, 1H, N*H*CH_2), 7.12-7.16 (m, 2H, ArH), 7.20-7.25 (m, 3H, ArH), 7.25-7.32 (m, 5H, ArH); δ_C (100 MHz, $CDCl_3$, 58 °C) 28.2, 38.6, 43.5, 56.4, 80.2, 126.8, 127.4, 127.6, 128.5,

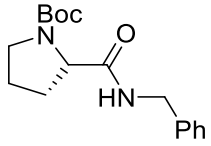
128.6, 129.3, 136.8, 137.8, 155.3, 171.0; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiracel Daicel OD): t_R (D) = 10.62 min (<1%), t_R (L) = 13.24 min (>99%).

Boc-L-Methionine-benzylamide 65b



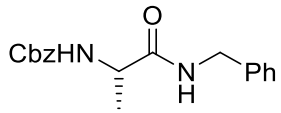
Yellow solid (266 mg, 79%); mp 98-100 °C (CH_2Cl_2); $[\alpha]_D^{25}$ −9.1 (*c* 1.1, CH_2Cl_2) [Lit.[135] $[\alpha]_D^{24}$ −9.2 (*c* 1.1, CH_2Cl_2)]; ν_{max} (solid/cm^{-1}) 3335 (N-H), 3314 (N-H), 3061, 3027, 2968, 2936 (C-H), 1679 (C=O), 1655 (C=O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.41 (s, 9H, $C(CH_3)_3$), 1.88-1.97 (m, 1H, CHC*H*H), 2.05 (s, 3H, CH_3S), 2.06-2.15 (m, 1H, CHCH*H*), 2.46-2.59 (m, 2H, CH_2S), 4.28 (app q, *J* 7.1, 1H, CH), 4.36 (dd, *J* 14.8, 5.8, 1H, C*H*HNH), 4.43 (dd, *J* 14.8, 5.9, 1H, CH*H*NH), 5.42 (br d, *J* 8.1, 1H, N*H*CH), 7.19-7.25 (m, 3H, ArH), 7.26-7.30 (m, 2H, ArH), 6.86 (br s, 1H, N*H*CH_2); δ_C (100 MHz, $CDCl_3$, 58 °C) 15.2, 28.3, 30.4, 32.0, 43.4, 54.1, 80.1, 127.3, 127.5, 128.5, 138.2, 155.7, 171.6; Found (ES): $[M+Na]^+$ 361.1567 $C_{17}H_{26}O_3N_2SNa$, requires 361.1562; HPLC (hexane/*i*-PrOH 92:8, 0.5 mL/min, Chiracel Daicel OD): t_R (D) = 9.28 min (<1%), t_R (L) = 12.48 min (>99%).

Boc-L-Proline-benzylamide 65c



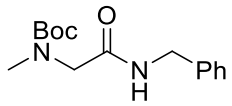
Yellow solid (186 mg, 61%); mp 124-125 °C (CH_2Cl_2) [Lit.[136] 125-126 °C]; $[\alpha]_D^{25}$ −77.0 (*c* 1.0, CH_2Cl_2) [Lit.[135] $[\alpha]_D^{24}$ −76.2 (*c* 1.0, CH_2Cl_2)]; ν_{max} (solid/cm^{-1}) 3303 (N-H), 2978, 2933, 2909, 2874 (C-H), 1682 (C=O), 1653 (C=O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.40 (s, 9H, $C(CH_3)_3$), 1.78-2.07 (m, 3H, C*H*$_2$CH$_2$NBoc and CH*H*CHNBoc), 2.25 (br s, 1H, C*H*HCHNBoc), 3.37-3.42 (m, 2H, CH_2NBoc), 4.24-4.30 (m, 1H, CHNBoc), 4.37 (dd, *J* 14.8, 5.6, 1H C*H*HNH), 4.46 (dd, *J* 14.8, 5.7, 1H, CH*H*NH), 6.82 (br s, 1H, NH), 7.18-7.30 (m, 5H, ArH); δ_C (100 MHz, $CDCl_3$, 58 °C) 24.1, 28.3 (2C), 43.3, 47.0, 60.6, 80.3, 127.2, 127.5, 128.5, 138.5, 155.2, 172.1; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiracel Daicel OD): t_R (D) = 13.08 min (1%), t_R (L) = 15.79 min (99%).

Cbz-L-Alanine-benzylamide 65d



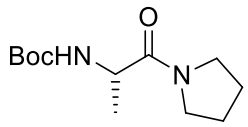
Yellow solid (245 mg, 78%); mp 138-139 °C (CH_2Cl_2) [Lit.[31] 140-141 °C]; $[\alpha]_D^{25}$ −8.0 (*c* 1.02, $CHCl_3$) [Lit.[31] $[\alpha]_D^{22}$ −8.1 (*c* 1.3, $CHCl_3$)]; ν_{max} (solid/cm^{-1}) 3286 (N-H), 3059, 3035, 2975, 2930 (C-H), 1682 (C=O), 1641 (C=O); δ_H (500 MHz, $CDCl_3$) 1.37 (d, *J* 6.9, 3H, CH_3), 4.28-4.32 (m, 1H, CH), 4.34 (dd, *J* 15.0, 5.7, 1H, C*H*HPh), 4.41 (dd, *J* 15.0, 5.6, 1H, CH*H*Ph), 4.98 (d, *J* 12.1, 1H, OC*H*H), 5.01 (d, *J* 12.1, 1H, OCH*H*), 5.68 (br d, *J* 6.5, 1H, N*H*CH), 6.88 (br s, 1H, N*H*CH_2), 7.18-7.35 (m, 10H, ArH); δ_C (125 MHz, $CDCl_3$) 18.9, 43.5, 50.7, 67.0, 127.5, 127.7, 128.1, 128.3, 128.6, 128.7, 136.2, 138.1, 156.1, 172.5; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiracel Daicel AD): t_R (L) = 5.13 min (95%), t_R (D) = 7.88 min (5%).

Boc-Sarcosine-benzylamide 65e



Yellow solid (265 mg, 95%); mp 82-84 °C (CH_2Cl_2) [Lit.[137] 83-85 °C]; ν_{max} (solid/cm^{-1}) 3310 (N-H), 3067, 2978, 2931 (C-H), 1664 (C=O), 1685 (C=O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.40 (s, 9H, $C(CH_3)_3$), 2.90 (s, 3H, CH_3N), 3.83 (s, 2H, CH_2CO), 4.41 (d, *J* 5.9, 2H, CH_2NH), 6.52 (br s, 1H, NH), 7.19-7.24 (m, 3H, ArH), 7.25-7.31 (m, 2H, ArH); δ_C (100 MHz, $CDCl_3$, 58 °C) 28.2, 35.7, 43.3, 53.4, 80.6, 127.3, 127.5, 128.6, 138.2, 155.9, 169.1; Found (EI): $[M]^+$ 278.16290 $C_{15}H_{22}O_3N_2$, requires 278.16249.

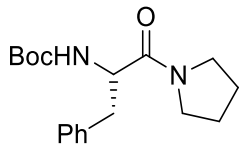
Boc-L-Alanine pyrrolidine amide 66a



Colourless oil (135 mg, 59%); $[\alpha]_D^{25}$ −6.4 (*c* 1.1, $CHCl_3$) [Lit.[31] $[\alpha]_D^{24}$ −6.8 (*c* 1.1, $CHCl_3$)]; ν_{max} (film/cm^{-1}) 3300 (N-H), 2976, 2936, 2879 (C-H), 1705 (C=O), 1636 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24 (d, *J* 6.8, 3H, CH_3CH), 1.36 (s, 9H, $C(CH_3)_3$), 1.76-1.84 (m, 2H, C$H_2$$CH_2$N), 1.91 (app qn, *J* 6.8, 2H, C$H_2$$CH_2$N), 3.31-3.39 (m, 2H, CH_2N), 3.41-3.49 (m, 1H, C*H*HN), 3.51-3.58 (m, 1H, CH*H*N), 4.37 (app qn, *J* 6.8, 1H,

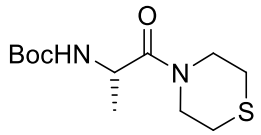
CH), 5.50 (br d, *J* 7.8, 1H, NH); δ_C (100 MHz, $CDCl_3$) 18.6, 24.1, 26.0, 28.3, 45.9, 46.2, 47.8, 79.3, 155.1, 171.2; Found (EI): $[M+H]^+$ 243.17132 $C_{12}H_{23}O_3N_2$, requires 243.17086; HPLC measured as benzoyl derivative (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiracel Daicel OD): t_R (D) = 15.79 min (<1%), t_R (L) = 23.58 min (>99%).

Boc-L-Phenylalanine pyrrolidine amide 66b



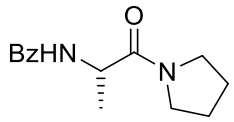
Colourless oil (115 mg, 37%); $[\alpha]_D^{25}$ +37.2 (*c* 1.0, $CHCl_3$) [Lit.[31] $[\alpha]_D^{20}$ +37.5 (*c* 1.0, $CHCl_3$)]; ν_{max} (film/cm^{-1}) 3432 (N-H), 2979, 2880 (C-H), 1702 (C=O), 1631 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (s, 9H, $C(CH_3)_3$), 1.47-1.77 (m, 4H, 2×C*H*$_2$C*H*$_2$N), 2.52-2.59 (m, 1H, C*H*HN), 2.90-3.01 (m, 2H, CH_2Ph), 3.25-3.46 (m, 3H, C*H*$_2$NCH*H*), 4.53-4.61 (m, 1H, CH), 5.49 (br d, *J* 8.6, 1H, NH), 7.16-7.28 (m, 5H, ArH); δ_C (100 MHz, $CDCl_3$) 24.0, 25.7, 28.3, 40.2, 45.7, 46.2, 53.6, 79.5, 126.8, 128.3, 129.4, 136.6, 155.1, 170.0; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiracel Daicel OD): t_R (D) = 10.09 min (4%), t_R (L) = 13.21 (96%).

Boc-L-Alanine thiomorpholine amide 66c



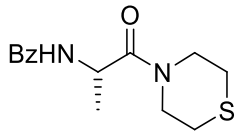
Yellow solid (113 mg, 41%); mp 65-68 ˚C (CH_2Cl_2); $[\alpha]_D^{25}$ −3.8 (*c* 1.03, $CHCl_3$); ν_{max} (solid/cm^{-1}) 3317 (N-H), 2980, 2927 (C-H), 1699 (C=O), 1638 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (d, *J* 6.8, 3H, C*H*$_3$CH), 1.43 (s, 9H, $C(CH_3)_3$), 2.53-2.61 (m, 2H, CH_2S), 2.63-2.76 (m, 2H, CH_2S), 3.65-3.75 (m, 2H, CH_2N), 3.80-3.89 (m, 1H, C*H*HN), 3.99-4.08 (m, 1H, CH*HN*), 4.59 (app qn, *J* 7.2, 1H, CH), 5.52 (br d, *J* 8.0, 1H, NH); δ_C (100 MHz, $CDCl_3$) 19.3, 27.3, 27.9, 28.4, 44.8, 46.1, 48.1, 79.6, 155.0, 171.3; Found (EI): $[M]^+$ 274.13515 $C_{12}H_{22}O_3N_2S$, requires 274.13456; HPLC measured as benzoyl derivative (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiracel Daicel OD): t_R (D) = 22.20 min (8%), t_R (L) = 31.86 min (92%).

Benz-L-Alanine-pyrrolidine amide 66d



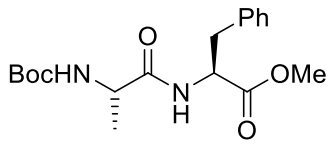
White solid (118 mg, 49%); mp 89-91 ˚C (PE/EtOAc); ν_{max} (solid/cm^{-1}) 3301 (N-H), 3061, 2975, 2877 (C-H), 1724 (C=O), 1629 (C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (d, *J* 6.8, 3H, C*H*$_3$CH), 1.81-1.89 (m, 2H, C*H*$_2$CH$_2$N), 1.96 (quintet, *J* 6.7, 2H, C*H*$_2$CH$_2$N), 3.39-3.54 (m, 3H, CH$_2$N and C*H*HN), 3.65 (dt, *J* 10.1, 6.7, 1H, CH*H*N), 4.90 (quintet, *J* 7.0, 1H, CH), 7.34-7.40 (m, 2H, ArH), 7.41-7.47 (m, 2H, ArH and NH), 7.77-7.81 (m, 2H, ArH); δ_C (100 MHz, $CDCl_3$) 18.3, 24.1, 26.0, 46.1, 46.4, 47.3, 127.1, 128.4, 131.5, 134.1, 166.4, 171.0; Found (ES): $[M-H]^+$ 245.1290 $C_{14}H_{17}N_2O_2$, requires 245.1291; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiracel Daicel OD): t_R (D) = 17.08 min (2%), t_R (L) = 28.56 min (98%).

Benz-L-Alanine-thiomorpholine amide 66e



White solid (120 mg, 45%); mp 137-138 ˚C (PE/EtOAc); ν_{max} (solid/cm^{-1}) 3310 (N-H), 3059, 2981, 2918 (C-H), 1631 (C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (d, *J* 6.9, 3H, CH_3), 2.52-2.77 (m, 4H, 2 × CH_2S), 3.69-3.80 (m, 2H, CH_2N), 3.89 (ddd, *J* 2.8, 6.6, 14.0, 1H, C*H*HN), 4.04 (ddd, *J* 2.8, 6.6, 13.3, 1H, CH*H*N), 5.07 (quintet, *J* 6.9, 1H, C*H*CH$_3$), 7.37-7.51 (m, 4H, ArH and NHBz), 7.78-7.83 (m, 2H, ArH); δ_C (100 MHz, $CDCl_3$) 19.1, 27.4, 27.9, 44.9, 45.6, 48.2, 127.1, 128.5, 131.6, 134.0, 166.4, 171.1; Found (ES): $[M-H]^+$ 277.1011 $C_{14}H_{17}N_2O_2S$, requires 277.1011; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiracel Daicel OD): t_R (D) = 24.26 min (4%), t_R (L) = 34.28 min (96%).

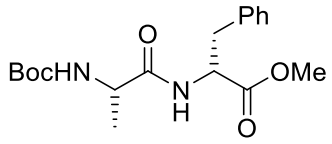
Boc-L-Ala-L-Phe-OMe 67a



Yellow solid (208 mg, 64%); mp 82-84 ˚C (CH_2Cl_2) [Lit.[138] 85-86 °C]; $[\alpha]_D^{25}$ +23.2 (*c* 1.01, $CHCl_3$) [Lit.[139] $[\alpha]_D$ +23.0 (*c* 0.61, $CHCl_3$)]; ν_{max} (solid/cm^{-1}) 3285 (N-H), 3061,

3030, 2926 (C-H), 1636 (C=O), 1547 (C=O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.27 (d, *J* 7.0, 3H, C*H*$_3$CH), 1.41 (s, 9H, (C*H*$_3$)$_3$C), 3.04 (dd, *J* 13.9, 6.6, 1H, C*H*HPh), 3.12 (dd, *J* 13.9, 6.1, 1H, CH*H*Ph), 3.64 (s, 3H, OCH_3), 4.13 (quintet, *J* 7.0, 1H, C*H*CH_3), 4.81 (dt, *J* 7.6, 6.3, 1H, C*H*CH_2), 5.16 (br d, *J* 7.6, 1H, N*H*$CHCH_2$), 6.71 (br d, *J* 7.3, 1H, N*H*$CHCH_3$), 7.08-7.12 (m, 2H, ArH), 7.15-7.26 (m, 3H, ArH); δ_C (100 MHz, $CDCl_3$, 58 °C) 18.1, 28.2, 38.0, 50.4, 51.9, 53.3, 79.9, 126.9, 128.4, 129.2, 136.0, 155.3, 171.7, 172.4.

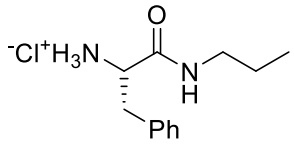
Boc-L-Ala-DL-Phe-OMe 67b



Yellow solid (136 mg, 42%); mp 93-95 ˚C (CH_2Cl_2); $[\alpha]_D^{25}$ −58.9 (*c* 0.99, $CHCl_3$); ν_{max} (solid/cm^{-1}) 3283 (N-H), 3254 (N-H), 3134, 3060, 3024 (C-H), 1655 (C=O), 1599 (C=O), 1544 (C=O); δ_H (600 MHz, $CDCl_3$) 1.27 (d, *J* 7.1, 3H, C*H*$_3$CH), 1.42 (s, 9H, (C*H*$_3$)$_3$C), 3.06 (dd, *J* 13.8, 6.3, 1H, C*H*HPh), 3.13 (dd, *J* 13.8, 5.7, 1H, CH*H*Ph), 3.70 (s, 3H, OCH_3), 4.18 (br t, *J* 7.1, 1H, C*H*CH_3), 4.85 (m, 1H, C*H*CH_2), 5.04 (br d, *J* 5.5, 1H, N*H*$CHCH_2$), 6.70 (br s, 1H, N*H*$CHCH_3$), 7.10 (d, *J* 7.1, 2H, ArH), 7.20-7.24 (m, 1H, ArH), 7.25-7.29 (m, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 18.6, 28.4, 38.0, 50.0, 52.5, 53.2, 80.2, 127.2, 128.7, 129.4, 135.9, 155.5, 171.9, 172.4; Found (ES): $[M+Na]^+$ 373.1720 $C_{18}H_{26}O_5N_2Na$, requires 373.1739.

6.6. Characterisation of unprotected amino acid amides

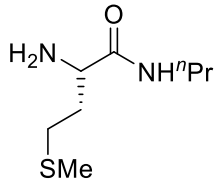
(*S*)-2-Amino-3-phenyl-*N*-propylpropanamide hydrochloride 77a



Off-white solid (118 mg, 90%); mp 150-151 °C [Lit.[140] 155 °C]; $[\alpha]_D^{25}$ +21.7 (*c* 0.62, MeOH) [Lit.[140] $[\alpha]_D$ +62.9 (*c* 0.62, MeOH)]; ν_{max} (solid/cm^{-1}) 3342 (N-H), 2876 (C-H), 1656 (C=O); δ_H (600 MHz, DMSO-d_6) 0.73 (t, *J* 7.5, 3H, CH_3), 1.23-1.36 (m, 2H, C*H*$_2$$CH_3$), 2.86-2.92 (m, 1H, C*H*HPh), 2.99-3.09 (3H, m, CH*H*Ph and NHC*H*$_2$), 3.97 (br s, 1H, C*H*CH_2), 7.22-7.27 (m, 3H, ArH), 7.28-7.33 (m, 2H, ArH), 8.40 (br s, 3H, $NH_3^+Cl^-$), 8.55 (br t, *J* 5.5, 1H, N*H*CH_2); δ_C (150 MHz, DMSO-d_6) 11.4, 22.0, 37.0,

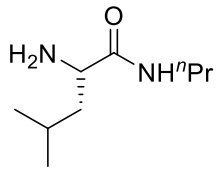
40.4, 53.5, 127.1, 128.4, 129.5, 135.1, 167.5; Found (CI): $[M\text{-}Cl]^+$ 207.149184 $C_{12}H_{19}N_2O$, requires 207.14974

(*S*)-2-Amino-4-(methylthio)-*N*-propylbutanamide 77b



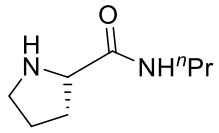
Colourless oil (77 mg, 81%); ν_{max} (solid/cm^{-1}) 3349 (N-H), 2901 (C-H), 1648 (C=O); δ_H (600 MHz, $CDCl_3$) 0.83 (t, *J* 7.4, 3H, CH_3), 1.44 (sextet, *J* 7.3, 2H, C*H*$_2$CH$_3$), 1.49 (br s, 2H, NH_2), 1.63-1.70 (m, 1H, C*H*HCH), 2.01 (s, 3H, SCH_3), 2.01-2.08 (m, 1H, CH*H*CH), 2.51 (t, *J* 7.4, 2H, C*H*$_2$S), 3.11 (q, *J* 6.9, 2H, NHC*H*$_2$), 3.38 (dd, *J* 4.7, 8.1, 1H, CH), 7.27 (br s, 1H, NH); δ_C (150 MHz, $CDCl_3$) 11.5, 15.4, 22.9, 30.7, 34.3, 40.8, 54.4, 174.6; Found (CI): $[M+H]^+$ 191.121334 $C_8H_{19}N_2SO$, requires 191.12181.

(*S*)-2-Amino-4-methyl-*N*-propylpentanamide 77c



Colourless oil (87 mg, 82%); ν_{max} (solid/cm^{-1}) 3325 (n-H), 2849 (C-H), 1661 (C=O); δ_H (600 MHz, $CDCl_3$) 0.83-0.87 (m, 6H, C*H*$_3$CH$_2$ and C*H*$_3$CH), 0.89 (d, *J* 6.4, 3H C*H*$_3$), 1.24-1.29 (m, 1H, C*H*(CH$_3$)$_2$), 1.33-1.49 (m, 4H, NH_2 and C*H*$_2$CH$_3$), 1.58-1.70 (m, 2H, C*H*$_2$CH), 3.30 (dd, *J* 3.8, 9.8, 1H, C*H*NH_2), 3.13 (app. q, *J* 6.6, 2H, NHC*H*$_2$), 7.30 (br s, 1H, NH); δ_C (150 MHz, $CDCl_3$) 11.5, 21.4, 22.9, 23.5, 24.9, 40.7, 44.2, 53.6, 175.7; Found (CI): $[M+H]^+$ 173.165643 $C_9H_{21}N_2O$, requires 173.16539.

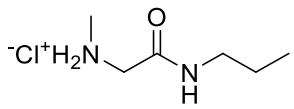
(*S*)-*N*-propylpyrrolidine-2-carboxamide 77e



Colourless oil (67 mg, 86%); $[\alpha]_D^{25}$ −63.2 (*c* 1.0, MeOH); ν_{max} (solid/cm^{-1}) 3325 (N-H), 2899 (C-H), 1660 (C=O); δ_H (600 MHz, $CDCl_3$) 0.84 (t, *J* 7.4, 3H, CH_3), 1.40-1.49 (m, 2H, C*H*$_2$CH$_3$), 1.57-1.67 (m, 2H, CHCH$_2$C*H*$_2$), 1.82 (app sextet, *J* 6.4, 1H, CHC*H*H),

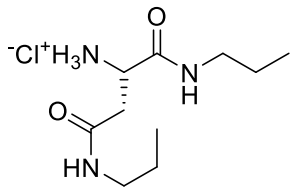
2.00-2.29 (m, 2H, NH and CHCH*H*), 2.81 (dt, *J* 6.3, 10.2, 1H, C*H*HNH), 2.93 (dt, *J* 6.8, 10.2, 1H, CH*H*NH) 3.06-3.16 (m, 2H, CONHCH_2), 3.64 (dd, *J* 5.3, 9.2, 1H, CH), 7.60 (br s, 1H, CONH); δ_C (150 MHz, $CDCl_3$) 11.4, 23.0, 26.3, 30.9, 40.6, 47.3, 60.6, 175.2; Found (CI): $[M+H]^+$ 157.134661 $C_8H_{17}N_2O$, requires 157.13409.

2-(Methylamino)-*N*-propylacetamide hydrochloride 77f



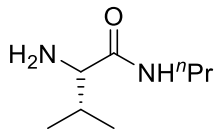
White solid (72 mg, 84%); mp 128-129 °C; ν_{max} (solid/cm^{-1}) 3340 (N-H), 2901 (C-H), 1659 (C=O); δ_H (600 MHz, DMSO-d_6) 0.86 (t, *J* 7.3, 3H, C$H_3$$CH_2$), 1.43 (sextet, *J* 7.3, 2H, C$H_2$$CH_3$), 2.52 (s, 3H, C$H_3$$NH_2^+Cl^-$), 3.07 (m, 2H, C$H_2$$CH_2CH_3$), 3.65 (s, 2H, C$H_2$NH), 8.56 (br s, 1H, NH), 8.99 (br s, 2H, $NH_2^+Cl^-$); δ_C (150 MHz, DMSO-d_6) 11.4, 222, 32.6, 40.4, 48.9, 164.8; Found (CI): $[M-Cl]^+$ 131.117931 $C_6H_{15}N_2O$, requires 131.11844.

(*S*)-2-Amino-*N*^{1},*N*^{4}-dipropylsuccinamide hydrochloride 77g



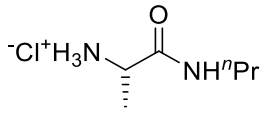
Off-white solid (89 mg, 68%); mp 165-167 °C; ν_{max} (solid/cm^{-1}) 3342 (N-H), 3280 (N-H), 2960, 2930, 2873 (C-H), 1660 (C=O), 1646 (C=O); δ_H (600 MHz, DMSO-d_6) 0.84 (td, *J* 1.9, 7.4, 6H, 2 × CH_3), 1.41 (septet, *J* 6.9, 4H, 2 × C$H_2$$CH_3$), 2.63 (dd, *J* 7.5, 16.1, 1H, CHC*H*H), 2.68 (dd, 5.5, 16.1, 1H, CHCH*H*), 2.96-3.13 (m, 4H, 2 × CH_2), 4.01 (br s, 1H, CH), 8.22 (br s, 3H, $NH_3^+Cl^-$), 8.30 (br t, *J* 5.5, 1H, NH), 8.46 (br t, *J* 5.5, 1H, NH); δ_C (150 MHz, DMSO-d_6) 11.4, 11.5, 22.1, 22.2, 35.9, 40.4, 40.5, 49.5, 167.7, 168.2; Found (CI): $[M-Cl]^+$ 216.170142 $C_{10}H_{22}N_3O_2$, requires 216.17120.

(*S*)-2-Amino-3-methyl-*N*-propylbutanamide 77k



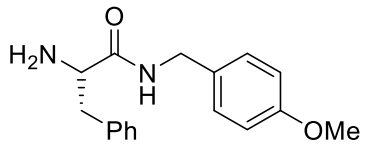
White solid (84 mg, 95%); mp 78-80 °C; $[\alpha]_D^{25}$ −3.8 (*c* 1.0, MeOH); ν_{max} (solid/cm^{-1}) 3311 (N-H), 2900 (C-H); 1645 (C=O); δ_H (600 MHz, $CDCl_3$) 0.73 (t, *J* 7.0, 3H, C*H*$_3$CH), 0.84 (t, *J* 7.4, 3H, C*H*$_3$CH$_2$), 0.90 (d, *J* 7.0, 3H, C*H*$_3$CH), 1.35 (br s, 2H, N*H*$_2$), 1.44 (sextet, *J* 7.4, 2H, C*H*$_2$CH$_3$), 2.16-2.23 (m, C*H*(CH$_3$)$_2$), 3.06-3.20 (m, 3H, C*H*NH$_2$ and C*H*$_2$NH), 7.31 (br s, 1H, NH); δ_C (150 MHz, $CDCl_3$) 11.5, 16.1, 19.8, 23.0, 30.9, 40.7, 60.2, 174.4; Found (CI): $[M+H]^+$ 157.149348 $C_8H_{19}N_2O$, requires 159.14974.

(*S*)-2-Amino-*N*-propylpropanamide hydrochloride 77l



White solid (60 mg, 71%); mp 197-198 °C; ν_{max} (solid/cm^{-1}) 3330 (N-H), 2850 (C-H), 1650 (C=O); δ_H (600 MHz, DMSO-d_6) 0.86 (t, *J* 7.4, 3H, C*H*$_3$CH$_2$), 1.34 (d, *J* 7.2, 3H, C*H*$_3$CH), 1.43 (sextet, *J* 7.2, 2H, C*H*$_2$CH$_3$), 3.01-3.12 (m, 2H, C*H*$_2$NH), 3.79 (br quint, *J* 6.0, 1H, C*H*), 8.21 (br s, 3H, $NH_3^+Cl^-$), 8.49 (br t, *J* 5.5, 1H, NH); δ_C (150 MHz, DMSO-d_6) 11.4, 17.3, 22.2, 40.4, 48.2, 169.3; Found (CI): $[M-Cl]^+$ 131.118930, $C_6H_{15}N_2O$, requires 131.11844.

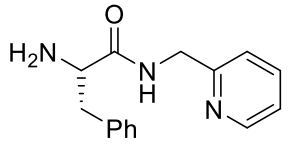
(*S*)-2-Amino-*N*-(4-methoxybenzyl)-3-phenylpropanamide 78b



White solid (122 mg, 86%); mp 78-80 °C; $[\alpha]_D^{25}$ +3.9 (*c* 1.0, MeOH); ν_{max} (solid/cm^{-1}) 3295 (N-H), 2890 (C-H), 1670 (C=O); δ_H (600 MHz, $CDCl_3$) 1.42, (br s, 2H, NH_2), 2.73 (dd *J* 9.2, 13.7, 1H, C*H*HPh), 3.29 (dd, *J* 4.1, 13.7, 1H, CH*H*Ph), 3.63 (dd, *J* 4.1, 9.2, 1H, C*H*NH$_2$), 3.79 (s, 3H, CH_3), 4.33-4.41 (m, 2H, C*H*$_2$NH), 6.83-6.86 (m, 2H, ArH), 7.14-7.18 (m, 2H, ArH), 7.20-7.26 (m, 3H, ArH), 7.28-7.32 (m, 2H, ArH), 7.52 (br s, 1H, NH); δ_C (150 MHz, $CDCl_3$) 41.1, 42.7, 55.4, 56.6, 114.1, 126.9, 128.8, 129.2,

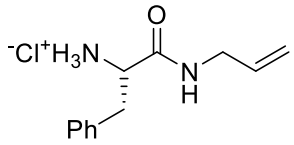
129.5, 130.6, 138.0159.0, 174.1; Found (CI): $[M+H]^+$ 285.160994 $C_{17}H_{21}N_2O_2$, requires 285.16030.

(*S*)-2-Amino-3-phenyl-*N*-(pyridin-2-ylmethyl)propanamide 78c



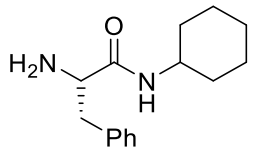
Light brown solid (112 mg, 88%); mp 109-110 °C; $[\alpha]_D^{25}$ −6.1 (*c* 1.0, MeOH); ν_{max} (solid/cm^{-1}) 3351 (N-H), 2872 (C-H), 1640 (C=O); δ_H (600 MHz, $CDCl_3$) 1.63 (br s, 2H, NH_2), 2.73 (dd, *J* 9.5, 13.8, 1H, PhC*H*H), 3.30 (dd, *J* 4.0, 13.8, 1H, PhCH*H*), 3.68 (dd, *J* 4.0, 9.5, 1H, C*H*CO), 4.57 (d, *J* 5.3, 2H, CONHCH_2), 7.18 (dd, *J* 5.2, 7.0, 1H, ArH), 7.20-7.25 (m, 4H, ArH), 7.27-7.31 (m, 2H, ArH), 7.64 (td, *J* 1.6, 7.7, 1H, ArH), 8.17 (br s, 1H, NH), 8.53 (d, *J* 4.4, 1H, ArH); δ_C (150 MHz, $CDCl_3$) 41.2, 44.5, 56.8, 122.1, 122.4, 126.9, 128.8, 129.4, 136.9, 138.1, 149.3, 157.0, 174.5; Found (CI): $[M+H]^+$ 256.144138 $C_{15}H_{18}N_3O$, requires 256.14499.

(*S*)-*N*-Allyl-2-amino-3-phenylpropanamide hydrochloride 78f



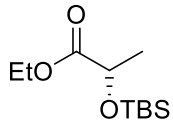
Brown solid (107 mg, 89%); mp 125-126 °C; $[\alpha]_D^{25}$ −6.0 (*c* 1.0, MeOH); ν_{max} (solid/cm^{-1}) 3280 (N-H), 2983 (C-H), 1650 (C=O); δ_H (600 MHz, DMSO-d_6) 3.05 (d, *J* 7.2, 2H, CH_2CH), 3.61-3.67 (m, 1H, NHC*H*H), 3.71-3.77 (m, 1H, NHCH*H*), 4.01 (m, 1H, C*H*$NH_3^+Cl^-$), 4.98-5.02 (m, 2H, CH_2=CH), 5.64-5.71 (m, 1H, C*H*=CH_2), 7.23-7.29 (m, 3H, ArH), 7.30-7.34 (m, 2H, ArH), 8.40 (br m, 3H, $NH_3^+Cl^-$), 8.68 (br m, 1H, NH); δ_C (150 MHz, DMSO-d_6) 37.0, 40.9, 53.5, 115.7, 127.1, 128.5, 129.5, 134.3, 135.1, 167.6; Found (CI): $[M-Cl]^+$ 205.133821 $C_{12}H_{17}N_2O$, requires 205.13409.

(*S*)-2-Amino-*N*-cyclohexyl-3-phenylpropanamide 77h



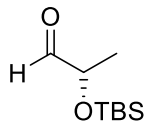
Pale brown solid (85 mg, 65%); mp 95-97 °C [Lit.[141] 96 °C]; $[\alpha]_D^{25}$ −15.7 (*c* 0.2, $CHCl_3$); ν_{max} (solid/cm^{-1}) 3400 (N-H), 2845 (C-H), 1649 (C=O); δ_H (600 MHz, $CDCl_3$) 1.05-1.19 (m, 3H, 3 × Cy-H), 1.29-1.49 (m, 4H, NH_2 and 2 × Cy-H), 1.55-1.61 (m, 1H, 1 × Cy-H), 1.63-1.70 (m, 2H, 2 × Cy-H), 1.80-1.88 (m, 2H, 2 × Cy-H), 2.69 (dd, *J* 9.1, 13.7, 1H, C*H*H), 3.22 (dd, *J* 4.3, 13.7, 1H, CH*H*), 3.55 (dd, *J* 4.3, 9.1, 1H, C*H*NH_2), 3.69-3.77 (m, 1H, C*H*NH), 7.08 (br d, *J* 7.2, 1H, NH), 7.18-7.24 (m, 3H, ArH), 7.27-7.31 (m, 2H, ArH); δ_C (150 MHz, $CDCl_3$) 24.9, 25.6, 33.1, 33.2, 41.2, 47.7, 56.5, 126.9, 128.8, 129.4, 138.1, 173.3; Found (CI): $[M+H]^+$ 247.180811 $C_{15}H_{23}N_2O$, requires 247.18104.

Ethyl (*S*)-2-((tert-butyldimethylsilyl)oxy)propanoate 80



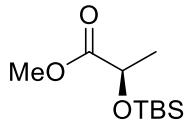
tert-Butylchlorodimethylsilane (16.0 g, 0.11 mol, 1.2 equiv.), was added to a stirring solution of *S*-ethyl lactate (10 mL, 0.09 mol, 1 equiv.) and imidazole (9.0 g, 0.13 mol, 1.4 equiv.) in DMF (88 mL). The solution was stirred for 30 min at rt, water (150 mL) was added and the reaction mixture extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give **80** as a colourless oil (20.49 g, 0.088 mol, 98%); δ_H (400 MHz, $CDCl_3$) 0.07 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.40 (d, *J* 6.8, 3H, C*H*$_3$CH), 3.73 (s, 3H, CH_3O), 4.31 (q, *J* 6.8, 1H, C*H*CH_3), 4.11-4.25 (m, 2H, C*H*$_2CH_3$); δ_C (100 MHz, $CDCl_3$) -5.3, -5.0, 14.2, 18.3, 21.3, 25.7, 60.7, 68.5, 174.1.

(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propanal (*S*)-81



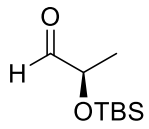
Diisobutylaluminium hydride (44 mL, 1.1 M in cyclohexane, 48.4 mmol, 1.6 equiv.) was added dropwise (20 mL/h) to a stirring solution of ester **80** (7 g, 30.1 mmol, 1 equiv.) in Et_2O (200 mL) at -100 °C. After completion of addition, the reaction was stirred for 10 min at -78 °C then quenched by dropwise addition of MeOH (2 mL) and H_2O (5 mL). After warming to rt and stirring for 1.5 h Na_2SO_4 and $MgSO_4$ were added and the suspension stirred for 15 min, then filtered through a short plug of celite and silica eluting with Et_2O. The filtrate was concentrated under reduced pressure and the residue distilled to give aldehyde (*S*)-**81** as a colourless liquid (4.56 g, 24.2 mmol, 80%); bp 79-81 °C (19 Torr) [Lit.[142] 67-68 °C (14 Torr)]; δ_H (600 MHz, $CDCl_3$) 0.08 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.27 (d, *J* 6.9, $CHCH_3$), 4.08 (qd, *J* 1.2, 6.9, $CHCH_3$), 9.60 (d, *J* 1.2, CHO); δ_C (150 MHz, $CDCl_3$) -4.7, -4.6, 18.3, 18.6, 25.8, 73.9, 204.4.

Methyl (*R*)-2-((*tert*-butyldimethylsilyl)oxy)propanoate



tert-Butylchlorodimethylsilane (18.0 g, 0.12 mol, 1.2 equiv.), was added to a stirring solution of *R*-methyl lactate (10 mL, 0.10 mol, 1 equiv.) and imidazole (10.0 g, 0.15 mol, 1.5 equiv.) in DMF (90 mL). The solution was stirred for 30 min at rt, water (150 mL) was added and the reaction mixture extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the ester as a colourless oil (17.85 g, 81.7 mmol, 82%); δ_H (400 MHz, $CDCl_3$) 0.07 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.28 (t, *J* 7.1, 3H, CH_3CH_2), 1.40 (d, *J* 6.8, 3H, CH_3CH), 4.34 (q, *J* 6.8, 1H, $CHCH_3$), 4.11-4.25 (m, 2H, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) -5.3, -5.0, 18.3, 21.4, 25.7, 68.4, 51.8, 51.9, 174.6.

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)propanal (*R*)-81



Diisobutylaluminium hydride (47 mL, 1.1 M in cyclohexane, 51.7 mmol, 1.6 equiv.) was added dropwise (20 mL/h) to a stirring solution of methyl (*R*)-2-((*tert*-butyldimethylsilyl)oxy)propanoate (7 g, 32.1 mmol, 1 equiv.) in Et_2O (200 mL) at -100 °C. After completion of addition, the reaction was stirred for 10 min at -78 °C then quenched by dropwise addition of MeOH (2 mL) and H_2O (5 mL). After warming to rt and stirring for 1.5 h Na_2SO_4 and $MgSO_4$ were added and the suspension stirred for 15 min, then filtered through a short plug of celite and silica eluting with Et_2O. The filtrate was concentrated under reduced pressure and the residue distilled to give aldehyde (*R*)-**81** as a colourless liquid (4.35 g, 23.1 mmol, 72%); bp 83-86 °C (28 Torr); δ_H (600 MHz, $CDCl_3$) 0.08 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.27 (d, *J* 6.9, $CHCH_3$), 4.08 (qd, *J* 1.0, 6.8, $CHCH_3$), 9.60 (d, *J* 1.0, CHO); δ_C (150 MHz, $CDCl_3$) -4.72, -4.66, 18.3, 18.6, 25.8, 73.9, 204.4.

7. Appendix

7.1. Appendix 1 – Determination of enantiomeric excess by HPLC and derivatisation

Compounds **6h** and **6i** were converted to the corresponding *N*-benzoyl derivatives **6k** and **6l** as described below in order to measure the enantiomeric ratio.

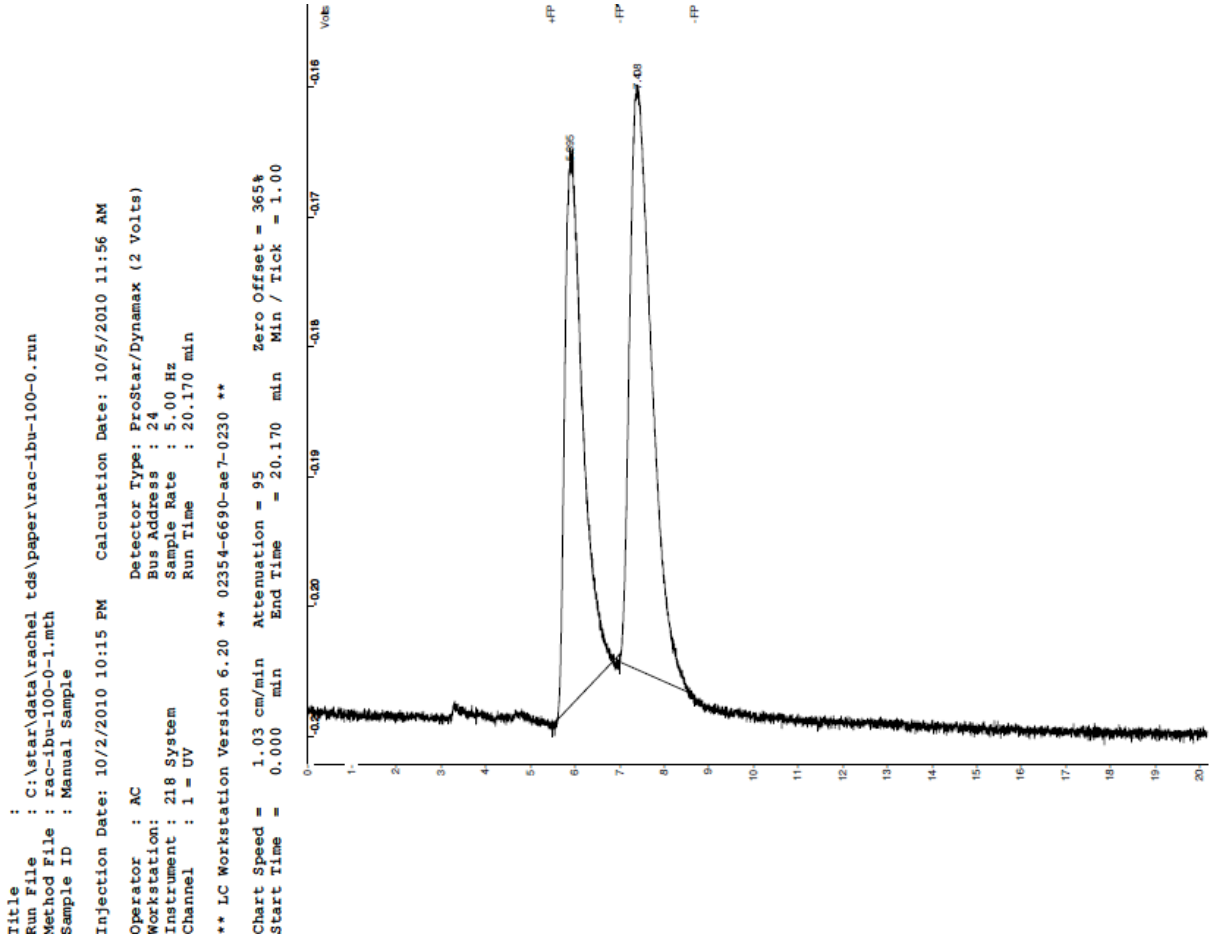
Representative Procedure for Boc deprotection

Boc-L-Alanine pyrrolidine amide was stirred in a 1:1 solution of TFA and CH_2Cl_2 (5 ml) for 1 h. The reaction mixture was the concentrated *in vacuo* to yield the crude salt. The product was carried forward to the next step without further purification.

Representative Procedure for benzoyl protection

Benzoyl chloride (2 equiv.) was added dropwise to L-alanine pyrrolidine amide TFA salt (1 equiv.) and triethylamine (3 equiv.) in CH_2Cl_2 at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then diluted with CH_2Cl_2, washed with water (10 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (PE-EtOAc 2:1) to yield the *N*-benzoyl amino acid amide.

(±)-*N*-Benzyl-2-(4-isobutylphenyl)propanamide



Print Date: Tue Oct 05 13:18:30 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\rac-ibu-100-0.run
Method File : rac-ibu-100-0-1.mth
Sample ID : Manual Sample

Injection Date: 10/2/2010 10:15 PM Calculation Date: 10/5/2010 11:56 AM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 = UV

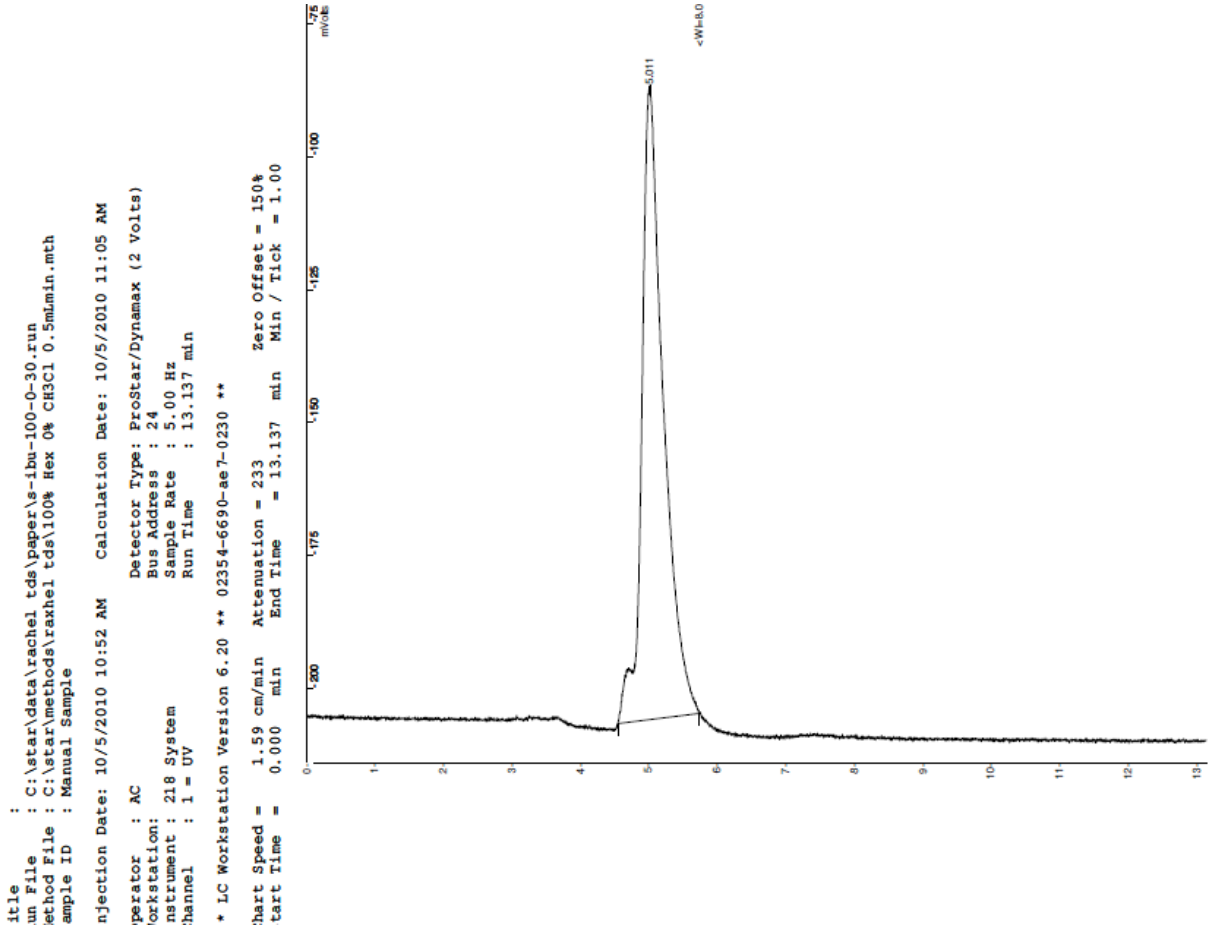
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 20.170 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		43.5612	5.895	0.000	1194116	BB	26.2	
2		56.4388	7.408	0.000	1547124	BB	31.5	
	Totals:	100.0000		0.000	2741240			

(*S*)-*N*-Benzyl-2-(4-isobutylphenyl)propanamide 58s



Print Date: Tue Oct 05 13:19:27 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\s-1bu-100-0-30.run
Method File : C:\star\methods\raxhel tds\100% Hex 0% CH3Cl 0.5mLmin.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 10:52 AM Calculation Date: 10/5/2010 11:05 AM

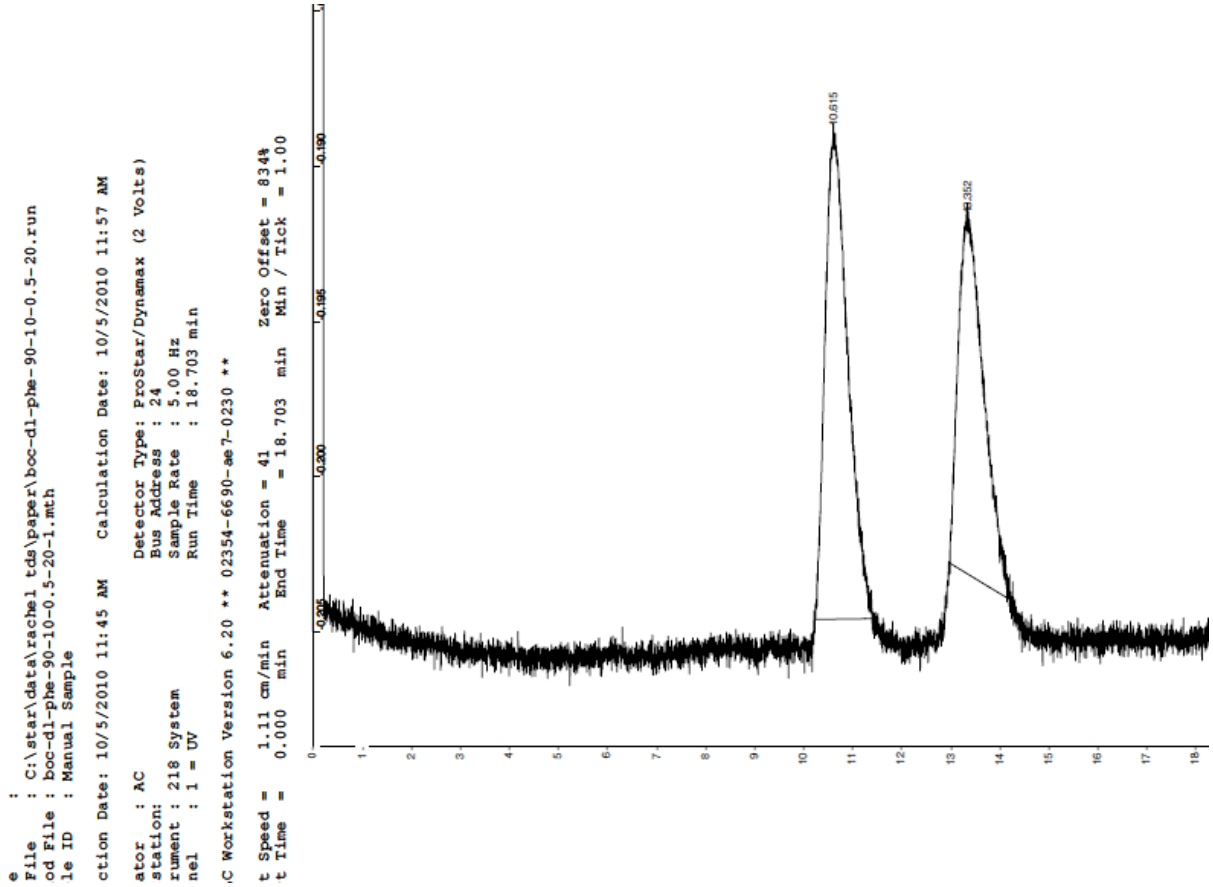
Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 - UV Run Time : 13.137 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		100.0000	5.011	0.000	2624127	BB	19.0	
	Totals:	100.0000		0.000	2624127			

Boc-DL-Phenylalanine-benzylamide



Print Date: Tue Oct 05 13:08:07 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\boc-dl-phe-90-10-0.5-20.run
Method File : boc-dl-phe-90-10-0.5-20-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 11:45 AM Calculation Date: 10/5/2010 11:57 AM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV

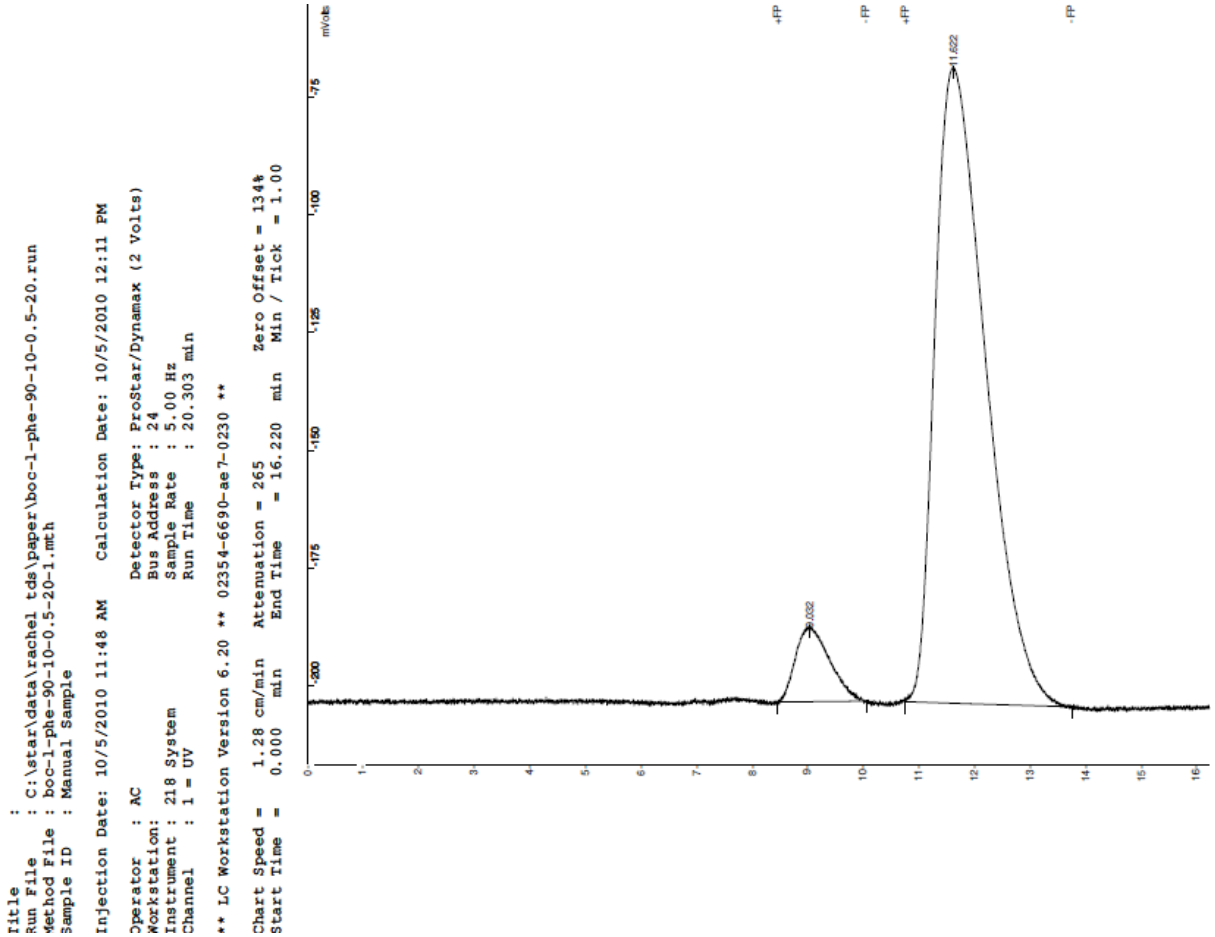
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 18.703 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		54.8020	10.615	0.000	505270	BB	29.9	
2		45.1980	13.352	0.000	416721	BB	31.0	
	Totals:	100.0000		0.000	921991			

Boc-L-Phenylalanine-benzylamide 65a



Print Date: Tue Oct 05 12:55:10 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\boc-l-phe-90-10-0.5-20.run
Method File : boc-l-phe-90-10-0.5-20-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 11:48 AM Calculation Date: 10/5/2010 12:11 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 = UV
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 20.303 min

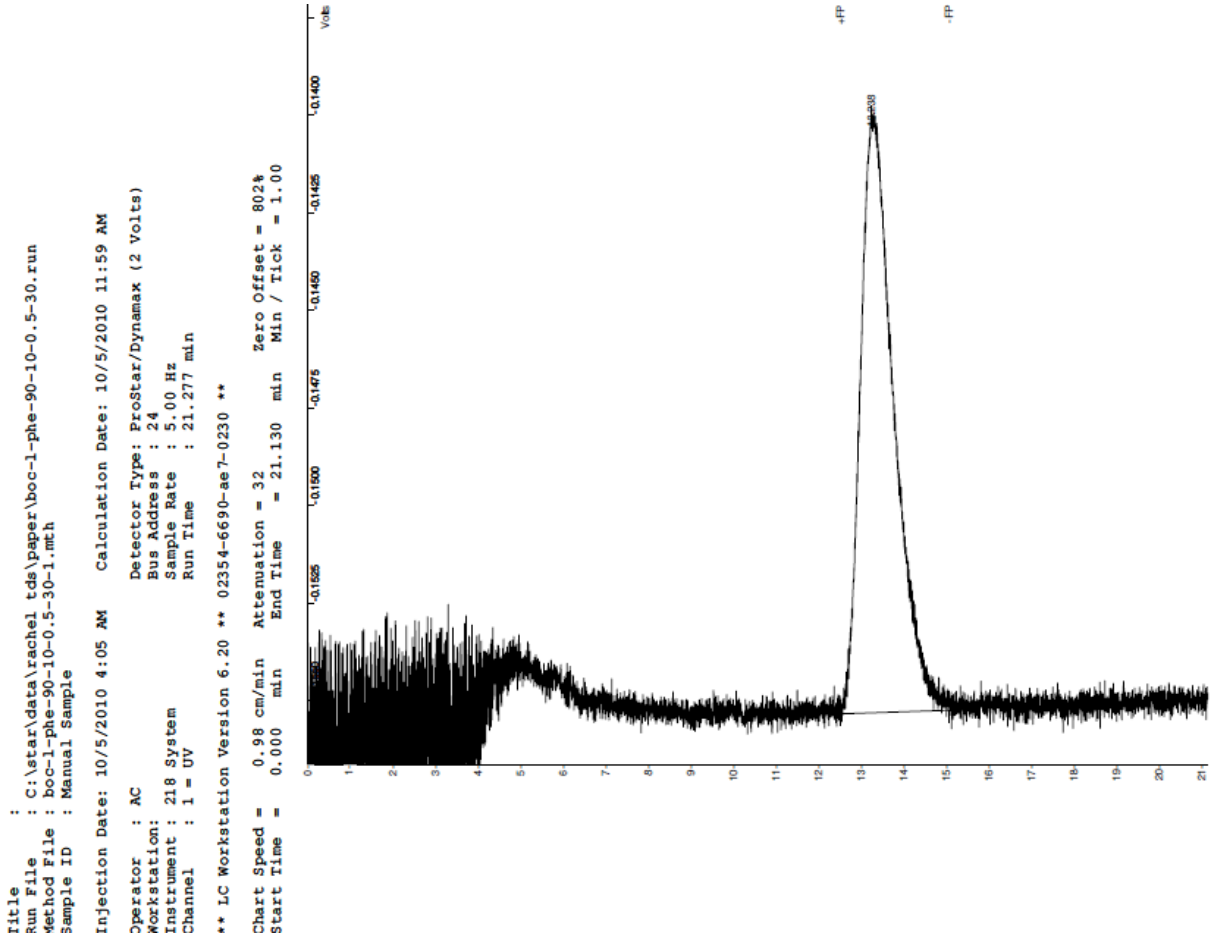
** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		7.3005	9.032	0.000	674385	BB	40.5	
2		92.6995	11.622	0.000	8563088	BB	59.5	
	Totals:	100.0000		0.000	9237473			

Total Unidentified Counts : 9237473 counts

Boc-L-Phenylalanine-benzylamide 65a (8 h reaction time)



Print Date: Tue Oct 05 13:08:48 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\boc-l-phe-90-10-0.5-30.run
Method File : boc-l-phe-90-10-0.5-30-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 4:05 AM Calculation Date: 10/5/2010 11:59 AM

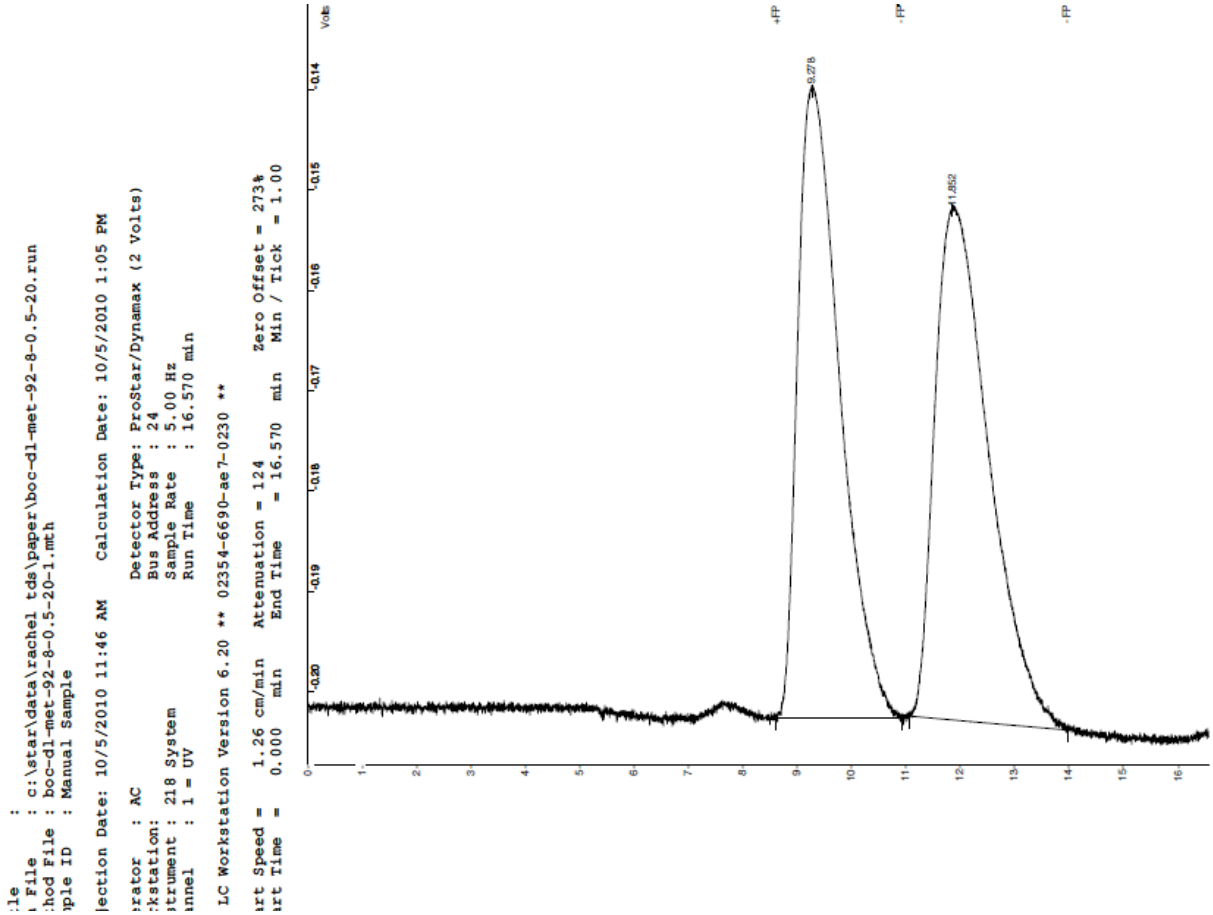
Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 - UV Run Time : 21.277 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		100.0000	13.238	0.000	835578	BB	48.4	
Totals:		100.0000		0.000	835578			

Boc-DL-Methionine-benzylamide



Print Date: Tue Oct 05 13:05:35 2010 Page 1 of 1

Title :
Run File : c:\star\data\rachel tds\paper\boc-dl-met-92-8-0.5-20.run
Method File : boc-dl-met-92-8-0.5-20-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 11:46 AM Calculation Date: 10/5/2010 1:05 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV

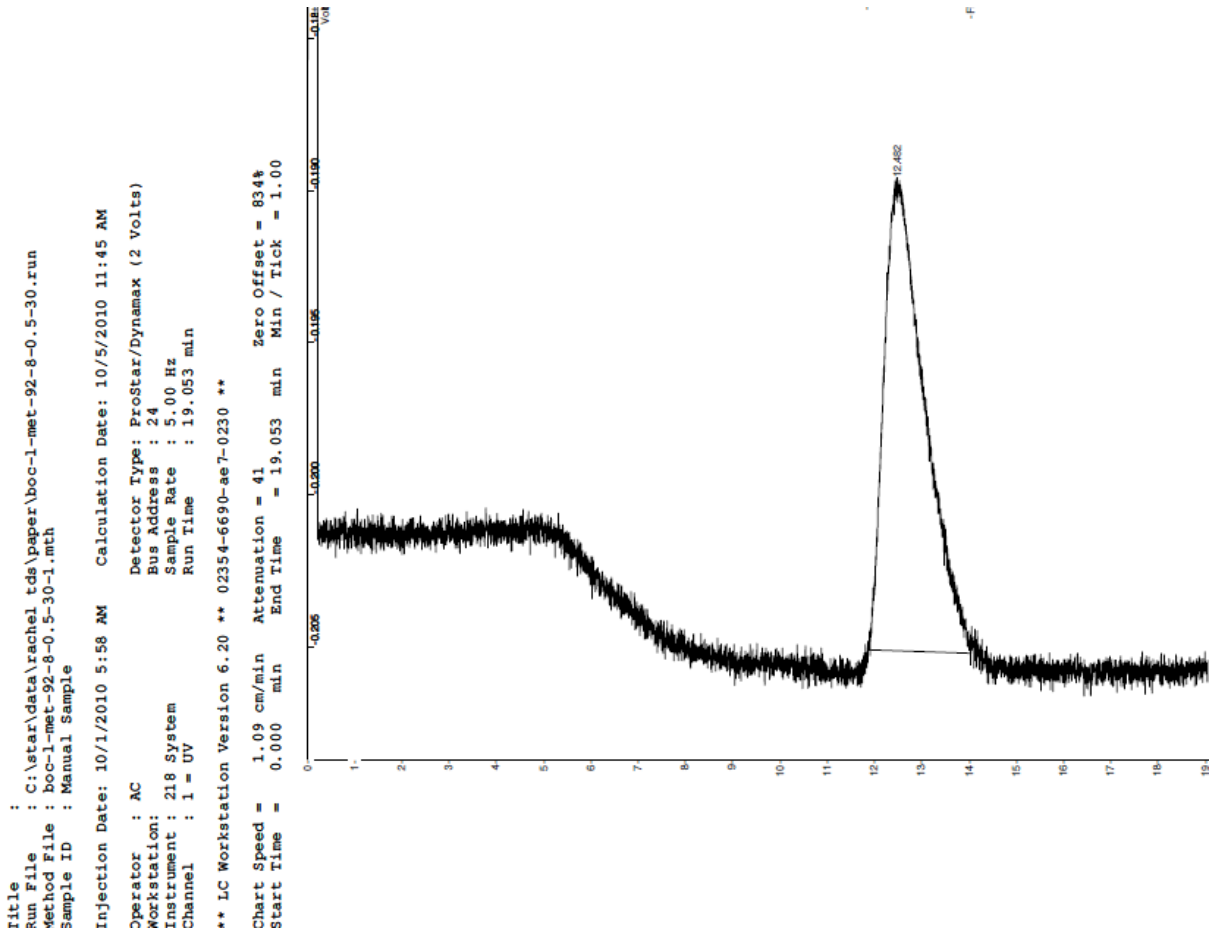
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 16.570 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		49.0595	9.278	0.000	3391570	BB	49.7	
2		50.9406	11.852	0.000	3521614	BB	62.9	
	Totals:	100.0001		0.000	6913184			

Boc-L-Methionine-benzylamide 65b



Print Date: Tue Oct 05 13:06:20 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\boc-l-met-92-8-0.5-30.run
Method File : boc-l-met-92-8-0.5-30-1.mth
Sample ID : Manual Sample

Injection Date: 10/1/2010 5:58 AM Calculation Date: 10/5/2010 11:45 AM

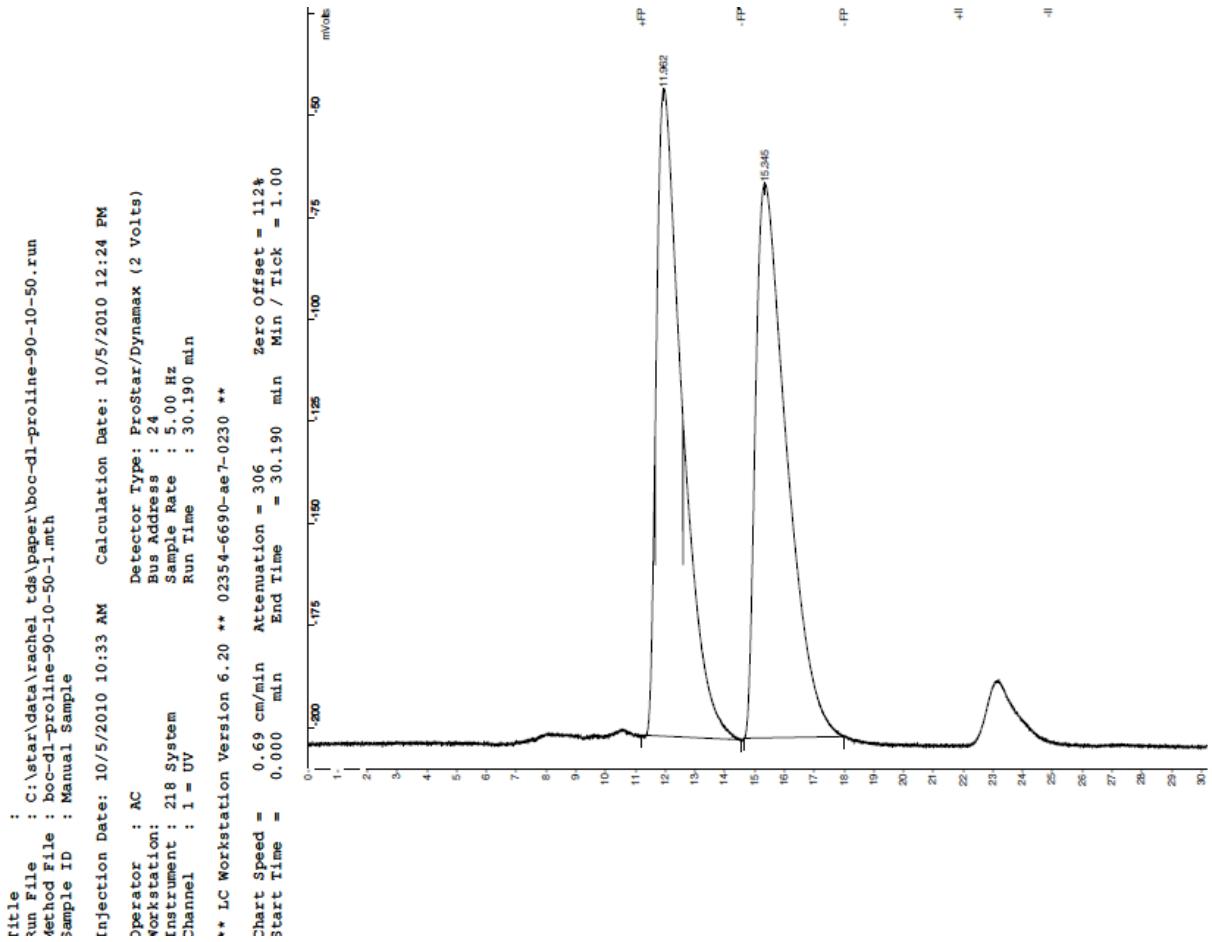
Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 - UV Run Time : 19.053 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		100.0000	12.482	0.000	919716	BB	55.2	
Totals:		100.0000		0.000	919716			

Boc-DL-Proline-benzylamide



Print Date: Tue Oct 05 13:14:30 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\boc-dl-proline-90-10-50.run
Method File : boc-dl-proline-90-10-50-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 10:33 AM Calculation Date: 10/5/2010 12:24 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV

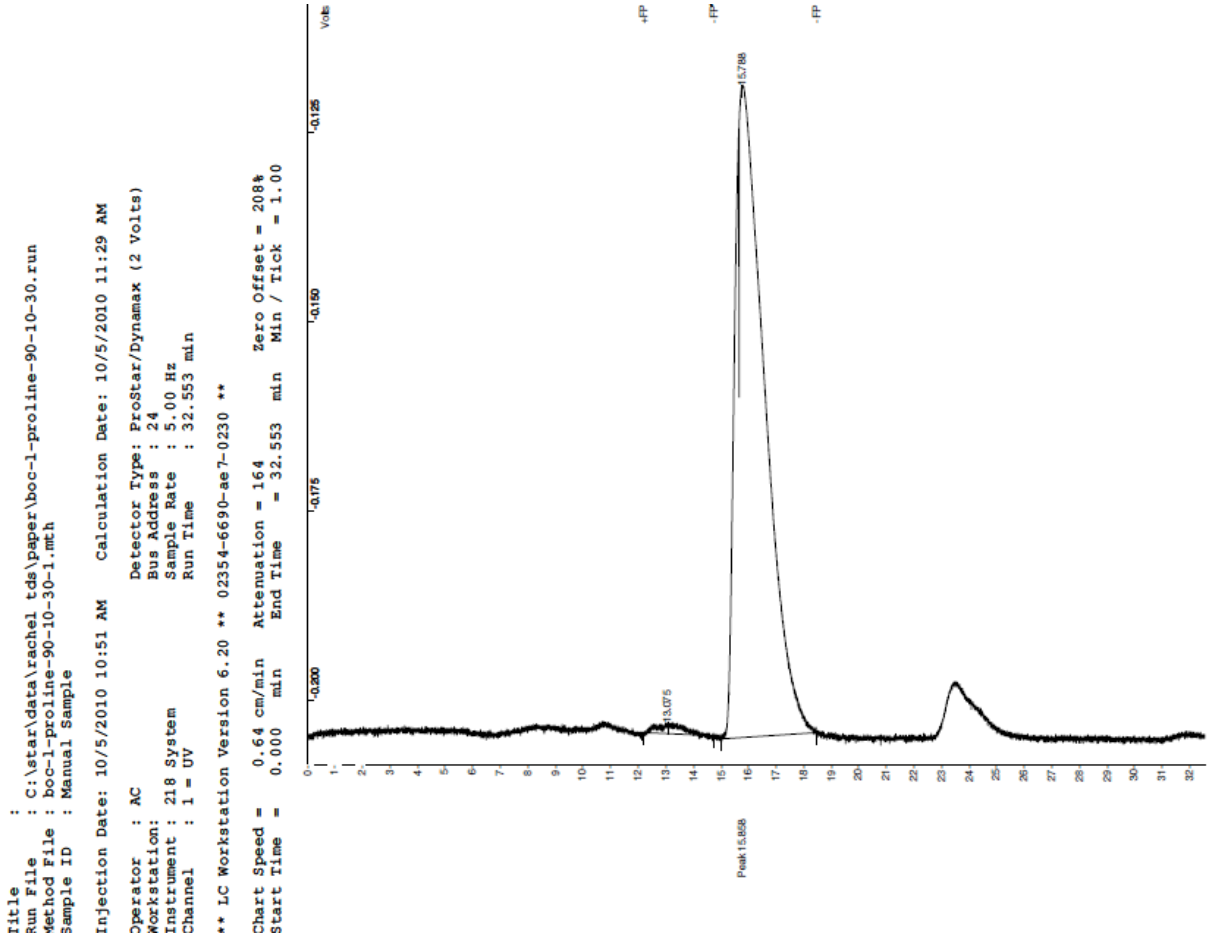
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 30.190 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		49.3556	11.962	0.000	9605417	BB	54.5	
2		50.6444	15.345	0.000	9856222	BB	67.0	
	Totals:	100.0000		0.000	19461639			

Boc-L-Proline-benzylamide 65c



Print Date: Tue Oct 05 13:13:45 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\boc-l-proline-90-10-30.run
Method File : boc-l-proline-90-10-30-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 10:51 AM Calculation Date: 10/5/2010 11:29 AM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV

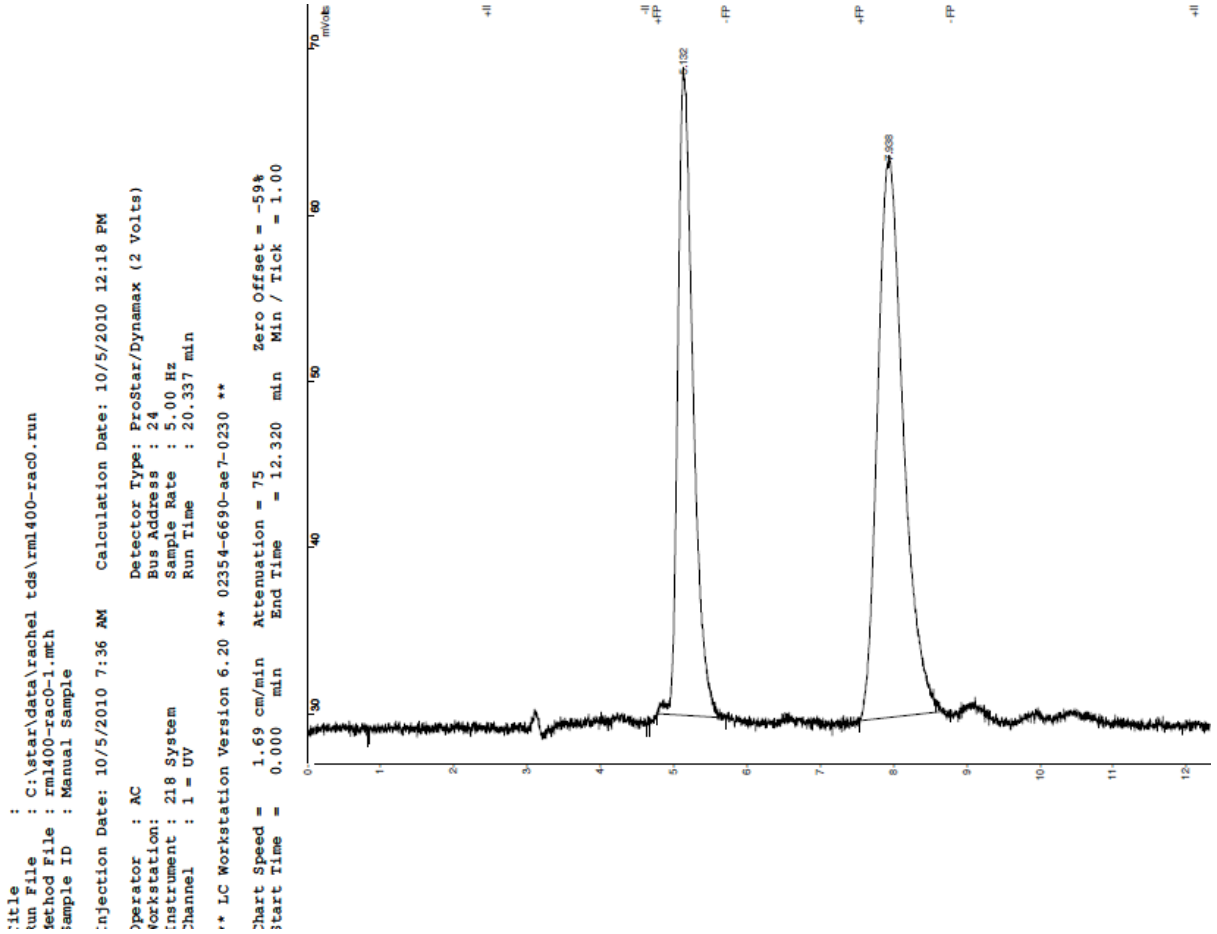
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 32.553 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		1.2271	13.075	0.000	80230	BB	2.9	
2	Peak 15.858	98.7729	15.788	-0.031	6458176	BB	71.4	
	Totals:	100.0000		-0.031	6538406			

Cbz-DL-Alanine-benzylamide



Print Date: Tue Oct 05 13:16:14 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\rml400-rac0.run
Method File : rml400-rac0-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 7:36 AM Calculation Date: 10/5/2010 12:18 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV

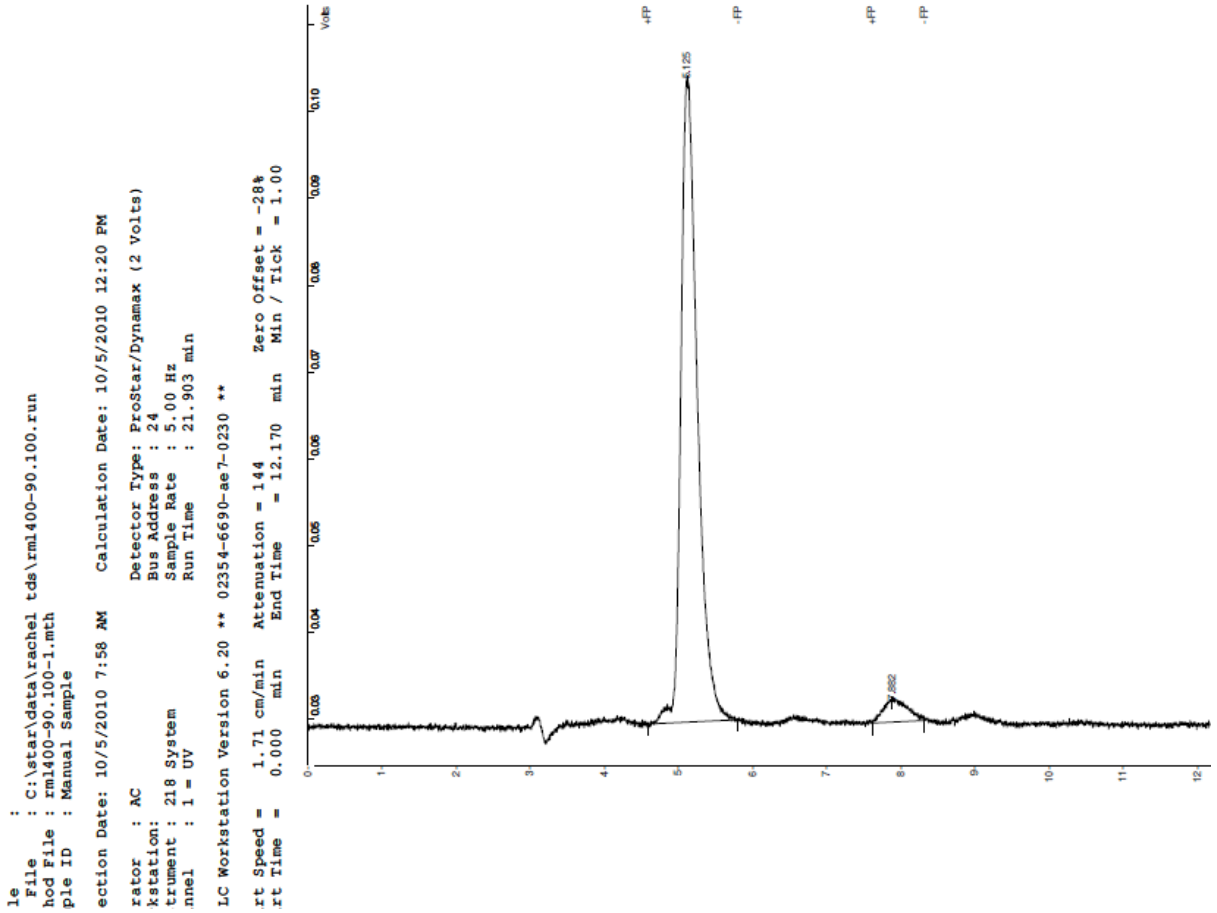
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 20.337 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		40.5417	5.132	0.000	562471	BB	13.0	
2		59.4583	7.938	0.000	824918	BB	22.3	
	Totals:	100.0000		0.000	1387389			

Cbz-L-Alanine-benzylamide 65d



Print Date: Tue Oct 05 13:16:37 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\rml400-90.100.run
Method File : rml400-90.100-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 7:58 AM Calculation Date: 10/5/2010 12:20 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV

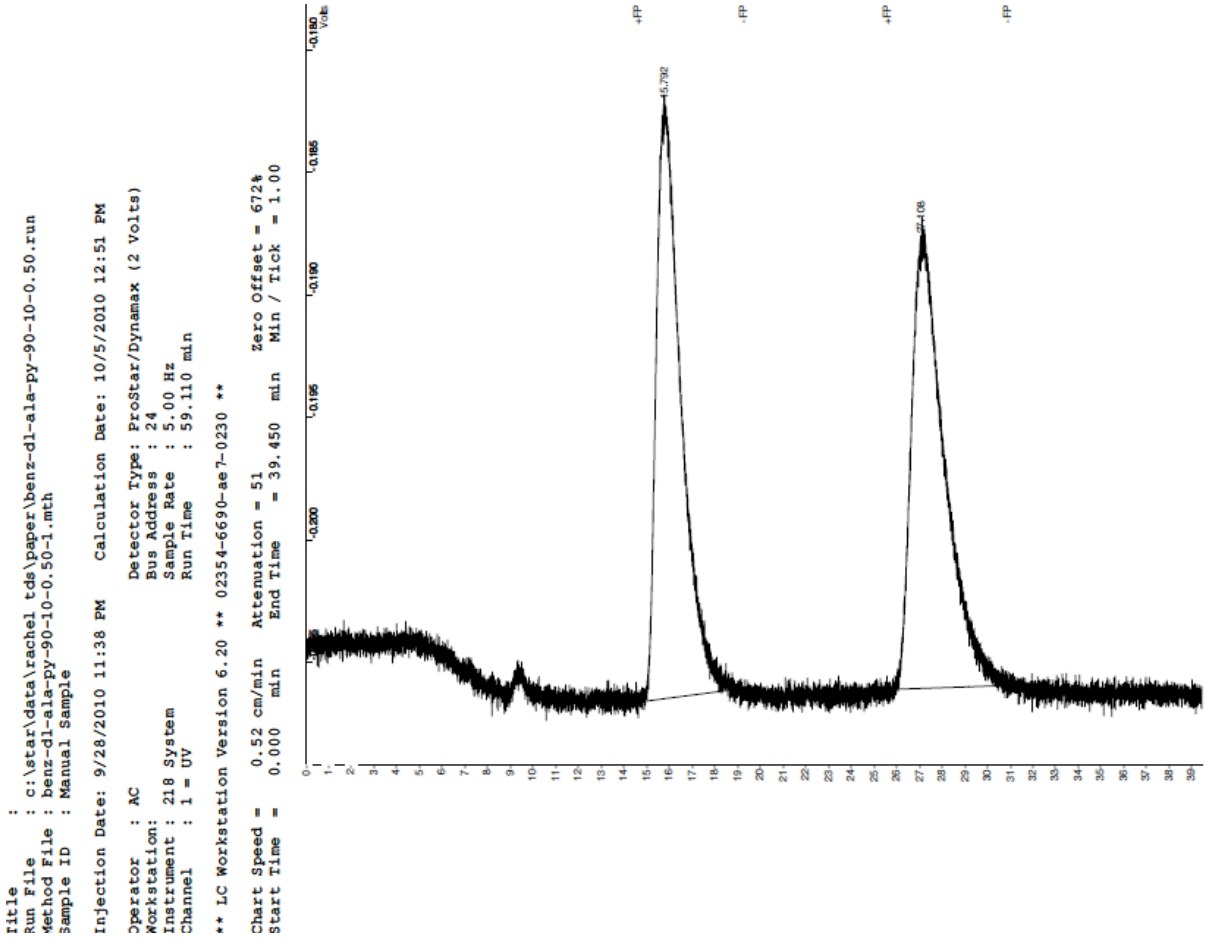
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 21.903 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		95.0551	5.125	0.000	1148915	BB	13.7	
2		4.9449	7.882	0.000	59768	BB	20.2	
	Totals:	100.0000		0.000	1208683			

Bz-DL-Alanine pyrrolidine amide



Print Date: Tue Oct 05 12:57:18 2010 Page 1 of 1

Title :
Run File : c:\star\data\rachel tds\paper\benz-dl-ala-py-90-10-0.50.run
Method File : benz-dl-ala-py-90-10-0.50-1.mth
Sample ID : Manual Sample

Injection Date: 9/28/2010 11:38 PM Calculation Date: 10/5/2010 12:51 PM

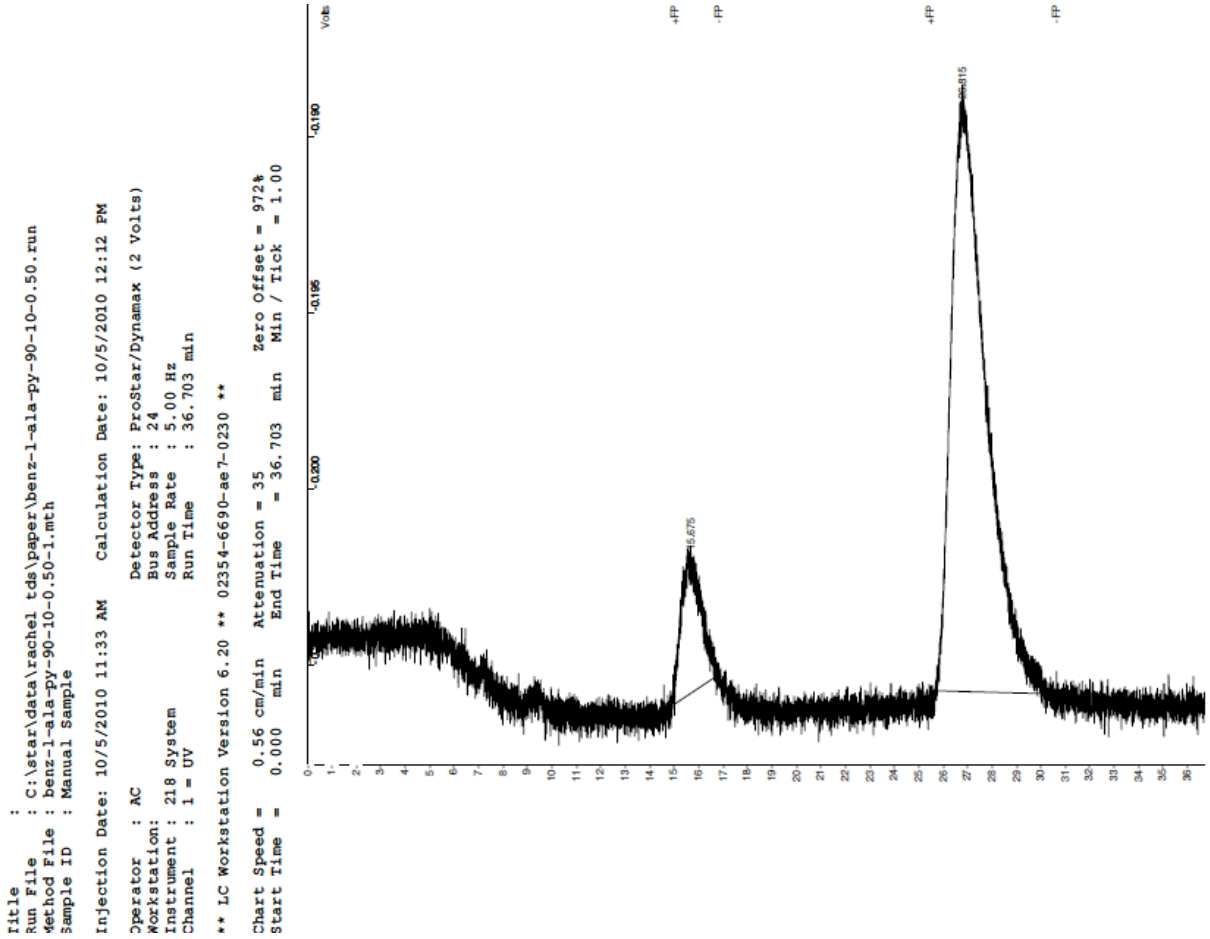
Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 - UV Run Time : 59.110 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		49.7030	15.792	0.000	1846888	BB	66.3	
2		50.2970	27.108	0.000	1868960	BB	83.7	
	Totals:	100.0000		0.000	3715848			

Bz-L-Alanine pyrrolidine amide 66d (obtained from 66a)



Print Date: Tue Oct 05 13:01:28 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\benz-l-ala-py-90-10-0.50.run
Method File : benz-l-ala-py-90-10-0.50-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 11:33 AM Calculation Date: 10/5/2010 12:12 PM

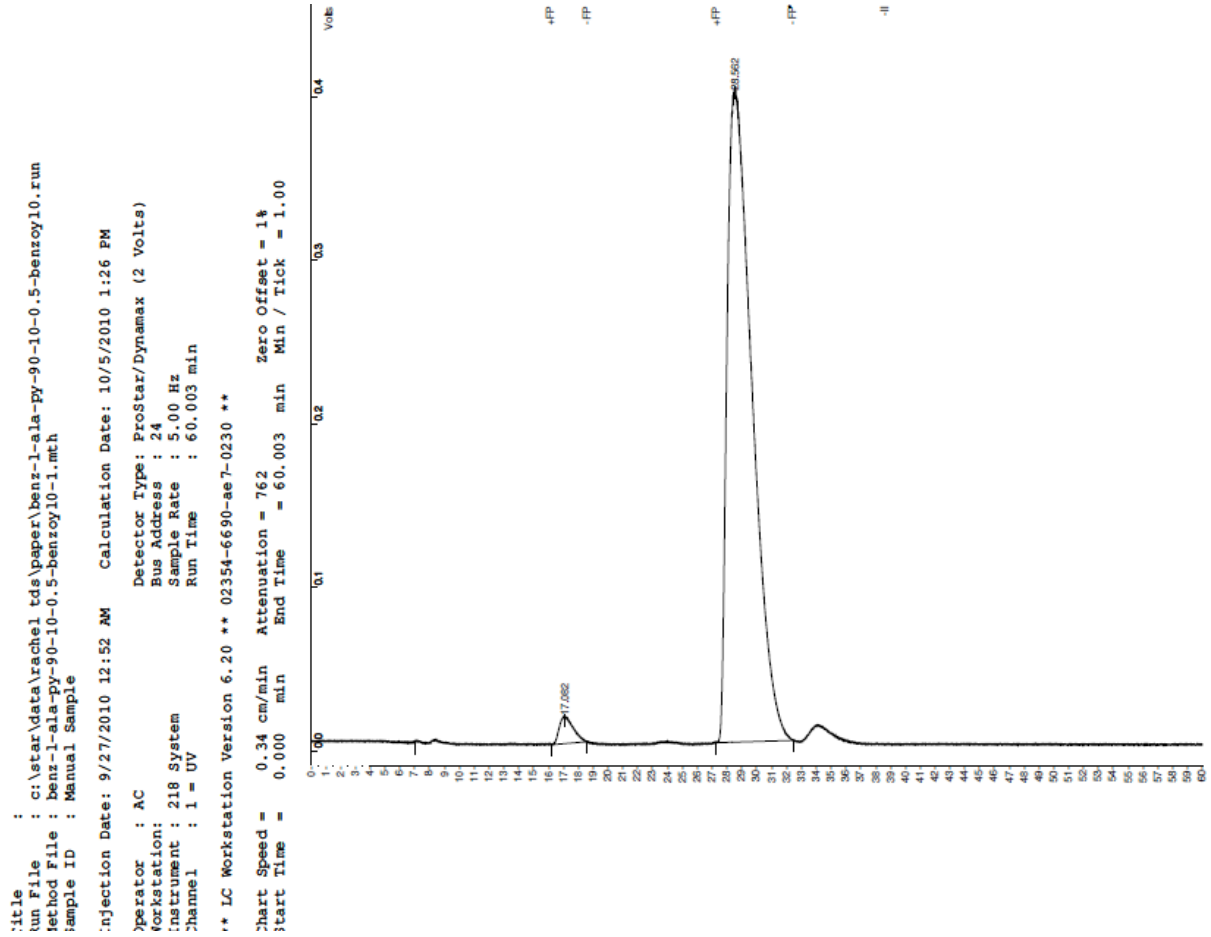
Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 = UV Run Time : 36.703 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		11.8045	15.675	0.000	221509	BB	50.8	
2		88.1955	26.815	0.000	1654964	BB	85.5	
	Totals:	100.0000		0.000	1876473			

Bz-L-Alanine pyrrolidine amide 66d (Directly from *N*-benzoyl alanine)



Print Date: Tue Oct 05 13:17:12 2010 Page 1 of 1

Title :
Run File : c:\star\data\rachel tds\paper\benz-l-ala-py-90-10-0.5-benzoyl0.run
Method File : benz-l-ala-py-90-10-0.5-benzoyl0-1.mth
Sample ID : Manual Sample

Injection Date: 9/27/2010 12:52 AM Calculation Date: 10/5/2010 1:26 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 60.003 min

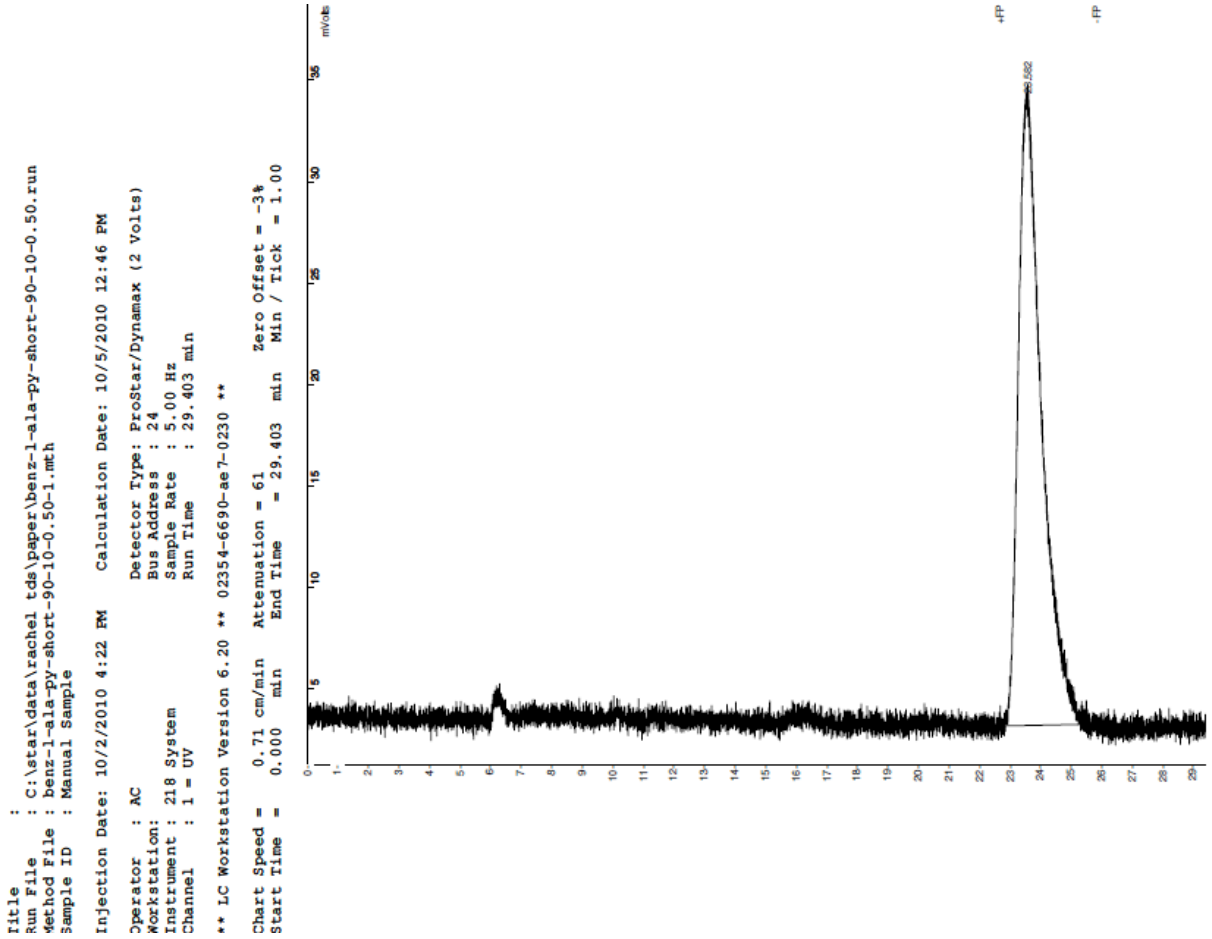
** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		2.2581	17.082	0.000	1070689	BB	61.8	
2		97.7419	28.562	0.000	46345164	BB	110.7	
	Totals:	100.0000		0.000	47415853			

Total Unidentified Counts : 47415852 counts

Bz-L-Alanine pyrrolidine amide 66d (obtained from 6h; 8 h reaction time)



Print Date: Tue Oct 05 13:01:52 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\benz-l-ala-py-short-90-10-0.50.run
Method File : benz-l-ala-py-short-90-10-0.50-1.mth
Sample ID : Manual Sample

Injection Date: 10/2/2010 4:22 PM Calculation Date: 10/5/2010 12:46 PM

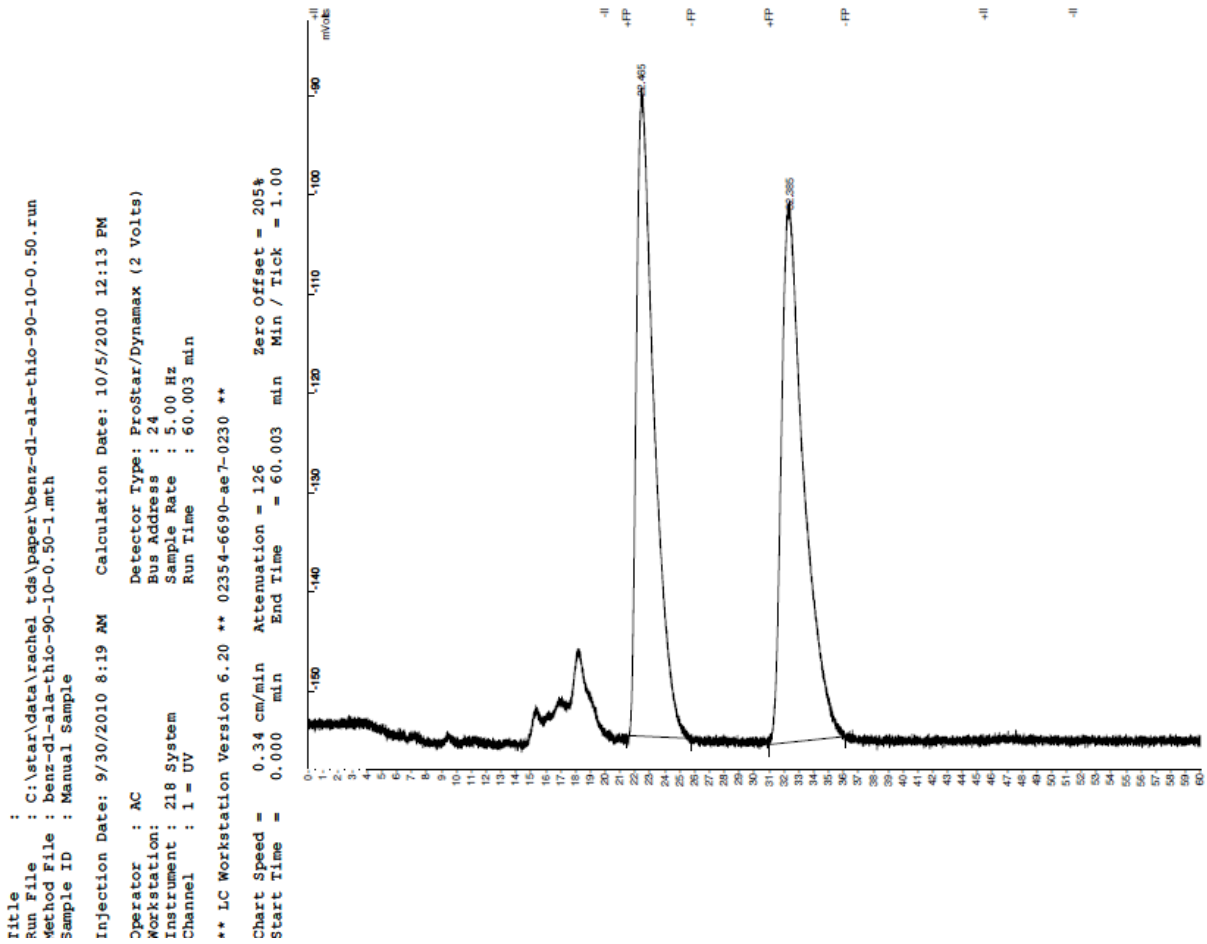
Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 - UV Run Time : 29.403 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		100.0000	23.582	0.000	1660522	BB	45.4	
	Totals:	100.0000		0.000	1660522			

Bz-DL-Alanine thiomorpholine amide



Print Date: Tue Oct 05 13:02:36 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\benz-dl-ala-thio-90-10-0.50.run
Method File : benz-dl-ala-thio-90-10-0.50-1.mth
Sample ID : Manual Sample

Injection Date: 9/30/2010 8:19 AM Calculation Date: 10/5/2010 12:13 PM

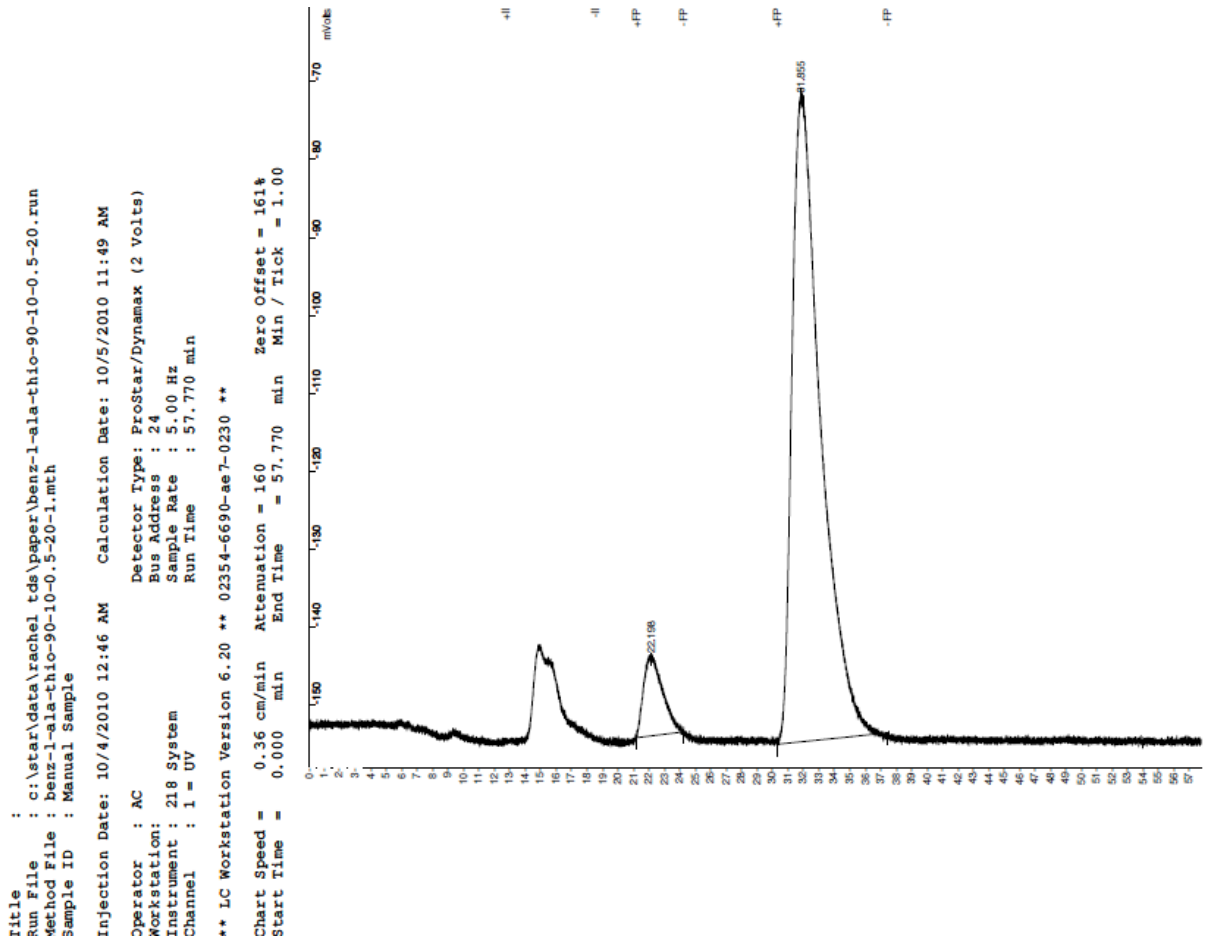
Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 - UV Run Time : 60.003 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		48.5606	22.465	0.000	5356351	BB	73.2	
2		51.4394	32.385	0.000	5673891	BB	91.1	
	Totals:	100.0000		0.000	11030242			

Bz-L-Alanine thiomorpholine amide 66e (obtained from 66c)



Print Date: Tue Oct 05 12:54:28 2010 Page 1 of 1

Title :
Run File : c:\star\data\rachel tds\paper\benz-l-ala-thio-90-10-0.5-20.run
Method File : benz-l-ala-thio-90-10-0.5-20-1.mth
Sample ID : Manual Sample

Injection Date: 10/4/2010 12:46 AM Calculation Date: 10/5/2010 11:49 AM

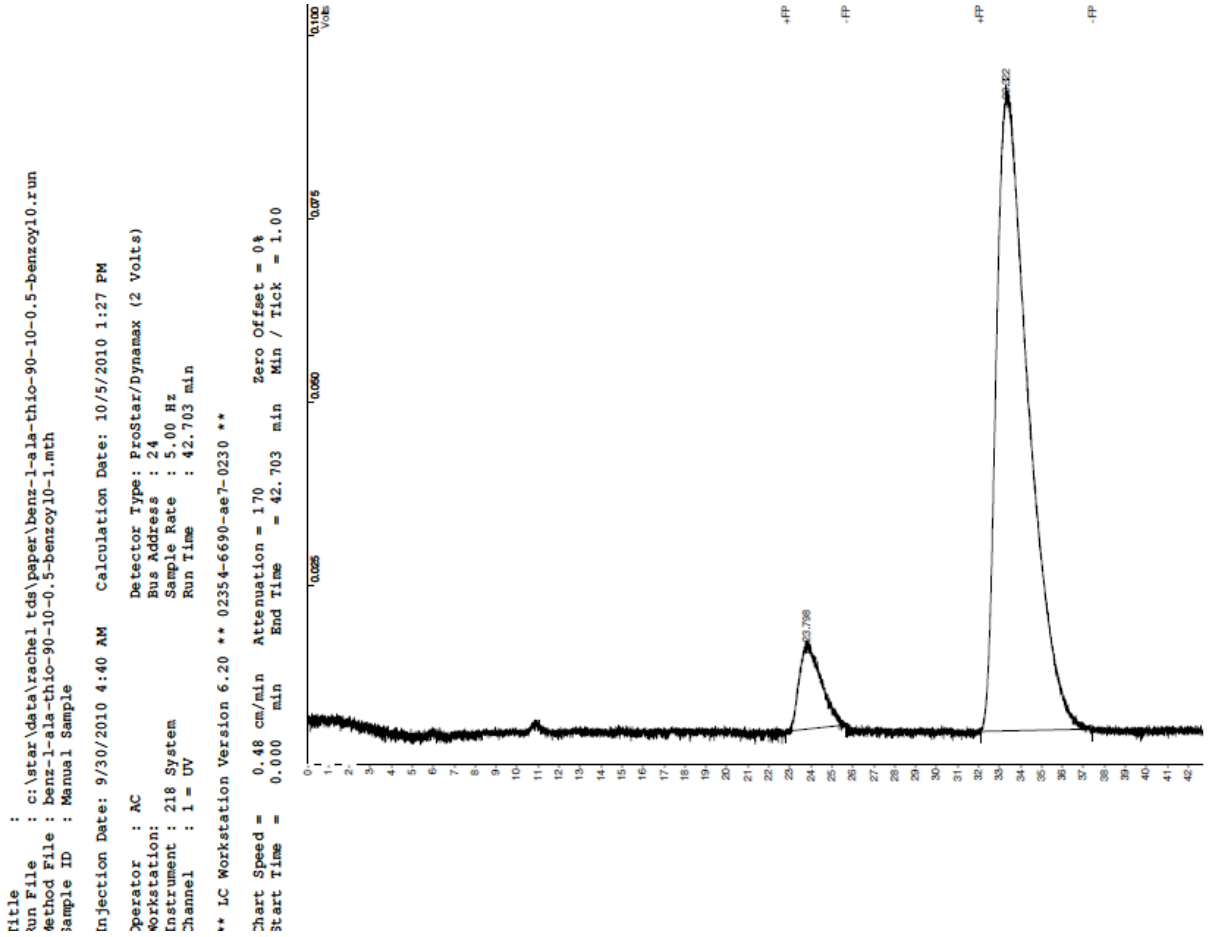
Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 - UV Run Time : 57.770 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		7.6265	22.198	0.000	879805	BB	80.3	
2		92.3735	31.855	0.000	10656364	BB	112.2	
	Totals:	100.0000		0.000	11536169			

Bz-L-Alanine thiomorpholine amide 66e (directly from *N*-benzoyl alanine)



Print Date: Tue Oct 05 13:16:25 2010 Page 1 of 1

Title :
Run File : c:\star\data\rachel tds\paper\benz-l-ala-thio-90-10-0.5-benzoyl0.run
Method File : benz-l-ala-thio-90-10-0.5-benzoyl0-1.mth
Sample ID : Manual Sample

Injection Date: 9/30/2010 4:40 AM Calculation Date: 10/5/2010 1:27 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 = UV
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 42.703 min

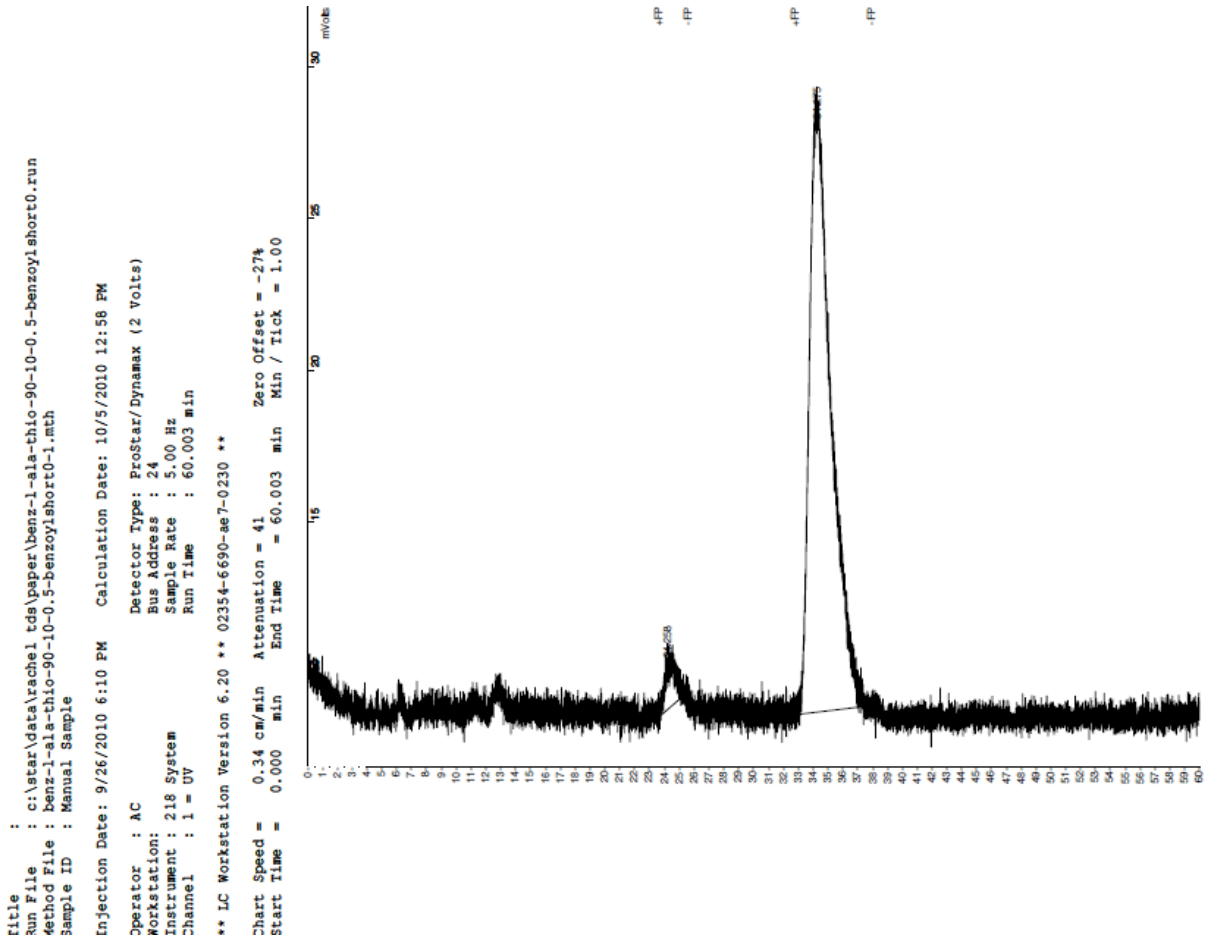
** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		8.2508	23.798	0.000	835734	BB	68.9	
2		91.7492	33.322	0.000	9293362	BB	96.1	
	Totals:	100.0000		0.000	10129096			

Total Unidentified Counts : 10129096 counts

Bz-L-Alanine thiomorpholine amide 66e (directly from *N*-benzoyl alanine; 8 h reaction time)



Print Date: Tue Oct 05 12:59:51 2010 Page 1 of 1

Title :
Run File : c:\star\data\rachel tds\paper\benz-l-ala-thio-90-10-0.5-benzoylshort0.run
Method File : benz-l-ala-thio-90-10-0.5-benzoylshort0-1.mth
Sample ID : Manual Sample

Injection Date: 9/26/2010 6:10 PM Calculation Date: 10/5/2010 12:58 PM

Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 - UV Run Time : 60.003 min

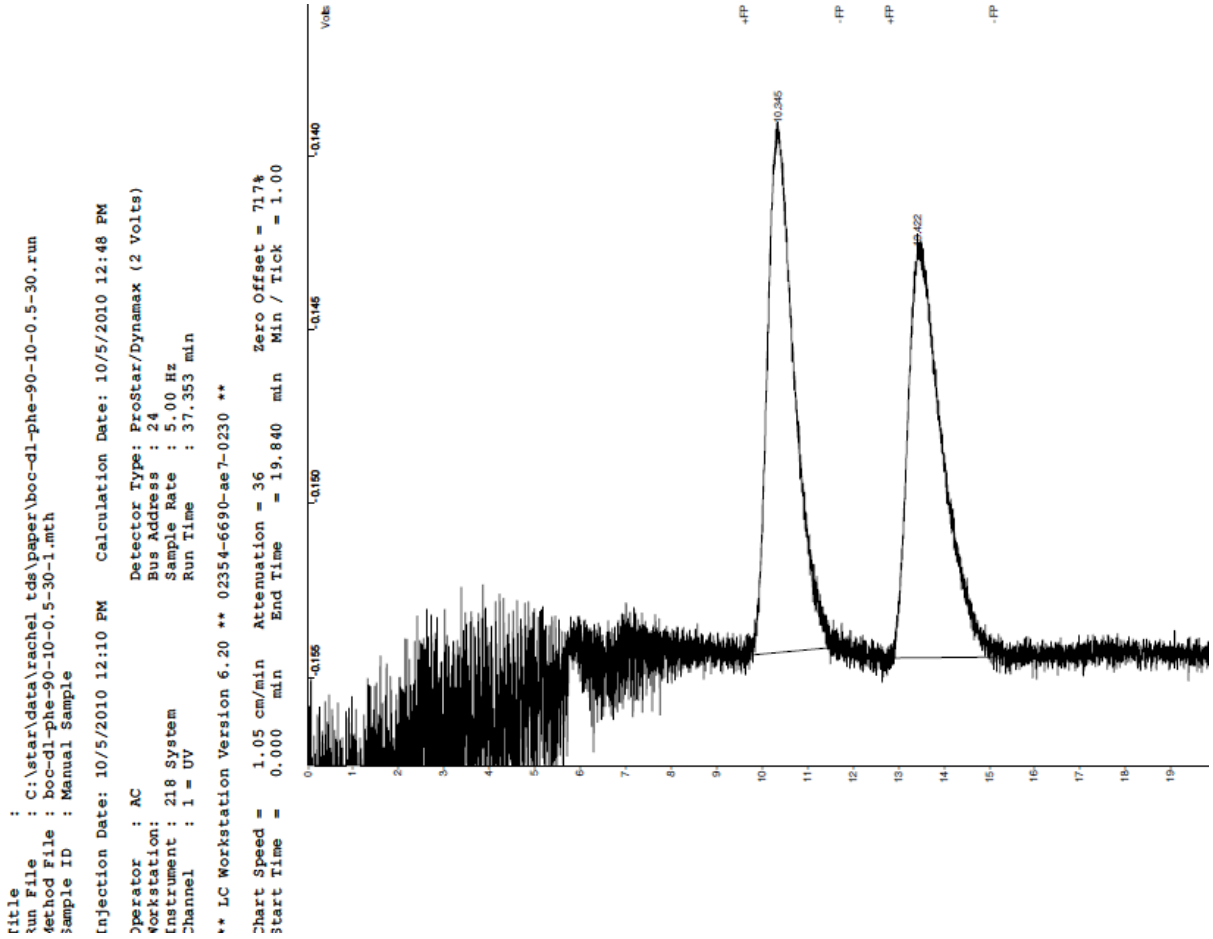
** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		3.7822	24.258	0.000	80261	BB	4.4	
2		96.2178	34.275	0.000	2041845	BB	85.3	
	Totals:	100.0000		0.000	2122106			

Total Unidentified Counts : 2122106 counts

Boc-DL-Phenylalanine pyrrolidine amide



Print Date: Tue Oct 05 12:55:52 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\boc-dl-phe-90-10-0.5-30.run
Method File : boc-dl-phe-90-10-0.5-30-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 12:10 PM Calculation Date: 10/5/2010 12:48 PM

Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 = UV Run Time : 37.353 min

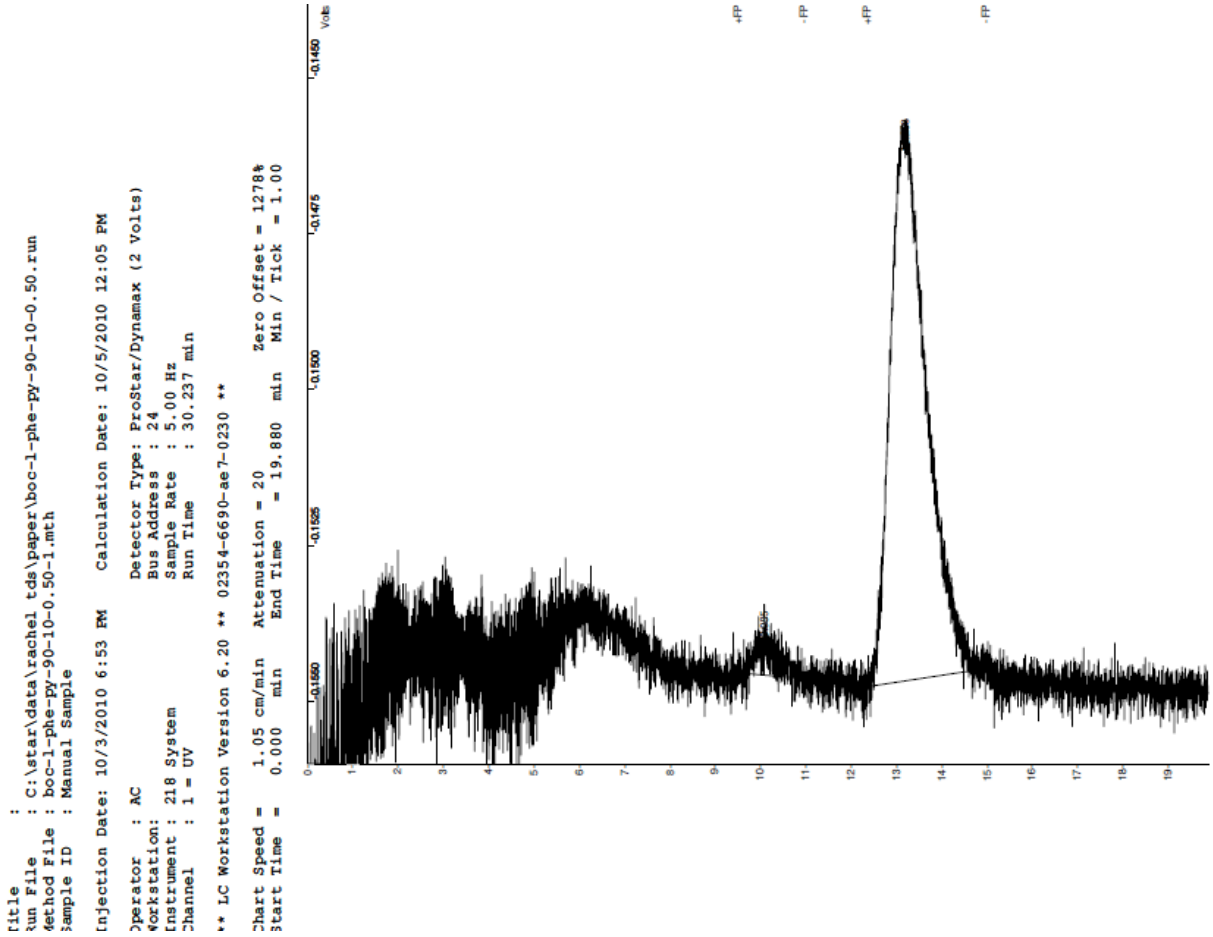
** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		50.1391	10.345	0.000	630998	BB	36.6	
2		49.8609	13.422	0.000	627496	BB	45.9	
	Totals:	100.0000		0.000	1258494			

Total Unidentified Counts : 1258494 counts

Boc-L-Phenylalanine pyrrolidine amide 66b



Print Date: Tue Oct 05 12:56:49 2010 Page 1 of 1

Title :
Run File : C:\star\data\rachel tds\paper\boc-l-phe-py-90-10-0.50.run
Method File : boc-l-phe-py-90-10-0.50-1.mth
Sample ID : Manual Sample

Injection Date: 10/3/2010 6:53 PM Calculation Date: 10/5/2010 12:05 PM

Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 - UV Run Time : 30.237 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

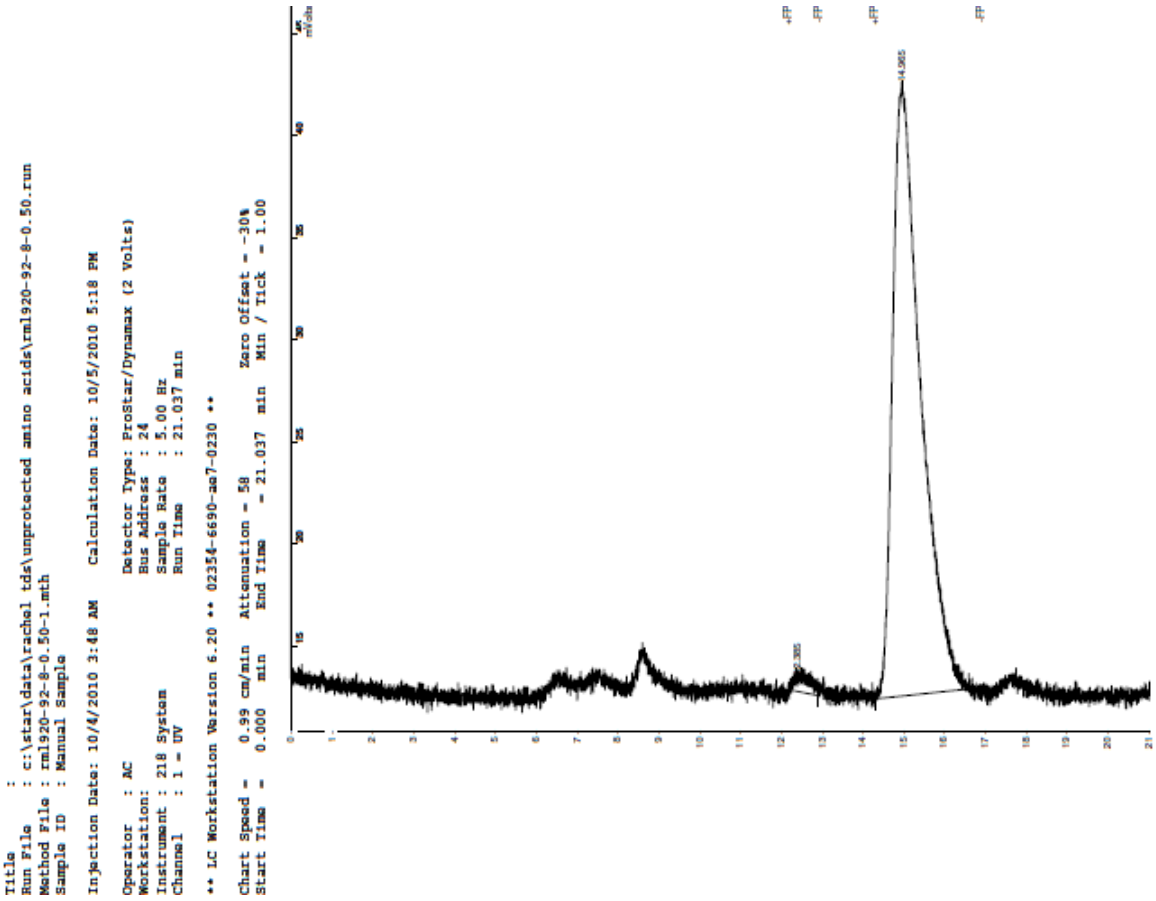
Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		3.7329	10.085	0.000	19136	BB	1.7	
2		96.2671	13.208	0.000	493486	BB	48.0	
	Totals:	100.0000		0.000	512622			

Total Unidentified Counts : 512621 counts

7.2. Appendix 2 – HPLC and NMR spectra for aldehyde 81 method development

Boc-L-Methionine-benzylamide 65b for aldehyde 81 comparison



Print Date: Tue Oct 05 17:13:50 2010 Page 1 of 1

Title :
Run File : c:\star\data\rachel tds\unprotected amino acids\rml920-92-8-0.50.run
Method File : rml920-92-8-0.50-1.mth
Sample ID : Manual Sample

Injection Date: 10/4/2010 3:48 AM Calculation Date: 10/5/2010 5:18 PM

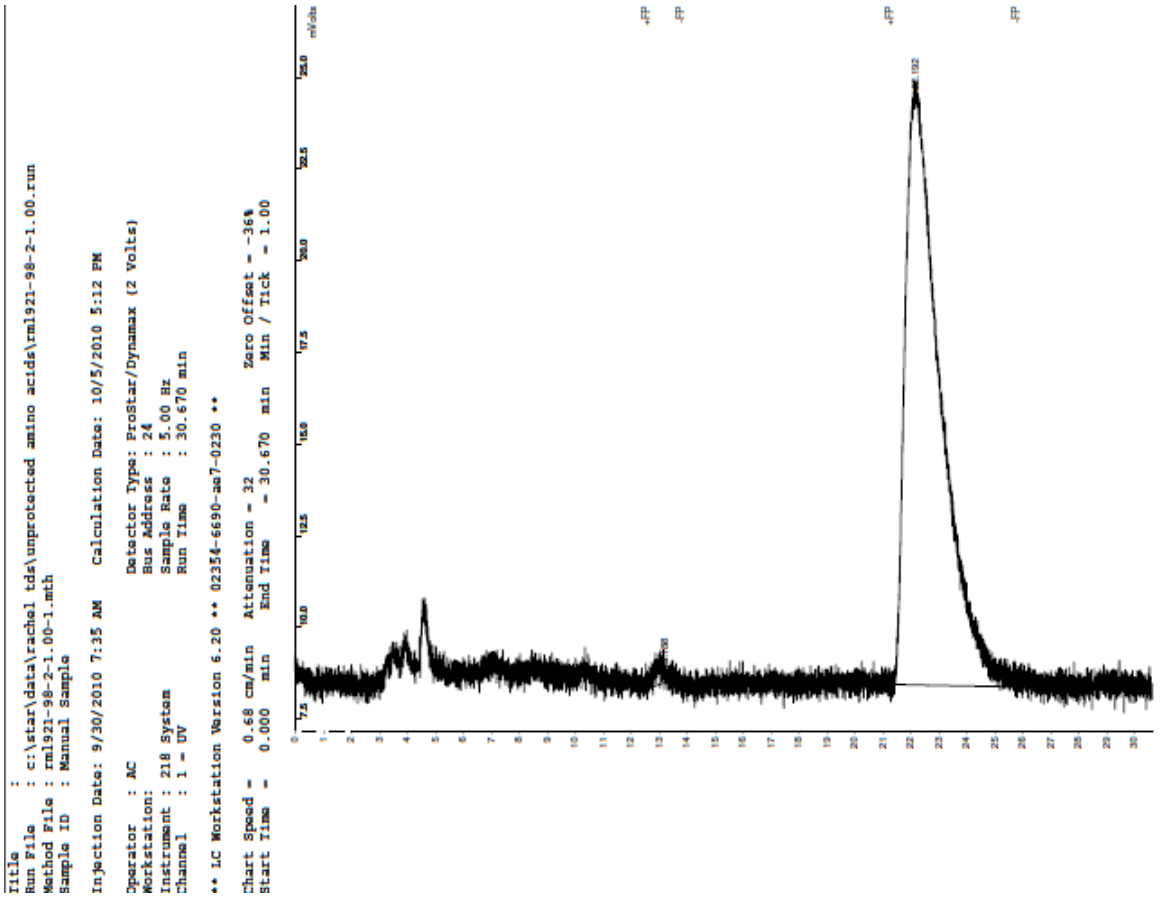
Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 21.037 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		1.6603	12.385	0.000	24171	BB	0.5	
2		98.3397	14.965	0.000	1431657	BB	43.2	
	Totals:	100.0000		0.000	1455828			

Boc-L-Alanine benzylamide for aldehyde 81 comparison



Print Date: Tue Oct 05 17:13:07 2010 Page 1 of 1

Title :
Run File : c:\star\data\rachel tds\unprotected amino acids\rm1921-98-2-1.00.run
Method File : rm1921-98-2-1.00-1.mth
Sample ID : Manual Sample

Injection Date: 9/30/2010 7:35 AM Calculation Date: 10/5/2010 5:12 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 = UV

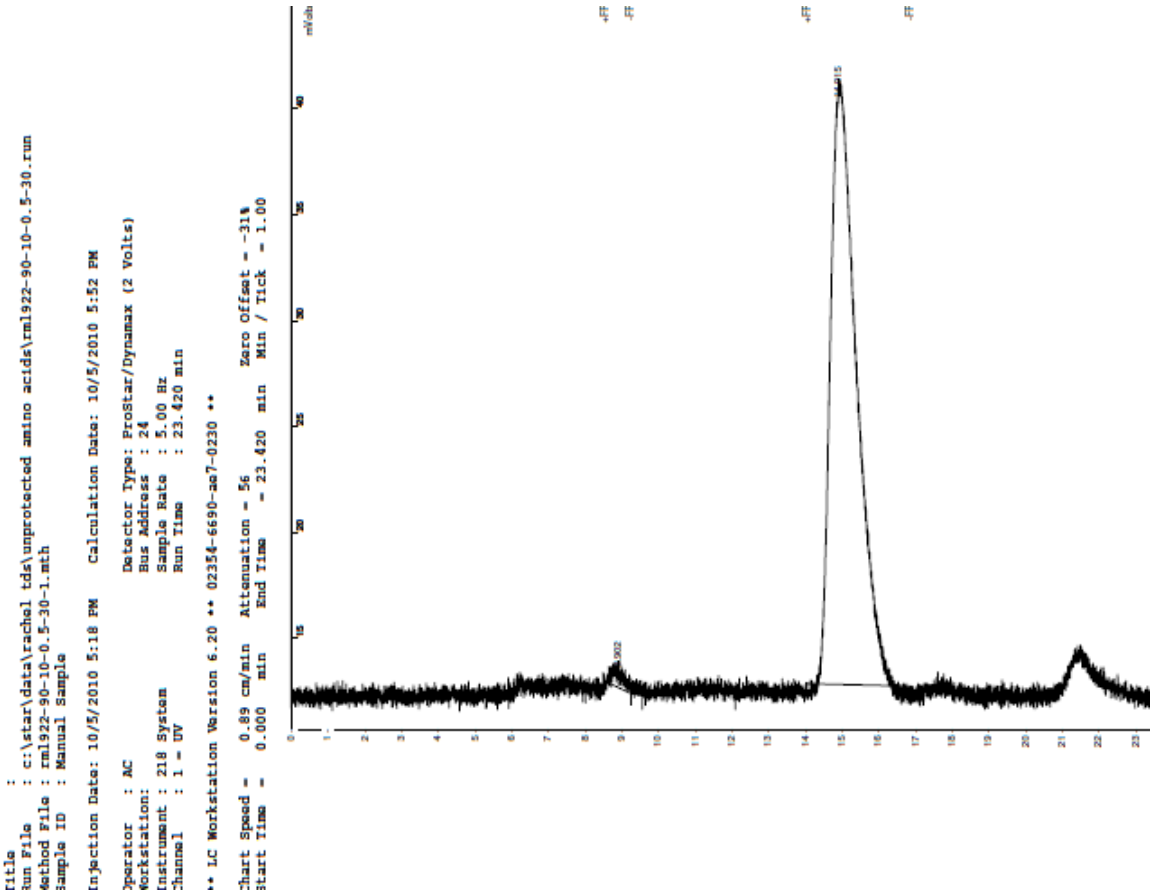
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 30.670 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		0.9707	13.188	0.000	13881	BB	0.3	
2		99.0293	22.192	0.000	1416128	BB	76.2	
	Totals:	100.0000		0.000	1430009			

Boc-L-Phenylalanine-benzylamide 65a for aldehyde 81 comparison



Print Date: Tue Oct 05 17:14:32 2010 Page 1 of 1

Title :
Run File : c:\star\data\rachel tds\unprotected amino acids\rml922-90-10-0.5-30.run
Method File : rml922-90-10-0.5-30-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 5:18 PM Calculation Date: 10/5/2010 5:52 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV

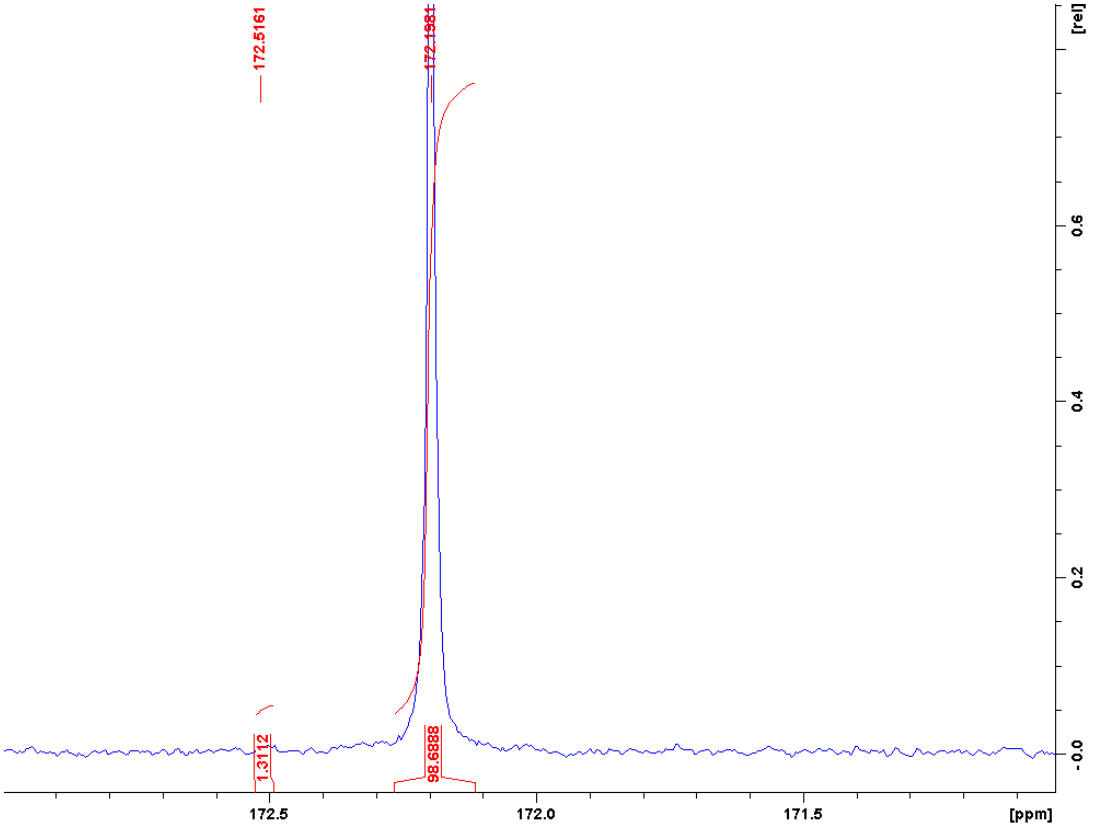
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 23.420 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

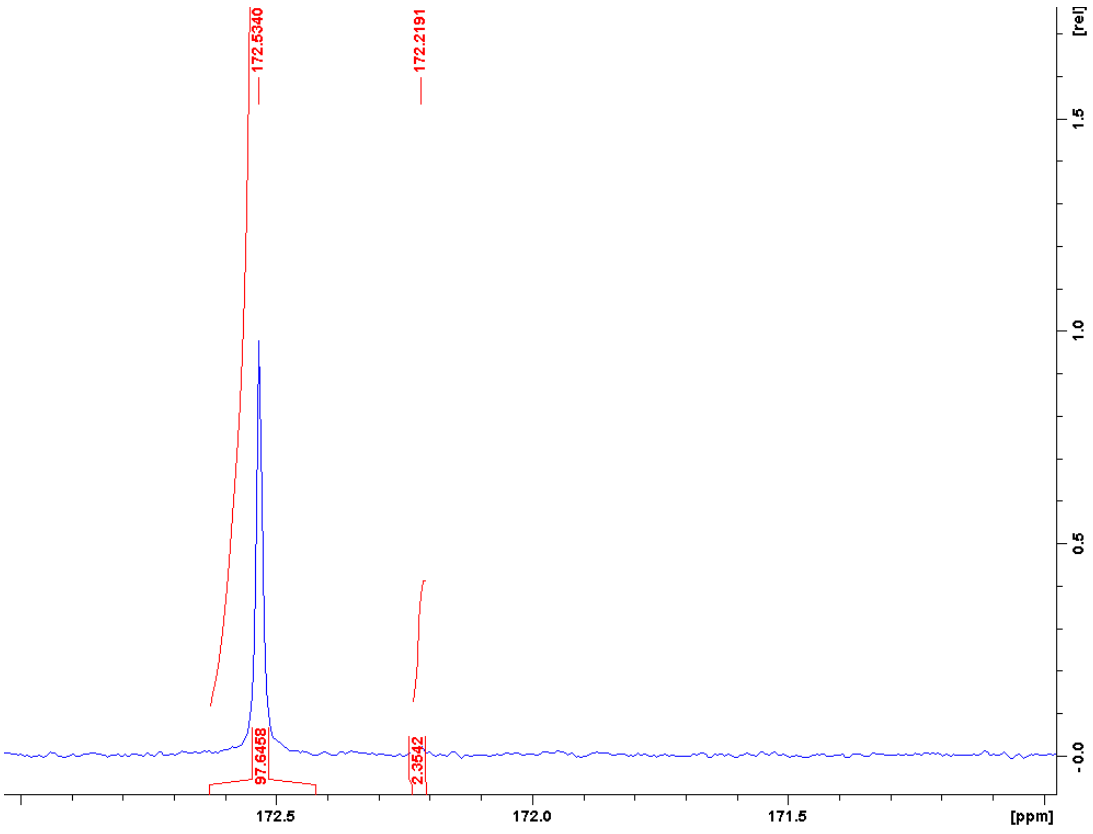
Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		1.2955	8.902	0.000	18165	BB	0.5	
2		98.7045	14.915	0.000	1384045	BB	44.7	
	Totals:	100.0000		0.000	1402210			

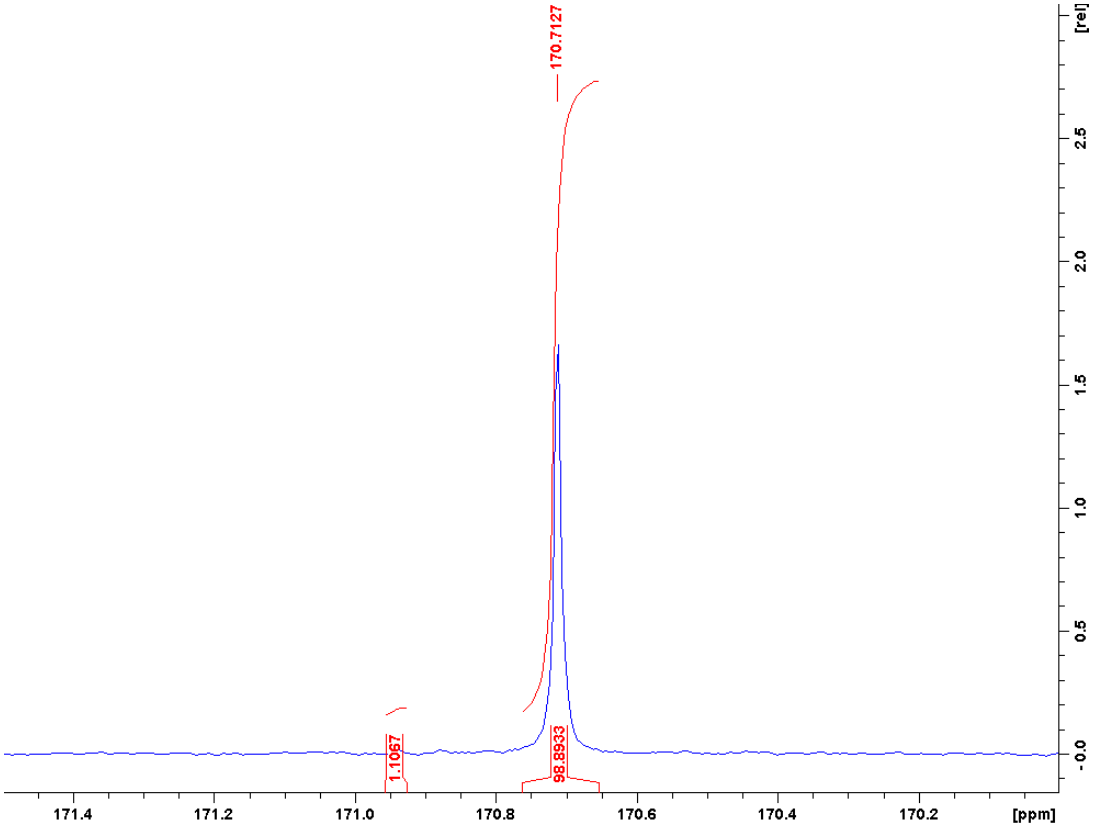
L-Methionine-benzylamide 65b imine with aldehyde (*R*)-81



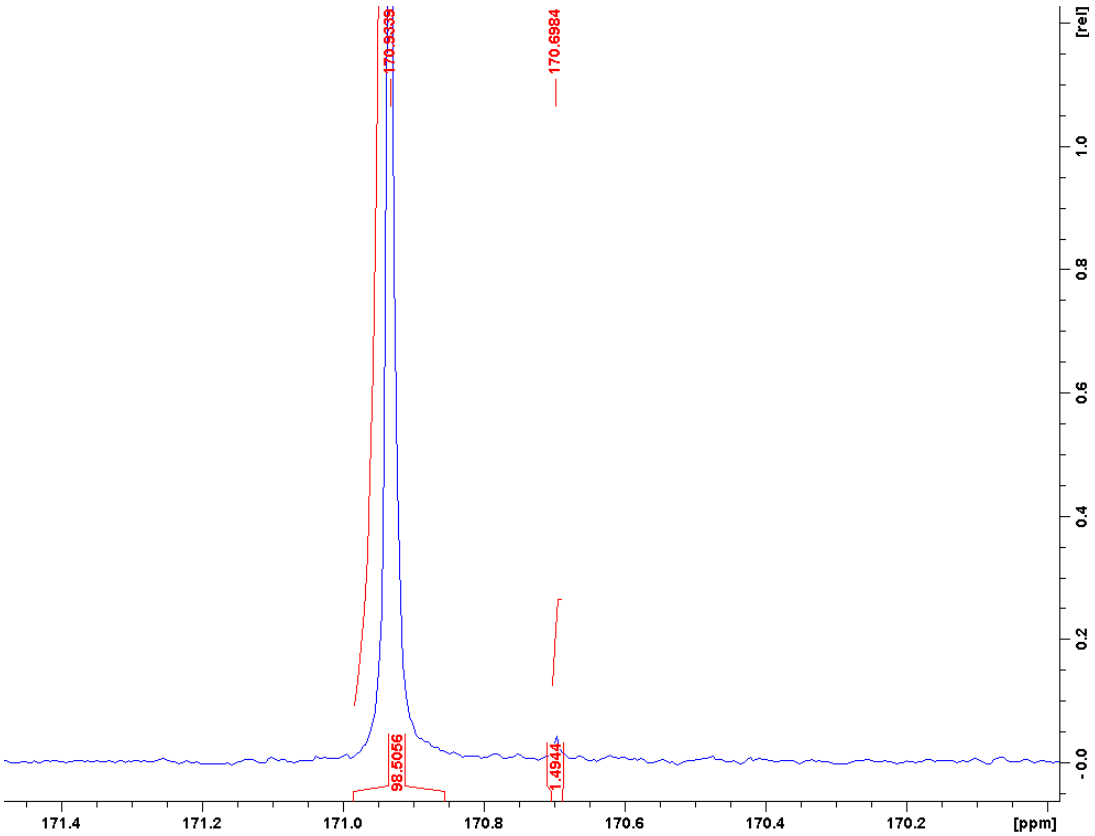
L-Methionine-benzylamide 65b imine with aldehyde (*S*)-81



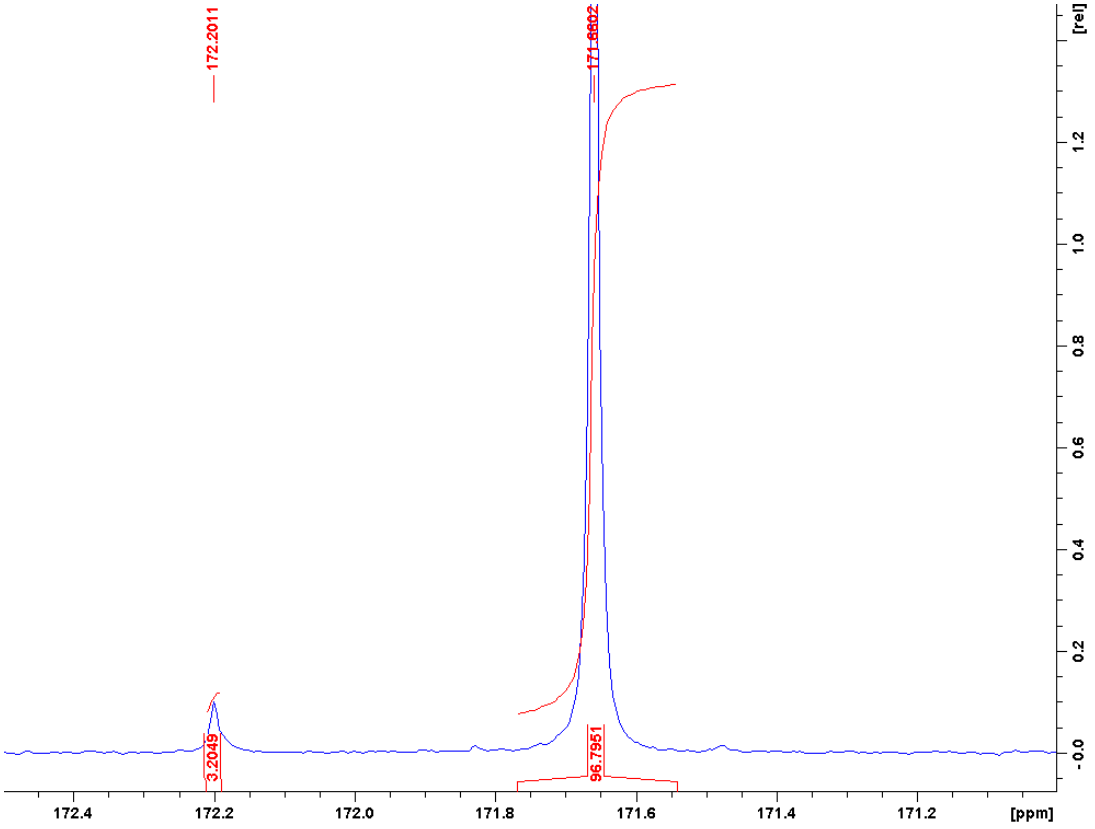
L-Alanine-benzylamide imine with aldehyde (*R*)-81



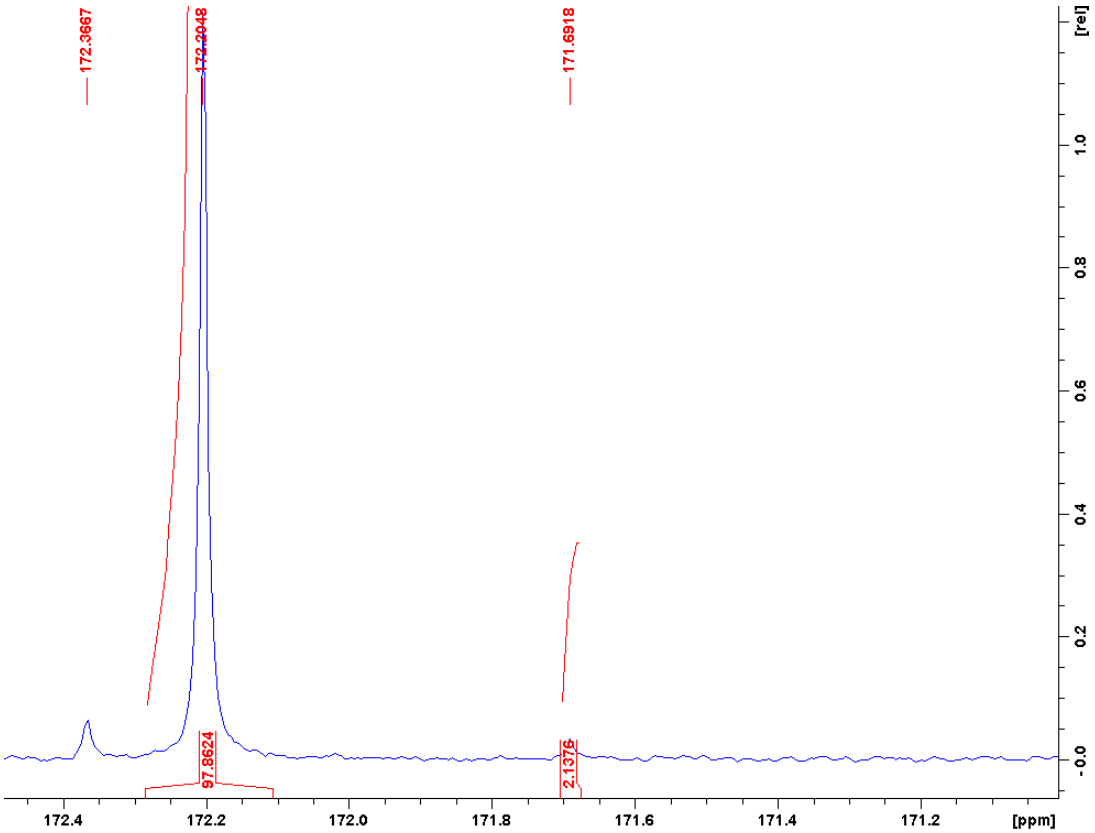
L-Alanine-benzylamide imine with aldehyde (*S*)-81



L-Phenylalanine-benzylamide 65a imine with aldehyde (*R*)-81

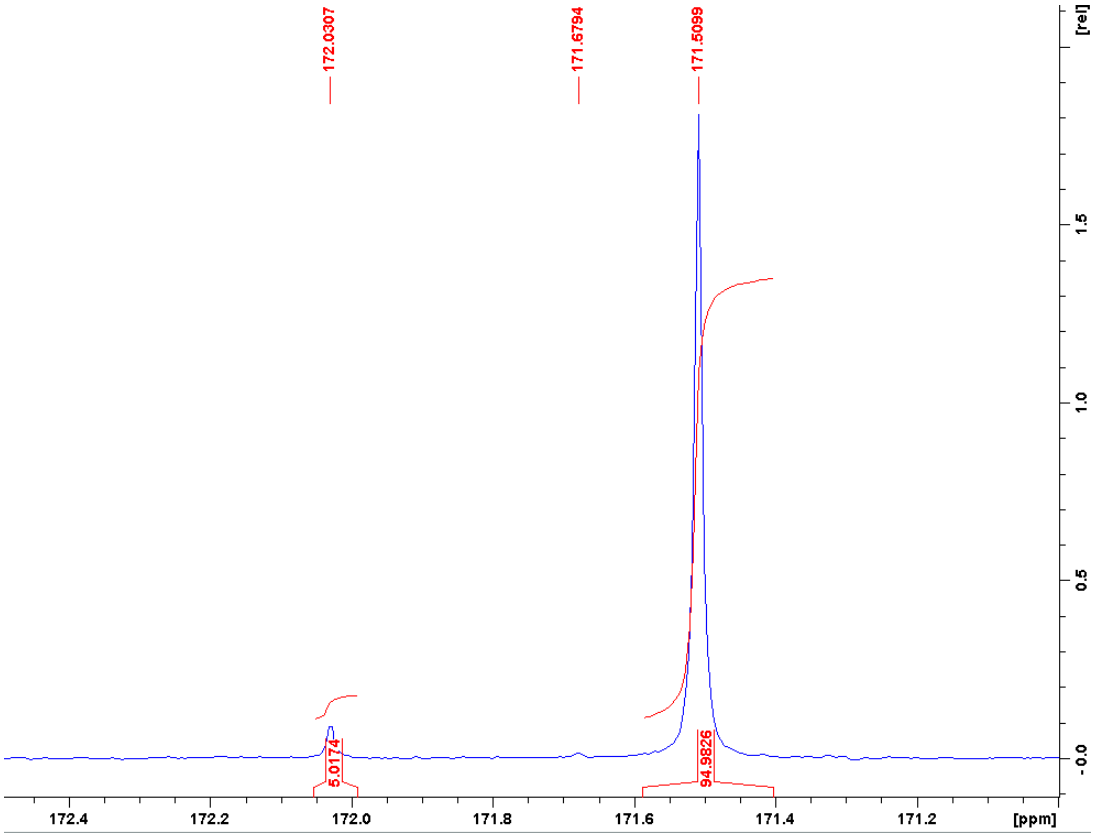


L-Phenylalanine-benzylamide 65a imine with aldehyde (*S*)-81

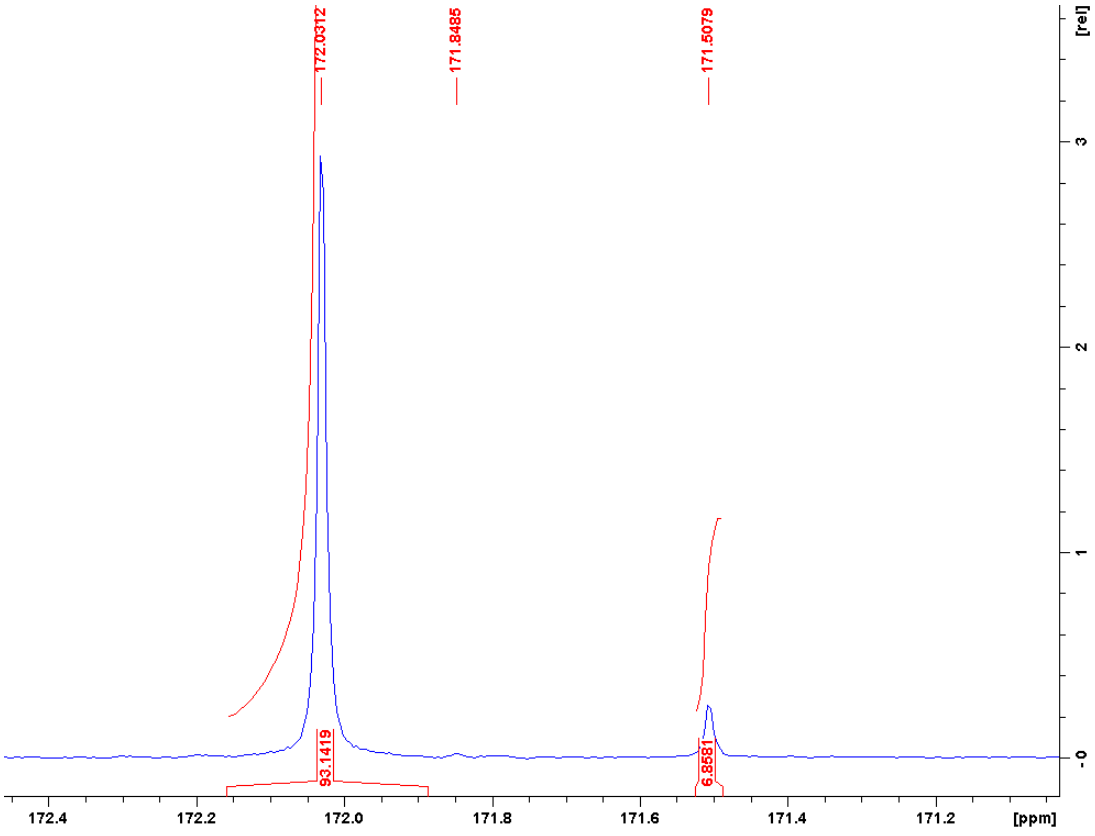


7.3. Appendix 3 – ^{13}C-NMR spectra for er determination

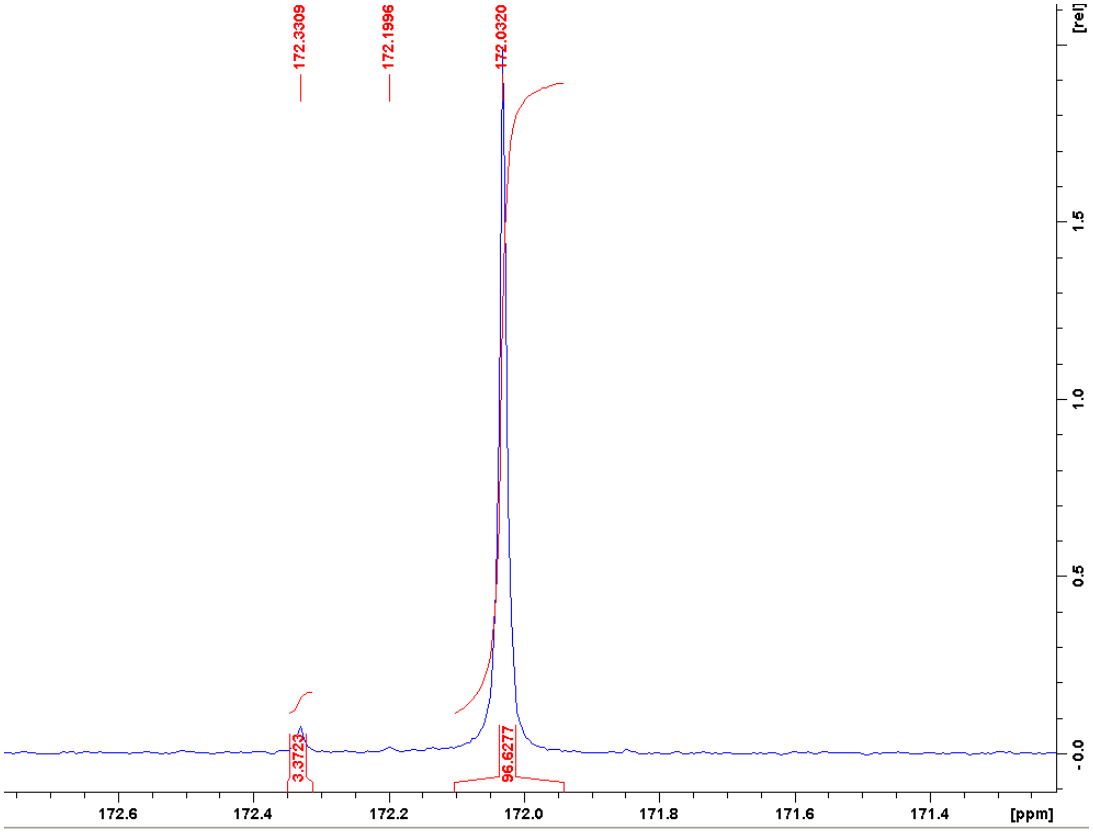
(*S*)-2-Amino-3-phenyl-*N*-propylpropanamide 77a – (*R*)-81



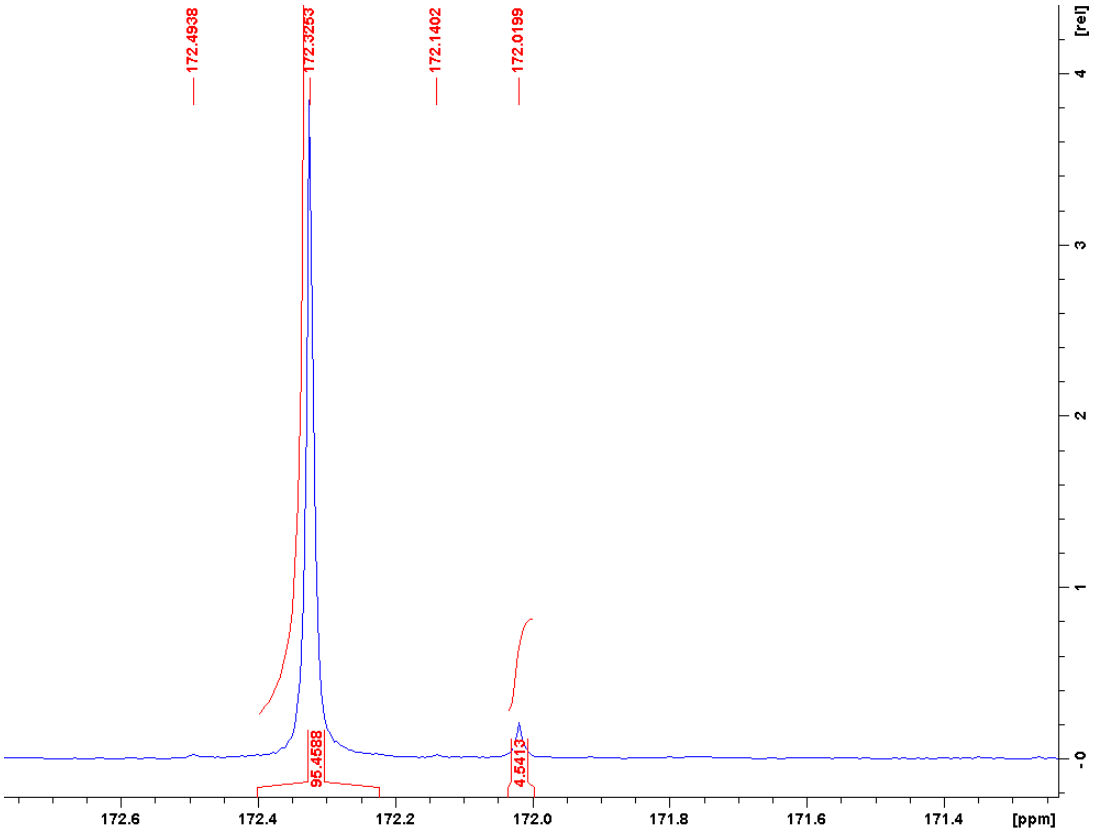
(*S*)-2-Amino-3-phenyl-*N*-propylpropanamide 77a – (*S*)-81



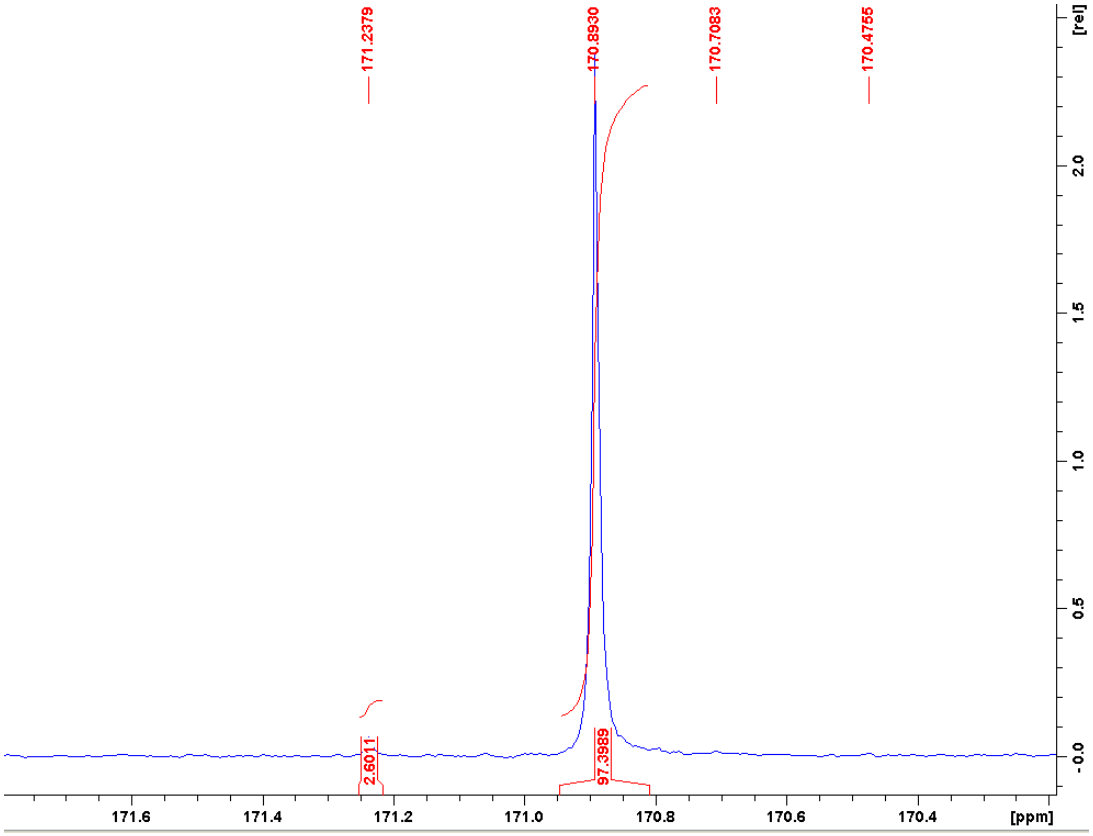
(*S*)-2-Amino-4-(methylthio)-*N*-propylbutanamide 77b – (*R*)-81



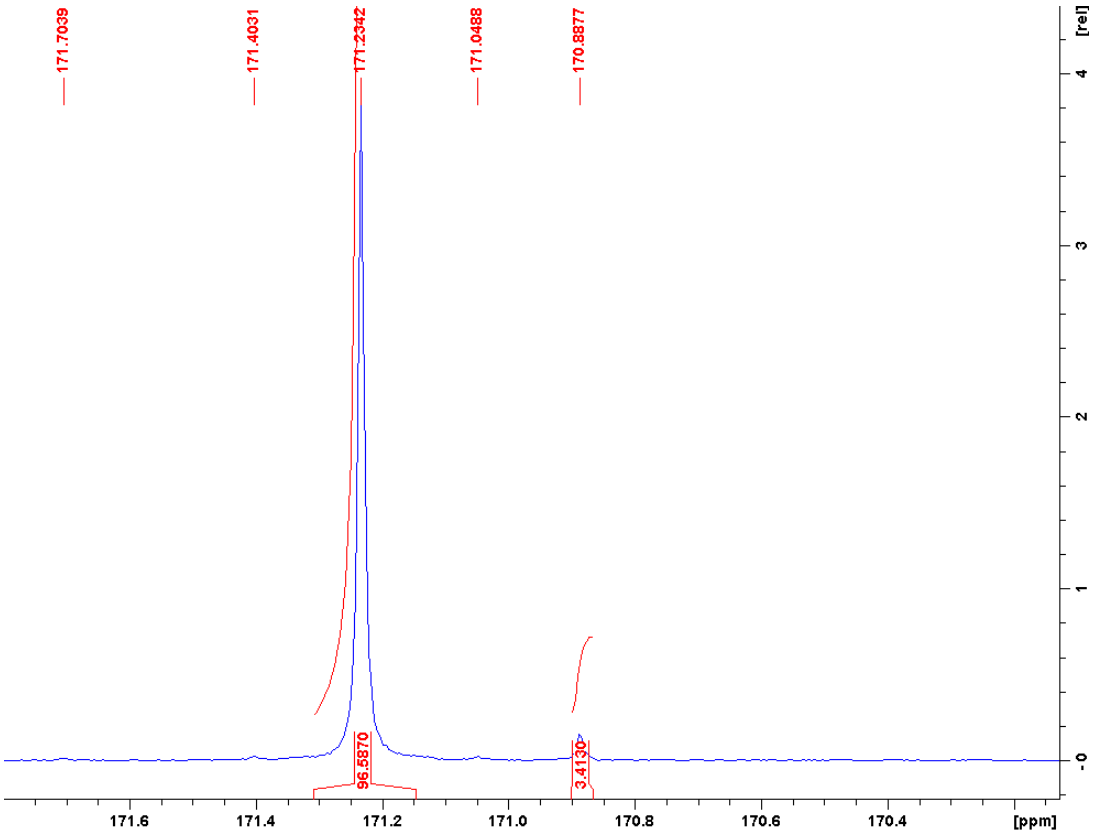
(*S*)-2-Amino-4-(methylthio)-*N*-propylbutanamide 77b – (*S*)-81



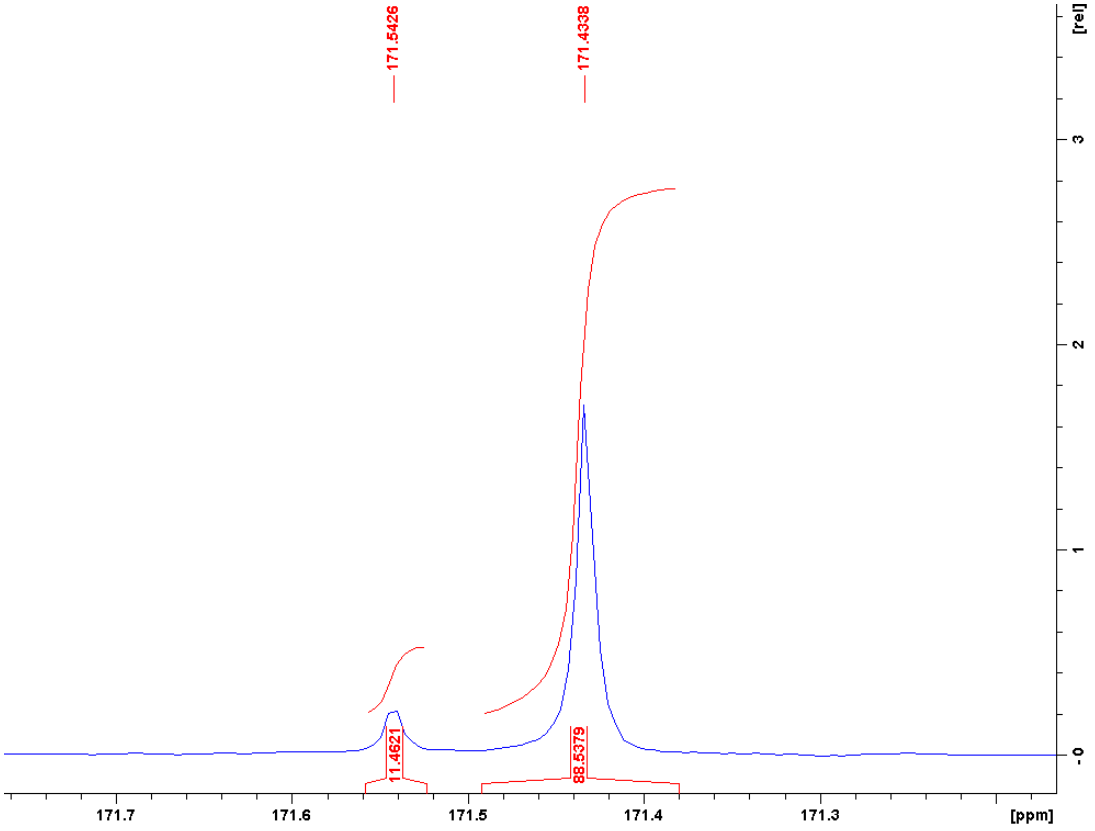
(*S*)-2-Amino-4-methyl-*N*-propylpentanamide 77c – (*R*)-81



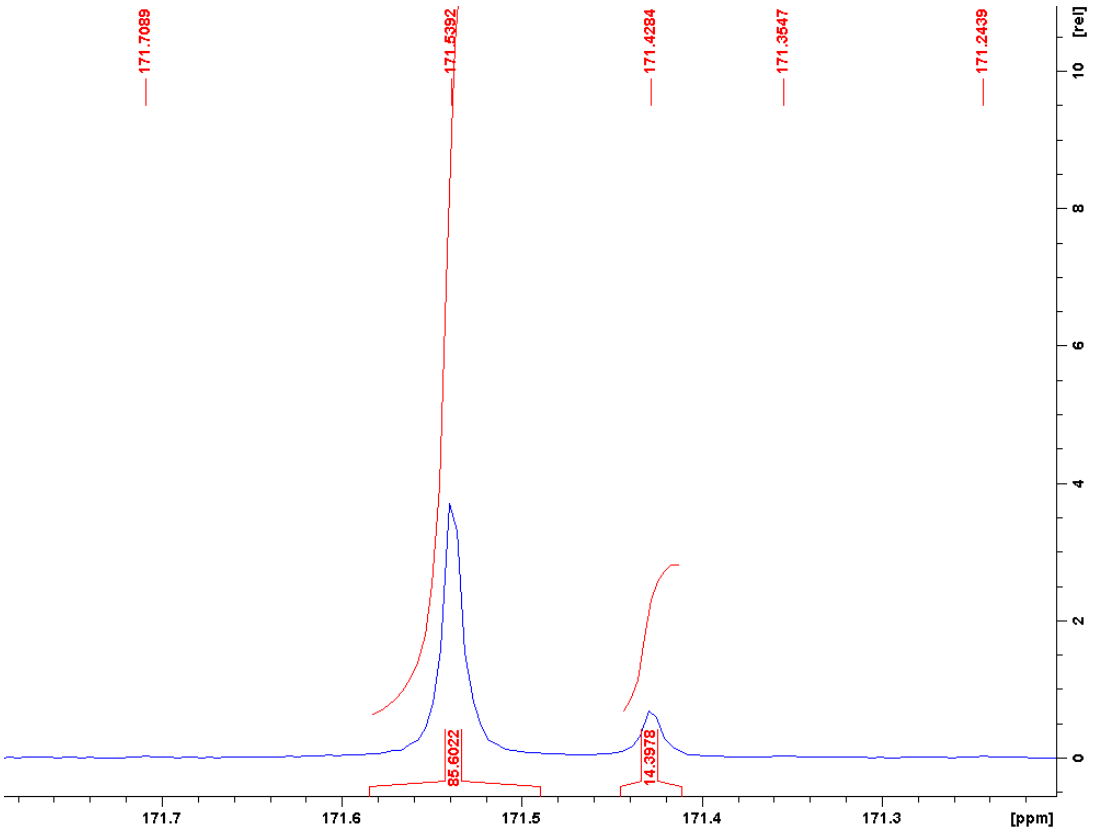
(*S*)-2-Amino-4-methyl-*N*-propylpentanamide 77c – (*S*)-81



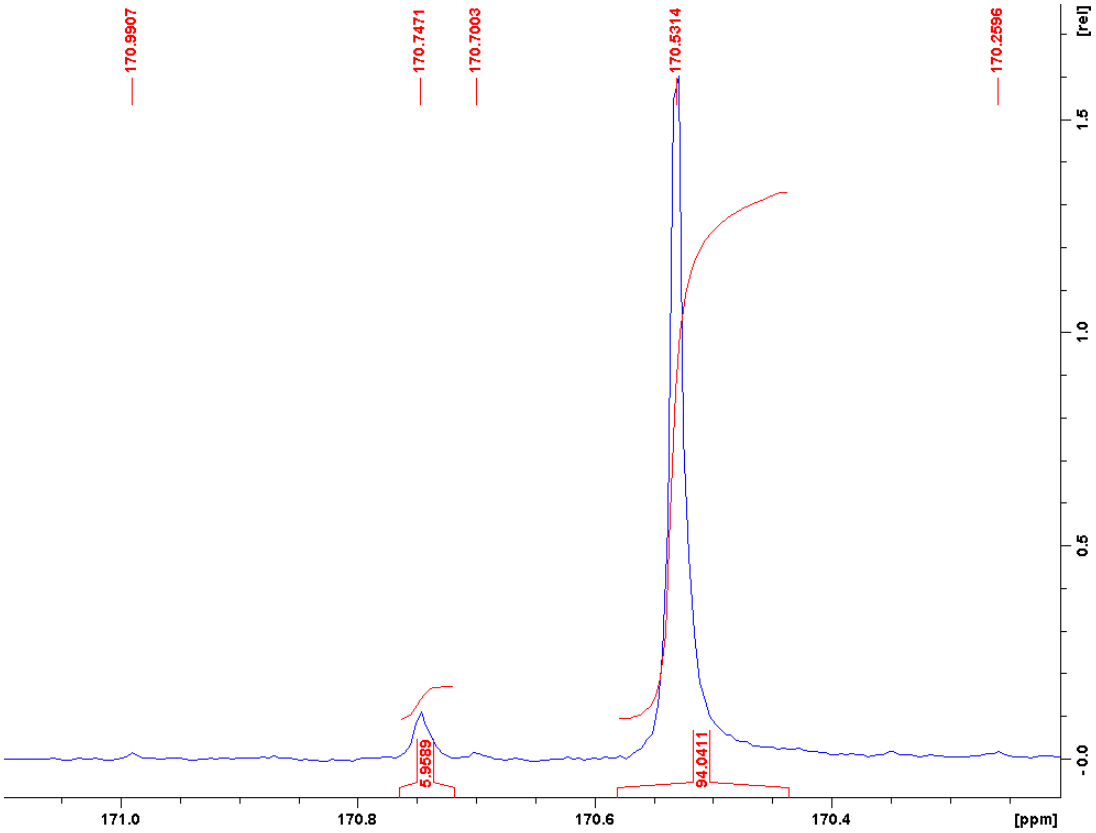
(*S*)-2-amino-3-methyl-*N*-propylbutanamide 77k – (*R*)-81



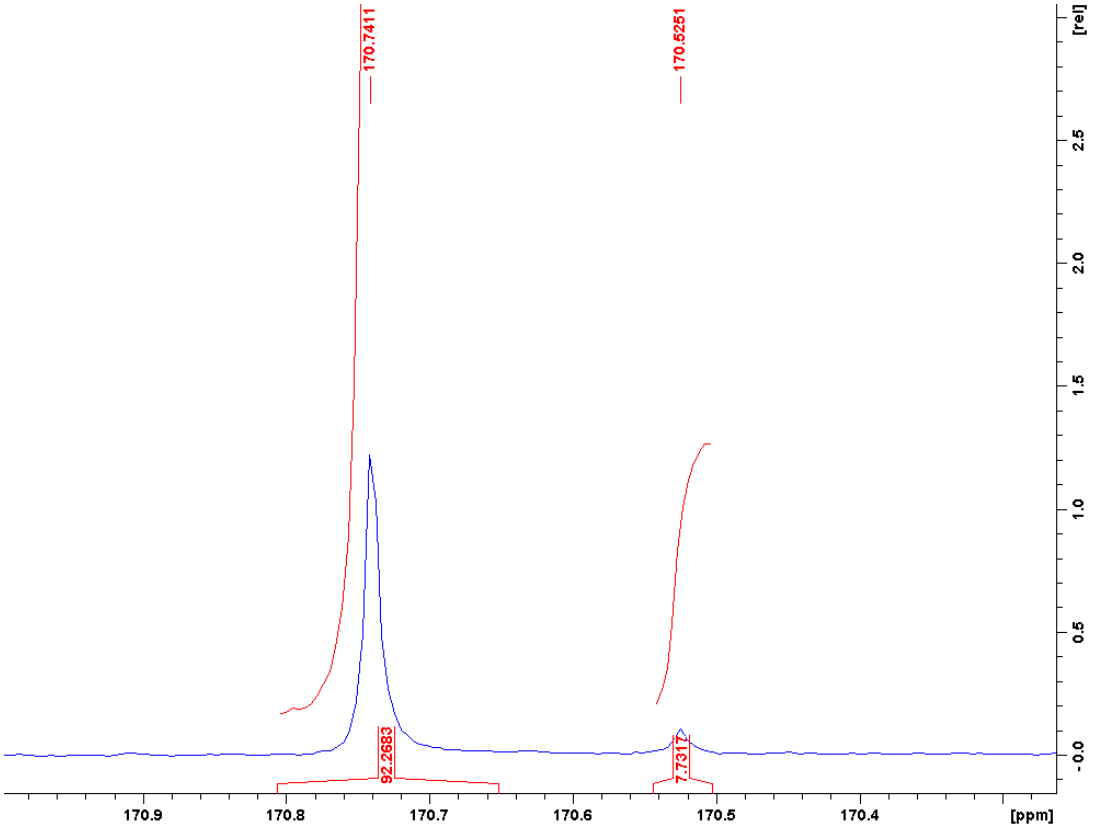
(*S*)-2-amino-3-methyl-*N*-propylbutanamide 77k – (*S*)-81



(*S*)-2-Amino-*N*-propylpropanamide 77l – (*R*)-81

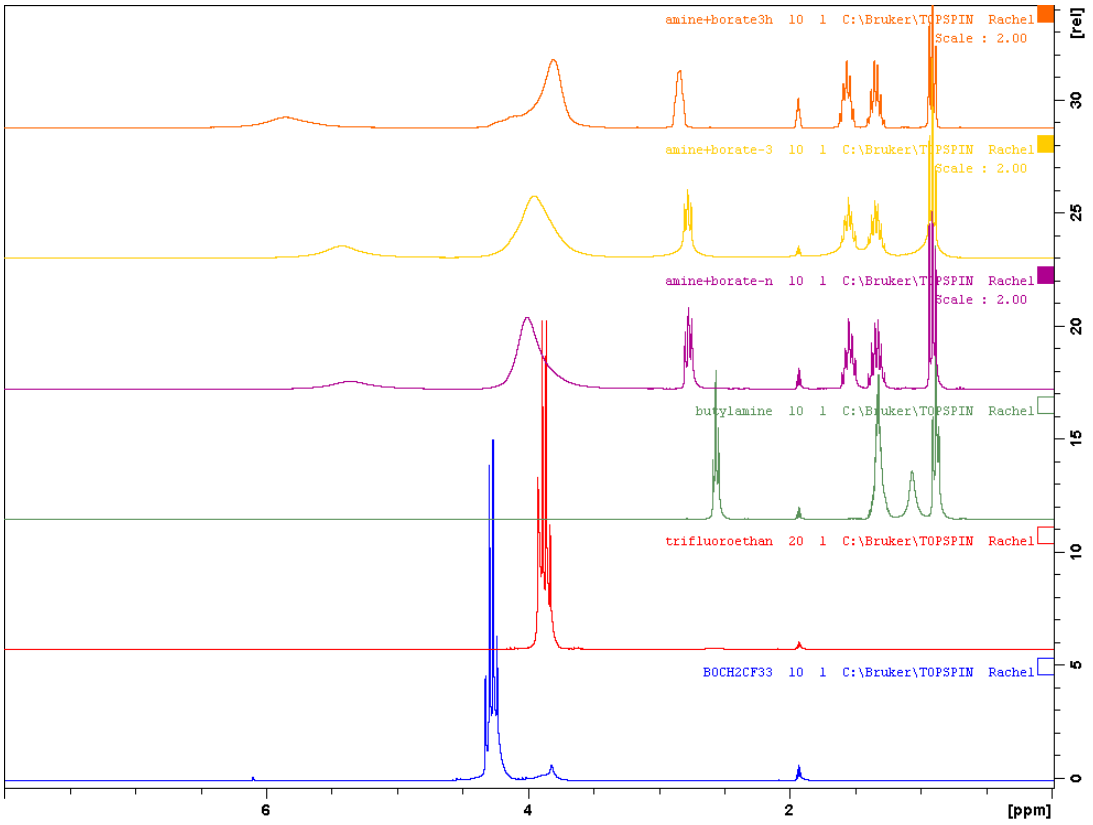


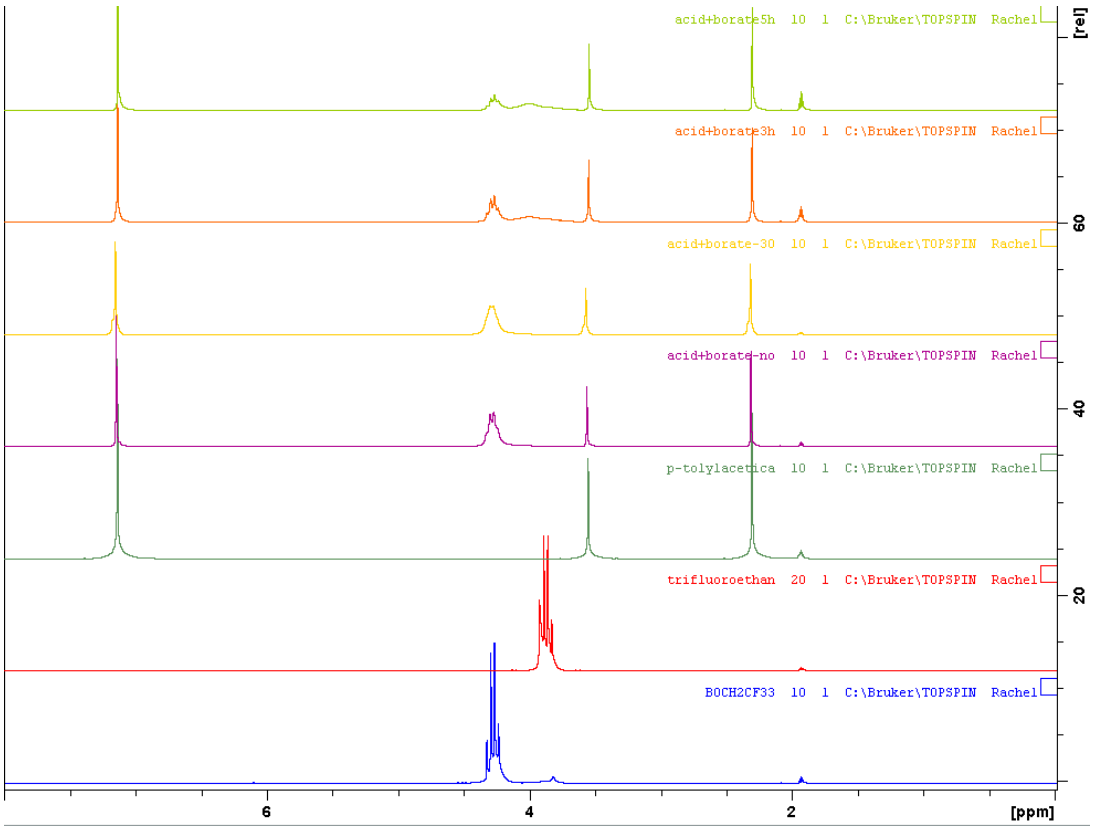
(*S*)-2-Amino-*N*-propylpropanamide 77l – (*S*)-81

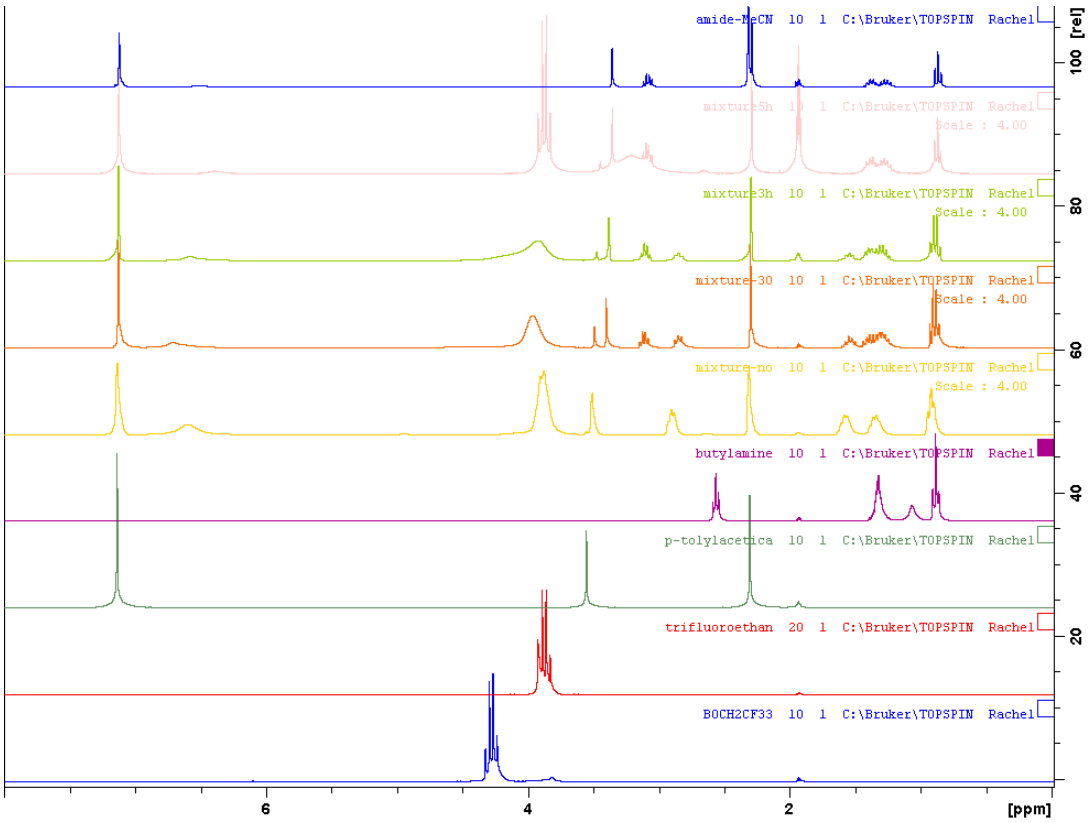


7.4. Appendix 4 – NMR study spectra

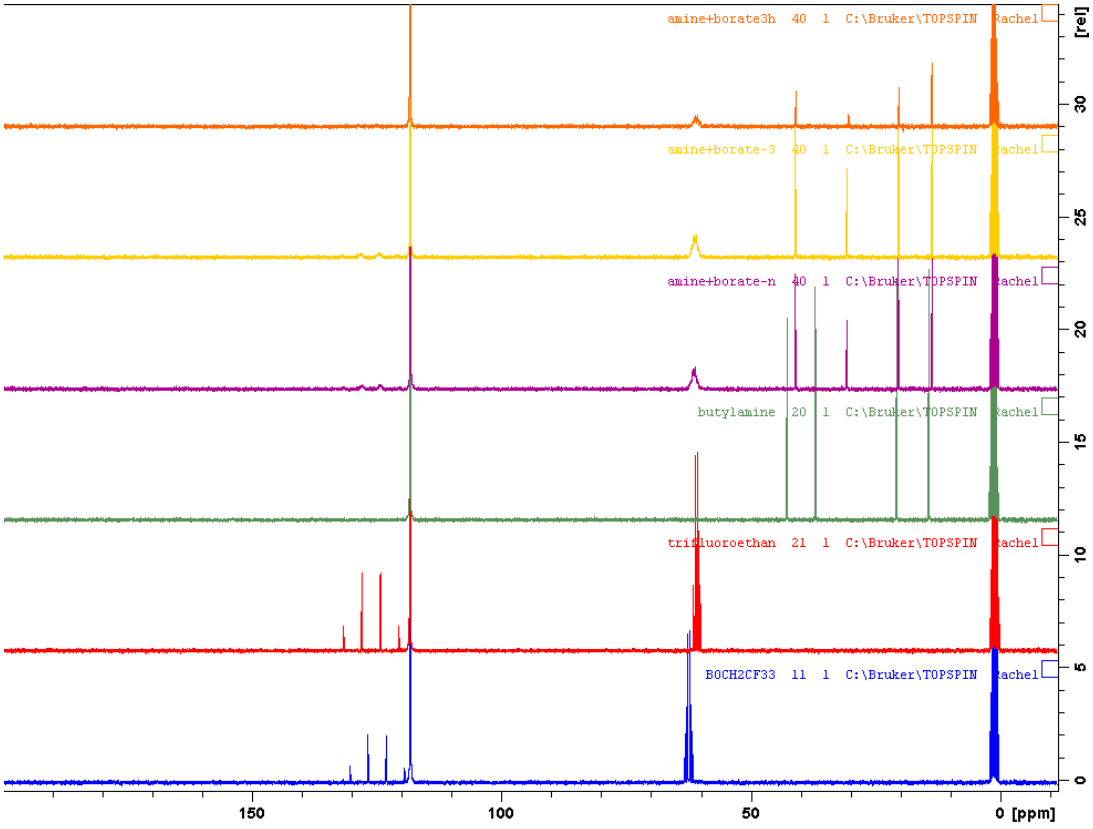
^{1}H-NMR study

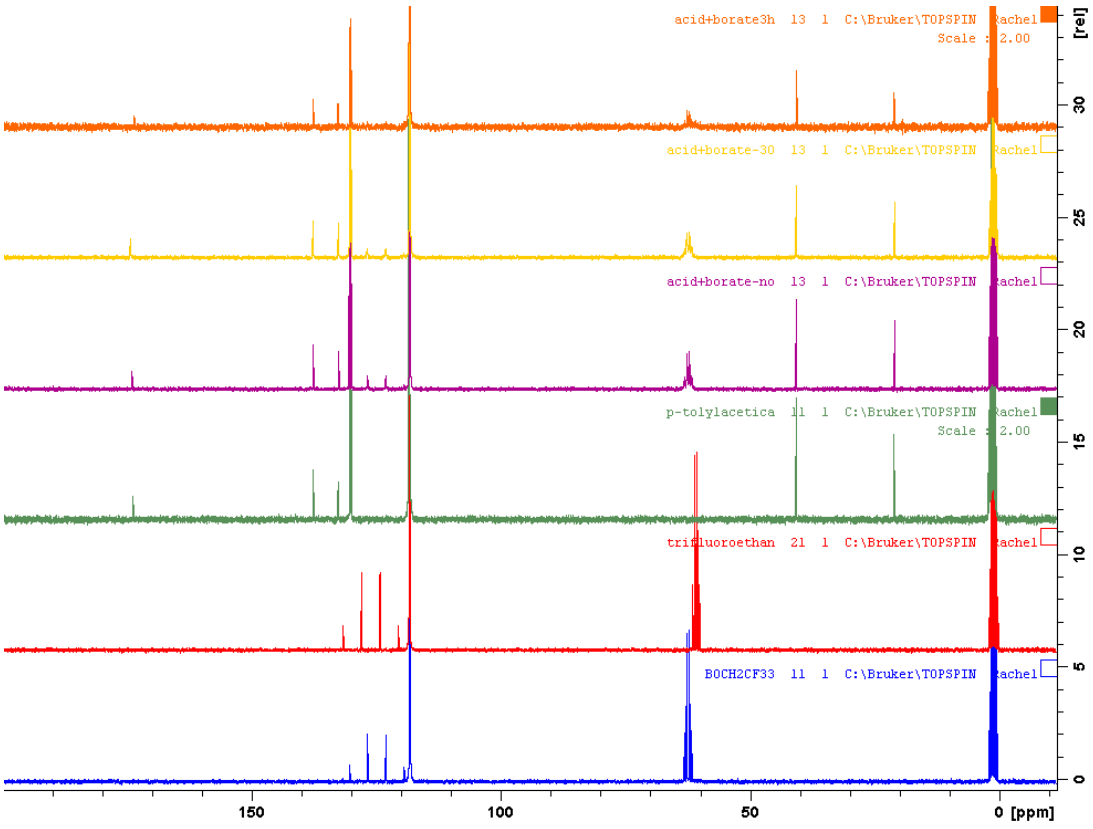


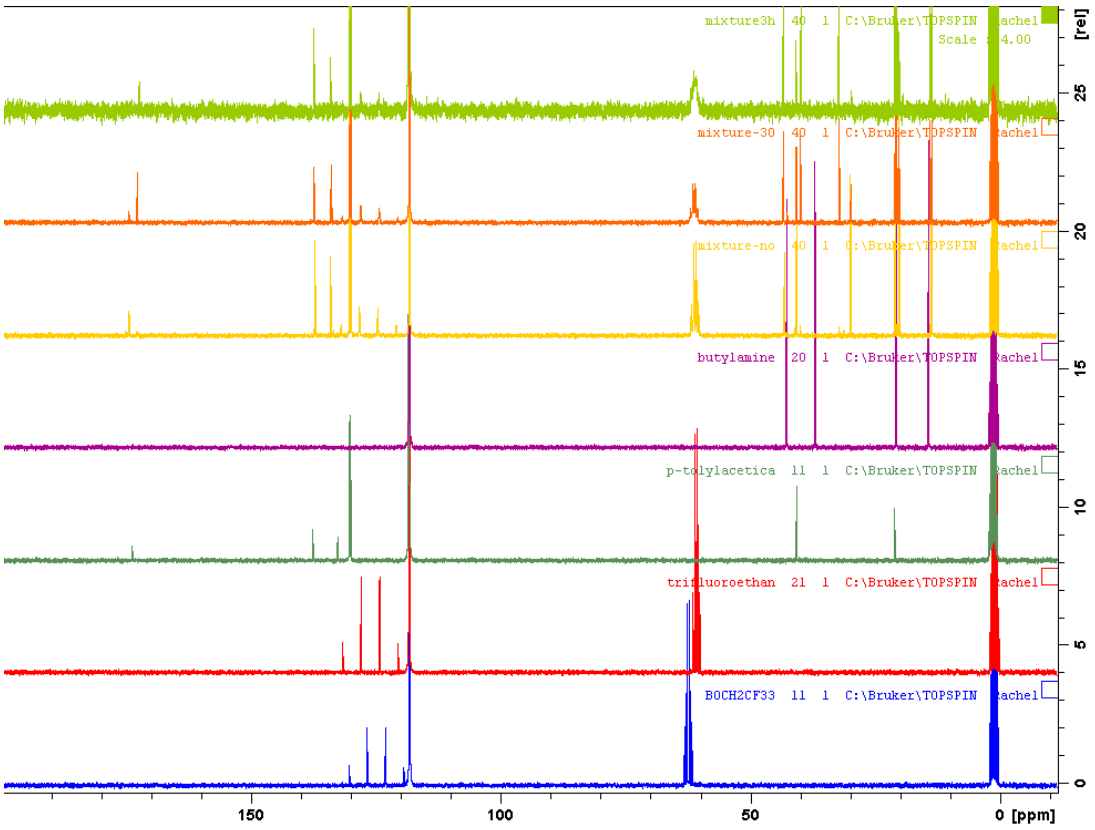



amide-MeCN 10 1 C:\Bruker\TOPSPIN Rachel
mixture5h 10 1 C:\Bruker\TOPSPIN Rachel
Scale : 4.00
mixture3h 10 1 C:\Bruker\TOPSPIN Rachel
Scale : 4.00
mixture-30 10 1 C:\Bruker\TOPSPIN Rachel
Scale : 4.00
mixture-no 10 1 C:\Bruker\TOPSPIN Rachel
Scale : 4.00
butylamine 10 1 C:\Bruker\TOPSPIN Rachel
p-tolylacetica 10 1 C:\Bruker\TOPSPIN Rachel
trifluoroethan 20 1 C:\Bruker\TOPSPIN Rachel
BOCH2CF33 10 1 C:\Bruker\TOPSPIN Rachel
100 [rel]
80
60
40
20
6
4
2
[ppm]

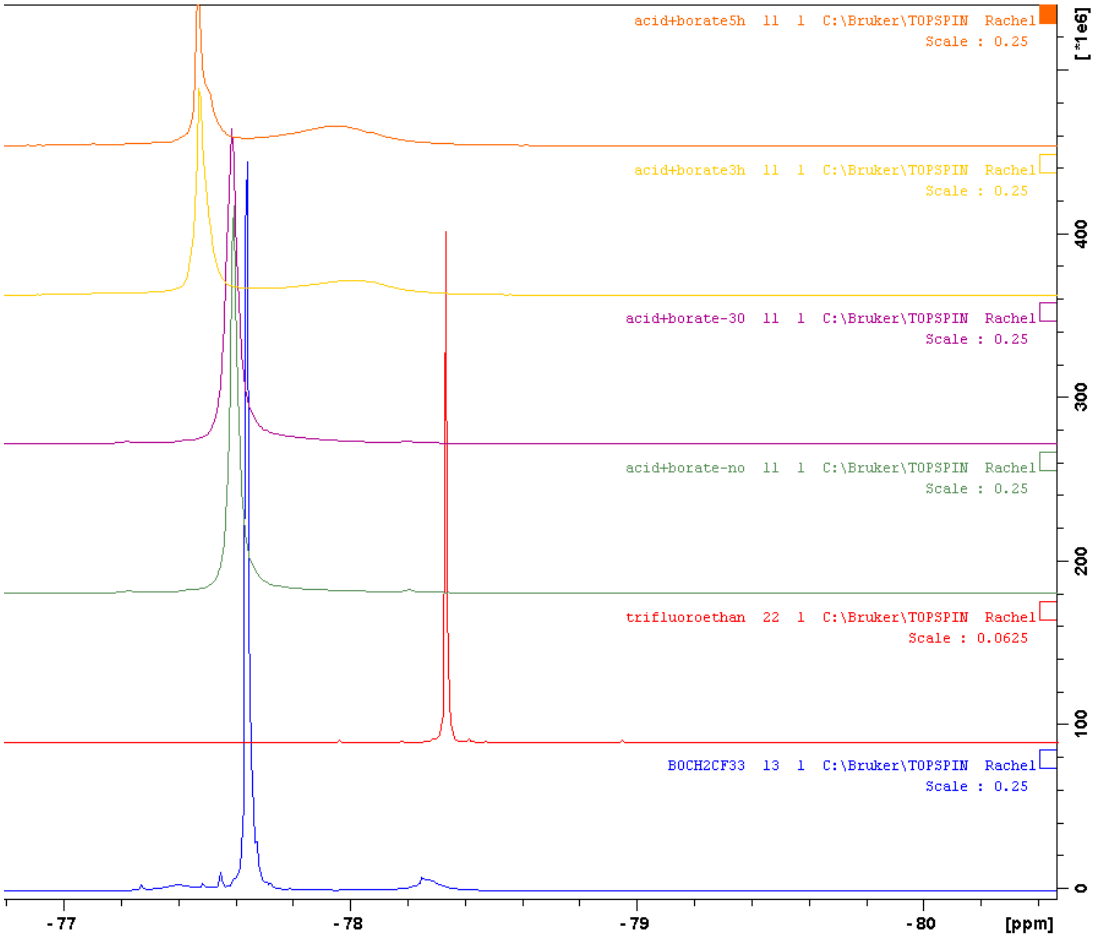
^{13}C-NMR study

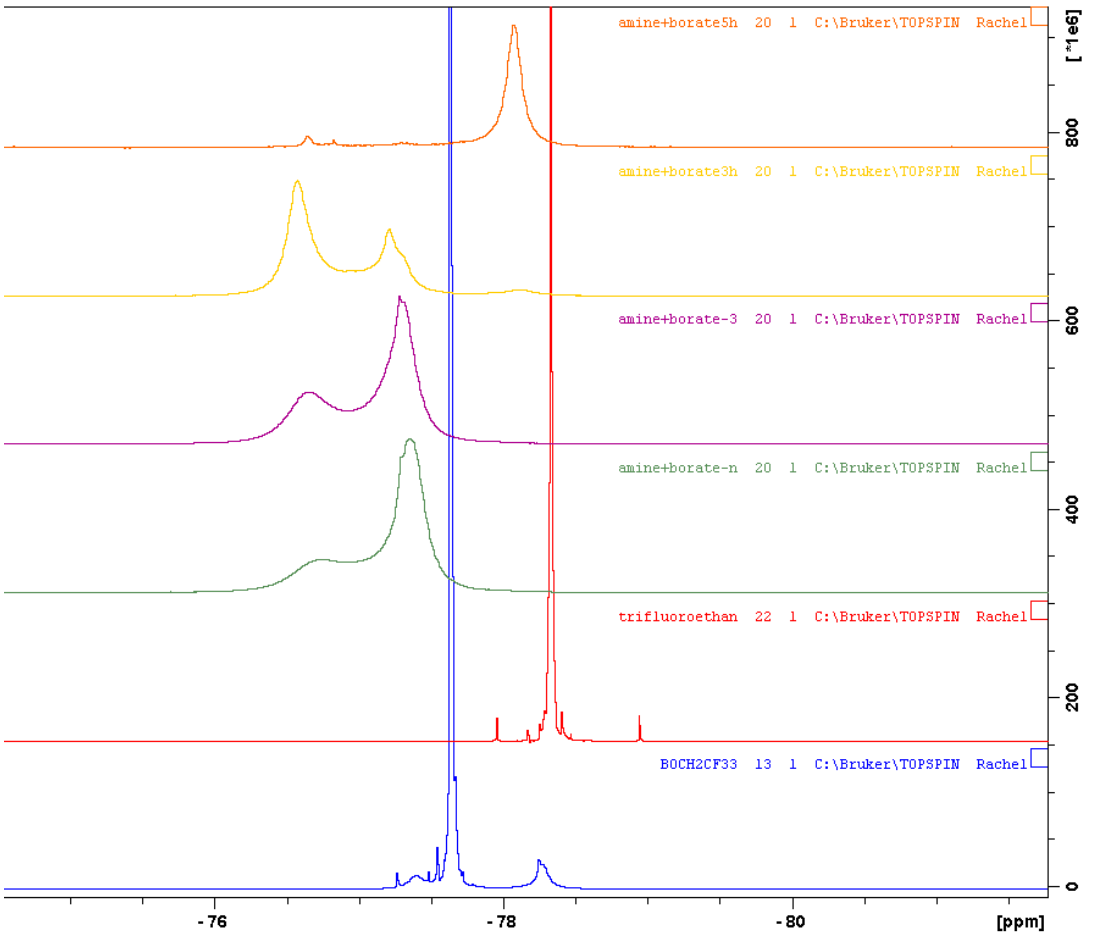


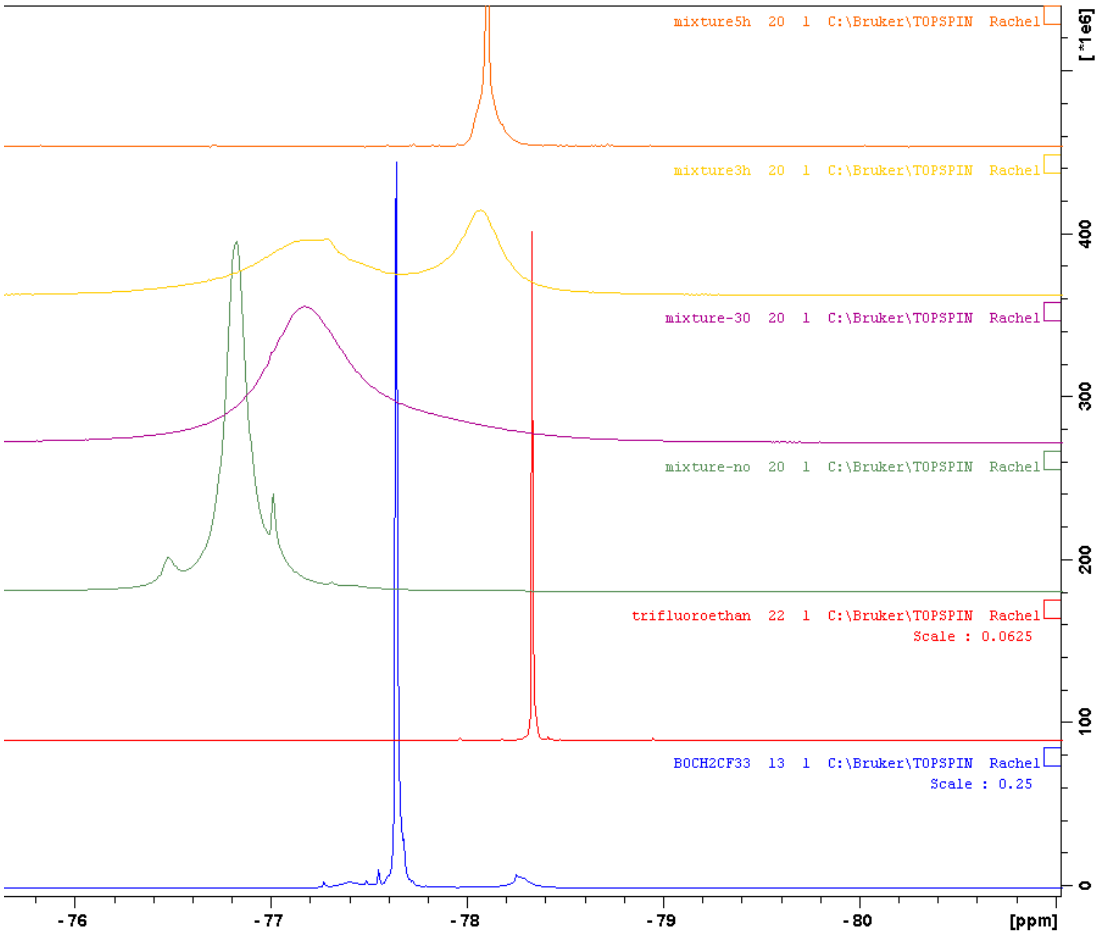



mixture3h 40 1 C:\Bruker\TOPSPIN Rachel
Scale : 4.00
mixture-30 40 1 C:\Bruker\TOPSPIN Rachel
mixture-no 40 1 C:\Bruker\TOPSPIN Rachel
butylamine 20 1 C:\Bruker\TOPSPIN Rachel
p-tolylacetica 11 1 C:\Bruker\TOPSPIN Rachel
trifluoroethan 21 1 C:\Bruker\TOPSPIN Rachel
BOCH2CF33 11 1 C:\Bruker\TOPSPIN Rachel
[rel]
25
20
15
10
5
0
150
100
50
0 [ppm]

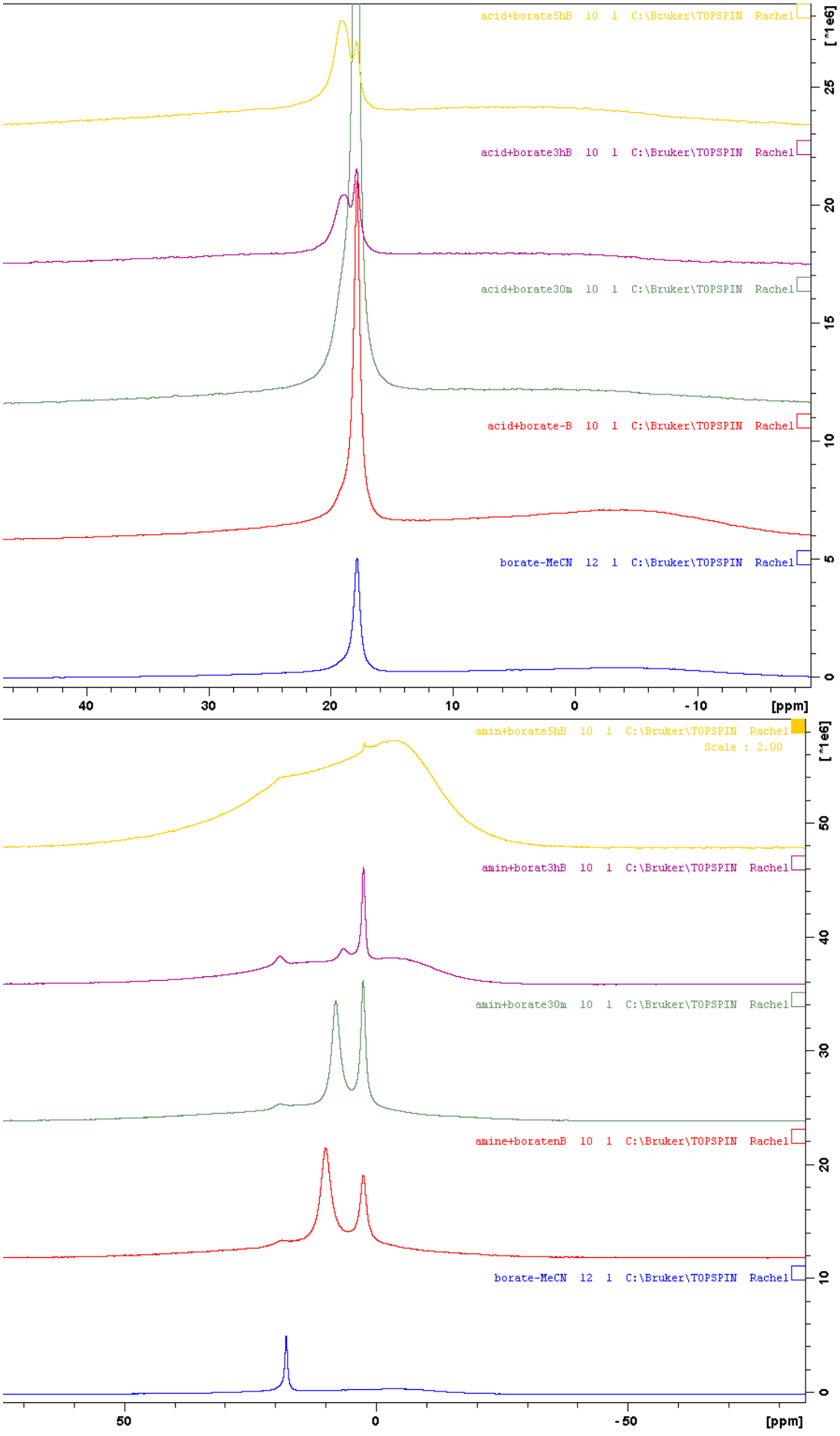
^{19}F-NMR study

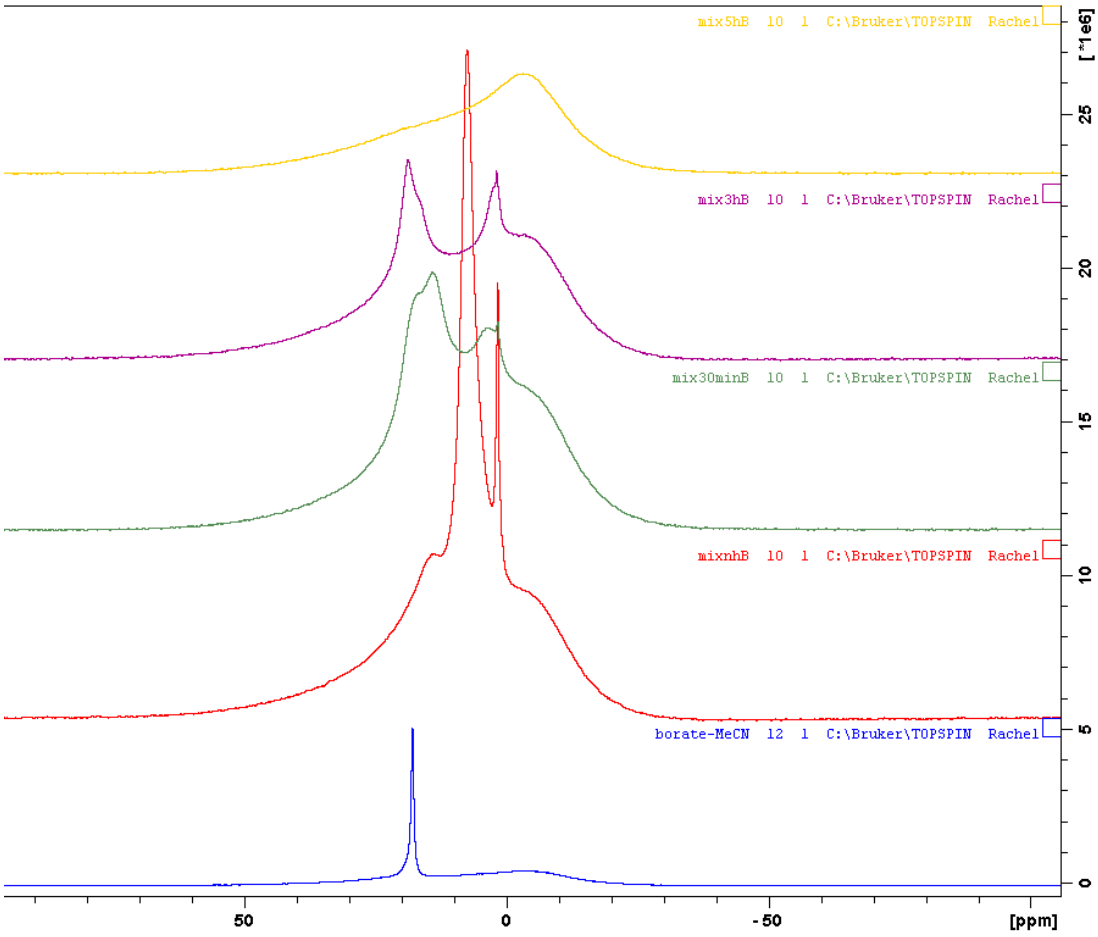





mixture5h 20 1 C:\Bruker\TOPSPIN Rachel
mixture3h 20 1 C:\Bruker\TOPSPIN Rachel
mixture-30 20 1 C:\Bruker\TOPSPIN Rachel
mixture-no 20 1 C:\Bruker\TOPSPIN Rachel
trifluoroethan 22 1 C:\Bruker\TOPSPIN Rachel
Scale : 0.0625
BOCH2CF33 13 1 C:\Bruker\TOPSPIN Rachel
Scale : 0.25
[*1e6]
400
300
200
100
0
-76
-77
-78
-79
-80
[ppm]

^{11}B-NMR study




mix5hB 10 1 C:\Bruker\TOPSPIN Rachel
mix3hB 10 1 C:\Bruker\TOPSPIN Rachel
mix30minB 10 1 C:\Bruker\TOPSPIN Rachel
mixnhB 10 1 C:\Bruker\TOPSPIN Rachel
borate-MeCN 12 1 C:\Bruker\TOPSPIN Rachel
[*1e6]
25
20
15
10
5
0
50
0
-50
[ppm]

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