Study and Development of Boron-mediated Amidation Reactions

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Declaration

I, Valerija Karaluka 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 acknowledged and indicated in this thesis.

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Abstract

This thesis discusses the study and further developments of boron-mediated amidation reactions.

Chapter I introduces the conventional and recent methods and developments for the direct amidation of carboxylic acids and their derivatives. An overview of boron-mediated transformations is also given with the focus on stoichiometric methods and boronic acid catalysts.

Chapter II describes the utilisation of $B(OCH_2CF_3)_3$ in the synthesis of medicinally-relevant amides, selective monoacylation of symmetrical diamines, and amidation of unprotected amino acids. Design of Experiments (DoE) is applied as the optimisation method for the improvement of efficiency of the amidation reaction and therefore the yield of one of the medicinally relevant amides. Furthermore, a convenient derivatisation method of amino amide products is applied to determine enantiopurity of the products.

Chapter III discusses investigations performed with the aim of understanding boron-mediated amidation reactions. A spectroscopic study is provided along with the proposed tentative mechanism.

Chapter IV describes the design and synthesis of a potential boronic acid amidation catalyst, which incorporates a borate moiety.

Conclusions and future developments as well as an outlook of the applications of borates in organic synthesis are described in Chapter V.

Chapter VI provides experimental details of this work and full characterisation of compounds synthesised throughout this project.

Chapter VII contains an appendix that includes chiral HPLC and spectroscopic data from Marfey's reagent derivatisation of chiral amino acid amide products. Moreover, spectra from ^{11}B NMR study of boron-mediated amidations and the DoE study for the optimisation of decarboxylation of amino acids are included.

Contents

Abbreviations

Ac	Acetyl
ACS	American Chemical Society
Ar	Aryl
aq.	Aqueous
PyBOP®	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
Bz	Benzoyl
Bn	Benzyl
BSA	Bistrimethylsilylacetamide
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate,
bp	Boiling point
9-BBN	9-Borabicyclo(3.3.1.)nonane
Bu	Butyl
Boc	*tert*-Butyloxycarbonyl
CDI	Carbonyldiimidazole
Cbz	Carboxybenzyl
cat.	Catalytic
CI	Chemical ionisation
conc.	Concentration/concentrated
conv.	Conversion
Cy	Cyclohexyl
CPME	Cyclopentyl methyl ether
Cp	Cyclopropyl

DFT	Density functional theory
DoE	Design of experiments
dr	Diastereomeric ratio
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DIBAL-H	Diisobutylaluminium hydride
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N,N*-Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMSO-d_6	Dimethyl sulfoxide, deuterated
EI	Electron ionisation
ES	Electron spray
EWG	Electron withdrawing group
ee	Enantiomeric excess
er	Enantiomeric ratio
EEDQ	2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
Et	Ethyl
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	Equivalents
HFA	Hexafluoroacetone
HPLC	High-performance liquid chromatography
HOBt	1-Hydroxybenzotriazole
IR	Infra-red
i	Iso
IPA	Isopropyl alcohol
Lit.	Literature
MR	Marfey's reagent

mp	Melting point
m	Meta
MOM	Methoxymethyl acetal
Me	Methyl
MTHP	4-Methyltetrahydropyran
MW	Microwave
mg	Milligram
mL	Millilitre
mmol	Millimole
min	Minutes
MS	Molecular sieves
MW	Molecular weight
NCA	*N*-Carboxy anhydride
NMP	*N*-Methyl-2-pyrrolidone
MIDA	*N*-methyliminodiacetic acid
T3P®	*n*-Propanephosphonic acid anhydride
NMR	Nuclear magnetic resonance
OVAT	One variable at a time
OPRD	Organic Process Research and Development
o	Ortho
p	Para
ppm	Parts per million
Ph	Phenyl
Pr	Propyl
Pg	Protecting group
quant.	Quantitative
RF	Radiofrequency

RDS	Rate determining step
RT	Room temperature
TAME	*tert*-Amyl methyl ether
TBS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBME	*tert*-Butyl methyl ether
tert	Tertiary
THF	Tetrahydrofuran
TDBTU	*N,N,N′,N′*-Tetramethyl-*O*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)uronium tetrafluoroborate
TLC	Thin layer chromatography
TFA	Trifluoro acetic acid
UV	Ultraviolet

Acknowledgements

First of all, I would to thank Dr Tom Sheppard for giving me an opportunity to work in his group and making it such a wonderful experience. Tom's support and encyclopaedic knowledge of chemistry, which I probably will never be able to match, has helped me through these years immensely. I would also like to thank my industrial supervisor, Dr Matt Badland, for supporting me throughout this project and providing valuable advice during my time in Pfizer labs. A big thank you goes to Dr Mike Porter for his patience with me during my fruitless attempts at learning computational chemistry.

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Last and never the least, I would like to thank Gareth, whom I have been fortunate enough to meet just at the start of this entire experience, for his humour and silliness that kept me sane and made my approach to life so much more optimistic; I look forward to all travels and future adventures together.

«Что бы ни говорили пессимисты,

земля все же совершенно прекрасна,

а под луною и просто неповторима.»

М. А. Булгаков

To my brother, Sasha, and my baby sister, Veronika

1. Introduction

The amide bond is an extremely important and commonly occurring linkage both in nature and synthetic chemistry. Not only is it an essential part of the protein build up, it is also recognised by the pharmaceutical industry as a crucial functional group for the synthesis of biologically active compounds and drugs. In 2005, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCI PR) was established with the view to collectively identifying research areas needing the development of greener approaches in organic synthesis.[1] The synthesis of amide bonds was nominated as the transformation that required the most improvements in atom economical reagents. Upon analysis of drug candidates it was discovered that amide-forming reactions were used in the synthesis of 65% of the molecules under the survey.[1] A more recent study that reviewed publications by three large pharmaceutical companies; AstraZeneca, Pfizer, and GSK, found that 16% of the reported routes to drug targets involved an amidation reaction.[2] To date, about 25% of top-selling drugs contain an amide linkage (selected examples in Figure 1).[3,4]

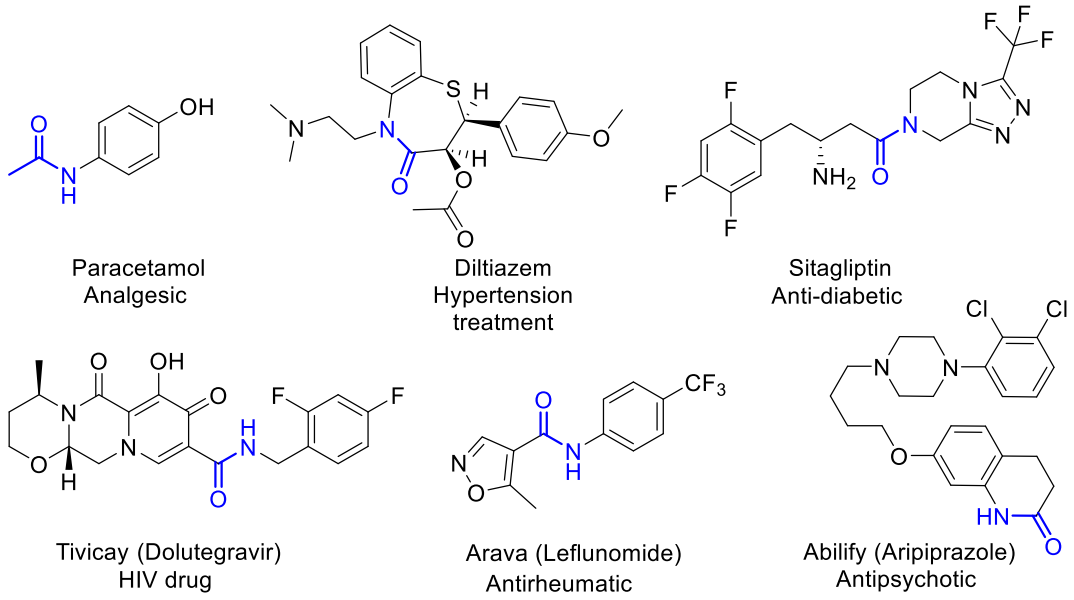
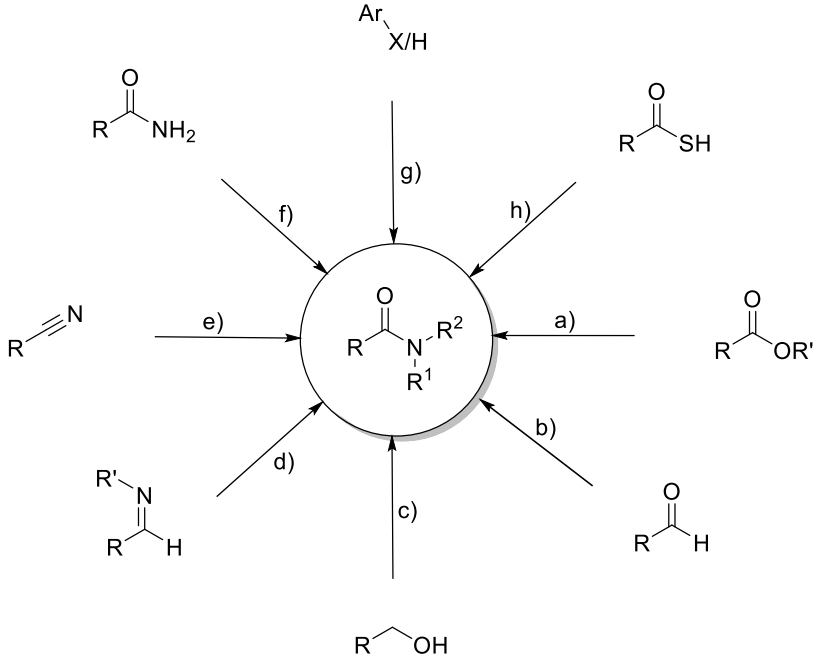


Figure 1 Examples of amide-containing drug molecules

As pointed out by Bode and Pattabiraman, due to the vast number of approaches to amide formation, it may often be not considered as a synthetic challenge.[5] However, the most commonly used procedures, although general in the application, make use of toxic and wasteful reagents, which often are too harsh for other functionalities to be tolerated. Consequently, there have been numerous developments in this area using a vast array of starting precursors to amides, and introducing a large variety of

activating agents and catalysts with the aim of overcoming some or all of these disadvantages.

The ultimate challenge is the development of methodologies that are scalable, inexpensive, and environmentally friendly. A vast number of developments were reported introducing greener procedures and utilising a wide range of starting materials. Many excellent reviews[6–10] highlight these methods which employ different starting pre-cursors to amides, such as esters,[11–14] aldehydes,[15–17] alcohols,[16,18,19] oximes,[20,21] nitriles,[22] primary amides,[23–25] metal-catalysed oxidation of alkyl or CO insertion,[26–28] thioesters,[29] etc. (Scheme 1).



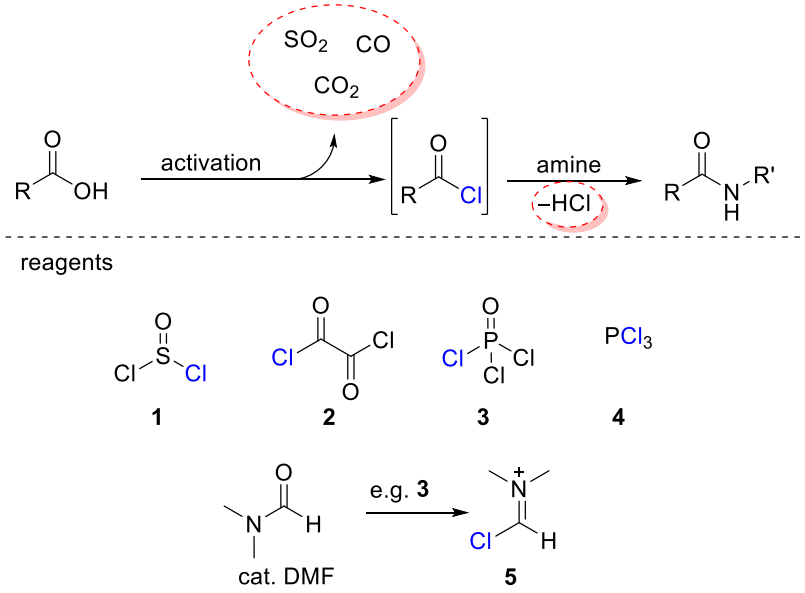
Scheme 1 Alternative routes to amides from a variety of starting materials; Selected examples of recent methods used for the amide synthesis: a)[14] Jamieson *et al.*: Amine (1 equiv.), CF_3CH_2OH (20 mol%), K_3PO_4 (1 equiv.), 1,4-dioxane (2 M), 125 °C, 0.5 h; b)[17] Kokotos *et al.*: (i) $PhCOCO_2H$ (10 mol%), DIAD (0.6 equiv.), 2 × 15 W household lamps, RT, 1.5 - 48 h; (ii) Amine (1 equiv.), CH_2Cl_2 (0.75 M), RT, 24 h; c)[30] Yang *et al.*: Amine (1.2 equiv.), $[PyPS]_3PW_{12}O_{40}$ (2 mol%), TBHP (3 equiv.), 90 °C, MW (700 W); d)[20] Pantoş *et al.*: $Pd(en)(NO_3)_2$ (10 mol%), MeOH (60 °C) or H_2O (80 °C), 3.5 - 16 h; e)[22] Qu *et al.*: Thiolate-Diiron complex (30 mol%), $HBF_4{\cdot}Et_2O$ (30 mol%), acetone (0.15 M), RT, 2 h; f)[23] Gamba-Sánchez *et al.*: Amine (0.6 equiv.), $Fe(NO_3)_3{\cdot}9H_2O$ (5 mol%), toluene (1.7 M), reflux; g)[27] Deng *et al.*: Amine (2 equiv.), CuI (10 mol%), PivOH (0.62 M), 120 °C, 48 h, O_2; h)[29] Liebeskind *et al.*: Amine (1.3 equiv.), BSA (1 equiv.), THF, RT, 3 - 24 h

Amongst these methods, however, the direct coupling of carboxylic acids and amines remains the most benign and desirable approach due to their ubiquity in contrast to other building blocks (1595 of carboxylic acids available on Sigma Aldrich vs. 1387 esters, 1171 aldehydes, 1134 alcohols, 658 nitriles, 415 amides).[31]

Most classical approaches, particularly in the large scale preparation of amides, rely on carboxylic acids being pre-activated or transformed into more reactive

derivatives, such as acyl chlorides or anhydrides.[4,32] In fact, a study performed in 2006 by Carey *et al.* looking into the most commonly performed reactions by the three major pharmaceutical companies, identified that acylation of the amine to amide accounted for approximately 2/3 of these; more importantly, all of these reactions utilised procedures using stoichiometric reagents to pre-activate the carboxylic acids.[32]

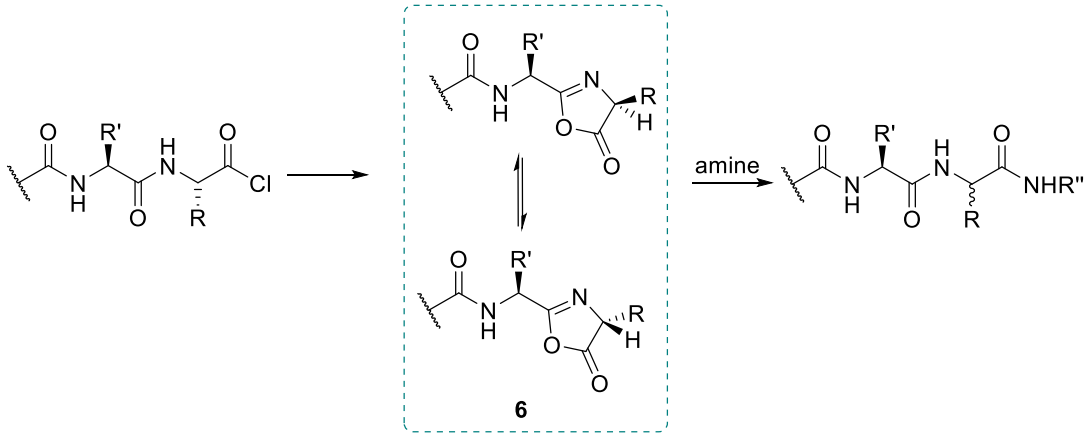
Acyl chlorides are the most commonly used activated derivatives of carboxylic acids. Formation of an acyl chloride is a convenient method for the pre-activation of carboxylic acid as it is done *in situ*, and is fast and quantitative. A good selection of reagents for acyl chloride synthesis is available, such as thionyl chloride **1**, oxalyl chloride **2**, phosphorus oxychloride **3**, phosphorus trichloride **4**, and Vilsmeier reagent **5** which can be formed from **1**, **2** or **3** with catalytic amounts of DMF (Scheme 2).[33,34]



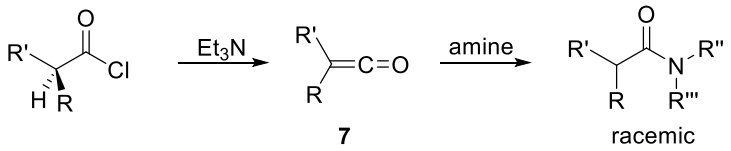
Scheme 2 A selection of reagents for the preparation of acyl chlorides *in situ*

This method accounts for 40% of the amidation reactions used in the synthesis of candidate drug molecules.[1] The major drawback, however, is that the chlorinating reagents and the acid chlorides are incredibly hazardous and moisture sensitive, therefore their use on a large scale is not desirable. Moreover, toxic waste and greenhouse gases are released as by-products in stoichiometric amounts (Scheme 2). This may not be a safety issue, as a simple basic scrubbing would neutralise the waste, but it certainly is not a suitable method for acid-sensitive substrates. For example, the use of acyl chlorides is limited in the synthesis of peptides due to the risk of protecting group removal (e.g. Boc group on amines or ester hydrolysis) as

well as racemisation *via* the formation of oxazolones **6** when the peptide is activated (Scheme 3).[33] Moreover, racemisation may occur under basic conditions, e.g. in the presence of Et_3N, which is used to quench HCl produced during the reaction, leading to the formation of ketenes **7** (Scheme 4).



Scheme 3 Epimerisation of the dipeptide product *via* oxazolone formation



Scheme 4 Ketene-mediated racemisation of the amide product

The second most popular approach, accounting for up to 36% of the methods employed in large scale amidation amongst surveyed drug molecules, is the use of carbodiimides such as *N,N'*-dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (EDCI·HCl) (Figure 2).[4,34]

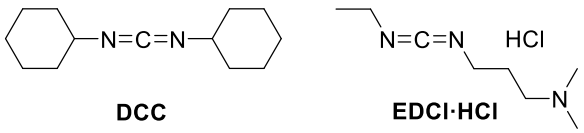
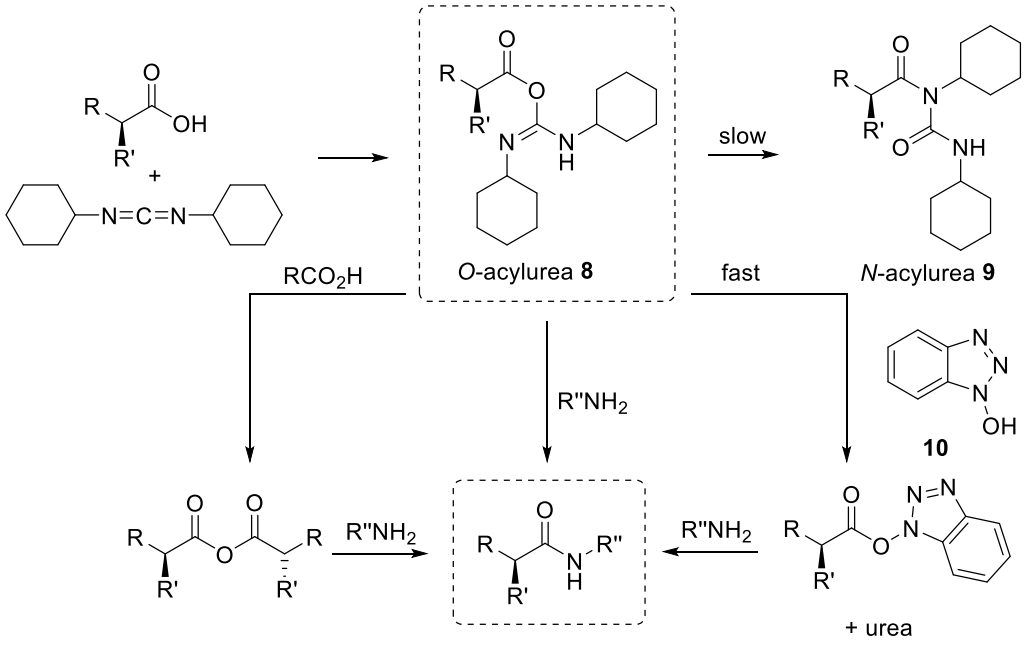


Figure 2 Carbodiimides as stoichiometric amidation reagents

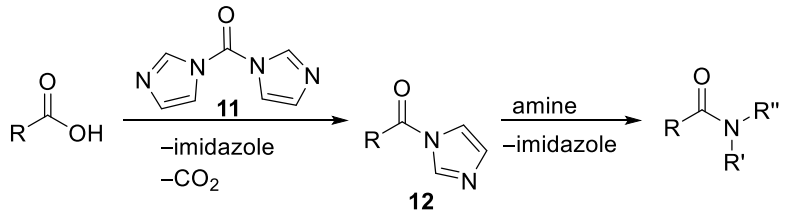
DCC is a commonly used coupling reagent due to its low cost, but the major drawback, apart from health hazards, is the production of by-products (urea) that are difficult to separate from the desired amide product. Morevover, the *O*-acylurea **8**, formed from the carboxylic acid and carbodiimide, is prone to epimerisation or may rearrange into the unreactive *N*-acylurea **9** (Scheme 5). Carboxylic acids with an α-stereo centre are particularly at risk of racemisation.[34,35] HOBt **10** is often used as an additive to prevent epimerisation of **8**, but this brings an extra hazard as this

reagent is shock sensitive.[34] Although the use of EDC for the activation of carboxylic acids results in lower epimerisation rates of chiral products, and its urea by-product is much easier to remove making its use more attractive for drug synthesis, it is much more expensive making its use in large scale preparation less desirable.[34]



Scheme 5 Routes and by-products formed during DCC-mediated amidation

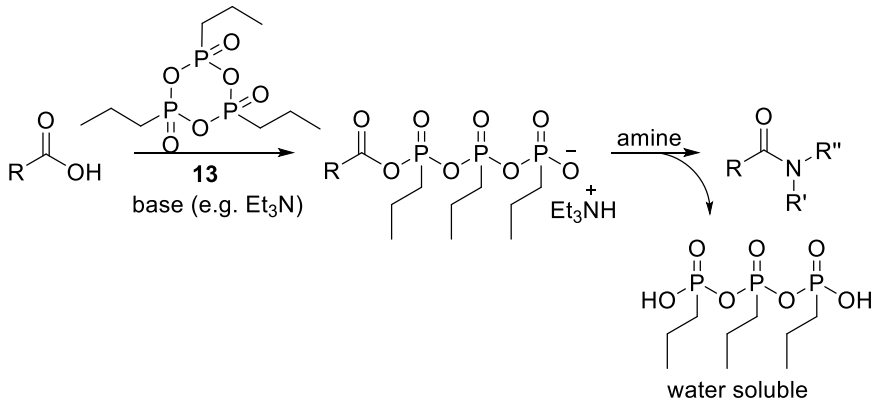
CDI **11** is another commonly used reagent, particularly in large scale synthesis, as it is inexpensive and easy to handle, and the imidazole by-product can be easily removed in the work-up (Scheme 6). However, the reagent is moisture sensitive and also has a limited scope when it comes to the coupling of aromatic amines (aniline derivatives) with the pre-activated intermediate **12**.[36]



Scheme 6 CDI-mediated amidation

More recently, *n*-propanephosphonic acid anhydride (T3P®) **13** has emerged as a useful amidation reagent. It was initially used in peptide synthesis only, but was later found to have a large variety of general applications, including amide synthesis directly from carboxylic acids (Scheme 7).[37] T3P® is easy to handle as it is provided as a 50% w/w or v/v solution in most common organic solvents. Its main advantage over the more conventional amidation reagents is the low propensity for product

epimerisation, which is particularly attractive in peptide synthesis.[38] However, the cost of T3P® is still quite high for large scale synthesis (Table 1).



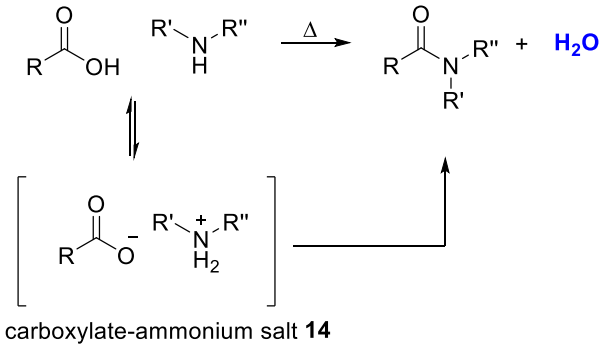
Scheme 7 T3P®-mediated amidation

Coupling Reagent	Yield (%)	Rate of epimerisation
T3P® (£932 per mol; 50% wt in EtOAc)	86.6	1.8
EDC/HOBt (£1.8k + £211 per mol)	67.3	11.1
DCC/HOBt (£37 + £211 per mol)	60.5	5.9
HATU (£18.8k per mol)	58.6	21.1
EEDQ (£727 per mol)	12.0	27.3
PyBOP® (£13.4k per mol)	63.4	14.2
TDBTU (£11.3k per mol)	97.7	1.1

Table 1 Comparison in cost (as sold from Sigma Aldrich), yields, and epimerisation of coupling reagents commonly used in peptide synthesis

1.1 Recent developments in the direct amidation of carboxylic acids

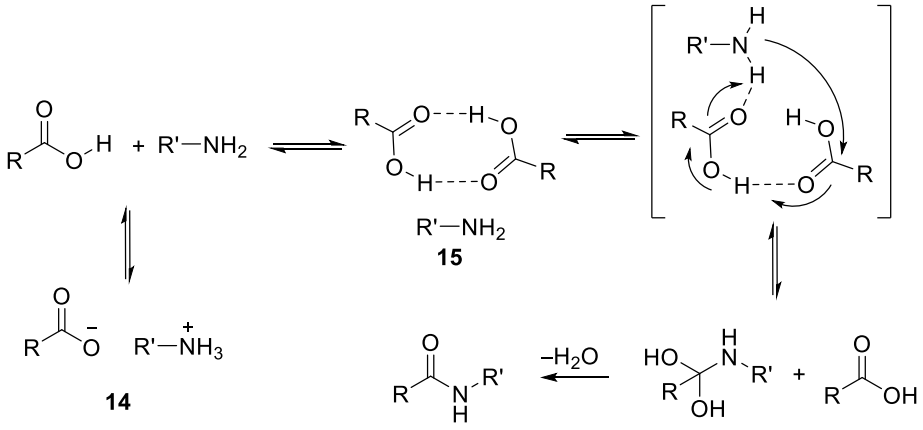
Ideally, the simplest approach to the amide linkage is the condensation of a carboxylic acid and an amine, where only water would be produced as the by-product (Scheme 8). In principle, this could be achieved under thermal conditions. However, in practice this approach is not feasible due to the believed formation of the unreactive carboxylate-ammonium salts **14** (Scheme 8).



Scheme 8 "Ideal" amidation reaction

The first report on the direct thermal amidation dates back to 1858, however, due to the harsh conditions required, few further developments were made, and therefore this area remained somewhat under-developed.[33,39,40] The scope was limited to only thermally stable, structurally simple substrates.[41] This eliminated the majority of pharmaceutically relevant amides. However, in recent years it has been established that the propensity of the ammonium-carboxylate mixture to form an amide depends on other reaction conditions, i.e. polarity of the solvent, efficacy of water removal, and reactivity of the substrates.

In 2011, Whiting *et al.* proposed a plausible mechanism of thermal amidation based on their observations from calorimetric and NMR experiments, and DFT calculations (Scheme 9).[41]

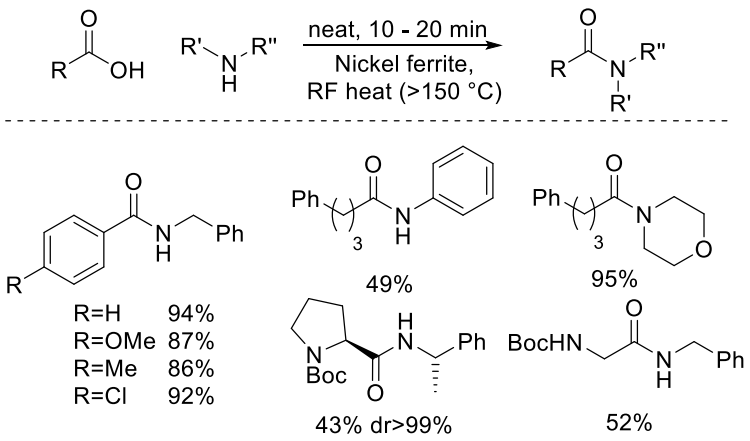


Scheme 9 Proposed mechanism of thermal amidation aided by H-bonding activation of the carboxylic acid supported by DFT calculations

It was determined that the ammonium-carboxylate salt **14** formation does occur, particularly with a strong acid-amine pair. There was a clear correlation between the strength of the acid and heat output when it was mixed with an amine. For the strong acids, higher degree of salt precipitation was also observed. Interestingly, the reactivity was higher for acids with lower pKa values. The link between the basicity

and reactivity of amines was less clear, and perhaps was more dependent on steric and electronic effects. For example, benzylamine was shown to be the most reactive, which was proposed to be due to the "benzylic effect".[41] The postulated mechanism suggested the formation of H-bonded dimeric species **15** that activated the carbonyl for the attack by the amine, which could then proceed to form the amide by the elimination of water.[41] They also established that the reaction was unlikely to be driven by the excess of acid or base in contrast to the esterification process. Moreover, it was concluded that the zwitterionic species **14** were not a part of the direct amidation. In all experiments, efficient water removal was necessary for the reaction to proceed catalyst free.

Microwave-assisted (MW) and radiofrequency (RF) heated reactions have been amongst major recent developments to aid the direct condensation between amines and carboxylic acids, which significantly shorten reaction times and improve yields.[42,43] In 2013, Rebrov *et al.* used RF heating in solvent free conditions to successfully synthesise a selection of amides with good scope (Scheme 10).

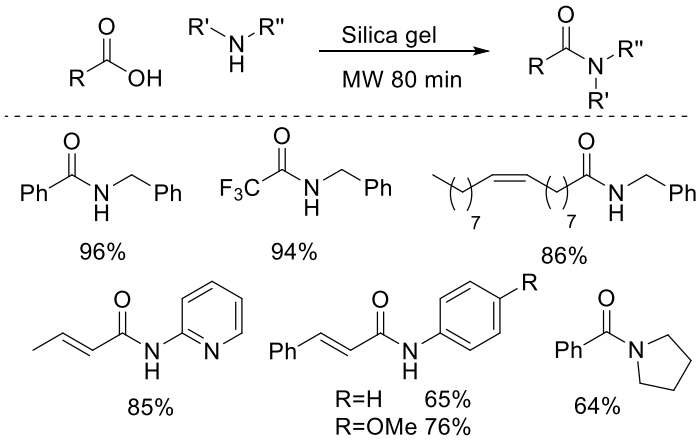


Scheme 10 Examples of RF-mediated thermal amidation

The developed procedure used the coupling of AC magnetic fields with the absorbing magnetic nickel ferrite as the heat source, which allowed the reaction mixture to be heated between 150-220 °C.[44] The products were often isolated by simple recrystallisation or filtration through a short pad of silica, and the heat source could be recycled by magnetic separation. This procedure benefited from very short reaction times leading to high yields of products.

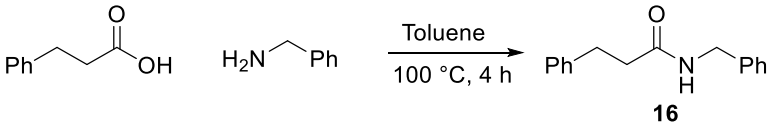
In 2015, Gamba-Sánchez *et al.* reported MW-mediated direct amidation using silica gel as a solid support. The methodology also benefited from short reaction times and simplicity of the operational setup. No solvent was required, making the procedure more environmentally benign, although pre-loading of the reactants onto

the silica was necessary with the aid of ethyl acetate.[45] Most often, products were isolated by a simple aqueous work-up. Good yields were obtained with a range of carboxylic acids, including unsaturated examples, and a variety of primary and secondary amines. Aniline derivatives, and even unreactive 2-aminopyridine also worked well (Scheme 11).



Scheme 11 Selected examples for solvent-free thermal amidation with silica

Williams and co-workers explored the possibility of lowering the temperature of thermal amidation, and hypothesised that the unreactive salts were less likely to form in non-polar solvents which made it more likely for the reaction to occur more efficiently.[46] Indeed, after 20 hours at reflux in toluene, a full conversion to the amide product **16** was achieved without the aid of drying methods (molecular sieves or azeotropic water removal).



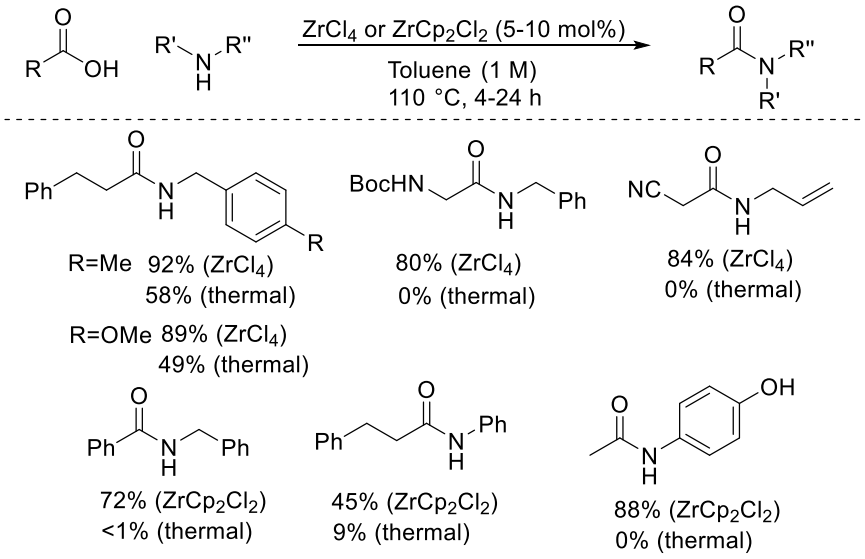
Scheme 12 Comparison of zirconium salt catalysts with thermal amidation

Catalyst	Conversion (%)
No catalyst	20
$FeCl_2$ (20 mol%)	100
$ZrCl_4$ (20 mol%)	100
$ZrCl_4$ (5 mol%)	83
$TiCl_4$ (20 mol%)	100
$TiCl_4$ (5 mol%)	26
$ZrCp_2Cl_2$ (5 mol%)	100

Table 2 Catalyst screen for the direct amidation catalysed by metal salts

Importantly, polar solvents such as water and DMSO resulted in no product at all.[46] During this study, the group also identified zirconium salts to be good catalysts for the direct amidation which reduced the reaction time required for thermal amidation.[46] From the catalyst screen, $ZrCl_4$ and $ZrCp_2Cl_2$ were selected as the best catalysts and only 5 mol% loading was required for the conversion to **16** in 83% and 100% respectively after 4 hours. Moreover, several other transition metal salts were found to catalyse the direct amidation (Table 2).

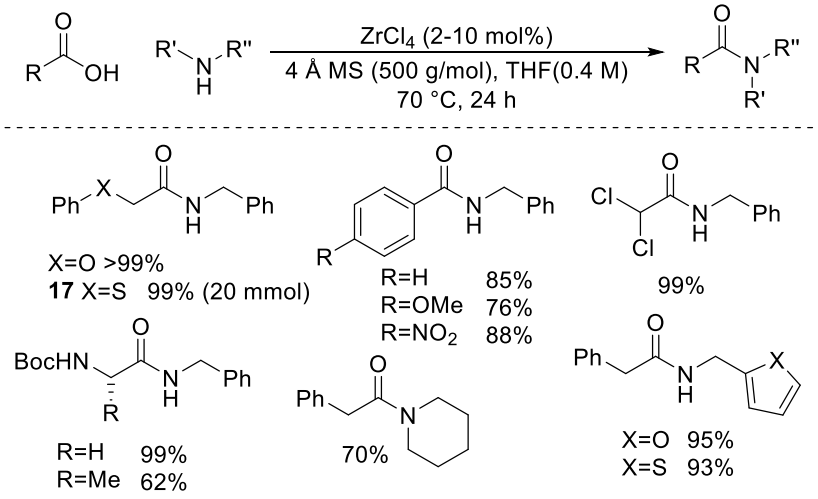
The scope was then explored with and without the catalyst, and in all cases, the catalyst improved the rate of the reaction. A variety of functionalities tolerated the conditions, including heterocyclic compounds, amino acid derivatives, showing no racemisation, and electron-donating and withdrawing aromatic substituents. Aniline and benzoic acid were less reactive in the presence of $ZrCl_4$ catalysts, but the yields could be improved by using the more expensive $ZrCp_2Cl_2$ instead (Scheme 13). Importantly, these examples highlighted the efficiency of the catalysts, as very low conversions were observed without the use of the catalysts.[46]



Scheme 13 Selected examples of zirconium catalysed amidation by Williams *et al.*

At the same time, Adolfsson *et al.* also reported the use of 2-10 mol% $ZrCl_4$ for direct amidation.[47] By introducing 4 Å molecular sieves as the drying agent, it was possible to lower the reaction temperature to 70 °C with anhydrous THF as the solvent. This meant that the degree of the background reaction was significantly lower than reported by Williams in toluene.[46] In the examples given, either the acid or amine counterpart was used in a slight excess. The reaction demonstrated excellent scope with regards to carboxylic acid; functional groups such as nitro, halogens, ethers and thioethers were well tolerated. Carboxylic acids with electron-

withdrawing groups resulted in better yields, and heterocyclic and secondary amines were also high yielding. No examples of weakly nucleophilic amines, such as aniline derivatives, were given, however. Large scale (20 mmol) preparation of amide **17** was demonstrated, although this example highlights the limitation of the methodology, which is the use of large quantity of molecular sieves (250 g per mol on large scale, Scheme 14).



Scheme 14 Adolfsson's[47] method of zirconium-mediated amidation, selected examples

With regards to the mechanism of Zr-mediated amidation, Adolfsson has proposed three possible modes of activation: a) a classical Lewis-acidic activation at the carbonyl (Figure 3a); b) simultaneous activation at the carbonyl and the leaving hydroxyl group (Figure 3b); c) formation of the Zr carboxylate (Figure 3c).[47]

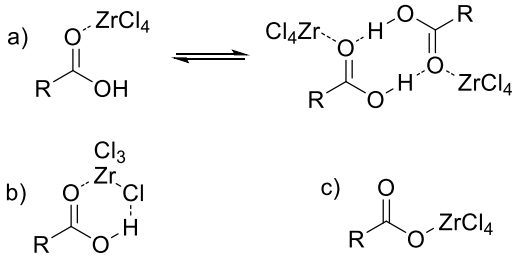
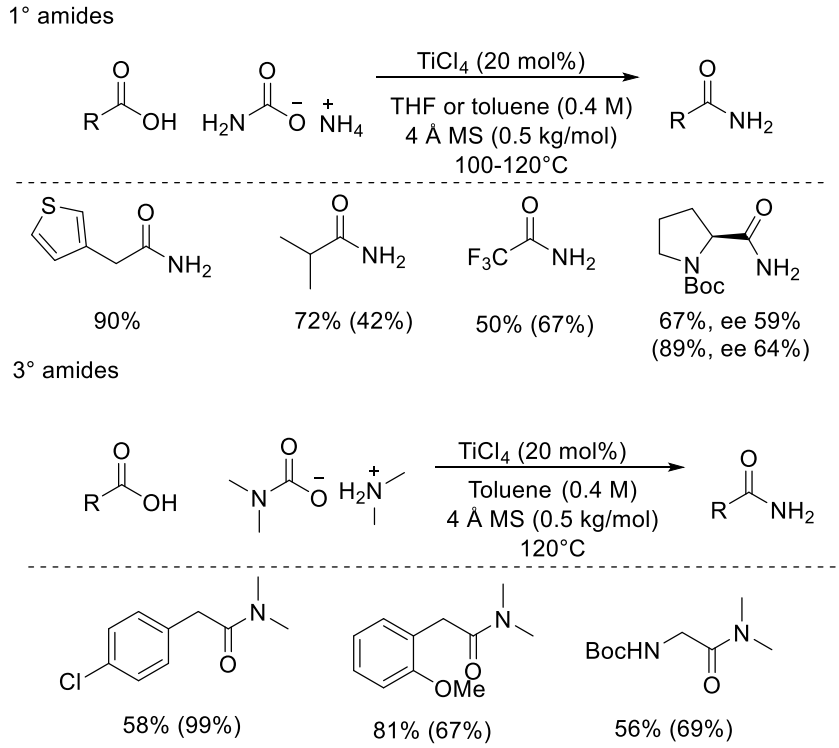


Figure 3 Proposed Zr-activated intermediates; a Lewis-acidic activation.; b. Simultaneous activation of the carbonyl moiety and hydroxyl group; c. Activation of the acid moiety making a better leaving group

Later that year, Adolfsson *et al.* published further updates using $TiCl_4$ and $ZrCl_4$ in the direct amidation of non-activated carboxylic acids.[48] The group extended the scope to the formation of primary and tertiary with carbamates and carboxylic acids (Scheme 15). Thermal conversion to amides was also monitored, and was found to be negligible or very low. Aromatic carboxylic acids gave higher primary amide yields with $TiCl_4$ as a catalyst than with $ZrCl_4$. Although no racemisation was

observed with $ZrCl_4$ at 70 °C in the synthesis of secondary amides (Scheme 15), higher temperature conditions led to near complete racemisation of the prolinamide product.



Scheme 15 Selected examples of primary and tertiary amides synthesised with $TiCl_4$ catalyst; yields and enantiomeric excess values in parenthesis represent the reaction catalysed by $ZrCl_4$

The group also explored other metal catalysts for the amidation, and identified $Ti(O^iPr)_4$ as a good catalyst which is inexpensive and easy to handle (Table 3).[49]

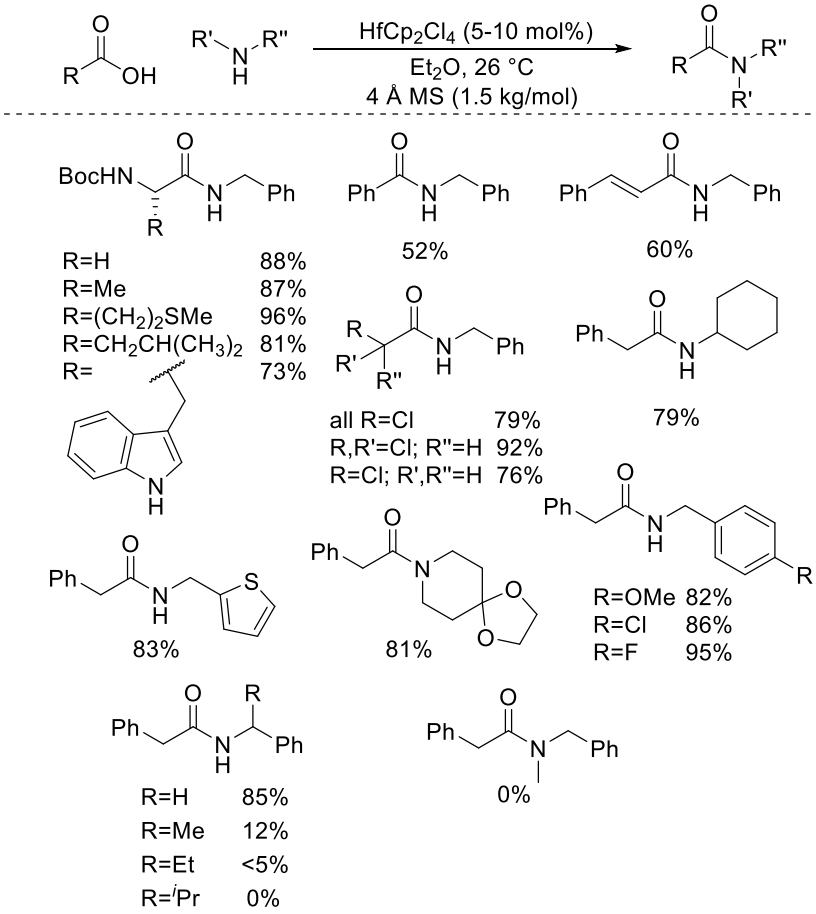
Catalyst	Yield (%)
No catalyst	10
$ZrCl_4$	>99
$Zr(OEt)_4$	93
$Zr(O^tBu)_4$	93
$TiCl_4$	68
$Ti(O^iPr)_4$	91
$Ti(OBu)_4$	89
$Hf(O^tBu)_4$	89
$Nb(OEt)_5$	88

Table 3 Catalyst screen for the direct amidation of phenylacetic acid (1.2 mmol) and benzylamine (1 mmol) with 10 mol% catalyst loading in anhydrous THF at 70 °C with 4 Å MS (0.5 kg/mol)

In 2015, Adolfsson reported the use of a more expensive, but equally efficient $HfCp_2Cl_2$ as a catalyst for the amidation at room temperature.[50] This was developed

with an aim to avoid the risk of racemisation, particularly of α-stereocentres in carboxylic acids, associated with reactions at high temperatures. However, an even larger amount (1.5 kg/mol) of molecular sieves was used, which makes this method less appealing in terms of sustainability.

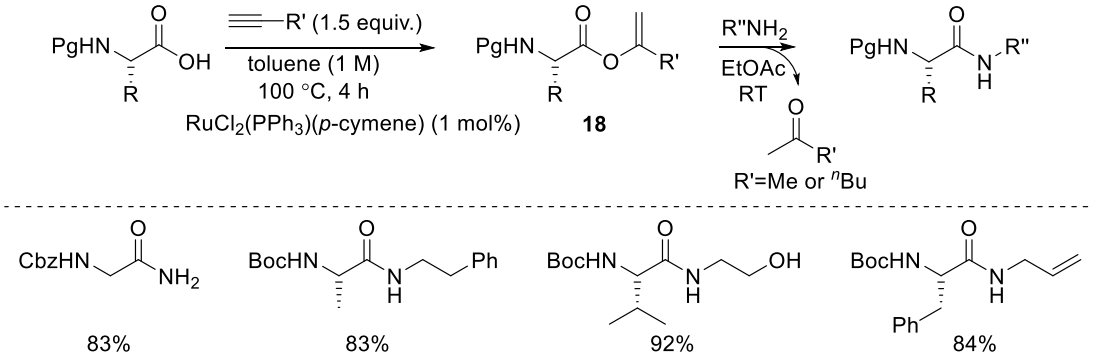
Good yields were attained with protected amino acids in the presence of an excess of primary amines; all enantiomeric excess values were reported to be above 99% (Scheme 16). However, reactions of carboxylic acids failed with sterically demanding amines. The yields of amides were dependent on the reaction concentration, which varied for each individual carboxylic acid.[50]



Scheme 16 Hf-catalysed amidation at room temperature

Gooßen *et al.* have recently reported a one-pot procedure for amide synthesis using ruthenium complexes in tandem with acetylene or ethoxyacetylene to activate carboxylic acids.[51] The methodology of Ru-mediated activation of carboxylic acids with alkynes was developed in 1991 by Dixneuf *et al.* and applied in the synthesis of amino acid amides and dipeptides (Scheme 17). The alkyne used was either propyne or hex-1-yne, and the resulting enol ester **18** was isolated before being subjected to the reaction with amino acid esters or ammonia with the only by-

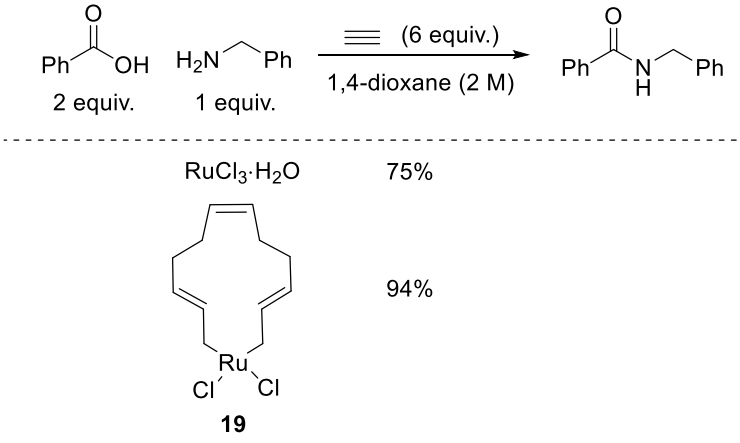
product from the reaction being acetone or 2-hexanone.[52,53] The reaction conditions were mild and high retention of enantiomeric purity was reported, and the amides were isolated in excellent yields.



Scheme 17 Selected examples of ethoxyacetylene activated amidation of carboxylic acids

In 1993, Kita *et al.* introduced the use of ethoxyacetylene as the activating group, producing ethyl acetate as the only waste by-product from the acylation reaction. The scope was extended from amino acids to a large variety of carboxylic acids with amines and alcohols as nucleophiles resulting in excellent yields.[54]

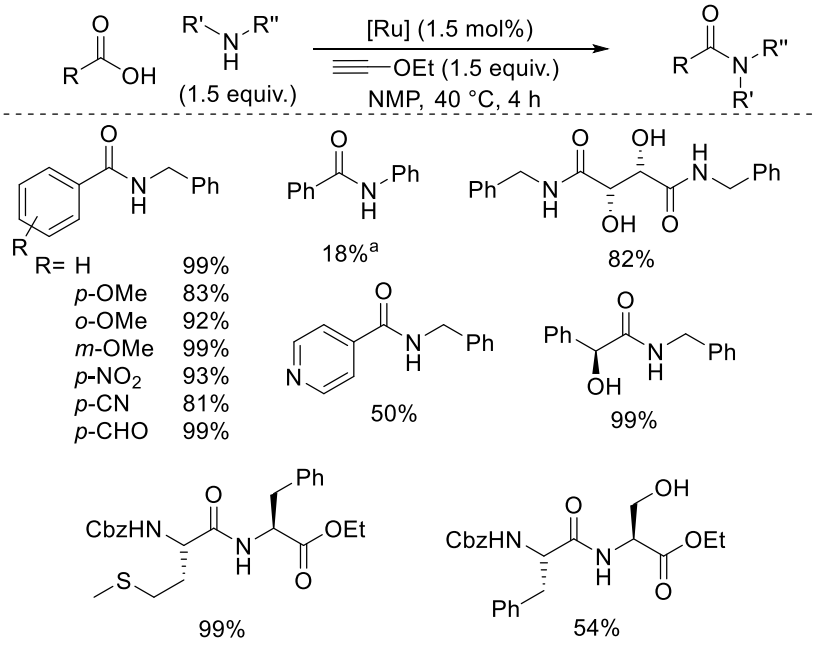
Gooßen then further developed the above procedures to be one-pot, aiming solely at the production of amides. The Ru catalysts used in the previous reports were ineffective in the activating step with acetylene, however, Gooßen found that simple $RuCl_3$ led to high conversions to the desired enol ester. Further optimisation studies identified catalyst **19** to be of even higher activity than $RuCl_3$ (Scheme 18).



Scheme 18 Catalyst comparison for acetylene-mediated activation

The scope of amides synthesised using acetylene was quite limited due to the low solubility of alkylammonium carboxylate salts in dioxane. Moreover, acetylene was ineffective as an activator when it was compared against the previously established protocols by Kita *et al.* However, the newly developed conditions using

ethoxyacetylene in NMP as the solvent resulted in higher overall yields in contrast to the two-step protocols. The scope included aromatic and heteroaromatic carboxylic acids, and a range of primary and secondary amines. Diverse moieties, such as free hydroxyl, halogens, esters, aldehydes, and amides, were well tolerated by the reaction conditions. The methodology was also extended to the synthesis of protected dipeptides isolated in good to excellent yields (Scheme 19). The reaction of aniline with benzoic acid resulted in a lower yield of 18%, however, and required harsher conditions.[51]

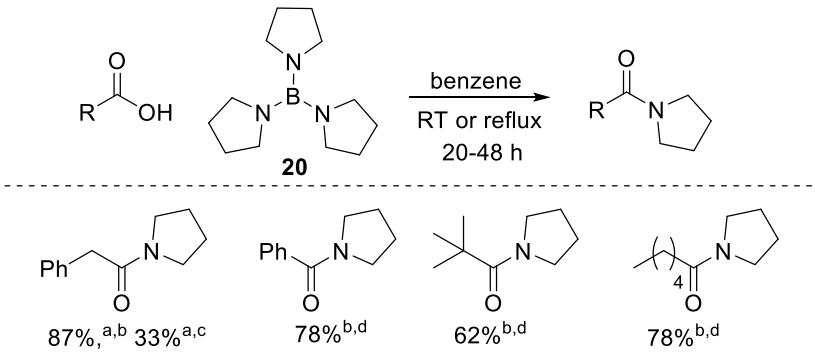


Scheme 19 Amide scope of atom-economical Ru-catalysed amidation; a. The reaction performed at 80 °C for 6 h

1.2 Boron-mediated amidation

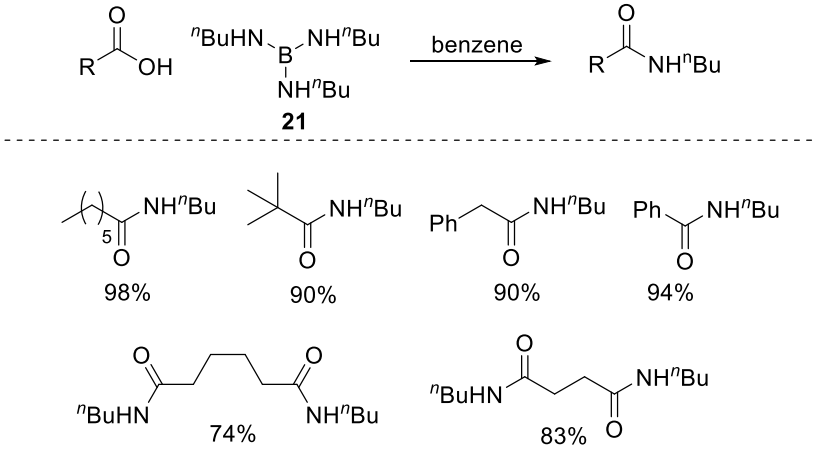
1.2.1 Stoichiometric boron reagents

The role of boron in amidation reactions first became evident in 1965 when Pelter *et al.* reported the use of trispyrrolidinoborane **20** as a stoichiometric reagent for the direct amidation of a carboxylic acid without the need of an additional catalyst (Scheme 20).[55]



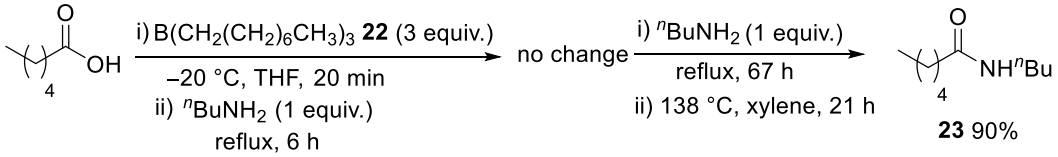
Scheme 20 The scope of amidation using tris(pyrrolidino)borane **20**; a. room temperature; b. 1 equiv. **20**; c. 1/3 equiv. **20**; d. benzene reflux

It was found that a full equivalent of **20** was required for full conversion into the corresponding amide product. If 1/3 equivalents of the **20** was used, only 33% of amide was obtained at room temperature. For the less reactive carboxylic acids (e.g. R=Ph, ^{t}Bu), refluxing benzene as well as prolonged reaction times were necessary. The group then extended the scope of the reaction to trismonoalkylaminoborane **21** as amidation reagents therefore giving access to secondary amides (Scheme 21).[56] Furthermore, the reaction was performed with dicarboxylic acids to yield di-amide products.[56] Good yields were obtained in all cases, although an excess of **21** was required.



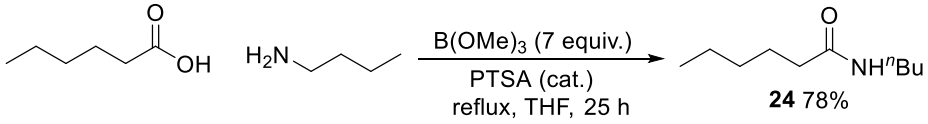
Scheme 21 Tris(monoalkylamino)borane **21** for direct amidation of carboxylic acids

In 1969, the group explored a variety of different boron-containing reagents; including alkylboranes and boronic esters or borates.[57] By mixing trioctylborane **22** with a carboxylic acid followed by the addition of an amine, amide **23** was obtained in 90% yield, but only after prolonged heating (Scheme 22).



Scheme 22 Exploring boron reagents for amidation: trioctylborane **22** for amide synthesis

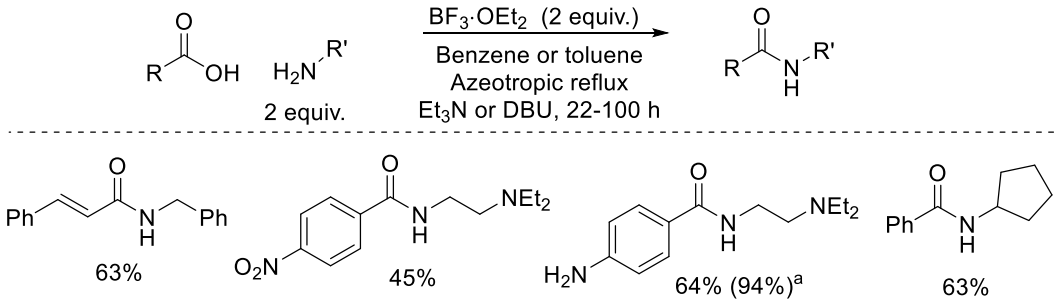
Trimethylborate was also tested as an amidation reagent and it was found that in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA), the corresponding amide could be produced in 78% yield with no or little ester product observed (Scheme 23).



Scheme 23 Trimethylborate as amidation reagent

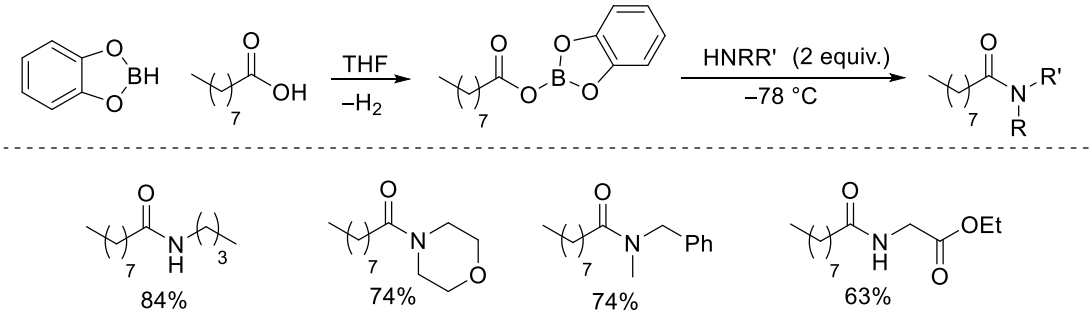
It was initially envisaged that this method could be applied to peptide synthesis. However, to their disappointment, the conversions into the test amide **24** were undesirably low and the need for the reaction to be heated did not allow this procedure to be used for peptide synthesis. Therefore, no further advancements were made to investigate further general scope of these reagents.[57]

The relative success of the boron-mediated amidation, however, gained attention in later years, and other groups started exploration of the stoichiometric use of boron reagents. In 1975, Tani *et al.* used boron trifluoride etherate as an amidation reagent, in refluxing benzene or toluene with an excess of amine and $BF_3{\cdot}OEt_2$ reagent.[58] The presence of an organic base such as triethylamine or DBU was beneficial at accelerating the reaction rate. The scope was wider than investigated before, selected examples are shown in Scheme 24.



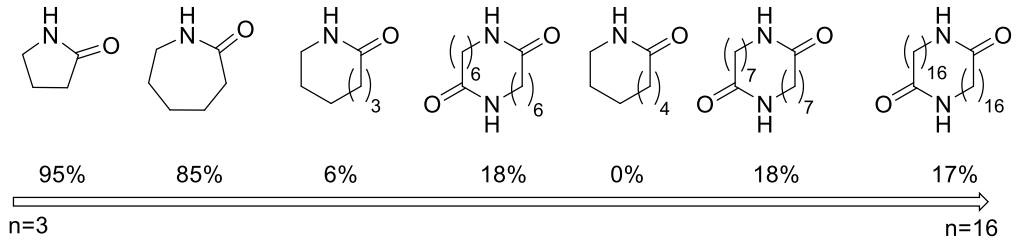
Scheme 24 Selected amides synthesised using $BF_3{\cdot}OEt_2$; a. 70 h heat

Ganem *et al.* explored the use of catecholborane to give access to acyloxyboranes furnished with carboxylic acids.[59] The pre-activated acid was then reacted with a variety of amines and showed to have a relatively wide scope (Scheme 25).



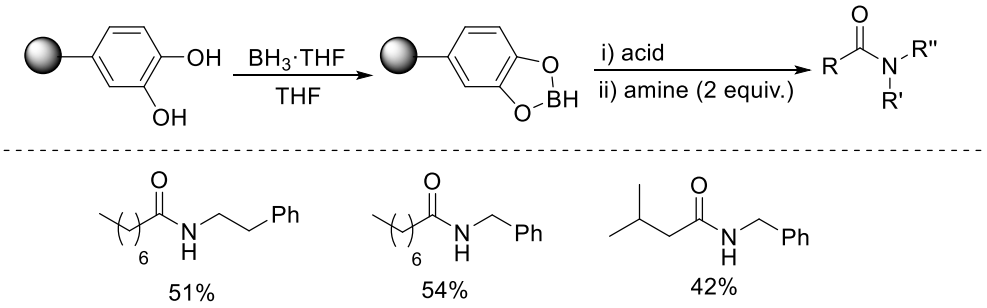
Scheme 25 Selected examples of catecholborane mediated amidation

The reaction was also applied to the synthesis of macrolactams, with excellent yields obtained on 5 and 7-membered rings, but the yields were lower for larger sizes, where dimer cyclisation reaction was more preferential (Scheme 26).



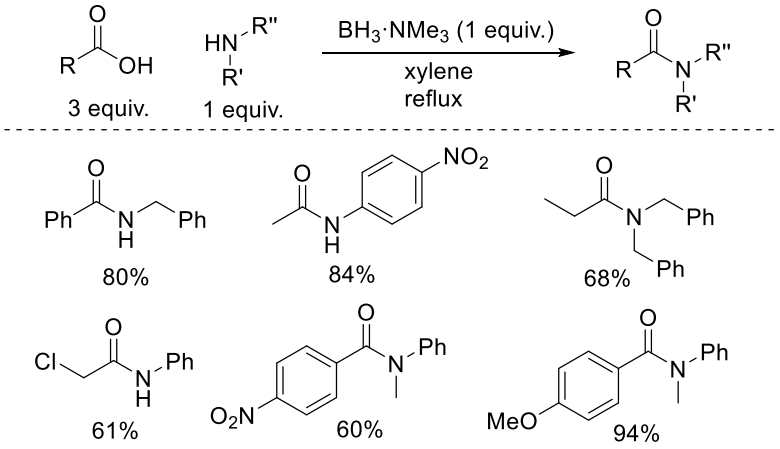
Scheme 26 Examples of macrolactam synthesis using catecholborane

In 2002, Wang *et al.* further developed the application of catecholborane by introducing solid support to the pendant catechol (Scheme 27).[60] Although yields were moderate and the scope studied very small, the purification of amide products was simplified by the ease of separation from the borane reagent.



Scheme 27 Solid-supported catecholborane amidation

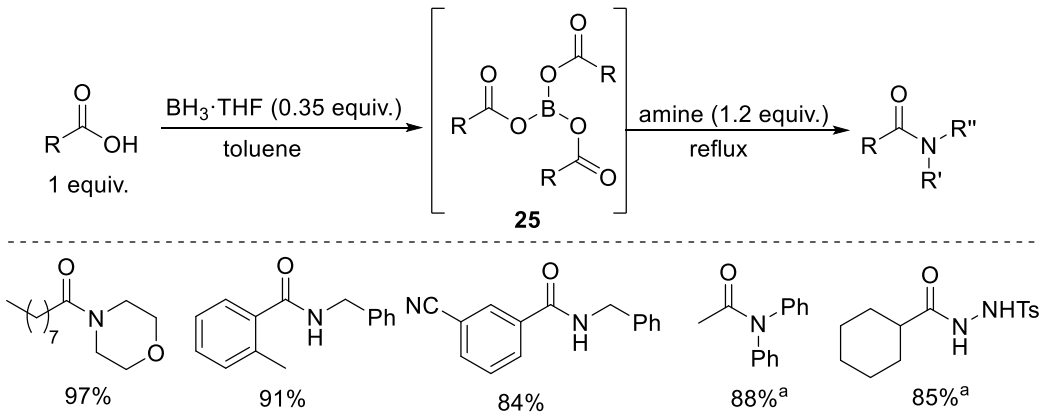
In 1983, Trapani and co-workers discovered that upon refluxing a 1:1:3 mixture of amine, trimethylamine-borane complex and carboxylic acid in xylene, amide formation was observed.[61] The reaction proceeded well with a wide variety of carboxylic acids and amines, but was less successful for carboxylic acids with electron-withdrawing substituents (Scheme 28).



Scheme 28 Selected examples of borane-trimethylamine mediated amidation

Interestingly, if the ratio of the reactants was changed to 1:2:2 amine:borane:acid, the reaction proceeded further to reduce the amide products to tertiary amines.

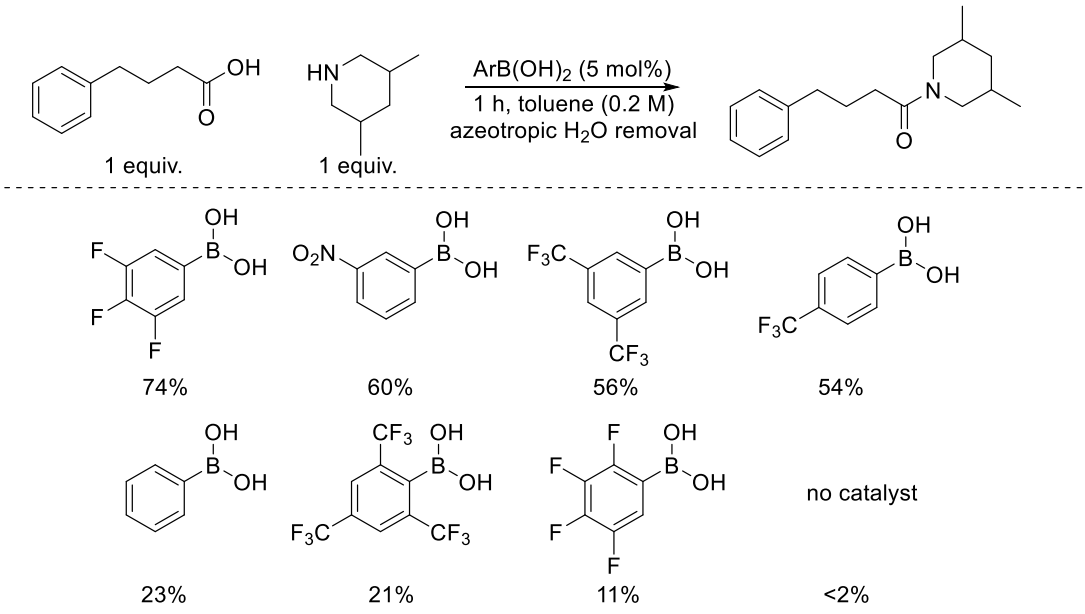
In 2007, Huang *et al.* reported the use of borane-THF or borane-dimethylsulfide to activate carboxylic acids in a reaction with a variety of nucleophiles, including amines to yield amides.[62] The group suggested the formation of triacyloxyborane **25**, but no evidence was provided to support this. It was found that no reaction occurred at room temperature, but amidation proceeded well at reflux in toluene. This method worked well for aliphatic and aromatic carboxylic acids, including with cyano functionality; and a range of amines, including secondary and bulky amines (Scheme 29).



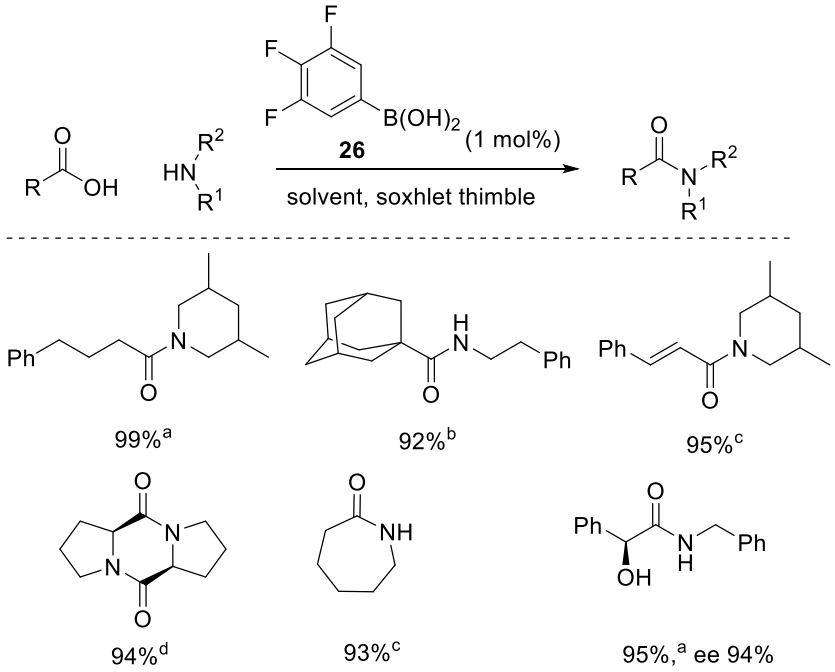
Scheme 29 Selected examples of borane-THF mediated amidation; a. 3 equivalents of carboxylic acid used to 1 equivalent of amine

1.2.2 Boron catalysts in amidation

In search of more water-stable and catalytic amidation reagents, Yamamoto pioneered the use of electron-poor aryl boronic acids as catalysts in amidation reactions in 1996.[63] 3,4,5-Trifluorobenzeneboronic acid **26** was found to be the most suitable catalyst, of the electron-poor boronic acids studied, for promoting condensation between an amine and carboxylic acid (Scheme 30).



Scheme 30 Comparison of a selection of boronic acids in the direct amidation of carboxylic acid

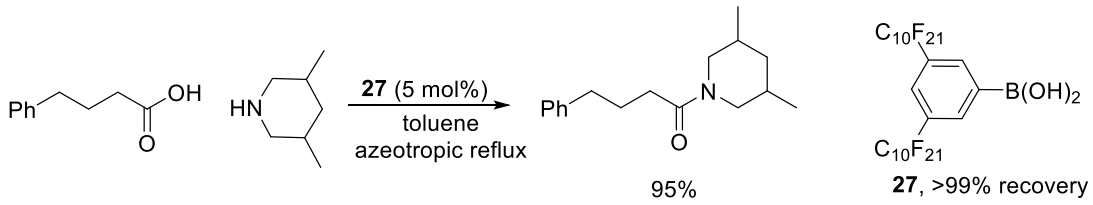


Scheme 31 Selected examples of **26**-mediated amidation; a. toluene used as the solvent; b. mesitylene used as the solvent; c. xylene sued as the solvent; d. anisole used as the solvent

The catalyst showed a promising scope, including with bulky and unreactive carboxylic acids (Scheme 31). In some cases, a thermal background reaction might be expected, however, no background yields were reported for comparison.

Following these results, Yamamoto *et al.* reported **26**-catalysed polycondensation of carboxylic acids with amines, including synthesis of nylon-6,6, although high temperatures (300 °C) were required.[64]

In order to improve the recyclability of boronic acids, the group successfully showed that introduction of long fluorous tails into the structure enabled easy recovery of the boronic acid by extraction into fluorous solvents (Scheme 32).[65] Boronic acid **27** was chosen, as it showed high yields and was the easiest to recover.

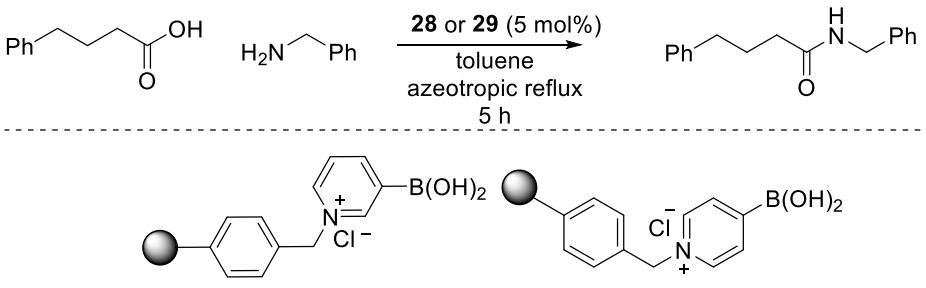


Scheme 32 Amidation using boronic acid **27** with fluorous tail

In a contribution to further developments of boronic acid-catalysed amidations, Wang *et al.* reported the synthesis and application of solid-phase arylboronic acids in which 3-pyridinium boronic acids were bound to polystyrene, which simplified the

isolation of products and catalyst recovery.[66] Experiments on recyclability of the catalyst showed that catalytic activity was not diminished after three uses.

In 2005, Yamamoto also reported that 4-borono-*N*-methylpyridinium salts were better and more thermally stable catalysts than that studied by Wang *et al.*[67] The salt was used to directly catalyse the amidation reaction in the presence of ionic liquid [emim][OTf] as a biphasic counterpart to toluene to ease the recovery of the catalyst. It could then be reused without significant loss of catalytic activity. The solid support was then employed and the catalyst tested against Wang's catalyst **28** showing clear improvements in activity with the catalyst **29** (Scheme 33).



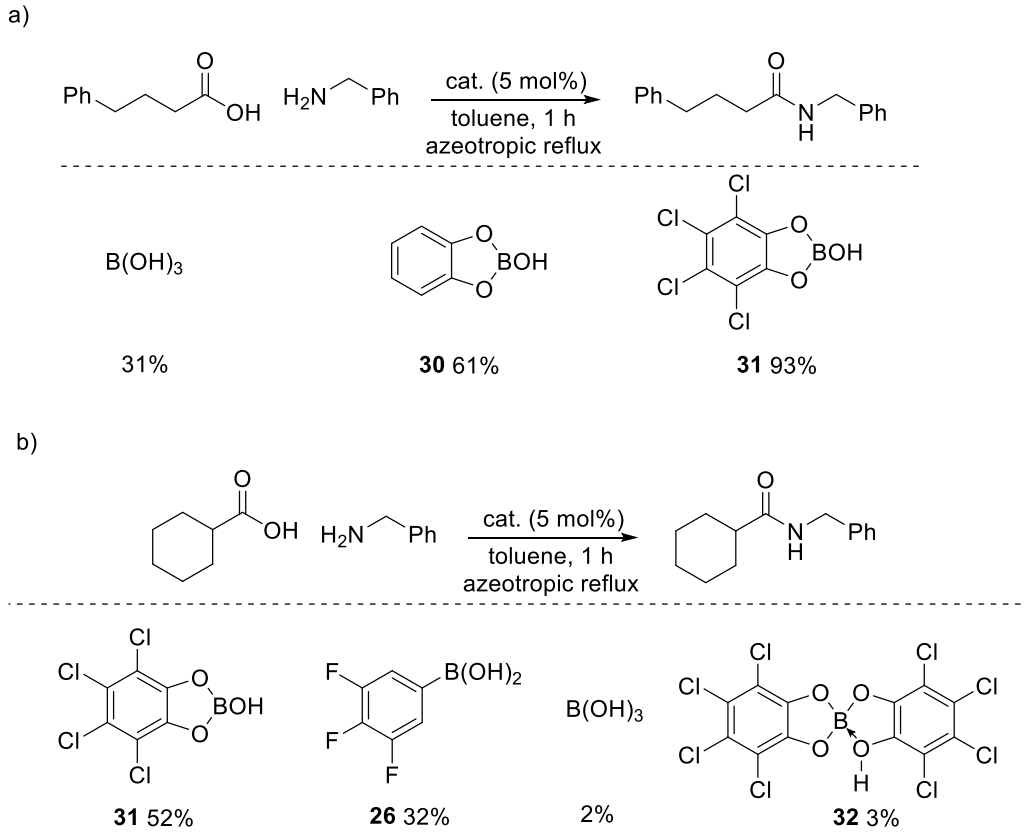
No. of uses	Yield	Yield
1	98%	98%
2	98%	98%
3	94%	98%
4	88%	98%
5	74%	96%

Scheme 33 Comparison of recyclability and activity of resin-supported pyridinium boronic acids

It was found that catalyst **28** was gradually losing its catalytic activity, and after five times of use, the conversion to the corresponding amide product decreased from 98% to 74%. They observed that the catalyst was undergoing decomposition, as boric acid was detected in the recovered catalyst mixture. On the other hand, no loss of activity was observed in Yamamoto's catalyst **29**, and after five cycles, the yield was not affected (Scheme 33).[68]

Yamamoto also investigated Ganem's catecholborane procedure and proposed that under the conditions developed by the group, catecholhydroxyborane **30** could be a useful dehydrating amidation reagent (Scheme 34a). The catalyst was prepared by azeotropic reflux of a catechol with boric acid, which was then used directly in the amidation reaction. Indeed, **30** led to 61% conversion into the amide, in contrast to

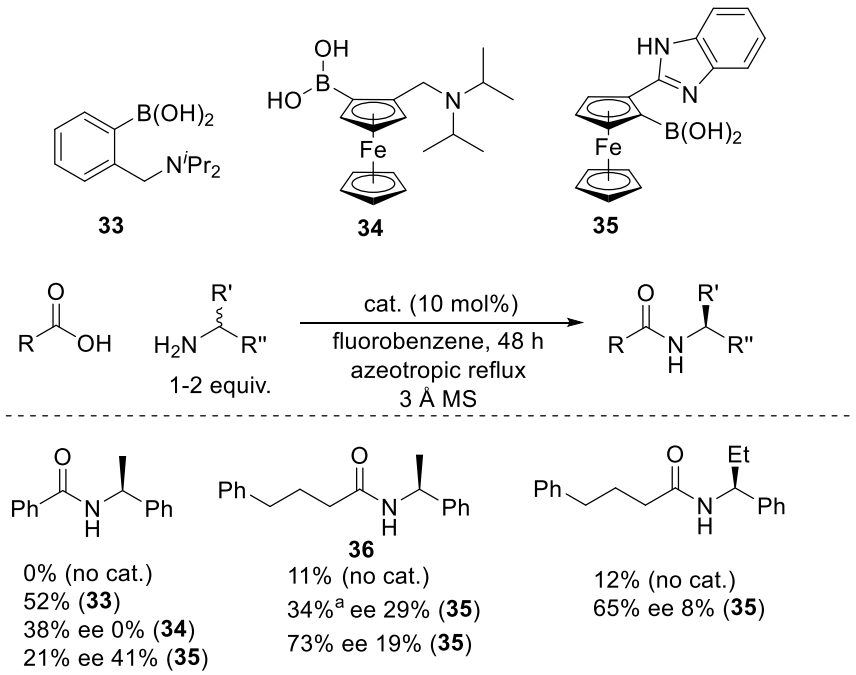
boric acid with only 31% conversion. Introducing an electron-poor catechol **31** led to 93% conversion. Importantly, the catalyst **31** showed a much better activity for sterically demanding carboxylic acids than boronic acid **26** and boric acid (Scheme 34b).[69]



Scheme 34 Comparison of boron-containing catalysts for amidation

Importantly, very little or no conversion was observed when catechol was mixed directly with the reaction mixture, presumably because the active catalyst **31** was not formed.

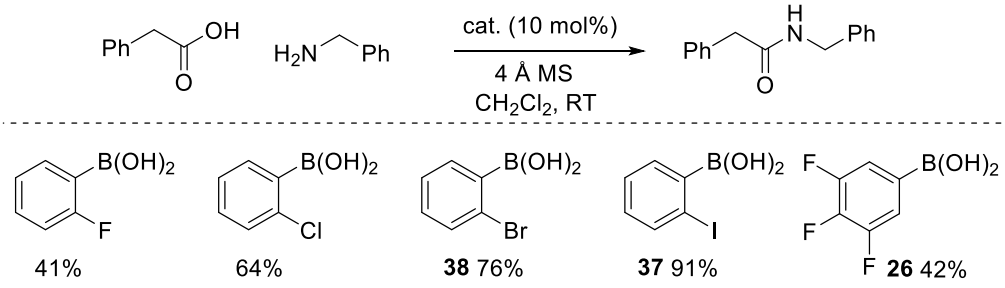
Although all the above reactions had a relatively good scope, all procedures were limited due to high temperatures required for the successful amidation. Efforts in decreasing the reaction temperatures were made by Whiting *et al.* by using bifunctional arylboronic acid **33** in refluxing fluorobenzene at 85 °C. Furthermore, chiral derivatives of **33** were synthesised by incorporating a ferrocene core (boronic acids **34** and **35**), which were used for the kinetic resolution of racemic amines in the asymmetric synthesis of amides (Scheme 35).



Scheme 35 Kinetic resolutions of amines using bifunctional boronic acid catalysts; a. Yield after 12 hours

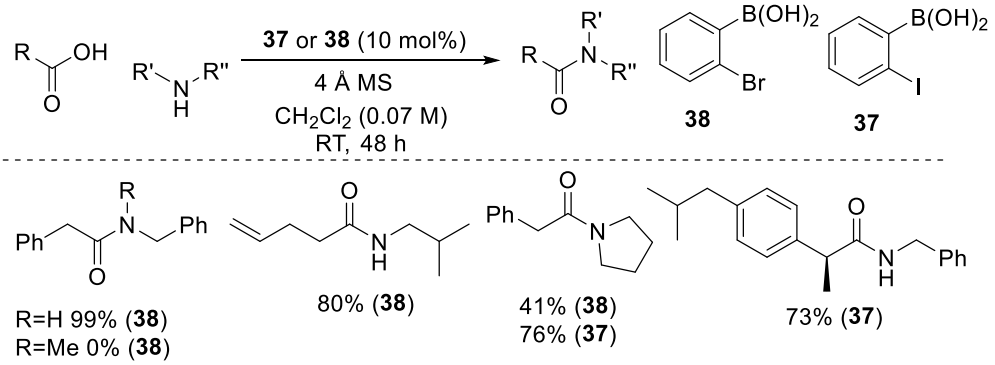
The catalyst **34**, although more active than **35**, did not afford the enantiomeric resolution of the amide products; the catalyst **35**, however, successfully introduced chirality into the amide product, but only moderate yields were observed. Importantly, the reaction was also time-sensitive as demonstrated by the drop in ee value after 48 h from 29% ee (after 12 h) to 19% ee of the product **36** (Scheme 35).[70]

In 2008, Hall and co-workers reported a procedure for the amidation catalysed by *ortho*-haloarylboronic acids at room temperature.[39] The reaction required the use of molecular sieves as a means for water removal, however. Upon studying over 45 *ortho*-substituted boronic acids, the best activity was exhibited by *o*-iodophenylboronic acid **37** (Scheme 36). In contrast, Yamamoto's boronic acid **26** led to only 42% conversion under the same conditions.



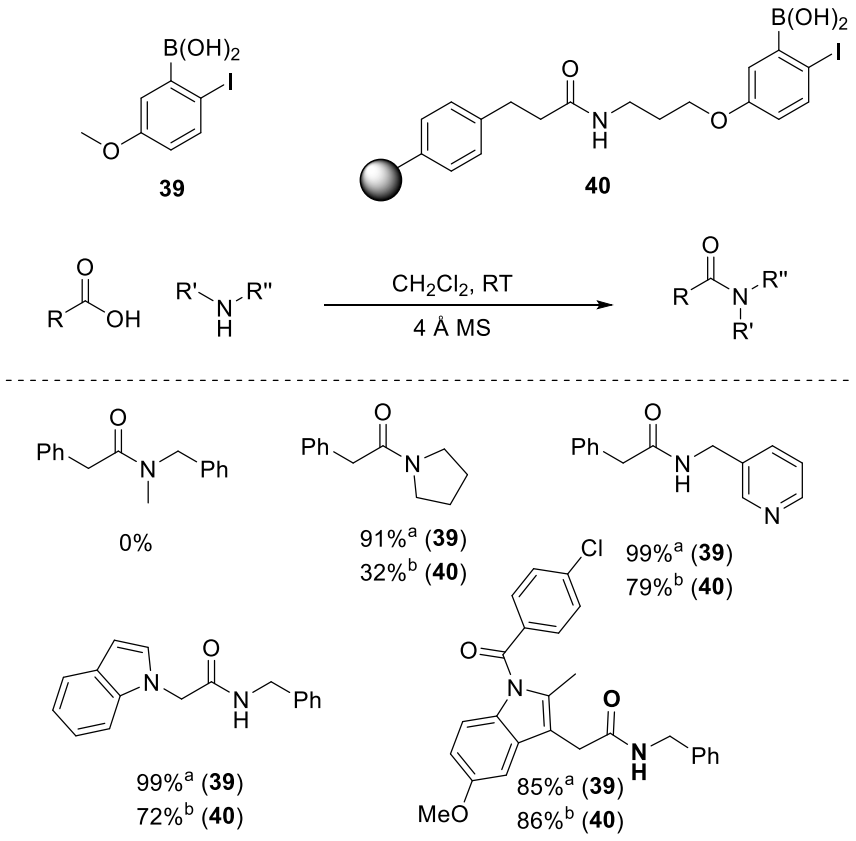
Scheme 36 *Ortho*-substituted boronic acids in the direct amidation at room temperature

A range of aromatic and aliphatic carboxylic acids reacted in good yields, however, benzoic acid was not reactive under the conditions even at higher temperatures (50 °C) and higher catalyst loading (Scheme 37).



Scheme 37 Selected examples of **37** and **38**-mediated amidation

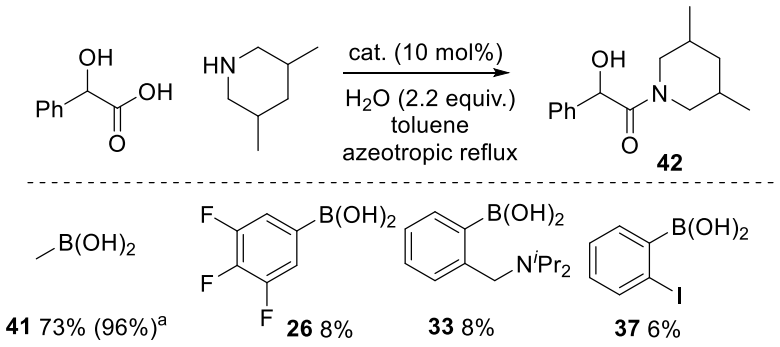
In 2012, Hall *et al.* reported an improvement to the catalyst **37** by introducing a methoxy group to the structure (**39**), which significantly enhanced the catalytic activity of the boronic acid (Scheme 38).[71] Later, the methoxy group was substituted with the solid support (**40**) in order to ease purification of the amide product by filtration and the recovery of the catalyst (Scheme 38).[72]



Scheme 38 Comparison of the catalytic activity of **39** and a resin-bound derivative **40**; a. Reaction performed in CH_2Cl_2 (0.07 M); b. Reaction performed in CH_2Cl_2 (0.1 M)

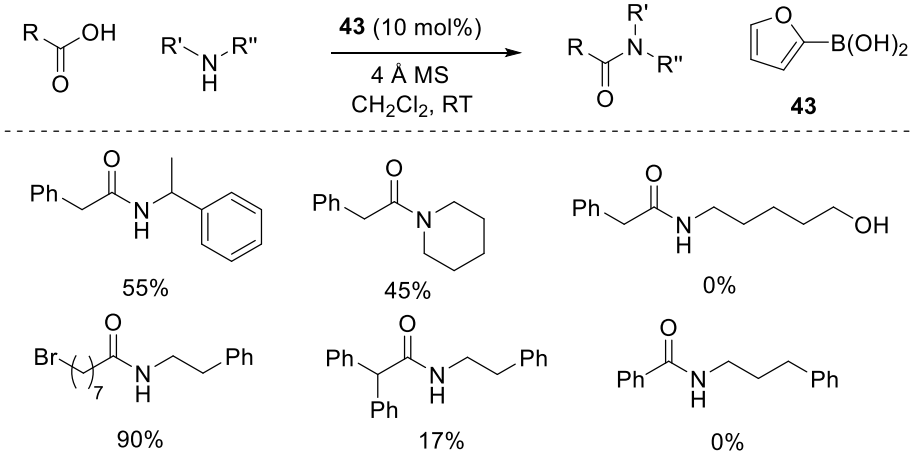
However, the scope was still limited to non-bulky amines and no conversion to the corresponding amide was observed with *N*-methylbenzylamine. The catalyst **39** was generally superior to the solid-supported derivative **40**, however, the purification of the amides was improved.

The scope of the aforementioned boronic acids suffered from low activity with α-hydroxycarboxylic acids often resulting in low conversions to the desired amides; this issue was subsequently addressed by Ishihara *et al.* in 2013 by using methylboronic acid **41** as the catalyst.[73] Where boronic acids **26**, **33**, and **37** were almost inactive, 73% yield of the amide **42** was obtained with the catalytic amounts of **41** (Scheme 39).



Scheme 39 Methylboronic acid-mediated amidation of α-hydroxycarboxylic acids; a. Reaction performed in the presence of benzoic acid (10 mol%)

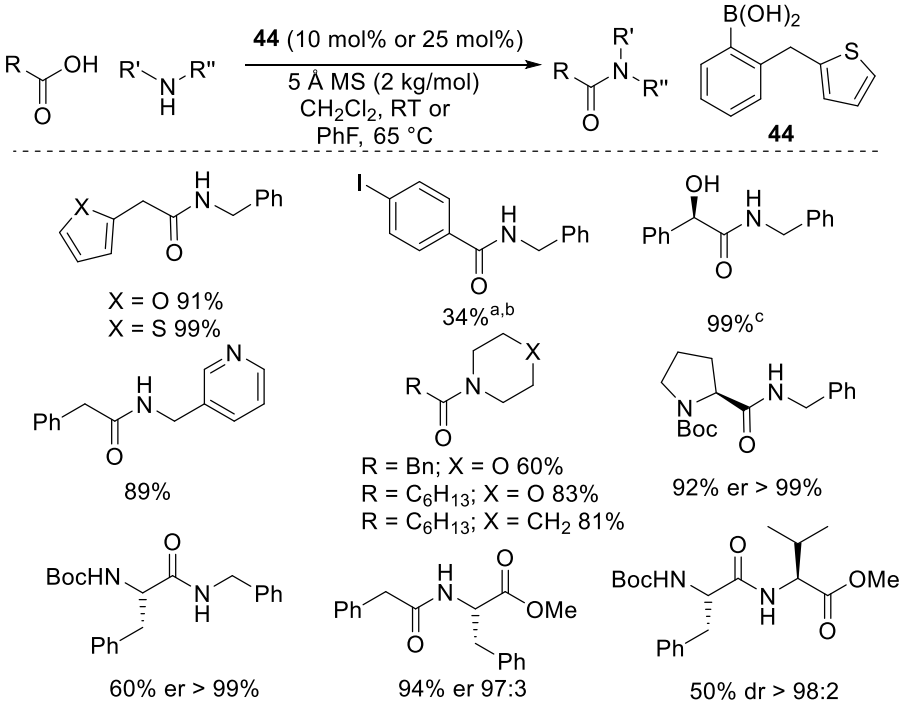
Good yields were obtained for the majority of tested acids with low racemisation observed in case of enantiopure examples.[73] Following Hall's success at decreasing the reaction temperature for successful amidation, Chen *et al.* investigated a series of heteroarylboronic acids, and found that 2-furanylboronic acid **43** was an efficient and inexpensive catalyst (Scheme 40).[74]



Scheme 40 Selected examples of amides synthesised with catalyst **43**

The scope included sterically hindered and secondary amines, as well as electron-rich and poor benzylamines; functionalised carboxylic acid examples were also given (Scheme 40). However, the reaction failed in case of bulky carboxylic acids and no amide was obtained with benzoic acid.

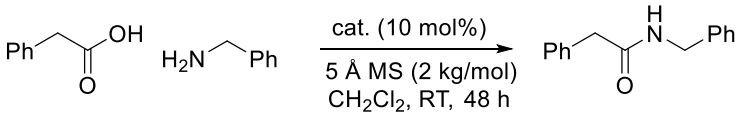
Recently, Blanchet *et al.* further explored the activity of heteroaryl boronic acids with a thiophene moiety. Boronic acid **44** with a pendant thiophene was found to be effective at room temperature amidation, including synthesis of protected amino acid amides (Scheme 41).[75] The reaction conditions employed 5 Å molecular sieves as a means of drying.

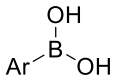


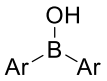
Scheme 41 Selected examples of amides synthesised by thiophene boronic acid **44**

A wide scope was investigated, although no examples of less reactive amines, such as anilines was shown.[75] In case of mandelic acid, no enantiomeric ratio was given, so it is unknown whether the amide had racemised. Higher temperature and catalyst loading was required for coupling of protected amino acids with benzylamine or phenylacetic acid. *N*-Boc-L-Phe gave amide in moderate yield, but in all cases, a good er value was maintained. More importantly, it was possible to synthesise dipeptide Boc-L-Phe-L-Val-OMe in 50% yield using the above conditions and catalyst **44**. Nonetheless, the procedure severely suffered from the requirement of a large amount of molecular sieves, which ultimately is unsatisfactory from a sustainability point of view.

This breakthrough was followed by a further report by Blanchet *et al.* using borinic acids in the synthesis of dipeptides and amides.[76] Upon analysis of a series of commercially available boronic acids and borinic acid derivatives, it was observed that the yields were consistently higher in all cases when the reaction was catalysed by a borinic acid (Scheme 42).





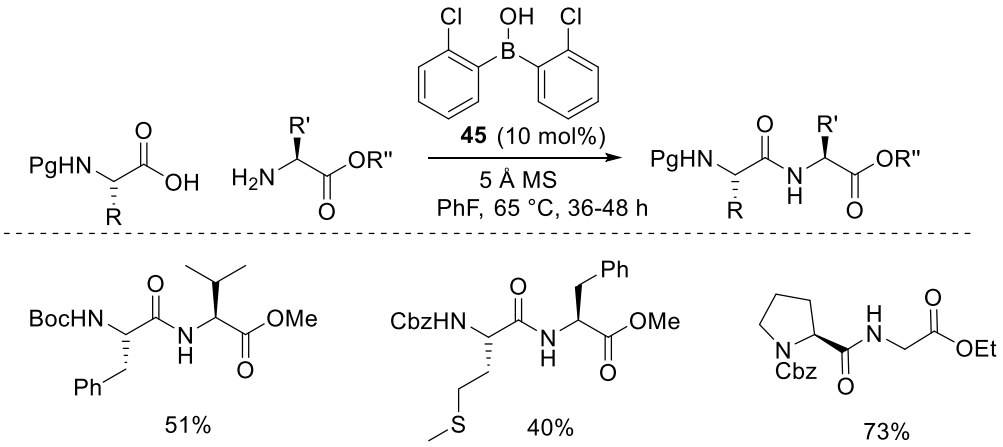


1	Ph	13%	19%
2	o-Tol	5%	15%
3	4-^{t}BuC$_6$H$_4$	0%	59%
4	4-OMeC$_6$H$_4$	4%	45%
5	3-OMeC$_6$H$_4$	5%	39%

Scheme 42 Comparison of boronic acids vs. derivative borinic acids in direct amidation

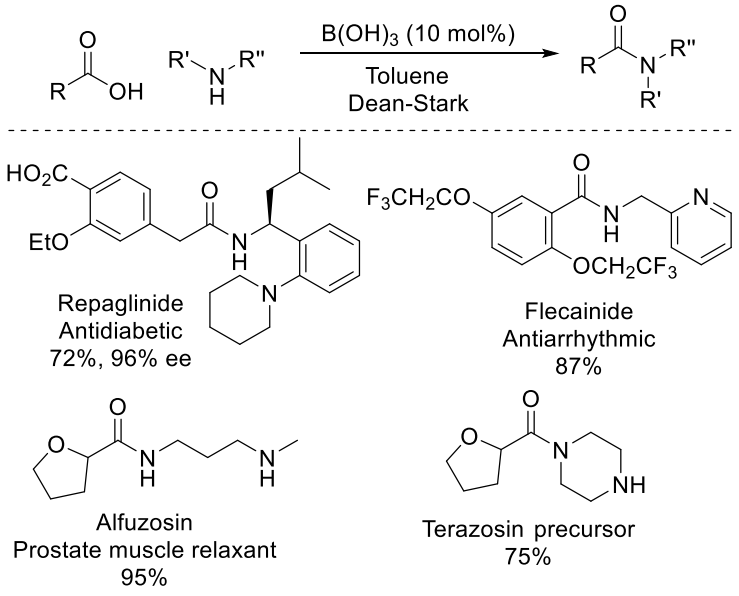
Encouraged by the results, *ortho*-halogen-substituted phenylborinic acids were further investigated, although no comparison with sister boronic acids was provided in this case. The selection of aryl substituents was inspired by Hall's work published in 2008.[39] 2-Chlorophenylborinic acid **45** was found to give the best results. A similar catalyst with fluoro substituents in place of chloro was monitored by ^{19}F NMR before and after the amidation reaction to confirm that the catalyst was indeed borinic acid and not boronic acid that could be formed from protodeboronation of one of the aryl groups.[76] The ^{19}F NMR spectrum suggested the presence on the borinic acid after the reaction, however, it was not reported whether an internal standard was used for fair comparison.

With the catalyst in hand, the scope of dipeptide synthesis was investigated. In this case, the reaction was performed in PhF at 65 °C to give moderate to good yields of a wide variety of dipeptides (Scheme 43).



Scheme 43 Selected examples of dipeptides synthesised with borinic acid **45**

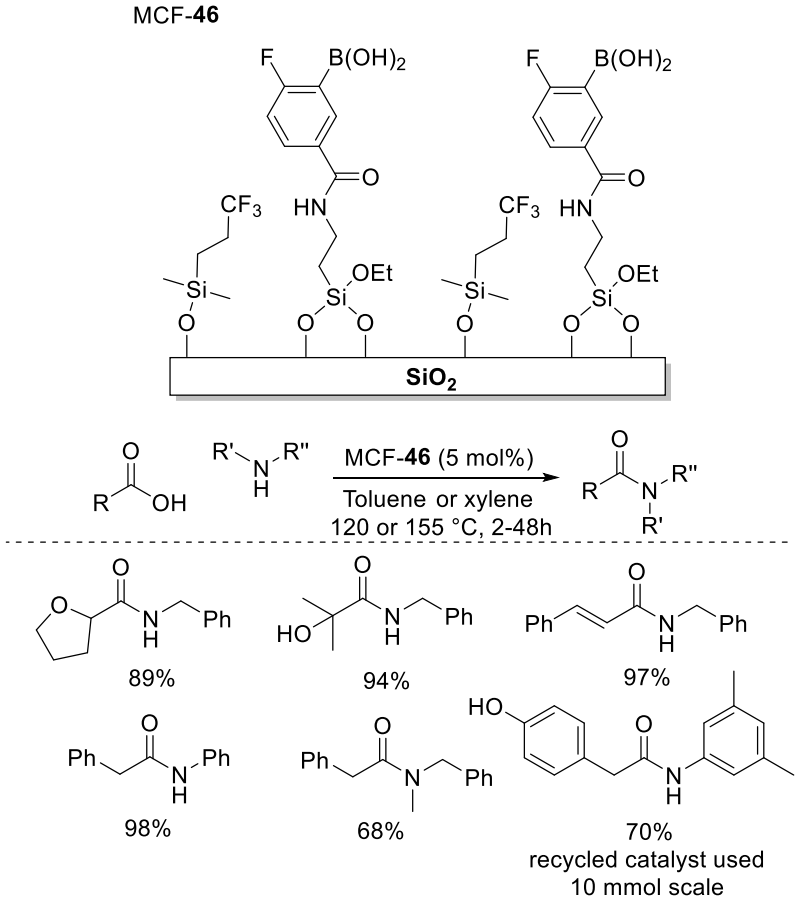
Boric acid is the simplest boron-containing catalyst that has been shown to be a versatile amidation catalyst under appropriate conditions. The main limitation of the reagent is its poor solubility in reaction solvents, however, it works well with efficient azeotropic reflux in toluene. In 2005, Tang reported a simple protocol employing boric acid as an excellent general amidation catalyst with only 1-5 mol% required for successful conversion into a variety of amides.[77] The reaction worked well with a wide variety of substrates, including poorly reactive anilines. The biggest advantage of using boric acid is the scalability, as it is a cheap, safe to use, and an easily accessible reagent. In 2007, Bandichhor reported the synthesis of pharmaceutical compounds on large scale using boric acid catalysis (Scheme 44).[78]



Scheme 44 Boric acid-catalysed synthesis of drug molecules

Importantly, the reaction was shown to be selective for monoacylation, resulting in the terazosin precursor in 75% yield, which could be further functionalised on the free amine to produce the drug.[78]

In 2014, Lee *et al.* developed a heterogenous silica-supported (MCF-mesocellular siliceous foam) boronic acid catalyst **46** with an intention to simplify the recovery of the catalyst.[79] The reaction was performed using fairly standard conditions heating in non-polar solvents such as toluene and xylene. Mainly aromatic examples of acids and aniline derivatives for the amine were given and these gave amides in good to excellent yields (Scheme 45).

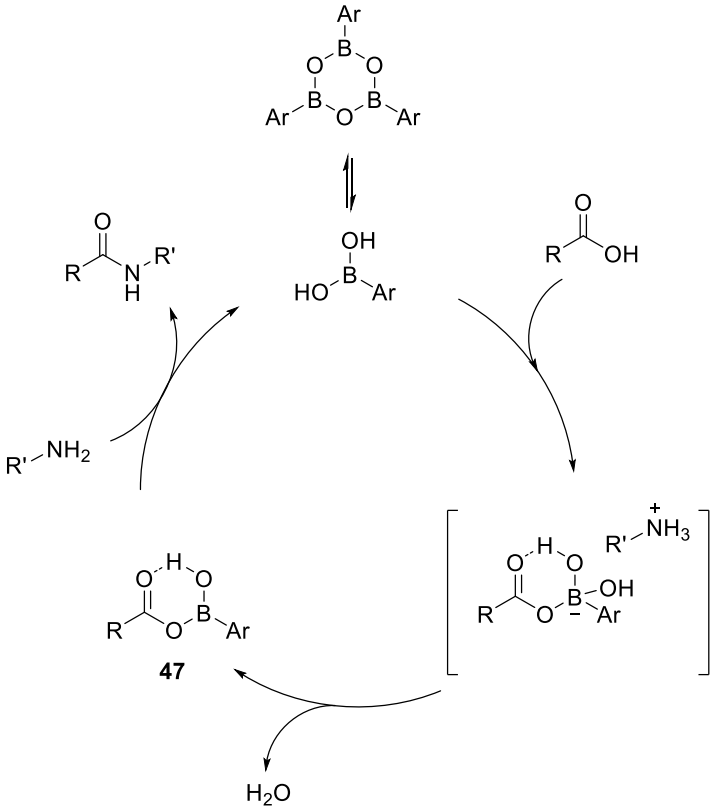


Scheme 45 Solid-supported boronic acid catalysed amidation

The recyclability of the catalyst was also demonstrated, and it was shown that the activity was not lost after five cycles with yields of the amide from phenylacetic acid and benzylamine over 98%.

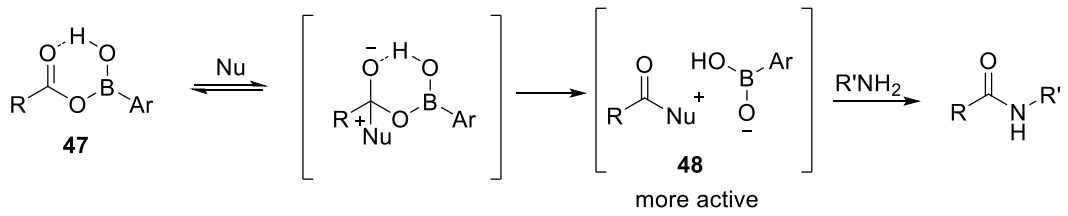
Throughout years of development of the boronic acid catalysed condensation of carboxylic acids with amines, there has been a general agreement, supported by computational studies, that the mechanism proceeded *via* the formation of

acyloxyboron species **47** where the boronic acid activated the carboxylic acid (Scheme 46).[71,80,81]



Scheme 46 Generally accepted proposed mechanism of boronic acid-mediated amidation

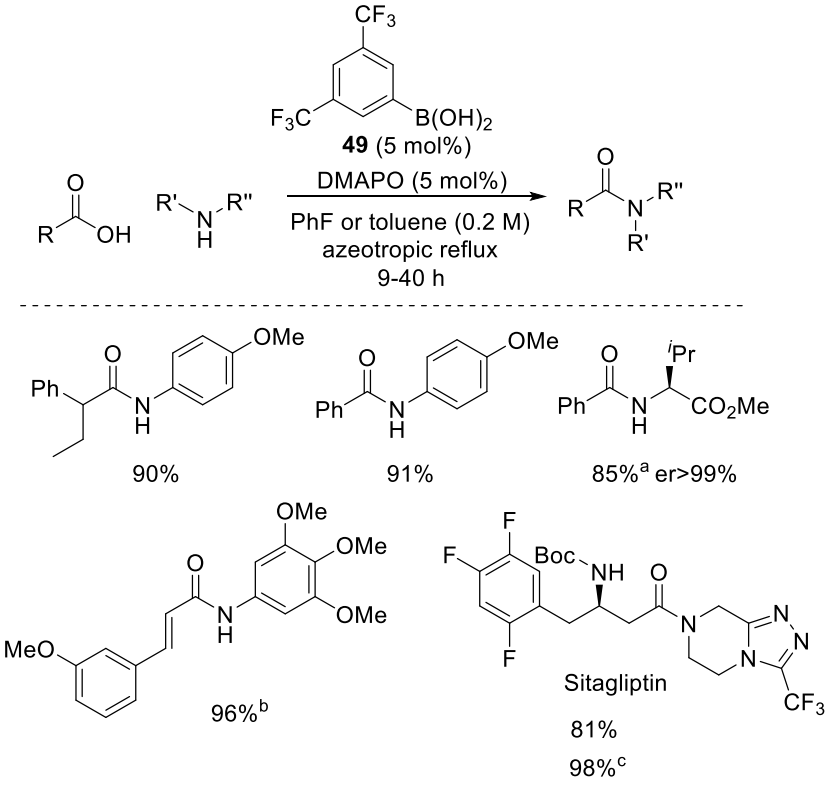
In 2016, Ishihara *et al.* hypothesised that secondary activation of anhydride **47** with a nucleophilic additive (**48**) would increase the rate of amide formation (Scheme 47).[82]



Scheme 47 Proposed alternative activation of a boronic acid

For this purpose, the group developed a procedure using *N,N*-dimethylaminopyridine *N*-oxide (DMAPO) to promote boronic acid **49**-catalysed amidation in non-polar solvents, such as fluorobenzene, toluene, and benzene (Scheme 48). The reaction scope included unreactive aniline derivatives, and bulky and conjugated carboxylic acids. Moreover, they demonstrated the synthesis of Boc-protected Sitagliptin, an antidiabetic drug, in excellent yields using different boronic acids (**49** and **39** (Hall's catalyst)). However, no examples were given with

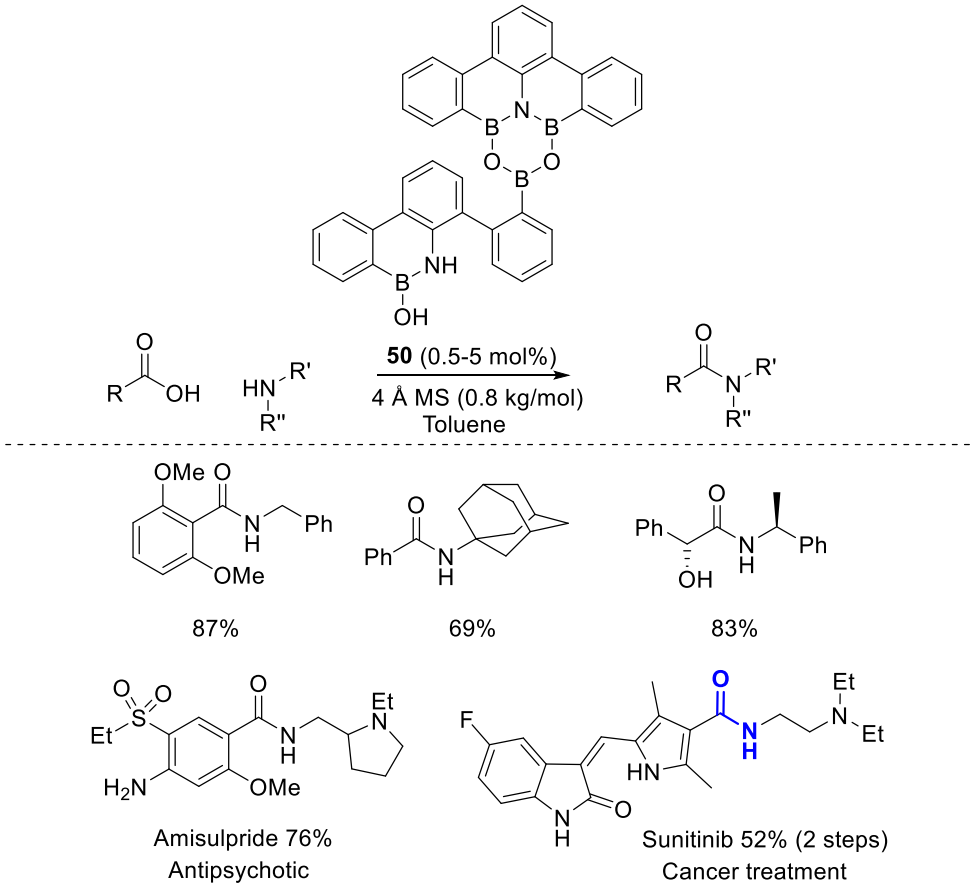
strongly electron withdrawing functionalities (nitro, cyano moieties) to demonstrate their tolerance to the reaction conditions.



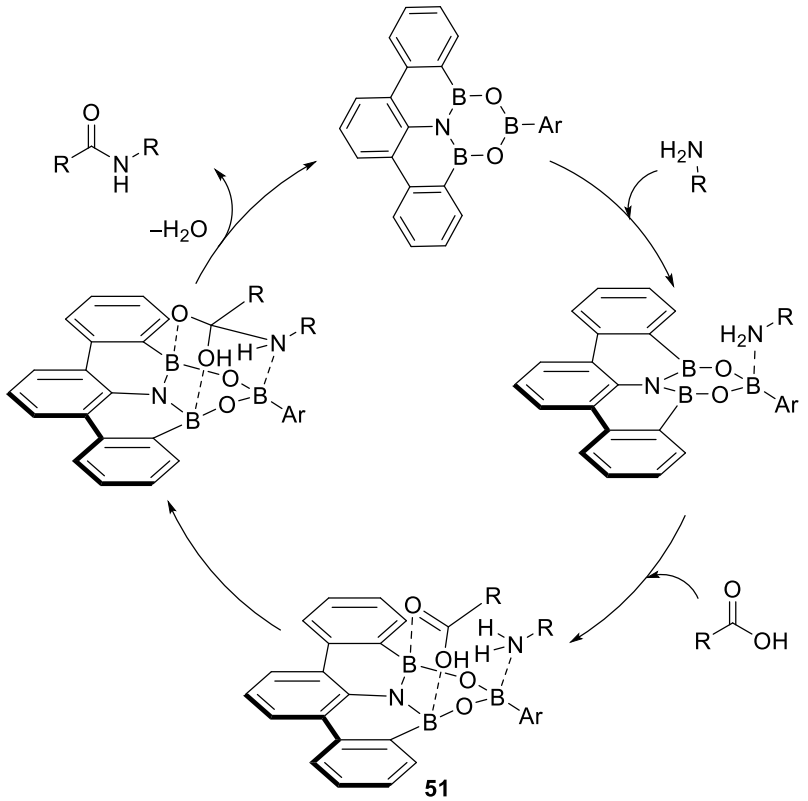
Scheme 48 Scope of boronic acid-DMAPO cooperative catalysis; a. 20 mol% of both catalysts used; b. 10 mol% of both catalysts used; c. **39** used as the catalyst

Most recently, Kumagai and Shibasaki *et al.* presented a novel boron-containing amidation catalyst with B_3NO_2 ring system.[83] Despite the lengthy synthetic route incorporating moisture and air sensitive catalysts and reactants, the catalyst **50** was used in small catalytic quantities to produce a large variety of highly functionalised and poorly reactive substrates with particular focus on sterically demanding examples (Scheme 49).

The success of the reaction was explained through the proposed catalytic cycle, where all three boron atoms in the ring participate in the amidation; two of the borons activating the carboxylic acid and the third delivering the amine. The intermediate complex **51** acts as the “surface” on which the amidation can take place (Scheme 50).



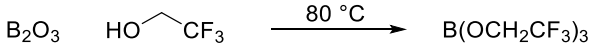
Scheme 49 Sterically demanding amide synthesis using B_3NO_2 catalyst



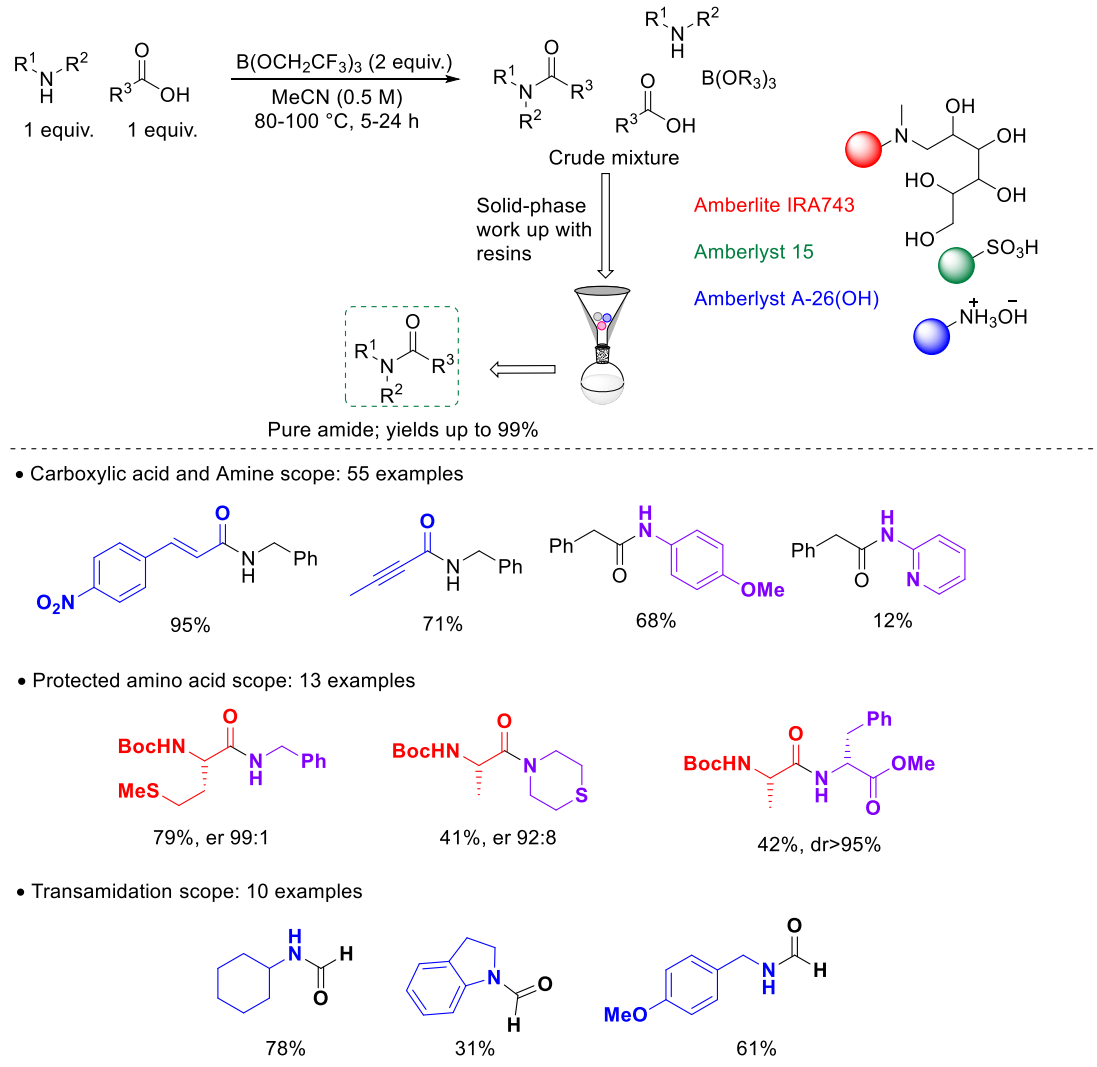
Scheme 50 Proposed catalytic cycle for the amidation with **50**

1.3 Project background and aims

The Sheppard group has reported $B(OCH_2CF_3)_3$ as an effective reagent for the direct amidation of carboxylic acids, and it is now commercially available from Sigma-Aldrich.[84] There are several efficient methods of making the reagent in the lab, and the method using boric anhydride with trifluoroethanol, adopted within the Sheppard group, is particularly useful for large scale (100 g) preparation (Scheme 51). It is a greener and less hazardous approach than one previously performed in the group using BBr_3 and 2,2,2-trifluoroethanol. The final product is purified by distillation and usually is isolated in up to 40% yield.



Scheme 51 Improved synthesis of the borate reagent



Scheme 52 Scope of $B(OCH_2CF_3)_3$-mediated direct amidation in MeCN

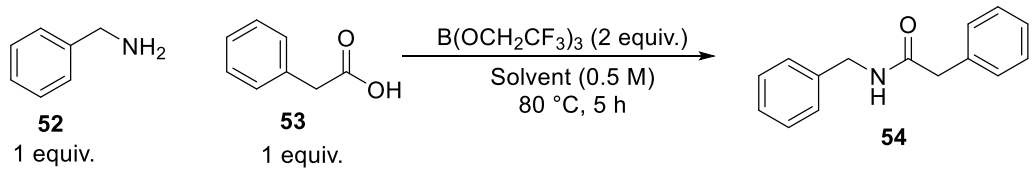
The reagent exhibited a wide scope with a large variety of carboxylic acids and amines (55 examples with up to 99% yield), as well as protected amino acids (13 examples). Moreover, transamidation of primary amides with DMF was demontrated.[84] The major development of this procedure involved incorporation of solid-phase work-up using resins to simply scavenge residual carboxylic acid, amine, and boron with Amberlyst® 15, Amberlyst® A26(OH), and Amberlite® IRA743 respectively (Scheme 52). Moreover, the reagent was shown to work for the direct amidation of unprotected amino acids.[85]

This thesis describes further developments of the $B(OCH_2CF_3)_3$-mediated amidation reactions with a focus on the synthesis of medicinally relevant amides, monoacylated symmetrical diamines, and unprotected amino acid amides. Furthermore, investigations towards understanding the mechanistic aspects of boron-mediated amidations are discussed.

2. $B(OCH_2CF_3)_3$-mediated amidation reactions

2.1 Synthesis of medicinally relevant amides

In preliminary studies on borates as a class of amidation reagents, solvent scope was investigated only with trimethyl borate, and acetonitrile was found to be the most suitable.[86] Therefore, acetonitrile was used in all further investigations with $B(OCH_2CF_3)$. However, when it came to less reactive and highly functionalised amine or carboxylic acid substrates, the reaction was less effective and lower yields were observed (Scheme 52, *vide supra*). It was decided to revisit the solvent screen to test a variety of solvents with greener profile or higher boiling points (Table 4). All reactions were performed with benzylamine **52** and phenylacetic acid **53** using 2 equivalents of $B(OCH_2CF_3)_3$ at 80 °C for 5 hours, and the yield was determined by isolating the final product **54** using the solid-phase work-up with resins, *vide infra*.



52
1 equiv.

53
1 equiv.

54

Entry	Solvent	b.p.	Yield[a]
1	**MeCN**[b]	**82 °C**	**87%**
2	MeCN[c]	82 °C	18%[c]
3	DMSO[b]	189 °C	35%[b]
4	EtOAc	77 °C	50%
5	**Cyclopentyl methyl ether (CPME)**	**106 °C**	**87%**
6	2-methyl THF	80 °C	56%
7	*tert*-Butyl methyl ether (TBME)	56 °C	53%
8	THF	66 °C	58%
9	4-Methyltetrahydropyran (MTHP)	105 °C	43%
10	***tert*-Amyl methyl ether (TAME)**	**86 °C**	**88%**

Table 4 Solvent screen for the amidation of highly functionalised acids and amines; a. Isolated yield; b. Reaction performed by Rachel Lanigan; c. Reaction performed in MeCN without $B(OCH_2CF_3)_3$ for 15 h[86]

DMSO (entry 3), being a polar and high boiling solvent, was found to be unsuitable for successful amidation with only 35% yield of amide **54** isolated. Ethyl acetate (entry 4) resulted in a moderate 50% yield and no competing amidation of the ester was observed. It is worth noting, however, that background reaction occurs between **52** and **53** on heating at 80 °C in MeCN in the absence of borate; previous experiments in the Sheppard group found that 18% yield of **54** was observed after 15 h.[86] Therefore, some of the yields could be higher for that reason. Ethereal

solvents showed promise with yields ranging from 43% to 88%, although this varied depending on the solvent. 2-Methoxytetrahydropyran (MTHP, entry 9) led to a moderate yield, and instant precipitation of the carboxylate-ammonium salt was observed upon mixing reactants in the solvent. However, both cyclopentyl methyl ether (CPME) and *tert*-amyl methyl ether (TAME) (entries 5 and 10, respectively) were shown to be excellent solvents for the reaction.

We decided to proceed with CPME as it was less expensive and higher boiling than TAME (£65.70 vs. £97.80 for 1L on Sigma Aldrich), which would allowing to perform reactions at higher temperatures for less reactive substrates. Importantly, CPME emerged as a safer and more sustainable alternative to other ethereal solvents when it became commercially available in 2005.[87] The main advantage, aside from a high boiling point (Table 4) is low risk for the formation of peroxides, narrow explosion range, and overall stability; all these factors make it an attractive solvent particularly for industrial processes.[87] With the solvent in hand, we went on to study the scope of medicinally relevant, highly functionalised substrates for amidation. The substrates were provided to the Sheppard group by GSK and contained building blocks or precursors for medicinally relevant structures, such as examples represented in Figure 4.

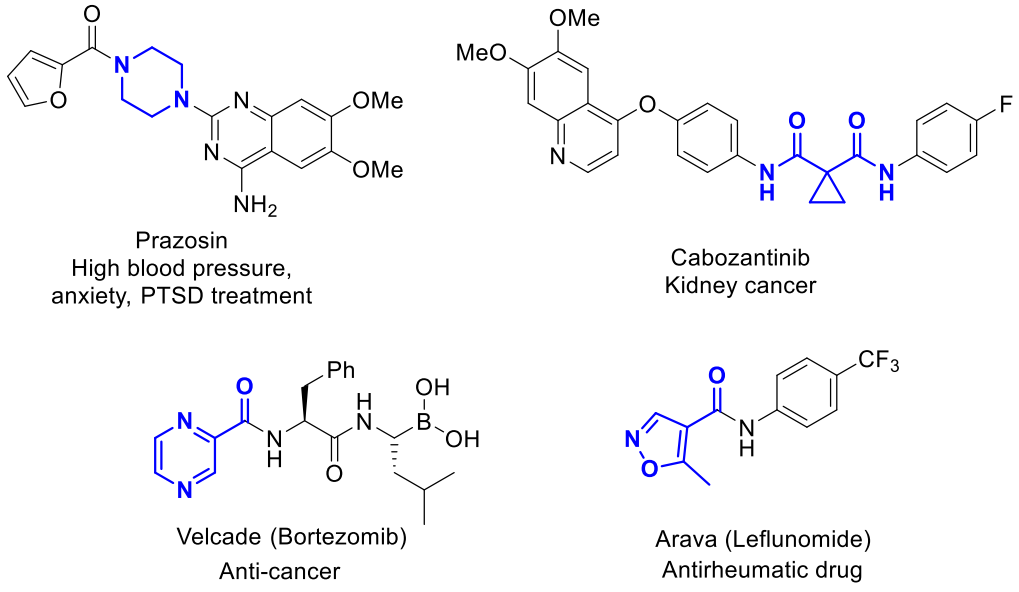
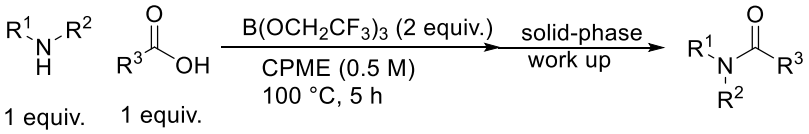


Figure 4 Commercially available drugs containing highly functionalised amides

The previously optimised conditions (concentration, equivalents of reactants, $B(OCH_2CF_3)_3$ amount) were maintained, but the reaction temperature was increased from 80 °C to 100 °C as the building blocks were often less reactive (poorly nucleophilic amines) (Scheme 53). For example, the reaction to obtain

amide **55c** led to a significant improvement in the yield from 38% to 69% (*vide infra*, Scheme 54).

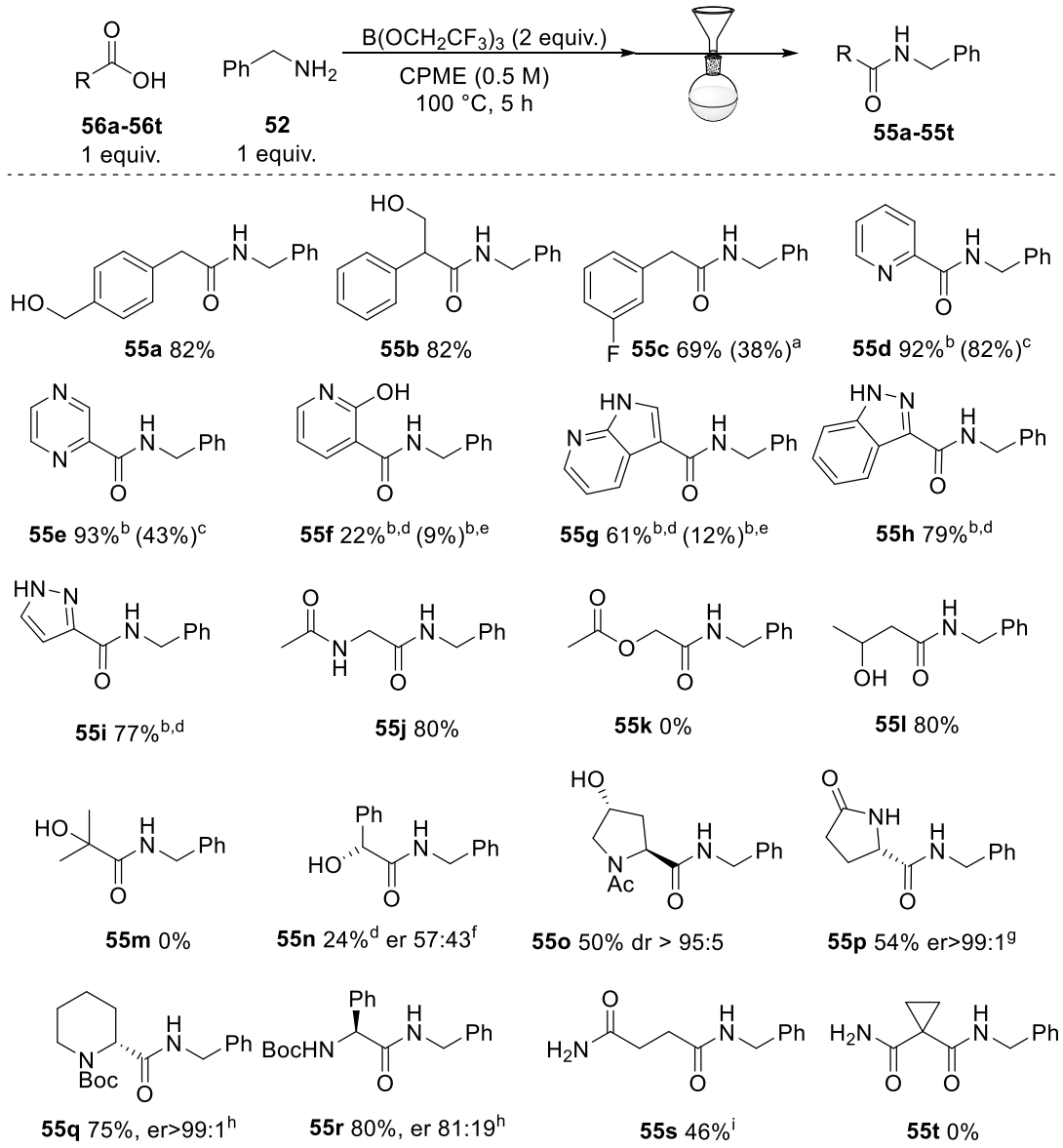


Scheme 53 Optimised conditions for amidation using $B(OCH_2CF_3)_3$ in CPME

The scope of the reaction was tested by reacting a highly functionalised acid or amine with benzylamine or phenylacetic acid respectively to provide good comparison between the substrates of interest. Unless otherwise stated, the amides were isolated by the solid-phase work up developed in the Sheppard group.[85] Upon completion, the mixture was diluted with EtOAc (3 mL) and water (0.5 mL) and stirred with acid scavenging basic resin Amberlyst® A26(OH), amine scavenging acidic resin Amberlyst® 15, and boron scavenger Amberlite® IRA743. In cases when the amine or acid substrates contained an acid-sensitive group (other than the amine moiety undergoing amidation), the residual acid/amine and boron were removed by Amberlyst® A26(OH) and Amberlite® IRA743, but amine scavenger Amberlyst® 15 was not used and any unreacted amine/acid was separated by flash column chromatography to yield pure amide.

Scope of highly functionalised carboxylic acids

Representative amides made from medicinally relevant carboxylic acids are shown below (Scheme 54).



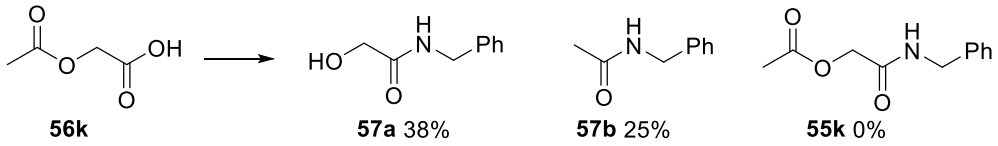
Scheme 54 Scope of acids in amidation reaction with benzylamine. All reactions were carried out on 0.5 mmol scale at 100 °C for 5 h in CPME followed by solid phase work up unless otherwise stated; a. Reaction carried out at 80 °C for 5 h; b. Purified by flash column chromatography; c. Purified by solid-phase work up with Amberlite® IRC86 as amine scavenger; d. Reaction carried out at 125 °C for 24 h in a sealed carousel tube; e. Isolated yield under standard conditions (100 °C, 5 h); f. er determined using chiral HPLC; g. er determined using chiral shift reagent; h. er determined using Marfey's reagent (see Chapter 2.2.3); i. Product isolated by recrystallisation

Generally, reactions of substituted phenylacetic acids **56a-56c** gave good yields under optimum conditions (100 °C, 5 h). The reaction was tolerant of free hydroxyl groups and amides **55a**, **55b**, **55l** were isolated in good yields. The hydroxyl proline derivative **55o** was obtained in a moderate yield with no racemisation of the product.

However, the reaction conditions were less suitable for carboxylic acid substrates with an α-hydroxyl moiety; the reaction of acid **56m** resulted in a very complicated mixture of decomposition by-products, whereas mandelic acid **56n** only reacted under forcing conditions, and low yield along with a significant degree of racemisation was observed.

Nitrogen containing heterocyclic amides **55d-55e** were isolated in excellent yields. In addition, purification of the amides was attempted using a less acidic resin Amberlite® IRC-86, containing a carboxylic acid moiety, however, a significant decrease in the isolated yield, particularly for the amide **55e** (93% to 43% decrease) with two nitrogen atoms in the heterocycle, was observed. Stronger and prolonged heating (125 °C, 24 h) was required to isolate amides **55f-55i** in good yields. When subjected to 100 °C and 24 h heat, only 9% of amide **55f** and 12% of **55g** was obtained.

An acyl-protected glycine derivative reacted well to give 80% yield of **55j**. Interestingly, **55k** was not isolated due to side-reaction of benzylamine with the ester group, resulting in amides **57a** and **57b** instead (Scheme 55).

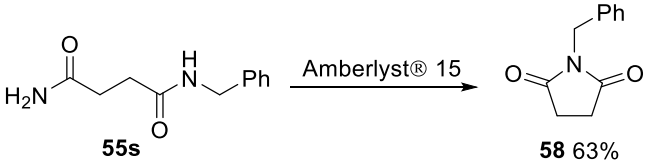


56k **57a** 38% **57b** 25% **55k** 0%

Scheme 55 Products of amidation of **56k**

Cyclic substrates **56p** and **56q** with stereocentres at the carboxylic acid moiety did not undergo racemisation and resulted in good yields of amides. However, the enantiomeric ratio of Boc-protected phenylglycine **56r**, known to be prone to racemisation, decreased to 81:19 upon reacting under standard conditions.

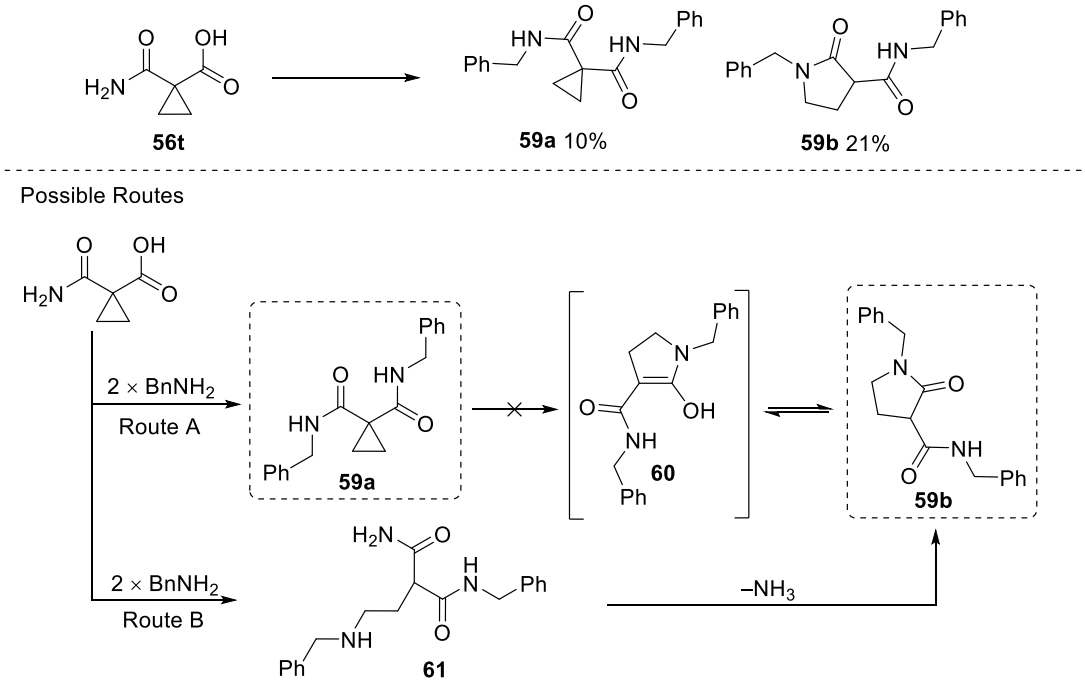
Succinamic acid **56s** gave a modest yield of 48%, however, the product **55s** was isolated by recrystallisation as when the acidic resin was used, it resulted in cyclisation of the amide product **55s** into the corresponding *N*-benzylsuccinimide **58** (Scheme 56).



55s **58** 63%

Scheme 56 Cyclisation of **55s** after acidic resin work-up

Synthesis of the amide **55t** failed due to side-reactions resulting in amides **59a** and **59b** instead (Scheme 57).



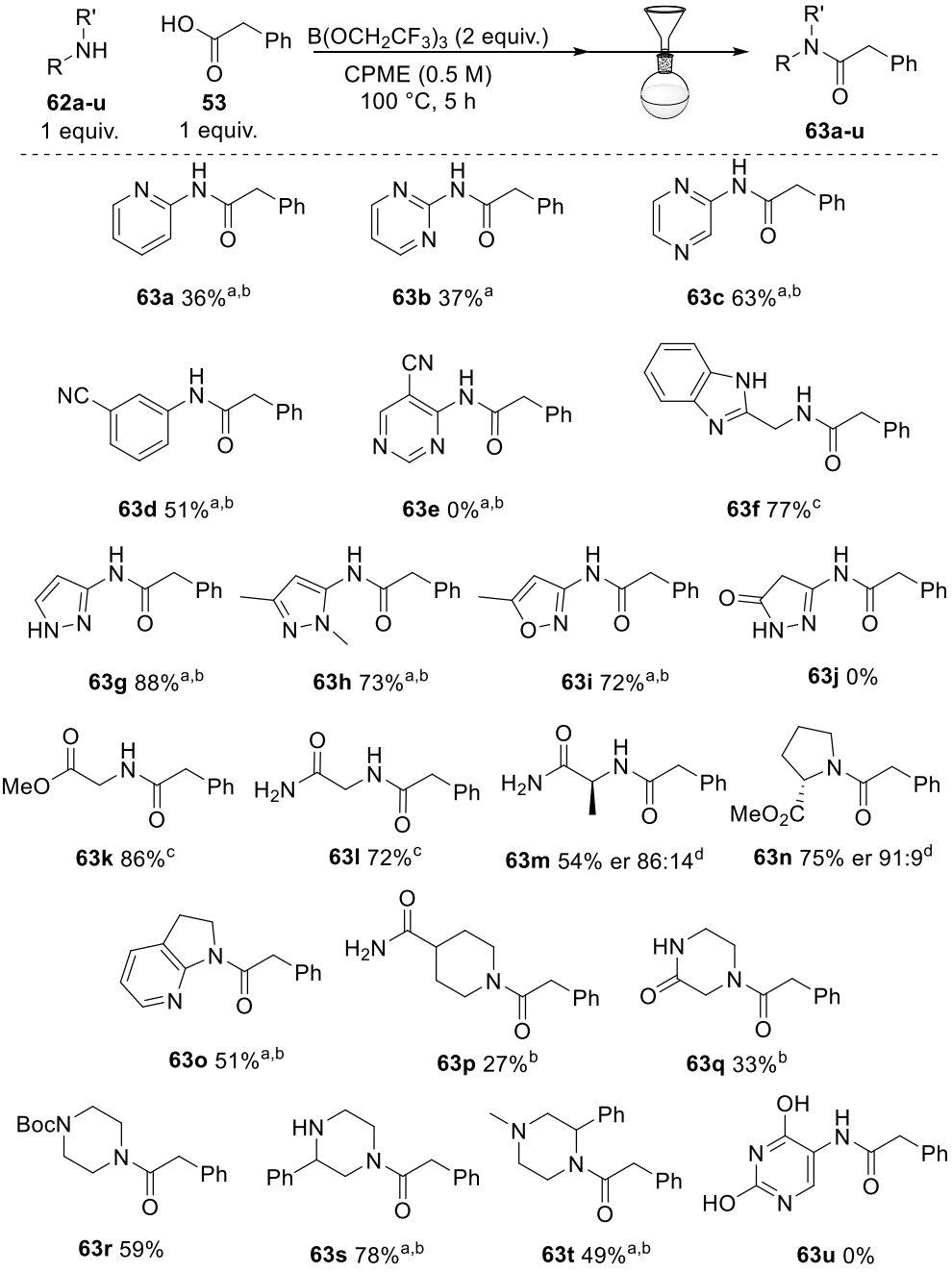
Scheme 57 Products of amidation of **56t**

Transamidation using $B(OCH_2CF_3)_3$ to activate primary amides has previously been observed and reported by the Sheppard group.[86,84] In the example of **56t**, however, the mechanism of formation of **59b** is unclear. The work-up with an acidic resin did not interfere with **59a** to promote the formation of **59b** as the crude NMR suggested that both amides were present in the mixture at the end of the reaction prior the work-up. The desired amide **55t** was not observed, however. Taking into account that **59b** is the major product in the reaction, it is possible that after the formation of **59a** *via* transamidation of the primary amide and amidation of the carboxylic acid, internal rearrangement could take place in order to release the ring strain (*via* **60**) and form a more stable five-membered amide **59b**. Alternatively, a direct formation of **59b** could be achieved *via* a competing pathway where benzylamine attacks the cyclopropane ring in **56t**, again driven by the ring strain release, to form **61** followed by elimination of ammonia to yield **59b** (Scheme 57). However, formation of **60** *via* **59a** was ruled out as subjecting the amide **59a** to longer heating time or resubmitting to the amidation conditions in the presence of $B(OCH_2CF_3)_3$ did not yield amide **59b**, suggesting that routes A and B are competing pathways. The reaction was repeated at a lower temperature (100 °C) to test whether transamidation could be avoided, and form the target amide **55t** instead. However, when subjected to our standard conditions (100 °C, 5 h), the major product was still

59b, with only **59a** present as a by-product (ratio 9:1) in a much lower overall yield of ~5%.

Scope of highly functionalised amines

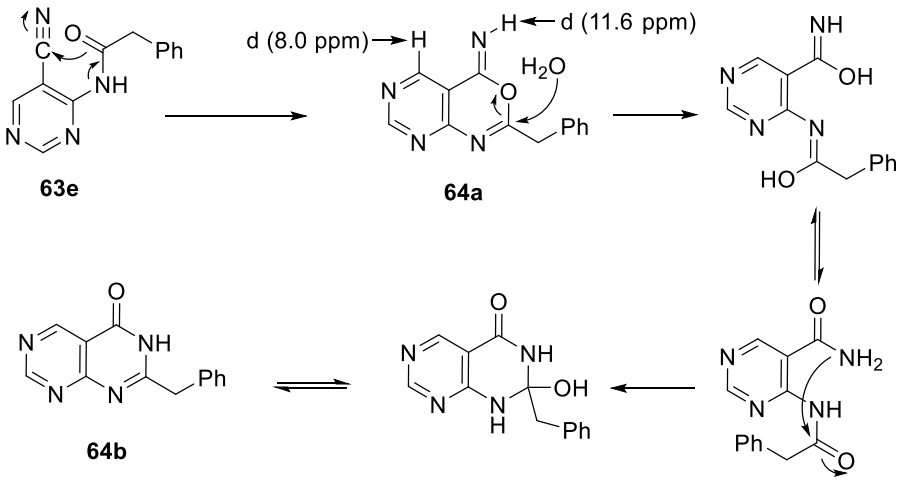
We then moved on to investigate the scope of medicinally relevant amine building blocks (Scheme 58).



Scheme 58 Scope of amines in amidation reaction with phenylacetic acid. All reactions were carried out on 0.5 mmol scale at 100 °C for 5 h in CPME followed by solid phase work up unless otherwise stated; a. Purified by flash column chromatography; b. Reaction carried out at 125 °C for 24 h in a sealed carousel tube; c. For 1 equiv. RNH_2.HCl salt, 1 equiv. NEt_3 was added; d. er determined using chiral HPLC

Harsher conditions were usually required in the examples presented above due to the poorly nucleophilic amines tested. The 6-member heterocyclic amides **63a-63c** were obtained in relatively low to moderate yields even at 125 °C after 24 hours. Importantly, however, the amide **63a** was obtained in a higher yield (36% vs 12%) under these conditions than in previous reactions done in MeCN (100 °C), highlighting the importance of increased temperature for less reactive substrates. In all cases, 6-membered heterocyclic amides were isolated using flash column chromatography, as it had been previously established (*vide supra*) that a less acidic resin Amberlite© IRC86 also led to the undesired scavenging of the product.

Aniline derivative **62d** with *meta*-nitrile group gave amide **63d** in 51% yield. However, an aromatic heterocyclic amine with an ortho-nitrile group to the amine moiety did not yield the desired amide **63e** and side-reactions were observed instead. The majority of **62e** was unreactive to amidation. Unfortunately, we were unable to separate the by-products and it is therefore not possible to determine their structure with certainty. The NMR data of the crude mixture suggested that a side-reaction had occurred at the nitrile moiety. This could possibly result in cyclisation which could lead to the proposed structure **64a** (Scheme 59).



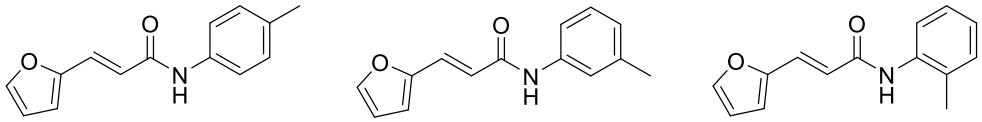
Scheme 59 Possible side-reaction of amide **63e**

It is also possible that in the presence of water, **64a** could rearrange further to **64b**. However, due to the excess of $B(OCH_2CF_3)_3$ used in the reaction, any water liberated as the result of initial amidation of **62e** could be consumed to hydrolyse the borate and therefore the formation of **64b** would not be favourable. Moreover, the strong NMR shifts downfield supported **64a** as the more likely structure.

5-Membered heterocycles all gave good yields of amides **63g**-**63i**. However, amine **62j** did not afford the product, most likely due to poor solubility in the reaction

solvent. Similarly, amide **63u** was not obtained as the amine was completely insoluble in the reaction solvent. Amino acid ester or amide derivatives (**62k-62n**) gave reasonable yields of **63k**-**63n**, with some racemisation observed for amides **63m** and **63n**. Pleasingly, secondary amines gave moderate to good yields of amides **63o**-**63t**, and no transamidation was observed for the amide **63p**. The *tert*-butyloxycarbonyl (Boc) protecting group in amine **62r** was well tolerated under the reaction conditions and work-up procedure resulting in 59% yield of amide **63r**.

The reaction scope was further extended to the synthesis of three potential positive allosteric modulators of the α7 nicotinic acetylcholine receptor for biological testing in the Millar group of UCL (Figure 5). The use of the α7 nicotinic acetylcholine receptor allosteric modulators has been widely researched as a potential to develop therapeutics for the treatment of schizophrenia.[88] The para-methyl aniline derivative **65** (PAM-2)[88] has previously been reported to have strong affinity for the receptors,[89–91] and more recently was shown to reverse negative and cognitive symptoms of schizophrenia induced by administration of ketamine to rats.[88]



65 nr[a] 54%[b]

66 nr[a] 30%[b]

67 nr[a] 35%[b]

Figure 5 Synthesis of potential positive allosteric modulators; reaction conditions: a. 1 equiv amine and acid stirred for 5 h in CPME at 100 °C in the presence of $B(OCH_2CF_3)_3$ (2 equiv.); b. heated at 125 °C for 24 h.

None of the target amides were obtained when substrates were subjected to standard conditions (100 °C, 5 h) most likely due to low reactivity of aniline derivatives. Increasing the heat and reaction time, however, afforded amides **65**-**67** in moderate yields.

Reaction of diamines using $B(OCH_2CF_3)_3$

Diamines are useful substrates with a variety of applications. For example, symmetrical aliphatic diamines are used as spacers, particularly in biologically active substrates.[92] The piperazine moiety is often an important scaffold for drug molecules, as the nitrogen atoms can be functionalised with different groups (Figure 6).[93]

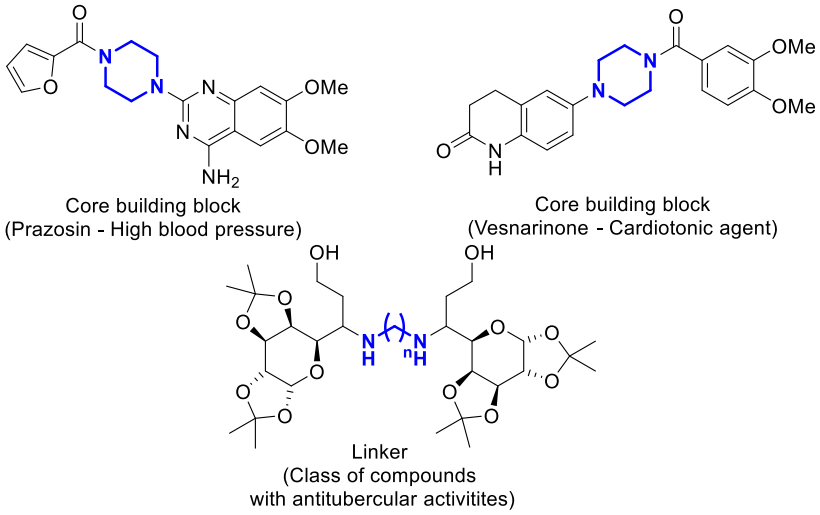
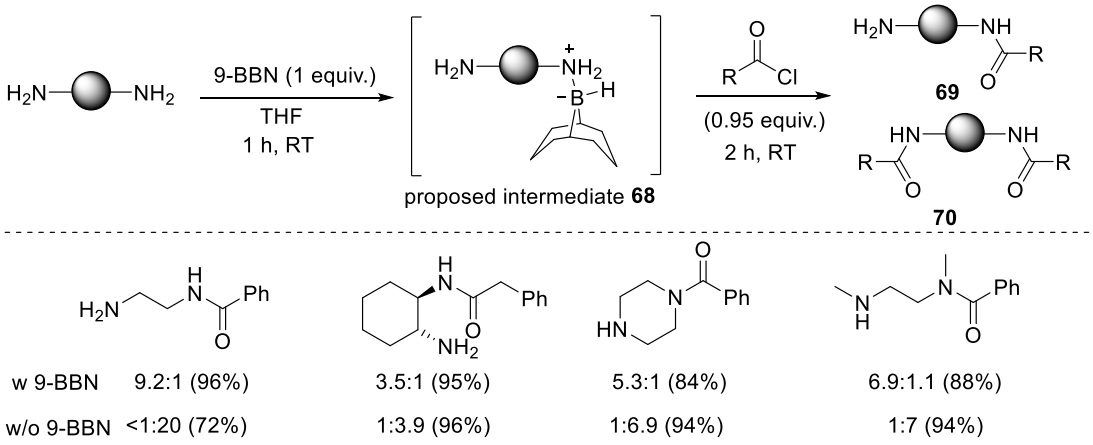


Figure 6 Selected examples of compounds containing a diamine moiety

Amidation of unsymmetrical diamines is quite a routine procedure and the selectivity often relies upon steric or electronic effects. The starting diamine can be tuned to afford a high degree of selectivity. For example, primary amines are often more reactive than secondary, which would afford the selective functionalisation of one over the other. Symmetrical diamines, on the other hand, present a bigger challenge, as no such effects are at hand and therefore other approaches need to be used. Statistically, when one equivalent of diamine is reacted with one equivalent of carboxylic acid, it is expected that 50% of the product would be mono-acylated product, 25% diamide, and another 25% the unreacted diamine.[92,93] This, however, according to reports, is rarely the case and even in excess of diamine, the major product is often diamide.[92] To achieve monoacylation, procedures often rely on selective protection followed by functionalisation, and finally with deprotection of one amine group. It was also found that using fairly unreactive acylating agents (e.g. acid anhydride vs. acid chloride) together with slow addition under high dilution conditions improved the selectivity of the reaction, as it has been shown that the first acylation occurred significantly more rapidly than the second one, which is due to the second non-acylated amines becoming less nucleophilic.[93,94]

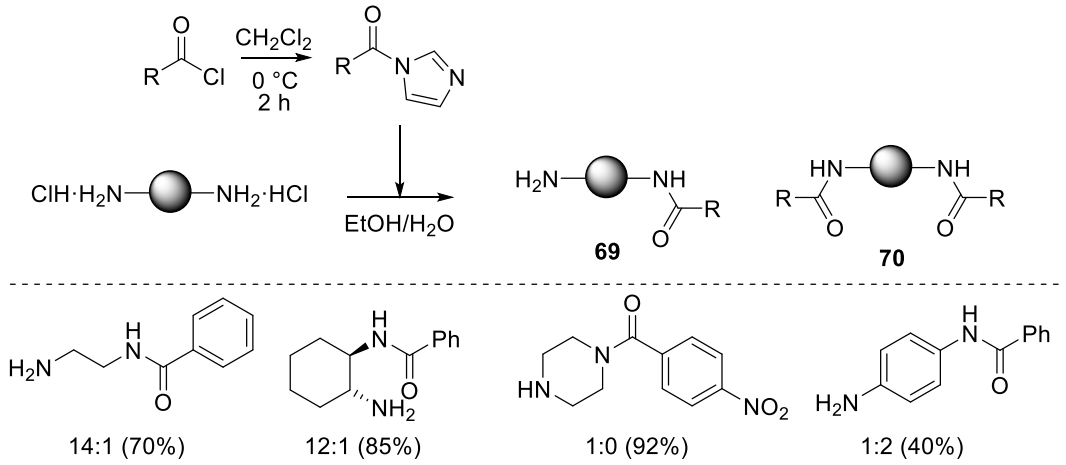
A different approach is the desymmetrisation of the diamine. One such method was developed in 2003 by Wang *et al.*; it was reported that 9-BBN could be used to form a complex **68** with one of the amines thus leaving only one amine group available for the reaction with a variety of acyl chlorides (Scheme 60).[95] Importantly, if no 9-BBN was used, the major product was diamide.



Scheme 60 9-BBN mediated monoacylation, selected examples. Overall yield in parenthesis. Ratio is **69:70** mono:di acylation product

In 2010, Kaushik *et al.* reported a more practical and tolerant method by using imidazole to tame the reactivity of acyl chlorides, therefore allowing the selective monoamidation of diamine hydrochlorides in EtOH/water at room temperature (Scheme 61).[96] The development came from the observation that when the acid and diamine were mixed together in the presence of tosyl imidazole, the tosyl transfer to only one amine group occurred, which led the group to test imidazole in the activation of the acyl group.

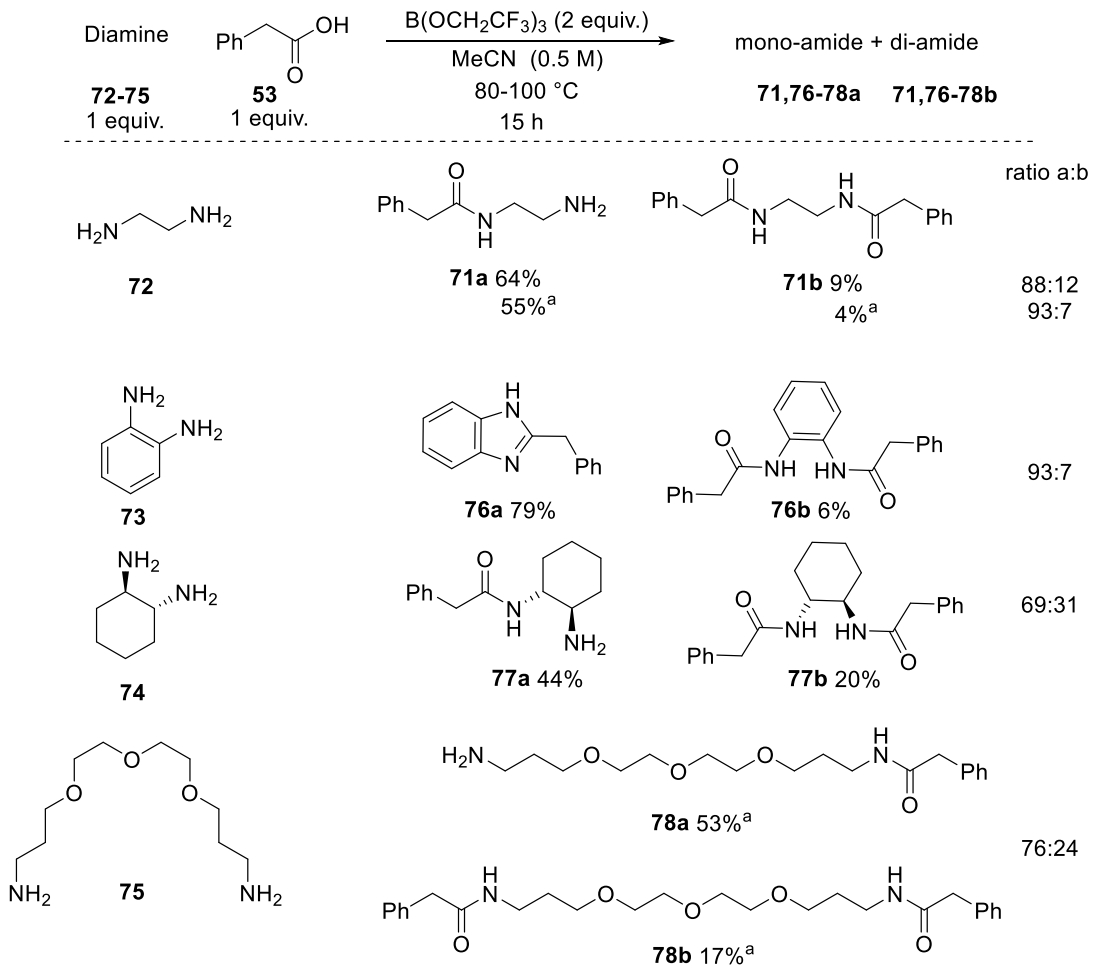
The scope was shown for aliphatic primary and secondary amines with aromatic acylating counterparts. 1,4-Diaminobenzene was the only aromatic diamine example, but in this case, diacylation was the preferred reaction.



Scheme 61 Imidazole as a reagent for selective monoacylation; ratio is **69:70** mono:diamidation products

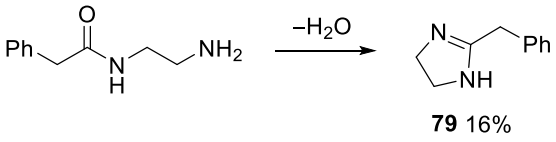
Later, Kaushik improved the protocol by using CDI as an activating agent of carboxylic acids, making the procedure more sustainable. Once formed, the acylating agent was then reacted with diamines in brine solution, and the product was obtained within 5 minutes with high selectivity for monoacylated products.[97]

In previous experiments in the Sheppard group, ethylenediamine was reacted with phenylacetic acid,[85] and good selectivity for mono-acylation was observed by NMR (95:5 of **71a**:**71b**). It was therefore decided to extend the scope to more diamines in a reaction with phenylacetic acid. Reactions were either performed using previously optimised conditions (MeCN, 80 °C)[84] or those applied to the synthesis of medicinally relevant amides in CPME, *vide supra* (Scheme 62).



Scheme 62 The scope of mono-acylation; diamine (1 equiv.) was mixed with phenylacetic acid (1 equiv.) in MeCN (0.5 M) with $B(OCH_2CF_3)_3$ (2 equiv.) and stirred at 80-100 °C for 15 h. Products isolated by flash column chromatography; a. Reaction performed in CPME

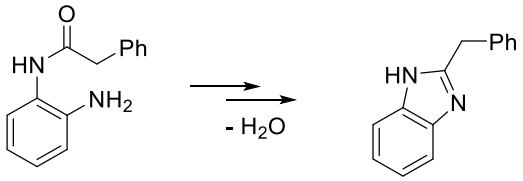
Pleasingly, the reaction showed promise for selective mono-acylation. In all cases, the major product was mono-amide with good to excellent yields obtained. Importantly, when the reaction of ethylenediamine was performed in CPME, higher selectivity for the monoamidation product **71a** was observed, however, the yield of the monoamide **71a** was decreased by the formation of cyclised product **79** (Scheme 63).



Scheme 63

Similarly, the amidation of 1,2-diaminobenzene **73** resulted in dehydration, but in this case, only cyclised by-product **76a** was isolated instead of mono-amide

(Scheme 64). The low yield of diamide **76b** also supports that the cyclisation from **76c** may have been facile, and occurred more rapidly than the diacylation reaction.



76c **76a**

Scheme 64 Cyclisation of **76c**

Amine **74** showed less selectivity for the selective acylation, resulting in 69:31 ratio of **77a**:**77b** respectively. Similarly, a long diamine linker **75** gave good overall amidation yield with selectivity 76:24 of **78a**:**78b**.

2.1.1 Design of Experiments study

During the investigation of the amine scope in the amidation of medicinally important substrates, it was observed that 2-aminopyridine **62a** showed a 3-fold increase in the yield with phenylacetic acid in CPME at 125 °C compared to MeCN at 100 °C (entry 1, Table 4),[84] suggesting that the increase in temperature is indeed beneficial for the higher yield for this reaction. In an attempt to further improve the procedure and optimise the conditions to suit more challenging unreactive substrates, it was decided to perform a “Design of Experiments” (DoE) study on this reaction.

Traditionally, the optimisation of the reaction is performed by varying one factor at a time (i.e. temperature, reactant concentration, time, solvent, etc.), which is also called an “OVAT” approach (one variable at a time). This may obviously be a lengthy process. It may also be difficult to arrive to optimum conditions as it heavily depends on the pre-optimisation starting point, which means that one may be far away from uncovering the best conditions possible. Moreover, OVAT does not incorporate interactions between variables, which may be an important factor for the outcome of a reaction.

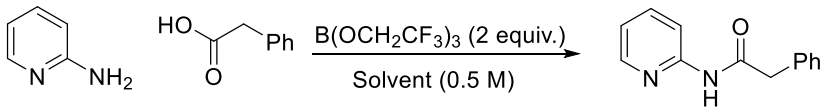
A DoE study is a statistical model used for the optimisation of a reaction. In contrast to traditional optimisation methods, the DoE approach enables simultaneous evaluation and variation of parameters of interest therefore giving a picture of the entire “reaction space”.[98] This approach significantly reduces the number of experiments required to optimise a reaction, and also gives a deeper insight into the reaction because it takes into account and identifies interactions amongst the

parameters.[99,100] For this reason, it is now routinely used by process chemists in industry, however, less so in academia. This issue has been highlighted in OPRD and it has been suggested that DoE methods should be a part of curriculum in universities.[101]

There are five main points to be considered before starting a DoE:[100]

1. Defining the goal of an experiment – e.g. improving the yield of the reaction.
2. Consideration of all factors/variables that can affect the reaction, e.g. temperature, reaction time, reactant amounts, solvents, etc.
3. Planning of experiments
4. Running the experiments
5. Data analysis; using the DoE software (MODDE 10 software was used for the analysis of data produced).

Before planning the experiments for the DoE on the 2-aminopyridine-phenylacetic acid reaction, it was necessary to determine what factors should be included in the design. Aside from the variables already present in the reaction, i.e. temperature, time, solvent, concentration, equivalents of reactants and the borate reagent, we decided to test whether dropwise delivery of $B(OCH_2CF_3)_3$ could be beneficial to the improvement of the yield (Table 5).



62a 1 equiv. **53** 1 equiv. **63a**

Entry	Solvent	Temperature	Conditions	Yield
1[a]	MeCN	100 °C	Standard	12%
2	CPME	125 °C	Standard	36%
3	CPME	125 °C	Dropwise addition of borate	(39%)
4	CPME	125 °C	Dropwise addition of borate/acid mixture	(40%)
5	CPME	125 °C	Dropwise addition of borate, Et_3N added to the reaction mixture	(60%)

Table 5 NMR yields in parenthesis, determined against pentachlorobenzene as internal standard; a. result obtained by Rachel Lanigan[84]

Dropwise addition of $B(OCH_2CF_3)_3$ to the reaction mixture did not seem to significantly improve the yield (entry 3). It has previously been observed that a basic environment is beneficial for increased yields and therefore we tested if slow

addition of carboxylic acid together with the borate could help, however, the yield did not improve either (entry 4). However, introducing Et_3N to the reaction mixture improved the yield, suggesting that basic environment in the reaction mixture may be responsible for the increased yield after all.

For this DoE optimisation, seven different factors were chosen, and two different solvents were varied – CPME and propionitrile, a higher boiling alternative to MeCN (Table 6).

Variable	Low	Middle	High
Amine-acid equiv. ratio	1:3	1:1	3:1
$B(OCH_2CF_3)_3$ (equiv.)	0.5	1.75	3
Et_3N (equiv.)	0.1	1.55	3
Rate of addition[a]	1	26	51
Temperature (°C)	80	102.5	125
Initial solvent volume in reaction mixture (mL)	0.5	1.25	2
Initial solvent volume in $B(OCH_2CF_3)_3$ solution (mL)	0.5	1.25	2

Table 6 a. Setting on a syringe pump; 1 is the slowest, 0.254 mL h^{-1}; 52 fastest 13 mL h^{-1} of a 5 mL syringe. For full details of each experiment see experimental section 6.4

Having seven variables and two solvents to be varied led to 16 experiments covering low/high ranges and 3 centre point experiments giving 19 in total. For accuracy of the results, stock solutions of all reagents were used. The NMR was collected on 600 MHz Bruker, and NMR yields were determined using 1,4-dimethoxybenzene as an internal standard. After all the experiments were performed and data analysed, the results were processed using MODDE 10 software by Dr Tom Sheppard (with the help of Dr Paul Murray). The software highlighted four parameters to be the most important in this reaction (Figure 7).

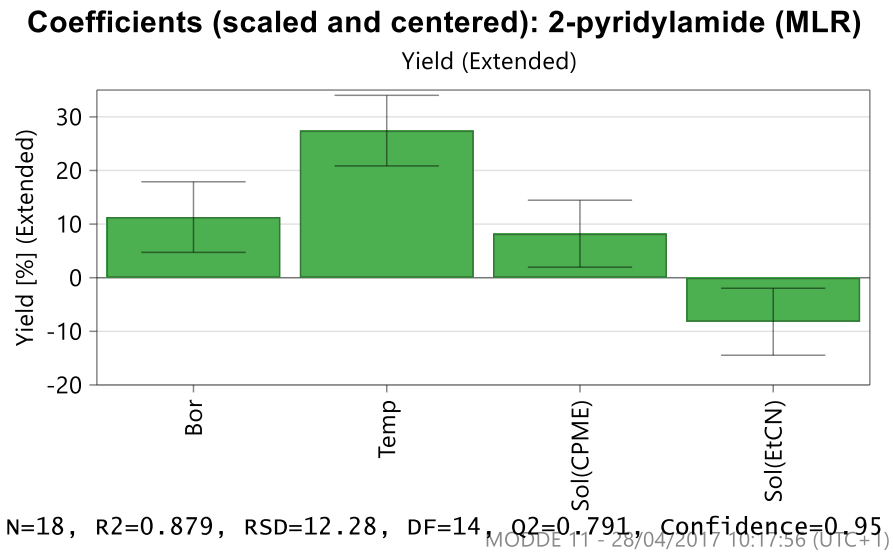
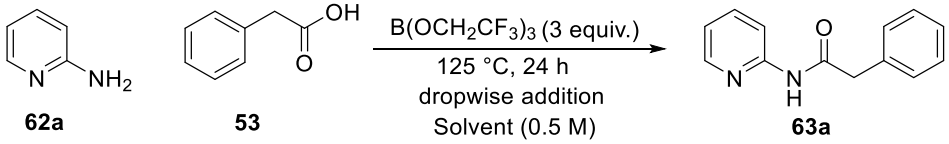


Figure 7 Graph representing the most improtant factors of the reaction

The most important factor, unsurprisingly, was shown to be temperature leading to 27% increase in the yield of the amide product **63a** on average when the reaction was performed at the higher temperature of 125 °C instead of 102.5 °C. The amount of $B(OCH_2CF_3)_3$ was the second most significant factor with a larger excess beneficial to the success of the reaction. Finally, CPME was more suitable as a solvent, and EtCN was determined as a poor solvent leading to lower overall yields.

With the new optimised conditions in hand, we went on to apply them to the reaction and isolate the products (Table 7).



Entry	Conditions	Yield
1	3 equiv. Et_3N, CPME	58%
2	3 equiv. Et_3N, Bu_2O (bp 142 °C)	74%
3	3 equiv. **53**, 3 equiv. Et_3N, CPME	83% (100%)
4	3 equiv. **62a**, 0.1 equiv. Et_3N, CPME	84% (100%)

Table 7 All experiments performed on 1 mmol scale, 1 equiv. of amine and acid unless otherwise stated; NMR conversion in parenthesis

Initially, the model did not determine the importance of excess of either amine or carboxylic acid in the reaction. However, when we moved on to obtaining isolated yields with the optimised conditions, it was found that the yield was lower when equimolar amounts of reactants were used with only 58% isolated yield (entry 1). It

was possible to improve the yield to 74% by switching to dibutyl ether as a solvent, which has similar properties to CPME, but has a higher boiling point (entry 2). This further emphasises the importance of temperature for the success of this reaction. Increasing equivalents of either acid or amine led to full conversion to amide with 83% and 84% isolated yields (entry 3 and 4).

2.2 Direct amidation of unprotected amino acids

2.2.1 Background

The amino acid moiety is important not only in peptide science and as a building block in nature, but also is present in an abundance of drug structures and ligands (Figure 8).

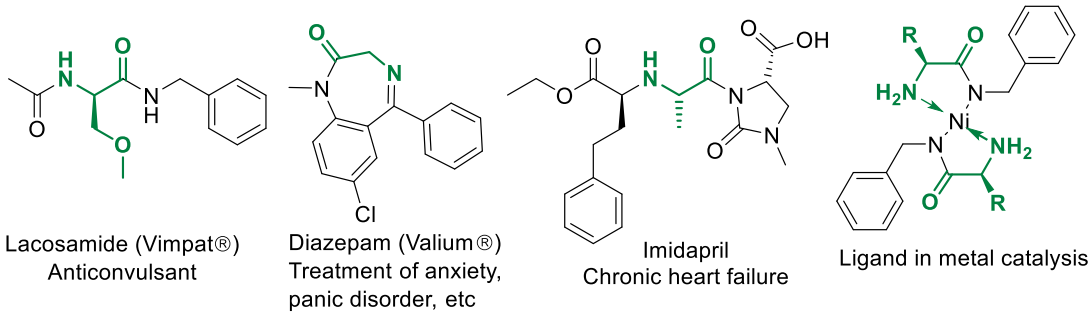


Figure 8 Selection of drugs and ligands containing amino amide functionality

The majority of synthetic routes employing amino acids usually concentrate on the application to peptide synthesis. This, however, heavily relies on protecting group chemistry as there is a danger of self-condensation reaction, leading to polymerisation, that cannot be controlled. The *N*-moiety can be protected by a large variety of groups, such as Boc (MW 116), Fmoc (MW 238), Cbz (MW 150), etc (Figure 9). The use of protecting groups, however, is highly inefficient as it adds extra cost and steps for the protection, purification and deprotection of the amino acid undergoing acylation adding to the poorer atom economy of the overall reaction.

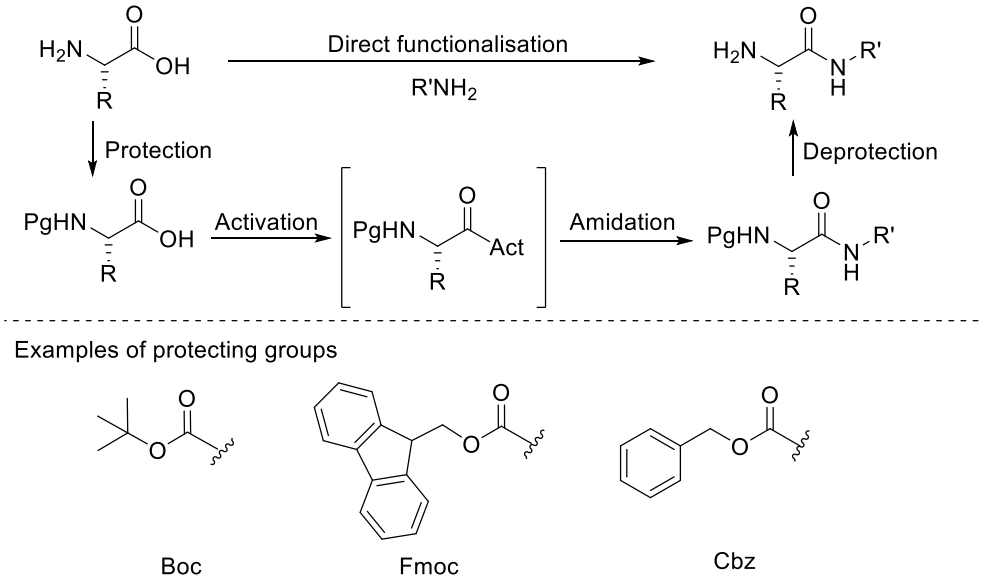
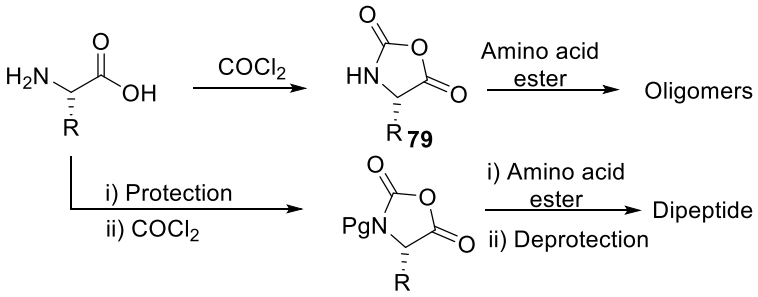


Figure 9 Commonly used amino acid protecting groups

Depending on the compound undergoing the transformation, not all may be compatible with the protection/deprotection conditions; Boc is usually removed with acid treatment, e.g. TFA; Fmoc requires base for removal (often 2° amines are used); Cbz is generally cleaved with hydrogenation.[102]

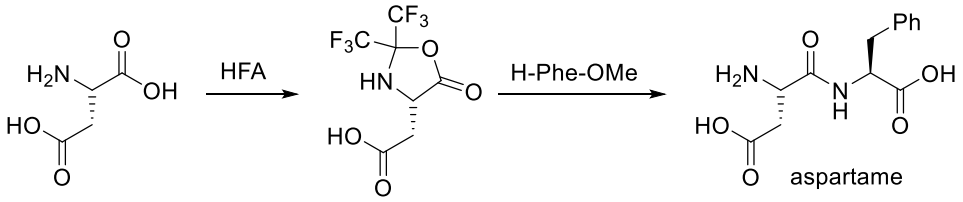
The amidation protocols that avoid the necessity to protect an amine moiety are scarce. In order to achieve direct amidation, the amine functionality needs to be "protected" by the catalyst or reagent used to aid the reaction, simultaneously with activation of the carboxylic acid moiety.[103,104] To our knowledge, there are only few publications addressing this problem and even fewer that succeeded in developing a practical approach to amino acid amide synthesis.[103–106]

Initially, attempts to synthesise an amide from an unprotected amino acid used a simultaneous protection-activation approach by making *N*-carboxy anhydride **79** (NCA approach). In the first known example, phosgene was used to activate the carboxylic acid, but it did so to such extent, that uncontrollable formation of oligo- and polymers was observed instead of the desired di-peptide (Scheme 65).[107] Therefore, to tame the reactivity, *N*-protection was still required upon activation with phosgene.[103,104]



Scheme 65 First attempts at direct amidation of unprotected amino acids to furnish peptides

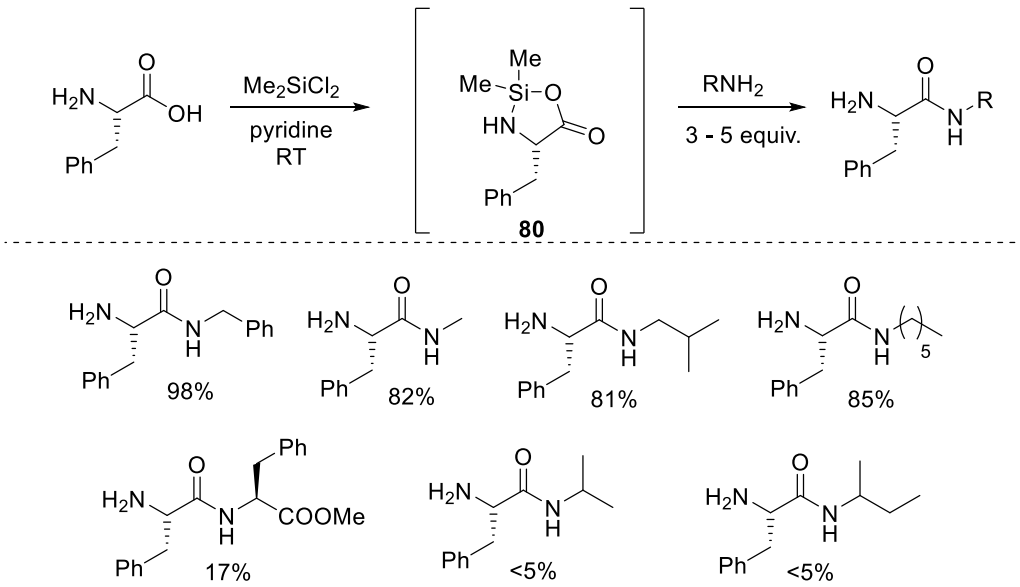
Burger *et al.*[107,108] reported the use of gaseous hexafluoroacetone (HFA) in a similar approach to activate and protect an amino acid. The group successfully produced aspartame, a commonly used sweetener, in 72% yield using this methodology (Scheme 66). Importantly, the reaction was selective to the α-carboxylic acid only, rationalising the importance of a chemoselective simultaneous protection-activation strategy.



Scheme 66 Simultaneous activation-protection approach using HFA

However, the procedure was severely limited by the cost and safety issues associated with gaseous HFA, particularly in application to large scale synthesis of amides.

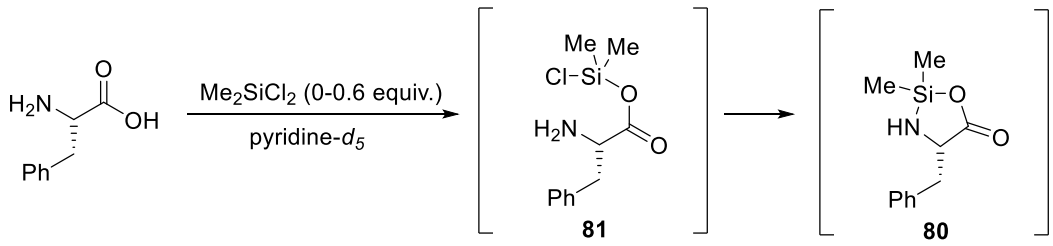
In 2002, a similar approach was further exploited by Liskamp *et al.* using dichloroalkyl silanes to produce activated amino acids of type **80** (Scheme 67). [103]



Scheme 67 Dichlorodialkylsilanes as reagents for the amidaiton of unprotected amino acids, selected examples

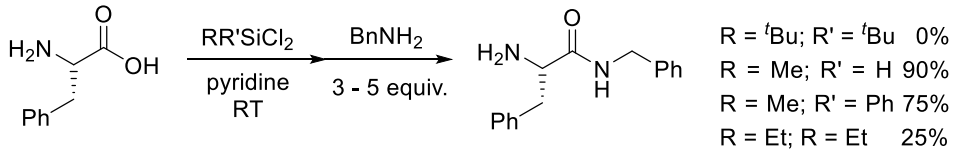
The reaction of L-Phe with benzylamine proceeded well at room temperature in pyridine both as a solvent and to scavenge HCl liberated from the reaction of Me_2SiCl_2 with an amino acid. Heating the reaction resulted in poorer yields, however, with no conversion observed at reflux. The scope was limited to primary amines, and any bulk on the α-carbon of the amine drastically reduced the reactivity resulting in amide yields dropping below 5% (Scheme 67). An attempt to make aspartame was also unsatisfactory with only 17% of dipeptide obtained. In all examples, enantiomeric ratio values were not discussed.

An attempt was made to isolate the reactive intermediate **80**, but it was too unstable and therefore indirect evidence was gathered to elucidate the mechanism of the reaction. The reaction did not proceed with benzoic acid or with *N*-protected L-Phe in the presence of Me_2SiCl_2 as the amidation reagent, suggesting that incorporation of silicone between amine and carboxylic acid moieties was necessary for the activation of an acid. Furthermore, titration of L-Phe with Me_2SiCl_2 revealed the formation of a linear intermediate **81** by NMR analysis which then cyclised to give **80** (Scheme 68).



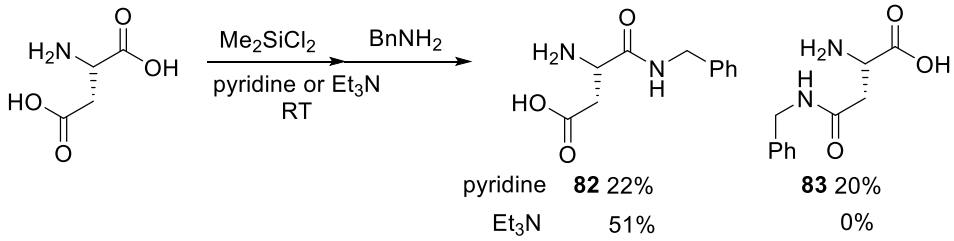
Scheme 68 Observed intermediate **81** in the formation of **80**

Further attempts to improve the reaction were made by varying alkyl groups on the silane reagent, but it was found that dichlorodimethylsilane was indeed the best reagent (Scheme 69).



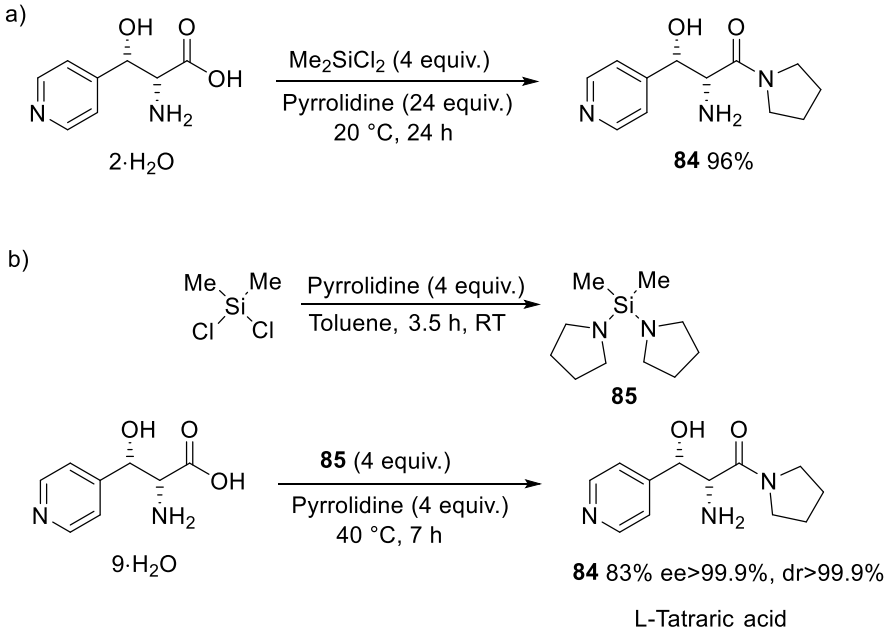
Scheme 69 Investigation of varying alkyl group of the silane reagent

The reaction was also applied to the amidation of sarcosine and β-alanine, which proceeded to give good yields of 80% and 60%, respectively. The reaction with L-Asp in pyridine gave an approximately 1:1 mixture of mono-amidation products **82** and **83**. However, using Et_3N as the solvent and base increased the selectivity for the desired product **82** (Scheme 70).



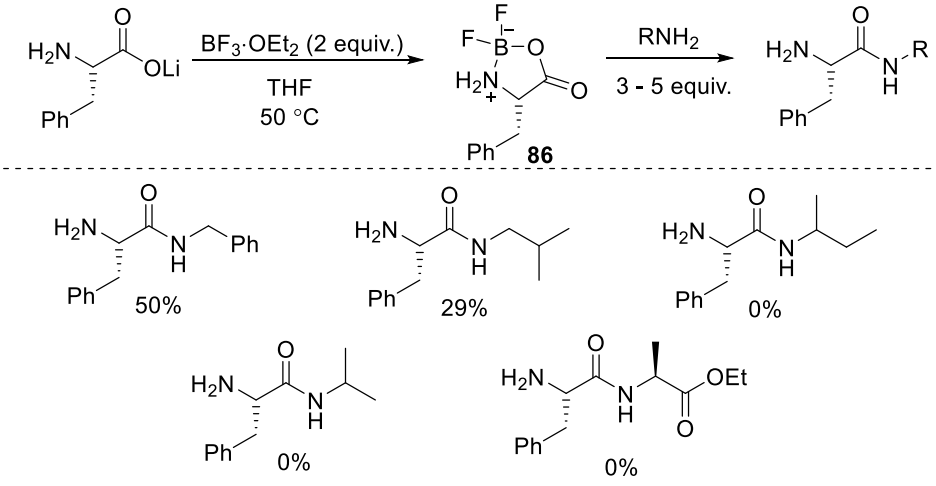
Scheme 70 Controlled amidation of aspartic acid

In 2015, this method was successfully applied by Schmidt and Rossano *et al.* in the large scale preparation of a candidate drug **84** used in the treatment of chronic pain.[109] Initially, a smaller scale reaction was performed using similar conditions to ones developed by Liskamp *et al.* with pyrrolidine as the solvent and nucleophile (Scheme 71a). The process was improved further by pre-forming silane species **85** from Me_2SiCl_2 and pyrrolidine, thus reducing the equivalents of pyrrolidine used. When the reaction was performed on a 450-gram scale, gentle heat was applied and therefore the reaction time was reduced to 7 hours to obtain the desired product **84** in 83% yield with no loss of enantiomeric purity (Scheme 71b).



Scheme 71 Large scale synthesis of drug **84** using Liskamp's method

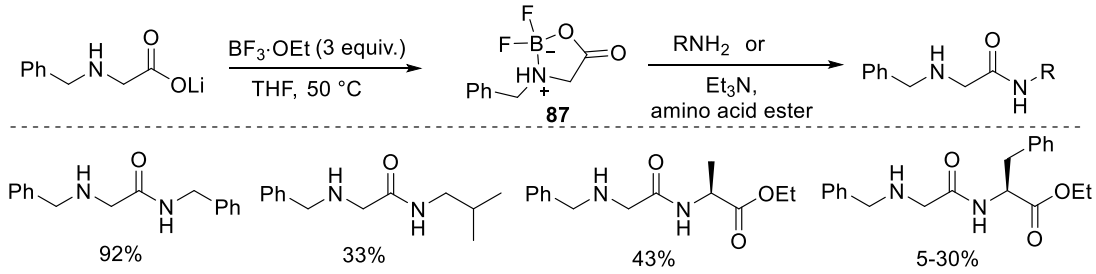
The Liskamp group also investigated the use of boron trifluoride diethyl etherate using the protection-activation approach in 2005.[104] In this case, lithium salts were prepared from an amino acid to aid solubility in the solvent of choice, THF. An intermediate **86** was stable enough to be isolated by flash column chromatography. When L-Phe lithium salt was subjected to amidation with benzylamine, 50% yield of the corresponding amide was obtained (Scheme 72).



Scheme 72 Selected examples from direct amidation of unprotected L-Phe using $BF_3 \cdot OEt_2$ as simulaneous protecting-activating reagent

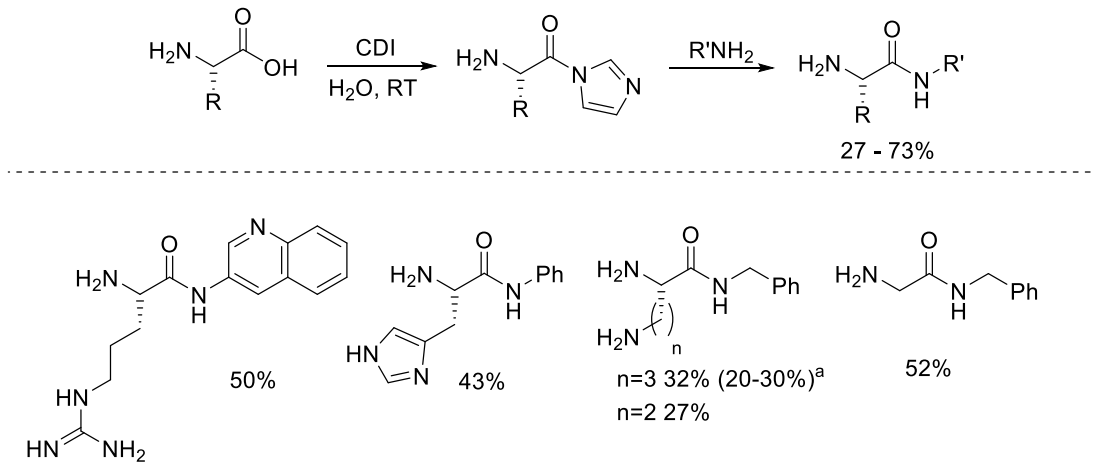
Unfortunately, the reaction was not tolerant to any steric bulk at the primary carbon of the amine and no amides were isolated. An attempt to make a dipeptide also failed. As before, the reaction worked with L-Asp lithium salt, but the reaction was

selective for the amidation of the side-chain carboxylic acid moiety resulting in 30% of the amide **83**.[104] Better reactivity was observed with benzyl-protected glycine (Scheme 73), which was proposed to be due to the more reactive and less stable intermediate **87** (making it more likely to ring-open). A series of dipeptides was synthesised in poor to moderate yields.



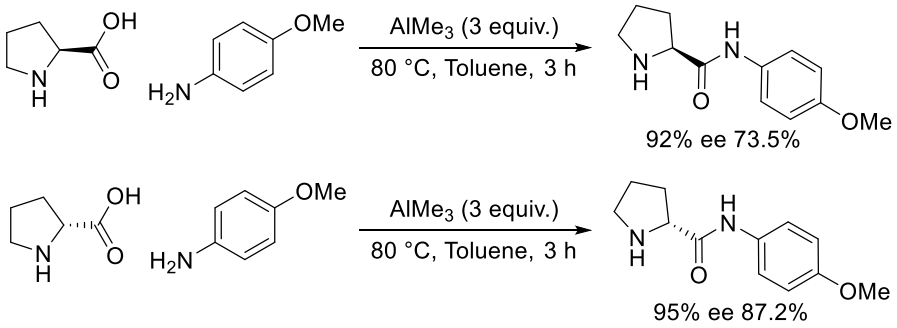
Scheme 73 Further scope of $BF_3{\cdot}OEt_2$-mediated amidation

A different strategy was investigated by Jain *et al.*, where amidation was performed at room temperature in water with CDI as an activating agent for the carboxylic acid moiety.[106] The scope was tested on five polar amino acids (Scheme 74) and mainly limited to water soluble amines.



Scheme 74 CDI-mediated amidation of unprotected amino acids in water; a. lactomisation by-product observed in the reaction

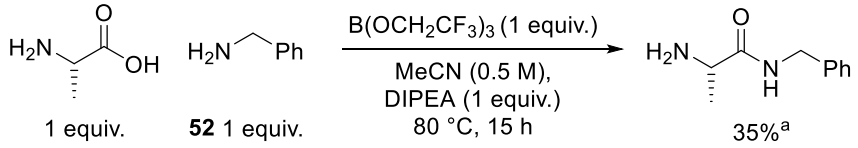
More recently, Li *et al.*[110] have used $AlMe_3$ as the Lewis acid for the direct amidation of unprotected proline with p-anisidine. Although the product yields were excellent, a high level of racemisation was observed (Scheme 75).



Scheme 75 $AlMe_3$ as an amidation reagent for unprotected proline

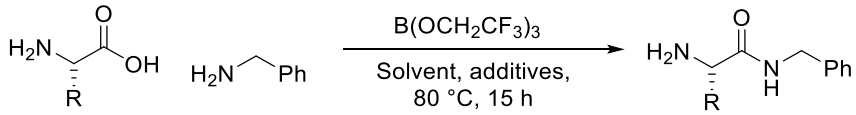
2.2.2 Previous work in the Sheppard group

Preliminary studies carried out in the Sheppard group have shown that $B(OCH_2CF_3)_3$ aids the formation of an amide bond between an unprotected L-Ala and benzylamine **52** (Scheme 76). No conversion was observed in the absence of Hünig's base, however.[84,111]



Scheme 76 First test experiment using $B(OCH_2CF_3)_3$ in amidation of L-Ala with benzylamine a. Conversion determined by ^1H NMR

Following this observation, a PhD student, Dr Rachel Lanigan, in the Sheppard group, concentrated on the optimisation of the reaction conditions to extend the scope to all proteinogenic amino acids (Scheme 77).[85] An extensive screen of solvents, varying reaction concentrations, temperatures, reaction time, and additives was performed, and it was found that the reaction gave the best results at 80 °C with an excess of amine (3 equiv.) and $B(OCH_2CF_3)_3$ (3 equiv.) in 15 hours (entry 10, Table 8). Importantly, base was not required as long as the amine was used in excess to the amino acid. The reaction conditions could be tuned by increasing the temperature and indeed using base to improve the yield, which could be useful if a more valuable amine was to be used (entries 6, 9). Both MeCN and CPME were selected as suitable solvents since they gave similar yields. Importantly, $B(OMe)_3$ did not perform well under these conditions, and the corresponding amide was obtained in only 9% yield (entry 11).

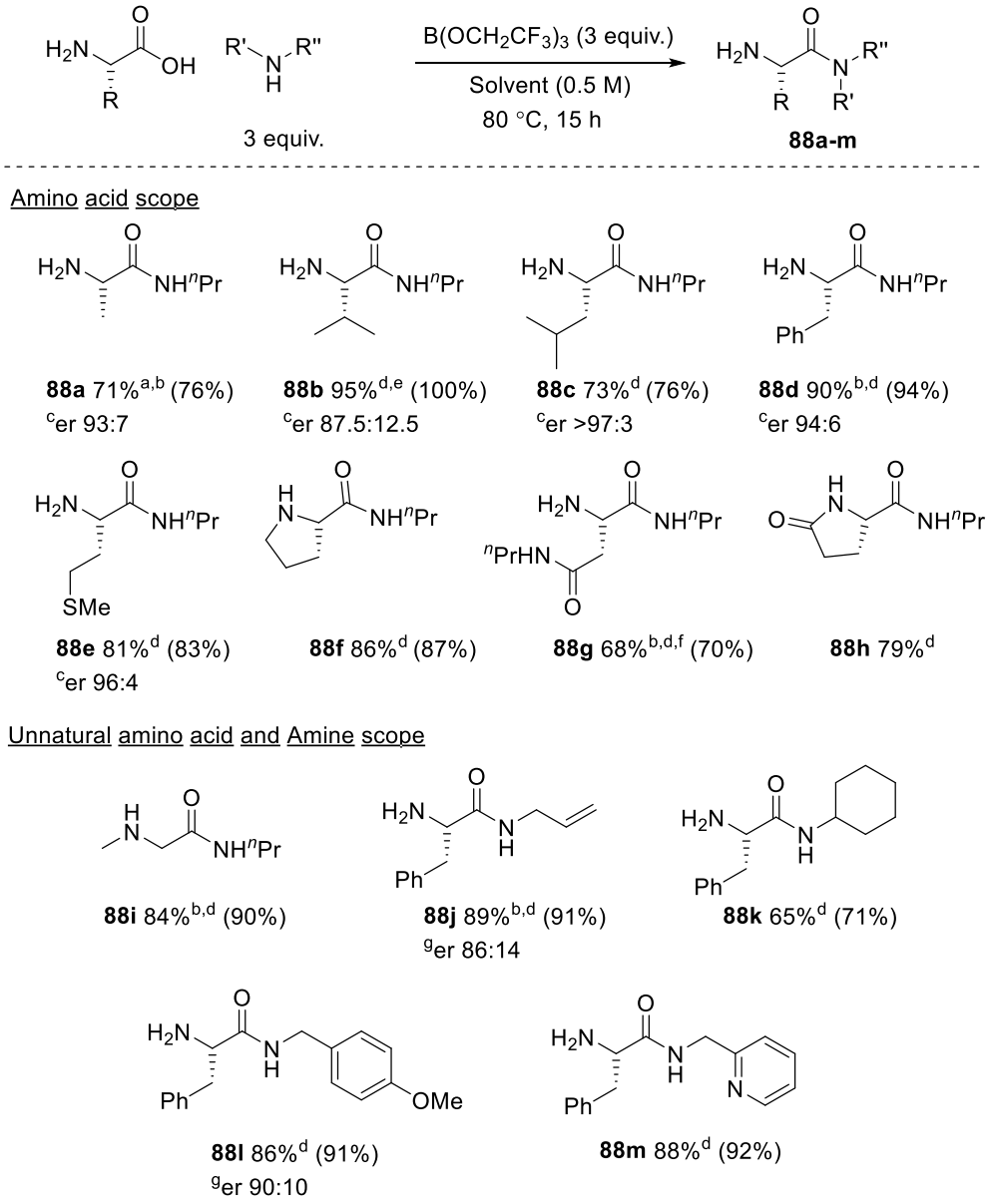


Scheme 77 Optimum conditions for direct amidation of unprotected amino acids

Entry	R	$B(OCH_2CF_3)_3$ (equiv.)	Solvent	Additive (equiv.)	Yield (%)
1	Me	2	MeCN	DIPEA (1 equiv.)	(65%)
2	Me	2	MeCN	-	(12%)
3	Me	2	MeCN	$BnNH_2$ (0.5 equiv.)	(36%)
4	Me	3	MeCN	DIPEA (1 equiv.)	(71%)
5	CH_2Ph	3	CPME[a]	DIPEA (1 equiv.)	69%
6	CH_2Ph	3	CPME[b]	DIPEA (1 equiv.)	89%
7	CH_2Ph	3	CPME	DIPEA (1 equiv.)	65%
8	CH_2Ph	3	CPME	DIPEA (1 equiv.)	61%
9	CH_2Ph	3	CPME	DIPEA (1 equiv.), $BnNH_2$ (2 equiv.)	86%
10	CH_2Ph	3	CPME	$BnNH_2$ (2 equiv.)	95%
11	CH_2Ph	3[c]	CPME	-	9%

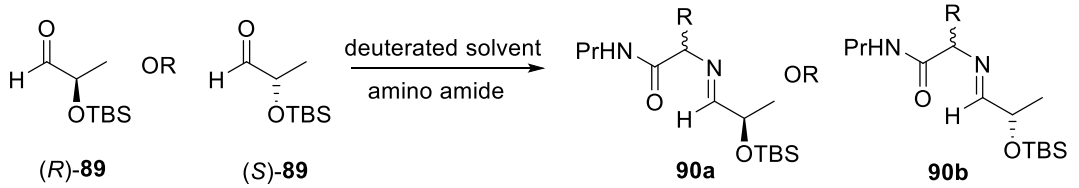
Table 8 A summary of the optimisation of $B(OCH_2CF_3)_3$-mediated amidation of unprotected amino acids; a. Reaction performed at 100 °C; b. Reaction performed at 125 °C; c. $B(OMe)_3$ used instead of $B(OCH_2CF_3)_3$

The scope of the reaction was tested by coupling natural and unnatural amino acids with propylamine as well as a selection of amines with L-Phe. Scheme 78 represents isolated amides.[85] A solid-phase work up procedure was used to isolate the amide products, excluding the use of Amberlyst® 15 because of the presence of free amine moiety. Volatile propylamine was used to aid purification of the final product by simple solid-phase work up followed by the evaporation of the amine. Other amides were usually isolated as HCl salts or by trituration.[85]



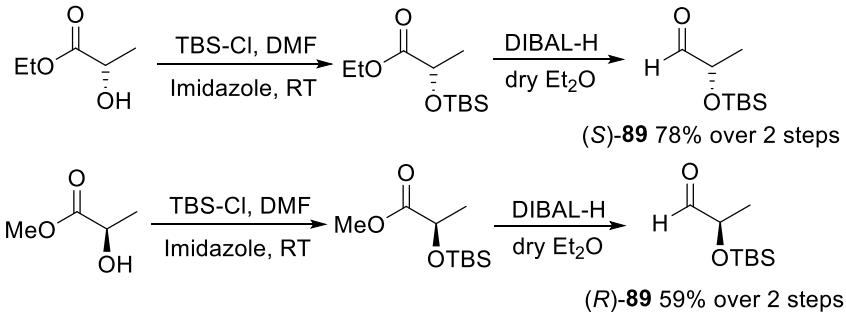
Scheme 78 Amino amide scope synthesised using optimised conditions for direct amidation of unprotected amino acid; a. MeCN used as a solvent; b. isolated as HCl salt; c. er determined using chiral aldehyde method; d. CPME used as a solvent; e. 125 °C; f. propylamine (6 equiv.), $B(OCH_2CF_3)_3$ (4 equiv.); g. er determined using chiral HPLC;

During this study, a novel method for determination of enantiopurity of chiral amino amides was developed using chiral aldehyde reagents (*S*)-**89** and (*R*)-**89** to derivatise the amide products (Scheme 79).[85,112]



Scheme 79 Imine formation between 2-((*tert*-butyldimethylsilyl)oxy)propanal and amino amide

A two-step synthesis starting from TBS protection of enantiopure ethyl or methyl lactate, followed by the reduction of ester moiety to aldehyde by DIBAL-H led to (*R*)-**89** and (*S*)-**89** (Scheme 80).[112]



Scheme 80 The synthesis of chiral aldehydes developed in the Sheppard group for determination of enantiomeric ratios of amino amides

Aldehydes (*S*)-**89** and (*R*)-**89** reacted quantitatively with an unprotected amine moiety of the amino amide and formed diastereomers. The enantiopurity was then measured by ^{13}C NMR integrating the imine peaks arising from the formation of imines **90a** and **90b**.[85,112]

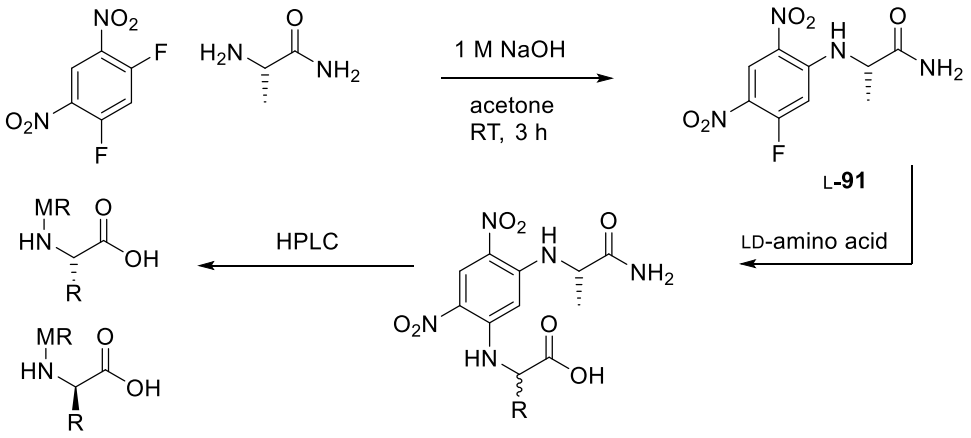
The aldehyde derivatisation method worked for some of the amino acid amides (**88a-e**), but unfortunately not for other substrates (**88g**, **88j-m**) due to the signals for the imine peak being inseparable in ^{13}C NMR.[85] Additionally, the starting aldehydes **89** were generally quite unstable and had to be stored in the freezer for a relatively short amount of time, as after 1 month some degree of decomposition was observed.[112] For accurate results, a fresh sample was therefore required.

The investigation performed by the previous PhD student concentrated mainly on the optimisation of the reaction conditions to obtain the best conversion to the products, and due to time restrictions in that project, some of the amides were not isolated.

The aim of the work presented in this thesis was to expand the amidation scope further to unnatural amino acids and amines, as well as isolate other natural amino acid amide products in order to determine their enantiopurity (described in Section 2.2.4). A different approach was applied to derivatise the chiral products to overcome the limitations associated with the aldehyde method, which is discussed in Section 2.2.3.

2.2.3 Marfey's reagent for derivatisation of chiral unprotected amino acid amides to determine enantiomeric ratio

1-Fluoro-2,4,-dinitrophenyl-5-L-alaninamide L-**91**, also known as Marfey's reagent (MR) was introduced by Peter Marfey in 1984 as a convenient indirect method for determination of the enantiopurity of proteins, peptides and amino acids by HPLC. It can be easily synthesised by a substitution of one of the reactive fluorine atoms on 1,5-difluoro-2,4-dinitrobenzene (FFDNB) by L-alaninamide in high yields (76% as reported by Marfey).[113] The reagent possesses another reactive fluorine atom which can be substituted by a chiral amino acid under alkaline conditions. This reaction is rapid and quantitative and therefore is a reliable method.[114–116] The resulting diastereomers can then be separated by HPLC allowing the enantiopurity of the amino acid to be determined (Scheme 81).



Scheme 81 The use of L-Marfey's reagent (L-**91**) in amino acid derivatisation

In 1993, Calmes *et al.* attempted this method with a series of chiral benzylic amines.[117] To their disappointment, an attempt to resolve the amines using HPLC failed for some of the amines or separation was too poor to determine er with accuracy, which led them to investigate alternative ways to determine enantiopurity. This led the group to explore the potential of NMR derivatisation, which was the first known case of doing so with Marfey's reagent.

They firstly tested racemic amine **92** which was derived with L-**91** (Figure 10). The ^{1}H NMR spectra in $CDCl_3$ did not show any separation of diastereomeric peaks, however, DMSO-d_6 resulted in a more complex spectrum with some of the peaks easily identifiable. The methyl peak of the product **93** did not provide an opportunity to determine enantiomeric ratio, as it overlapped with the methyl group of L-**91** which was used in excess to the amine **92** to ensure full conversion to **93**. However, it was possible to use the aromatic signal **H^2** of the derived L-**91**.

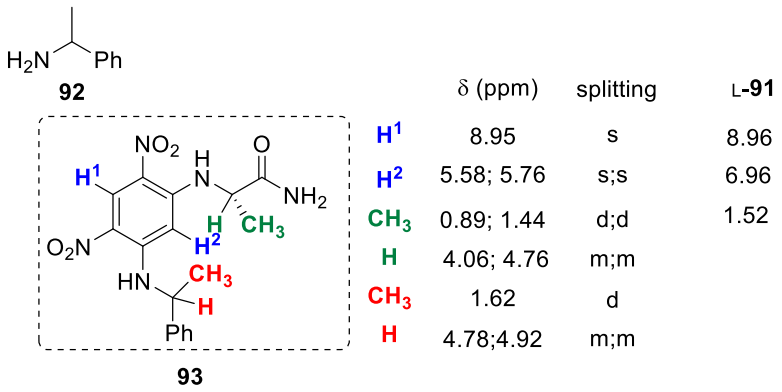


Figure 10 An example of analysis of peaks by ^{1}H NMR to determine enantiomeric ratio of chiral amine **92**

To further demonstrate the generality of this method, other amines were derivatised. As in the above example, the main identifiable peak was H^2. Amines containing an aromatic group were successfully derivatised and different diastereomers were easily separable by NMR. However, the two tested aliphatic amines (1-methylpropyalmine and 1-cyclohexyl ethylamine) did not show any separation. This was explained to be due to the π- π interaction in the aromatic amines and L-**91** that led to the successful separation.[117]

It was therefore decided to examine the use of Marfey's reagent as a derivatising agent for the amino acid amides. For comparable and reliable derivatisation of the amino amides, it was decided to make the original Marfey's reagent L-**91** as well as its D-isomer (D-**91**) (Figure 11). This would also enable us to avoid the synthesis of the racemic sample of amino amide products.

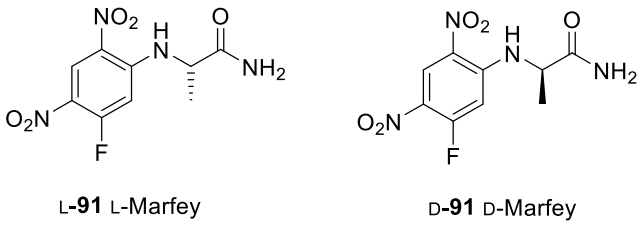


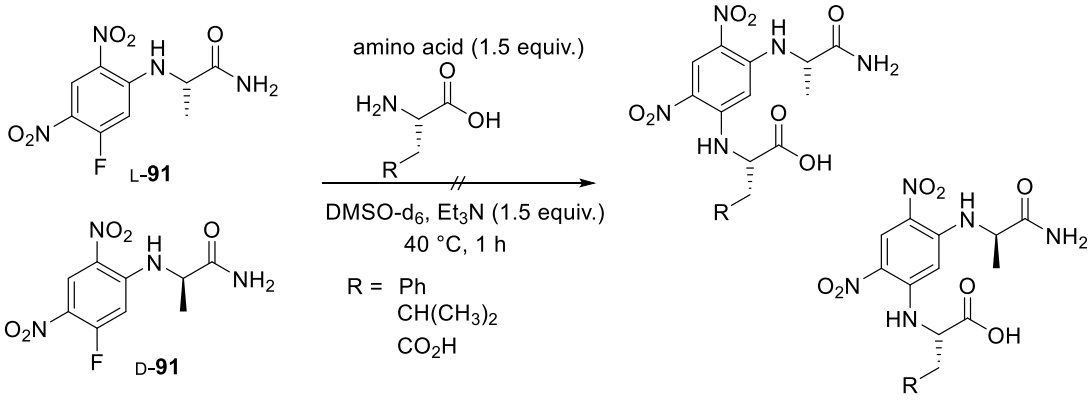
Figure 11 Marfey reagents

The synthesis followed the procedure described in the original paper by Marfey.[113] The synthesis consisted of one step (Scheme 81, *vide supra*), and the reaction was complete in 1 hour, the product was isolated by recrystallisation. The reaction yielded two bright yellow crystalline compounds in good yields (63% L-**91**; 67% D-**91**).[113]

The main requirement of an indirect enantio-resolution of chiral compounds is that the derivatising agent must be enantiomerically pure for accurate results.[114,115] To

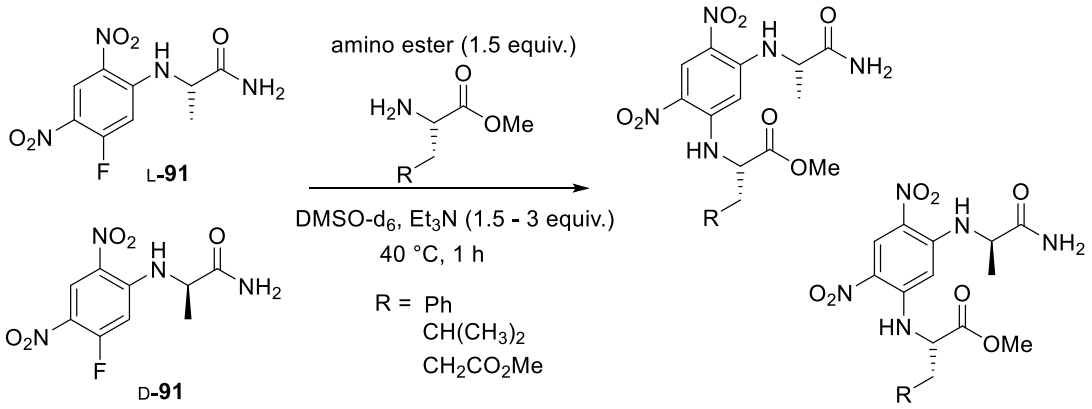
test the enantiopurity of the two MR's reagents, a normal phase chiral HPLC was attempted, however, the reagent was completely insoluble in Hex/IPA mixture, and therefore this method was unsuitable.

We therefore used the NMR approach by reacting both L-**91** and D-**91** with a selection of L-amino acids, namely L-Phe, L-Leu, and L-Asp (Scheme 82). Assuming that the amino acids are homochiral, the enantiopurity of L-**91** and D-**91** could be determined by NMR. The amino acids were used in slight excess (1.5 equiv.) to ensure full consumption of the Marfey's reagents, and DMSO-d_6 was the solvent of choice. However, all reactions either failed to go to completion or react at all due to poor solubility of the amino acids in DMSO-d_6. Increasing the temperature or adding more triethylamine did not improve the conversion sufficiently.



Scheme 82 Derivatisation of Marfey reagents with amino acids

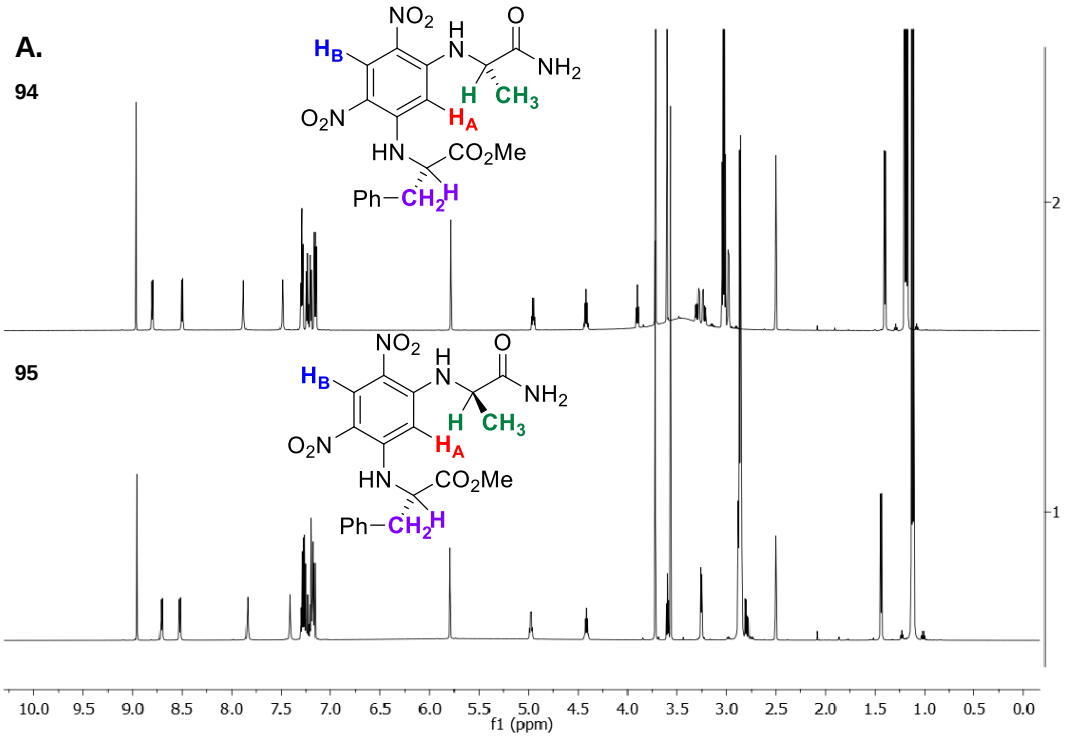
It was therefore decided to use ester derivatives of the amino acids instead to aid solubility (Scheme 83).

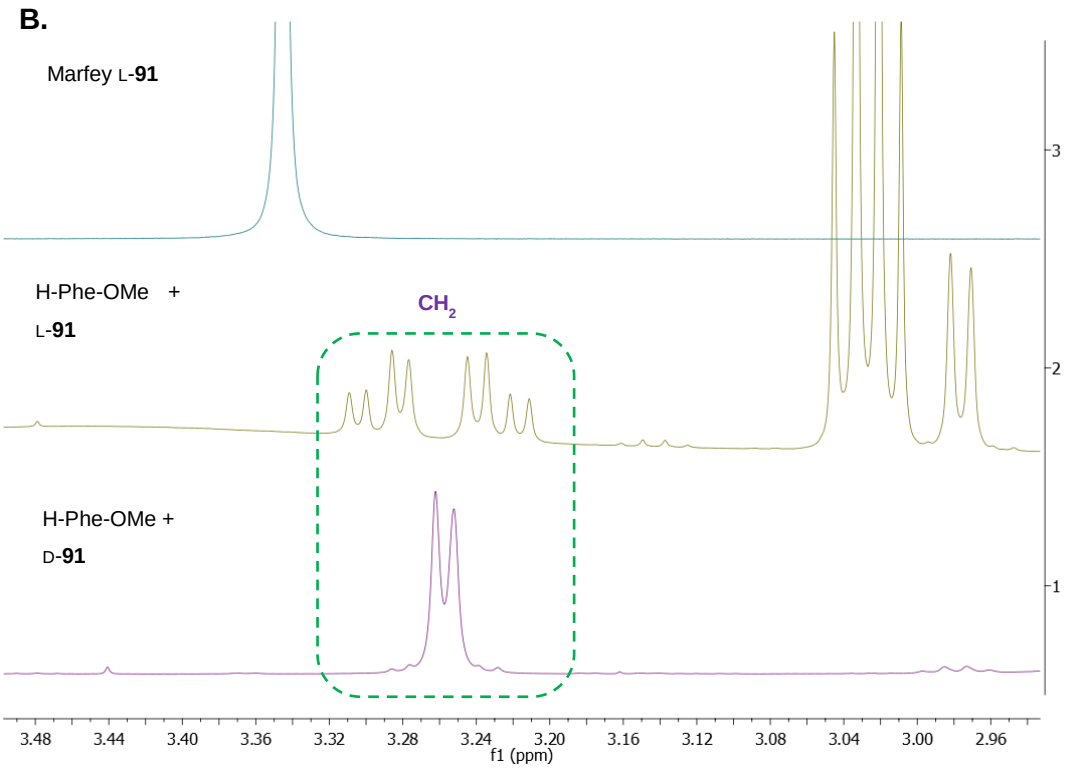


Scheme 83 Derivatisation of Marfey reagents with amino acid esters

All reactions successfully went to completion. The enantiopurity of L-**91** and D-**91** was determined by ^{1}H NMR. An estimate of enantiopurity was based on the

comparison of the spectra of two diastereomers synthesised from the same amino acid ester. Only a single diastereomer was observed in each case suggesting that L-**91** and D-**91** were enantiomerically pure (Figure 12**A**-**C**).





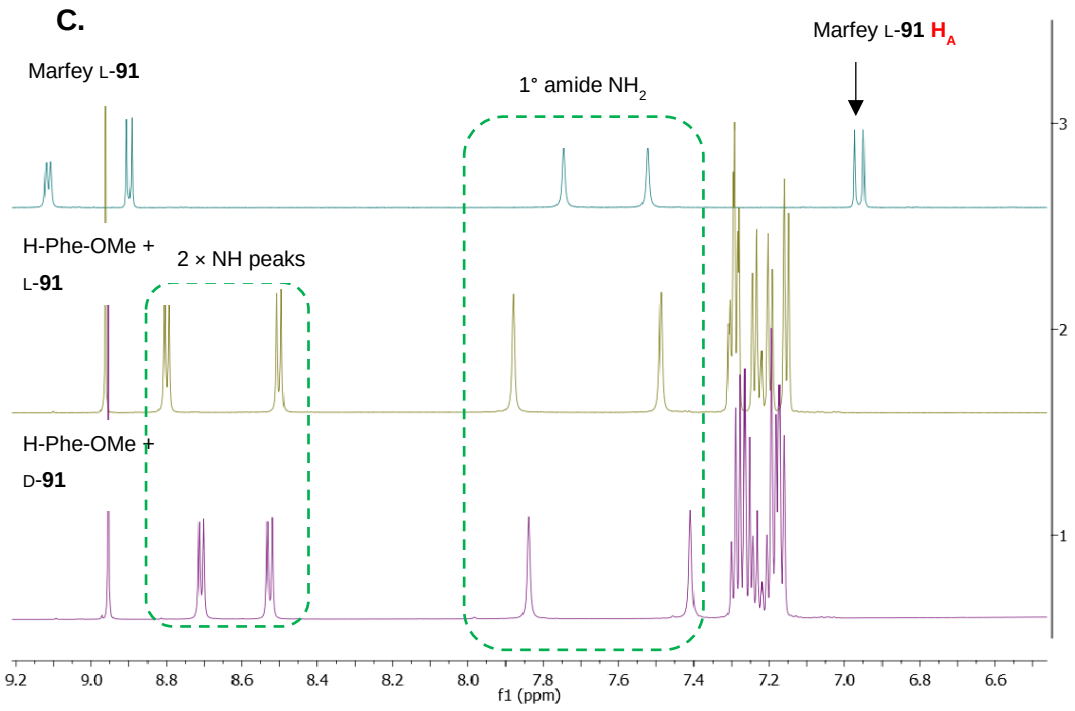


Figure 12 A. ^{1}H NMR spectra of H-Phe-OMe coupled with **L-91** and **D-91**; **B.** Zoomed in region to CH_2 peak in each **94** and **95** to show the difference in splitting; **C.** Comparison of coupled Marfey with H-Phe-OMe vs. Marfey **L-91** to show the consumption of **L-91** and the shift of amide peaks

Only a slight difference was visible in the shift of the H_A proton (Δ0.01 ppm), however, there was a definite difference of the splitting of CH_2 protons. When the (*S,S*) diastereomer was formed, the protons split in a diastereotopic pattern (Figure 12**B.**) Whereas with the (*R,S*) diastereomer, it is not pronounced. In either of the spectra, the CH_2 from the opposite diastereomer **95** was not visible.

The difference in the shifts was also evident in ^{13}C NMR, which further confirmed that both L-**91** and D-**91** were enantiomerically pure (Figure 13).

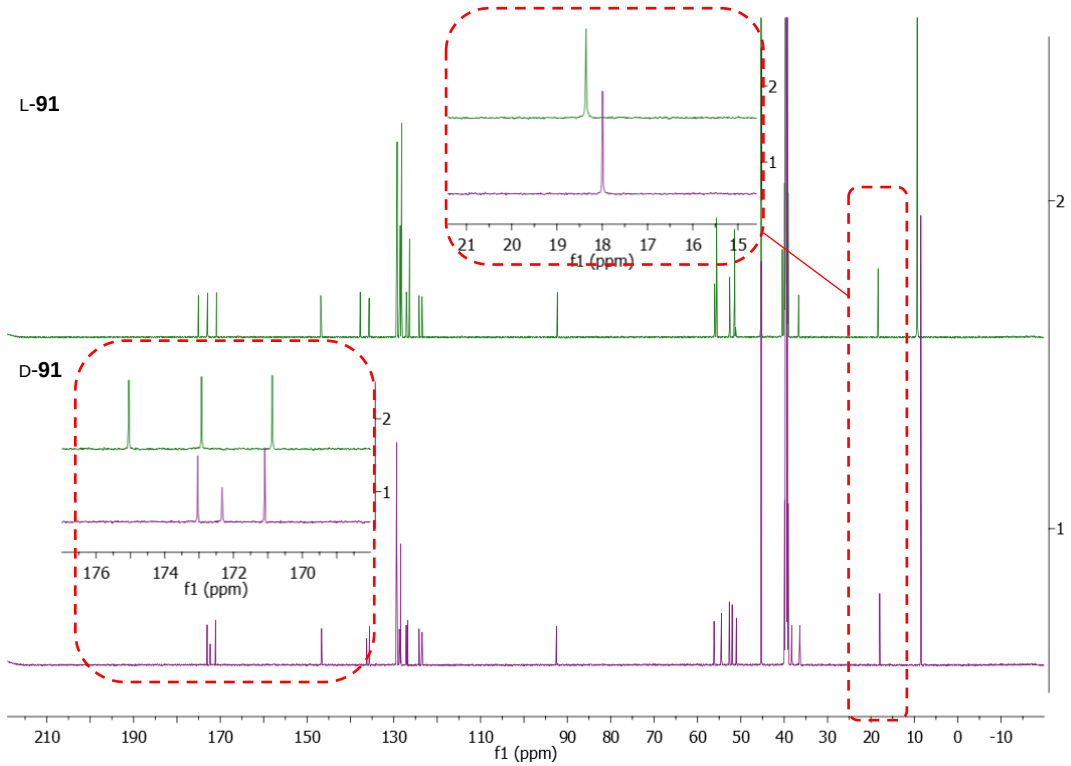


Figure 13 Difference in ^{13}C NMR shifts of L-**91** and D-**91** with H-Phe-OMe

The reagents were then used to determine the purity of the amino amides made by the amidation reaction of unprotected amino acids discussed in Section 2.2.4, *vide infra*. A similar procedure was used, but with the Marfey's reagent in excess relative to the chiral amino acid amide to ensure full conversion into the derivatised product. The enantiopurity was determined by integrating the same peaks rising from two different diastereomers and taking the average of the two. Both L-**43** and D-**43** were used to ensure the accuracy of the reading. Representative spectra of the amino amide **98f** with high er (>99%) and amino amide **103d** with low er is given below (Figure 14).

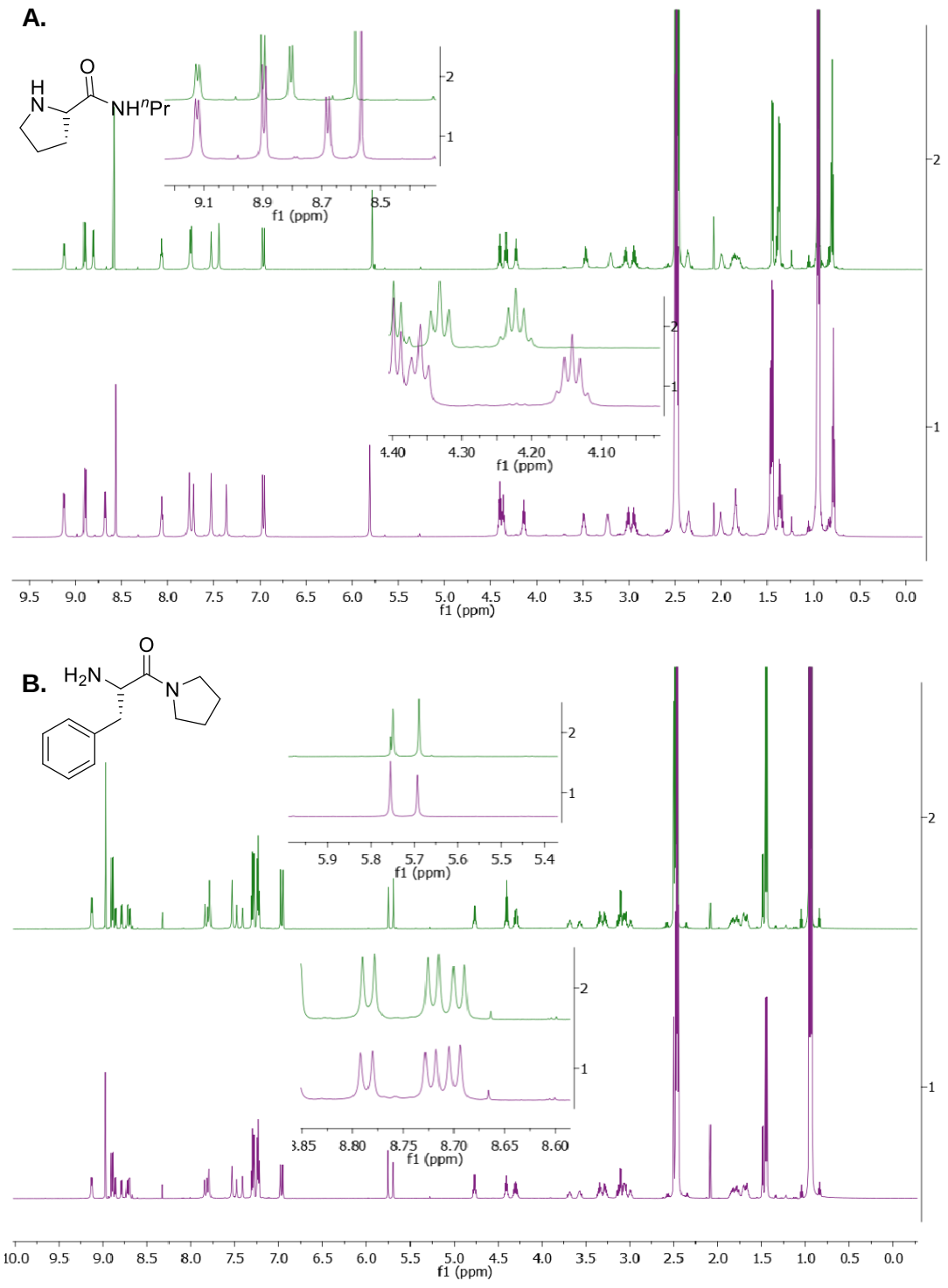
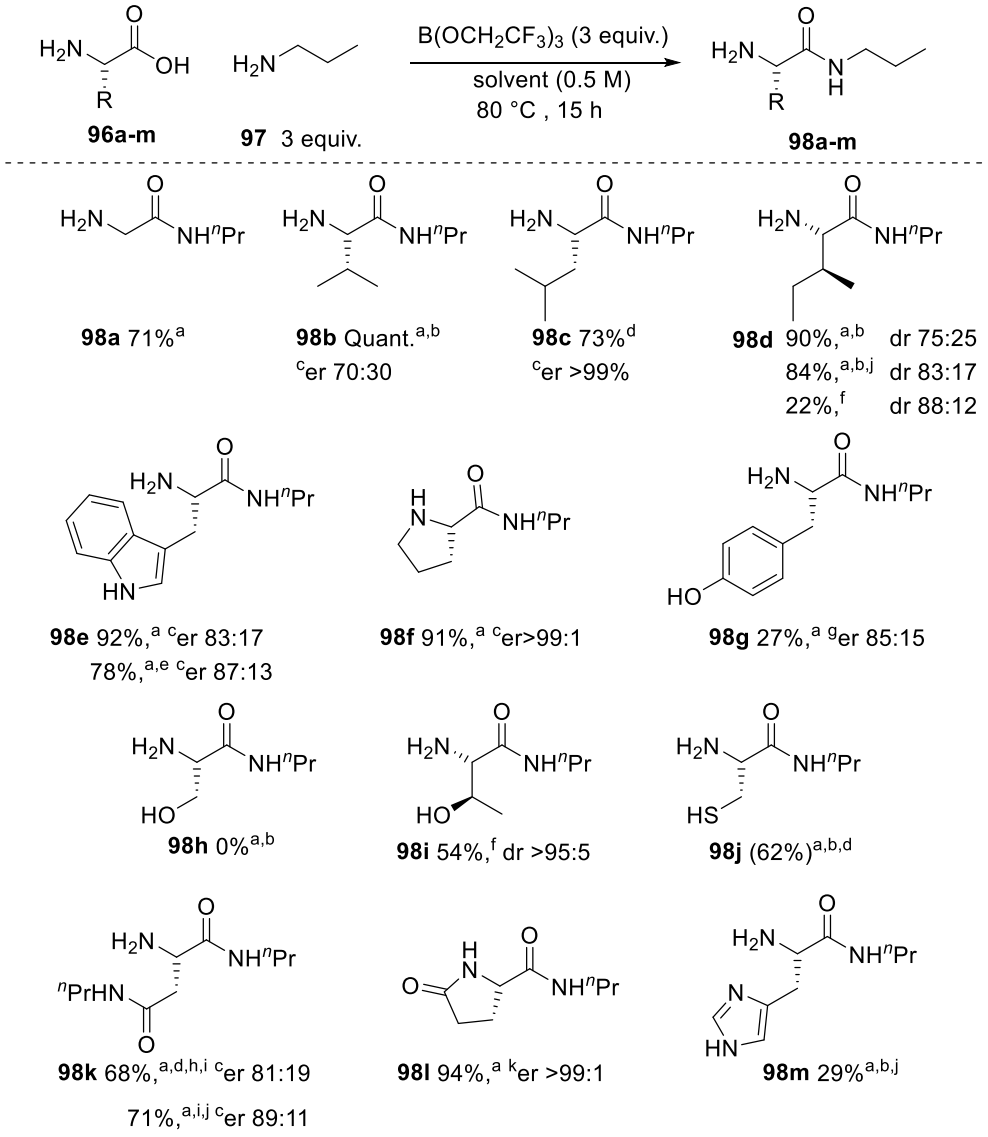


Figure 14 Representative spectra using Marfey's analysis: **A.** amino amide **98f**, er > 99%; **B.** amino amide **103d**, er 53:47

2.2.4 Scope of direct amidation of unprotected amino acids

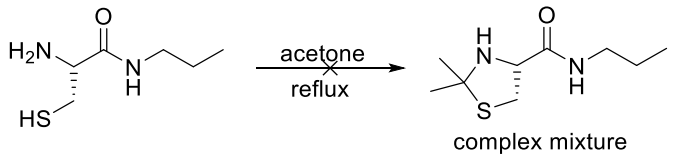
As discussed in Section 2.2.2, the full scope of proteinogenic amino acids had been tested by Rachel Lanigan with NMR yields determined; only 7 of the 22 amino acid amides were isolated and therefore the enantiopurity of these products was not known.[85] The aldehyde method was used to derivatise some of the isolated products, however, it did not work for many of the examples (*vide supra*). For that reason, Marfey's reagent was used to derivatise the products. The previously optimised procedure was used for the synthesis of amides presented below (Scheme 84). Enantiopurity was determined for all amides using Marfey's reagent, including the examples that failed with the aldehyde method.



Scheme 84 Proteinogenic amino acid scope; a. CPME; b. 125 °C; c. Marfey's reagent used for er determination; d. Synthesised by Rachel Lanigan; e. 5 h; f. MeCN; g. HPLC used for er determination; h. Isolated as HCl salt; i. 4 equiv. of borate and 6 equiv. of propylamine used; j. Dropwise addition of $B(OCH_2CF_3)_3$; k. Shift reagent used for er determination

Non-polar amino acids with an aliphatic chain generally gave good yields of amino amides (**98a-98d**), although isoleucine required strong heat to obtain high conversion, which led to a high degree of epimerisation. Dropwise addition of $B(OCH_2CF_3)_3$ improved the dr quite significantly, however. At 80 °C, epimerisation was even lower, but the lower temperature led to a poor yield of 22%. Similarly, valine amide **98b** underwent some racemisation most likely due to high reaction temperature (125 °C) used to obtain high conversion to the product. Tryptophan amide (**98e**) was isolated in excellent yield, but with erosion of enantiopurity; reducing the reaction to 5 hours resulted in an improvement of er with good yield of the amide **98e**. Proline (**96f**) was an excellent substrate for the direct amidation, and no racemisation of the product was observed. Tyrosine amide **98g** was isolated in a much lower yield than the observed NMR conversion of 48%.[85] This could be due to the phenolic moiety, which could be scavenged by the resins thus reducing the overall yield. This was supported by the fact that numerous attempts of this reaction resulted in highly inconsistent yields, depending on whether resins were used in the work-up procedure. Moreover, we were unable to determine the er using Marfey's reagent, possibly due to the competing reaction by the phenol moiety, and therefore the purity was determined by chiral HPLC.

Unfortunately, serine completely failed to give the desired product **98h** with a complex mixture of by-products observed. Interestingly, structurally very similar threonine gave amide **98i** in a moderate yield, despite the presence of a hydroxyl moiety. The formation of cysteine amide **98j** was previously observed by NMR with good conversion,[85] but we were unable to isolate the final product. An attempt to protect the thiol group by forming an acetal between the thiol and amine group was not successful (Scheme 85).[118] An unidentified foul-smelling complicated mixture was obtained, which we could not identify by NMR; an attempt to purify the product by column chromatography was not fruitful either.

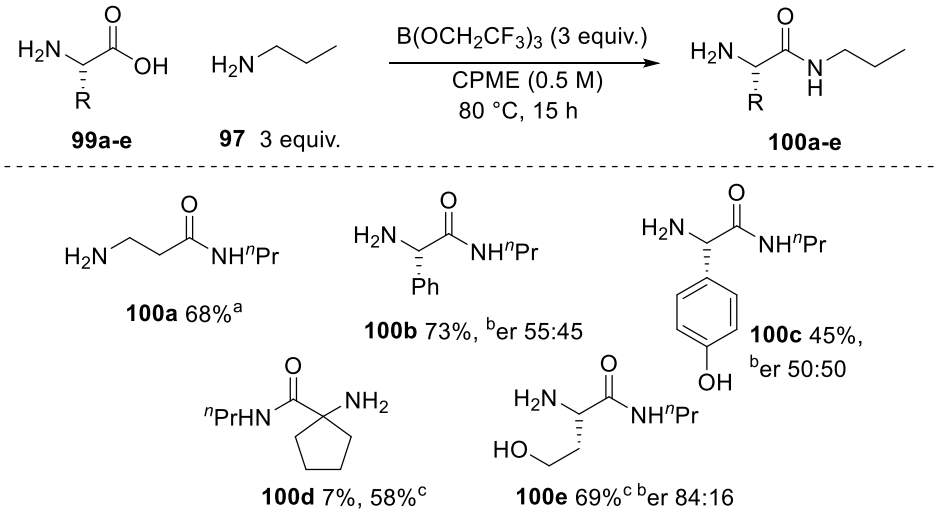


Scheme 85 Cysteine moiety protection attempt with acetone

Aspartic acid **96k** and glutamic acid **96l** gave high yields of the corresponding amide products. Glutamic acid underwent cyclisation with the free amine, whereas no cyclic by-product was observed in case of aspartic acid. Amide **98k** racemised to some extent, but we were able to improve it to 89:11 by adding the borate dropwise

to the reaction mixture. Enantiopurity of **98l** was determined using a chiral shift reagent,[119] as there were no amine moiety to use Marfey's method of derivatisation. Histidine **96m** gave a low yield, and the product had to be isolated by flash column chromatography due to numerous impurities present even after the solid phase work-up.

Six unnatural amino acids were also tested (Scheme 86).



Scheme 86 Amidation scope of unnatural amino acids; a. MeCN (0.5 M); b. er determined using Marfey's reagent; c. 125 °C;

β-Alanine **99a** gave a good yield of amide and is comparable in reactivity to glycine. Although phenylglycine amide **100b** was isolated in a good yield, full racemisation of the product was observed. Hydroxyl derivative **100c** resulted in a lower yield, possibly due to the same issue as with tyrosine amide **98g** whereby phenol moiety was being scavenged by the resin work-up. Strong heat was required to achieve high conversion of amino acid **99d** to the desired amide. Pleasingly, homoserine gave amide **100e** in a good yield and despite higher temperature required only a limited amount of racemisation was observed. It was previously determined that no amidation of L-serine **96h** took place. This could be due to the orientation of the β-hydroxyl group allowing for coordination to the borate, thus preventing the activation of the carboxylic acid (Figure 15).

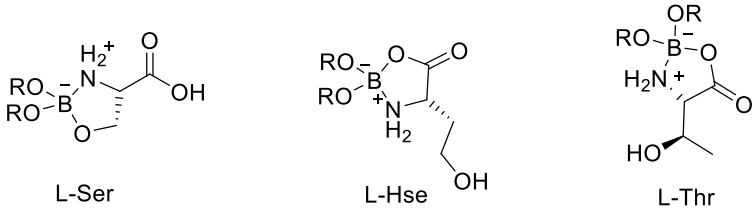
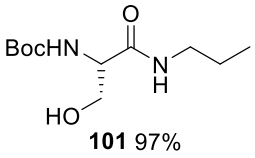


Figure 15 Proposed coorination of borate to L-Ser **96h**, L-Hse **99e**, and L-Thr **96i**

This was supported by the fact that the amidation worked well for Boc protected serine, resulting in 97% yield of the amide **101** (Figure 16).

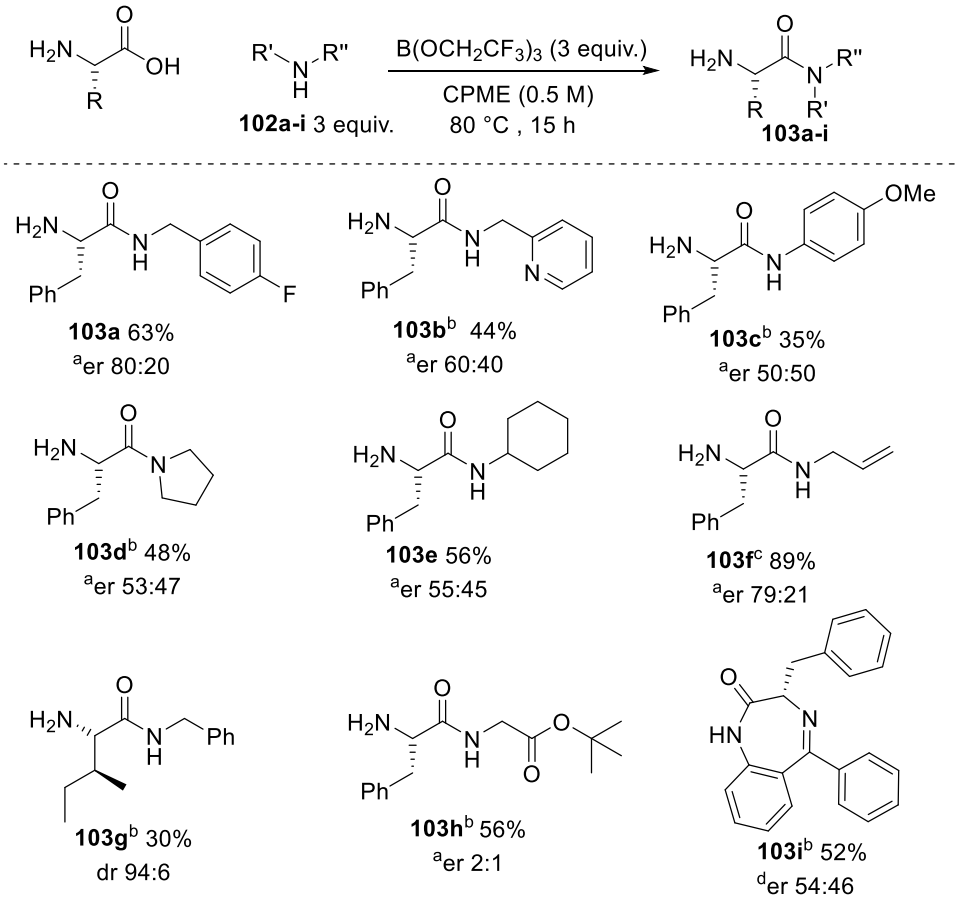


101 97%

Figure 16 Boc-protected serine amidation

In contrast to L-Ser, homoserine **99e** would be more stable as a 5-membered intermediate and therefore cyclise with the amino group and not the hydroxyl in the γ-position. In the case of threonine **96i**, it is possible that the coordination of the borate is favoured between the acid and amine moiety and not the hydroxyl, therefore enabling the activation for the amidation of **6i**.

The scope of the reaction was then tested with respect to an amine partner (Scheme 87).

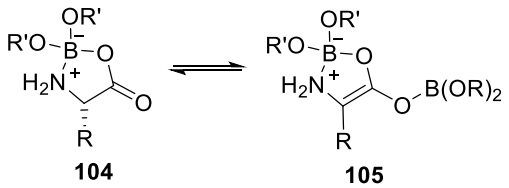


Scheme 87 Amine scope of direct amidation of unprotected amino acids; a. er determined using Marfey's reagent; b. 125 °C; c. isolated as HCl salt; d. er determined using chiral HPLC

Unfortunately, most examples suffered from varying degrees of racemisation. A good yield was obtained for the benzylamine derivative with electron withdrawing fluorine moiety with some racemisation of the product (**103a**). The reaction also tolerated a pyridine substituent resulting in 44% of the amide **103b**. Unfortunately, the product went through an almost full racemisation. *p*-Anisidine **102c** was not reactive and only 35% of amide was obtained under forcing conditions (125 °C), which resulted in full loss of enantiopurity. Pyrrolidine **102d** was a good substrate in terms of conversion to the product at 125 °C, although complete racemisation was observed in this example too. Similarly, L-Phe fully racemised with its cyclohexylamine partner even at 80 °C resulting in er 55:45 of the amide **103e**. Allylamine **102f**, however, resulted in excellent conversion although with some loss of enantiopurity. Unlike with propylamine **97**, little epimerisation was observed in the reaction of L-Ile with benzylamine even at high temperatures. However, only 30% yield of the desired product **103g** was obtained.

An attempted synthesis of a dipeptide proceeded well with 56% of L -Phe-Gly-O^{t}Bu **103h** isolated. In this case, due to the strong heat, racemisation of the amide was also observed. We were also able to synthesise a benzodiazepine derivative, which belongs to a class of anxiolytic drugs, from 2-aminobenzophenone and L-Phe in 52% yield, albeit under forcing conditions, which again led to a near full racemisation of the final product **103i**.

High racemisation levels observed using stoichiometric $B(OCH_2CF_3)_3$ is the major limitation of this methodology. The reason behind it could either be a relatively high reaction temperature required for good conversion to amide products, or perhaps due to the proposed formation of the intermediate cyclic boron enolate **104** leading to the racemisation (Scheme 88). It is unknown, however, whether the latter is indeed the case, and if so, whether the high temperatures would aid the formation of **105** consequently leading to the erosion of enantiopurity.

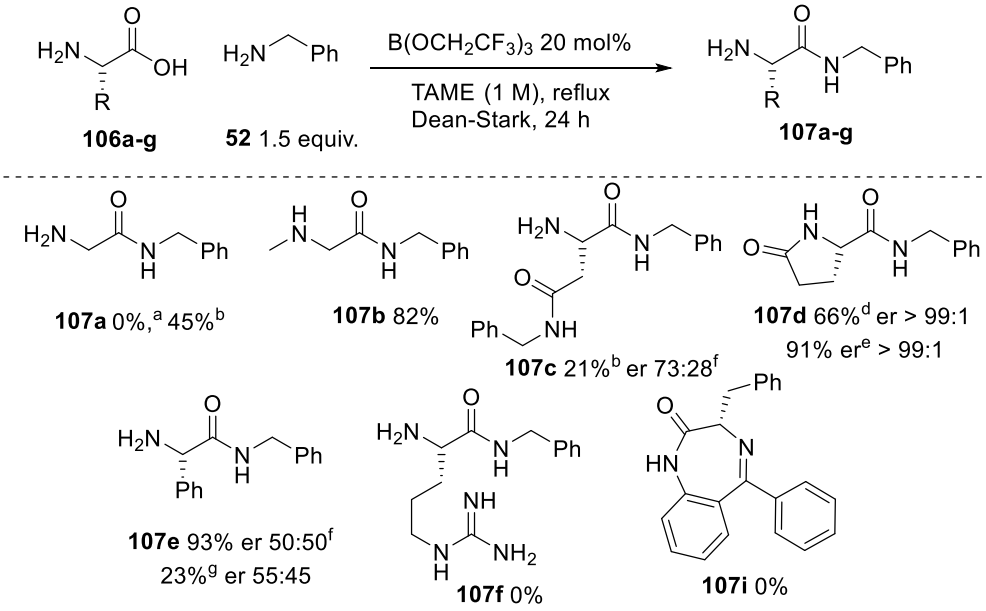


Scheme 88 Possible cyclysation with borate resulting in racemisation of amino amide products

During this work, another member of the Sheppard group, Marco Sabatini, developed a catalytic procedure using 20 mol% of $B(OCH_2CF_3)_3$ and Dean-Stark as the means for water removal.[120] In this case, TAME, which had previously shown to

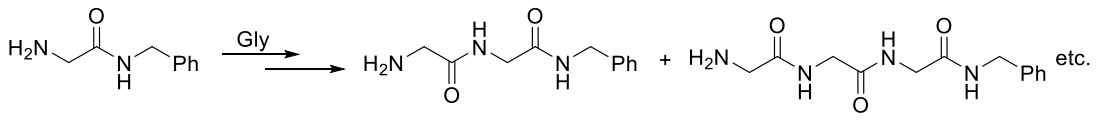
be a good solvent for stoichiometric amidation under standard conditions (*vide supra*, Section 2.1, Table 4), was selected as the reaction solvent as it resulted in improved yields of the amide products. Importantly, the boiling temperature of TAME is 86 °C, which might be beneficial in amino acid amidation for the conservation of higher levels of enantiopurity.

Following the optimised conditions, some of the unprotected amino acids were tested (other amino acids were tested by Marco Sabatini) (Scheme 89). Benzylamine was used in this case, as propylamine would evaporate in an open system and therefore a significant excess would have been required.



Scheme 89 Catalytic method for amino amide synthesis; a. Polymerisation observed; b. 3 equiv. amine used; d. 0.33 M in TAME; e. er determined using chiral shift reagent; f. determined using Marfey's reagent; g. 5 h

Unfortunately, the first limitation of this method became evident when a competitive reaction of the amino amide **107a** with glycine leading to a mixture of di- and tri-amides was noted (Scheme 90).



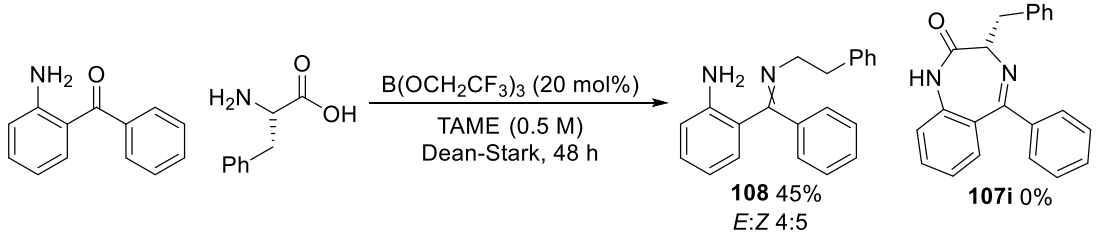
Scheme 90 Polymerisation of glycine amide

Using 3 equivalents of benzylamine, however, prevented self-condensation of the amino amide **107a** to a higher extent and the product was isolated in 45% yield. The isolation of the product was complicated by the poor separation of **107a** and **52** and

therefore benzylamine was removed by Kugelrohr distillation; this would not be a suitable method for chiral substrates, however. Unsurprisingly, the issue of polymerisation was not observed in the case of sarcosine with a secondary amine moiety and the product **107b** was isolated in 82% yield.

L-Asp amide **107c** was isolated in a low 21% yield with significant loss of enantiopurity, which was higher [loss] than in an example of the amide **98k** produced with propylamine and stoichiometric $B(OCH_2CF_3)_3$. No lactamisation of the side-chain carboxylic acid with the free amine occurred. During the optimisation studies performed by Marco Sabatini, it was observed that a concentrated reaction mixture was beneficial for the faster rate. Indeed, the amide **107d** was isolated in 66% yield after 24 hours when the reaction was performed at a concentration of 0.33 M in TAME, whereas at 1 M, it went up to 91%. In both cases, cyclisation of glutamic acid side-chain and free amine was observed. Unfortunately, the amide **107e** fully racemised to even a higher degree that in the stoichiometric reaction. Reducing the reaction time only resulted in a much lower yield with a similar deterioration of enantiopurity. Highly polar arginine did not react at all, perhaps due to poor solubility in the reaction solvent.

To our surprise, an attempt to make benzodiazepine **107i**, using the catalytic method, failed. The reaction resulted in decarboxylation of L-Phe yielding imine **108** in 45% yield instead (Scheme 91).



Scheme 91 An attempted synthesis of benzodiazepine, resulting in decarboxylation by-product **108**

3. Mechanistic studies on boron-mediated amidation

3.1 Background

3.1.1 Boronic acid-mediated amidation

Since the discovery in 1965 by Pelter *et al.* that trisaminoboranes were able to react with a carboxylic acid directly to form an amide without the necessity of an additional catalyst, boron-based reagents have found a wide use in amidation chemistry.[55] Consequently, numerous boron reagents for amidation have been developed at three boron oxidation levels, ranging from boric acid and borates to boronic acids, and even borinic acids, examples of which were discussed in the introduction (Figure 17). Naturally, efforts to elucidate the mechanisms of the boron mediated amidation have been made.

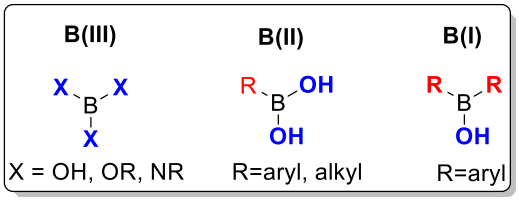
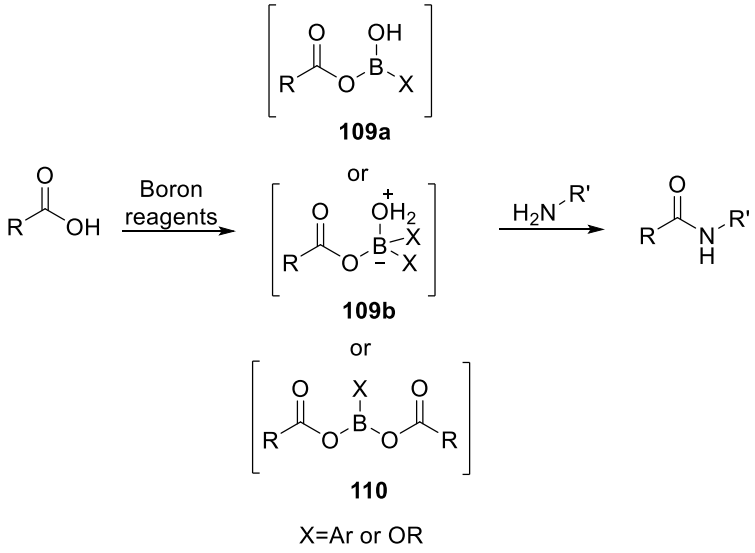


Figure 17 Oxidation states of boron compounds

To date, a general agreement in the literature is that boron acts as a Lewis acid and activates the carboxylic acid through an acyloxyboron intermediate **109** (trigonal **a** or tetrahedral **b**) or diacyloxyboron **110** (Scheme 92).

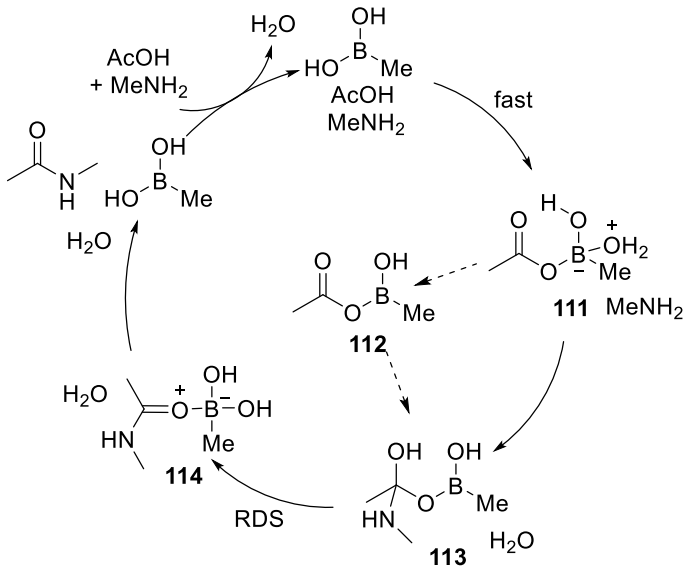


Scheme 92 Proposed activation of carboxylic acids with boron

The mechanism for boronic acid catalysed amidation was first proposed by Yamamoto *et al.* in 1996. The authors reported the isolation and partial

characterisation (by ^{1}H NMR and IR) of the monoacyloxyboron species **109**, which was proposed to be the activating intermediate for the amidation. More recently, however, Whiting *et al.* reported the observation of the diacyloxyboron species **110** identified by mass spec with no evidence of **109** being detected.[121]

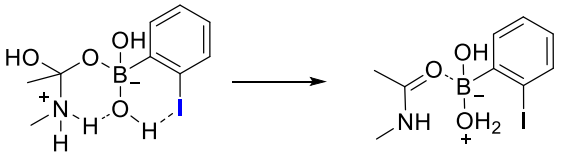
To support the proposed mechanisms on the boronic acid-mediated amidations, Marcelli investigated methyl boronic acid-catalysed amidation of acetic acid and methylamine using computational methods in the gas phase (Scheme 93).



Scheme 93 Boronic acid-mediated amidation mechanism proposed by Marcelli

The less energetically demanding pathway proceeded *via* neutral reactants and not ionised reactants (acetic acid and methylamine, and not acetate and methylammonium). Also, monoacyloxyboron intermediate **111** was found to be favoured over **110**. The formation of **111** was reported to be relatively low in energy indicating it as a fast process. It was not possible to locate the energy for the pathway from **111** to the tricoordinate acyloxyboron **112**, but it was determined that the reaction of the tetracoordinate intermediate **113** with methylamine was less energetically demanding than that of tricoordinate **112**. The rate determining step was found to be the formation of the boron-bound amide from the corresponding hemiaminal **114**.[81]

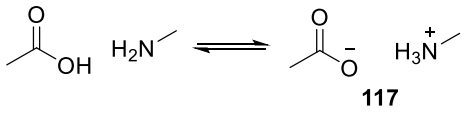
Marcelli also investigated possible mechanistic reasons for the increased catalytic activity of *o*-iodoarylboronic acid **37**, developed by Hall *et al.*, over other arylboronic acids.[39,81] It was shown that during the rate determining step (formation of **116** from **115**), the iodine atom provided stabilisation to the transition state *via* an intramolecular hydrogen bond between the hydroxyl and iodine (Scheme 94).



115 **116**

Scheme 94 Iodine-stabilised transition state for enhanced catalytic activity

Later, Fu *et al.* re-examined Marcelli's study by performing calculations to take into account solvent (dichloroethane) effects.[80] The study also investigated the mechanism for the amidation of acetic acid and methylamine catalysed by phenylboronic acid in dichloroethane. Firstly, the authors determined that the most stable form between the amine and the acid in dichloroethane was as separate molecules and not as salt **117**, which has been reported to disfavour condensation to form the amide product (Scheme 95).[80]

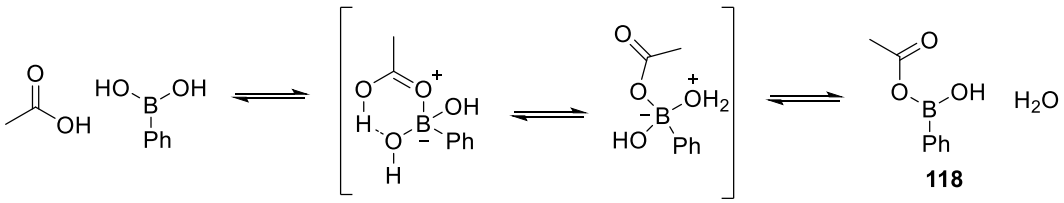


117

Scheme 95 Favoured form of amine and acid in the amidation reaction

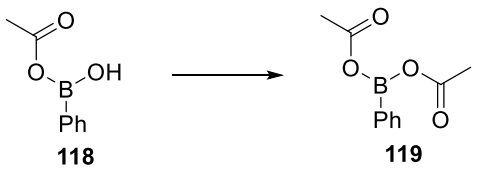
The energies for the formation of acyloxyboron **118** were examined next (Scheme 96).

Acyloxyboron formation



118

Diacyloxyboron formation



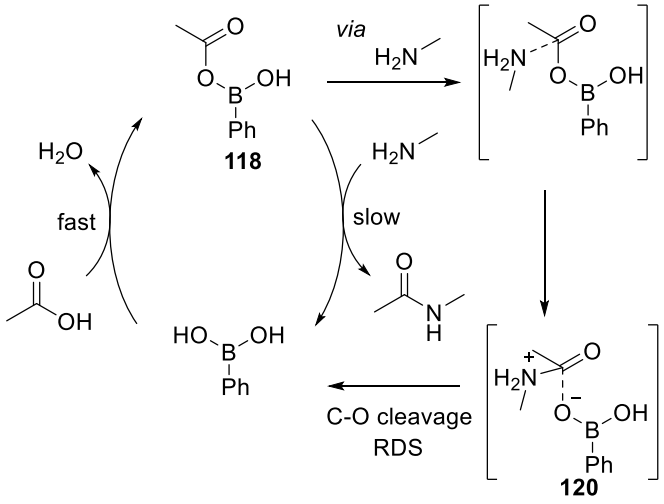
118 **119**

Scheme 96 Proposed activation states with boronic acid

This step was found to be kinetically favourable, but highly thermodynamically unfavourable, which meant that the equilibrium lay strongly to the reactants side. However, the reaction was determined to proceed easily at room temperature when water removal took place favouring the formation of **118**. This supports the fact that

all methodologies developed for boronic acid-mediated amidation require some form of water removal; either azeotropically or with the aid of molecular sieves. It was also established that the formation of diacyloxyboron **119**, although feasible, was unlikely and energetically more demanding, making the acyloxyboron **118** the more likely reaction intermediate (Scheme 96).[80]

The authors then investigated the reaction of **118** with an amine followed by amidation. The formation of the C-N bond was found to be facile with **118**. The rate determining step in the reaction was calculated to be the C-O bond cleavage of the intermediate **120** to produce the amide product (Scheme 97).



Scheme 97 Proposed mechanism of boronic acid-catalysed amidation

Fu also examined the exceptional catalytic activity of *o*-iodoarylboronic acid. In contrast to Marcelli's observations, Fu *et al.* did not observe O-H···I hydrogen bond stabilisation.[80] As an alternative, the authors attributed the activity to the orbital overlap between sp^2 orbital of the iodine atom and the p orbital of the boron, which was said to stabilise the transition state **121** and therefore decrease the energy barrier for the amide bond formation (Figure 18).

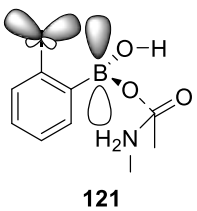
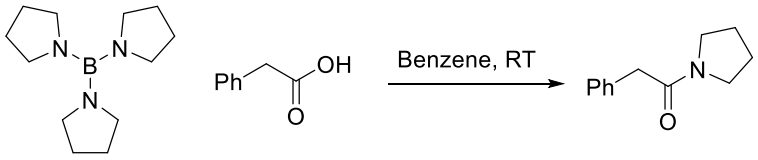


Figure 18 Fu's explanation of iodophenylboronic acid enhanced activity as the catalyst

3.1.2 Investigations of B(III)-mediated amidations

To our knowledge, fewer reports are available investigating the amidation mechanisms at the B(III) oxidation level (borates, trisaminoboranes, etc.). As discussed in the introduction (*vide supra*, Section 1.2.1), Pelter *et al.* demonstrated that trispyrrolidinoborane **20** reacted with carboxylic acids to give the corresponding amides in good yields without the requirement for an additional catalyst.[55] Phenylacetic acid **53** gave the amide **122** at room temperature with 1 equivalent of **20** in 87% yield. However, using 1/3 equivalent of **20** (i.e. 1 equiv. of the amine per carboxylic acid) led to a maximum 33% yield, even upon prolonged reaction times (Scheme 98).

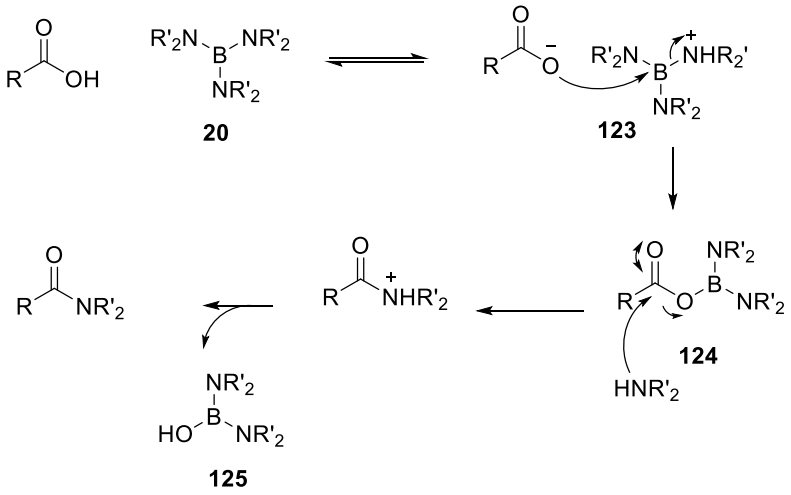


20	**53**	**122**
1 equiv.	1 equiv.	87%
1/3 equiv.	1 equiv.	33%

Scheme 98 Pelter's amidation reaction using **20**

It is important to point out, however, that the only experiment that was performed was at room temperature with phenylacetic acid. Although it was noted that initial interaction of **20** and **53** produced an exotherm, heat was required for better yields with less reactive carboxylic acids and therefore any future reactions were done at reflux in benzene with 1 equiv. of **20** (Scheme 20, Section 1.2). The effect of increased temperature on the amide yield with 0.33 equiv. of **20** was not investigated.

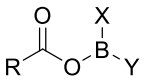
The proposed mechanism proceeded *via* the initial formation of salt **123**, followed by the expulsion of one amine group by carboxylate on the boron atom to give acyloxyboron intermediate **124** (Scheme 99).



Scheme 99 Proposed mechanism of trisaminoborane-mediated amidation

Finally, a nucleophilic attack by the liberated amine at the “activated” carbonyl led to the formation of the amide and boron species **125**.

From this observation, the authors investigated the application of pre-forming acyloxyboron species of a general formula **126** for an easy activation of carboxylic acids to yield amides at room temperature (Figure 19).

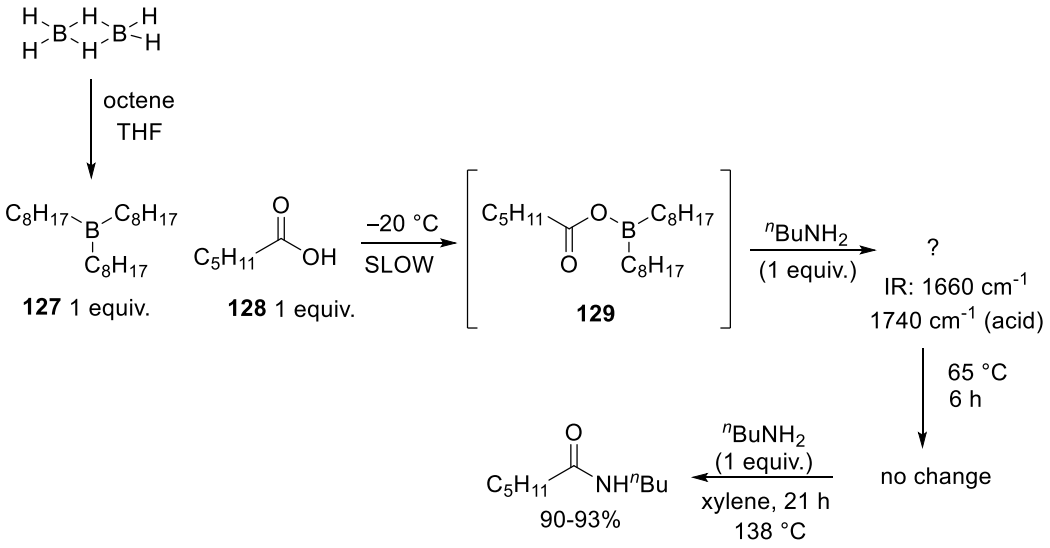


126

X,Y = alkyl, alkoxy, amino

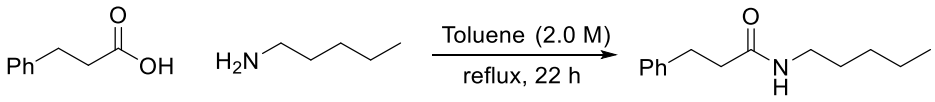
Figure 19 A general proposed activation of carboxylic acids

Trioctylborane **127** was firstly reacted with caproic acid **128** in an attempt to access **129** (Scheme 100).



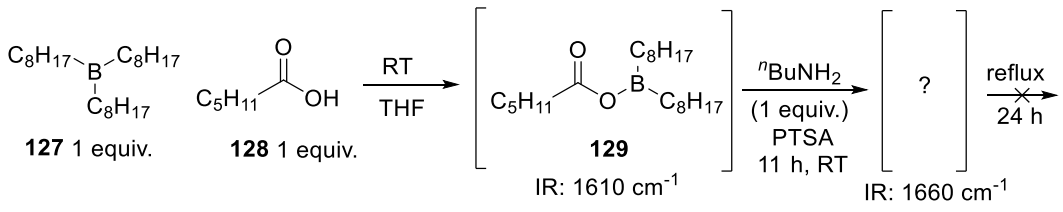
Scheme 100 Trioctylborane activation of a carboxylic acid for amidation

Borane **127** was prepared *in situ* by the addition of oct-1-ene to diborane. Caproic acid **128** was then added at −20 °C, at which point only weak conversion to acyloxyboron species **129** was suggested. Upon addition of butylamine, no amide or carboxylate formation was reported, and IR stretches for the free carboxylic acid (1740 cm^{-1}) and unspecified species at 1660 cm^{-1} were identified. Only prolonged and harsh heating with added equivalents of butylamine in xylene resulted in excellent conversion to the amide product. This, however, might suggest that the amide isolated was just the product of thermal amidation reaction, as this is expected for simple non-functionalised acids and amines, for example Williams *et al.* showed that successful amidation takes place in refluxing toluene (Scheme 101).[46]



Scheme 101 Williams' thermal amidation method

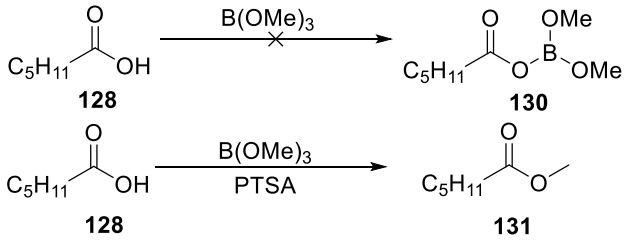
When the acid **128** and **127** were mixed at room temperature, an immediate formation of **129** was proposed (Scheme 102).



Scheme 102 Room temperature formation of acyloxyboron species **129**

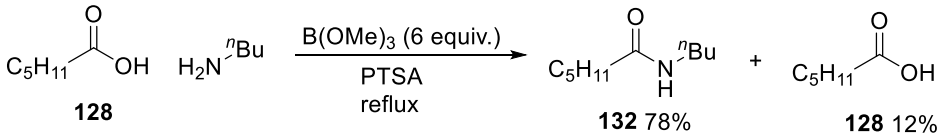
Subsequent addition of the amine caused some reaction (but not amidation) and the IR for C=O shifted from 1610 cm^{-1} to 1660 cm^{-1}. When PTSA was added and the mixture was stirred for 11 hours at room temperature, no amide formation was observed. After reflux (24 h at 68 °C) no amide was isolated, but the unknown species were reported to be highly susceptible to hydrolysis. The authors did not specify the products of hydrolysis, however, it can be suggested that the acid **128** and butylamine were recovered. Despite the authors' statement that no carboxylate ammonium salt was formed (as no evidence to confirm or contradict this was provided), this result further supports that carboxylate ammonium salt formation occurred and therefore the product only formed with strong heat.

Due to the lack of success with alkylboranes, the authors moved on to test trimethylborate as the amidation reagent. When trimethylborate was mixed with caproic acid **128** in an attempt to form acyloxyboron **130**, no interaction was observed. However, when PTSA was added to the mixture, a rapid formation of ester **131** was observed (Scheme 103).



Scheme 103 Trimethylborate interaction with a carboxylic acid

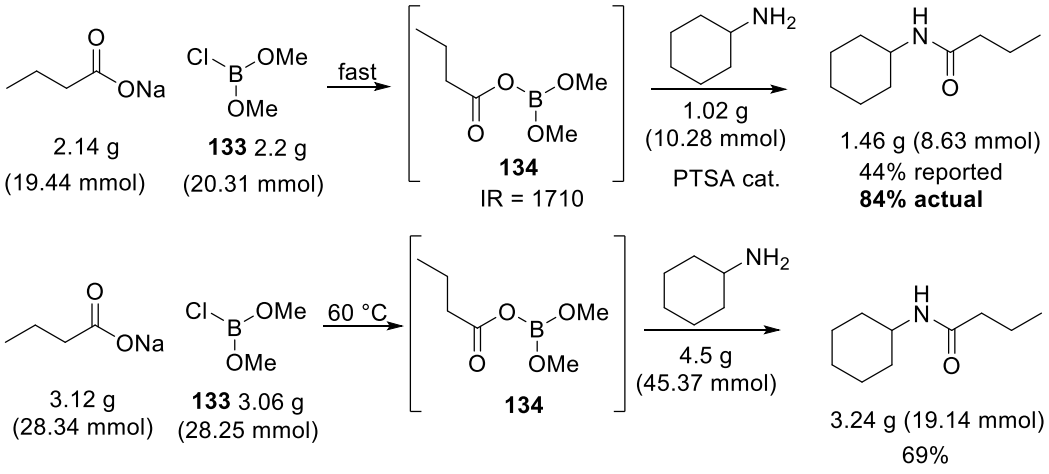
The amide **132** was formed when **128** and butylamine were heated in the presence of trimethylborate and catalytic amounts of PTSA to yield 78% of the amide **132** with 12% hexanoic acid recovered (Scheme 104).



Scheme 104 Trimethylborate-mediated amidation by Pelter *et al.*

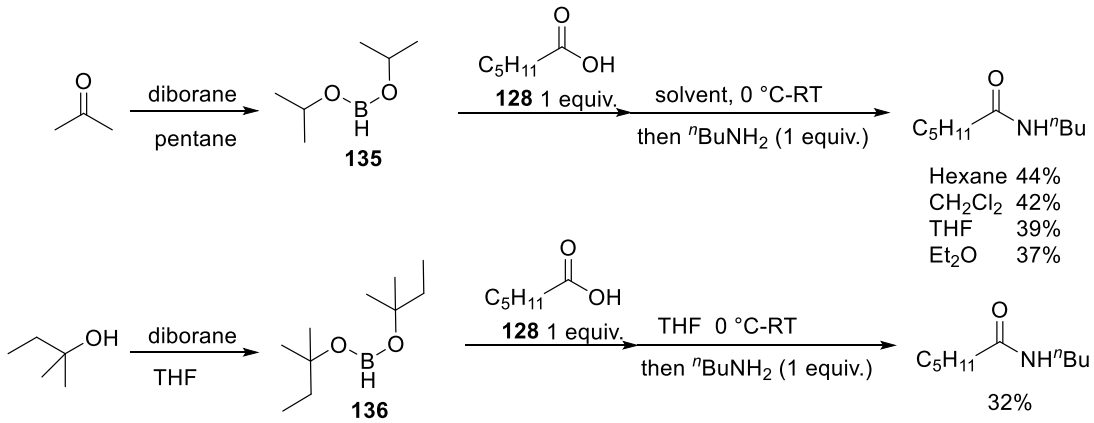
However, strong heat was required for high conversions to the corresponding amide and therefore this method was deemed unsuitable for the preparation of peptides, which was the main aim of their investigations.[57]

Pelter *et al.* hypothesised that using B-chlorodimethylborate **133** and pre-mixing it with carboxylic acid to form acyloxyboron species **134**, would enable an easier acylation of the amine at room temperature (Scheme 105).



Scheme 105 B-chlorodialkoxy boranes for carboxylic acid amidation

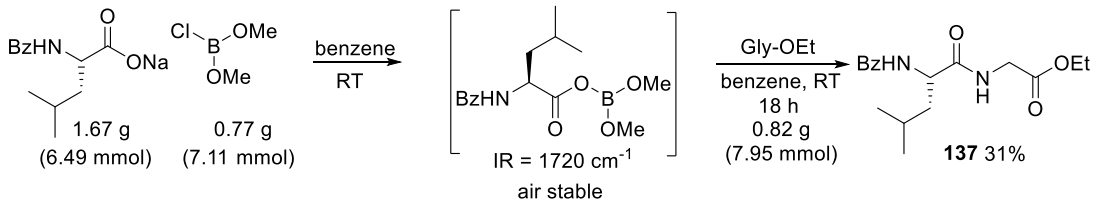
To their disappointment, although the reaction proceeded smoothly, the yield of the corresponding amide was reported to be 44%. Heating the reaction mixture increased the yield to 69%. Upon analysis of their report, we noted a few discrepancies between the main text and the details in the experimental section; the calculated yield reported by the authors did not match the experimental yield from the provided values for the amount of reagents used. In the experimental, the limiting reagent was said to be the amine, which would lead to 84% yield. However, the yield determined by the authors accounted for the acid as the limiting reagent. This, however, might simply be a misprint, as the reaction was also attempted with dialkoxyboranes **135** and **136**, and in either cases the yields were consistently below 50% (Scheme 106).[57]



Scheme 106 Examples of dialkoxyborane-mediated amidation

Moreover, varying solvents for the reaction with **135** did not result in improvement. It is therefore unclear whether the yield inconsistency was due to an inaccurate mass of the amine given in the experimental section, or if the yield was calculated using acid **128** as the limiting reagent, which was used in excess with respect to the amine.

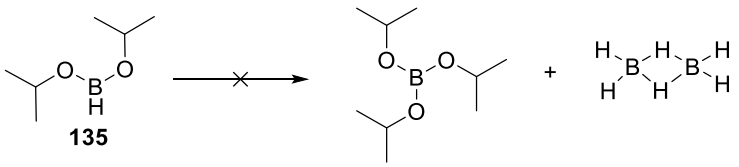
The synthesis of dipeptide **137** was also attempted with a low yield (31%) observed at room temperature without racemisation of the product (Scheme 107).[57] When heated, however, full racemisation of the product occurred, but no yields were given in that case.



Scheme 107 Attempted dipeptide synthesis with B-chlorodimethoxyborane

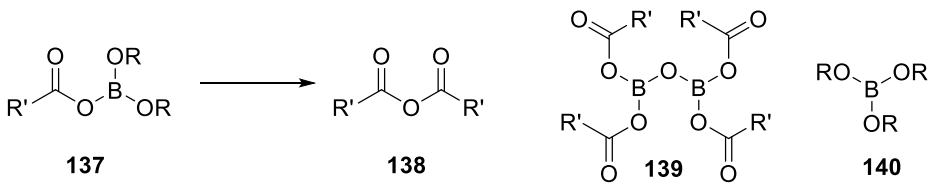
Pelter *et al.* then explored the potential reasons for decreased yields in the follow up paper.[122] The authors hypothesised and subsequently tested the possible reasons for low conversions observed from the amidation of acyloxyborates.

An inefficient synthesis of dialkoxyboranes (e.g. **135** and **136**, Scheme 106) was ruled out as the reason for the low yields as it was found that this reaction was 97% efficient. This type of compound was also found to be stable to disproportionation and therefore did not form borate and borane (e.g. **135** in Scheme 108).[122]



Scheme 108 Possible decomposition of dialkoxyboranes

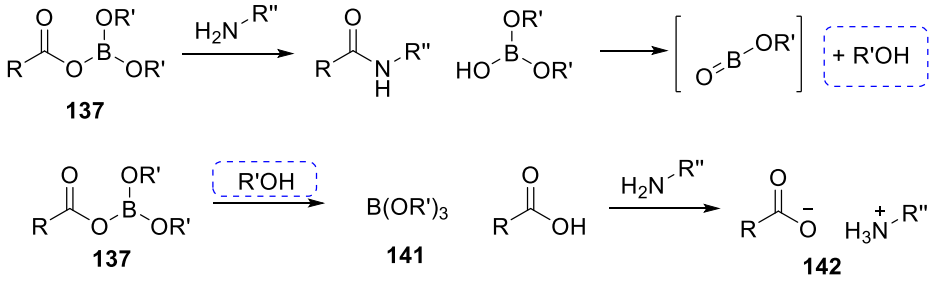
The second reason alluded to the acyloxyboranes **137** being decomposed prior the amidation, either *via* the reduction of the carboxylic acid to the corresponding alcohol by the residual dialkoxyborane or through rearrangement into different unreactive boron species (acid anhydride **138,** and **139**, **140**) (Scheme 109).[122]



Scheme 109 Proposed decomposition of acyloxyboron species

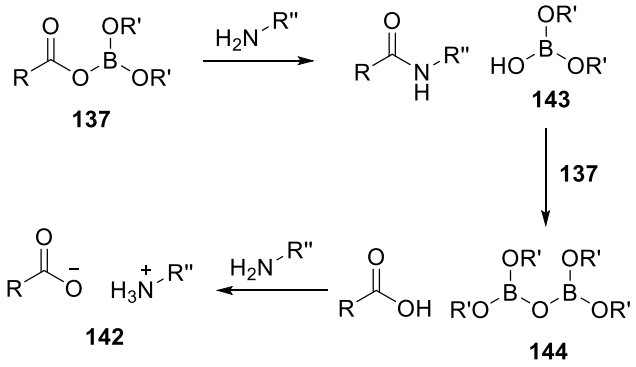
However, on the timescale of the control experiments, loss of caproic acid to reduction was found to be less than 5%. Moreover, possible intermediates (e.g. acid anhydride **138**) tested during this investigation were considered improbable to be formed in this type of the reaction and therefore were not the cause for low amide yields.[122]

A final investigation tested a few possibilities whereby either amine or liberated alcohol destroyed the active species **137** through nucleophilic attack at boron and not carbonyl. If that were the case, a mole of alcohol could be liberated after the first amidation cycle, which subsequently would attack the acyloxyboron to yield borate **141** and a carboxylic acid (Scheme 110). The acid could then form an unreactive salt **142** with the amine, therefore reducing the overall yield of the amide.



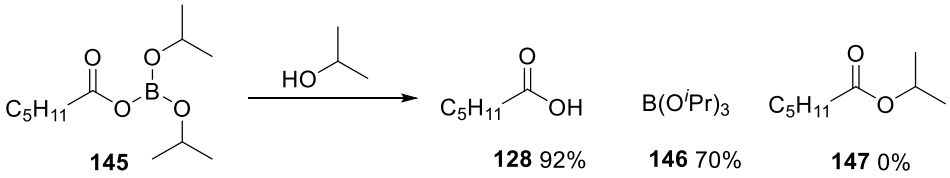
Scheme 110 Possible side-reaction of acyloxyboron intermediate

Alternatively, the amidation may be followed by the formation of **143** which can react with another acyloxyboron to make an unreactive anhydride **144** with carboxylic acid liberated to form the salt **142** with an amine (Scheme 111).



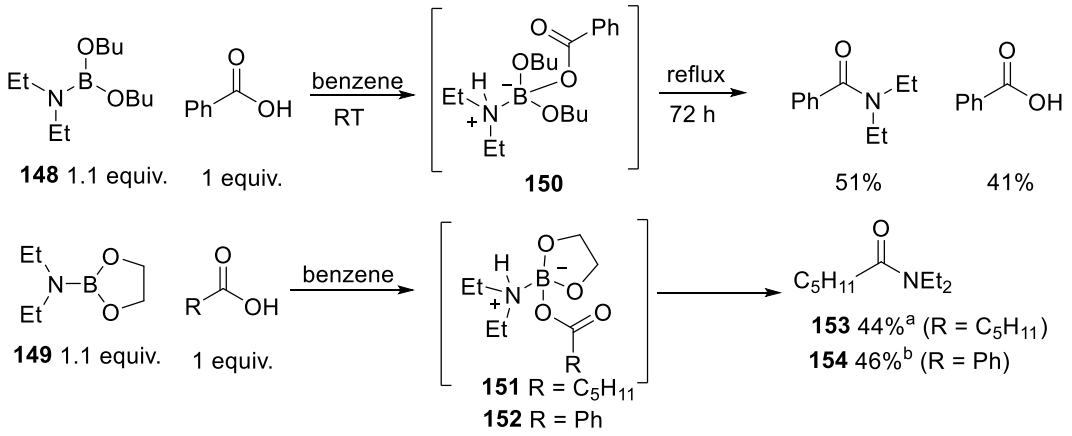
Scheme 111 Side-reactions of acyloxyboron **137**

When IPA was added to **145**, **128** was isolated in 92% yield alongside borate **146** in 70%. No formation of ester **147** was observed meaning that the alcohol attacked exclusively at the boron centre (Scheme 112).



Scheme 112 Test reaction of **145** with alcohol

The authors then tested the reactivity of dialkoxyaminoboranes **148** and **149** in amidation in case they formed if an amine attacked in a similar manner to alcohol (Scheme 113).



Scheme 113 Interaction if aminodialkoyboranes with carboxylic acids a. RT, 14 days; b. reflux, 72 h

The reaction of the acid with **148** and **149** was exothermic giving IR bands at 1670-1700 cm^{-1} which disappeared over times during amide formation. The salt **150** was reported to form between **148** and benzoic acid, which the authors isolated and partially characterised by ^{1}H NMR and IR. Interestingly, when **150** was isolated first and then re-subjected to heat, the corresponding amide was formed in only 17%

yield after 118 hours.[122] Similarly, when caproic acid and benzoic acid were reacted with **149**, only 44% and 46% of the corresponding amides **153** and **154** were isolated.

Despite these observations, when the reaction was performed by pre-forming the acyloxyboron first, no formation of salts such as **150**-**152** was noted, meaning that this was not the reason for lower yields.[122]

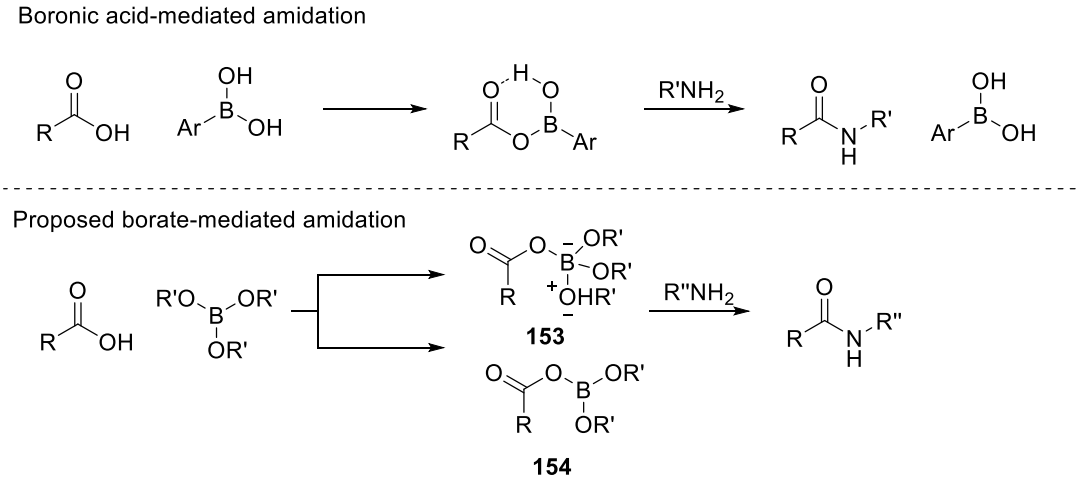
Based on their investigation, the main reason for low conversions was attributed to the formation of borates **141** as a result of nucleophilic attack by the liberated alcohol (Scheme 110). This possibility is feasible, as it is known that borates, despite being excellent reagents for amidation, require elevated temperatures for the reaction to work.

3.2 Understanding boron-mediated amidation

3.2.1 Previous mechanistic work in the Sheppard group

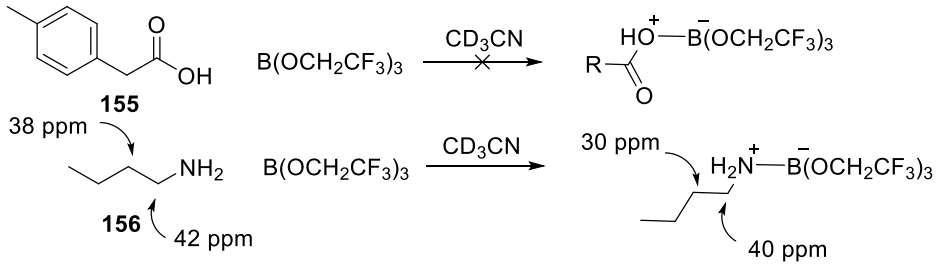
It was important to investigate the mechanism of the borate-mediated amidation to gain a better understanding of the process and use this knowledge in the design of an improved catalyst.

An investigation of $B(OCH_2CF_3)_3$-mediated amidation was initiated by a previous PhD student in the Sheppard group.[85] Initially, it was hypothesised that the mechanism could proceed *via* a generally accepted mechanism of boronic acids through the formation of acyloxy species **153** or **154** followed by the addition of amine to form amide (Scheme 114).



Scheme 114 Proposed borate-mediated amidation mechanism

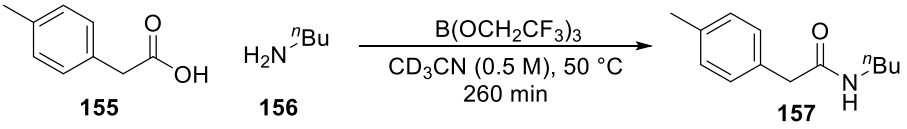
An NMR study was conducted with $B(OCH_2CF_3)_3$ mixed with tolylacetic acid **155** and butylamine **156** to investigate interactions between the reagents. Surprisingly, there was no interaction observed by NMR upon mixing the acid and borate reagent without an additional activation such as removal of water. On the other hand, quite a strong interaction resulted when borate was mixed with the amine, which was determined by the change in ^{13}C NMR shift (Scheme 115).



Scheme 115 Interaction of borate with acid and amine

This result was in agreement with Pelter's study using the $B(OMe)_3$ system, where no interaction was observed between caproic acid and trimethylborate, unless catalytic amounts of PTSA were added with ester formation taking place in that case.

The rate study was performed by a previous PhD student in the Sheppard group investigating rate dependence on the concentration of A. acid **155**; B. amine **156**; and C. borate (Figure 20).[85]



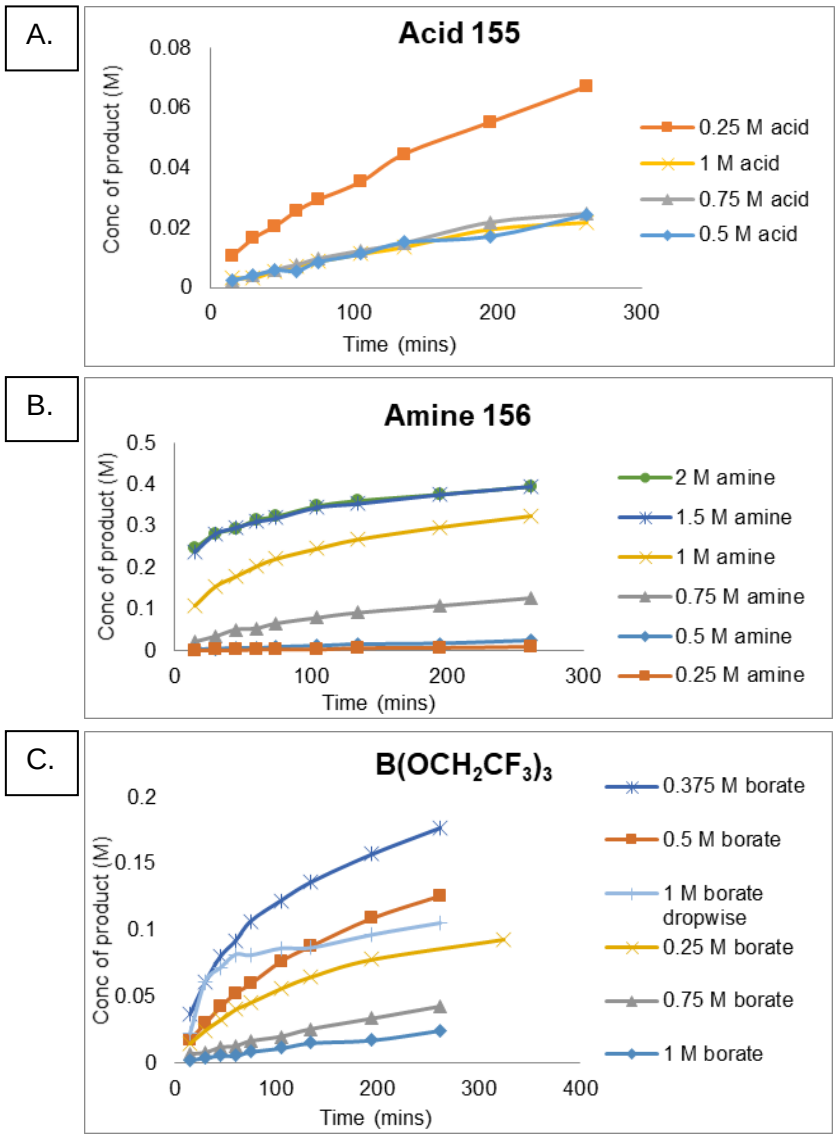
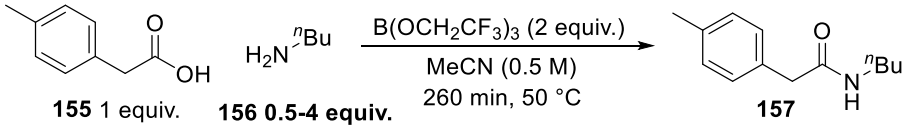
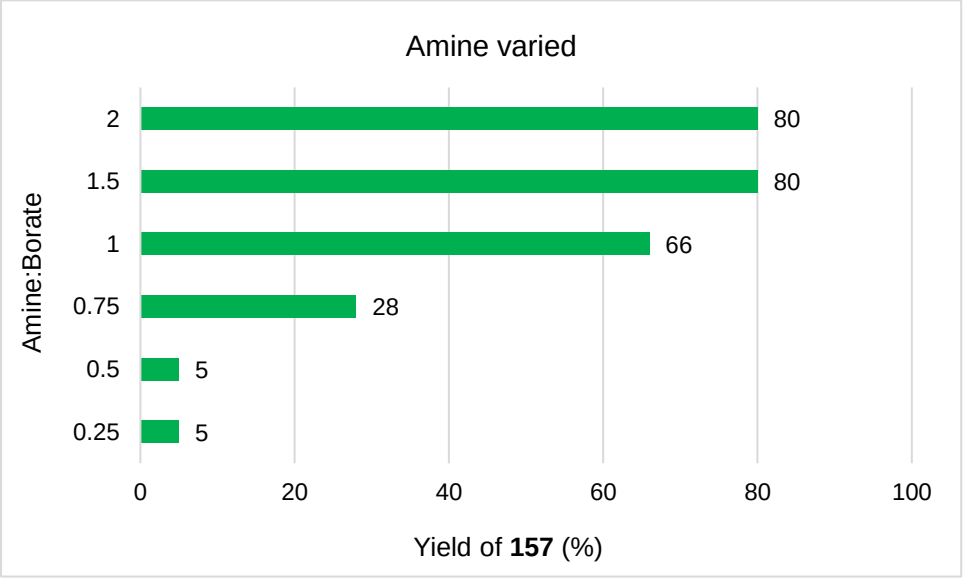


Figure 20 Adapted from a thesis by Rachel Lanigan.[85] Reactions were performed in 1 mL CD_3CN at 50 °C with 1 equiv. of **155** and **156**, 2 equiv. $B(OCH_2CF_3)_3$ unless otherwise stated: Full conversion at 0.5 M product; Graphs of reaction dependence on varying concentrations of A. acid varied (0.25 M product with 0.25 M acid); B. amine (0.25 M product with 0.25 M amine); C. borate;

The results suggested that excess of amine **156** relative to the acid **155** was beneficial for the increased rate of conversion to the amide **157** (Figure 20A,B). Importantly, there was some correlation between the amount of borate and **156**; if the amine was used in excess relative to the borate reagent, the rate was significantly faster leading to higher conversions over a given amount of time.[85]

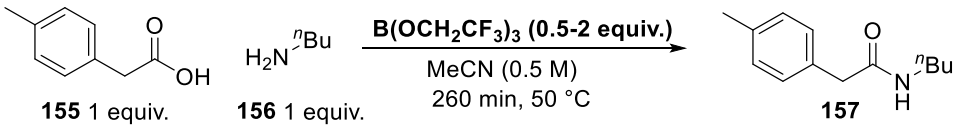
This link can be visualised by re-interpreting the results as the relative ratio of equivalent of amine:borate vs. the yield of **157** after 260 min (Graphs 1 and 2).



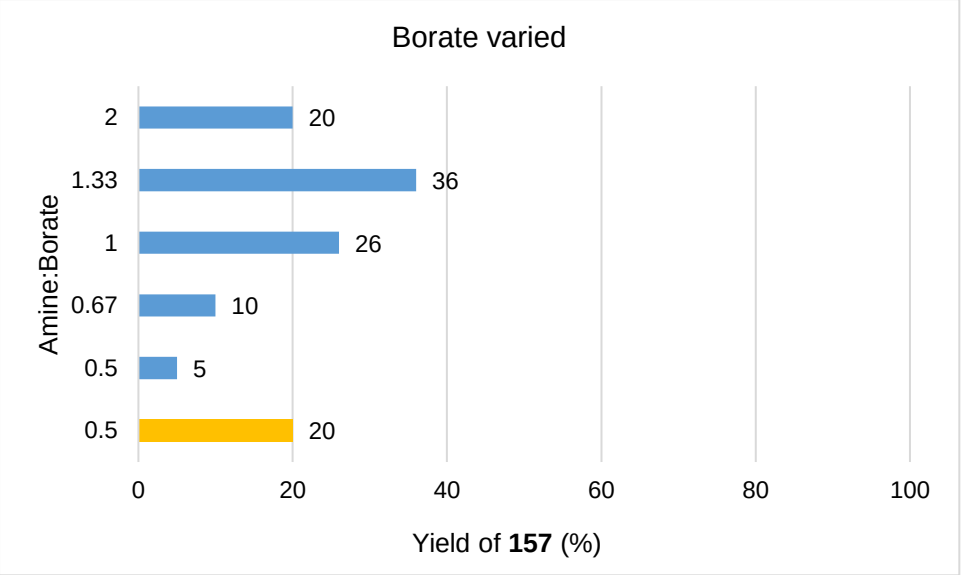


Graph 1 Dependence of yield of the amide vs. Relative ratio of equivalent of Amine:Borate;

As demonstrated, there is a clear decrease in the amide yield when the reaction mixture contains less amine than borate. It is also important to point out that yields are much higher than in the reaction with varied borate (Scheme 116, *vide infra*), because excess **156** to the acid **155** is also used. Once the yield drops to 5% (at ratio 0.5 and 0.25, Graph 1), not only the borate is in excess relative to the amine, but also the acid.



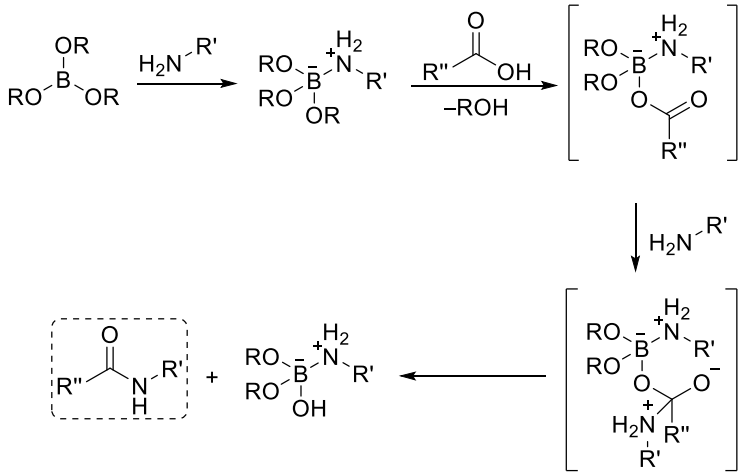
Scheme 116



Graph 2 Dependence of yield of the amide vs. Relative ratio of equivalent of Amine:Borate; Orange = borate added dropwise

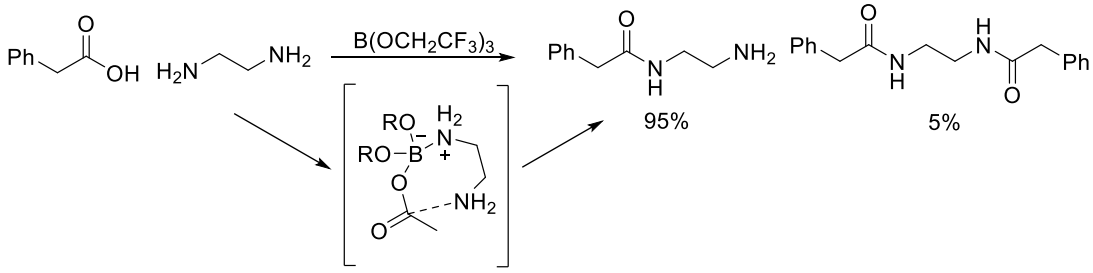
With the varied borate concentration, a similar pattern is followed. However, there also is an “optimum” amount of borate (Graph 2, 0.375 M borate). The yields of **157** were lower in this instance, as 1:1 **155**:**156** was used in this reaction. Importantly, when the borate was added dropwise to the reaction mixture, thus keeping the relative concentration of borate lower that the amine at the start of the reaction, the yield was higher (20%) after 4 hours.

The above observations suggest that a second equivalent of the amine is required for the reaction, which supports the proposed mechanism below (Scheme 117).



Scheme 117 Proposed mechnism for borate-mediated amidation

Moreover, the selectivity for monoacylation offered by the borate reagent in the reaction of symmetrical diamines with carboxylic acids further supported the above observations (Scheme 118).



Scheme 118 Selective monoacylation of diamine mediated by borate

Finally, computational evidence was presented, comparing the energy path of the reaction of $B(OMe)_3$ **158** vs. $B(OMe)_2(NHMe)$ **159** in the reaction with acetic acid (Figure 21).

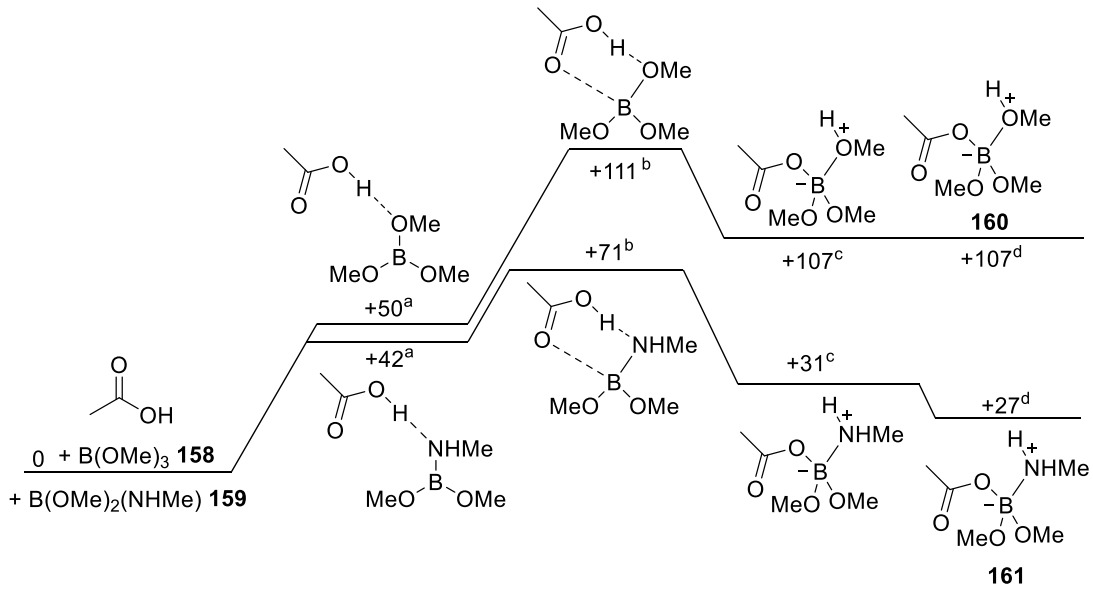


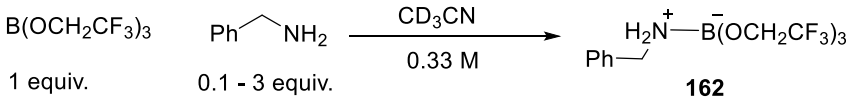
Figure 21 Computational comparison of **160** and **161** as active species for amidaiton; a. hydrogen-bonded complex; b. Transition state; c. Local minimum; d. Global minimum.

It was shown that overall the formation of the species **161** with an amine substituent was energetically more favourable than the formation of **160**. (Figure 21).

3.2.2 B(III)-mediated amidation NMR study

This project was devoted to further investigations of the boron-mediated amidation reactions using spectroscopic experiments, particularly ^{11}B NMR.

We firstly decided to investigate in more detail the species formed in the reaction between $B(OCH_2CF_3)_3$ and an amine. Upon mixing $B(OCH_2CF_3)_3$ with varied amounts of benzylamine from 0.1 equivalents to 3 equivalents, and monitoring by ^{11}B NMR, it is evident that the species formed is indeed **162** (Scheme 119, Figure 22). When the ratio of the amine and the borate is 1:1, a sharp signal for tetrahedral species at ~ 1 ppm is detected by ^{11}B NMR (Figure 22). This shift is unchanged and the peak remains sharp even with the excess of amine to borate, suggesting that there is no further interchange between amine and alcohol substituents on the boron, and that species **162** is stable once formed (Figure 22). As the amount of amine is decreased, the peak shifts towards the $B(OCH_2CF_3)_3$ signal, suggesting that an equilibrium is taking place, which is in agreement with previous observations reported by Landesman *et al.* on the interaction of amines with borates.[123]



Scheme 119

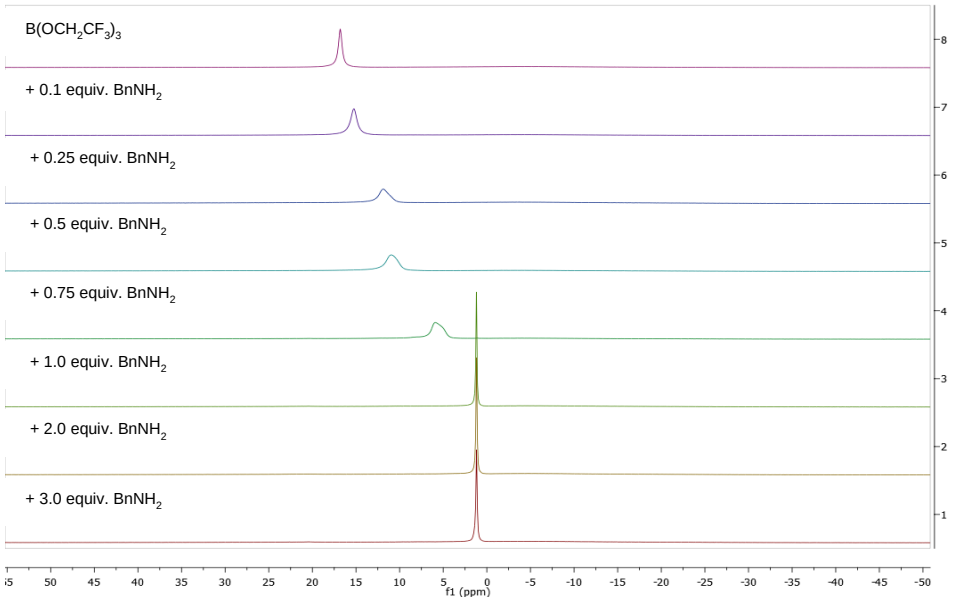
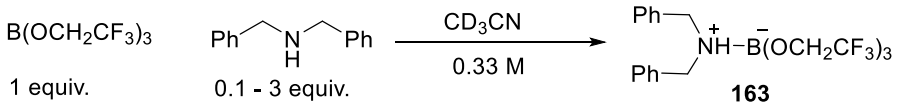


Figure 22 Titration study of borate with benzylamine

Similarly, when secondary amine was used, formation of **163** was observed (Figure 23).



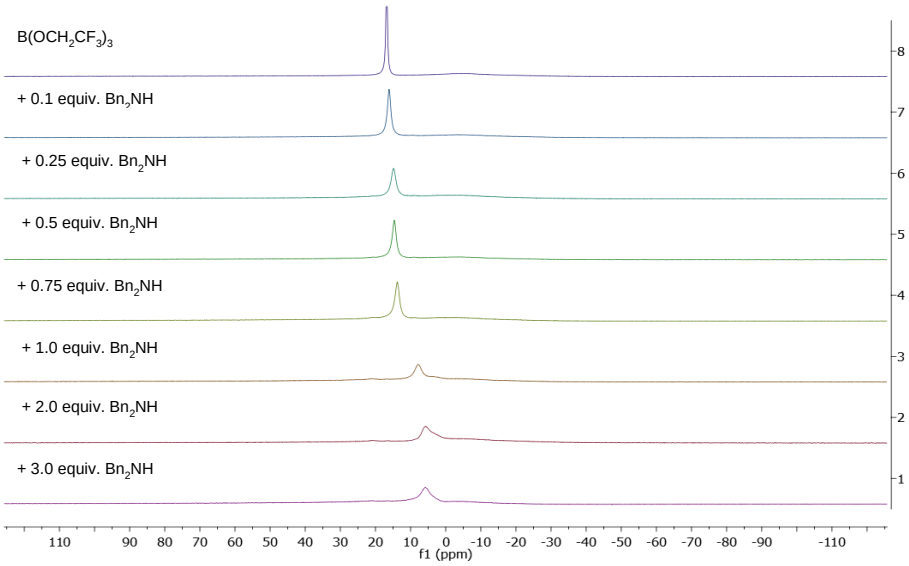
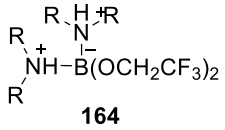


Figure 23 Titration study of borate with dibenzylamine

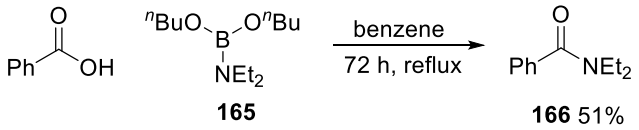
In both cases, no trifluoroethanol was liberated when equimolar or excess of benzylamine was added as determined by ^{19}F NMR (Appendix 7.2.1, Figure 44). From these observations, it is clear that at 1:1 ratio of the borate to an amine, tetrahedral species **162** and **163** are formed without expulsion of other substituents on the boron (i.e. trifluoroethanol in this case). Only one amine group attacks the boron centre and therefore species such as **164** does not form (Figure 24).



164

Figure 24 An unlikely intermediate in the interaction between an amine and borate

It is therefore possible that **163** is an intermediate in the $B(OCH_2CF_3)_3$-mediated amidation reaction. However, it is also possible that **163** is an off-cycle species, and the actual intermediate is the trigonal derivative $B(NR_2)(OR')_2$. This is partially supported by the reactivity of **165**, as reported by Pelter *et al.*, which reacted with benzoic acid to give 51% of the amide **166** after 72 h reflux in benzene (Scheme 120).[122]



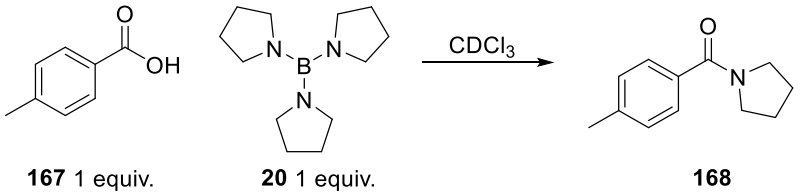
165 **166** 51%

Scheme 120 Pelter's amidation of benzoic acid with **165**

Interestingly, this interaction is not evident or detectable by ^{11}B NMR when $B(OMe)_3$ was mixed with an amine, even upon heating to 60 °C, which could support the reason why $B(OMe)_3$ is less effective reagent for amidation than $B(OCH_2CF_3)_3$.

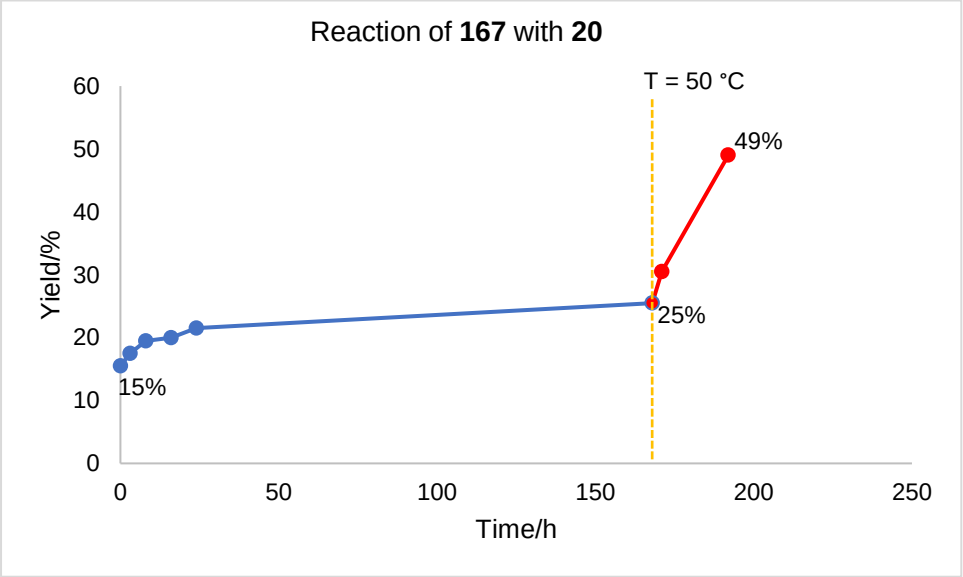
We then moved on to repeating some of the experiments reported by Pelter *et al.* to get a wider picture of the events during the trisaminoborane-mediated amidation by using NMR as the means of investigation. All experiments were performed at room temperature in $CDCl_3$ or CD_3CN as solvents in the presence of the internal standard (1,3,5-trimethoxybenzene or 1,4-dimethoxybenzene) used to quantify the amide formed in the reaction. Measurements were taken from the mixing point of the trisaminoborane and acid and at regular time intervals. ^{11}B NMR was used to gain an understanding of what potential species could be involved during the process.

The first experiment was performed using toluic acid **167** with trispyrrolidinoborane **20** (Scheme 121).



167 1 equiv. **20** 1 equiv. **168**

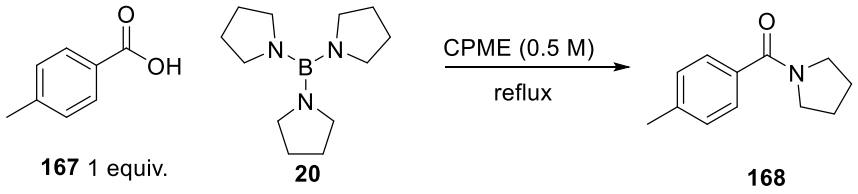
Scheme 121



Graph 3 Amide **168** formation over 7 days. Blue plot denotes the reaction performed at room temperature; Red shows the yield of **168** when the reaction was heated at 50 °C.

To our surprise, an immediate formation of the product **168** was observed resulting in 15% yield after approximately 5 minutes. The reaction, however, slowed down with no significant improvement in the yield after 7 days. When the same reaction was heated to 50 °C, however, the rate of the amide formation increased leading to 49% overall yield (25% increase from the heating point in 24 hours) of the amide **168**.

The reaction was also performed at reflux in CPME using varying amounts of borane **20** (Table 9).



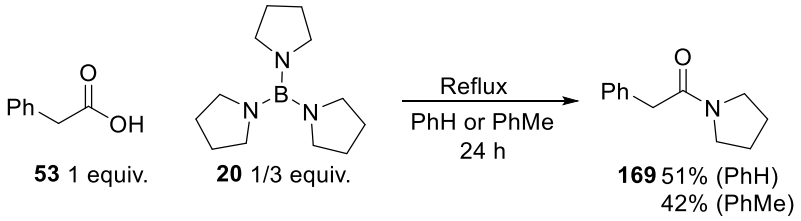
167 1 equiv. **20** **168**

Entry	Conditions	Yield (%)
1	24 h, 110°C (1 equiv. **20**)	90
2	24 h, 110 °C (0.33 equiv. **20**)	40
3	96 h, 110°C (0.33 equiv. **20**)	85
4	24 h, 100 °C (0.33 equiv. **20**) + CF_3CH_2OH	65

Table 9 Various reactions of toluic acid with **20**

After 24 hours, nearly quantitative yield was obtained with 1 equivalent of **20** (entry 1), and to our surprise, 40% with 1/3 equivalent (entry 2). Longer reaction times (entry 3) led to a further increase in yield to 85%. Using trifluoroethanol as an additive also improved the yield to 65% after 24 hours (entry 4).

The increase in temperature led to an improved yield when 1/3 equiv. of **20** was used. However, the conditions for this reaction were different to the ones reported by Pelter *et al.*, in which case benzene was used as a solvent. It was therefore important to test these conditions as well. The reaction was performed in benzene and toluene with 0.33 equiv. of **20** and phenylacetic acid **53** (Scheme 122).



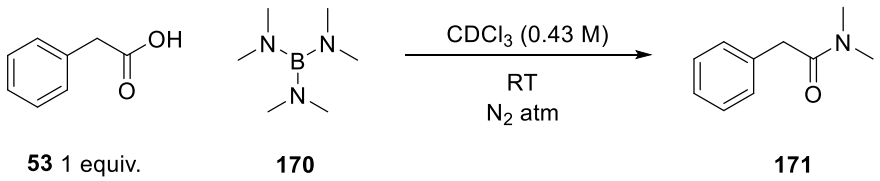
53 1 equiv. **20** 1/3 equiv. **169** 51% (PhH) 42% (PhMe)

Scheme 122 Heated reaction of 0.33 equiv. of **20** with phenylacetic acid

Pleasingly, both reactions resulted in moderate yields of **169**, and above 33%, which was in agreement with the result obtained in CPME.

We then moved on to studying boron intermediates produced in the reaction with trisaminoboranes by ^{11}B NMR. Trispyrrolidinoborane **20** purchased from Sigma-Aldrich was not very pure with free pyrrolidine present, and therefore it was decided to use tris(dimethylamino)borane **170** for the future experiments with phenylacetic acid.

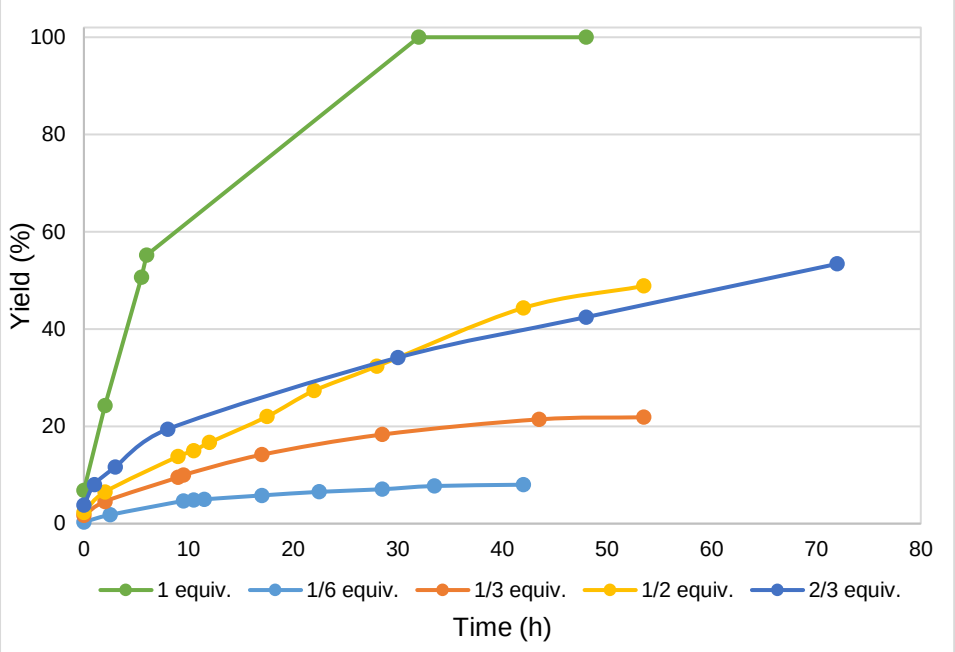
All reactions were performed on a 0.3 mmol scale in $CDCl_3$ (0.43 M) with 1,4-dimethoxybenzene as an internal standard (Scheme 123). The ratio of **170** to **53** was varied from 1:6 to 1:1 equivalents.



53 1 equiv. **170** **171**

Scheme 123 NMR study using varying equivalents of **170** in direct amidation of **53**

The NMR yields are plotted in Graph 4.



Graph 4 NMR yields of the amide **141** measured over the reaction time-course with varying equivalents of **170** to 1 equiv. of **53**

As previously observed with **20**, the reaction reached completion after 48 hours at room temperature with 1 equivalent of **170**. Faster reaction occurred with more trisaminoborane **170**. In all cases an immediate product formation was observed, although less than with **20** (only 6% conv. with 1 equiv. **170**). When **170** was used in less than 1 equivalent, the reaction did not proceed as rapidly, and after 50 hours with 1/3 equivalents of the reagent, the yield only reached 22% of the amide **171**.

The reactions were followed by ^{11}B NMR to examine the boron species formation with 1:1 equivalents (Figure 25, Graph 5) and 1/3:1 equivalents (Figures 27 and 28, *vide infra*) of **170**:**53**. For the reaction of 1:1 equivalents of **170** and **53**, five different species were formed (0.75 ppm was an unidentifiable impurity) (Figure 25).

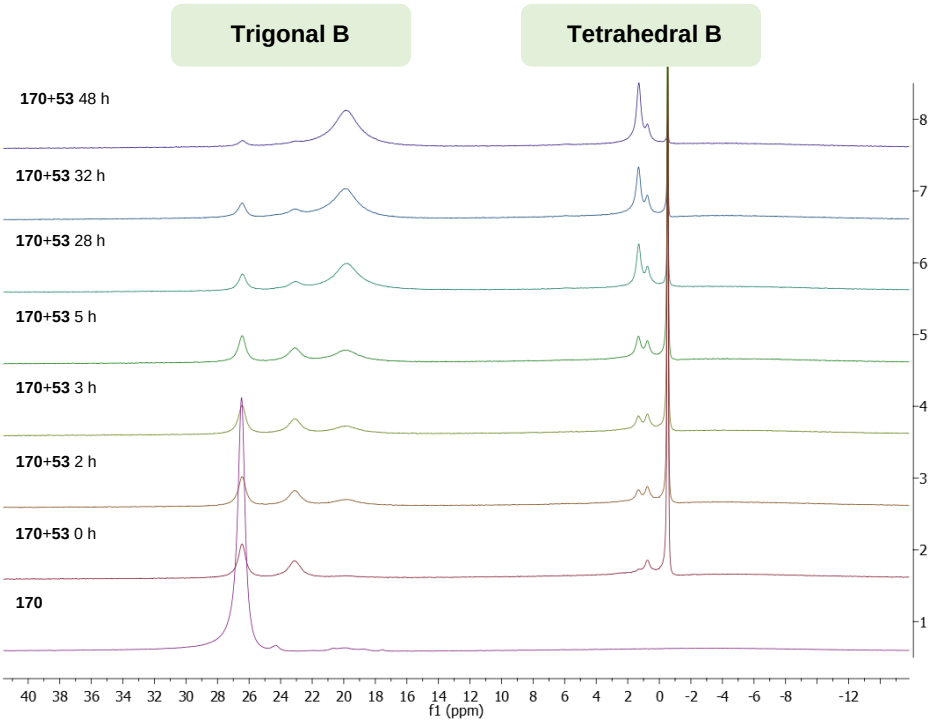
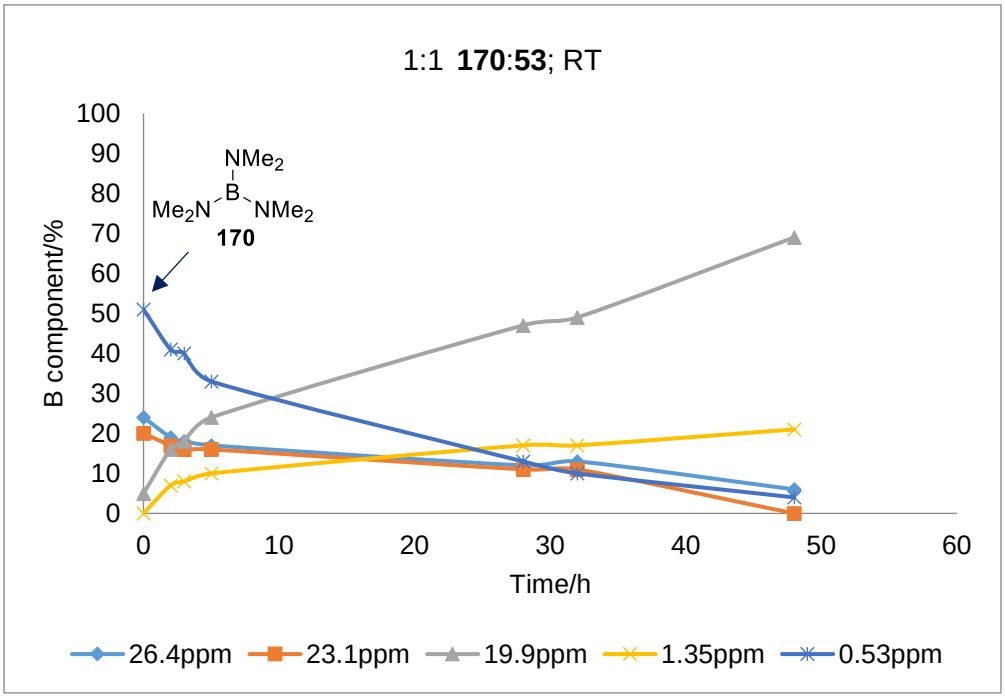


Figure 25 ^{11}B NMR of 1:1 reaction with **53**:**170** over time



Graph 5 Boron species present during the reaction of **170** with **53**

The proposed structures are summarised in Table 10. Where possible, literature ^{11}B NMR shifts were provided for the proposed structures or their derivatives.

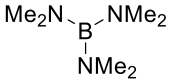
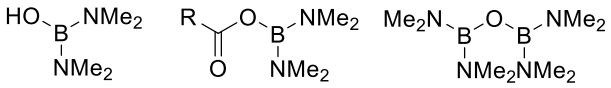
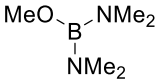
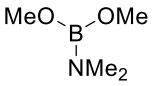
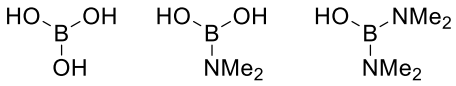
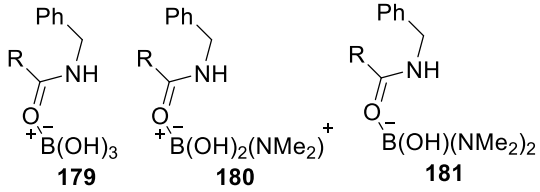
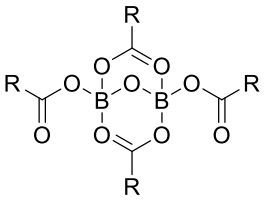
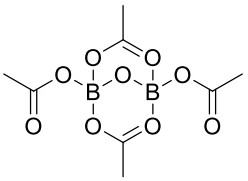
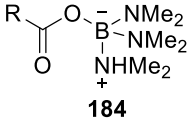
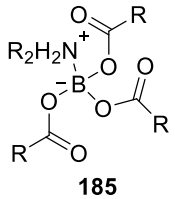
^{11}B NMR (ppm)	Proposed structures	Lit. ^{11}B NMR (ppm)
26.4	 **170**	27.3 ($CDCl_3$)[124]
23.1	 **172** **173** **174**	**174**: 27.5 ($CDCl_3$)[125] **175**:[126] 25.1  **175** **176**:[126] 21.3  **176**
19.9	 **177** **178** **172**	**175**:[126] 25.1 **177**: 19.9 (CD_3CN)[127] 17.9 ($CHCl_3$)[128]
1.35	 **179** **180** **181**  **182** R = Bn	**183**:[129] 2.11  **183** 1.69 (observed)
0.53	 **184**  **185**	

Table 10 Proposed species formed during the amidation reaction of **53** with borane **170**

Over 48 hours, borane **170** at 26 ppm decreased as the reaction proceeded to form the amide product **171**. Upon mixing **53** and **170**, an immediate formation of the peak at 0.53 ppm was observed, which could be the acyloxy species **184**. This is supported by the full disappearance of the carbonyl peak of **53** at 176 ppm (172 ppm appears) and a big shift of the CH_2 peak from 40.8 ppm to 43.0 ppm in ^{13}C NMR at 0 h (Appendix 7.2.2, Figure 46).

The boron species at 23.1 ppm may be the result of the immediate formation of the amide **171**. If that is the case, then the possible species are the hydrolysis product of one of the amines on **170** leading to **172** or **174**. However, the reported ^{11}B NMR shift for **174** is at 27.5 ppm,[125] which is higher than the observed shift. On the other hand, a similar to **172** compound **175** with a methoxy substituent was reported to appear at 25.1 ppm.[126] Alternatively, the peak at 23.1 ppm could be a trigonal derivative of **184** with one equivalent of dimethylamine directly substituted by the carboxylic acid (**173**), which is justified by its disappearance over the reaction course.

The signal at 1.35 ppm increases over the course of the reaction, and is likely to be boric acid with the amide product (**179**) chelated which is partially supported by the shift of all product peaks in contrast to the actual product alone in the NMR tube (Appendix 7.2.2, Figure 48). This is supported by the fact that at the end of the reaction, only the species at 19.9 pmm and 1.35 ppm were present (i.e. full conversion to the amide product). It cannot be determined with certainty as to what the identities of both are, but the signal at 19.9 ppm could potentially be due to boric acid **177**, as stoichiometric quantities of water are formed from the amidation. The mixture was spiked with boric acid (dissolved in $CDCl_3$:DMF-d_7) to confirm the observation (Figure 26).

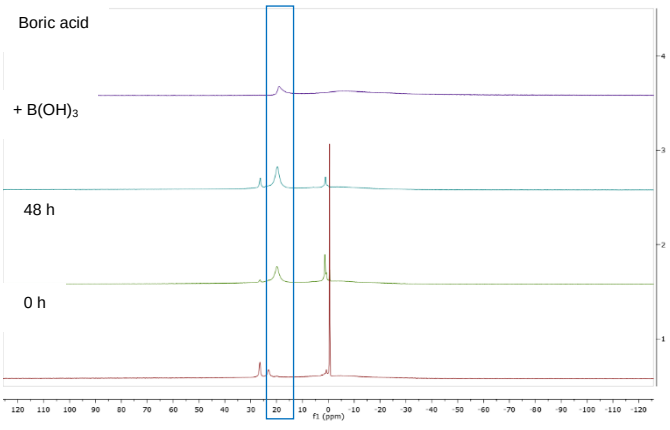


Figure 26 Spiking experiment to test for boric acid in the reaction mixture

The peak in the crude sample aligns with the spiked sample. This, however, is not definitive proof for the identity of this species. However, the reported ^{11}B shifts for **177** usually appear around 19 ppm.

However, 2 equivalents of dimethylamine would be remaining in the reaction mixture. And it is therefore possible that a combination of **177**, **178** and **172** could be present at 19.9 and **179**-**181** at 1.35 ppm.

When 1/3 equiv. of **170** was mixed with **53**, only one tetrahedral boron species formed at ~ 0.53 ppm (Figure 27). After 36 hours, it is slowly consumed to form new species at 1.35 ppm, at which point the amide yield is 21%, which could be the same or similar species to **179** (Table 10).

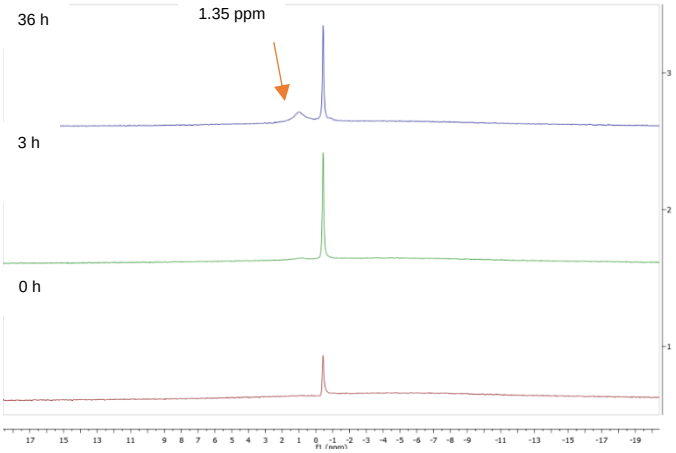


Figure 27 ^{11}B NMR species during the reaction of 0.33:1 equiv. of **170** with **53**

Upon heating to 50 °C, the species at 1.35 ppm appear faster, which is attributed to the faster formation of the amide **171**, as when no tetrahedral species at 0 ppm is remaining (after 24 h), the conversion to the amide is 33% (Figure 28, Graph 6).

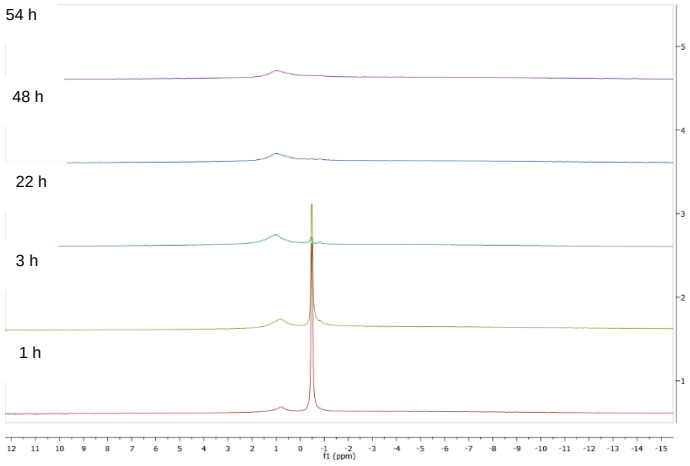
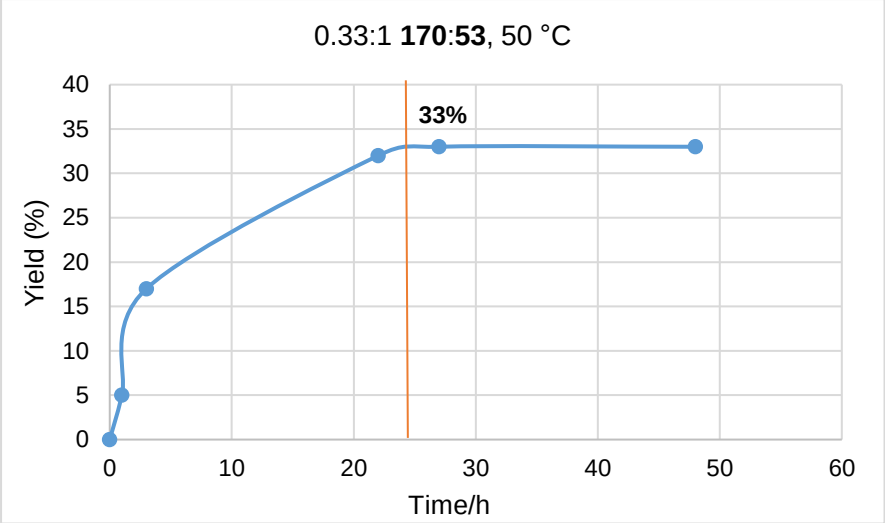
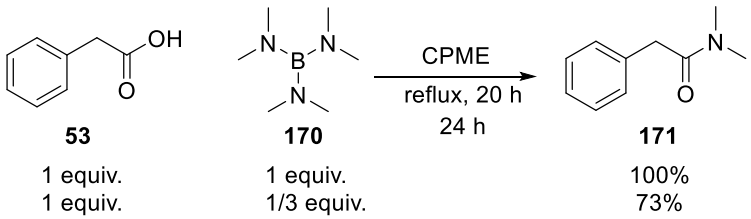


Figure 28 ^{11}B NMR species during the reaction of 0.33:1 equiv. of **170** with **53** at 50 °C



Graph 6 Amide **171** formation with 0.33 equiv. of **170**

In a similar way to the borane **20**, 73% yield of the amide **171** was obtained when the reaction was performed in CPME with 1/3 equiv. of **170** (Scheme 124).

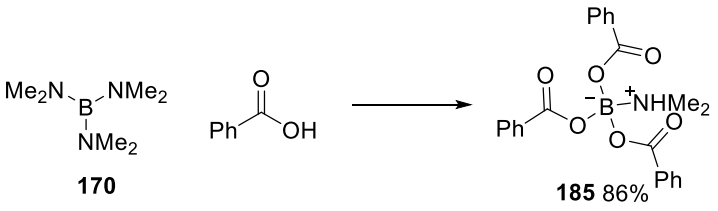


Scheme 124 Yield comparison of amidation with 1 equiv. and 0.33 equiv. of **170** at reflux in CPME

Only negligible instant formation of the amide **171** was observed with 0.33 equiv. of **170**, which could explain the absence of species at 23 ppm (or such a small amount was present that it did not show up on the spectrum as the peak is broad).

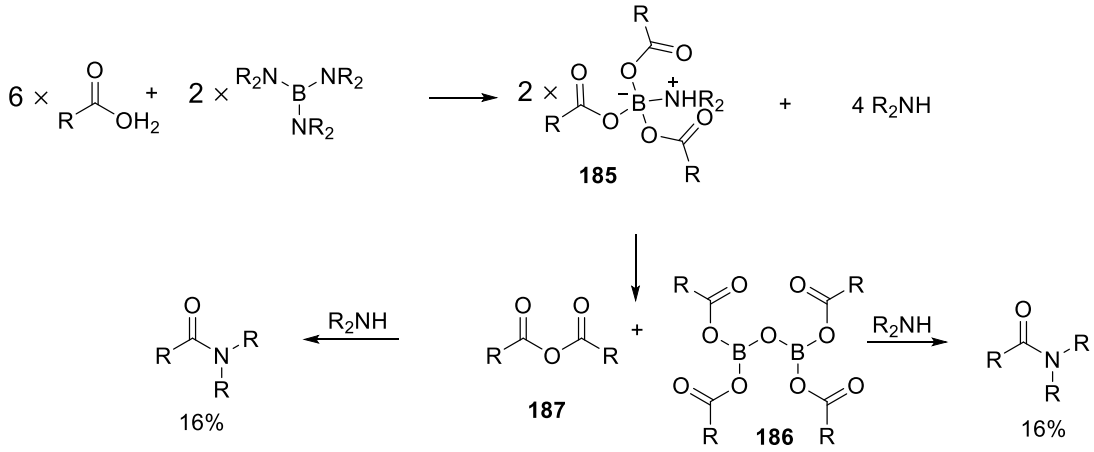
From the results above, it is evident that species at 1.35 ppm are not reactive to form the amide at RT. The fact that the amide is formed when heat is applied, however, means that this species contain both amine and the acid (either by coordination or directly bonded to boron).

Pelter *et al.* explained the conversions to 33% of the amide with 0.33 equivalent of trisaminoborane **170** by the formation of the salt **185**, which the authors isolated and partially characterised upon mixing benzoic acid with **170** (Scheme 125).[130]



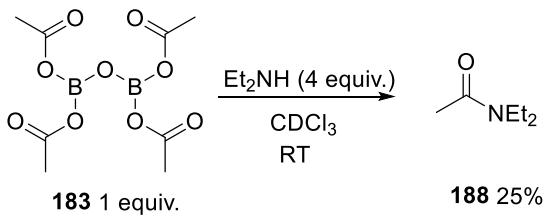
Scheme 125 Observed formation of salt **185** by Pelter *et al.*

This was then said to rearrange to **186** and acid anhydride **187**, which would explain the formation of 33% yield of the amide due to the stoichiometry of the intermediates involved when 1/3 equivalents of trisaminoborane is used (Scheme 126).



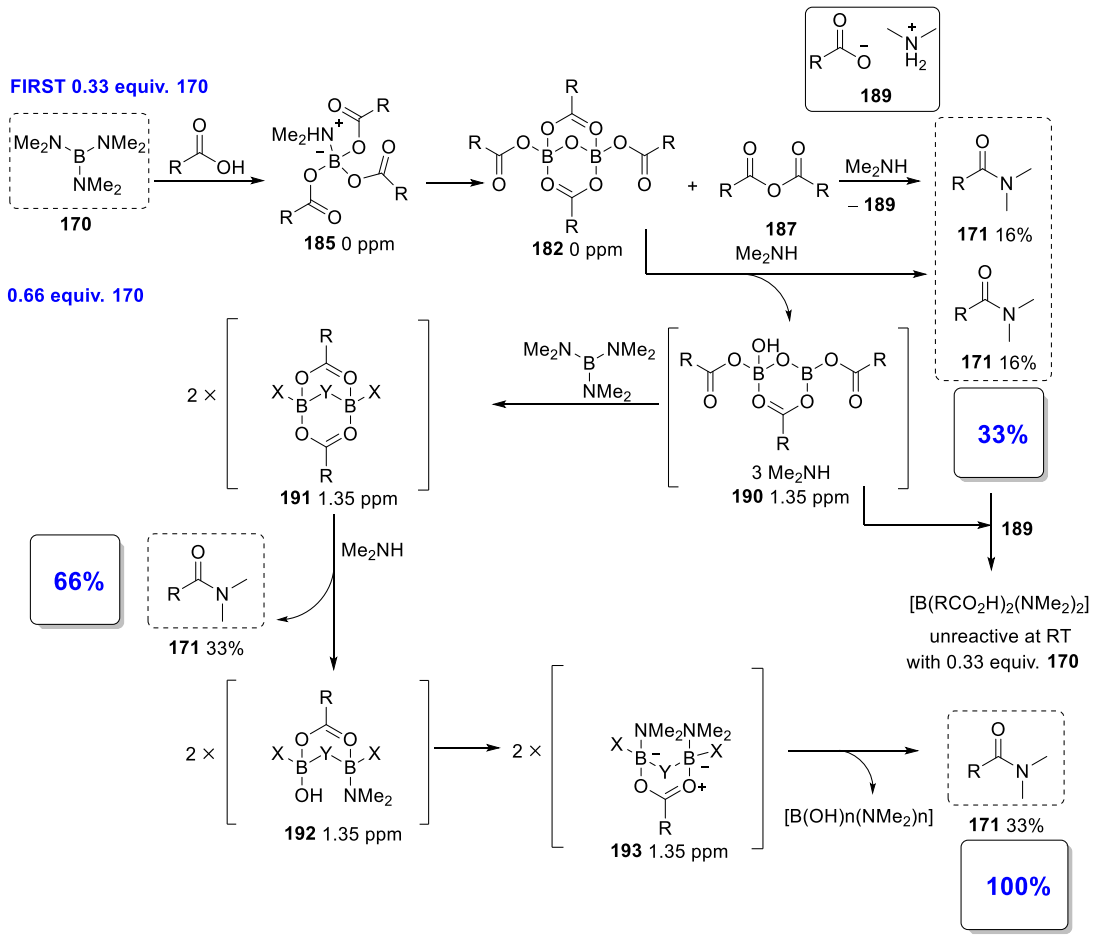
Scheme 126 Proposed mechanism with 0.33 equiv. of **170** by Pelter

When we reacted **183** with diethylamine, 22% yield of the amide **188** formed between the time the amine was added and the NMR spectrum collected (Scheme 127). However, the reaction reached 25% yield of **188** after 24 hours and remained unchanged after 48 hours.



Scheme 127 Reaction of **183** with an amine; Yield determined using 1,4-dimethoxybenzene as internal standard

Based on the above observations and Pelter's reports,[57,122,130] it is possible to propose a tentative reaction pathway of trisaminoboranes with carboxylic acids (Scheme 128).



Scheme 128 Reactivity map of **170**-mediated amidation reaction

We propose that a similar pathway is followed (at least initially) with 1 and 0.33 equiv. of **170**. Pelter proposed the formation of **182** and anhydride **187** *via* **185** as a possible explanation for only 33% yield of the amide forming.[130] We have shown that the reaction of **183** and diethylamine yields 25% of the amide **188**, which means that only one acyloxy group reacts to form the amide product. It is therefore possible, that during amidation, the species **190** and by-product **189** form an unreactive tetrahedral boron species (1.35 ppm by ^{11}B NMR). Analysing ^{1}H NMR spectrum at the end of the reaction with 0.33 equiv. of **170**, we found that 67% of unreacted amine-acid salt **189** are present in the mixture in correct stoichiometry (Figure 29).

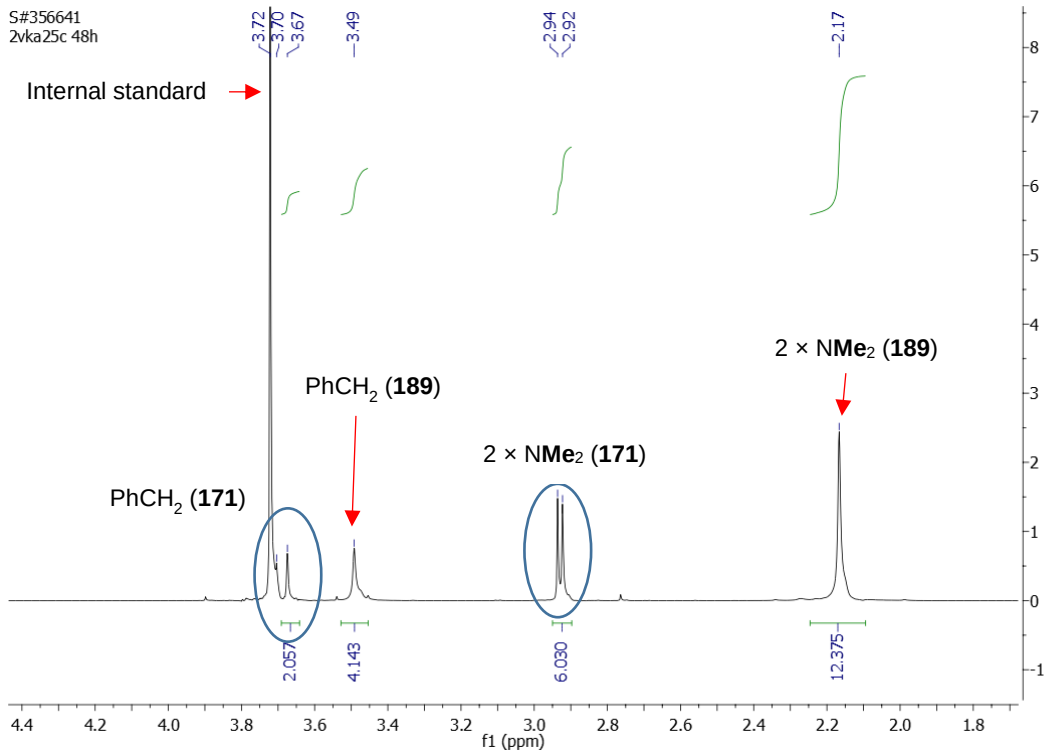


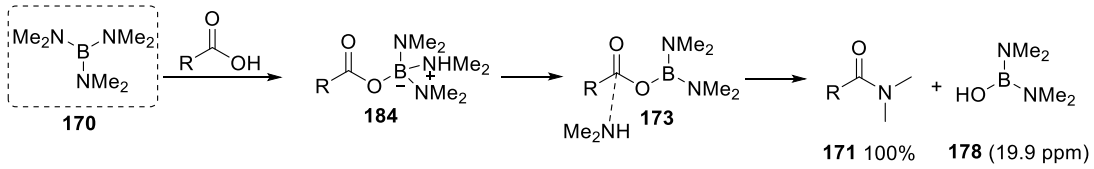
Figure 29 Species observed by ^{1}H NMR at the end of the reaction with 0.33 equiv. of **170**

Moreover, the presence of anhydride **187** could explain an immediate formation of the amide product upon mixing the acid and **170**.

With 1 equiv. of **170**, further rearrangement to reactive species (e.g. **191**) may be possible, which could lead to the full conversion of the amide **171** *via* the expulsion of two carboxylic acid moieties at a time, which could be replaced on the boron atom by the excess of dimethylamine present in reaction mixture to produce proposed reactive species of type **192** and **193** (Scheme 128). The identities of any of the intermediates are unknown. However, from the observation of the reactivity of the bridged species **183**, where only one of the activated carboxylic acids reacted with an amine, it is likely that all the consecutive steps would involve some form of such activated species. We propose that the acyloxy group may be replaced by an amine (i.e. X = NMe_2, for **191**, **192** and **193**) thus retaining the bridged boron species for further amidation.

With 1 equivalent of **170**, 1:1 acid to boron is present in the reaction mixture. Both trigonal (19.9 ppm) and tetrahedral (1.35 ppm) species are observed by ^{11}B NMR, which are likely to be **172**, **177**, or **178** (or a mixture) for 19.9 ppm, and any form of **184** with the amide product coordinating to the boron atom (at 1.35 ppm) (Table 10).

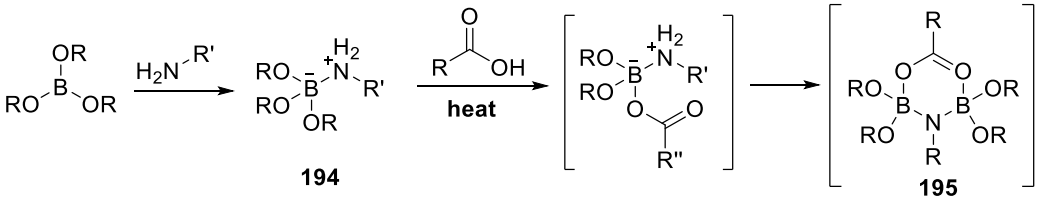
Another possible route to full conversion to the amide product with 1 equiv. of **170**, which was proposed by Pelter *et al.*, is presented in Scheme 129.[55]



Scheme 129 Alternative amidation mechanism with 1 equiv. of **170**

Although possible, this route is unlikely to be followed, as Pelter *et al.* found that species of this type are inefficient amidation catalysts, usually leading to conversions <50% (*vide supra*). Moreover, Gerrard *et al.* have observed that acyloxyboron species are prone to dimerisation or disproportionation, leading to the formation of bridged species (e.g. **182**) and borates, which essentially takes back to the first mechanistic explanation presented in Scheme 128.[131,132]

Based on the above observations, it is also possible that borates could proceed *via* a comparable mechanism (Scheme 130).



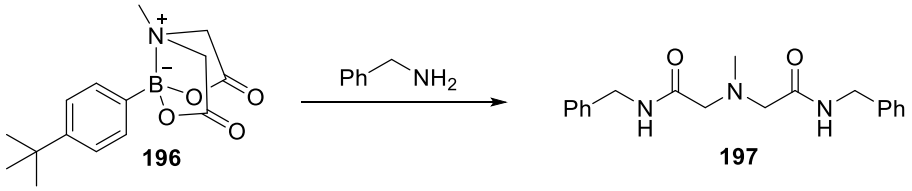
Scheme 130 Proposed reaction pathway with borate-mediated amidation

The initial formation of the salt **194** might indeed somewhat deactivate the borate, however, with heat (as the reaction does not really occur at RT), the formation of "acyloxyboron" is then likely to rearrange to a bridged derivative **195**. The bridging through the amine would occur as no water is present at this stage, which could also explain why the amide yields over a given time were lower when borate was in excess to the amine (*vide supra*, Graphs 1 and 2).

3.2.3 Experiments with MIDA boronate

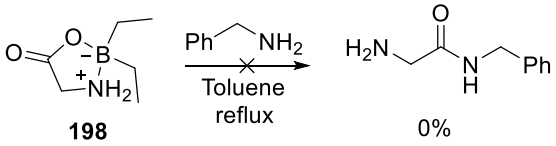
It has been generally accepted that acyloxyboron species are effective amidation reagents, which was supported by computational studies and some experimental evidence (*vide supra*). The mechanisms for boronic acid-mediated amidation proposed the activation of the carboxylic acid *via* the formation of acyloxyboron species **109**.

In order to test the reactivity of acyloxyboron compounds as acylating reagents, a brief study using MIDA boronate **196** was undertaken. If the computational predictions are correct, then it is expected that **196** would react with an amine at room temperature to form the amide **197** or its mono-amide derivative (Scheme 131).



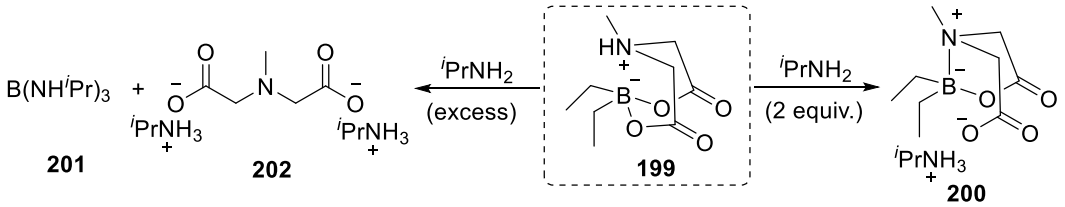
Scheme 131 MIDA boronate reaction with benzylamine

Previous reports on the MIDA borinate derivatives (i.e. B(I) oxidation level) have shown that such compounds were poor amidation reagents, however. In 1982, Zwanenburg *et al.* reported that **198** was recovered almost quantitatively after refluxing with benzylamine in toluene (Scheme 132).



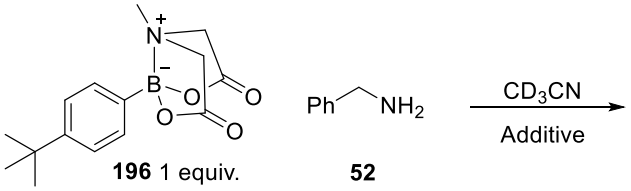
Scheme 132 Reaction of MIDA borinate derivative **198** at reflux with benzylamine

A similar result was also reported by Garrigues *et al.* in 1986 with MIDA borinate derivative **199**; when **199** was mixed with $^{i}PrNH_2$ in DMF at room temperature, no amidation took place and instead salt **200** was isolated.[133] Importantly, if an excess of the amine was used, the authors reported the formation of trisaminoborane **201** and MIDA salt **202** (Scheme 133).



Scheme 133 Reported reaction of MIDA borinate **199** with amine

We therefore tested similar reactions using MIDA boronate **196** (Table 11).



196 1 equiv. **52**

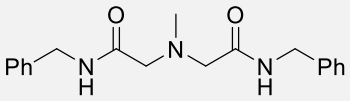
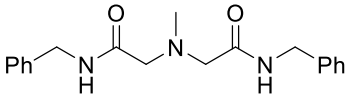
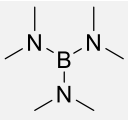
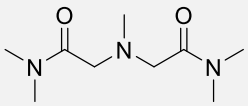
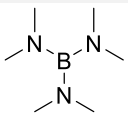
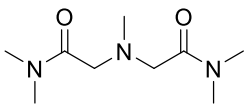
Entry	**52** (equiv.)	Additive (equiv.)	Product	Amide yield (%)
1	2	N/A	 **203**	18[a] 78[b]
2	2	$B(OCH_2CF_3)_3$ (1 equiv.)	 **203**	0[a] 88[b]
3	0	 **170** (1 equiv.)	 **204**	< 5[a]
4	2	 **170** (1 equiv.)	 **204**	44[a]

Table 11 Test reactions with MIDA boronate **196**; a. 7 days at RT; b. the reaction was performed in CPME at reflux for 24 h

All reactions were performed in CD_3CN or $CDCl_3$ at room temperature and monitored by ^{1}H and ^{13}C NMR as well as ^{11}B NMR in an attempt to identify potential boron intermediates unless otherwise stated.

When benzylamine was added to **196**, no clear interaction was observed by ^{11}B NMR or ^{1}H NMR (Appendix 7.2.3, Figure 49). The reaction proceeded very slowly with the appearance of the product in <5% yield after 48 hours. After 7 days, approximately 18% yield of the amide **203** was formed (Figure 30).

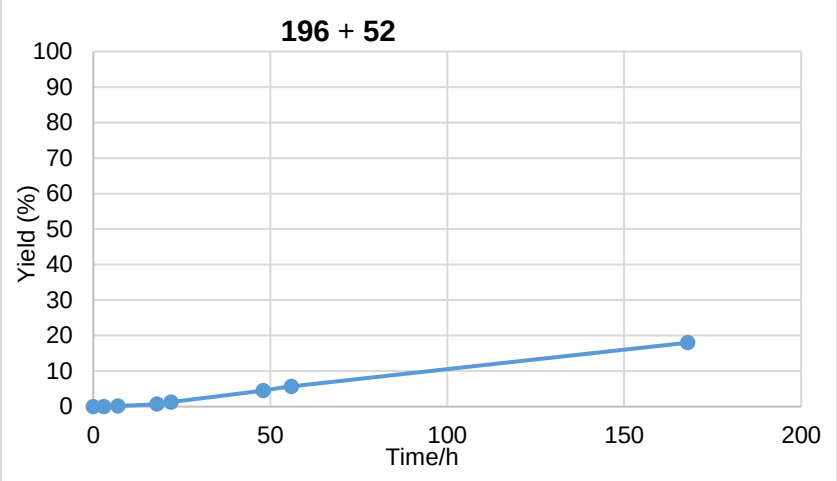
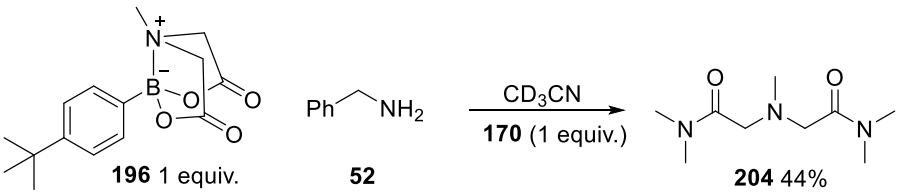


Figure 30 Reaction of MIDA **196** with amine over 7 days

When the reaction was performed in CPME at reflux, however, 78% yield of the amide **203** was formed after 24 h. The addition of $B(OCH_2CF_3)_3$ with the amine to **196** did not yield the desired product at room temperature (entry 2). The borate did not interact with **196** according to ^{11}B NMR (Appendix 7.2.3, Figure 50), and once the amine was added, the borate shifted to the tetrahedral boron species at 1 ppm which indicated the formation of the salt **162**. However, when the reaction was subjected to reflux in CPME, the yield of the amide **203** improved to 88% in contrast to when no borate was added (entry 2). Similarly, barely any amide formation was observed in the presence of borane **170** (entry 3). No apparent interaction was observed by ^{11}B NMR with only **170** being hydrolysed to possibly boric acid over time (Appendix 7.2.3, Figure 51). To our surprise, 44% of the amide **204** was formed after 7 days when **170** and benzylamine were added to **196** (Scheme 134, Figure 31).



Scheme 134 Unexpected amide **204** formation in presence of **170** and **52** with MIDA **196**

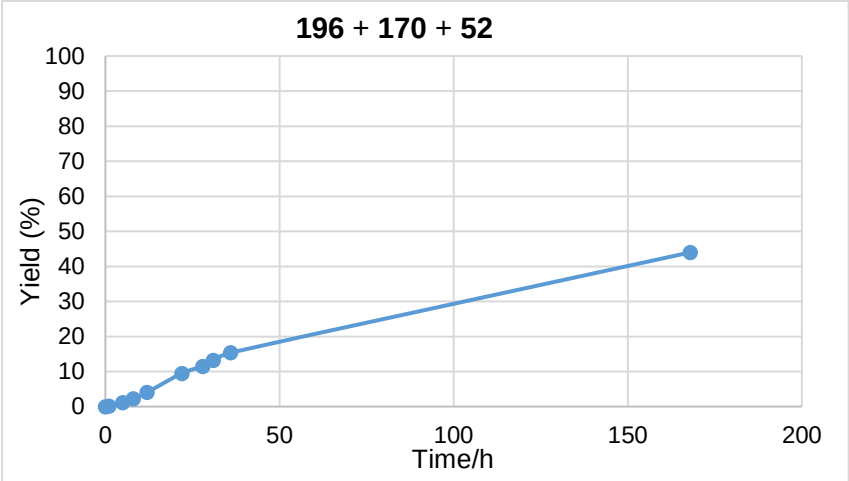


Figure 31 Reaction of MIDA **196** with amine and borane **170** over 7 days

The formation of the amide **203** was not observed in the reaction mixture. It was not possible to identify any boron species formed during this reaction, apart from hydrolysis by-products of **170** as the spectrum produced a complex mixture of products (11 species by ^{11}B NMR). Upon initial interaction, two trigonal boron species formed, but it is not possible to identify the nature of those (Appendix 7.2.3, Figure 52).

From these observations, we began to speculate that boron nitrogen coordination is of importance in the boron-mediated amidation mechanisms and that cooperative catalysis might be taking place. A suggested intermediate **205** could form to facilitate the amidation by delivering the amine (coordinated to one boron) to the carboxylic acid, which could be coordinated to the second boron, in an intramolecular fashion (Figure 32). This could explain the outcome of the reaction of MIDA boronate **196** with benzylamine and **170**, if, for example, the proposed species **206** is formed *in situ* (Figure 32).

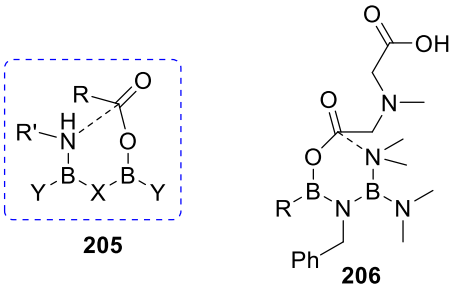


Figure 32 Proposed activation intermediates for the amidation reaction

During the course of this work, a paper was published reporting on the novel efficient amidation catalyst **50** (generating the proposed intermediate **51**), discussed in the introduction (*vide supra*), developed by Kumagai *et al.* (Figure 33).[83]

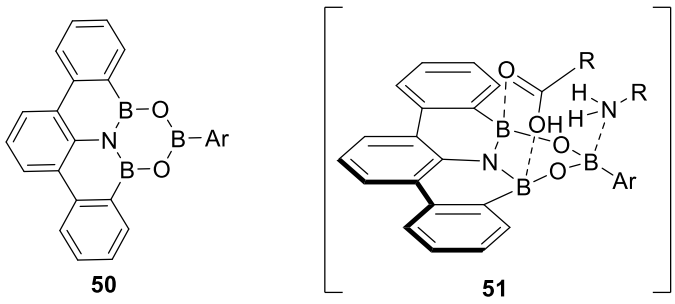
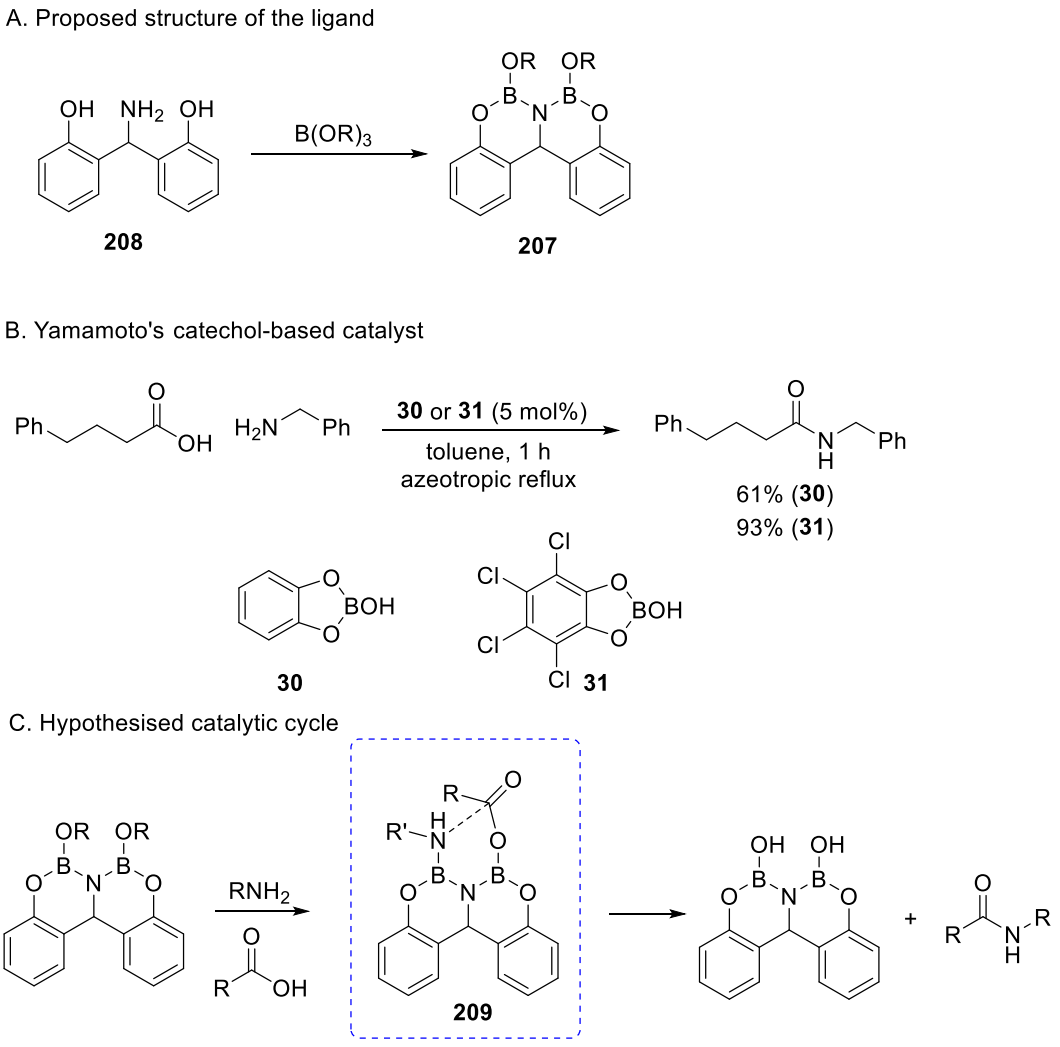


Figure 33 Kumagai's catalyst

Our observations on the dual boron cooperation could therefore explain the high catalytic activity of **50**, which was proposed to act as a surface for coordinating both amine and acid thus performing amidation in intramolecular fashion (Figure 33, **51**).

3.2.4 Synthesis of B-N-B ligand

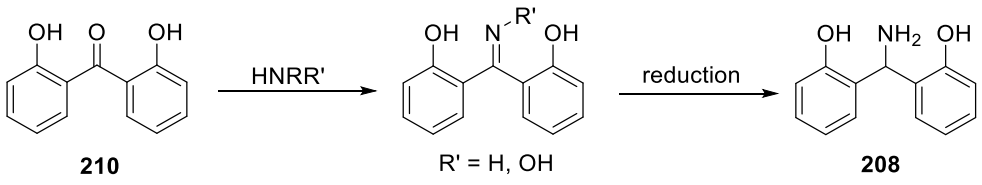
Based on the observations on possible cooperative boron interactions for the amidation, we decided to the test this hypothesis and develop a ligand which could be attached to the borate reagents with the aim of improving reactivity. The synthesis of a compound **207** was proposed as the first-generation catalyst (Scheme 135A). It was envisaged that such a ligand might act in a similar manner to catecholborol **30** successfully employed by Yamamoto *et al.* in a catalytic manner for the amidation reaction (Scheme 135B).[69] However, in case of **207** two boron centres would be available for intramolecular reaction *via* the proposed intermediate **209**, making the delivery of an amine to the carboxylic acid more efficient, much like Kumagai's catalyst **50** (Scheme 135C).



Scheme 135 Hypothesised synthesis of a dual boron catalyst

The ligand **208**, however, was not commercially available and therefore needed to be synthesised.

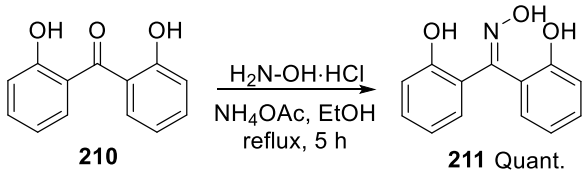
The most convenient route would be by the reductive amination of a benzophenone derivative **210** (Scheme 136).



Scheme 136 Proposed synthetic route to **208**

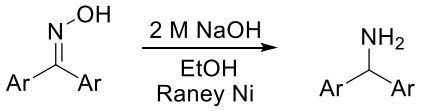
The most commonly reported routes from benzophenones to amines are the reduction of the corresponding oximes, synthesised from benzophenones and hydroxylamine in the presence of a base. The reaction of **210** with hydroxylamine

hydrochloride in the presence of NH_4OAc proceeded smoothly and the desired oxime **211** was isolated in quantitative yield (Scheme 137).



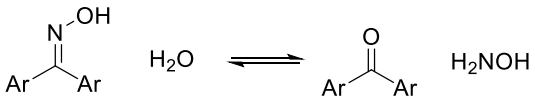
Scheme 137 Oxime synthesis

Only one literature precedent for the reduction of **211** was reported by Lawson *et al.* in 1968.[134] The researchers adopted a procedure developed earlier by Staskun *et al.* using Raney Nickel in a strongly alkaline reaction mixture to reduce oximes to amines (Scheme 138).[135]



Scheme 138 RaNi-mediated reduction of an oxime

However, due to lack of experimental details, we were unable to reproduce the results and no conversion to the desired product was observed. Mainly unreacted starting material **211** was recovered and the presence of ketone by-product **210** was detected. Staskun has highlighted that this was the case when heat was applied, proposing that the hydroxylamine, released in equilibrium, was decomposed by Raney Ni (Scheme 139).[135]

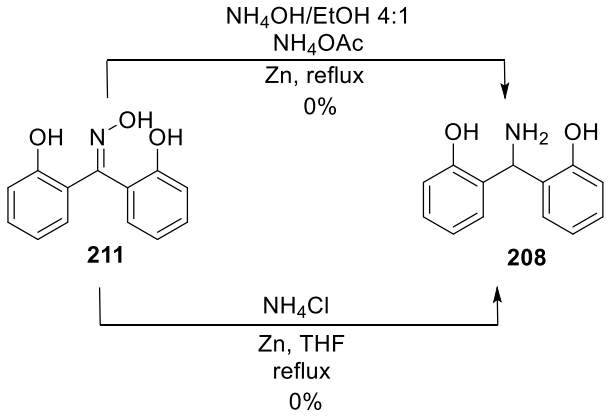


Scheme 139 Possible decomposition of oxime

The reaction for the substrate **211** was performed at room temperature, however. Introduction of hydrogen environment and increasing the pressure to 50 Psi with or without heating did not push the reaction to the desired product either, only resulting in **211** and **210**.

We therefore decided to revisit the literature and attempt other methods reported for similar substrates. The most common approach for the reduction of benzophenone derived oximes was *via* Zn-mediated reduction. Most reported procedures use zinc in an ammonia solution for reduction,[136] however, with the substrate **211** the reaction did not work and only ketone product **210** was isolated (Scheme 140). Zn-mediated reduction for a relatively similar structure, but with only one hydroxyl group

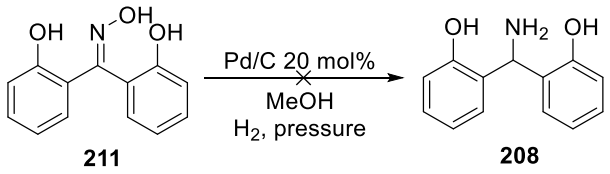
on the ortho position using dry conditions and ammonium chloride as the hydride source was also attempted.[137] Unfortunately, this method was not suitable for the reduction of **211** and no conversion to the amine **208** was observed (Scheme 140).



211 **208**

Scheme 140 Attempted Zn-mediated reduction

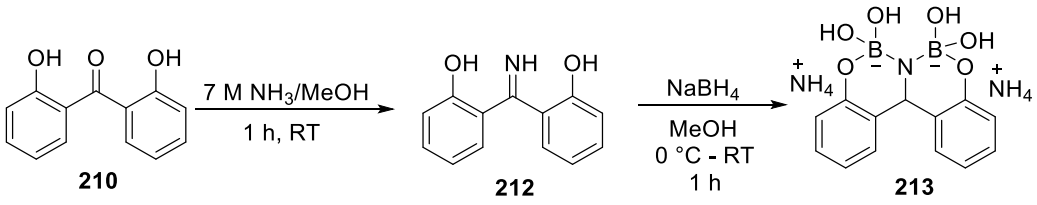
Palladium on carbon is often applied to the reduction of oximes, and this method has been previously used on similar systems and was therefore tested on oxime **211** (Scheme 141).



211 **208**

Scheme 141 Attempted Pd/C-mediated amidation

The reaction proved unsuccessful and no product was obtained even with increased catalysts loading, pressure (50 Psi), and temperature (reflux). As the reduction of the oxime **211** proved to be troublesome, it was decided to make a more reactive imine **212**. The imine was synthesised using 7 M NH_3 solution in methanol, which proceeded successfully to full conversion. The crude product was then used directly in the reduction using $NaBH_4$ in methanol (Scheme 142).



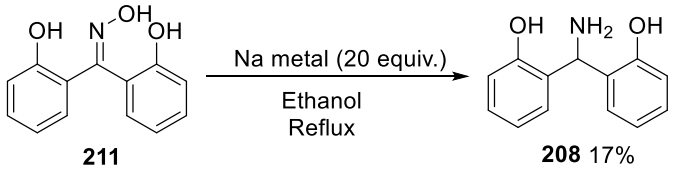
210 **212** **213**

Scheme 142 Successful imine reduction with $NaBH_4$

Pleasingly, the reaction proceeded successfully with an almost immediate reduction into the desired amine. However, ^{11}B NMR suggested that boric acid incorporated

itself into the ligand with ammonia counterion making the salt **213**, which made the compound highly insoluble. Attempts to break it out of the chelation were not successful. An attempt to replace the boric acid with $B(OCH_2CF_3)_3$ or trimethyl borate did not work either, as well as simple Dean-Stark reflux of the compound in the presence of an alcohol (methanol or trifluoroethanol). It was decided to test **213** in the amidation reaction as a catalyst anyway, since boron had incorporated itself already, which would make this procedure very efficient and cheap. Unfortunately, the catalyst had no activity whatsoever perhaps due to poor solubility, *vide infra* (entry 7, Table 12).

Sodium metal reduction of **211** in refluxing ethanol was attempted next (Scheme 143).

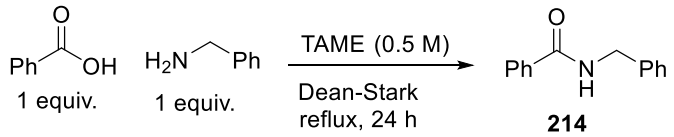


211 **208** 17%

Scheme 143 Successful synthesis of the ligand **208**

The reaction was successful and the desired amine **208** was isolated in 17% yield. A large excess of sodium was required for the reaction to go this far, however, which would not be a practical approach for the large scale synthesis of the ligand. This, however, produced enough material to work with.

The ligand was then subjected to the reaction conditions used for the catalytic amidation with $B(OMe)_3$ using a Dean-Stark as a method for water removal (Table 12).



Entry	$B(OMe)_3$	208	Conditions	Yield
1	10 mol%	-	15 h	27%
2	10 mol%	-	24 h	61% (53%)
3	10 mol%	5 mol %	$B(OMe)_3$ and **208** pre-mixed and refluxed for 1 h, 15 h reaction	28%
4	10 mol%	5 mol%	$B(OMe)_3$ and **208** pre-mixed and refluxed for 3 h	47% (42%)
5	10 mol%	5 mol%	**208** added to the reaction mixture, 15 h reaction	25%
6	10 mol%	5 mol% **213**	$B(OMe)_3$ and **213** pre-mixed and refluxed for 3 h	36%
7	-	5 mol % **213**	**213** added to the reaction mixture	0%
8	-	-	-	0%

Table 12 Yields determined using 1,4-dimethoxybenzene as internal standard; isolated yields in parenthesis

The ligand was mixed with $B(OMe)_3$, which alone is a relatively inefficient catalyst for the amidation using these conditions (entries 1 and 2).

To our disappointment, the ligand did not offer any improvement in the conversion to the product **214**, and only seemed to reduce the activity of the catalyst. Therefore, the best conversion was observed when $B(OMe)_3$ was used alone with 53% yield of **214** isolated (entry 2).

Due to time constraints, this project was not pursued further. It is possible that the catalyst **207** is deactivated once the amine is added to the reaction mixture, resulting in a similar salt to **213**. One possible improvement could be *via* tuning the aromatic ring with electron-withdrawing groups to improve the reactivity. This has been previously demonstrated by Ishihara and Yamamoto *et al.* where the catalytic activity of catecholborol **30** was improved with the introduction of chloro substituent on the aromatic ring to afford the catalyst **31** (Scheme 135B, *vide supra*).[69]

4. Synthesis of a hybrid catalyst

It was hypothesised that an appropriately designed catalyst, a hybrid of boronic acid and borate, could offer a solution to overcoming the disadvantages that both borate reagents and boronic acids carry. Boronic acids, although used catalytically, usually require highly dilute conditions and non-polar solvents, which somewhat limits the substrate scope. Borates, particularly $B(OCH_2CF_3)_3$ (*vide supra*), have shown a good substrate scope in both CPME and MeCN allowing access to a wide range of heavily functionalised amides as well as the direct amidation of unprotected amino acids. However, the recovery of the borate reagent at the end of the reaction is not possible due to the hydrolysis into boric acid. Moreover, it was found that the conditions were often not compatible with substrates prone to racemisation. We therefore envisaged the synthesis of a catalyst of general structure **215** with pendant "arms" bearing hydroxyl moiety to on the sides of arylboronic acid, therefore resembling both classes of reagents (Figure 34).

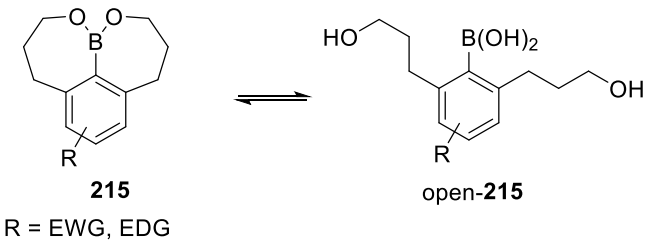
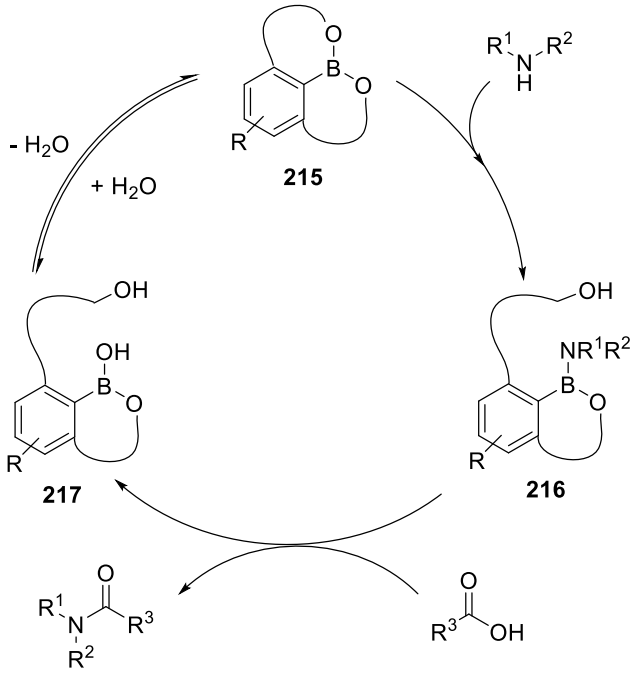


Figure 34 Proposed hybrid catalyst structure

The electronics of the catalyst could then be tuned with different substituents on the aromatic ring or the side arms. It was proposed that the length of the arm would be suitable for the lactonisation to occur for the prevention of oligomer formation under high concentration of the reaction, but also be unstable enough to open the boronic acid moiety for the catalyst to be active for amidation.

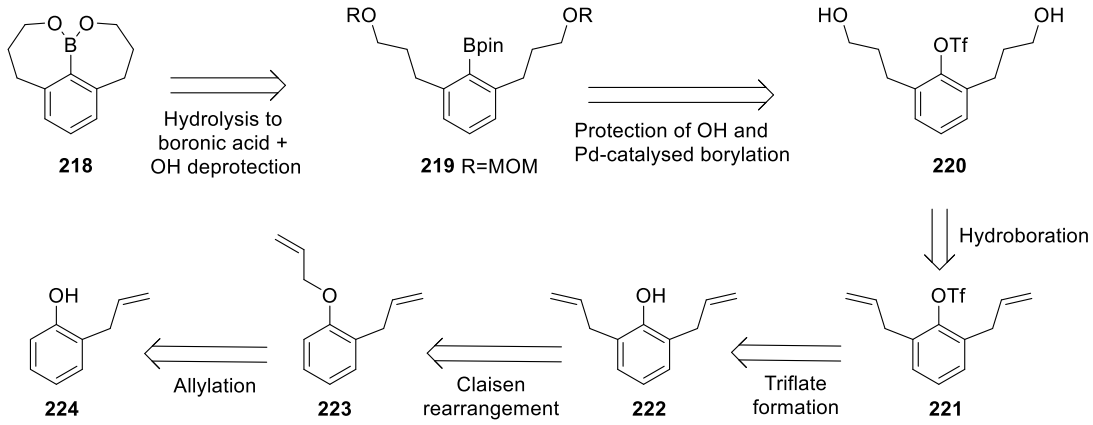
The proposed catalytic cycle is represented in Scheme 144.



Scheme 144 Proposed catalytic cycle of the hybrid catalyst **215**

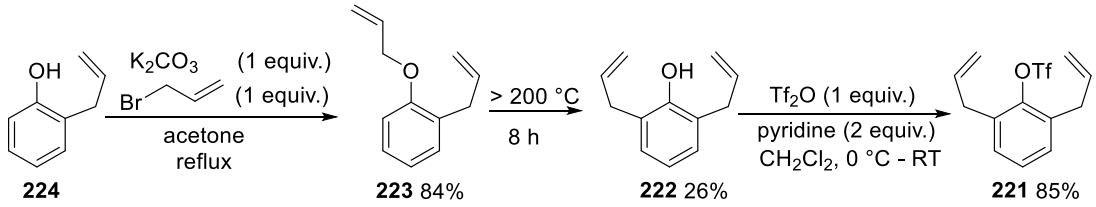
It was hypothesised that after amine could coordinate to **215** in a similar manner to interaction with borates. This would then be followed by the amidation of a carboxylic acid producing a ring-opened catalyst **217**, which subsequently can re-cyclise *via* loss of water molecule to regenerate the catalyst **215**.

We firstly focused our attention on the synthesis of arylboronic acid **218** without additional substituents on the aromatic ring. Since an aromatic compound with a halo or phenol moiety and pendant arms on either side already attached was not commercially available, we sought to synthesise the target catalyst **218** *via* the route represented in Scheme 145.



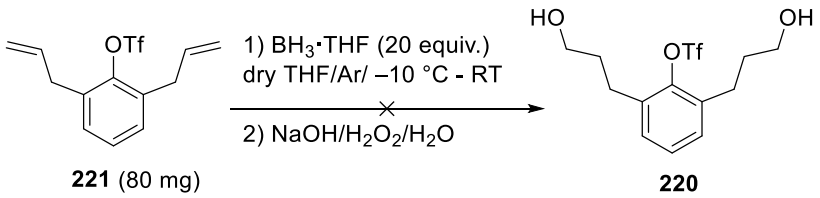
Scheme 145 Retrosynthetic route to the first generation hybrid catalyst **218**

The aromatic triflate **221** was synthesised using the reported route by Edwards *et al.*.[138] in 18% yield over three steps on 20 g scale (Scheme 146). The successful allylation of **224** was followed by the less efficient Claisen rearrangement reaction. The yield of **222** was significantly lowered by the presence of a large amount of decomposition, possibly *via* polymerisation. The next step, reaction of **222** with triflic anhydride, however, proceeded well and the product **221** was isolated in 85% yield.



Scheme 146 The route to **221** reported by Edwards *et al.*.

We then proceeded to the hydroboration of **221**. In our first trial it was decided to use 0.5 M BH_3·THF reagent to synthesise **221** following the procedure reported by Shi *et al.* on a similar substrate, containing a methoxy group instead of the triflate moiety.[139] Unfortunately, with this procedure the desired product **220** was not obtained (Scheme 147).



Scheme 147 Attempted hydroboration using BH_3

After purification by flash column chromatography, two unexpected products were isolated with some recovery of starting material **221** in 23% yield and phenol **222** in 21% yield. 8-Allylchroman-3-ol **225** was isolated as the major product in 39% yield. It is unclear as to how the formation of **225** occurred, however, the BH_3 reagent was clearly unselective to the hydroboration at the terminal end of the alkene. It is difficult to state with certainty the exact structure of the second isolated compound, but all data collected suggested the structure **226**. A possible explanation to the formation of **226** is that the BH_3·THF reagent is BHT stabilised (which contains the *tert*-butyl group), which may have interacted with the main reaction leading to the formation of **226**.

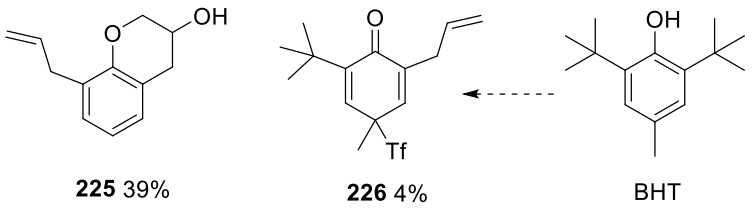
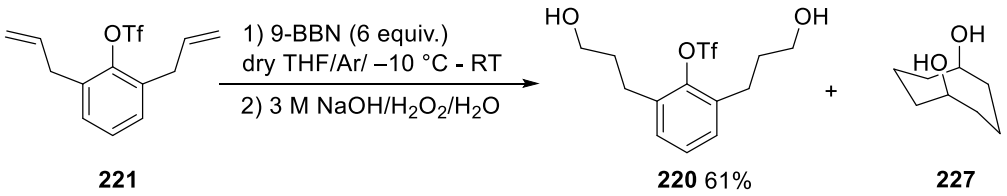


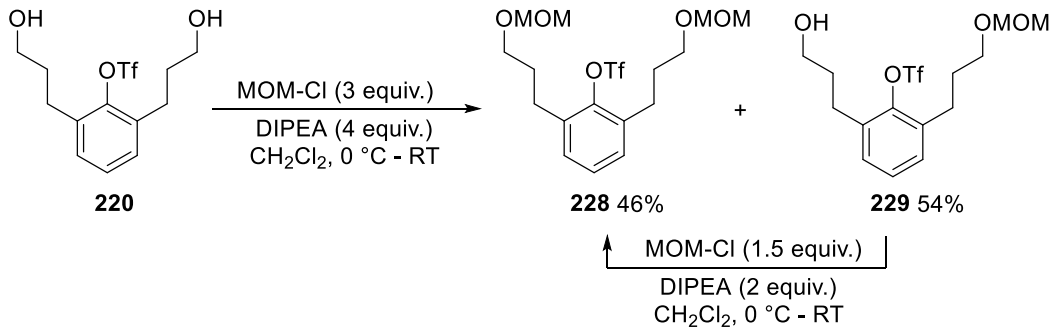
Figure 35 Unexpected by-products isolated from hydroboration of **221** using BH_3

We therefore used a bulkier hydroborating agent 9-BBN to ensure hydroboration occurred on the terminal end of the alkene. A procedure reported by Ganton and Kerr was adopted,[140] which in their case was applied to a similar compound, but with only one allylic group attached to the aromatic ring. Pleasingly, this reaction worked well giving 61% yield of the product **220** (Scheme 148).



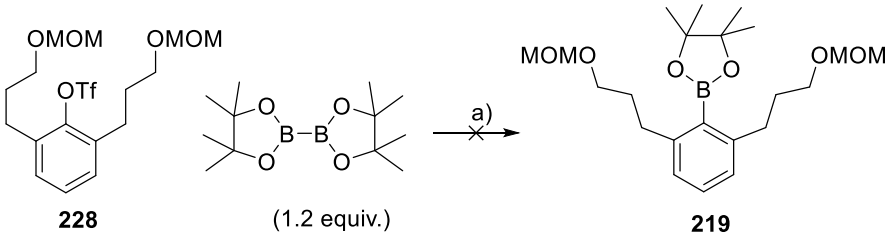
Scheme 148 Successful hydroboration using bulkier 9-BBN

The hydroxyl groups were then protected using MOM-Cl to yield **228** in 46% yield and **229** with MOM group on only one of the hydroxyl isolated in 54% yield, presumably formed because the reaction did not reach completion (Scheme 149). The second hydroxyl could then be protected using the same conditions resulting in quantitative overall yield.



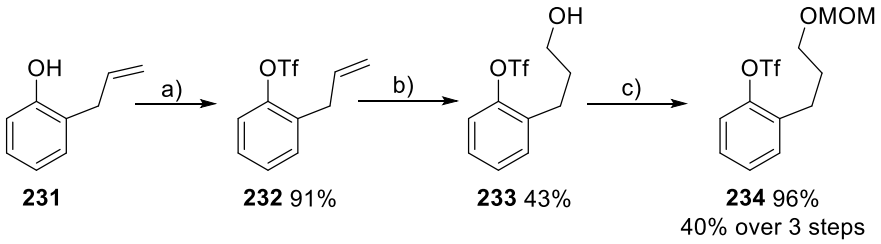
Scheme 149 Protection of hydroxyl groups with MOM

Finally, **228** was subjected to a Pd-catalysed borylation reaction (Scheme 150). The most common conditions used for a variety of systems react triflates with bis(pinacolato)borane in the presence of KOAc in 1,4-dioxane. An initial attempt at the synthesis of **219** did not yield positive results, as the triflate **228** was completely unreactive and remained in the reaction mixture after 4 days at reflux.



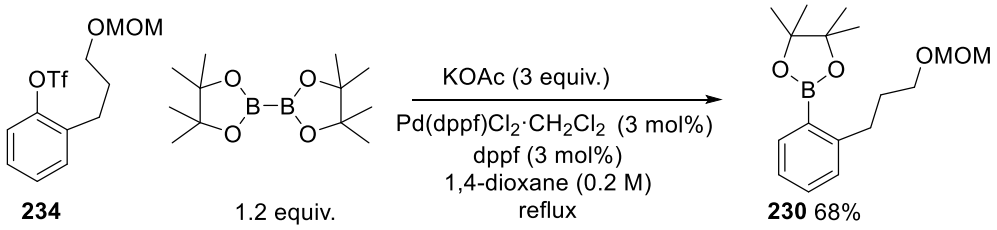
Scheme 150 Attempted Pd-catalysed borylation; a) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (3 mol%), dppf (3 mol%), KOAc (3 equiv.), dioxane (0.2 M), reflux

It was decided to test the reaction of a less sterically hindered substrate **230** bearing only one *ortho*-allyl group (Scheme 151). The synthetic route to **230** was similar to **219** but avoiding allylation of phenol followed by the Claisen rearrangement. The synthesis of **234** proceeded smoothly with 40% yield over three steps.



Scheme 151 Trial synthetic route with one sidearm; a) Tf_2O (1.1 equiv.), pyridine (1.5 equiv.), CH_2Cl_2, 0 °C-RT; b) 9-BBN (3 equiv.), THF, −10 °C - RT, then 3 M $NaOH/H_2O_2/H_2O$; c) MOM-Cl (1.5 equiv.), DIPEA (2 equiv.), CH_2Cl_2, 0 °C - RT

To our satisfaction, when subjected to the same borylation conditions, the borylation worked well and the product **230** was isolated in 68% yield (Scheme 151).



Scheme 152 Test borylation of a less bulky substrate **230**

Encouraged by the positive result, we repeated the reaction, but with higher catalyst loading (20 mol%). Unfortunately, after 4 days of reflux, mostly starting material was isolated alongside with by-product **235** in 29% yield (Figure 36).

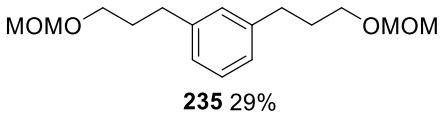
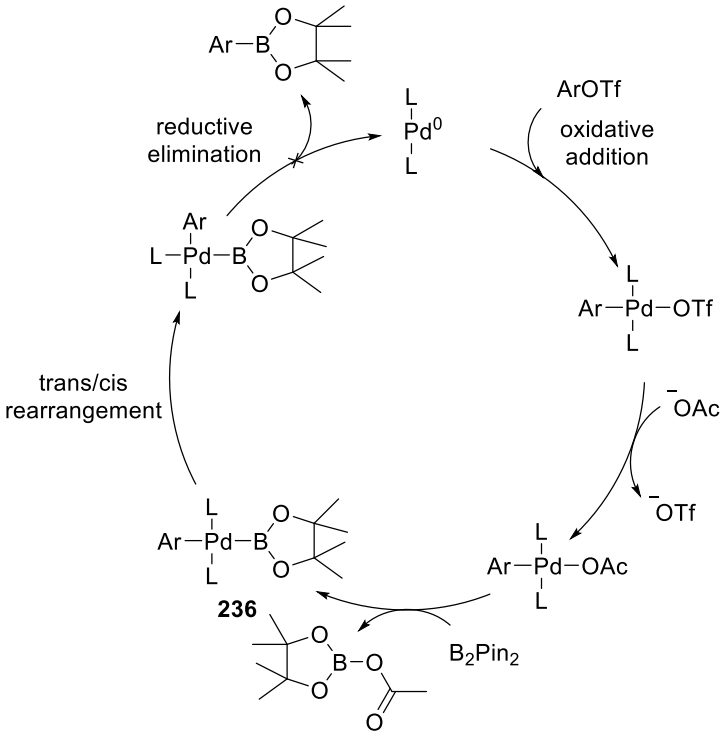


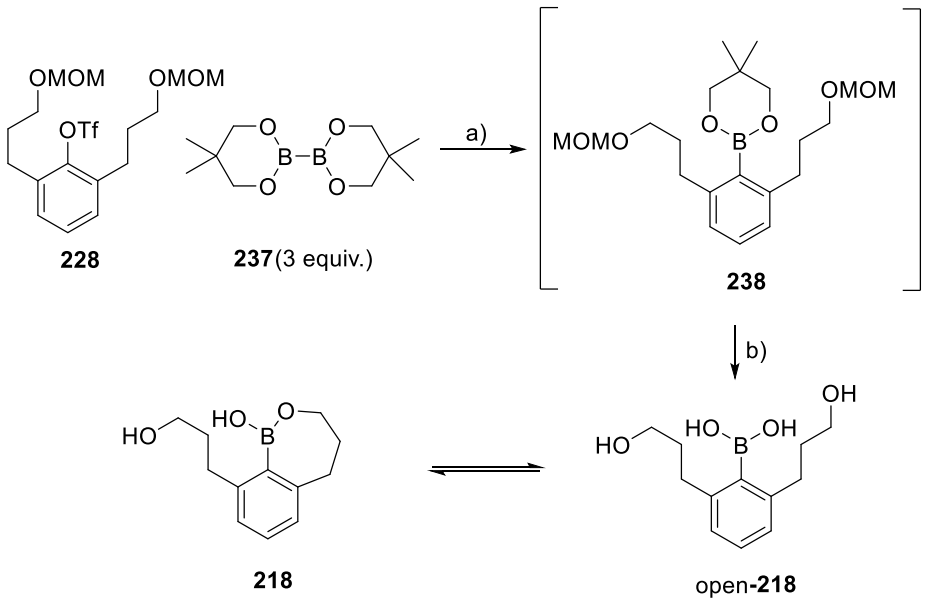
Figure 36 Major product from borylation of **228**

This suggests that although Pd was able to perform the oxidative addition between the aryl ring and the triflate, and perhaps incorporation of the boron occurred, either the trans/cis rearrangement of the Pd complex **236**, or the reductive elimination step was disfavoured due to the sterically hindered position on the aryl ring (Scheme 153).



Scheme 153 Proposed mechanistic explanation of failed borylation

For the next attempt, a less bulky bis(neopentyl glycolato)diboron **237** was used. To our satisfaction, the desired product **238** was formed. The crude mixture was directly subjected to HCl hydrolysis in methanol at reflux and the deprotected product was then purified by flash column chromatography to yield the desired boronic acid **218** in 27% yield over two steps (Scheme 154).



Scheme 154 Successful borylation using a less bulky diboron followed by deprotection to yield target catalyst **218**; a) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10 mol%), dppf (10 mol%), KOAc (5 equiv.), dioxane (0.2 M), reflux, 2 days; b) 3 M HCl/MeOH, reflux, 5 h

Boronic acid **218** exists mainly in an open form **218.1** in the presence of water, whereas form **218.2** is favoured when no water is present (Figure 37).

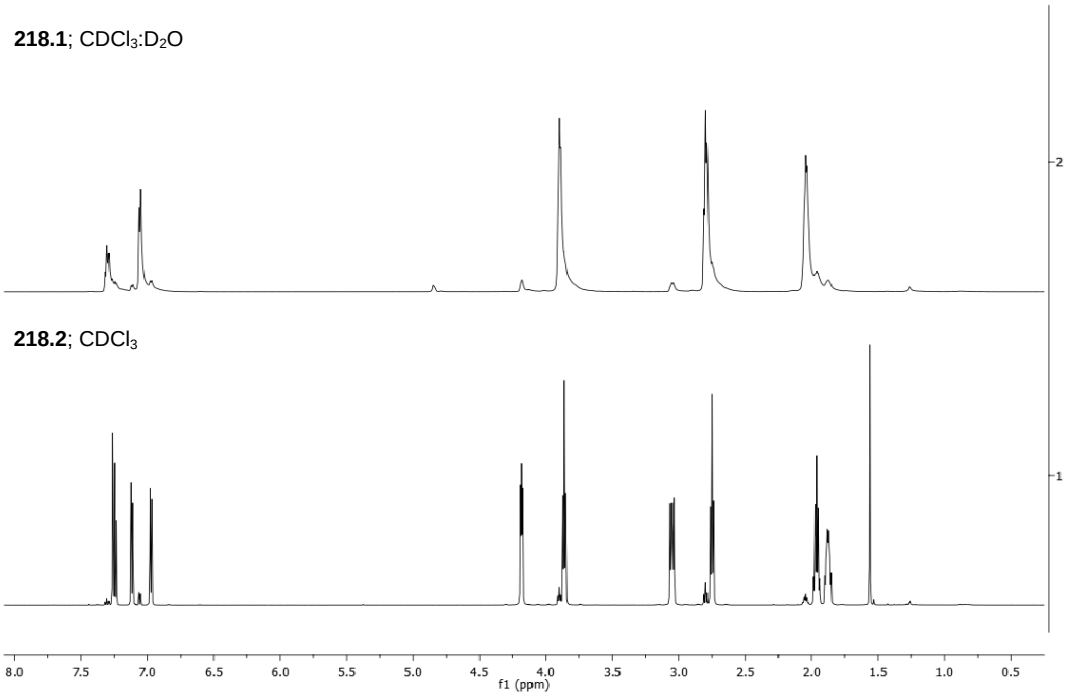
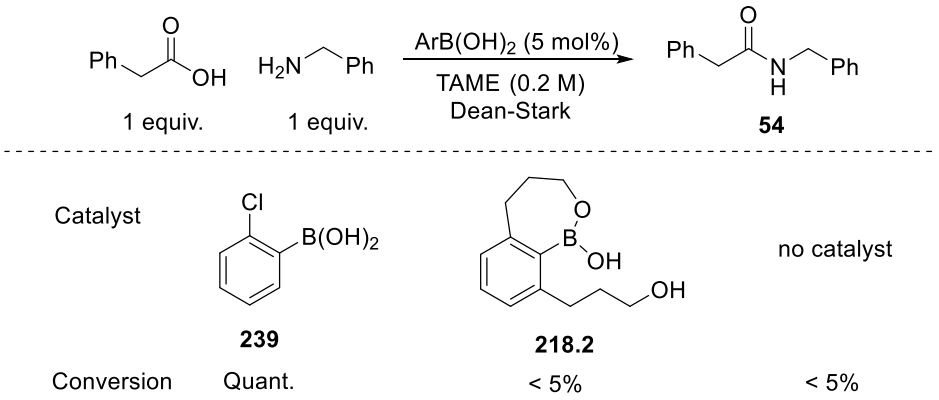


Figure 37 ^1H NMR of boronic acid **218** in $CDCl_3$:D_2O (**218.1**) and in $CDCl_3$ only (**218.2**)

When ^1H NMR was collected in $CDCl_3$:D_2O, the major peaks appear to be for the symmetric conformation **218.1** with water hydrolysing ester to boronic acid.

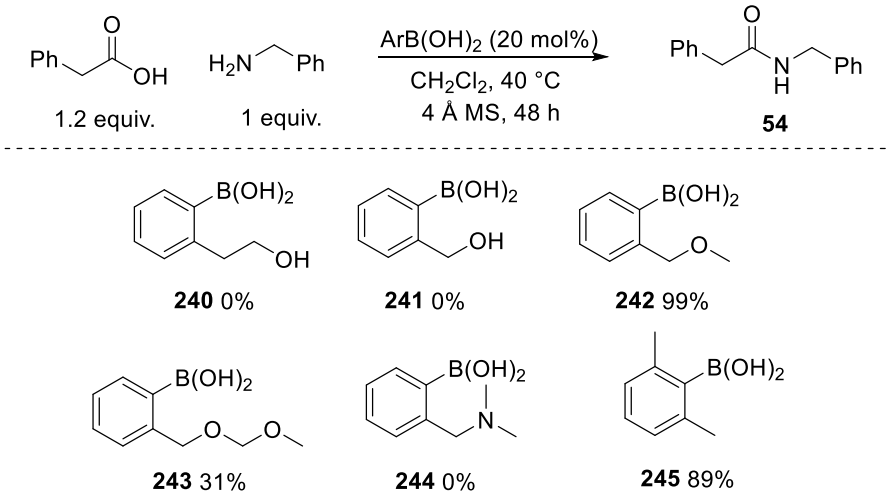
However, lactonisation of only one of the arms is favoured forming an unsymmetrical **218.2** in $CDCl_3$ without additional water (Figure 37).

The hybrid catalyst was then tested using Yamamoto's[63] previously reported conditions for boronic acid catalysis with azeotropic water removal, but in TAME as a solvent (to avoid background reaction), and compared against 2-chlorophenyl boronic acid **239**, which had previously been shown to have good catalytic activity by Hall *et al.*[39] in amidation at room temperature in CH_2Cl_2 (Scheme 155). Boronic acid **239** resulted in an excellent conversion to the amide **54**. Unfortunately, less than 5% product was obtained with the catalyst **218**, which essentially meant that it exhibited no catalytic activity, as the same result was obtained without the catalyst.



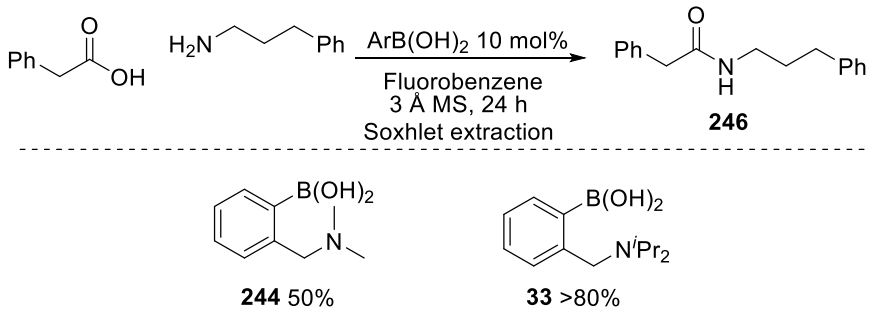
Scheme 155 Testing the reactivity of the catalyst **218.2** against 2-chlorophenylboronic acid **239**. Yields determined by ^{1}H NMR using 1,4-dimethoxybenzene as internal standard

This outcome is in part supported by observations previously made by Hall *et al.* using boronic acids with similar structures (Scheme 156).[39] Before the group arrived at *ortho*-halogen boronic acids being good amidation catalysts, they performed a large study on a variety of *ortho*-substituted arylboronic acids (> 40), including "hydroxyl arms". Arms that contained nucleophilic moieties, such as non-bulky amines (**244**) and free hydroxyl groups (**240-241**) had limited activity unless protected to prevent coordination to boron. Boronic acid **242** with the methyl ether group on the side-arm, on the other hand, resulted in full conversion to the desired product **54**.



Scheme 156 Hall's reported ortho-substituted arylboronic acids in amidation reaction

A higher reactivity of boronic acid **244** was observed by Whiting *et al.* when subjected to reflux in fluorobenzene, resulting in 50% conversion to the amide **246**. However, the much bulkier amine arm in boronic acid **3** led to over 80% conversion under the same conditions (Scheme 157).[121]



Scheme 157 Whiting's boronic acids with pendant arms

This suggests that the "hybrid" catalyst **218** might benefit from the presence of bulky protecting groups or methyl ether to avoid the strong coordination to boron, which heavily restricts the catalytic activity of the boronic acid. Alternatively, tuning the aromatic ring or the side-arms with a more electron withdrawing moiety might also favour the instability of the lactone and aid the catalytic activity.

Unfortunately, due to time constraints, these possibilities were not investigated, and might be addressed in the future.

5. Conclusions & Future Work

This thesis has focused on further developments of $B(OCH_2CF_3)_3$-mediated amidation and mechanistic investigations of boron-mediated amidation reaction, followed by attempts in the synthesis of improved boron-based catalysts.

Applications of $B(OCH_2CF_3)_3$ and outcomes of this project are summarised in Figure 38.

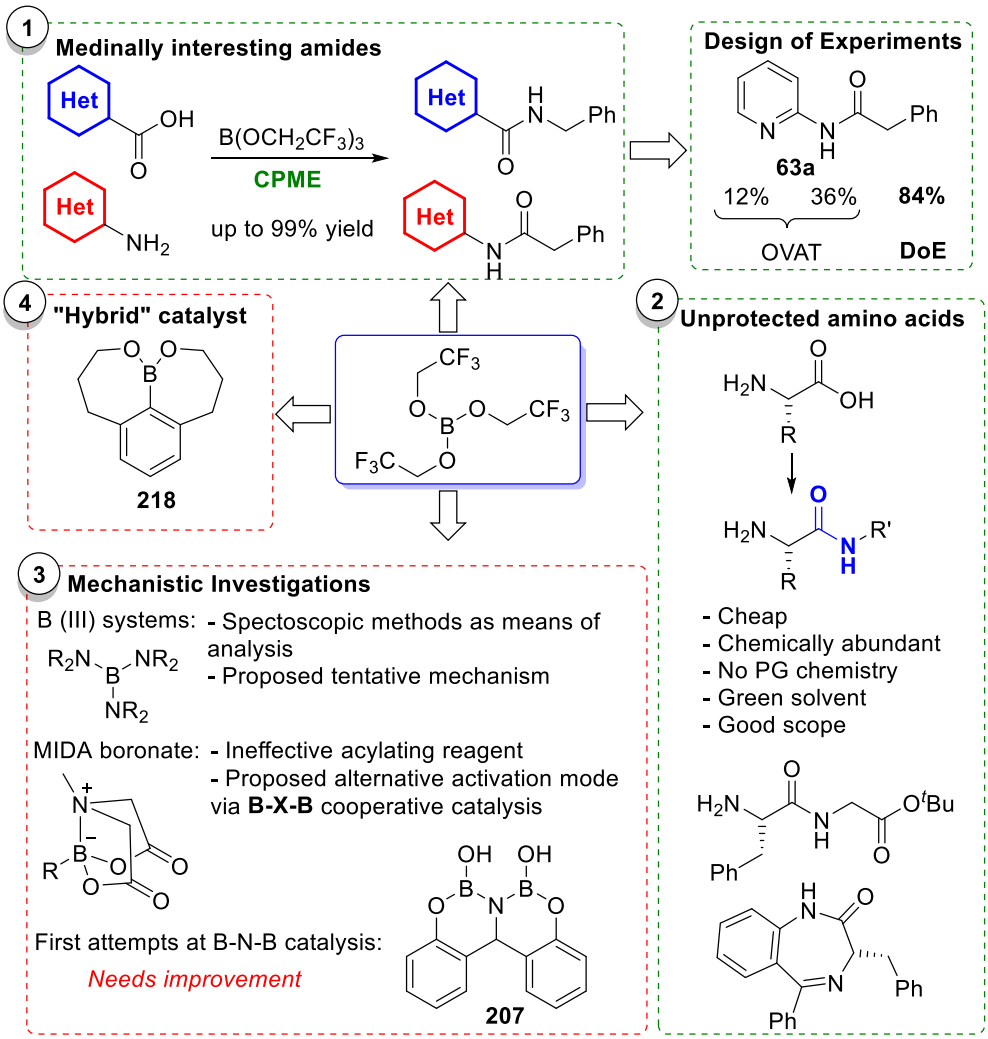


Figure 38 Project map

1. Medicinally interesting amides

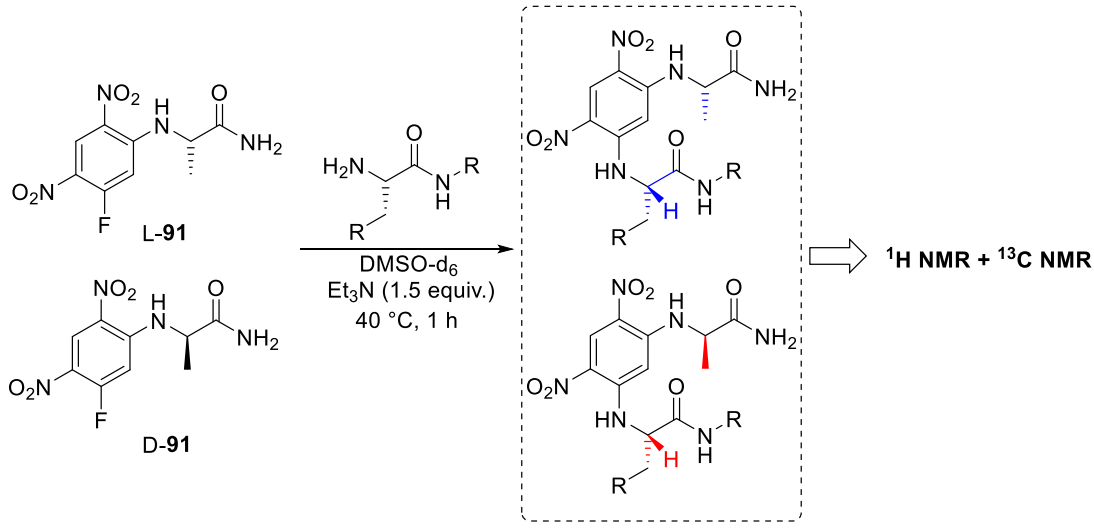
The synthesis of medicinally relevant highly functionalised amides (36 examples) was demonstrated using $B(OCH_2CF_3)_3$ employing a greener alternative solvent to MeCN, CPME.[141] Moreover, we successfully applied an emerging optimisation method, Design of Experiments, to improve the efficiency of the borate-mediated amidation reaction to form the amide **63a**. It was shown that temperature had a significant impact on the conversion to the product. Although the software did not

detect the importance of the relative equivalents of acid and amine, it was found that an excess of one or the other was beneficial for high conversion to the product; 100% conversion (84% isolated yield) was obtained when 3 equivalents of the acid or amine was used at 125 °C in CPME with 3 equivalents of $B(OCH_2CF_3)_3$ after 24 hours. However, the amine:acid ratio could be decreased to 1:1 whilst retaining high conversions to the product when the reaction temperature was increased to 140 °C using Bu_2O as the solvent.

Moreover, the scope of selective monoacylation of symmetrical diamines was investigated with good selectivity for monoamide products observed in several examples.

2. Unprotected amino acids

$B(OCH_2CF_3)_3$ was also shown to be a good reagent for the direct amidation of unprotected amino acids.[85,142] An extensive scope was investigated, with a dipeptide and benzodiazepine derivative synthesised. Due to the necessity of a convenient method for determination of enantiopurity of the products, an efficient derivatisation procedure was applied using Marfey's reagents L-**91** and D-**91** (Scheme 158).



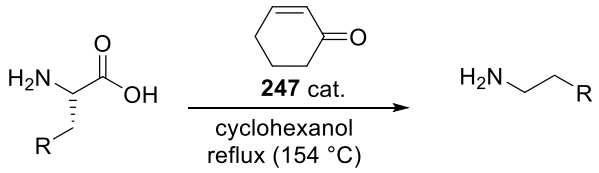
Scheme 158 Marfey's reagent for derivatisation of amino amide products

It is a fast and simple method which was reliable and applicable to the majority of the amino amide products synthesised. Unfortunately, this has revealed the major limitation of the borate-mediated amidation of unprotected amino acids – high levels of racemisation were observed in many cases. Although the majority of the amino amides were obtained in good yields, the racemisation is an issue that needs to be addressed further.

Some of the amino acid amides were synthesised catalytically with 20 mol% $B(OCH_2CF_3)_3$ with the aid of Dean-Stark for water removal (developed by Marco Sabatini[120]). Unfortunately, the method did not offer a solution to prevent the racemisation issue, and in some cases, the enantiopurity eroded to an even higher degree than with the stoichiometric method. Interestingly, when the catalytic method was applied to the synthesis of benzodiazepine derivative **107i**, it was found that decarboxylation of the amino acid took place instead of the cyclisation giving imine **108** in 45% yield (Scheme 91, *vide supra*).

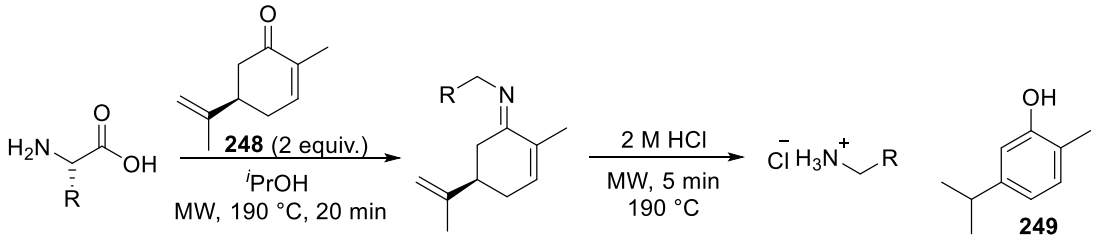
Decarboxylation of amino acids is a well-established process, which gives access to a variety of amines that are important in biological structures. The majority of procedures rely on thermally-assisted decarboxylation with the aid of a carbonyl group: an aldehyde or a ketone.[134,143–145] Enzyme catalysed decarboxylation is also widely used.[146,147]

In 1968, Lawson *et al.* used a range of benzophenones in the synthesis of Schiff bases *via* thermal decarboxylation of amino acids.[134] In 1986, Hashimoto *et al.* reported 2-cyclohexene-1-one **247** as an efficient catalysts for decarboxylation of α-amino acids in refluxing cyclohexanol (Scheme 159)I.[143]



Scheme 159 Decarboxylation of amino acids with the aid of **247**

More recently, Morrison *et al.* used (*R*)-carvone **248**, an essential oil derived from caraway seeds, as the catalyst for decarboxylation of amino acids assisted by MW heat (Scheme 160).[145]

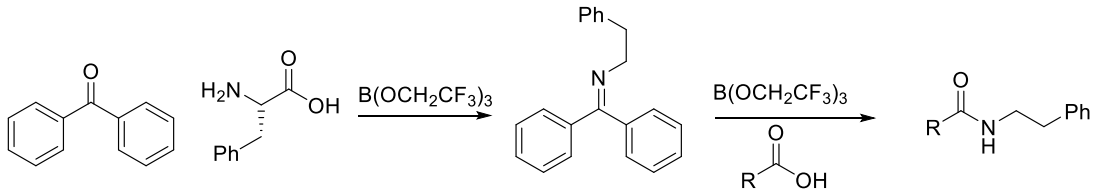


Scheme 160 (*R*)-carvone mediated decarboxylation

The procedure was rapid and simple with 12 of the 20 natural amino acids successfully converted to biogenic amines. However, the hydrolysis step to obtain

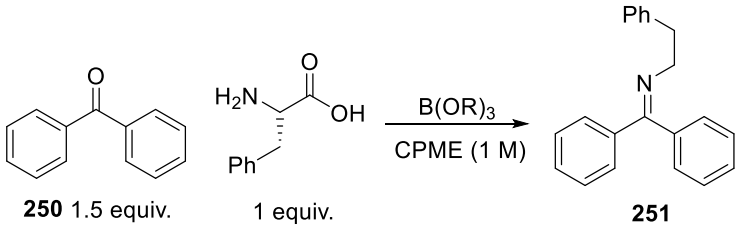
amides also resulted in isomerisation of carvone to **249**, making the procedure not recyclable.

With $B(OCH_2CF_3)_3$, however, lower reaction temperatures were used for the successful decarboxylation and therefore in the future this could be further optimised to reduce prolonged reaction times and use a less expensive ketone (e.g. benzophenone). Ultimately, a one-pot procedure for decarboxylation followed by acylation of the amine could be developed (Scheme 161).



Scheme 161 Proposed one-pot synthesis of amides with biogenic amines

We tested whether benzophenone **250**, being a cheaper substrate, could be used for decarboxylation instead of 2-aminobenzophenone (Table 13).



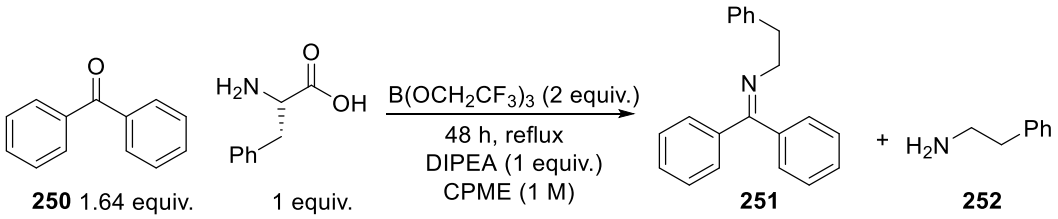
Entry	Borate	Method	Yield (%)[a]
1	$B(OCH_2CF_3)_3$ (20 mol%)	Reflux, 4 days	76
2	$B(OCH_2CF_3)_3$ (20 mol%)[b]	Reflux, 4 days	50
3	0	125 °C, 2 days; DIPEA	32
4	0	125 °C, 2 days	7
5	$B(OCH_2CF_3)_3$ (2 equiv.)	125 °C, 2 days	76
6	$B(OH)_3$ (2 equiv.)	125 °C, 2 days	17%
7	$B(OMe)_3$ (2 equiv.)	125 °C, 2 days	30%

Table 13 Test reactions with varying conditions for decarboxylation of L-Phe; a. Yields determined by ^1H NMR using 1,4-dimethoxybenzene as internal standard; b. Bu_2O used as the solvent;

When catalytic amounts of the borate were used, the reaction proceeded well, but over prolonged reaction time (entry 1). Reaction in Bu_2O at higher temperature was not beneficial (entry 2). Importantly, decarboxylation also occurred at higher temperatures in CPME without the catalyst in 32% yield after 2 days in the presence of DIPEA (entry 3). Without the additives, decarboxylation was inefficient and only

7% yield of **251** was observed (entry 4). Increasing the number of equivalents of $B(OCH_2CF_3)_3$ resulted in 76% yield over 2 days (entry 5). Boric acid and trimethylborate were also tested to provide comparison and determine whether a cheaper alternative to $B(OCH_2CF_3)_3$ could be used (entries 6 and 7). However, $B(OCH_2CF_3)_3$ remained the best reagent for this purpose.

A brief DoE study was undertaken in an attempt to optimise the decarboxylation reaction with the aim of developing a catalytic decarboxylation with respect to both benzophenone and $B(OCH_2CF_3)_3$ (Appendix 7.3). MODDE 10 was used for the processing of the results (performed by Dr Tom Sheppard). According to the model, an excess of benzophenone was essential for higher conversions. Moreover, 2 equivalents of borate and the presence of DIPEA also favoured higher conversion to the product. Concentration was found to be an unimportant factor. The software suggested the following conditions with the prediction of 83% overall yield of imine **251** and amine **252** (Scheme 162).



Scheme 162 Optimum conditions predicted by DoE

However, when we repeated the reaction, a complex mixture of by-products was formed; non-decarboxylated product **253**, amidation product **254**, and imine **251** which was inseparable from the by-products (Figure 39). This development was late in the project and therefore was not pursued further.

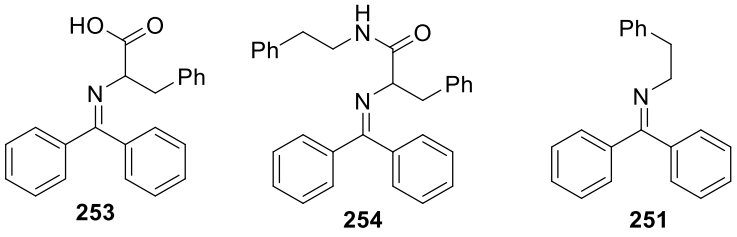


Figure 39 By-products from “optimum” decarboxylation reaction

Future work could include further investigations in potentially developing a one-pot procedure, or an efficient sequential method whereby post isolation of a biogenic amine, a series of biologically relevant amides could be synthesised, e.g.

moschamine, a precursor to natural product montamine with anti-cancer activity (Figure 40).[148]

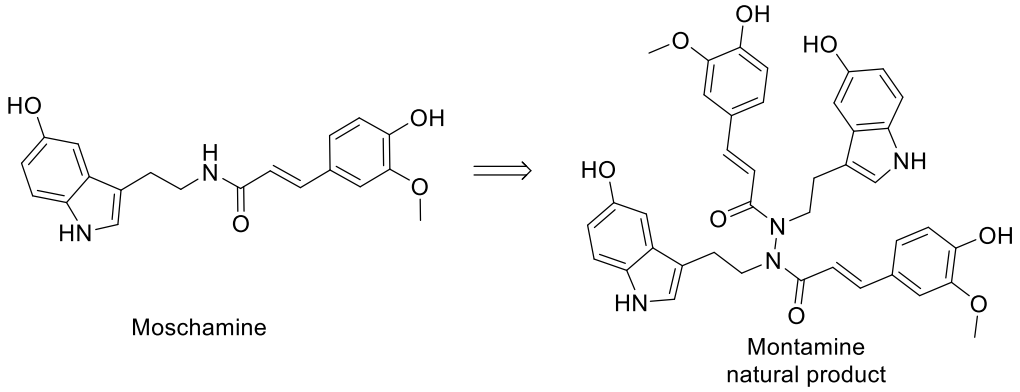


Figure 40 An example of amides with biological activity containing biogenic amines

3. Mechanistic investigations

Possible boron-mediated amidation mechanisms were investigated on different systems: trisaminoboranes and MIDA boronate-type acylating reagents. With the aid of an NMR study (^{1}H, ^{13}C and ^{11}B) it was possible to propose possible boron intermediates present during the amidation of carboxylic acids with trisaminoboranes. This led to the proposal of a tentative mechanism for trisaminoborane amidation, which subsequently provided an explanation for $B(OCH_2CF_3)_3$-mediated amidation. It was proposed that the activation of the carboxylic acids occurs *via* bridged boron species of type **193** and not through the generally accepted acyloxyboron species **109**, as these had been shown to be poor acylating agents as well as not stable to dimerisation (Figure 41).

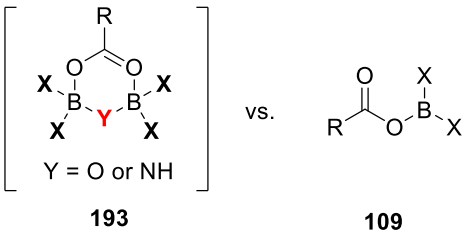
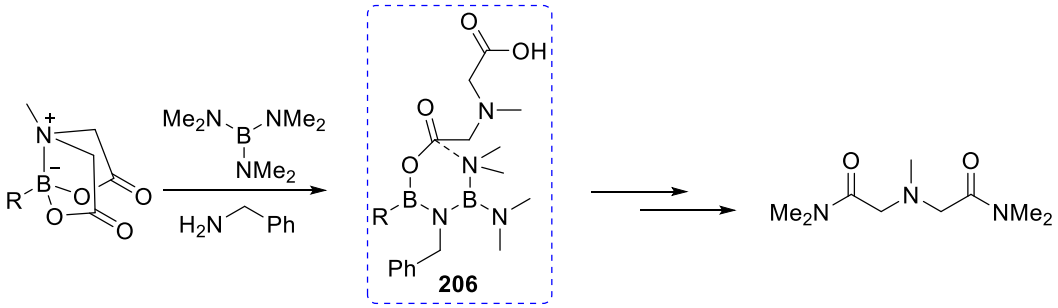


Figure 41 Proposed B-X-B transition state for carboxylic acid activation

In the future, a computational study could provide a better insight on the proposed structures and predict the likelihood of their formation. This would provide a good idea of the relative energy barriers for their formation as well as comparison with the acyloxy species.

Moreover, a study with MIDA boronate suggested that dual cooperative boron catalysis might be important for amidation *via* the proposed intermediate **206** (Scheme 163).



Scheme 163 Explanation of cooperative boron-mediated amidation

Hence, we hypothesised that an appropriately designed catalyst incorporating two boron atoms could improve the activity of the borates (Figure 42).

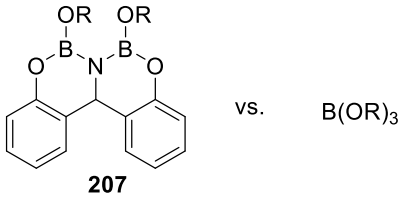


Figure 42 Proposed novel catalyst for amidation

Moreover, such a ligand had the potential of improving the recyclability of the catalyst. Unfortunately, the first-generation catalyst was not successful for this purpose and in the future, manipulations of the ligand would be required. Considerations to be made are the synthesis of a less strongly chelating ligand, e.g. **255** *via* introduction of electron withdrawing groups such as chloro; or introduction of a less rigid system, e.g. a boronic acid-type catalyst **256** (similar to Kumagai's catalyst 50, but with two reactive boron centres) (Figure 43).

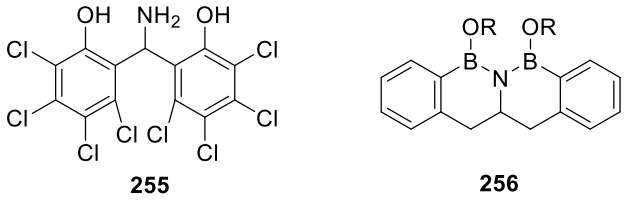


Figure 43 Proposed improved ligands for the boron-catalysed amidation

4. Hybrid catalyst

A novel “hybrid” catalyst was also synthesised in an attempt to overcome the drawbacks of borates and boronic acids. Unfortunately, the first generation catalyst was not useful in the amidation. At this stage of the $B(OCH_2CF_3)_3$-mediated amidation development (with catalytic procedure optimised),[120] further investigations of boronic acids of this type are less practical. It has been shown that hydroxyl arms deactivate the catalyst, and manipulations of the substituents will result in a lengthy process making it expensive.

However, through the introduction of bulkier moieties on the hydroxyl groups to avoid strong coordination of the side-arms to the boronic acid moiety, a practical solution to the deactivation of the catalyst might be provided. Alternatively, the aryl ring may be tuned with, e.g. strongly electron withdrawing groups, to destabilise the strong coordination of the side-arms to the boronic acid. This could be a viable design improvement as it is already known that electron poor boronic acids are usually better catalysts in the amidation.

Several similar structures could be synthesised, which may have less stability in the cyclised form and therefore an improved catalytic activity (Figure 44).

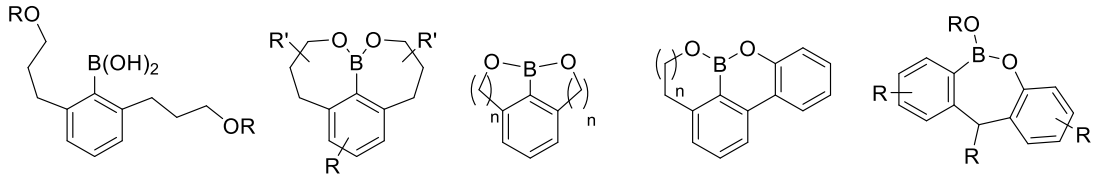


Figure 44 Possible “hybrid” catalysts

6. Experimental

6.1 General methods

All reagents and solvents were purchased and used as supplied unless otherwise stated. All carboxylic acids and amines for medicinally interesting amide synthesis were provided by GSK and used as supplied unless otherwise stated. Borate ester $B(OCH_2CF_3)_3$ was prepared using the literature procedure.[84] All reactions were carried out at atmospheric pressure with stirring and under ambient atmosphere unless otherwise indicated. All resins were washed with EtOAc, Et_2O and CH_2Cl_2 and dried *in vacuo* prior to use. All reactions were monitored by TLC or ^1H NMR. TLC plates used were pre-coated with silica gel 60 F254 on aluminium (Merck KGaA). The spotted TLCs were visualised by UV light (254 nm or 365 nm) or chemically stained ($KMnO_4$). Flash column chromatography purification was performed using silica gel (Merck silica gel, 40-60 μm) or using a Biotage Isolera flash purification system with either Biotage SNAP or GraceResolv flash cartridges prepacked with silica gel (40-60 μm). $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}, concentration (*c*) in g per 100 mL. ^1H NMR and ^{13}C NMR spectra were recorded at 300, 400, 500, or 600 MHz (for ^1H) and 75, 100, 125 or 150 MHz (for ^{13}C) on a Bruker AMX300, AMX400 or JEOL ECS 400 Delta, AMX500, or AMX600 at ambient temperature, unless otherwise indicated. ^{11}B NMR spectra was recorded at 128 MHz on a Bruker AMX400 or JEOL ECS 400 Delta at ambient temperature. ^{19}F NMR was recorded at 282 MHz on a Bruker AMX300 or at 376 MHz on JEOL ECS 400 Delta. Deuterated solvents for NMR detection used were $CDCl_3$, CD_3OD, DMSO-d_6, or CD_3CN as stated. Peaks are assigned as singlet (s), doublet (d), triplet (t), quintet (qn), sextet (sx), septet (sept), or multiplet (m). Coupling constants of diastereotopic geminal (AB) protons coupled to an additional nucleus (X) are reported as J_{AB}, J_{AX}, J_{BX}. ^1H and ^{13}C shifts are reported in parts per million (ppm) and compared against residual solvent signals: $CDCl_3$ (δ = 7.26 ppm, s; 77.2 ppm, t), CD_3OD (δ_H 4.87, s and 3.31, qn; δ_C 49.1 ppm, sept), DMSO-d_6 (δ_H 2.56 ppm, qn; δ_C 39.5 ppm, sept), or CD_3CN (δ_H 1.94 ppm, qn; 1.4 ppm, sept and δ_C 118.7 ppm, s); ^1H and ^{13}C shifts relative to TMS are calibrated using residual solvents peak. ^{11}B NMR shifts are calibrated relative to $BF_3{\cdot}Et_2O$; and ^{19}F NMR relative to $CFCl_3$. Coupling constants (*J*) are quoted in Hertz (Hz) to one decimal place. Mass spectrometry was performed on VG70 SE (EI, CI, ES modes). Infra-red spectra were obtained using a Perkin-Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode, all frequencies given in reciprocal centimetres (cm^{-1}). Melting points were measured with a Gallenkamp heating block and are uncorrected.

6.2 General procedures

6.2.1 Preparation of $B(OCH_2CF_3)_3$

A suspension of B_2O_3 (100 g, 1.44 mol) in 2,2,2-trifluoroethanol (210 mL, 2.88 mol) was stirred at 80 °C for 24 h. Upon completion, the reaction mixture was allowed to cool and then filtered to remove excess boric anhydride. The filtrate was purified by distillation to give $B(OCH_2CF_3)_3$ as a clear liquid (116 g, 0.36 mol, 38%); bp 125-129 °C; δ_H (600 MHz, $CDCl_3$) 4.23 (q, J = 8.6 Hz, 6H); δ_C (150 MHz , $CDCl_3$) 61.8 (q, J = 36.3 Hz), 123.3 (q, J = 278.4 Hz); LRMS (EI): 309 ($[M]^+$, 100); Data in agreement with the literature.[84]

6.2.2 General Procedure (1) for the synthesis of medicinally relevant amides

All reactions were performed on a 0.5-1.0 mmol scale unless otherwise indicated. $B(OCH_2CF_3)_3$ (2.0 equiv.) was added to a solution of carboxylic acid (1.0 equiv.) and amine (1.0 equiv.) in CPME (0.5 M). The resulting mixture was then stirred at either 100 °C for 5 h or at 125 °C for 24 h unless otherwise stated. Upon completion, the reaction mixture was diluted with EtOAc (4 mL) and water (0.5 mL). Unless otherwise stated, Amberlyst® A26(OH) (200 mg), Amberlyst® 15 (200 mg) and Amberlite® IRA743 (200 mg) were added to the mixture and it was stirred for 30 min. The mixture was then dried ($MgSO_4$), filtered and washed with EtOAc (3 × 15 mL). The filtrate was concentrated *in vacuo* to yield the desired amide product.

6.2.3 General Procedure (2) for the direct amidation of unprotected amino acids

Method A: All reactions were performed on a 0.5-2.0 mmol scale. An unprotected amino acid (1 equiv.) and propylamine (3 equiv.) were stirred at 80 °C or 125 °C (as stated) in CPME (0.5 M, unless stated otherwise) with $B(OCH_2CF_3)_3$ (3 equiv.) for 5 or 15 h. Upon completion, the mixture was diluted with EtOAc or CH_2Cl_2 (3 mL) and water (0.5 mL). Amberlite® IRA743 and Amberlyst® A26(OH) were added and stirred for 30 min. The mixture was dried ($MgSO_4$) and then filtered. The solids were washed with EtOAc (3 × 20 mL) and the product concentrated *in vacuo.* The volatile propylamine was removed *in vacuo*.

Method B: A solution of $B(OCH_2CF_3)_3$ (646 µL, 3.0 mmol, 3.0 equiv.) in CPME (1 mL, unless stated otherwise) was added dropwise to a mixture of an unprotected amino acid (1.0 mmol, 1.0 equiv.) and propylamine (247 µL, 3.0 mmol, 3.0 equiv.) in CPME (1 mL) over 1 h at 80 °C or 125 °C. The resulting mixture was stirred for 5-15 h. Upon completion, the mixture was diluted with EtOAc or CH_2Cl_2 (3 mL) and water (0.5 mL). Amberlite® IRA 743 and Amberlyst® A26(OH) were added and stirred for

30 min. The mixture was dried ($MgSO_4$) and then filtered. The solids were washed with EtOAc (3 × 20 mL) and the product concentrated *in vacuo.* The volatile propylamine was removed *in vacuo* by the addition of $CHCl_3$ to get the clean product. Amides with different amines were either triturated with Et_2O, recovered as HCl salt, or purified by flash column chromatography as stated.

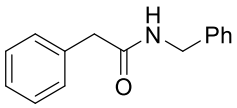
Method C: L-Phenylalanine (165 mg, 1 mmol, 1.0 equiv.) and an amine (3 mmol, 3.0 equiv.) were stirred at 80 °C unless otherwise stated in CPME (2 mL, 0.5 M) with $B(OCH_2CF_3)_3$ (646 µL, 3 mmol, 3.0 equiv.) for 15 h. Upon completion, the mixture was diluted with EtOAc or CH_2Cl_2 (3 mL) and water (0.5 mL). Resins Amberlite® IRA743 and Amberlyst® A26(OH) were added and stirred for 30 min. The mixture was dried ($MgSO_4$) and then filtered. The solids were washed with EtOAc (3 × 20 mL) and the product concentrated *in vacuo.* The product was then either triturated with Et_2O, recovered as HCl salt, or purified by flash column chromatography as stated.

Method D: An amino acid (5 mmol, 1 equiv.) and benzylamine (0.82 mL, 7.5 mmol, 1.5 equiv., unless otherwise stated) were stirred at 86 °C in TAME (5 mL, 1.0 M, unless otherwise stated) with azeotropic removal of water using Dean-Stark, with $B(OCH_2CF_3)_3$ (215 µL, 1 mmol, 20 mol%) for 24 h. Upon completion, the mixture was concentrated *in vacuo* and the crude product was purified by flash column chromatography.

6.3 Characterisation of amides

6.3.1 Medicinally relevant amides

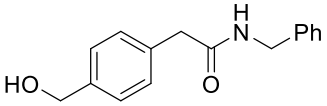
_N_-Benzyl-2-phenylacetamide 54



Prepared according to General Procedure (1) at 100 °C for 5 h to yield a white solid (98 mg, 87%); mp 119-120 °C [lit.[86] 118-120 °C]; ν_{max} (solid/cm^{-1}) 3284 (N-H), 3062, 3031, 1635 (C=O), 1546; δ_H (600 MHz, $CDCl_3$) 7.39-7.21 (m, 9H, ArH), 7.18 (d, J = 7.2 Hz, 1H, ArH), 5.69 (s, 1H, NH), 4.42 (d, J = 5.8 Hz, 2H, CH_2NH), 3.64 (s, 2H, $COCH_2$); δ_C (150 MHz, $CDCl_3$) 171.0 (C=O), 138.2, 134.8, 129.6, 129.2, 128.8, 127.6, 127.6, 44.0 (CH_2), 43.7 (CH_2); LRMS (EI): 225 ([M]$^+$, 100). Data in agreement with the literature.[86]

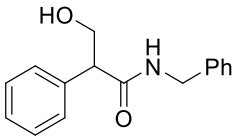
Carboxylic acid scope

_N_-Benzyl-2-(4-(hydroxymethyl)phenyl)acetamide 55a



Prepared according to General Procedure (1) at 100 °C for 5 h to yield a white solid (103 mg, 82%); mp 156-158 °C; ν_{max} (solid/cm^{-1}) 3310 (br, O-H), 3276 (N-H), 3055, 3026, 2917, 2872, 1644 (C=O), 1540; δ_H (600 MHz, $CDCl_3$) 7.35-7.33 (m, 2H, ArH), 7.32-7.26 (m, 5H, PhH), 7.18-7.15 (m, 2H, ArH), 5.67 (s, 1H, NH) 4.69 (s, 2H, CH_2, HOCH_2), 4.42 (d, J = 5.8 Hz, 2H, PhCH_2), 3.63 (s, 2H, $COCH_2$); δ_C (150 MHz, $CDCl_3$) 170.9, 140.2, 138.2, 134.2, 129.8, 128.8, 127.8, 127.7, 127.6, 65.1, 43.7, 43.6; LRMS (EI): 256 ([M+H]$^+$, 70), 121 ([M-C_8H_8NO]$^+$, 30), 104 ([M-OH-C_8H_8NO]$^+$, 90), 91 ([M-$C_9H_{10}NO_2$]$^+$, 100); HRMS: Found (EI): [M]$^+$ 255.12501 $C_{16}H_{17}NO_2$, requires 255.12593.

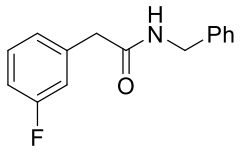
_N_-Benzyl-3-hydroxy-2-phenylpropanamide 55b



Prepared according to General Procedure (1) at 100 °C for 5 h to yield a white solid (104 mg, 82%); mp 117-119 °C; ν_{max} (solid/cm^{-1}) 3264, 1645, 1556; δ_H (600 MHz, $CDCl_3$) 7.35 (t, J = 7.1 Hz, 2H, ArH), 7.30-7.24 (m, 6H, ArH), 7.16 (d, J = 7.1 Hz, 2H,

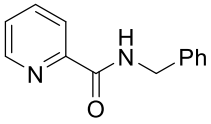
ArH), 5.79 (br s, 1H, NH), 4.46 (dd, J_{AB} = 14.9 Hz; J_{AX} = 5.9 Hz, 1H, ArCH_AH$_B$), 4.40 (dd, J_{AB} = 14.9 Hz; J_{BX} = 5.9 Hz, 1H, ArCH$_A$$H_B$), 4.18 (dd, J_{AB} = 11.1 Hz; J_{AX} = 8.8 Hz, 1H, CH_AH$_B$OH), 3.79 (dd, J_{AB} = 11.1 Hz; J_{BX} = 4.4 Hz, 1H, CH$_A$$H_B$OH), 3.71 (dd, J_{AX} = 8.8 Hz; J_{BX} = 4.4 Hz, 1H, ArCH$_X$); δ_C (150 MHz, $CDCl_3$) 173.6, 137.9, 136.7, 129.3, 128.8, 128.6, 128.1, 127.6, 127.6, 65.1, 54.5, 43.6; LRMS (CI): 256 ([M+H]$^+$, 100); HRMS: Found (CI): [M+H]$^+$ 256.13338 $C_{16}H_{18}NO_2$, requires 256.13375.

_N_-Benzyl-2-(3-fluorophenyl)acetamide 55c



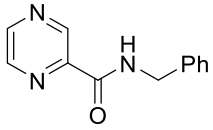
Prepared according to General Procedure (1) at 100 °C for 24 h to yield an off-white solid (70 mg, 69%); mp 94-96 °C; ν_{max} (solid/cm^{-1}) 3281 (N-H), 3066, 3032, 2926, 1636 (C=O), 1589, 1544; δ_H (600 MHz, $CDCl_3$) 7.33-7.26 (m, 4H, ArH), 7.20-7.19 (m, 2H, ArH), 7.01-6.98 (m, 3H, ArH), 5.87 (s, 1H, NH), 4.41 (d, J = 5.8 Hz, 2H, NHCH_2), 3.58 (s, 2H, COCH_2); δ_C (150 MHz, $CDCl_3$) 170.3 (*C*=O), 163.1 (d, $^1J_{CF}$ = 247 Hz, Ar*C*F), 138.1, 137.24 (d, $^3J_{CF}$ = 8.0 Hz, Ar*C*), 130.6 (d, $^3J_{CF}$ = 8.0 Hz, Ar*C*H), 128.8, 127.7, 127.7, 125.2 (d, $^4J_{CF}$ = 3.4 Hz, Ar*C*H), 116.5 (d, $^2J_{CF}$ = 21.4 Hz, Ar*C*H), 114.5 (d, $^2J_{CF}$ = 20.8 Hz, Ar*C*H), 43.8 (*C*H$_2$), 43.5 (d, $^4J_{CF}$ = 1.6 Hz, *C*H$_2$); LRMS (EI): 243 ([M]$^+$, 75), 91 ([M-C_8H_7FNO]$^+$, 100); HRMS: Found (EI): [M]$^+$ 243.10577 $C_{15}H_{14}FNO$, requires 243.10594.

_N_-Benzylpicolinamide 55d



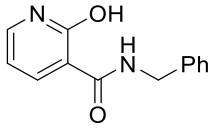
Prepared according to General Procedure (1) at 100 °C for 5 h and the product purified by flash column chromatography (CH_2Cl_2:EtOAc:Et_3N 1:0:0 to 0:1:0.01) to yield an off-white solid (39 mg, 92%); mp 85-87 °C [lit.[11] 87-90 °C]; ν_{max} (solid/cm^{-1}) 3302 (N-H), 2923, 1657 (C=O), 1522, 1454; δ_H (600 MHz, $CDCl_3$) 8.50 (ddd, J = 4.7, 1.6, 1.0 Hz, 1H, NCH), 8.41 (s, 1H, NH), 8.24 (dt, J = 7.8, 1.0 Hz, 1H, COCCH), 7.86 (td, J = 7.8, 1.6 Hz, 1H, COCCHC*H*), 7.43 (ddd, J = 7.8, 4.7, 1.0 Hz, 1H, COCNCHC*H*), 7.38-7.34 (m, 4H, Ph), 7.29-7.25 (m, 1H, Ph), 4.68 (d, J = 6.1 Hz, 2H, CH$_2$); δ_C (150 MHz, $CDCl_3$) 164.4, 149.9, 148.2, 138.3, 137.5, 128.8, 128.0, 127.6, 126.4, 122.5, 43.6; HRMS: Found (EI): [M]$^+$ 212.09398 $C_{13}H_{12}N_2O$, requires 212.09496. Data in agreement with the literature.[11]

***N*-Benzylpyrazine-2-carboxamide 55e**



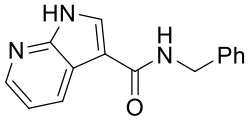
Prepared according to General Procedure (1). In this reaction Amberlyst® 15 was not used. The reaction was performed at 100 °C for 5 h to yield a white solid (99 mg, 93%); mp 116-118 °C [lit.[149] 114-115 °C]; ν_{max} (solid/cm^{-1}) 3368 (N-H), 3029, 2930, 2851, 1669 (C=O), 1514, 1453; δ_H (600 MHz, $CDCl_3$) 9.45 (d, *J* = 1.5 Hz, 1H, COCCH), 8.74 (d, *J* = 2.4 Hz, 1H, COCNCH), 8.50 (dd, *J* = 2.4, 1.5 Hz, 1H, COCCHNCH), 8.13 (s, 1H, NH), 7.39-7.28 (m, 5H, Ph), 4.68 (d, *J* = 6.1 Hz, 2H, CH_2); δ_C (150 MHz, $CDCl_3$) 163.0, 147.5, 144.7, 144.5, 142.7, 137.8, 128.9, 128.0, 127.8, 43.6; LRMS (CI): 214 ([M+H]$^+$, 100), 106 ([M-$C_5H_4N_2O$]$^+$, 20), 91 ([M-$C_5H_4N_3O$]$^+$, 45); HRMS: Found (EI): [M+H]$^+$ 214.09791 $C_{12}H_{12}N_3O$, requires 214.09804. Data in agreement with the literature.[149]

***N*-Benzyl-2-hydroxynicotinamide 55f**



Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography (CH_2Cl_2 to MeOH:CH_2Cl_2 0.02:0.98) to yield a white solid (10 mg, 22%); mp 199-201 °C [lit.[150] 190-192 °C]; ν_{max} (solid/cm^{-1}) 3231 (br, O-H), 1661 (C=O), 1551; δ_H (600 MHz, $CDCl_3$) 9.93 (s, 1H, NH), 8.66 (dd, *J* = 7.2, 2.2 Hz, 1H, NCHCHC*H*), 7.47 (dd, *J* = 6.3, 2.2 Hz, 1H, NCH), 7.38-7.26 (m, 5H, ArH), 6.54 (dd, *J* = 7.2, 6.3 Hz, 1H, NCHC*H*), 4.68 (d, *J* = 5.8 Hz, 2H, CH_2); δ_C (150 MHz, $CDCl_3$) 163.9 (*C*=O or *C*-OH), 163.8 (*C*=O or *C*-OH), 145.7, 138.7, 137.6, 128.7, 127.7, 127.3, 121.7, 108.1, 43.5; LRMS (CI): 229 ([M+H]$^+$, 100), 91 ([M-$C_6H_5N_2O_2$]$^+$, 35). Data in agreement with the literature.[150]

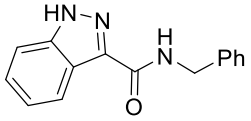
***N*-Benzyl-1*H*-pyrrolo[2,3-b]pyridine-3-carboxamide 55g**



Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography (Petrol: CH_2Cl_2 1:1 to EtOAc) to yield a white solid (77 mg, 61%); mp 201-202 °C; ν_{max} (solid/cm^{-1}) 3135 (N-H), 3105 (N-H), 3029, 2512, 1615 (C=O), 1525, 1452; δ_H (600 MHz, MeOD) 8.53 (d, *J* = 7.6 Hz, 1H,

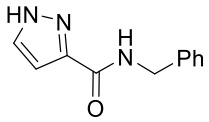
COCCCHCHC*H*), 8.26 (d, *J* = 3.5 Hz, 1H, COCCC*H*), 8.07 (s, 1H, NHCOCC*H*NH), 7.38-7.26 (m, 4H, ArH), 7.22 (t, *J* = 6.9 Hz, 2H, COCCCHC*H*), 4.58 (s, 2H, PhCH_2NH); δ_C (150 MHz, MeOD) 167.2, 149.4, 144.5, 140.6, 131.4, 129.6, 129.5, 128.5, 128.1, 120.5, 118.3, 111.0, 43.9; LRMS (ES): 252 ([M+H]$^+$, 100); HRMS: Found (ES): [M+H]$^+$ 252.1128 $C_{15}H_{14}N_3O$, requires 252.1137.

_N_-Benzyl-1_H_-indazole-3-carboxamide 55h



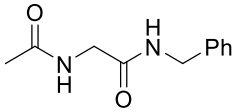
Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography (EtOAc:CH_2Cl_2 1:9) to yield a white solid (99 mg, 79%); mp 173-174 °C [lit.[151] 158 °C decomposition]; ν_{max} (solid/cm^{-1}) 3406 (N-H), 3183, 3083, 2920, 1645 (C=O), 1541; δ_H (600 MHz, $CDCl_3$) 10.48 (s, 1H, NH), 8.44 (d, *J* = 8.2 Hz, 1H, ArH), 7.49-7.29 (m, 9H, ArH), 4.71 (d, *J* = 6.0 Hz, 2H, CH_2); δ_C (150 MHz, $CDCl_3$) 162.8, 141.4, 139.5, 138.4, 128.9, 128.0, 127.6, 127.5, 123.1, 122.8, 122.1, 109.9, 43.2; LRMS (ES): 252 ([M+H]$^+$, 100); HRMS: (ES): Found 252.0916 $C_{15}H_{14}N_3O$, requires 252.0899.

_N_-Benzyl-1_H_-pyrazole-3-carboxamide 55i



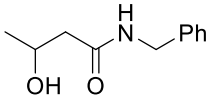
Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography (CH_2Cl_2 to EtOAc) to yield a white solid (78 mg, 77%); mp 151-152 °C [lit.[152] 149-150 °C]; ν_{max} (solid/cm^{-1}) 3228 (N-H), 3029, 2952, 1639 (C=O), 1549, 1453; δ_H (600 MHz, $CDCl_3$) 7.60 (d, *J* = 1.8 Hz, 1H, COCC*H*), 7.37-7.31 (m, 4H, ArH), 7.30-7.26 (m, 1H, ArH), 7.23 (br s, 1H, NH), 6.89 (d, *J* = 1.8 Hz, 1H, COCCHC*H*), 4.63 (d, *J* = 6.0 Hz, 2H, PhCH_2NH); δ_C (150 MHz, $CDCl_3$) 161.7, 138.2, 130.7. 130.6, 128.8, 128.0, 127.6, 106.3, 43.4; LRMS (CI): 202 ([M+H]$^+$, 100), 91 ([M-$C_4H_4N_3O$]$^+$, 55); HRMS: Found (CI): [M+H]$^+$ 202.08205 $C_{11}H_{12}N_3O$, requires 202.09804.

2-Acetamido-*N*-benzylacetamide 55j



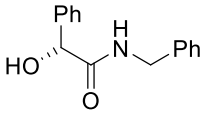
Prepared according to General Procedure (1) at 100 °C for 5 h to yield a white solid (166 mg, 80%); mp 139-141 °C [lit.[153] 140-142 °C]; ν_{max} (solid/cm^{-1}) 3322 (N-H), 3245 (N-H), 3196, 3065, 2927, 1633 (C=O), 1538; δ_H (600 MHz, DMSO-d_6) 8.36 (s, 1H, NH), 8.14 (s, 1H, NH), 7.32-7.22 (m, 5H, ArH), 4.27 (d, J = 5.8 Hz, 2H, PhCH_2), 3.70 (d, J = 5.8 Hz, 2H, PhCH$_2$NHCOCH_2), 1.85 (s, 3H, CH$_3$); δ_C (150 MHz, DMSO-d_6) 169.7, 169.1, 139.5, 128.3, 127.2, 126.8, 42.2, 42.0, 22.6; HRMS: Found (EI): [M]$^+$ 206.10500 $C_{11}H_{14}N_2O_2$, requires 206.10553. Data in agreement with the literature.[153]

***N*-Benzyl-3-hydroxybutanamide 55l**



Prepared according to General Procedure (1) at 100 °C for 5 h, the product was flushed through a short silica column (CH_2Cl_2) to remove impurities present in the starting carboxylic acid to yield a white solid (154 mg, 80%); mp 65-67 °C [lit.[154] 65-66 °C]; ν_{max} (solid/cm^{-1}) 3358 (O-H), 3275 (N-H), 2969, 2907, 1638 (C=O), 1553; δ_H (600 MHz, $CDCl_3$) 7.31-7.26 (m, 5H, Ph), 6.28 (s, 1H, NH), 4.44 (d, J = 5.7 Hz, 2H, PhCH_2), 4.21-4.18 (m, 1H, CHOH), 2.37 (dd, J_{AB} = 15.4 Hz; J_{AX} = 2.7 Hz, 1H, COCH_AH$_B$), 2.30 (dd, J_{AB} = 15.4 Hz; J_{AX} = 8.8 Hz; 1H, COCH$_A$$H_B$), 1.22 (d, J = 6.3 Hz, 3H, Me); δ_C (150 MHz, $CDCl_3$) 172.4, 138.1, 128.9, 127.9, 127.7, 65.0, 44.0, 43.5, 23.0; LRMS (CI): 194 ([M+H]$^+$, 100). Data in agreement with the literature.[154,155]

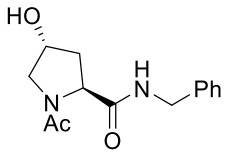
(*R*)-*N*-Benzyl-2-hydroxy-2-phenylacetamide 55n



Prepared according to General Procedure (1) at 125 °C for 24 h to yield a white solid (41 mg, 24%, er 57:43, determined using chiral HPLC); mp 95-96 °C [lit.[156] 94-96 °C]; $[\alpha]_D$ −5.6 (*c* 0.23, MeOH, 20 °C); ν_{max} (solid/cm^{-1}) 3381 (br), 3224, 1658, 1528; δ_H (600 MHz, $CDCl_3$) 7.43-7.24 (m, 8H, Ph), 7.20-7.15 (m, 2H, Ph), 6.57 (s, 1H, NH), 5.05 (s, 1H, CHOH), 4.43 (dd, J_{AB} = 14.9 Hz; J_{AX} = 6.0 Hz, 1H, PhCH_AH$_B$), 4.39 (dd, J_{AB} = 14.9 Hz; J_{BX} = 6.0 Hz, 1H, PhCH$_A$$H_B$), 3.75 (s, 1H, OH); δ_C (150 MHz,

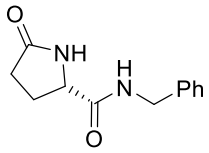
$CDCl_3$) 172.1, 139.4, 137.8, 129.1, 128.9, 128.9, 127.8, 127.7, 127.0, 74.4, 43.7; LRMS (ES): 505 ([2M+Na]$^+$, 20), 242 ([M+H]$^+$, 100); HRMS: Found (ES): [M+H]$^+$ 242.1108 $C_{15}H_{16}NO_2$, requires 341.1181. Data in agreement with the literature.[156]

(*2S,4R*)-1-Acetyl-*N*-benzyl-4-hydroxypyrrolidine-2-carboxamide 55o



Prepared according to General Procedure (1) at 100 °C for 24 h to yield a white solid (131 mg, 50%); mp 160-162 °C [lit.[149] 147-148 °C]; $[\alpha]_D$ −25.3 (*c* 1.05, MeOH, 20 °C) [lit.[149] $[\alpha]_D$ −32.7 (*c* 1.5, MeOH, 20 °C); ν_{max} (solid/cm^{-1}) 3264 (br), 3085, 2908, 1660, 1619, 1576; δ_H (600 MHz, DMSO-d_6; a mixture of 2:1 trans:cis rotamers; where possible, asterisk (*) denotes the minor rotamer peak) 8.71* (t, *J* = 5.9 Hz, 1H, NH), 8.40 (t, *J* = 6.0 Hz, 1H, NH), 7.34-7.20 (m, 5H, Ph), 5.12 (d, *J* = 3.9 Hz, 1H, OH), 5.03* (d, *J* = 3.9 Hz, 1H, OH), 4.41* (t, *J* = 7.5 Hz, 1H, COC*H*), 4.33-4.27 (m, 2H, C*H*OH and NAcC*H*H), 4.23-4.21 (m, 2H, $PhCH_2$); 3.64 (dd, *J* = 10.5, 4.7 Hz, 1H, NAcCH*H*), 3.46* (d, *J* = 12.0 Hz, 1H, NAcCH*H*), 3.36-3.34 (m, 1H, COC*H*), 2.18-2.14* (m, 1H, COCHCH*H*), 2.03 (ddd, *J* = 12.0, 8.2, 3.9 Hz, 1H, COCHCH*H*), 1.99-1.94* (m, 1H, COCHC*H*H), 1.99-1.94 (s, 3H, Me), 1.90-1.84 (m, 1H, COCHC*H*H), 1.77* (s, 3H, Me); δ_C (150 MHz, DMSO-d_6) 172.0*, 171.9, 168.9*, 168.7, 139.6, 139.3*, 128.4*, 128.2, 127.3, 126.9*, 126.8, 126.6, 68.6, 67.3*, 59.4*, 58.4, 55.7, 54.3*, 42.2*, 41.8, 40.3*, 38.4, 22.5, 21.6*; LRMS (ESI+): 263 ([M+H]$^+$, 100); HRMS: Found (ESI+): [M+H]$^+$ 263.1398 $C_{14}H_{19}N_2O_3$, requires 263.1396.

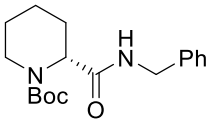
(*S*)-*N*-Benzyl-5-oxopyrrolidine-2-carboxamide 55p



Prepared according to General Procedure (1) at 100 °C for 5 h to yield a white solid (59 mg, 54%, er > 99%, determined using shift reagent); mp 134-135 °C [lit.[157] 138.3 °C]; $[\alpha]_D$ +218.1 (*c* 0.21, MeOH, 25 °C); ν_{max} (solid/cm^{-1}) 3276 (N-H), 3226 (N-H), 3097, 1681 (C=O), 1645 (C=O), 1574, 1419; δ_H (600 MHz, $CDCl_3$) 7.38 (s, 1H, NH), 7.29-7.19 (m, 5H, ArH), 4.37 (dd, J_{AB} = 14.7 Hz, J_{AX} = 5.7 Hz, 1H, PhCH_AH_B), 4.32 (dd, J_{AB} = 14.7 Hz, J_{BX} = 5.7 Hz, 1H, PhCH_AH_B), 4.09 (dd, *J* = 8.9, 4.5 Hz, 1H, COCH), 2.43-2.31 (m, 1H), 2.19 (m, 2H), 2.09 (m, 1H); δ_C (150 MHz, $CDCl_3$) 179.8, 172.4, 138.1, 128.8, 127.9, 127.6, 57.3, 43.5, 29.4, 25.9; LRMS (ES): 241 ([M+Na]$^+$,

100); HRMS: Found (ES): $[M+Na]^+$ 241.0943 $C_{12}H_{14}N_2O_2Na$, requires 241.0953. Data in agreement with the literature.[157]

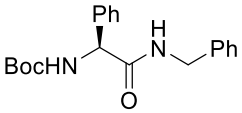
(*R*)-*Tert*-butyl 2-(benzylcarbamoyl)piperidine-1-carboxylate 55q



Mixture of rotamers: ^{1}H NMR obtained at 120 °C to eliminate rotamer signals; δ_C reported at ambient temperature for major rotamer.

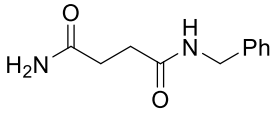
Prepared according to General Procedure (1) at 100 °C for 5 h to yield a yellow solid (240 mg, 75%, er > 99%, determined using Marfey's reagent); mp 94 -95 °C; $[\alpha]_D$ +21.2 (*c* 0.76, MeOH, 20 °C); ν_{max} (solid/cm^{-1}) 3315, 2978, 2931, 1672, 1659; δ_H (400 MHz, DMSO-d_6, 120 °C) 7.82 (br s, 1H, NH), 7.43-7.12 (m, 5H, Ph), 4.58 (dd, *J* = 6.0, 2.6 Hz, 1H, BocNCH), 4.33 (d, *J* = 6.0 Hz, 2H, $PhCH_2$), 3.87-3.79 (m, 1H), 3.12-3.09 (m, 1H), 2.08 (dd, *J* = 9.3, 6.8 Hz, 1H), 1.68-1.55 (m, 3H), 1.41 (s, 9H, 3 x CH_3 and m, 2H); δ_C (150 MHz, DMSO-d_6) 171.2, 154.9, 139.8, 128.2, 127.0, 126.7, 78.8, 54.7, 42.1, 41.0, 28.0, 27.2, 24.3, 19.9; LRMS (ES): 319 ($[M+H]^+$, 100); HRMS: Found (ES): $[M+H]^+$ 319.2013 $C_{18}H_{27}N_2O_3$, requires 319.2016.

(*S*)-*Tert*-butyl (2-(benzylamino)-2-oxo-1-phenylethyl)carbamate 55r



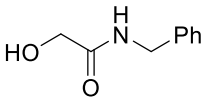
Prepared according to General Procedure (1) at 100 °C for 24 h to yield an off-white solid (272 mg, 80%, er 81:19, determined using Marfey's reagent); mp 126-128 °C; $[\alpha]_D$ +59.3 (*c* 0.34, MeOH, 20 °C); ν_{max} (solid/cm^{-1}) 3267 (N-H), 3087, 2909, 1658 (C=O), 1621 (C=O), 1572; δ_H (600 MHz, DMSO-d_6) 8.65 (t, *J* = 5.8 Hz, 1H, NH), 7.43 (d, *J* = 7.3 Hz, 2H, Ph), 7.33 (t, *J* = 7.3 Hz, 2H, Ph), 7.29 (d, *J* = 7.3 Hz, 1H, Ph), 7.28-7.23 (m, 2H, Ph), 7.21 (d, *J* = 7.2 Hz, 1H, Ph), 7.14 (d, *J* = 7.2 Hz, 2H, Ph), 5.20 (d, *J* = 8.5 Hz, 1H, C*H*CO), 4.29 (dd, J_{AB} = 15.6 Hz, J_{AX} = 6.2 Hz, 1H, PhCH_AH$_B$), 4.24 (dd, J_{AB} = 15.6 Hz, J_{BX} = 6.2 Hz, 1H, PhCH$_A$$H_B$), 1.39 (s, 9H, 3 × CH_3); δ_C (150 MHz, DMSO-d_6) 170.2, 155.0, 139.1, 138.8, 128.3, 128.2, 127.6, 127.3, 127.0, 126.8, 78.4, 58.0, 42.1, 40.1, 28.2; LRMS (ES): 341 ($[M+H]^+$, 100); HRMS: Found (ES): $[M+H]^+$ 341.1851 $C_{20}H_{25}N_2O_3$, requires 341.1859.

***N*^{1}-Benzylsuccinamide 55s**



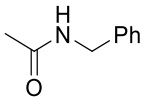
Prepared according to General Procedure (1) at 100 °C for 5 h. Resins were not used for the work-up and the product was recrystallised from hot methanol with addition of petrol to yield a white fluffy solid (94 mg, 46%); mp 193-194 °C [lit.[158] 194-195 °C]; ν_{max} (solid/cm^{-1}) 3377 (N-H), 3297 (N-H), 3187, 1654 (C=O), 1628 (C=O), 1539; δ_H (600 MHz, DMSO-d_6) 8.34 (t, J = 5.8 Hz, 1H, NH), 7.32-7.28 (m, 3H, Ph and NH), 7.25-7.21 (m, 3H, Ph), 6.76 (s, 1H, NH), 4.25 (d, J = 5.8 Hz, 2H, $PhCH_2$), 2.37-2.33 (m, 2H, CH_2), 2.33-2.30 (m, 2H, CH_2); δ_C (150 MHz, DMSO-d_6) 173.5, 171.5, 139.7, 128.3, 127.2, 126.7, 42.0, 30.6, 30.4; LRMS (FTMS): 207 ([M+H]$^+$, 100), 190 ([M-NH_2]$^+$, 50); HRMS: Found (FTMS): [M+H]$^+$ 207.1129 $C_{11}H_{15}N_2O_2$, requires 207.1128.

***N*-Benzyl-2-hydroxyacetamide 57a**



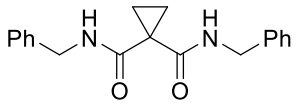
Prepared according to General Procedure (1) at 125 °C for 24 h and product isolated by flash column chromatography (CH_2Cl_2-EtOAc) to yield a white solid (34 mg, 38%); mp 103-104 °C [lit.[86] 102-103 °C]; ν_{max} (solid/cm^{-1}) 3317 (N-H), 3215 (s, O-H), 1633 (C=O), 1561, 1424; δ_H (600 MHz, $CDCl_3$) 7.39-7.15 (m, 5H, Ph), 6.88 (br s, 1H, NH), 4.47 (d, J = 5.9 Hz, 2H, $PhCH_2$), 4.12 (s, 2H, $COCH_2$), 3.12 (s, 1H, OH); δ_C (150 MHz, $CDCl_3$) 171.7, 137.8, 128.9, 127.9, 127.8, 62.3, 43.2; LRMS (CI): 166 ([M+H]$^+$, 100). Data in agreement with the literature.[86]

***N*-Benzylacetamide 57b**



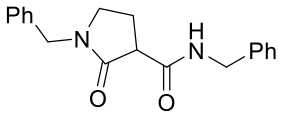
Prepared according to General Procedure (1) at 125 °C for 24 h and product isolated by flash column chromatography (CH_2Cl_2-EtOAc) to yield a white solid (20 mg, 25%); mp 60-62 °C [lit.[159] 60-62 °C]; ν_{max} (solid/cm^{-1}) 3284 (N-H), 3086, 3032, 2928, 1635 (C=O), 1548, 1491; δ_H (600 MHz, $CDCl_3$) 7.36-7.22 (m, 5H, ArH), 5.81 (s, 1H, NH), 4.42 (d, J = 5.7 Hz, 2H, CH_2), 2.02 (s, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 170.0, 138.3, 128.9, 128.0, 127.7, 43.9, 23.4; LRMS (CI): 150 ([M+H]$^+$, 100), 91 ([M-C_2H_4NO+H]$^+$, 25). Data in agreement with the literature.[159]

***N,N'*-Dibenzylcyclopropane-1,1-dicarboxamide 59a**



Prepared according to General Procedure (1) at 125 °C for 24 h and product isolated by flash column chromatography (CH_2Cl_2-EtOAc) to yield a white solid (15 mg, 10%); mp 99-100 °C; ν_{max} (solid/cm^{-1}) 3247, 3063, 3028, 2931, 1623; δ_H (600 MHz, $CDCl_3$) 7.37 (br s, 2H, 2 × NH), 7.33-7.25 (m, 10H, ArH), 4.44 (d, J = 5.7 Hz, 4H, 2 × $PhCH_2$), 1.43 (s, 4H, 2 × $COCCH_2$); δ_C (150 MHz, $CDCl_3$) 170.7, 138.0, 128.9, 127.8, 127.7, 43.9, 28.1, 16.9; LRMS (ES+): 309 ($[M+H]^+$, 100); HRMS: Found (ES); 309.1610 $C_{19}H_{21}N_2O_2$, requires 309.1603.

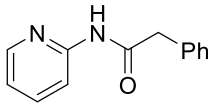
***N*,1-Dibenzyl-2-oxopyrrolidine-3-carboxamide 59b**



Prepared according to General Procedure (1) at 125 °C for 24 h and product isolated by flash column chromatography (CH_2Cl_2-EtOAc) to yield a white solid (32 mg, 21%); mp 109-111 °C; ν_{max} (solid/cm^{-1}) 3264 (N-H), 3031, 2923, 1689 (C=O), 1631 (C=O); δ_H (600 MHz, $CDCl_3$) 7.97 (br t, J = 6.1 Hz, 1H, NH), 7.37-7.27 (m, 8H, Ph), 7.22-7.20 (m, 2H, Ph), 4.56 (dd, J_{AB} = 14.9 Hz; J_{AX} = 6.1 Hz, 1H, $PhCH_AH_BNH$), 4.51-4.40 (m, 3H, $PhCH_AH_BNH$, $PhCH_2N$), 3.37 (t, J = 9.2 Hz, 1H, $COCHCO$), 3.29 (td, J = 9.6, 3.7 Hz, 1H, $PhCH_2NCHH$), 3.24 (dt, J = 9.6, 7.9 Hz, 1H, $PhCH_2NCHH$), 2.53-2.47 (m, 1H, $COCHCHH$), 2.33-2.27 (m, 1H, $COCHCHH$); δ_C (150 MHz, $CDCl_3$) 172.2, 167.9, 138.3, 135.8, 129.0, 128.8, 128.2, 128.0, 127.8, 127.5, 47.3, 47.0, 44.9, 43.66, 20.4; LRMS (ES+): 331 ($[M+Na]^+$, 100); HRMS: Found (ES): 331.1455 $C_{19}H_0N_2O_2Na$, requires 331.1423.

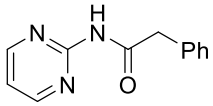
Amine scope

2-Phenyl-*N*-(pyridin-2-yl)acetamide 63a



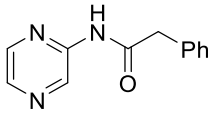
Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography (EtOAc:$CH_2Cl_2$1:4 - EtOAc) to yield a white solid (38 mg, 36%); mp 122-123 °C [lit.[84] 121-122°C]; ν_{max} (solid/cm^{-1}) 3234 (N-H), 3043, 1656 (C=O), 1535; δ_H (600 MHz, $CDCl_3$) 8.34 (s, 1H, NH), 8.26-8.17 (m, 2H, ArH), 7.71-7.63 (m, 1H, ArH), 7.38-7.34 (m, 2H, ArH), 7.33-7.29 (m, 3H, ArH), 7.01 (ddd, *J* = 7.3, 4.9, 0.8 Hz, 1H, ArH), 3.75 (s, 2H, $PhCH_2$); δ_C (150 MHz, $CDCl_3$) 169.8, 151.4, 147.7, 138.6, 134.1, 129.6, 129.3, 127.8, 120.0, 114.3, 45.0; HRMS: Found (ES): $[M+H]^+$ 213.1025 $C_{13}H_{13}N_2O$, requires 213.1028. Data in agreement with the literature.[84]

2-Phenyl-*N*-(pyrimidin-2-yl)acetamide 63b



Prepared according to General Procedure (1) at 100 °C for 24 h and the product purified by flash column chromatography (EtOAc:$CH_2Cl_2$1:4 to EtOAc) to yield a white solid (39 mg, 37%); mp 192-193 °C; ν_{max} (solid/cm^{-1}) 3212 (N-H), 3139, 3091, 3000, 2920, 1678 (C=O), 1578, 1520; δ_H (600 MHz, $CDCl_3$) 9.56 (s, 1H, NC*H*), 8.31 (d, *J* = 2.5 Hz, 1H, NC*H*), 8.17 (dd, *J* = 2.5, 1.6 Hz, 1H, NCHC*H*), 8.11 (br s, 1H, N*H*), 7.40-7.36 (m, 2H, Ph), 7.33-7.31 (m, 3H, Ph), 3.79 (s, 2H, CH_2); δ_C (150 MHz, $CDCl_3$) 169.7, 148.0, 142.1, 140.5, 137.1, 133.7, 129.6, 129.4, 128.0, 44.7; LRMS (CI): 214 ($[M+H]^+$, 100); HRMS: Found (CI): $[M+H]^+$ 214.09851 $C_{12}H_{12}N_3O$, requires 214.09804.

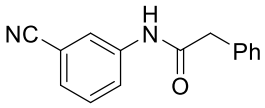
2-Phenyl-*N*-(pyrazin-2-yl)acetamide 63c



Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography (CH_2Cl_2-EtOAc) to yield a white solid (67 mg, 63%); mp 171-173 °C; ν_{max} (solid/cm^{-1}) 3207 (N-H), 3089, 1662, 1589, 1409; δ_H (600 MHz, $CDCl_3$) 9.55 (s, 1H, NH), 8.32 (d, *J* = 2.5 Hz, 1H, ArH), 8.20-8.16 (m, 1H,

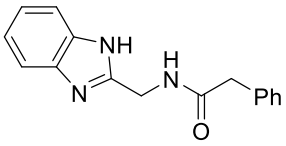
ArH), 7.72 (s, 1H, NHCC*H*), 7.43-7.39 (m, 2H, Ph), 7.37-7.32 (m, 3H, Ph), 3.80 (s, 2H, $PhCH_2$); δ_C (150 MHz, $CDCl_3$) 169.5, 147.9, 142.1, 140.5, 137.0, 133.5, 129.6, 129.6, 128.1, 44.8; LRMS (ES+): 214 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 214.0970 $C_{12}H_{12}N_3O$, requires 214.0980.

_N_-(3-Cyanophenyl)-2-phenylacetamide 63d



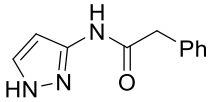
Prepared according to General Procedure (1) at 125 °C for 24 h to yield a yellow solid (60 mg, 51%); mp 152-153 °C [lit.[28] 156-157 °C]; ν_{max} (solid/cm^{-1}) 3321 (N−H), 2235 (C≡N), 1686 (C=O), 1589, 1546, 1423; δ_H (600 MHz, $CDCl_3$) 7.83 (s, 1H, N*H*), 7.62 (dt, *J* = 7.1, 2.2 Hz, 1H, ArH), 7.45-7.40 (m, 2H, ArH), 7.40-7.34 (m, 3H, Ph), 7.35-7.31 (m, 2H, Ph), 7.19 (br s, 1H, ArH), 3.76 (s, 2H, CH_2); δ_C (150 MHz, $CDCl_3$) 169.6, 138.6, 133.9, 129.9, 129.6, 129.5, 128.1, 128.0, 124.0, 123.0, 118.5, 113.1, 44.8; HRMS: Found (EI): $[M]^+$ 236.09399 $C_{15}H_{12}N_2O$, requires 236.09496. Data in agreement with the literature.[28,160]

_N_-((1*H*-Benzo[d]imidazol-2-yl)methyl)-2-phenylacetamide 63f



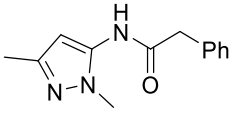
Prepared according to General Procedure (1) at 100 °C for 5 h and the product purified by flash column chromatography (7% MeOH/EtOAc) to yield an off-white fluffy solid (204 mg, 77%); mp 186-187 °C [lit.[161] 185-187 °C]; ν_{max} (solid/cm^{-1}) 3225 (N-H), 2985, 1650 (C=O), 1562, 1416; δ_H (600 MHz, DMSO-d_6) 12.26 (s, 1H, NH), 8.74 (t, *J* = 5.4 Hz, 1H, N*H*CO), 7.56 (d, *J* = 7.6 Hz, 1H, ArH), 7.45 (d, *J* = 7.5 Hz, 1H, ArH), 7.34-7.26 (m, 4H, ArH), 7.24-7.20 (m, 1H, ArH), 7.18-7.11 (m, 2H, ArH), 4.48 (d, *J* = 5.6 Hz, 2H, NHCH_2), 3.54 (s, 2H, $PhCH_2$); δ_C (150 MHz, DMSO-d_6) 174.5, 152.8, 139.1, 136.2, 130.6, 130.5, 129.9, 129.7, 128.4, 124.0, 116.1, 44.0, 38.7; LRMS (CI): 294 ($[M+C_2H_4]^+$, 10), 266 ($[M+H]^+$, 100); HRMS: Found (CI): $[M+H]^+$ 266.1294 $C_{16}H_{16}N_3O$, requires 266.1293. Data in agreement with the literature.[161]

2-Phenyl-*N*-(1*H*-pyrazol-3-yl)acetamide 63g



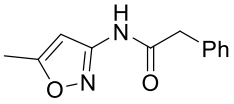
Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography (EtOAc:CH_2Cl_2 1:4 to EtOAc) to yield white solid (92 mg, 88%); mp 157-158 °C; ν_{max} (solid/cm^{-1}) 3291 (N-H), 3223, 3132, 3030, 1666 (C=O), 1579, 1488; δ_H (600 MHz, DMSO-d_6) 12.31 (s, 1H, NH), 10.61 (s, 1H, NH), 7.57 (s, 1H, CH), 7.37-7.29 (m, 4H, Ph), 7.25-7.23 (m, 1H, Ph), 6.46 (t, J = 2.0 Hz, 1H, CH), 3.59 (s, 2H, CH_2); δ_C (150 MHz, DMSO-d_6) 168.2, 147.3, 136.2, 129.1, 128.6, 128.3, 126.5, 95.9, 42.5; LRMS (ES+): 202 ([M+H]$^+$, 100); HRMS: Found (CI): [M+H]$^+$ 202.0979 $C_{11}H_{12}N_3O$, requires 202.0980.

***N*-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-2-phenylacetamide 63h**



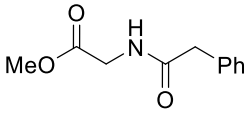
Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography (EtOAc:CH_2Cl_2 1:4 to EtOAc) to yield a white solid (84 mg, 73%); mp 110-111 °C [lit.[162] 111-112 °C]; ν_{max} (solid/cm^{-1}) 3249 (N-H), 2919, 1664 (C=O), 1529; δ_H (600 MHz, $CDCl_3$) 7.39-7.34 (m, 6H, ArH and NH), 5.97 (s, 1H, CH), 3.71 (s, 2H, $PhCH_2$), 3.45 (s, 3H, NCH_3), 2.16 (s, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 169.6, 147.4, 135.4, 134.2, 129.5, 129.4, 128.0, 99.7, 43.8, 35.1, 14.0; LRMS (CI): 230 ([M+H]$^+$, 100); HRMS: Found (CI): [M+H]$^+$ 230.12910 $C_{13}H_{16}N_3O$, requires 230.12934. Data in agreement with the literature.[162,163]

***N*-(5-Methylisoxazol-3-yl)-2-phenylacetamide 63i**



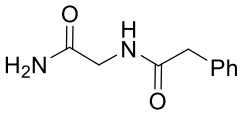
Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography (EtOAc:CH_2Cl_2 1:4 to EtOAc) to yield a white solid (78 mg, 72%); mp 165-166 °C; ν_{max} (solid/cm^{-1}) 3217 (N-H), 3088, 3033, 2971, 1702 (C=O), 1625, 1562, 1478; δ_H (600 MHz, $CDCl_3$) 9.15 (s, 1H, NH), 7.38-7.28 (m, 5H, ArH), 6.74 (s, 1H, CH, ArH), 3.76 (s, 2H, $PhCH_2$), 2.39 (s, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 170.2, 169.4, 158.3, 133.8, 129.6, 129.2, 127.8, 96.6, 44.3, 12.8; LRMS (ESI+): 239 ([M+Na]$^+$, 100), 217 ([M+H]$^+$, 20); HRMS: Found (ESI+): [M+H]$^+$ 217.0971 $C_{12}H_{13}N_2O_2$, requires 217.0977.

Methyl-2-(2-phenylacetamido)acetate 63k



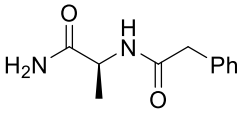
Prepared according to General Procedure (1) at 100 °C for 5 h to yield a white solid (179 mg, 86%); mp 84-85 °C [lit.[164] 82 °C]; ν_{max} (solid/cm^{-1}) 3243 (N−H), 3074, 2921, 2850, 1748 (C=O), 1639 (C=O), 1555; δ_H (600 MHz, MeOD) 7.34-7.27 (m, 4H, Ph), 7.24 (m, 1H, Ph), 3.93 (s, 2H, CH_2), 3.70 (s, 3H, OMe), 3.58 (s, 2H, $PhCH_2$); δ_C (150 MHz, MeOD) 174.6, 171.8, 136.6, 130.2, 129.6, 127.9, 52.6, 43.5, 42.0; HRMS: Found (EI): $[M]^+$ 207.08894 $C_{11}H_{13}NO_3$, requires 207.08954.

***N*-(2-Amino-2-oxoethyl)-2-phenylacetamide 63l**



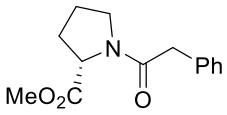
Prepared according to General Procedure (1) at 100 °C for 24 h to yield a white solid (139 mg, 72%); mp 170-172 °C; ν_{max} (solid/cm^{-1}) 3373 (N−H), 3319 (N−H), 3191 (N−H), 3063, 3032, 1641 (C=O), 1638 (C=O), 1541; δ_H (600 MHz, DMSO-d_6) 8.20 (t, J = 5.5 Hz, 1H, NH), 7.32 (s, 1H, NH), 7.30-7.25 (m, 4H, Ph), 7.23-7.19 (m, 1H, Ph), 7.03 (s, 1H, N*H*), 3.63 (d, J = 5.7 Hz, 2H, NHCH_2), 3.47 (s, 2H, $PhCH_2$); δ_C (150 MHz, DMSO-d_6) 170.9, 170.4, 136.4, 129.2, 128.2, 126.3, 42.1, 41.9; LRMS (ES+): 215 ([M+Na]$^+$, 100), 193 ([M+H]$^+$, 80); HRMS: Found (ES+): $[M+H]^+$ 193.0969 $C_{10}H_{13}N_2O_2$, requires 193.0977.

(*S*)-2-(2-Phenylacetamido)propanamide 63m



Prepared according to General Procedure (1) at 100 °C for 5 h to yield a white solid (55 mg, 54%, er 67:33, determined using chiral HPLC); mp 111-113 °C; ν_{max} (solid/cm^{-1}) 3359, 3274, 2977, 1640 (C=O), 1635 (C=O), 1535; $[\alpha]_D$ +36.3 (*c* 1.0, MeOH, 21.5 °C); δ_H (600 MHz, DMSO-d_6) 8.18 (d, J = 7.6 Hz, 1H, NH), 7.35 (br s, 1H, NH), 7.31-7.24 (m, 4H, ArH), 7.20 (t, J = 6.9 Hz, 1H, ArH), 6.99 (br s, 1H, NH), 4.20 (p, J = 7.2 Hz, 1H, CH), 3.46 (s, 2H, CH_2), 1.19 (d, J = 7.2 Hz, 3H); δ_C (150 MHz, DMSO-d_6) 174.3, 169.8, 136.5, 129.1, 128.2, 126.3, 48.0, 42.0, 18.6; LRMS (ES+): 229 ([M+Na]$^+$, 100), 207 ([M+H]$^+$, 50); HRMS: Found (ES+): $[M+Na]^+$ 229.0943 $C_{11}H_{14}N_2ONa$, requires 229.0953.

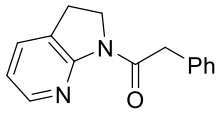
(*S*)-Methyl-1-(2-phenylacetyl)pyrrolidine-2-carboxylate 63n



A complex mixture of rotamers (~1:0.18). ^{1}H NMR shifts reported for both rotamers; ^{13}C NMR shifts reported for major rotamer.

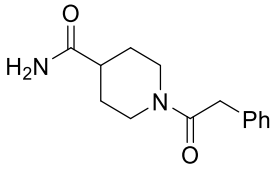
Prepared according to General Procedure (1) at 100 °C for 5 h to yield a colourless oil (93 mg, 75%, er 91:9, determined using chiral HPLC); $[\alpha]_D$ −57.6 (*c* 0.25, MeOH, 25 °C); ν_{max} (film/cm^{-1}) 2952, 2879, 1739 (C=O), 1640 (C=O), 1416; δ_H (600 MHz, $CDCl_3$) 7.31-7.19 (m, 5H, ArH), 4.49 (dd, *J* = 8.5, 4.1 Hz, 0.84H, NC*H*CH_2, major rotamer), 4.43 (dd, *J* = 8.5, 2.4 Hz, 0.16H, minor rotamer), 3.71-3.59 (3 × br s, 5H, CH_3 and CH_2), 3.59 (m, 1H), 3.48 (m, 1H), 2.15 (m, 1H), 2.01 (m, 1H), 1.93 (m, 2H); δ_C (150 MHz, $CDCl_3$) 172.9, 169.9, 134.5, 129.1, 128.7, 126.9, 59.0, 52.3, 47.4, 42.0, 29.3, 25.0; LRMS (ES+): 248 ([M+H]$^+$, 50); HRMS: Found (ES+): [M+H]$^+$ 248.1287 $C_{14}H_{18}NO_3$, requires 248.1287.

1-(2,3-Dihydro-1*H*-pyrrolo[2,3-b]pyridin-1-yl)-2-phenylethanone 63o



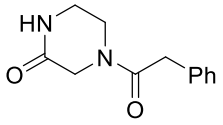
Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography (EtOAc:CH_2Cl_2 1:4 to EtOAc) to yield an orange oil (61 mg, 51%); ν_{max} (film/cm^{-1}) 3029 (N-H), 2915, 1650 (C=O), 1587, 1416; δ_H (600 MHz, $CDCl_3$) 8.16 (dd, *J* = 5.0, 0.9 Hz, 1H, ArH), 7.46 (dd, *J* = 7.6, 0.9 Hz, 1H, ArH), 7.42-7.38 (m, 2H, ArH), 7.29 (t, *J* = 7.6 Hz, 2H, ArH), 7.22 (t, *J* = 7.4 Hz, 1H, ArH), 6.89 (dd, *J* = 7.4, 5.1 Hz, 1H, ArH), 4.59 (s, 2H, $PhCH_2$), 4.12 (t, *J* = 8.6 Hz, 2H, NCH_2), 3.04 (t, *J* = 8.6 Hz, 2H, NCH_2CH_2); δ_C (150 MHz, $CDCl_3$) 170.9, 155.9, 146.1, 135.8, 133.6, 129.9, 128.4, 126.7, 126.3, 118.3, 46.0, 42.4, 24.3; LRMS (ES+): 239 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 239.1192 $C_{15}H_{14}N_2O$, requires 239.1184. Data in agreement with the literature.[165]

1-(2-Phenylacetyl)piperidine-4-carboxamide 63p



Prepared according to General Procedure (1) at 125 °C for 24 h to yield a white solid (33 mg, 27%); mp 137-139 °C; ν_{max} (solid/cm^{-1}) 3400 (N-H), 3205 (N-H), 2942, 1662 (C=O), 1636 (C=O); δ_H (400 MHz, $CDCl_3$) 7.37-7.22 (m, 5H, Ph), 5.49 (br s, 2H, NH_2), 4.63-4.57 (m, 1H), 3.94-3.86 (m, 1H), 3.73 (s, 2H, $PhCH_2$), 3.05-2.98 (m, 1H), 2.74-2.67 (m, 1H), 2.33 (tt, *J* = 11.3, 3.9 Hz, 1H, CH), 1.88 (br d, *J* = 13.5 Hz, 1H), 1.74 (br d, *J* = 13.5 Hz, 1H), 1.63-1.58 (m, 1H), 1.48-1.38 (m, 1H); δ_C (150 MHz, $CDCl_3$) 176.9, 169.6, 135.1, 128.9, 128.7, 127.0, 45.7, 42.3, 41.4, 41.2, 28.7, 28.5; LRMS (ES+): 247 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 247.1449 $C_{14}H_{19}N_2O_2$, requires 247.1447.

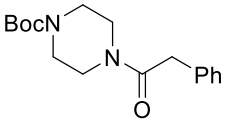
4-(2-Phenylacetyl)piperazin-2-one 63q



A mixture of two rotamers (1:0.88). Shifts for major rotamer described.

Prepared according to General Procedure (1) at 125 °C for 24 h to yield white solid (39 mg, 33%); mp 135-136 °C; ν_{max} (solid/cm^{-1}) 3218 (N-H), 2906, 2882, 1669 (C=O), 1624 (C=O), 1449; δ_H (400 MHz, DMSO-d_6, 120 °C) 7.72 (s, 1H, NH), 7.43-7.10 (m, 5H, Ph), 4.02 (s, 2H), 3.75 (s, 2H), 3.67 (t, *J* = 5.3 Hz, 2H), 3.19 (m, 2H); δ_C (150 MHz, $CDCl_3$) 169.9, 167.6, 134.3, 129.5, 129.1, 128.8, 49.1, 41.0, 40.7, 38.5; LRMS (ES+): 241 ([M+Na]$^+$, 100); HRMS: Found (ES+): [M+Na]$^+$ 241.0994 $C_{14}H_{14}N_2O_2Na$, requires 241.0953.

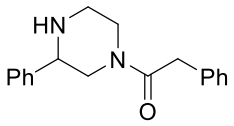
***Tert*-butyl-4-(2-phenylacetyl)piperazine-1-carboxylate 63r**



Prepared according to General Procedure (1) at 100 °C for 5 h to yield a white solid (90 mg, 59%); mp 114-116 °C [lit.[166] 113-115 °C]; ν_{max} (solid/cm^{-1}) 2979, 2921, 2858, 1696 (C=O), 1630 (C=O), 1496, 1454; δ_H (600 MHz, $CDCl_3$) 7.33-7.30 (m, 2H, Ph), 7.25-7.22 (m, 3H, Ph), 3.74 (s, 2H, $PhCH_2$), 3.63-3.59 (m, 2H, CH_2), 3.38-3.35 (m, 4H, 2 × CH_2), 3.23-3.19 (m, 2H, CH_2), 1.43 (s, 9H, ^{t}Bu); δ_C (150 MHz,

$CDCl_3$) 169.8, 154.6, 134.9, 129.0, 128.6, 127.1, 80.4, 46.0, 41.7, 41.3, 28.5; LRMS (CI): 305 ([M+H]$^+$, 20), 277 (10), 249 ([M–C_4H_7]$^+$, 100), 205 (10). Data in agreement with the literature.[166]

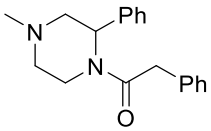
2-Phenyl-1-(3-phenylpiperazin-1-yl)ethanone 63s



A complex mixture of two rotamers (0.57:0.43). ^{1}H NMR shifts for rotamer combined integrations reported; where possible, major and minor rotamers are separated, reported as fractions (0.57:0.43) and denoted by a dagger (†) an asterix (*) respectively. All ^{13}C NMR peaks are reported.

Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography to yield a colourless oil (217 mg, 78%); ν_{max} (film/cm^{-1}) 3304 (N-H), 3027, 2907, 1631 (C=O); δ_H (600 MHz, $CDCl_3$) 7.44-7.21 (m, 9H, Ph), 7.15-7.12 (m, 1H, Ph), 4.67-4.63 (m, 0.53H and 0.47H, $NHCH_2CHH^†$ and $PhCHCHH^*$), 3.82-3.79* (m, 0.43H, $NHCH_2CHH$), 3.77-3.75 (m, 2 × 0.57H, $PhCHHCO^†$, $PhCHCHH^†$ and 2 × 0.43H, $PhCH_2^*$), 3.70† (d, J = 15.0 Hz, 0.57H, PhCHHCO), 3.66* (dd, J = 10.6, 3.0 Hz, 0.43H, CH), 3.25† (dd, J = 10.6, 2.8 Hz, 0.57H, CH), 3.17* (td, J = 12.9, 3.1 Hz, 0.43H, NHCHH), 3.09-7.06† (m, 0.57H, NHCHH), 3.02-2.99* (m, 0.43H, NHCHH), 2.97-2.95† (m, 0.57H, PhCHCHH), 2.79-2.77† (m, 2 × 0.57H, NHCHH and $NHCH_2CHH$), 2.66-2.63* (m, 0.43H, $NHCH_2CHH$), 2.60-2.57* (m, 0.43H, PhCHCHH), 1.95 (br s, 1H, NH); δ_C (150 MHz, $CDCl_3$) δ_C (150 MHz, $CDCl_3$) 169.6, 169.5, 141.3, 140.9, 135.4, 135.3, 129.0, 128.9, 128.8, 128.8, 128.7, 128.7, 128.1, 128.0, 127.1, 127.0, 127.0, 126.9, 60.9, 60.1, 53.9, 49.1, 46.6, 46.4, 46.0, 42.1, 41.5, 41.3; LRMS (EI): 280 ([M]$^+$, 100); HRMS: Found (EI): [M]$^+$ 280.1593 $C_{18}H_{20}N_2O$, requires 280.1576.

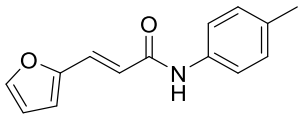
1-(4-Methyl-2-phenylpiperazin-1-yl)-2-phenylethanone 63t



Prepared according to General Procedure (1) at 125 °C for 24 h and the product purified by flash column chromatography to yield a colourless oil (145 mg, 49%); ν_{max} (film/cm^{-1}) 2939, 2689, 1633 (C=O); δ_H (400 MHz, DMSO-d_6, 120 °C) 7.39 (m, 2H, Ph), 7.33-7.21 (m, 8H, Ph), 5.54 (br s, 1H), 3.99 (d, J = 13.4 Hz, 1H), 3.83 (d, J = 15.2 Hz, 1H), 3.75 (d, J = 15.2 Hz, 1H), 3.32 (dt, J = 12.0, 1.7 Hz, 1H), 3.03 (td, J

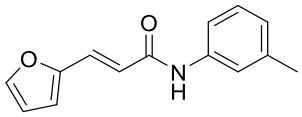
= 13.0, 3.3 Hz, 1H), 2.71 (ddt, *J* = 11.1, 3.4, 1.8 Hz, 1H), 2.25 (dd, *J* = 12.0, 4.3 Hz, 1H), 2.20 (s, 3H), 1.91 (td, *J* = 11.7, 3.4 Hz, 1H); δ_C (100 MHz, DMSO-d_6, 120 °C) 169.9, 140.8, 136.3, 129.4, 128.6, 128.5, 127.7, 126.9, 126.8, 57.7, 55.2, 52.8, 46.0, 45.6, 40.3; LRMS (ES+): 295 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 295.1798 $C_{19}H_{22}N_2O$, requires 295.1810.

(*E*)-3-(Furan-2-yl)-*N*-(p-tolyl)acrylamide 65



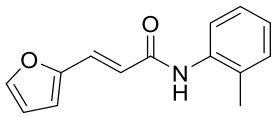
Prepared according to General Procedure (1) at 125 °C for 24 h to yield a white solid (118 mg, 54%); mp 154-155 °C; ν_{max} (solid/cm^{-1}) 3300 (N-H), 1659 (C=O), 1601 (C=C), 1561, 1510; δ_H (600 MHz, $CDCl_3$) 7.79 (br s, 1H, NH), 7.56-7.46 (m, 3H, 2 × ArH and COCHC*H*), 7.41 (br s, 1H, OCH), 7.12-7.10 (m, 2H, ArH), 6.52-6.50 (m, 2H, OCHCHC*H* and COC*H*), 6.44 (br s, 1H, OCHC*H*), 2.31 (s, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 164.2, 151.4, 144.3, 135.7, 134.1, 129.6, 128.8, 120.2, 118.9, 114.4, 112.4, 21.0; LRMS (ES+): 250 ($[M+Na]^+$, 100), 228 ($[M+H]^+$, 30); HRMS: Found (ES+): $[M+H]^+$ 228.1015 $C_{14}H_{14}NO_2$, requires 228.1025.

(*E*)-3-(Furan-2-yl)-*N*-(m-tolyl)acrylamide 66



Prepared according to General Procedure (1) at 125 °C for 24 h to yield a white solid (105 mg, 28%); mp 104-105 °C; ν_{max} (solid/cm^{-1}) 3263 (N-H), 1657 (C=O), 1610, 1547; δ_H (600 MHz, $CDCl_3$) 8.13 (s, 1H, NH), 7.51-7.49 (m, 2H, ArH and COCHC*H*), 7.44 (d, *J* = 7.1 Hz, 1H, ArH), 7.37 (d, *J* = 1.4 Hz, 1H, OCH), 7.17 (t, *J* = 7.8 Hz, 1H, ArH), 6.91 (d, *J* = 7.3 Hz, 1H, ArH), 6.58 (d, *J* = 15.2 Hz, 1H, COC*H*), 6.48 (br s, 1H, OCCH), 6.42 (br s, 1H, OCHC*H*), 2.27 (s, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 164.5, 151.4, 144.3, 139.0, 138.2, 128.9 (2 × C), 125.3, 120.9, 119.0, 117.4, 114.4, 112.4, 21.6; LRMS (ES+): 228 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 228.1020 $C_{14}H_{14}NO_2$, requires 228.1025.

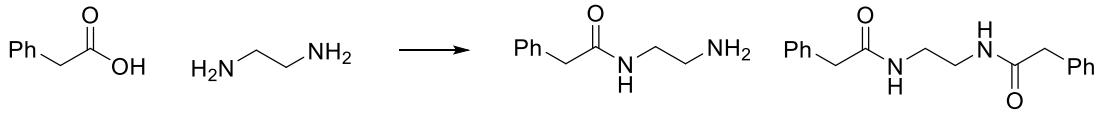
(*E*)-3-(Furan-2-yl)-*N*-(o-tolyl)acrylamide 67



Prepared according to General Procedure (1) at 125 °C for 24 h to yield an off-white solid (100 mg, 35%); mp 112-114 °C; ν_{max} (solid/cm^{-1}) 3243 (N-H), 3117, 1658 (C=O), 1584; δ_H (600 MHz, $CDCl_3$) 7.91 (br s, 1H, NH), 7.51 (d, *J* = 15.2 Hz, 1H, COCHC*H*), 7.43-7.42 (m, 2H, 2 × ArH), 7.24-7.14 (m, 2H, 2 × ArH), 7.08 (br s, 1H, ArH), 6.54-6.46 (m, 3H, COCH and 2 × ArH), 2.27 (s, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 164.2, 151.4, 144.4, 135.9, 130.6, 129.1 (2 × C), 126.9, 125.3, 123.3, 118.7, 114.5, 112.4, 18.0; LRMS (ES+): 228 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 228.1014 $C_{14}H_{14}NO_2$, requires 228.1025.

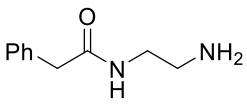
6.3.2 Diamines

Reaction of phenylacetic acid with ethylenediamine



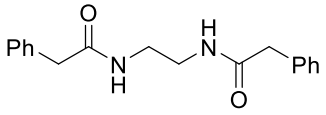
A solution of phenylacetic acid (272 mg, 2.00 mmol) and ethylenediamine (120 mg, 2.00 mmol) in MeCN (4 mL, 0.5 M) was stirred with $B(OCH_2CF_3)_3$ (1232 mg, 4.00 mmol) at 80 °C for 15 h. Upon completion, the reaction mixture was diluted with EtOAc (4 mL) and water (0.5 mL) and stirred with Amberlyst® A26(OH) and Amberlite® IRA743 for 30 min. The mixture was dried ($MgSO_4$), filtered, the solids were washed with EtOAc (3 × 50 mL). The products **71a** and **71** were then isolated by flash column chromatography (1% Et_3N/CH_2Cl_2-5% MeOH/1% Et_3N/CH_2Cl_2).

***N*-(2-Aminoethyl)-2-phenylacetamide 71a**



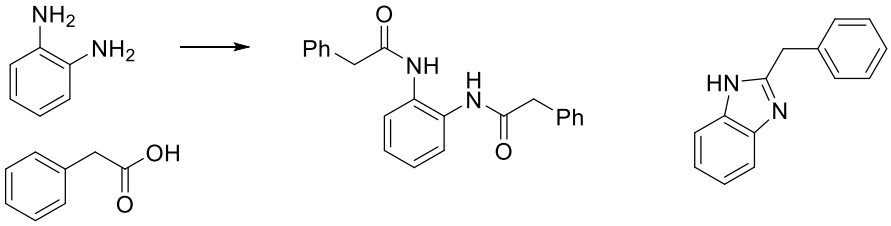
Off-white oily solid (228 mg, 64%); mp ~ 25 °C [lit.[167] 20-25 °C]; δ_H (600 MHz, $CDCl_3$) 7.37-7.22 (m, 5H), 5.89 (br s, 1H, NH), 3.58 (s, 2H, $PhCH_2$), 3.25 (q, *J* = 5.9 Hz, 2H, CONHC*H*$_2$), 2.75 (t, *J* = 6.0 Hz, 2H, NH_2CH_2), 1.36 (br s, 2H, NH_2); δ_C (150 MHz, $CDCl_3$) 171.4, 135.1, 129.52, 129.1, 127.4, 44.0, 42.3, 41.4; LRMS (ES+): 179 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 179.1191 $C_{10}H_{15}N_2O$, requires 179.1184. Data in agreement with the literature.[168]

***N,N'*-(Ethane-1,2-diyl)bis(2-phenylacetamide) 71b**



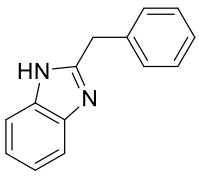
White solid (55 mg, 9%); mp 196-197 °C [lit.[169] 202 °C]; ν_{max} (solid/cm^{-1}) 3287 (N-H), 3084, 3063, 3032, 2922, 1636 (C=O), 1556 (C=C); δ_H (600 MHz, CD_3OD) 7.31-7.18 (m, 10H, Ar), 3.45 (s, 4H, 2 × NHC*H*$_2$), 3.27 (s, 4H, 2 × ArCH_2); δ_C (150 MHz, CD_3OD) 173.1 (C=O), 135.2, 129.0, 128.5, 126.9, 42.9, 39.0; HRMS: Found (EI): 296.15191 $C_{18}H_{20}N_2O_2$, requires 296.15248.

Reaction of phenylacetic acid with o-phenylenediamine



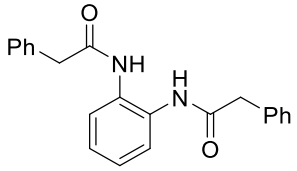
A solution of phenylacetic acid (137 mg, 1.0 mmol) and 1,2-diaminobenzene (110 mg, 1.0 mmol) in MeCN (2.0 mL, 0.5 M) was stirred with $B(OCH_2CF_3)_3$ (615 mg, 2.0 mmol) at 80 °C for 15 h. Upon completion, the reaction mixture was diluted with EtOAc (4 mL) and water (0.5 mL) and stirred with Amberlyst® A26(OH) and Amberlite® IRA743 for 30 min. The mixture was dried ($MgSO_4$), filtered, the solids were washed with EtOAc (3 × 50 mL). The products **76a** and **76b** were then isolated by flash column chromatography (CH_2Cl_2-2% MeOH/CH_2Cl_2).

2-Benzyl-benzimidazole 76a



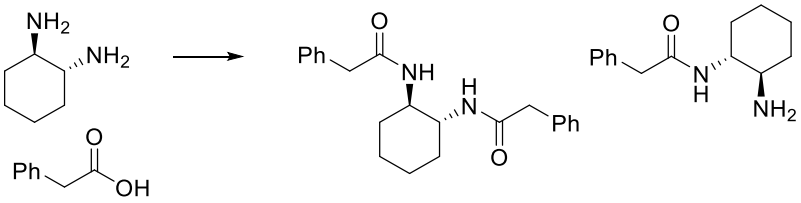
White solid (178 mg, 79%); mp 196-197 °C [lit.[170] 195-196 °C]; ν_{max} (solid/cm^{-1}) 2875 (C-H), 2734, 1536 (C=C), 1425; δ_H (600 MHz, DMSO-d_6) 12.36 (br s, 1H, NH), 7.51 (br s, 1H, NHCC*H*), 7.41 (br s, 1H, NCCH), 7.33-7.30 (m, 4H, Ph), 7.24-7.22 (m, 1H, Ph), 7.12 (br s, 1H, NHCCHC*H*), 7.11 (br s, 1H, NCCHC*H*), 4.16 (s, 2H, $PhCH_2$); δ_C (150 MHz, DMSO-d_6) 153.5, 143.5 (br), 137.7, 134.5 (br), 128.8, 128.5, 126.6, 121.6 (br), 121.0 (br), 118.3 (br), 111.0 (br), 35.0; LRMS (CI): 209 ([M+H]$^+$, 100); HRMS: Found (ES+): 209.1085 $C_{14}H_{13}N_2$, requires 209.1085. Data in agreement with the literature.[171]

***N,N'*-(1,2-Phenylene)bis(2-phenylacetamide) 76b**



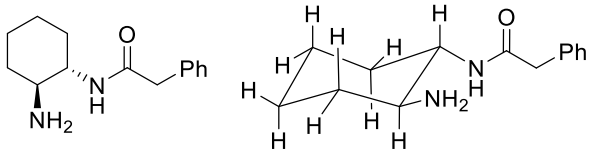
White solid (21 mg, 6%); mp 170-172 °C; ν_{max} (solid/cm^{-1}) 3211 (N-H), 2915, 1631 (C=O); δ_H (600 MHz, $CDCl_3$) 8.05 (d, J = 7.8 Hz, 1H, NH), 7.69-7.14 (m, 15H, Ar and 2 × NH), 3.60 (s, 4H, 2 × $PhCH_2$); δ_C (150 MHz, $CDCl_3$) 170.3, 134.5, 129.7, 129.4, 129.3, 127.9, 126.6, 125.4, 44.4; LRMS (ES+): 345 ([M+H]$^+$, 100); HRMS: Found (ES+): 345.1619 $C_{22}H_{21}N_2O_2$, requires 345.1603.

<u>Reaction of phenylacetic acid with 1,2-diaminocyclohexane</u>



A solution of phenylacetic acid (69 mg, 0.50 mmol) and (1*R*)-trans-1,2-cyclohexanediamine (56 mg, 0.49 mmol) in MeCN (1.0 mL, 0.5 M) was stirred with $B(OCH_2CF_3)_3$ (308 mg, 1.0 mmol) at 80 °C for 15 h. Upon completion, the reaction mixture was diluted with EtOAc (4 mL) and water (0.5 mL) and stirred with Amberlyst® A26(OH) and Amberlite® IRA743 for 30 min. The mixture was dried ($MgSO_4$), filtered, the solids were washed with EtOAc (3 × 50 mL). The products **77a** and **77b** were then isolated by flash column chromatography (EtOAc-5% MeOH/EtOAc).

***N*-((1*R*,2*R*)-2-Aminocyclohexyl)-2-phenylacetamide 77a**

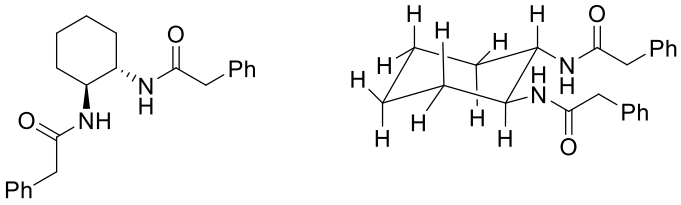


NMR suggests the equatorial arrangement of the amide and amine moieties. Where possible, proton peaks are assigned as equatorial and axial.

White solid (50 mg, 44%); mp 125-128 °C; $[\alpha]_D^{25}$ +12.1 (*c* 1.0, $CHCl_3$); ν_{max} (solid/cm^{-1}) 3289 (br N-H), 3062, 2929, 2855, 1639 (C=O), 1550; δ_H (600 MHz, $CDCl_3$) 7.38-7.31 (m, 2H, Ph), 7.31-7.22 (m, 3H, Ph), 5.51 (d, J = 8.3 Hz, 1H, NH), 3.60 (d, J_{AB} = 15.7 Hz, 1H, PhCH_AH$_B$), 3.56 (d, J_{AB} = 15.7 Hz, 1H, PhCH$_A$$H_B$), 3.52-

3.47 (m, 1H, NHCH_{ax}), 2.26 (td, J = 10.3, 4.0 Hz, 1H, NH_2CH_{ax}), 1.92-1.85 (m, 2H, NHCHC$H_{eq}H_{ax}$ and $NH_2CHCH_{eq}H_{ax}$), 1.80 (br s, 2H, NH_2), 1.69-1.61 (m, 2H, $NHCHCH_2CH_{eq}H_{ax}$ and $NH_2CHCH_2CH_{eq}H_{ax}$), 1.28-1.23 (m, 1H, $NHCHCH_2CH_{eq}H_{ax}$), 1.21-1.12 (m, 2H, $NH_2CHCH_2CH_{eq}H_{ax}$ and $NH_2CHCH_{eq}H_{ax}$), 1.00 (qd, J = 12.7, 3.6 Hz, 1H, $NHCHCH_{eq}H_{ax}$); δ_C (150 MHz, $CDCl_3$) 171.5, 135. 2, 129.4, 129.1, 127.4, 56.2, 55.4, 44.1, 35.1, 32.4, 25.1, 25.0; LRMS (CI): 233 ($[M+H]^+$, 100), 216 (30), 98 (20); HRMS: Found (CI): $[M+H]^+$ 233.16539 $C_{14}H_{21}N_2O$, requires 233.16539.

***N,N'*-((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(2-phenylacetamide) 77b**



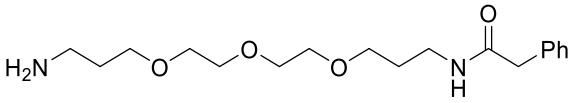
NMR suggests the equatorial arrangement of the amide and amine moieties. Where possible, proton peaks are assigned as equatorial and axial.

White solid (34 mg, 20%); mp 265-266 °C; $[\alpha]_D^{25}$ +65.4 (*c* 1.0, $CHCl_3$); ν_{max} (solid/cm^{-1}) 3291, 3259 (N-H), 2932, 1638 (C=O), 1542 (C=C), 1494; δ_H (600 MHz, $CDCl_3$) 7.33-7.28 (m, 4H, Ph), 7.26-7.22 (m, 2H, Ph), 7.16-7.12 (m, 4H, Ph), 5.85 (d, J = 5.2 Hz, 2H, 2 × NH), 3.58-3.53 (m, 2H, 2 × CONHC*H*), 3.35 (2 × d, J = 15.2 Hz, 4H, 2 × $PhCH_2$), 1.92-1.90 (m, 2H, 2 × NHCHC$H_{eq}H_{ax}$), 1.68-1.67 (m, 2H, 2 × $NHCHCH_2CH_{eq}H_{ax}$), 1.24-1.21 (m, 2H, 2 × $NHCHCH_2CH_{eq}H_{ax}$), 1.12-1.09 (m, 2H, 2 × $NHCHCH_{eq}H_{ax}$); δ_C (150 MHz, $CDCl_3$) 171.6 (C=O), 134.9, 129.4, 129.0, 127.4, 53.7, 43.9, 32.3, 24.7; LRMS (CI): 351 ($[M+H]^+$, 100); HRMS: Found (CI): $[M+H]^+$ 351.20725 $C_{22}H_{27}N_2O_2$, requires 351.20725.

Reaction of phenylacetic acid with 4,7,10-trioxa-1,13-tridecanediamine

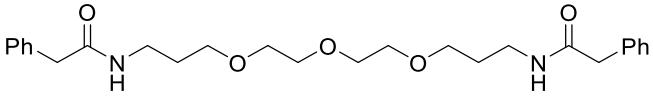
A solution of phenylacetic acid (136 mg, 1.0 mmol) and 4,7,10-trioxa-1,13-tridecanediamine (0.219 mL, 1.0 mmol) in CPME (2.0 mL, 0.5 M) was stirred with $B(OCH_2CF_3)_3$ (0.43 mL, 2.0 mmol) at 80 °C for 15 h. Upon completion, the reaction mixture was diluted with EtOAc (4 mL) and water (0.5 mL) and stirred with Amberlyst® A26(OH) and Amberlite® IRA743 for 30 min. The mixture was dried ($MgSO_4$), filtered, the solids were washed with EtOAc (3 × 50 mL). The products **78a** and **78b** were then isolated by flash column chromatography (CH_2Cl_2-20% MeOH/CH_2Cl_2).

***N*-(3-(2-(2-(3-Aminopropoxy)ethoxy)ethoxy)propyl)-2-phenylacetamide 78a**



Clear oil (178 mg, 53%); δ_H (600 MHz, $CDCl_3$) 7.32-7.27 (m, 2H, Ar), 7.25-7.19 (m, 3H, Ar), 6.51 (br s, 1H, NH), 3.58-3.54 (m, 2H, OCH_2), 3.54-3.47 (m, 8H, $PhCH_2$, 3 × OCH_2), 3.47-3.42 (m, 4H, $NHCH_2CH_2CH_2$ and $NH_2CH_2CH_2CH_2$), 3.28 (app q, J = 6.1 Hz, 2H, $NHCH_2$), 2.75 (t, J = 6.6 Hz, 2H, NH_2CH_2), 2.37 (br s, 2H, NH_2), 1.68 (app p, J = 6.1 Hz, 4H, $NHCH_2CH_2$ and $NH_2CH_2CH_2$); δ_C (150 MHz, $CDCl_3$) 171.1, 135.5, 129.5, 128.9, 127.1, 70.6 (2 × CH_2), 70.2, 70.1, 69.8, 69.6, 43.9, 39.7, 37.9, 32.8, 29.0; LRMS (ES+): 339 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 339.2282 $C_{18}H_{31}N_2O_4$, requires 339.2284. Data in agreement with the literature.[172]

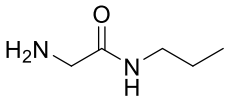
***N,N'*-(((Oxybis(ethane-2,1-diyl))bis(oxy))bis(propane-3,1-diyl))bis(2-phenylacetamide) 78b**



White solid (77 mg, 17%); mp 75-77 °C; ν_{max} (solid/cm^{-1}) 3243 (N-H), 3066, 2870, 1654 (C=O), 1545; δ_H (600 MHz, $CDCl_3$) 7.34-7.28 (m, 4H), 7.26-7.20 (m, 6H), 6.17 (br s, 2H, 2 × NH), 3.51-3.47 (m, 8H, 2 × $PhCH_2$ and 2 × OCH_2), 3.47-3.45 (m, 4H, 2 × OCH_2), 3.43 (t, J = 5.9 Hz, 4H, 2 × $NHCH_2CH_2CH_2$), 3.28 (app q, J = 6.3 Hz, 4H, 2 × $NHCH_2$), 1.71-1.64 (app p, J = 6.3 Hz, 4H, 2 × $NHCH_2CH_2$); δ_C (150 MHz, $CDCl_3$) 171.1, 135.4, 129.5, 129.0, 127.2, 70.5, 70.1, 69.9, 43.9, 38.0, 29.1; LRMS (ES+): 457 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 457.2698 $C_{26}H_{37}N_2O_5$, requires 457.2702. NMR data in agreement with the literature.[173]

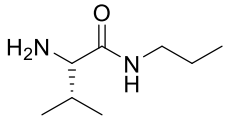
6.3.3 Unprotected amino acids

2-Amino-*N*-propylacetamide 98a



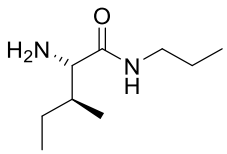
Prepared according to General Procedure (2), Method A, at 80 °C for 15 h to give a yellow oil (41 mg, 71%); ν_{max} (film/cm^{-1}) 3297, 2961, 2873, 1643 (C=O), 1539; δ_H (300 MHz, $CDCl_3$) 3.30 (s, 2H, $COCH_2$), 3.24 (m, 2H, $CONHCH_2$), 1.62 (br s, 2H, NH_2), 1.53 (m, 2H, CH_3CH_2), 0.93 (t, J = 7.4 Hz, 3H, CH_3); δ_C (75 MHz, $CDCl_3$) 172.8, 44.9, 40.8, 23.0, 11.5; LRMS (ES+): 117 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 117.1025 $C_5H_{13}N_2O$, requires 117.1028.

(*S*)-2-Amino-3-methyl-*N*-propylbutanamide 98b[85]



Prepared according to General Procedure (2), Method A, at 125 °C for 15 h to give a colourless oil (155 mg, 98%, er 70:30, determined using Marfey's reagent); ν_{max} (film/cm^{-1}) 3289, 2962, 2868, 1645 (C=O); δ_H (600 MHz, $CDCl_3$) 7.32 (br s, 1H, NH), 3.21-3.12 (m, 3H, NH_2CH and $NHCH_2$), 2.28-2.18 (m, 1H, $(CH_3)_2CH$), 1.49 (br s, 2H, NH_2), 1.48 (sx, J = 7.3 Hz, 2H, CH_3CH_2), 0.93 (d, J = 7.0 Hz, 3H, CH_3CH), 0.91-0.83 (m, 3H, CH_3CH_2), 0.77 (d, J = 7.0 Hz, 3H, CH_3CH); δ_C (150 MHz, $CDCl_3$) 174.2, 60.2, 40.8, 30.7, 23.1, 19.8, 16.1, 11.5; Data in agreement with the literature.[85]

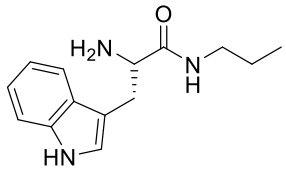
***(2S,3S)*-2-Amino-3-methyl-*N*-propylpentanamide 98d**



Prepared according to General Procedure (2), Method A, at 125 °C for 15 h to give a yellow oil (155 mg, 90%, dr 75:25) or method B, at 125 °C for 5 h to give a yellow oil (131 mg, 76%, dr 83:17); $[\alpha]_D^{20}$ +3.41 (*c* 1.2, MeOH); ν_{max} (film/cm^{-1}) 3325, 2899, 1660 (C=O); δ_H (600 MHz, $CDCl_3$, both diastereoisomers reported, where possible major (*) and minor (†) peaks are denoted) 7.41† (br s, 0.17H, NH), 7.30* (br s, 0.83H, NH), 3.29† (d, J = 3.2 Hz, 0.17H, COC*H*), 3.29† (d, J = 3.2 Hz, 0.17H, COC*H*), 3.24-3.08 (m, 2.70H), 2.05-2.02 (m, 0.17H), 1.96-1.89 (m, 0.83H), 1.52-

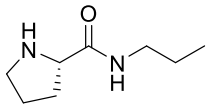
1.44 (m, 2.07H), 1.38-1.28 (m, 2.62H),0.72† (d, *J* = 6.9 Hz, 0.51H, C*H*$_3$CH), 0.84* (t, *J* = 7.4 Hz, 2.51H, C*H*$_3$CH$_2$CH$_2$NH), 1.27-1.20† (m, 0.34H, CH$_2$), 1.04* (m, 0.83H, CH$_3$CH$_2$C*H*), 0.91* (d, *J* = 7.0 Hz, 2.51H, C*H*$_3$CH), 0.87* (t, *J* = 7.4 Hz, 3.41H); δ_C (150 MHz, DMSO-*d*$_6$) 174.5, 59.4, 57.7, 40.1, 38.5, 37.9, 26.1, 23.8, 22.5, 22.5, 15.9, 13.6, 11.8, 11.6, 11.5, 11.4; LRMS (CI): 173 ([M+H]$^+$, 100); HRMS: Found (CI): [M+H]$^+$ 173.16480 $C_9H_{21}N_2O$, requires 173.16484.

(*S*)-2-Amino-3-(1*H*-indol-3-yl)-*N*-propylpropanamide 98e



Prepared according to General Procedure (2), Method A, at 80 °C for 15 h to give a brown oil (220 mg, 92%, er 83:17, determined using Marfey's reagent) or according to method B, at 80 °C for 5 h to yield a brown oil (191 mg, 78%, er 87:13, determined using Marfey's reagent); $[\alpha]_D^{25}$ +11.2 (*c* 0.95, MeOH, 25 °C); ν_{max} (film/cm^{-1}) 3261 (N-H), 2960, 2927, 2872, 1641 (C=O), 1522; δ_H (600 MHz, $CDCl_3$) 8.68 (s, 1H, ArNH), 7.64 (d, *J* = 8.0 Hz, 1H, Ar), 7.36 (d, *J* = 8.0 Hz, 1H, Ar), 7.32 (t, *J* = 5.6 Hz, 1H, CON*H*), 7.20-7.14 (m, 1H, Ar), 7.11-7.07 (m, 1H, Ar), 7.02 (d, *J* = 1.8 Hz, 1H, Ar), 3.69 (dd, J_{AX} = 9.0 Hz, J_{BX} = 4.2 Hz, 1H, COCH_X), 3.37 (dd, J_{AB} = 14.5, J_{AX} = 4.2 Hz, 1H, ArCH_AH$_B$), 3.21 (app q, *J* = 6.5 Hz, 2H, NHCH_2), 2.89 (dd, J_{AB} = 14.5 Hz, J_{BX} = 9.0 Hz, 1H, ArCH$_A$$H_B$), 1.51-1.45 (m, C$H_2CH_3$), 0.88 (t, *J* = 7.4 Hz, 3H, CH$_3$); δ_C (150 MHz, $CDCl_3$) 175.1, 136.6, 127.6, 123.4, 123.4, 122.2, 119.5, 119.0, 111.5, 55.8, 40.9, 31.0, 22.9, 11.5; LRMS (ES+): 246 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 246.1606 $C_{14}H_{20}N_3O$, requires 246.1606.

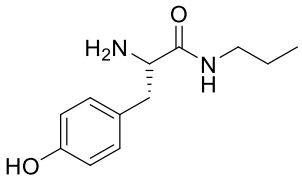
(*S*)-*N*-Propylpyrrolidine-2-carboxamide 98f



Prepared according to General Procedure (2), Method A, at 80 °C for 15 h to give a colourless oil (142 mg, 91%, er > 99:1, determined using Marfey's reagent); $[\alpha]_D^{25}$ −63.2 (*c* 1.0, MeOH); ν_{max} (film/cm^{-1}) 3325, 2899, 1660 (C=O); δ_H (600 MHz, $CDCl_3$) 7.60 (br s, 1H, CONH), 3.64 (dd, *J* = 9.2, 5.3 Hz, 1H, CH), 3.06-3.16 (m, 2H, CONHCH_2), 2.93 (dt, *J* = 10.2, 6.8 Hz, 1H, CH*H*NH), 2.81 (dt, *J* = 10.2, 6.8 Hz, 1H, C*H*HNH), 2.00-2.29 (m, 2H, NH and CHCH*H*), 1.82 (app sx, *J* = 6.4 Hz, 1H,

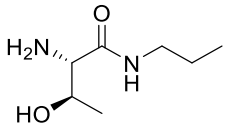
CHC*H*H), 1.57-1.67 (m, 2H, CHCH$_2$C*H*$_2$), 1.40-1.49 (m, 2H, C*H*$_2$CH$_3$), 0.84 (t, *J* = 7.4 Hz, 3H, CH$_3$); δ_C (150 MHz, CDCl$_3$) 175.2, 60.6, 47.3, 40.6, 30.9, 26.3, 23.0, 11.4; HRMS: Found (CI): [M+H]$^+$ 157.134661 $C_8H_{17}N_2O$, requires 157.13409.

(*S*)-2-Amino-3-(4-hydroxyphenyl)-*N*-propylpropanamide 98g



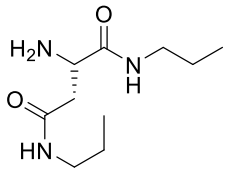
Prepared according to General Procedure (2), Method A, at 80 °C for 15 h to give a yellow oil (60 mg, 27%, er 85:15, determined using chiral HPLC); $[\alpha]_D^{25}$ +4.3 (*c* 0.63, MeOH); ν_{max} (film/cm^{-1}) 3291 (br, O-H), 2961, 2929, 1641 (C=O), 1512; δ_H (600 MHz, CDCl$_3$) 7.34 (t, *J* = 5.8 Hz, 1H, NH), 6.98 (d, *J* = 8.4 Hz, 2H, 2 × CH$_2$CC*H*), 6.79 (d, *J* = 8.4 Hz, 2H, 2 × OHCC*H*), 3.54 (dd, J_{AX} = 8.9 Hz, J_{BX} = 4.4 Hz, 1H, COCH_X), 3.18 (m, 2H, NHC*H*$_2$), 3.09 (dd, J_{AB} = 13.8 Hz, J_{BX} = 4.4 Hz, 1H, ArCH$_A$*H*$_B$), 2.61 (dd, J_{AB} = 13.8 Hz, J_{AX} = 8.9 Hz, 1H, ArC*H*$_A$H$_B$), 1.48 (m, 2H, C*H*$_2$CH$_3$), 0.86 (t, *J* = 7.4 Hz, 3H, CH$_3$); δ_C (150 MHz, CDCl$_3$) 175.1, 155.9, 130.4, 128.4, 115.9, 56.6, 41.1, 40.3, 22.8, 11.5; LRMS (ES+): 223 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 223.1443 $C_{12}H_{19}N_2O_2$, requires 223.1447.

(2*S*,3*R*)-2-Amino-3-hydroxy-*N*-propylbutanamide 98i



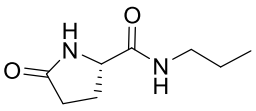
Prepared according to General Procedure (2), Method A, at 80 °C for 15 h in MeCN to give a yellow solid (43 mg, 54%, dr >99:1); mp 75-77 °C; $[\alpha]_D^{20}$ −11.9 (*c* 0.82, MeOH); ν_{max} (solid/cm^{-1}) 3323, 3278 (br O-H), 2962, 1646 (C=O), 1550; δ_H (600 MHz, CDCl$_3$) 7.44 (s, 1H, NH), 4.30-4.27 (m, 1H, COC*H*), 3.31-3.18 (m, 3H, CONHC*H*$_2$ and C*H*OH), 1.77 (br s, 1H, OH), 1.57-1.54 (m, 2H, C*H*$_2$CH$_3$), 1.20 (d, *J* = 6.5 Hz, 3H, C*H*$_3$CHOH), 0.94 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$); δ_C (150 MHz, CDCl$_3$) 173.7, 68.2, 59.5, 40.9, 23.0, 18.8, 11.5; LRMS (ES+): 161 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 161.1290 $C_7H_{17}N_2O_2$, requires 161.1290.

(*S*)-2-Amino-*N*^{1},*N*^{4}-dipropylsuccinamide 98k



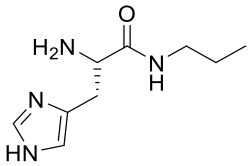
Prepared according to General Procedure (2), Method B, at 80 °C for 15 h and further purified by flash column chromatography (CH_2Cl_2:MeOH 9:1) to give a white solid (152 mg, 71%, er 89:11, determined using Marfey's reagent); mp 130-131 °C; $[\alpha]_D^{20}$ −17.4 (*c* 1.0, MeOH); ν_{max} (solid/cm^{-1}) 3278 (N-H), 2960, 2932, 2872 (C-H), 1633 (C=O), 1546; δ_H (600 MHz, $CDCl_3$) 7.64 (s, 1H, NH), 6.95 (s, 1H, NH), 3.63 (dd, J_{AX} = 8.0 Hz; J_{BX} = 4.3 Hz, 1H, NH_2CH_X), 3.18-3.09 (m, 4H, 2 × $CH_2CH_2CH_3$), 2.61 (dd, J_{AB} = 14.6 Hz; J_{BX} = 4.3 Hz, 1H, $CHCH_AH_B$), 2.45 (dd, J_{AB} = 14.6 Hz; J_{AX} = 8.0 Hz, 1H, $CHCH_AH_B$), 2.21 (s, 2H, NH_2), 1.46 (2 × sx, *J* = 7.4 Hz, 4H, 2 × CH_2CH_3), 0.86 (2 × t, *J* = 7.4, 6H, 2 × CH_3); δ_C (150 MHz, $CDCl_3$) 174.2, 171.3, 52.8, 41.2, 41.1, 40.8, 22.8, 22.8, 11.5, 11.5; LRMS (ES+): 216 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 216.1713 $C_{10}H_{22}N_3O_2$, requires 216.1712.

(*S*)-5-Oxo-*N*-propylpyrrolidine-2-carboxamide 98l



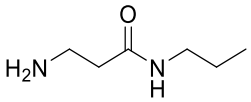
Prepared according to General Procedure (2), Method A, at 80 °C for 15 h to yield a white solid (161 mg, 94%, er 100%, determined using chiral shift reagent); mp 107-109 °C; $[\alpha]_D^{20}$ −11.3 (*c* 0.25, MeOH); ν_{max} (solid/cm^{-1}) 3289, 3090, 2961, 2931, 1695 (C=O), 1652 (C=O), 1552; δ_H (600 MHz, $CDCl_3$) 7.64 (s, 1H, CON*H*CH), 7.01 (t, *J* = 5.1 Hz, 1H, CON*H*CH_2), 4.12 (dd, *J* = 9.0, 4.7 Hz, 1H, CH), 3.20-3.16 (m, 2H, $CH_3CH_2CH_2$), 2.47-2.43 (m, 1H, CH_2CHHCH), 2.36-2.33 (m, 1H, CH_2CHHCH), 2.28-2.22 (m, 1H, $CHHCH_2CH$), 2.18-2.09 (m, 1H, $CHHCH_2CH$), 1.48 (app sx, *J* = 7.3 Hz, 2H, CH_3CH_2), 0.87 (t, *J* = 7.4 Hz, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 179.7, 172.2, 57.3, 41.4, 29.5, 26.1, 22.8, 11.5; LRMS (CI): 188 ([M+H+CH_4]$^+$, 100), 171 ([M+H]$^+$, 30); HRMS: Found (CI): [M+H]$^+$ 171.11281 $C_8H_{15}N_2O_2$, requires 171.11280.

(*S*)-2-Amino-3-(1*H*-imidazol-4-yl)-*N*-propylpropanamide 98m



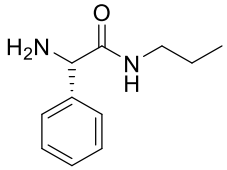
Prepared according to General Procedure (2), Method B, at 80 °C for 15 h and purified by flash column chromatography to yield a yellow oil (57 mg, 29%); $[\alpha]_D^{20}$ +5.5 (*c* 0.23, MeOH); ν_{max} (film/cm^{-1}) 3203, 3096, 2963, 2928, 1641 (C=O), 1562; δ_H (600 MHz, $CDCl_3$) 7.69 (t, *J* = 5.7 Hz, 1H, CONH), 7.52 (s, 1H, ArCH), 6.77 (s, 1H, NHC*H*), 3.60 (dd, J_{AX} = 8.2 Hz, J_{BX} = 4.4 Hz, 1H, COCH_X), 3.12 (app. q, *J* = 6.7 Hz, 2H, $CH_3CH_2CH_2$), 3.03 (dd, J_{AB} = 14.6 Hz, J_{BX} = 4.4 Hz, 1H, $ArCH_AH_B$), 2.79 (dd, J_{AB} = 14.6 Hz, J_{AX} = 8.2 Hz, 1H, $ArCH_AH_B$), 1.43 (app sx, *J* = 14.6 Hz, 2H, CH_3CH_2), 0.87 (t, *J* = 7.4 Hz, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 174.8, 135.3, 133.3, 118.8, 55.3, 41.0, 32.3, 22.8, 11.5; LRMS (CI): 197 ([M+H]$^+$, 100); HRMS: Found (CI): [M+H]$^+$ 197.13959 $C_9H_{17}N_4O$, requires 197.13969.

3-Amino-*N*-propylpropanamide 100a



Prepared according to General Procedure (2), Method A, at 80 °C for 15 h in MeCN to yield an off-white solid (88 mg, 68%); mp 122-125 °C; ν_{max} (solid/cm^{-1}) 3295, 2959, 2931, 2872, 1643 (C=O); δ_H (600 MHz, $CDCl_3$) 6.97 (s, 1H, NH), 3.23-3.20 (m, 2H, NHCH_2), 3.00-2.98 (m, 2H, COCH_2), 2.32-2.29 (m, 2H, NH_2CH_2), 1.52-1.49 (m, 2H, CH_3CH_2), 0.93-0.90 (m, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 172.6, 41.1, 38.7, 38.4, 23.0, 11.6; LRMS (ES+): 131 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 131.1183 $C_6H_{15}N_2O$, requires 131.1179.

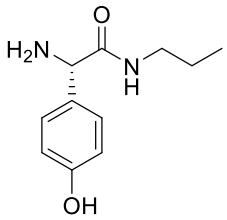
(*S*)-2-Amino-2-phenyl-*N*-propylacetamide 100b



Prepared according to General Procedure (2), Method A, at 80 °C for 15 h to yield a yellow oil (141 mg, 73%, er 55:45, determined using chiral HPLC); $[\alpha]_D^{25}$ +3.1 (*c*

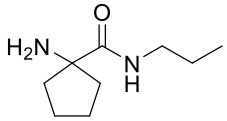
0.64, MeOH); ν_{max} (film/cm^{-1}) 3294 (N-H), 2961, 2929, 2873, 1647 (C=O), 1522; δ_H (300 MHz, $CDCl_3$) 7.43-7.25 (m, 5H, Ar), 7.07 (s, 1H, NH), 4.51 (s, 1H, COC*H*), 3.23-3.21 (m, 2H, NHCH_2), 2.01 (s, 2H, NH_2), 1.53-1.51 (m, 2H, CH_2CH$_3$), 0.89 (t, *J* = 7.4 Hz, 3H, CH_3); δ_C (75 MHz, $CDCl_3$) 173.0, 141.3, 129.0, 128.1, 127.0, 60.0, 41.1, 23.0, 11.5; LRMS (ES+): 193 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 193.1343 $C_{11}H_{17}N_2O$, requires 193.1341.

(*S*)-2-Amino-2-(4-hydroxyphenyl)-*N*-propylacetamide 100c



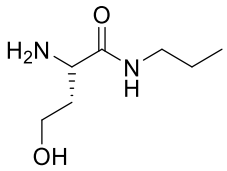
Prepared according to General Procedure (2), Method A, at 80 °C for 15 h and further purified by column chromatography to yield a yellow oil (94 mg, 45%, er 50:50, determined using Marfey's reagent); $[\alpha]_D^{25}$ +3.3 (*c* 0.06 MeOH); ν_{max} (film/cm^{-1}) 3332, 3243 (br, O-H), 2924, 1639 (C=O), 1511; δ_H (600 MHz, $CDCl_3$) 7.48 (t, *J* = 2.3 Hz, 1H, NH), 6.99 (d, *J* = 8.4 Hz, 2H, 2 × NH_2CHCC*H*), 6.50 (d, *J* = 8.4 Hz, 2H, 2 × OHCC*H*), 4.38 (s, 1H, COC*H*), 3.24-3.22 (m, 2H, NHCH_2), 1.55-1.53 (m, 2H, CH_2CH$_3$), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 174.4, 157.0, 131.3, 128.2, 116.2, 59.0, 41.3, 22.8, 11.5; LRMS (ES+): 209 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 209.1279 $C_{11}H_{17}N_2O$, requires 209.1290.

1-Amino-*N*-propylcyclopentanecarboxamide 100d



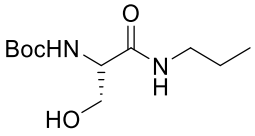
Prepared according to General Procedure (2), Method A, at 125 °C for 15 h to yield a yellow oil (98 mg, 58%); δ_H (600 MHz, $CDCl_3$) 7.80 (s, 1H, NH), 3.22 (app q, *J* = 6.7 Hz, 2H, NHCH_2), 2.26-2.23 (m, 2H, C*H*HCH_2CH_2C*H*H), 1.85 (td, *J* = 6.8, 3.4 Hz, 2H, CH*H*CH_2CH_2CH*H*), 1.80-1.73 (m, 2H, CH_2C*H*HC*H*HCH_2), 1.54 (app. sx, *J* = 7.3 Hz, 2H, CH_2CH$_3$), 1.47-1.42 (m, 2H, CH_2CH*H*CH*H*CH_2), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 177.3, 65.2, 41.1, 40.6, 24.5, 23.0, 11.5; LRMS (CI): 171 ([M+H]$^+$, 100); HRMS: Found (CI): [M+H]$^+$ 171.1491 $C_9H_{19}N_2O$, requires 171.1492.

(*S*)-2-Amino-4-hydroxy-*N*-propylbutanamide 100e



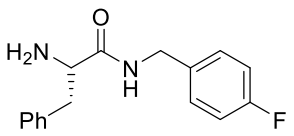
Prepared according to General Procedure (2), Method A, at 125 °C for 15 h to yield a yellow oil (111 mg, 69%, er 84:16, determined by Marfey's reagent); $[\alpha]_D^{25}$ +12.1 (*c* 0.62, MeOH); ν_{max} (film/cm^{-1}) 3287 (N-H), 3260 (br, O-H), 2966, 2836, 1645 (C=O), 1542; δ_H (300 MHz, $CDCl_3$) 3.81-3.79 (m, 2H, OHC*H*$_2$), 3.57 (t, *J* = 6.6 Hz, 1H, COC*H*), 3.23 (app. q, *J* = 6.5 Hz, 2H, NHC*H*$_2$), 2.17 (br s, 3H, NH_2 and OH), 1.95-1.91 (m, 1H, CHC*H*H), 1.84-1.82 (m, 1H, CHC*H*H), 1.55-1/53 (m, 2H, C*H*$_2$CH$_3$), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3); δ_C (75 MHz, $CDCl_3$) 175.3, 61.0, 54.6, 41.0, 38.0, 22.9, 11.5; LRMS (ES+): 161 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 161.1304 $C_7H_{17}N_2O_2$, requires 161.1290.

***tert*-Butyl (*S*)-(3-hydroxy-1-oxo-1-(propylamino)propan-2-yl)carbamate 101**



Prepared according to General Procedure (2), Method A to yield amide as a yellow solid (240 mg, 97%); ν_{max} (solid/cm^{-1}) 3397, 3316, 3267, 3102, 2967, 2933, 1705, 1649, 1571, 1523; δ_H (600 MHz, DMSO-*d*$_6$) 7.73 (s, 1H, NH), 6.55 (d, *J* = 8.1 Hz, 1H, CH), 4.79 (br app s, 1H, C*H*H), 3.92-3.89 (m, 1H, CH*H*), 3.51-3.50 (m, 2H, $CH_3CH_2CH_2$), 3.05-2.95 (m, 2H, CH_3CH_2), 1.38 (br s, 10H, 3 × CCH_3 and OH), 0.86-0.81 (m, 3H, CH_3); δ_C (150 MHz, DMSO-*d*$_6$) 170.1, 155.2, 78.1, 61.9, 56.9, 40.3, 28.2, 22.3, 11.3; LRMS (ES+): 268 ([M+Na]$^+$, 100), 515 ([2M+Na]$^+$, 50); HRMS: Found (ES+): [M+H]$^+$ 247.1677 $C_{11}H_{23}N_2O_4$, requires 247.1658.

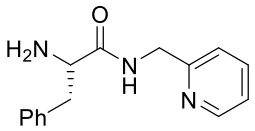
(*S*)-2-Amino-*N*-(4-fluorobenzyl)-3-phenylpropanamide 103a



Prepared according to General Procedure (2), Method C, at 80 °C for 15 h and purified by flash column chromatography (Petrol:EtOAc:Et_3N, 100:25:1) to yield a yellow oil (172 mg, 63 %, er 80:20, determined using Marfey's reagent); $[\alpha]_D^{20}$ +8.0

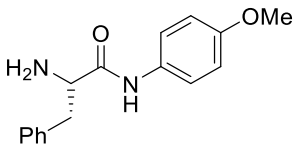
(*c* 0.40, MeOH); ν_{max} (film/cm^{-1}) 3285 (br, NH), 3028, 2925, 1648 (C=O), 1507; δ_H (600 MHz, $CDCl_3$) 7.63 (br s, 1H, NH), 7.30-7.17 (m, 9H, Ar), 4.41 (dd, J_{AB} = 14.8 Hz, J_{AX} = 6.0 Hz, 1H, ArCH_AH$_B$), 4.38 (dd, J_{AB} = 14.8, J_{BX} = 6.0 Hz, 1H, ArCH$_A$$H_B$), 3.68-3.65 (m, 1H, CH$_X$), 3.27 (dd, J_{AB} = 13.7 Hz, J_{AX} = 4.2 Hz, 1H, PhCH_AH$_B$), 2.76 (dd, J_{AB} = 13.7 Hz, J_{BX} = 9.0 Hz, 1H, PhCH$_A$$H_B$); δ_C (150 MHz, $CDCl_3$) 174.2, 162.2 (d, $^1J_{CF}$ = 245.5 Hz, Ar*C*F), 137.8, 134.3 (d, $^4J_{CF}$ = 3.2 Hz, ArC), 129.5, 129.5, 128.9, 127.0, 115.6 (d, $^2J_{CF}$ = 21.4 Hz, 2 × ArCH), 56.5, 42.5, 41.1; LRMS (ES+): 273 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 273.1403, $C_{16}H_{18}N_2OF$, requires 273.1403.

(*S*)-2-Amino-3-phenyl-*N*-(pyridin-2-ylmethyl)propanamide 103b



Prepared according to General Procedure (2), Method C, at 125 °C for 15 h and further purified by flash column chromatography to yield a light brown solid (112 mg, 44%, er 60:40, determined using Marfey's reagent); mp 109-110 °C; $[\alpha]_D^{25}$ −6.1 (*c* 1.0, MeOH); ν_{max} (solid/cm^{-1}) 3351 (N-H), 2872, 1640 (C=O); δ_H (600 MHz, $CDCl_3$) 8.53 (d, *J* = 4.4 Hz, 1H, Ar), 8.17 (br s, 1H, NH), 7.64 (td, *J* = 7.7, 1.6 Hz, 1H, Ar), 7.31-7.27 (m, 2H, Ar), 7.25-7.20 (m, 4H, Ar), 7.18 (dd, *J* = 7.0, 5.2 Hz, 1H, Ar), 4.57 (d, *J* = 5.3 Hz, 2H, CONHCH_2), 3.68 (dd, J_{AX} = 9.5 Hz, J_{BX} = 4.0 Hz, 1H, NH$_2$CH_X), 3.30 (dd, J_{AB} = 13.8 Hz, J_{BX} = 4.0 Hz, 1H, PhCH$_A$$H_B$), 2.73 (dd, J_{AB} = 13.8 Hz, J_{AX} = 9.5 Hz, 1H, PhCH_AH$_B$), 1.63 (br s, 2H, NH$_2$); δ_C (150 MHz, $CDCl_3$) 174.5, 157.0, 149.3, 138.1, 136.9, 129.4, 128.8, 126.9, 122.4, 122.1, 56.8, 44.5, 41.2; HRMS: Found (CI): [M+H]$^+$ 256.144138 $C_{15}H_{18}N_3O$, requires 256.14499.

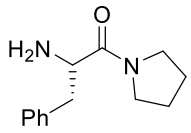
(*S*)-2-Amino-*N*-(4-methoxyphenyl)-3-phenylpropanamide 103c



Prepared according to General Procedure (2), Method C, at 125 °C for 24 h and further purified by flash column chromatography to yield a brown solid (95 mg, 35%, er 1:1, determined using Marfey's reagent); mp 88-90 °C [lit.[174] 89-90 °C for DL-**103c**); ν_{max} (solid/cm^{-1}) 3381, 3253, 1642 (C=O), 1536; δ_H (600 MHz, $CDCl_3$) 9.29 (s, 1H, NH), 7.58-7.43 (m, 2H, 2 × ArH), 7.37-7.29 (m, 2H, Ph), 7.26-7.18 (m, 3H,

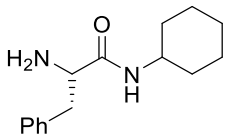
Ph), 6.93-6.77 (m, 2H, 2 × ArH), 3.77 (s, 3H, CH_3), 3.69 (dd, J_{AX} = 9.4 Hz, J_{BX} = 4.0 Hz, 1H, NH_2CH_X), 3.34 (dd, J_{AB} = 13.8 Hz, J_{BX} = 4.0 Hz, 1H, $PhCH_AH_B$), 2.77 (dd, J_{AB} = 13.8 Hz, J_{AX} = 9.4 Hz, 1H, $PhCH_AH_B$); δ_C (150 MHz, $CDCl_3$) 172.3, 156.4, 138.0, 131.1, 129.5, 128.9, 127.3, 121.3, 114.2, 56.9, 55.6, 40.9; LRMS (ES+): 271 ($[M+H]^+$, 100). Data in agreement with the literature.[175]

(*S*)-2-Amino-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one 103d



Prepared according to General Procedure (2), Method C, at 125 °C for 15 h and further purified by flash column chromatography (2% MeOH:CH_2Cl_2) to yield a brown oil (105 mg, 48%, er 53:47, determined using Marfey's reagent); $[\alpha]_D^{25}$ +6.1 (*c* 0.5, MeOH); ν_{max} (oil/cm^{-1}) 3033, 2969, 2884, 1673 (C=O), 1586; δ_H (600 MHz, $CDCl_3$) 7.28-7.26 (m, 2H, Ar), 7.22-7.18 (m, 3H, Ar), 3.71 (app t, *J* = 7.2 Hz, 1H, CH), 3.45 (dt, J_{AB} = 13.0 Hz, J_{AX} = 7.0 Hz, 1H, $PhCH_AH_B$), 3.39-3.30 (m, 2H, NCH_2), 2.93 (dd, J_{AB} = 13.0 Hz, J_{BX} = 7.4 Hz, 1H, $PhCH_AH_B$), 2.80-2.75 (m, 2H, NCH_2), 1.80-1.72 (m, 2H, NCH_2CH_2), 1.72-1.59 (m, 1H, NCH_2CH_2); δ_C (150 MHz, $CDCl_3$) 173.1, 137.9, 129.4, 128.6, 126.8, 55.2, 46.1, 45.9, 43.0, 26.0, 24.1; LRMS (ES+): 219 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 219.1491 $C_{13}H_{18}N_2O$, requires 219.1492.

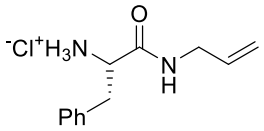
(*S*)-2-Amino-*N*-cyclohexyl-3-phenylpropanamide 103e



Prepared according to General Procedure (2), Method C, at 80 °C for 15 h and further purified by flash column chromatography (2% MeOH:CH_2Cl_2) to yield a brown solid (147 mg, 56%, er 55:45, determined using Marfey's reagent); mp 74-76 °C [lit.[176] 78-79 °C for DL-**103e**]; $[\alpha]_D^{25}$ −15.1 (*c* 0.20, $CHCl_3$, 25 °C); δ_H (600 MHz, $CDCl_3$) 7.33-7.18 (m, 5H, Ph), 7.08 (br s, 1H, NH), 3.76-3.73 (m, 1H, CONHC*H*), 3.56 (dd, J_{AX} = 9.1 Hz, J_{BX} = 4.3 Hz, 1H, $COCH_X$), 3.23 (dd, J_{AB} = 13.7 Hz, J_{BX} = 4.3 Hz, 1H, $PhCH_AH_B$), 2.69 (dd, J_{AB} = 13.7, J_{AX} = 9.1 Hz, 1H, $PhCH_AH_B$), 1.89-1.79 (m, 2H, 2 × CyH), 1.73-1.64 (m, 2H, 2 × CyH), 1.62-1.55 (m, 1H, CyH), 1.42-1.33 (m, 3H, NH_2 and CyH), 1.20-1.07 (m, 3H, 3 × CyH); δ_C (150 MHz, $CDCl_3$) 173.3, 138.1,

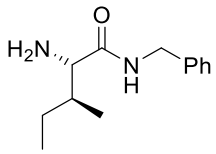
129.5, 128.8, 126.9, 56.5, 47.7, 41.2, 33.2, 33.1, 25.7, 24.9; LRMS (ES+): 247 ([M+H]$^+$, 100).

(*S*)-*N*-Allyl-2-amino-3-phenylpropanamide hydrochloride 103f



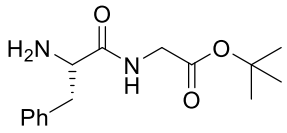
Prepared according to General Procedure (2), Method C, at 80 °C for 15 h and further isolated as HCl salt to yield a brown solid (107 mg, 89%, er 79:21, determined using Marfey's reagent); mp 125-126 °C; $[\alpha]_D^{25}$ −6.0 (*c* 1.0, MeOH); ν_{max} (solid/cm^{-1}) 3280 (N-H), 2983 (C-H), 1650 (C=O); δ_H (600 MHz, DMSO-d_6) 8.69-8.66 (br m, 1H, NH), 8.42-8.39 (br m, 3H, $NH_3^+Cl^-$), 7.34-7.30 (m, 2H, ArH), 7.29-7.23 (m, 3H, ArH), 5.71-5.64 (m, 1H, C*H*=CH_2), 5.02-4.98 (m, 2H, CH_2=CH), 4.03-4.00 (m, 1H, C*H*$NH_3^+Cl^-$), 3.71-3.77 (m, 1H, NHCH*H*), 3.61-3.67 (m, 1H, NHC*H*H), 3.05 (d, *J* = 7.2 Hz, 2H, CH_2CH); δ_C (150 MHz, DMSO-d_6) 167.6, 135.1, 134.3, 129.5, 128.5, 127.1, 115.7, 53.5, 40.9, 37.0; HRMS: Found (CI): [M-Cl]$^+$ 205.133821 $C_{12}H_{17}N_2O$, requires 205.13409.

(2*S*,3*S*)-2-Amino-*N*-benzyl-3-methylpentanamide 103g



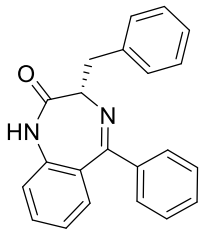
Prepared according to General Procedure (2), Method C, at 125 °C for 24 h and further purified by flash column chromatography to yield a colourless oil (67 mg, 30%, dr 94:6), ν_{max} (film/cm^{-1}) 3281, 3059, 2959, 2927, 2871, 1640 (C=O), 1518; δ_H (600 MHz, $CDCl_3$) 7.67 (br s, 1H, NH), 7.36-7.30 (m, 2H, Ph), 7.29-7.24 (m, 3H, Ph), 4.45 (d, *J* = 5.9 Hz, 2H, $PhCH_2$), 3.32 (d, *J* = 3.8 Hz, 1H, NH_2CH), 2.08-2.00 (m, 1H, CH), 1.51 (br s, 2H, NH_2), 1.41-1.36 (m, 1H, C*H*H), 1.13-1.02 (m, 1H, CH*H*), 0.97 (d, *J* = 7.0 Hz, 3H, CH_3CH), 0.90 (t, *J* = 7.0 Hz, 3H, CH_3CH_2); δ_C (150 MHz, $CDCl_3$) 174.4, 138.7, 128.8, 127.9, 127.5, 60.1, 43.2, 38.0, 23.8, 16.4, 12.1; LRMS (ES+): 221 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 221.1654 $C_{13}H_{21}N_2O$, requires 221.1650. Data in agreement with the literature.[177]

(*S*)-*Tert*-butyl 2-(2-amino-3-phenylpropanamido)acetate 103h



Prepared according to General Procedure (2), Method C, at 125 °C for 15 h and further purified by flash column chromatography (2% MeOH:CH_2Cl_2) to yield a colourless oil (157 mg, 56%, er 2:1, determined using Marfey's reagent); ν_{max} (film/cm^{-1}) 3303, 3026, 2974, 1736, 1667, 1517; δ_H (600 MHz, $CDCl_3$) 7.77 (br s, 1H, NH), 7.32-7.27 (m, 2H, Ar), 7.24-7.18 (m, 3H, Ar), 3.96 (dd, J_{AB} = 18.2 Hz, J_{AX} = 5.4 Hz, 1H, OCOC$H_A$$H_B$), 3.91 (dd, J_{AB} = 18.2 Hz, J_{BX} = 5.4 Hz, 1H, OCOC$H_A$$H_B$), 3.62 (dd, J_{AX} = 9.9 Hz, J_{BX} = 3.9 Hz, 1H, NH_2CH_X), 3.29 (dd, J_{AB} = 13.8 Hz, J_{BX} = 3.9 Hz, 1H, PhC$H_A$$H_B$), 2.65 (dd, J_{AB} = 13.8 Hz, J_{AX} = 9.9 Hz, 1H, PhC$H_A$$H_B$), 1.56 (s, 2H, NH_2), 1.46 (s, 9H, 3 × CH_3); δ_C (150 MHz, $CDCl_3$) 174.7, 169.2, 138.1, 129.4, 128.8, 126.9, 82.2, 56.6, 41.8, 41.0, 28.2; LRMS (ES+): 279 ([M+H]$^+$, 85), 223 ([M-^{t}Bu+2H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 279.1702 $C_{15}H_{23}N_2O_3$, requires 279.1703. Data in agreement with the literature.[178]

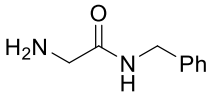
(*S*)-3-Benzyl-5-phenyl-1,3-dihydro-2*H*-benzo[e][1,4]diazepin-2-one 103i



A mixture of 2-aminobenzophenone (197 mg, 1 mmol, 1 equiv.), L-Phe (165 mg, 1 equiv., 1 mmol) and $B(OCH_2CF_3)_3$ (0.64 mL, 3 mmol, 3 equiv.) was stirred at 125 °C for 4 days and further purified by flash column chromatography (Petrol:EtOAc 70:30) to give a white solid (170 mg, 52%, er 54:46, determined used chiral HPLC); mp 189-190 °C; $[\alpha]_D^{20}$ +13.8 (*c* 1.0, $CHCl_3$); ν_{max} (solid/cm^{-1}) 3196, 2964, 1676 (C=O); δ_H (600 MHz, $CDCl_3$) 9.36 (2 × br s, ratio 0.69:0.29, 1H, NH), 7.52-7.47 (m, 3H, ArH), 7.43-7.41 (m, 3H, ArH), 7.38-7.34 (m, 2H, ArH), 7.34-7.27 (m, 3H, ArH), 7.23 (t, *J* = 6.8 Hz, 1H, ArH), 7.19-7.17 (m, 1H, ArH), 7.13 (t, *J* = 7.6 Hz, 1H, ArH), 3.82 (t, *J* = 6.7 Hz, 1H, CH), 3.68-3.58 (m, 2H, CH_2); δ_C (150 MHz, $CDCl_3$) 172.1 (minor CO), 172.0 (major CO), 169.4, 139.5, 139.4, 138.5, 131.8, 131.4, 130.4, 130.1, 130.0, 128.3, 128.3, 127.7, 126.3, 123.4, 121.3, 65.0, 37.8; LRMS (ES+):

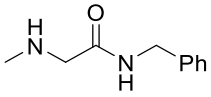
327 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 327.1498 $C_{22}H_{19}N_2O$, requires 327.1497.

2-Amino-*N*-benzylacetamide 107a



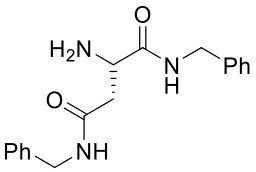
Prepared according to General Procedure (2), Method D with 3 equiv. of benzylamine used, and further purified by flash column chromatography (6% MeOH:CH_2Cl_2) to yield an amide as a white solid (369 mg, 45%); mp 140-143 °C (lit.[106] 142-144 °C); δ_H (600 MHz, MeOD) 7.34-7.27 (m, 4H, Ph), 7.26-7.22 (m, 1H, Ph), 4.40 (s, 2H, $PhCH_2$), 3.34 (s, 2H, NH_2CH_2); δ_C (150 MHz, MeOD) 174.3, 139.8, 129.6, 128.6, 128.3, 44.7, 44.0; LRMS (ES+): 165 ([M+H]$^+$, 100); Data in agreement with the literature.[106,179]

***N*-Benzyl-2-(methylamino)acetamide 107b**



Prepared according to General Procedure (2), Method D, and further purified by flash column chromatography (6% MeOH:CH_2Cl_2) to yield the amide as a yellow oil (730 mg, 82%); δ_H (600 MHz, $CDCl_3$) 7.53 (s, 1H, $PhCH_2NH$), 7.38-7.31 (m, 2H, Ph), 7.31-7.27 (m, 3H, Ph), 4.49 (d, J = 6.0 Hz, 2H, $PhCH_2$), 3.30 (s, 2H, $COCH_2$), 2.42 (s, 3H, CH_3); δ_C (150 MHz, $CDCl_3$) 171.5, 138.5, 128.8, 127.8, 127.5, 54.7, 43.1, 37.0; LRMS (ES+): 179 ([M+H]$^+$, 100); Data in agreement with the literature.[18]

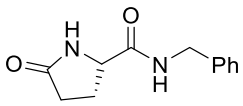
(*S*)-2-Amino-N^1,N^4-dibenzylsuccinamide 107c



Prepared according to General Procedure (2), Method D, and further purified by flash column chromatography to yield amide as a white solid (326 mg, 21%, er 72:28, determined using Marfey's reagent); mp 157-159 °C; ν_{max} (solid/cm^{-1}) 3273, 3082, 3059, 3028, 1627, 1543; δ_H (600 MHz, $CDCl_3$) 7.93 (t, J = 5.4 Hz, 1H, NH), 7.35-7.20 (m, 10H, ArH), 7.05 (s, 1H, NH), 4.38-4.26 (m, 4H, 2 × $PhCH_2$), 3.67 (dd, J_{AX} = 7.6 Hz, J_{BX} = 4.2 Hz, 1H, CH_X), 2.69 (dd, J_{AB} = 14.7 Hz, J_{BX} = 4.2 Hz, 1H,

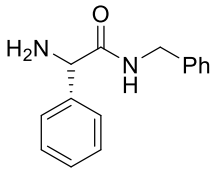
$CHCH_AH_B$), 2.58 (dd, J_{AB} = 14.7 Hz, J_{AX} = 7.6 Hz, 1H, $CHCH_AH_B$), 1.93 (s, 2H, NH_2); δ_C (150 MHz, $CDCl_3$) 174.1, 171.2, 138.4, 138.3, 128.8, 128.8, 127.8, 127.7, 127.5, 127.5, 52.8, 43.5, 43.3, 40.7; LRMS (ES+): 312 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 312.1713 $C_{18}H_{22}N_3O_2$, requires 312.1712.

(*S*)-*N*-Benzyl-5-oxopyrrolidine-2-carboxamide 107d



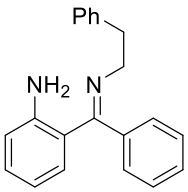
White solid (398 mg, 91%, er > 99%, determined using chiral shift reagent); Data consistent with **55p**.

(*S*)-2-Amino-N-benzyl-2-phenylacetamide 107e



Prepared according to General Procedure (2), Method D, heated for 5 h and further purified by flash column chromatography to yield a colourless oil (278 mg, 23%, er 55:45, determined using Marfey's reagent), $[\alpha]_D^{20}$ +5.8 (*c* 1.0, MeOH); or heated for 24 h and further purified by flash column chromatography to yield a colourless oil (1124 mg, 93%, er 50:50, determined using Marfey's reagent); ν_{max} (film/cm^{-1}) 3289, 2888, 1665, 1546; δ_H (600 MHz, $CDCl_3$) 7.47-7.21 (m, 10H, 2 × Ph), 4.59 (s, 1H, CH), 4.51-4.42 (m, 2H, $PhCH_2$); δ_C (150 MHz, $CDCl_3$) 173.0, 141.1, 138.4, 129.0, 128.8, 128.2, 127.8, 127.6, 127.0, 60.1, 43.4; Data in agreement with the literature.[180]

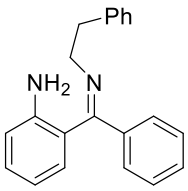
***E*-2-((Phenethylimino)(phenyl)methyl)aniline *E*-108**



Prepared according to General Procedure (2), Method D, and further purified by flash column chromatography to yield a yellow oil (303 mg, 20%); ν_{max} (film/cm^{-1}) 3452, 3207, 3021, 2917, 1681, 1609, 1572; δ_H (600 MHz, $CDCl_3$, *E*-**108**) 7.76-7.70 (m, 2H), 7.44-7.42 (m, 1H), 7.41-7.37 (m, 2H), 7.30-7.27 (m, 2H), 7.25-7.20 (m, 4H), 6.81 (td, *J* = 7.4, 1.0 Hz, 1H), 6.75 (dd, *J* = 7.5, 1.4 Hz, 1H), 6.73-6.72 (m, 1H), 3.78-

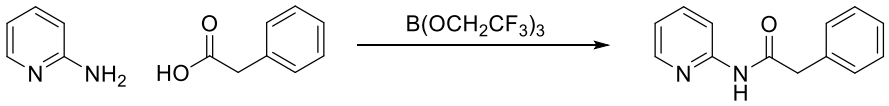
3.73 (m, 1H), 3.72-3.65 (m, 1H), 3.31 (s, 2H), 3.16-3.12 (m, 1H), 3.08-3.04 (m, 1H); δ_C (150 MHz, $CDCl_3$, *E*-**108**) 167.2, 143.2, 140.7, 138.9, 130.4, 129.7, 129.3, 128.6, 128.4, 128.1, 126.1, 122.3, 118.4, 115.6, 55.8, 37.7; LRMS (ES+): 301 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 301.1700 $C_{21}H_{20}N_2$, requires 301.1705.

***Z*-2-((Phenethylimino)(phenyl)methyl)aniline *Z*-108**



Prepared according to General Procedure (2), Method D, and further purified by flash column chromatography a yellow oil (369 mg, 25%); δ_H (600 MHz, $CDCl_3$, Z-**108**) 7.44-7.37 (m, 2H, Ph), 7.27-7.24 (m, 2H, Ph), 7.21-7.13 (m, 3H, Ph), 7.08 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1H, Ph), 7.06-6.96 (m, 3H, Ph), 6.73 (br s, 2H, NH_2), 6.72 (dd, *J* = 8.0, 1.5 Hz, 1H, Ph), 6.68 (dd, *J* = 8.0, 1.2 Hz, 1H, Ph), 6.44 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H, Ph), 3.54 (t, *J* = 7.2 Hz, 2H, NCH_2), 2.96 (t, *J* = 7.2 Hz, 2H, $PhCH_2$); δ_C (150 MHz, $CDCl_3$, Z-**108**) 172.1, 149.3, 140.7, 137.4, 133.3, 130.5, 129.0, 128.6, 128.4, 128.0, 127.5, 126.1, 119.8, 116.4, 115.4, 55.1, 38.1; LRMS (ES+): 301 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 301.1704 $C_{21}H_{20}N_2$, requires 301.1705.

6.4 DoE optimisation of amidation of 2-aminopyridine 62a with phenylacetic acid 53



62a **53** **63a**

The experimental design was set up using MODDE 10 software to investigate the effect of the following factors:

(Amine-Acid): Number of equivalents of amine **62a** – number of equivalents of acid **53**; -2 to +2.

Et_3N: Number of equivalents of triethylamine; 0.1 to 3 eq.

Borate: Number of equivalents of $B(OCH_2CF_3)_3$; 0.5 to 3 eq.

Vol: Volume of solvent used in the reaction flask; 0.5 mL to 2 mL.

Addition Rate: Rate of addition; set using the syringe pump from 1 (0.254 mLh^{-1}) to 51 (13 mLh^{-1}) in a 5 mL syringe.

Temp: Temperature; from 80 °C to 125 °C.

Solvent: Either CPME or EtCN.

Borate Vol: Volume of solvent used to prepare the borate reagent solution; from 0.5 mL to 2 mL.

The reaction was carried out using 1 mmol of the limiting reagent in each case (acid or amine).

General Procedure: A solution of borate reagent in CPME or EtCN was added dropwise *via* a syringe pump to a solution of amine, acid and Et_3N in CPME or EtCN in a sealed carousel tube at the required temperature. The reaction was maintained at the temperature for a total of 24 h (including addition time). Two aliquots were removed from the mixture, concentrated *in vacuo* and re-dissolved in an internal standard solution (1,4-dimethoxybenzene in DMSO-d_6, 0.5 M). They were then analysed separately by ^{1}H NMR to determine the yield of amide present. The average yield from the two samples was taken. All experiments and determined NMR yields are presented below (Table 14).

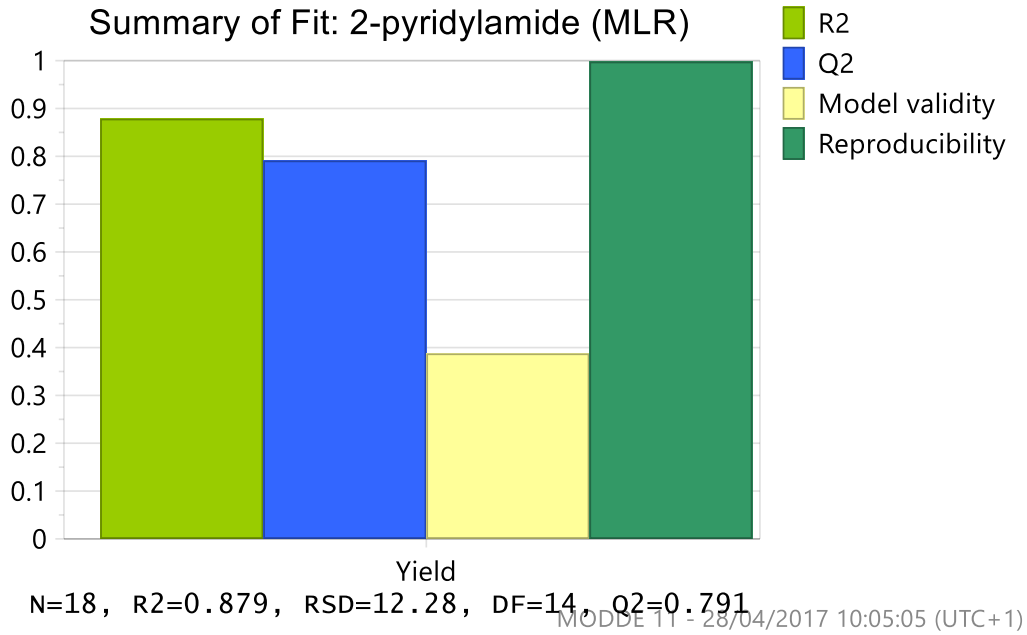
Run Order	Amine-Acid	Et_3N	Borate	Vol	Addition Rate	Temp	Solvent	Borate Vol	Yield
1	2	3	0.5	2	1	80	CPME	2	7
2	2	3	0.5	0.5	51	125	CPME	0.5	66
3	2	0.1	0.5	2	51	80	EtCN	0.5	9
4	0	1.55	1.75	1.25	26	102.5	CPME	1.25	49
5	2	3	3	2	51	125	EtCN	2	69
6	-2	0.1	0.5	0.5	1	80	CPME	0.5	12
7	2	0.1	3	0.5	51	80	CPME	2	9
8	0	1.55	1.75	1.25	26	102.5	CPME	1.25	47
9	-2	3	0.5	2	1	125	EtCN	0.5	26
10	-2	0.1	3	0.5	51	125	EtCN	0.5	75
11	-2	3	0.5	0.5	51	80	EtCN	2	5
12	-2	3	3	0.5	1	125	CPME	2	99
13	-2	0.1	0.5	2	51	125	CPME	2	78
14	-2	0.1	3	2	1	80	EtCN	2	14
15	2	0.1	0.5	0.5	1	125	EtCN	2	41
16	2	0.1	3	2	1	125	CPME	0.5	100
17	-2	3	3	2	51	80	CPME	0.5	31
18	2	3	3	0.5	1	80	EtCN	0.5	28

Table 14

A model was generated using the software which provided a good fit to the data.; ANOVA table is included below.

Yield	DF	SS	MS (variance)	F	p	SD
Total	18	49915	2773.06			
Constant	1	32512.5	32512.5			
Total corrected	17	17402.5	1023.68			31.9949
Regression	3	15291.7	5097.22	33.8068	**0.000**	71.3948
Residual	14	2110.85	150.775			12.279
Lack of Fit (Model error)	13	2108.85	162.219	81.1096	**0.087**	12.7365
Pure error (Replicate error)	1	2	2			1.41421
	N = 18	Q2 =	0.791	Cond. no. =	1.118	
	DF = 14	R2 =	0.879	RSD =	12.28	
		R2 adj. =	0.853			

Table 15



Optimised procedure for the preparation of 63a with an excess of amine

A solution of $B(OCH_2CF_3)_3$ (642 µL, 3.0 mmol) in CPME (0.5 mL) was added dropwise (0.254 mLh^{-1}) to a solution of 2-aminopyridine (282 mg, 3.0 mmol), phenylacetic acid (136 mg, 1.0 mmol) and Et_3N (14 µL, 0.1 mmol) in CPME (2 mL) in a sealed carousel tube. The mixture was heated at 125 ºC for 24 h (including the addition time). Upon completion, reaction mixture was diluted with EtOAc (5 mL), water (1 mL) and resins Amberlyst® A26(OH) (200 mg) and Amberlite® IRA743 (200 mg) were added and stirred for 30 min. $MgSO_4$ was then added, the solution was filtered and solids washed with EtOAc (3 × 15 mL) and the crude product was concentrated *in vacuo.* The product was further purified by flash column

chromatography (Petrol:EtOAc 4:1) to remove excess 2-aminopyridine and yield amide **63a** (178 mg, 84%).

Optimised procedure for the preparation of 63a with an excess of carboxylic acid

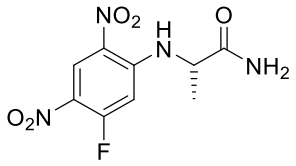
A solution of $B(OCH_2CF_3)_3$ (642 µL, 3.0 mmol) in CPME (2 mL) was added dropwise (0.254 mLh^{-1}) to a solution of 2-aminopyridine (94 mg, 1.0 mmol), phenylacetic acid (408 mg, 3.0 mmol) and Et_3N (418 µL, 3.0 mmol) in CPME (0.5 mL) in a sealed carousel tube. The mixture was heated at 125 ºC for 24 h (including the addition time). Upon completion, reaction mixture was diluted with EtOAc (5 mL), water (1 mL) and resins Amberlyst® A26(OH) (200 mg) and Amberlite® IRA743 (200 mg) were added and stirred for 30 min. $MgSO_4$ was then added, the solution was filtered and solids washed with EtOAc (3 × 15 mL) and the crude product was concentrated *in vacuo.* The product was further purified by flash column chromatography (Petrol:EtOAc 4:1) to remove unreacted 2-aminopyridine and yield amide **63a** (176 mg, 83%).

Optimised procedure for the preparation of 63a with equimolar quantities of acid and amine in Bu_2O

A solution of $B(OCH_2CF_3)_3$ (642 µL, 3.0 mmol) in Bu_2O (1 mL) was added dropwise (0.254 mLh^{-1}) to a solution of 2-aminopyridine (94 mg, 1.0 mmol), phenylacetic acid (136 mg, 1.0 mmol) and Et_3N (418 µL, 3.0 mmol) in Bu_2O (1 mL) in a sealed carousel tube. The mixture was heated at 140 ºC for 24 h (including the addition time). Upon completion, reaction mixture was diluted with EtOAc (5 mL), water (1 mL) and resins Amberlyst® A26(OH) (200 mg) and Amberlite® IRA743 (200 mg) were added and stirred for 30 min. $MgSO_4$ was then added, the solution was filtered and solids washed with EtOAc (3 × 15 mL) and the crude product was concentrated *in vacuo.* The product was further purified by flash column chromatography (Petrol:EtOAc 4:1) to remove unreacted 2-aminopyridine and yield amide **63a** (157 mg, 74%).

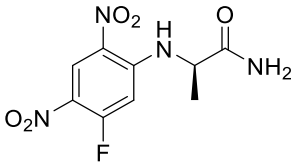
6.5 Marfey's reagent

(*S*)-2-((5-Fluoro-2,4-dinitrophenyl)amino)propanamide L-91[113]



L-Alaninamide (473 mg, 3.80 mmol) was dissolved in 1 M NaOH (3.9 mL) and the resulting mixture was dissolved in acetone (60 mL). $MgSO_4$ (10 g) was added and the resulting mixture was stirred for 3 h at room temperature. $MgSO_4$ was then filtered off. 1,5-Difluoro-2,4-dinitrobenzene (FFDNB) (668 mg, 3.27 mmol) was dissolved in acetone (15 mL). L-Alaninamide solution was then added dropwise to FFDNB and the solution was stirred for 0.5 h. Water (80 mL) was added and the crystals formed were filtered and washed with acetone/water mixture (3 × 15 mL). The product was obtained as bright yellow crystals (563 mg, 63%); mp 223-224 °C; ν_{max} (solid/cm^{-1}) 3439, 3339, 1670, 1632, 1580; $[\alpha]_D$ +54.0 (*c* 0.99, Acetone, 25°C); δ_H (600 MHz, DMSO-d_6) 9.11 (d, *J* = 6.7 Hz, 1H, N*H*), 8.90 (d, *J* = 8.1 Hz, 1H, C(NO_2)CH), 7.75 (s, 1H, CONH*H*), 7.52 (s, 1H, CON*H*H), 6.96 (d, *J* = 14.3 Hz, 1H, CFCH), 4.39 (p, *J* = 6.8 Hz, 1H, CH), 1.44 (d, *J* = 6.8 Hz, 3H, CH_3); δ_C (150 MHz, DMSO-d_6) 172.4 (C=O), 159.1 (d, J_{CF} = 266.7 Hz, C-F), 147.63 (d, J_{CF} = 14.1 Hz), 127.44 (d, J_{CF} = 15.4 Hz), 125.08 (d, J_{CF} = 9.6 Hz), 102.18 (d, J_{CF} = 27.1 Hz), 51.6, 18.4; LRMS (ES−): 270 ([M-H]$^-$, 100); HRMS: Found (ES−): [M-H]$^-$ 270.4001 $C_9H_7N_4O_5F$, requires 270.0411.

(*R*)-2-((5-Fluoro-2,4-dinitrophenyl)amino)propanamide D-91

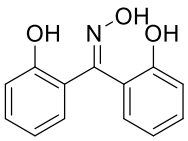


D-Alaninamide (472 mg, 3.79 mmol) was dissolved in 1 M NaOH (3.9 mL) and the resulting mixture was dissolved in acetone (60 mL). $MgSO_4$ (10 g) was added and the resulting mixture was stirred for 3 h at room temperature. $MgSO_4$ was then filtered off. 1,5-Difluoro-2,4-dinitrobenzene (FFDNB) (668 mg, 3.27 mmol) was dissolved in acetone (15 mL). D-Alaninamide solution was then added dropwise to FFDNB and the solution was stirred for 0.5 h. Water (80 mL) was added and the crystals formed were filtered and washed with acetone/water mixture (3 × 15 mL). The product was obtained as bright yellow crystals (596 mg, 67%); mp 223-224 °C;

ν_{max} (solid/cm^{-1}) 3442, 3338, 3190, 1670, 1631, 1579; $[\alpha]_D$ −60.0 (*c* 0.69, Acetone, 25°C); δ_H (600 MHz, DMSO-d_6) 9.11 (d, *J* = 6.7 Hz, 1H, N*H*), 8.90 (d, *J* = 8.1 Hz, 1H, C(NO_2)CH), 7.75 (s, 1H, CONH*H*), 7.52 (s, 1H, CON*H*H), 6.96 (d, *J* = 14.3 Hz, 1H, CFCH), 4.39 (p, *J* = 6.8 Hz, 1H, CH), 1.44 (d, *J* = 6.8 Hz, 3H, CH_3); δ_C (150 MHz, DMSO-d_6) 172.4 (C=O), 159.1 (d, J_{CF} = 266.7 Hz, C-F), 147.63 (d, J_{CF} = 14.1 Hz), 127.44 (d, J_{CF} = 15.4 Hz), 125.08 (d, J_{CF} = 9.6 Hz), 102.18 (d, J_{CF} = 27.1 Hz), 51.6, 18.4; LRMS (ES−): 270 ([M−H]$^-$, 100); HRMS: Found (ES−): [M−H]$^-$ 270.3989 $C_9H_7N_4O_5F$, requires 270.0411.

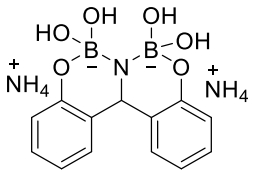
6.6 BNB system

Bis(2-hydroxyphenyl)methanone oxime 211



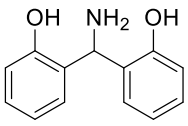
To a stirring solution of 2,2'-dihydroxybenzophenone (5 g, 23.6 mmol) and NaOAc (4.1 g, 50 mmol) in ethanol (120 mL) was added hydroxylamine hydrochloride (3.4 g, 50 mmol). The mixture was heated to reflux for 24 h. Upon completion, solvent was evaporated, re-dissolved in EtOAc (50 mL) and washed with water to remove salts. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford oxime **211** as an off-white solid (5.3 g, 98%); mp 102-104 °C (lit.[181] 113 °C); ν_{max} (solid/cm^{-1}) 3371 (O-H), 3234 (O-H), 1633, 1577 (C=C); δ_H (600 MHz, DMSO-d_6) 11.62 (s, 1H, N-OH), 11.49 (s, 1H, OH (near N-OH)), 9.58 (s, 1H, OH), 7.28 (td, *J* = 8.3, 1.7 Hz, 1H, ArH), 7.24-7.18 (m, 1H, ArH), 7.04 (dd, *J* = 7.5, 1.6 Hz, 1H, ArH), 6.95 (d, *J* = 8.2 Hz, 1H, ArH), 6.93-6.88 (m, 2H, ArH), 6.77-6.71 (m, 2H, ArH); δ_C (150 MHz, DMSO-d_6) 158.1, 157.4, 154.2, 130.0 (2 × C), 129.4, 129.4, 119.1, 118.9, 118.9, 118.7, 116.5, 115.7; LRMS (ES+): 230 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 230.0824 $C_{13}H_{12}O_3N$, requires 230.0817. Spectral data is in agreement with the literature.[181]

6,6,8,8-Tetrahydroxy-6*H*,8*H*,13b*H*-benzo[e]benzo[5,6][1,3,2]oxazaborinino[3,4-c][1,3,2]oxazaborinine-6,8-diuide ammonium salt 213



2,2'-Dihydroxybenzophenone (1.1g, 5.16 mmol, 1.0 equiv.) was dissolved in a cooled to 0 °C 7 M ammonia in MeOH solution (20 mL) and the mixture was allowed to warm to 25 °C over 20 min and stirred for 24 h. The solvent was then removed in vacuo and residue re-dissolved in MeOH (10 mL) cooled to 0 °C. $NaBH_4$ (727 mg, 19.2 mmol, 3.7 equiv.) was added portion-wise, keeping internal temperature below 10 °C. After the addition, the mixture was allowed to reach RT and stirred for 20 h. The reaction was then acidified with 1 M HCl and MeOH removed in vacuo. The aqueous phase was mixed with EtOAc (20 mL), and neutralised. The aqueous was extracted and washed with EtOAc (3 × 20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford **213** as a white solid (1.68 g, 97%); mp decomp. > 300 °C; ν_{max} (solid/cm^{-1}) 1581, 1486, 1459; δ_H (600 MHz, DMSO-d_6) 7.22 (dd, J = 7.4, 1.1 Hz, 2H, 2 × ArCH), 7.13-6.93 (m, 2H, 2 × ArCH), 6.77 (s, 2H, 2 × OH), 6.73-6.54 (m, 4H, Ph), 5.13 (s, 1H, NH_2CH); δ_C (150 MHz, DMSO-d_6) 155.2, 128.4, 126.6, 125.4, 117.6, 117.4, 54.4; LRMS (ES+): 337 ([M]$^+$, 100%);

2,2'-(Aminomethylene)diphenol 208

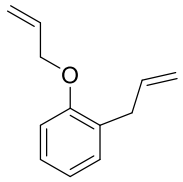


An oven-dried 500 mL 3-neck round-bottomed flask was fitted with a reflux condenser, stoppered and flushed with argon. Oxime **211** (5 g, 22 mmol) was dissolved in EtOH (300 mL) and heated to reflux. Sodium shavings (25 g, 1.09 mol) were added portionwise to refluxing solution over 2 h. When all sodium has dissolved, the mixture was allowed to cool to RT, quenched with sat. aq. NH_4Cl and extracted with EtOAc (3 × 300 mL). Organic phases were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield crude **208** as an orange oil. The product was further purified by flash column chromatography (petrol-EtOAc 40%) to afford yellow oil, which was further recrystallised from CPME to give product as a yellow solid (833 mg, 18%); mp 132-135 °C; ν_{max} (solid/cm^{-1}) 3361, 3287, 3146 (br), 1584; δ_H (600 MHz, MeOD) 7.09 (td, J = 8.1, 1.6 Hz, 2H, 2 × CH), 6.93 (dd, J = 7.6, 1.3

Hz, 2H, 2 × CH), 6.78 (dd, *J* = 8.1, 1.0 Hz, 2H, 2 × CH), 6.71 (td, *J* = 7.6, 1.0 Hz, 2H, 2 × CH), 5.55 (s, 1H, H_2NCH); δ_C (150 MHz, MeOD) 158.0, 129.5, 129.4, 129.1, 120.0, 117.0, 54.9; LRMS (ESI): 216 ($[M+H]^+$, 35%), 199 ($[M-NH_3]^+$, 100); HRMS: Found (ESI): $[M+H]^+$ 216.1019 $C_{13}H_{14}NO_2$, requires 216.1019.

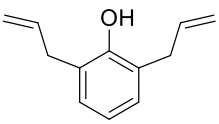
6.7 Hybrid catalyst

1-Allyl-2-(allyloxy)benzene 223[138]



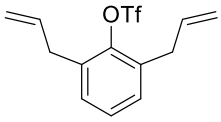
20 g scale: A round-bottomed flask equipped with a reflux condenser was flame-dried and flushed with argon prior use. A mixture of potassium carbonate (21.0 g, 0.150 mol), 2-allylphenol (20.5 g, 0.150 mol) and allylbromide (13.5 mL, 0.150 mol) was heated to reflux in acetone (40 mL) for 18 h. After cooling, the reaction was washed with water (150 mL) and the aqueous phase separated and extracted with diethyl ether (3 × 20 mL). The combined organic phases were then washed with sodium hydroxide (2 M, 50 mL) and dried ($MgSO_4$). The mixture was filtered and the solvent removed to yield **48** as a yellow liquid (21.5 g, 84%); ν_{max} (film/cm^{-1}) 3078, 2979, 2909, 1490, 1239; δ_H (600 MHz, $CDCl_3$) 7.18 (d, *J* = 7.4 Hz, 2H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.12-5.99 (m, 2H), 5.47-5.40 (m, 1H), 5.30-5.25 (m, 1H), 5.11-5.03 (m, 2H), 4.56 (d, *J* = 4.9 Hz, 2H, OCH_2), 3.44 (d, *J* = 6.6 Hz, 2H, CH_2); δ_C (150 MHz, $CDCl_3$) 156.3, 137.1, 133.7, 130.0, 129.1, 127.4, 120.8, 117.0, 115.5, 111.7, 68.8, 34.6; LRMS (CI): 175 ($[M+H]^+$, 100), 147 $[M-C_2H_3]^+$, 20), 133 $(M-C_3H_5]^+$, 50), 107 (30).

2,6-Diallylphenol 222[138]



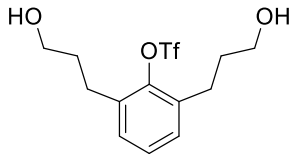
Neat **223** (21.5 g, 0.123 mol) was heated at 180 °C under argon atmosphere for 8 hours. The product was purified by flash column chromatography (Petrol-2% MeOH/CH_2Cl_2) to yield **222** as a yellow liquid (6.80 g, 32%); δ_H (600 MHz, $CDCl_3$) 7.03 (d, *J* = 7.5 Hz, 2H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.03 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 2H), 5.21-5.12 (m, 4H), 3.43 (d, *J* = 6.4 Hz, 4H); δ_C (150 MHz, $CDCl_3$) 152.8, 136.7, 128.9, 125.8, 120.8, 116.5, 35.4; LRMS (CI): 175 ($[M+H]^+$, 40), 133 ($[M-C_3H_5]^+$, 20).

2,6-Diallylphenyl trifluoromethanesulfonate 221[138]



Triflic anhydride (7.7 mL, 46.1 mmol) was added dropwise to an ice-cool solution of pyridine (4.7 mL, 57.7 mmol) and **222** (6.7 g, 38.0 mmol) in CH_2Cl_2 (127 mL). The solution was stirred for 17 h and then washed with water (50 mL), aq. HCl (0.1 M, 50 mL) and aq. Na_2CO_3 (0.1 M, 50 mL). The aqueous phase was dried ($MgSO_4$) and solvent removed *in vacuo* to yield **221** as a yellow oil (9.85 g, 85%); δ_H (600 MHz, $CDCl_3$) 7.27 (m, 1H, ArH), 7.19 (d, J = 7.6 Hz, 2H, ArH), 5.91 (ddt, J = 16.9, 10.1, 6.6 Hz, 2H, 2 × CH_2=C*H*), 5.15 (dd, 2H, J = 10.1, 1.4 Hz, 2 × CH_{cis}H$_{trans}$=CH), 5.12 (dd, J = 16.9, 1.4 Hz, 2H, 2 × CH$_{cis}$$H_{trans}$=CH), 3.52 (d, J = 6.6 Hz, 4H, 2 × CH_2=CHCH_2); δ_C (150 MHz, $CDCl_3$) 145.2, 135.1, 133.9, 129.6, 128.5, 118.6 (q, J_{CF} = 320 Hz), 117.6, 34.6; LRMS (CI): 306 ([M]$^+$, 20), 174 ([M-CF_3O_2S]$^+$, 100).

2,6-Bis(3-hydroxypropyl)phenyl trifluoromethanesulfonate 220

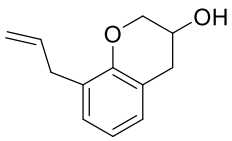


9-BBN method (small scale): To a solution of **221** (31 mg, 0.101 mmol) in dry THF (1.0 mL) under Ar environment was added 0.5 M 9-BBN (1.2 mL) at 0 °C. This reaction mixture was stirred whilst warming to RT over 3 h. The mixture was then cooled to 0 °C and 3 M aq. NaOH (1 mL) was added dropwise, followed by 30% aq. H_2O_2 (1.0 mL). The reaction mixture was then stirred for 3 h. Brine (2.0 mL) was added to hydrolyse boronate ester and stirred for 30 min. This mixture was then extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with 30% aq. $Na_2S_2O_2$, brine and then dried ($MgSO_4$), filtered and concentrated *in vacuo* to obtain a crude yellow oil. The product was then purified by flash column chromatography (0-100% Et_2O in petrol) to yield a colourless oil (21 mg, 61%); ν_{max} (film/cm^{-1}) 3349 (br, O-H), 2925, 2882, 1445, 1212; δ_H (600 MHz, $CDCl_3$) 7.27-7.19 (m, 3H, ArH), 3.69 (t, J = 6.4 Hz, 4H, 2 × OCH_2), 2.85-2.82 (m, 4H, 2 × $OHCH_2CH_2CH_2$), 1.93-1.87 (m, 4H, 2 × $OHCH_2CH_2$CH_2); δ_C (150 MHz, $CDCl_3$) 145.8, 135.7, 129.3, 128.6, 118.7 (q, J_{CF} = 320 Hz), 62.2, 33.0, 26.9; LRMS (ES): 343 ([M+H]$^+$, 100), 365 ([M+Na]+, 50); HRMS: Found (ES): [M+H]$^+$ 343.0833 $C_{13}H_{18}O_5F_3S$, requires 343.0827

9-BBN method (large scale): To a solution of **221** (9.85 g, 32.1 mmol) in dry THF (32 mL) under Ar environment was added 0.5 M 9-BBN (300 mL) at 0 °C (maintaining internal temperature at 0 °C) over 10 hours (CARE! The reaction is highly exothermic and on large scale the addition should be very slow). This reaction mixture was then stirred whilst warming to RT over 12 h. The mixture was then cooled to 0 °C and 3 M aq. NaOH (100 mL) was added dropwise, followed by 30% aq. H_2O_2 (100 mL) maintaining internal temperature below 10 °C. The reaction mixture was then stirred for another 10 h. Brine (2.0 mL) was added to hydrolyse boronate ester and stirred for 2 h. This mixture was then extracted with EtOAc (3 × 500 mL) and the combined organic phases were washed with 30% aq. $Na_2S_2O_2$, brine and then dried ($MgSO_4$), filtered and concentrated *in vacuo* to obtain a crude yellow oil. The product was purified by recrystallisation of excess of cyclononane-1,5-diol (by-product of 9-BBN hydrolysis) followed by purification with flash column chromatography (Et_2O) to yield a colourless oil (6.65 g, 60%); NMR data consistent with the above method.

BH_3/THF method: A solution of **221** (82 mg, 0.268 mmol) in anhydrous THF was cooled to –15 °C under argon atmosphere. BH_3.THF (0.51 mL, 5.35 mmol) was added dropwise to the reaction mixture and stirred or 3.5 hours. Aq. NaOH solution (1 M, 1.1 mL) was then added dropwise over 10 min followed by the dropwise addition of 30% H_2O_2 (0.33 mL) and water (0.1 mL). The reaction mixture was then allowed to stir at room temperature for 1 h and then heated at 40 °C for 2 h. After cooling the reaction mixture, brine (10 mL) was added and organic layer was separated. The aqueous phase was further extracted with THF (3 × 10 mL) and the combined organic phases were washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to yield crude mixture of products (~90 mg). The mixture was then purified by flash column chromatography (Petrol:EtOAc 1:0-0:1) to yield four products: **222** and **21** characterised above, and **225**, **226**.

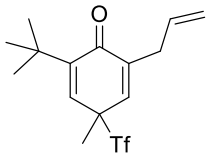
8-Allylchroman-3-ol 225



Colourless oil (20 mg, 39%); ν_{max} (film/cm^{-1}) 3352 (br, O-H), 2923, 1454; δ_H (600 MHz, $CDCl_3$) 7.04 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.81 (t, *J* = 7.5 Hz, 1H), 5.99-5.96 (m, 1H, R*H*C=CH_2), 5.10-5.06 (m, 2H, CH_2=CH), 4.94-4.85 (m, 1H,

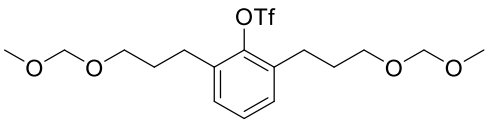
C*H*OH), 3.78-3.75 (m, 2H, OC*H*$_2$COH), 3.39-3.30 (m, 2H, CH$_2$=CHC*H*$_2$), 3.15-3.12 (m, 2H, C*H*$_2$), 2.01 (s, 1H, OH); δ_C (150 MHz, $CDCl_3$) 157.2, 136.5, 128.5, 126.3, 123.1, 121.9, 120.9, 115.7, 82.8, 65.1, 34.1, 31.7; LRMS (CI): 191 ([M+H]$^+$, 50), 173 ([M-OH]$^+$, 20), 147 ([M-C_2H_4O]$^+$, 100); HRMS: Found (CI): [M+H]$^+$ 191.10783 $C_{12}H_{15}O_2$, requires 191.10720.

2-Allyl-6-(*tert*-butyl)-4-methyl-4-((trifluoromethyl)sulfonyl)cyclohexa-2,5-dienone 226



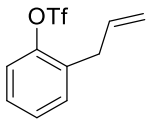
Pale yellow oil (3 mg, 4%); ν_{max} (film/cm^{-1}) 2956, 2923, 1719 (C=O), 1455; δ_H (600 MHz, $CDCl_3$) 6.86 (s, 1H), 6.54 (s, 1H), 5.97 (ddt, *J* = 16.9, 10.3, 6.5 Hz, 1H, CH$_2$C*H*), 5.21-5.12 (m, 2H), 3.37 (d, *J* = 6.5 Hz, 2H, CH$_2$CHC*H*$_2$), 1.57 (s, 3H, CH$_3$), 1.23 (s, 9H, ^{t}Bu); δ_C (150 MHz, $CDCl_3$) 186.7, 151.7, 147.4, 144.3, 136.4, 133.9, 126.6, 125.9, 116.9, 35.6, 29.6, 25.0; LRMS (EI): 336 ([M]$^+$, 100).

2,6-Bis(3-(methoxymethoxy)propyl)phenyl trifluoromethanesulfonate 228



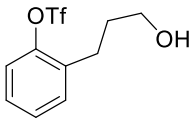
To an ice-cold solution of **220** (1.0 g, 2.92 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (12 mL) was added DIPEA (2.0 mL, 11.7 mmol) and MOM-Cl (0.66 mL, 8.76 mmol) under argon environment and left to stir at room temperature for 18 h. Upon completion, water was added (7 mL) and the product was extracted with EtOAc (3 × 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to obtain the crude product which was further purified using flash column chromatography (7:3 Petrol:EtOAc) to give the product as a colourless liquid (842 mg, 67%); ν_{max} (film/cm^{-1}) 3347, 3294, 2938, 2880, 1631; δ_H (600 MHz, $CDCl_3$) 7.25 (dd, *J* = 8.4, 6.7 Hz, 1H, ArH), 7.19 (d, *J* = 7.6 Hz, 2H, 2 × ArH), 4.63 (s, 4H, 2 × CH$_3$OC*H*$_2$), 3.56 (t, *J* = 6.3 Hz, 4H, 2 × OC*H*$_2$CH$_2$), 3.37 (s, 6H, 2 × CH$_3$), 2.88-2.82 (m, 4H, 2 × OCH$_2$CH$_2$C*H*$_2$), 1.96-1.88 (m, 4H, 2 × OCH$_2$C*H*$_2$CH$_2$); δ_C (150 MHz, $CDCl_3$) 145.9, 135.7, 129.2, 128.5, 118.7 (q, J_{CF} = 320 Hz), 96.6, 67.0, 55.3, 30.1, 27.3; LRMS (CI): 448 ([M+NH_4]$^+$, 100); HRMS: Found (CI): [M+NH_4]$^+$ 448.1612 $C_{17}H_{29}F_3NO_7S$, requires 448.1611.

2-Allylphenyl trifluoromethanesulfonate 232[140]



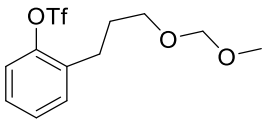
Triflic anhydride (1.00 mL, 6.0 mmol) was added dropwise to an ice-cool solution of pyridine (0.61 mL, 7.5 mmol) and 2-allylphenol (0.66 mL, 5.0 mmol) in CH_2Cl_2 (17 mL). The solution was stirred for 20 h and then washed with water (20 mL), aq. HCl (0.1 M, 20 mL) and aq. Na_2CO_3 (0.1 M, 20 mL). The aqueous phase was dried ($MgSO_4$) and solvent removed *in vacuo* to yield **232** as a colourless oil (1.45 g, 91%); ν_{max} (film/cm^{-1}) 2923 (C-H), 1665 (C=C), 1570, 1480; δ_H (600 MHz, $CDCl_3$) 7.37-7.24 (m, 4H, Ar), 5.93 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H, CH_2=C*H*), 5.16 (dd, *J* = 10.1, 1.3 Hz, 1H, C*H*$_{cis}$H$_{trans}$=CH), 5.13 (dd, *J* = 16.8, 1.3 Hz, 1H, CH$_{cis}$*H*$_{trans}$=CH), 3.49 (d, *J* = 6.6 Hz, 2H, ArCH_2); δ_C (150 MHz, $CDCl_3$) 148.0, 134.7, 132.9, 131.5, 128.5, 128.3, 121.5, 119.8 (q, J_{CF} = 320 Hz), 117.6, 34.1; Data in agreement with the literature.[140]

2-(3-Hydroxypropyl)phenyl trifluoromethanesulfonate 233[140]



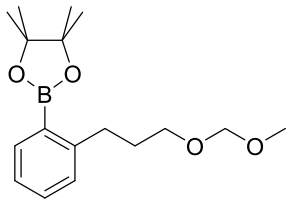
To a solution of **232** (1.21 g, 4.53 mmol) in dry THF (40 mL) under Ar environment was added 0.5 M 9-BBN (25 mL) at 0 °C. After the addition, the reaction mixture was stirred whilst warming to RT over 3 h. The mixture was then cooled to 0 °C and 3 M aq. NaOH (4.0 mL) was added dropwise, followed by 30% aq. H_2O_2 (2.0 mL). The reaction mixture was then stirred for 3 h. Brine (4.0 mL) was added to hydrolyse boronate ester and stirred for 30 min. This mixture was then extracted with EtOAc (3 × 50 mL) and the combined organic phases were washed with 30% aq. $Na_2S_2O_2$, brine and then dried ($MgSO_4$), filtered and concentrated *in vacuo* to obtain a crude yellow oil. The by-product cyclooctane-1,5-diol was recrystallised to separate the majority from the product **233**, filtered, and the resulting solution was concentrated *in vacuo* to yield crude **233** (NMR clean) as a colourless oil (559 mg, 43%); δ_H (600 MHz, $CDCl_3$) 7.39-7.21 (m, 4H), 3.69 (t, *J* = 6.3 Hz, 2H, Ar$CH_2CH_2CH_2$), 2.87-2.76 (m, 2H, ArCH_2), 1.93-1.88 (m, 2H, ArCH_2CH_2), 1.71 (s, 1H, OH); δ_C (150 MHz, $CDCl_3$) 148.2, 134.7, 131.4, 128.6, 128.1, 121.5, 118.7 (q, J_{CF} = 320.0 Hz), 62.0, 32.8, 26.4. The NMR data is in agreement with the literature.[140] The product was directly used in the next step without further purification.

2-(3-(Methoxymethoxy)propyl)phenyl trifluoromethanesulfonate 234



The crude triflate **233** (559 mg, 1.97 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (8.0 mL) and DIPEA (0.86 mL, 4.93 mmol) and MOM-Cl (0.23 mL, 2.95 mmol) were added dropwise under argon environment, and the resulting mixture was left to stir at room temperature for 15 h. Upon completion, water was added (5 mL) and the product was extracted with EtOAc (3 × 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to obtain the product as a colourless liquid (621 mg, 96%); δ_H (600 MHz, $CDCl_3$) 7.36-7.22 (m, 4H, Ar), 4.62 (s, 2H, CH_3OCH_2), 3.56 (t, J = 6.3 Hz, 2H, $CH_3OCH_2OCH_2$), 3.36 (s, 3H, CH_3), 2.86-2.74 (m, 2H, $ArCH_2$), 1.95-1.90 (m, 2H, $ArCH_2CH_2$); δ_C (150 MHz, $CDCl_3$) 148.2, 134.7, 131.3, 128.5, 128.0, 121.5, 118.7 (q, J_{CF} = 319.9 Hz), 96.5, 66.8, 55.3, 29.9, 26.8; The product was then directly used in the next step without further purification.

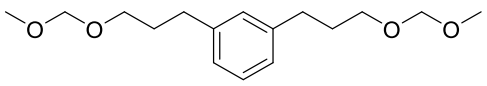
2-(2-(3-(Methoxymethoxy)propyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 230



To an oven-dried 3-necked flask under argon was added KOAc (294 mg, 3.0 mmol, 3.0 equiv.), **234** (310 mg, 0.94 mmol, 1.0 equiv.), B_2Pin_2 (279 mg, 1.1 mmol, 1.1 equiv.) in 1,4-dioxane (5 mL, 0.2 M). The resulting mixture was degassed with Ar bubbles for 20 min and dppf (17 mg, 0.03 mmol, 3 mol%) followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (24 mg, 0.03 mmol, 3 mol%) were added and heated to 100 °C for 17 h. The solution was then filtered through a pad of celite washing with EtOAc. The resulting solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (petrol:Et_2O 0-50%) to yield the product **230** as a clear liquid (208 mg, 68%); δ_H (600 MHz, $CDCl_3$) 7.79 (dd, J = 7.6, 1.3 Hz, 1H, Ar), 7.38-7.32 (m, 1H, Ar), 7.23-7.14 (m, 2H, Ar), 4.64 (s, 2H, CH_3OCH_2), 3.57 (t, J = 6.7 Hz, 2H, $CH_3OCH_2OCH_2$), 3.38 (s, 3H, CH_3O), 3.02-2.90 (m, 2H, $ArCH_2$), 1.90-1.85 (m, 2H,

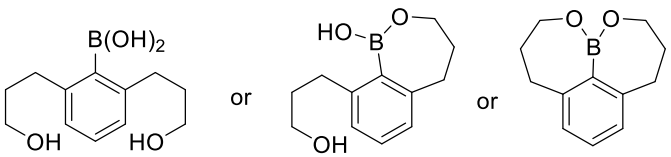
$ArCH_2CH_2$), 1.35 (s, 12H, 4 × CH_3); δ_C (150 MHz, $CDCl_3$) 155.7 (br), 149.2, 136.3, 131.0, 129.4, 125.3, 96.5, 83.6, 67.7, 55.2, 33.1, 32.5, 25.0.

1,3-Bis(3-(methoxymethoxy)propyl)benzene 235



To an oven-dried flask under argon was added KOAc (835 mg, 8.5 mmol, 4.2 equiv.), **228** (861 mg, 2.0 mmol, 1.0 equiv.), B_2Pin_2 (609 mg, 2.4 mmol, 1.2 equiv.) in 1,4-dioxane (10 mL, 0.2 M). The resulting mixture was degassed with Ar bubbles for 20 min and dppf (110 mg, 0.2 mmol, 10 mol%) followed by Pd(dppf)Cl_2·CH_2Cl_2 (163 mg, 0.2 mmol, 10 mol%) were added and heated to 100 °C for 2 days. The solution was then filtered through a pad of celite washing with EtOAc. The resulting solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (petrol:Et_2O 0-50%) to yield the unreacted **228** (547 mg) and product **235** as a clear liquid (162 mg, 29%); ν_{max} (film/cm^{-1}) 2924, 2877, 1605; δ_H (600 MHz, $CDCl_3$) 7.21 (t, *J* = 7.4 Hz, 1H, ArH), 7.05-7.01 (m, 3H, 3 × ArH), 4.64 (s, 4H, 2 × OCH_2O), 3.55 (t, *J* = 6.4 Hz, 4H, 2 × OCH_2CH_2), 3.38 (s, 6H, 2 × CH_3), 2.72-2.65 (m, 4H, 2 × $ArCH_2$), 1.95-1.89 (m, 4H, 2 × OCH_2CH_2); δ_C (150 MHz, $CDCl_3$) 142.1, 128.8, 128.5, 126.1, 96.6, 67.3, 55.3, 32.5, 31.6; LRMS (ES+): 305 ([M+Na]$^+$, 100); HRMS: Found (ES+): [M+Na]$^+$ 305.1741 $C_{16}H_{26}O_4Na$, requires 305.1729.

(2,6-Bis(3-hydroxypropyl)phenyl)boronic acid 218 (open, half-open, and closed forms)



218a **218b** **218c**

Boronic acid **218** is reported as a mixture of **218a**:**218b** 0.05:1 in $CDCl_3$, and as **218c** in solid form (used for mass spec). When ^{1}H NMR shifts are reported for **218b**, two arms are denoted as “open” to describe a free arm, and “closed” to describe the arm cyclised with boron. For ^{13}C NMR, peaks of major form **128b** reported only, C-B is not visible by NMR.

To an oven-dried flask under argon was added KOAc (1.29 g, 5 equiv., 13.1 mmol), **228** (750 mg, 1 equiv., 1.74 mmol), bis(neopentyl glycolato)diboron (1.18 g, 3 equiv., 5.22 mmol) in 1,4-dioxane (10 mL, 0.2 M). The resulting mixture was

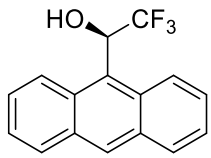
degassed with Ar bubbles for 20 min and dppf (96 mg, 10 mol%, 0.17 mmol) followed by Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (142 mg, 10 mol%, 0.17 mmol) were added and heated at 100 °C for 2 days. The solution was then filtered through a pad of celite washing with EtOAc. The resulting solution was washed with brine, extracted, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (Petrol-Et_2O 0-50%) to yield unreacted **228** (55 mg, 7%) and a mixture of partially deprotected and fully protected boronic acid **238** by-products (495 mg). The mixture was then mixed with 3 M methanolic HCl (10 mL) and heated to 60 °C for 15 h. After cooling, the solvent was evaporated and the crude mixture purified by flash column chromatography (petrol-Et_2O 30%) to yield **218** as a white solid (112 mg, 27%); mp 173-176 °C; ν_{max} (solid/cm^{-1}) 3049, 2952, 2847, 1591, 1569; δ_H (600 MHz, $CDCl_3$, **218b**, 5% of **218a** present) 7.25 (t, *J* = 7.6 Hz, 1H, ArH), 7.12 (d, *J* = 7.6 Hz, 1H, ArH), 6.97 (d, *J* = 7.4 Hz, 1H, ArH), 4.22-4.15 (m, 2H, OCH_2), 3.86 (t, *J* = 6.3 Hz, 2H, $HOCH_2$), 3.09-3.01 (m, 2H, $ArCH_2$(closed)), 2.75 (t, *J* = 7.0 Hz, 2H, $ArCH_2$(open)), 1.96 (app p, *J* = 6.7 Hz, 2H, $ArCH_2CH_2$(open)), 1.88 (ddd, *J* = 12.6, 10.0, 5.5 Hz, 2H, $ArCH_2CH_2$(closed)), 1.56 (s, 1H, OH); δ_C (150 MHz, $CDCl_3$) 146.9, 143.4, 129.8, 127.4, 125.4, 63.1, 62.5, 35.9, 33.8, 31.3, 30.4; δ_B (128 MHz, $CDCl_3$) 33.2; LRMS (ES+): 203 ([M(**218c**)+H]$^+$, 100); HRMS: Found (ES+): [M(**218c**)]$^+$ 202.1274 $C_{12}H_{15}O_2B$, requires 302.1280.

7. Appendix

7.1 Determination of enantiomeric purity of chiral amides by HPLC or derivatisation with Marfey's reagent and Chiral shift agent 257

Marfey's reagent method: 1 equiv. of chiral amide was mixed with 1.5 equiv. of L- and D-Marfey's reagent and 1.0 equiv. of Et_3N in DMSO-*d6*. The mixture was heated at 40 °C for 1 h before ^1H NMR spectrum was collected. This method was applied to amides **55q, 55r, 98b, 98c, 98e-f, 98k, 100c, 100e, 103a-f, 103h,** L**-91 and** D**-91**, **107c**, **107e**.

Chiral shift agent method:[182] 1 equiv. of amide and its racemic equivalent were mixed with 1.2 equiv. of *(R)*-(−)-1-(9-Anthryl)-2,2,2-trifluoroethanol **257** in $CDCl_3$ and the er was determined by ^1H NMR.



257

This method was used for **55p** and **98l**

Chiral HPLC: Chiral HPLC was used to determine er of amides **55n**, **63m**, **63n, 98g, 100b, 103i.**

Chiralcel OD-H was used for **55n** (^{n}Hex/^{i}PrOH; 80/20; 0.8 mL/min; 218 nm; R_t(R) = 6.03 min.

Chiralcel OD-1 was used for **63m** (^{n}Hex/^{i}PrOH; 90/10; 0.8 mL/min; 218 nm; R_t(S) = 16.56 min.

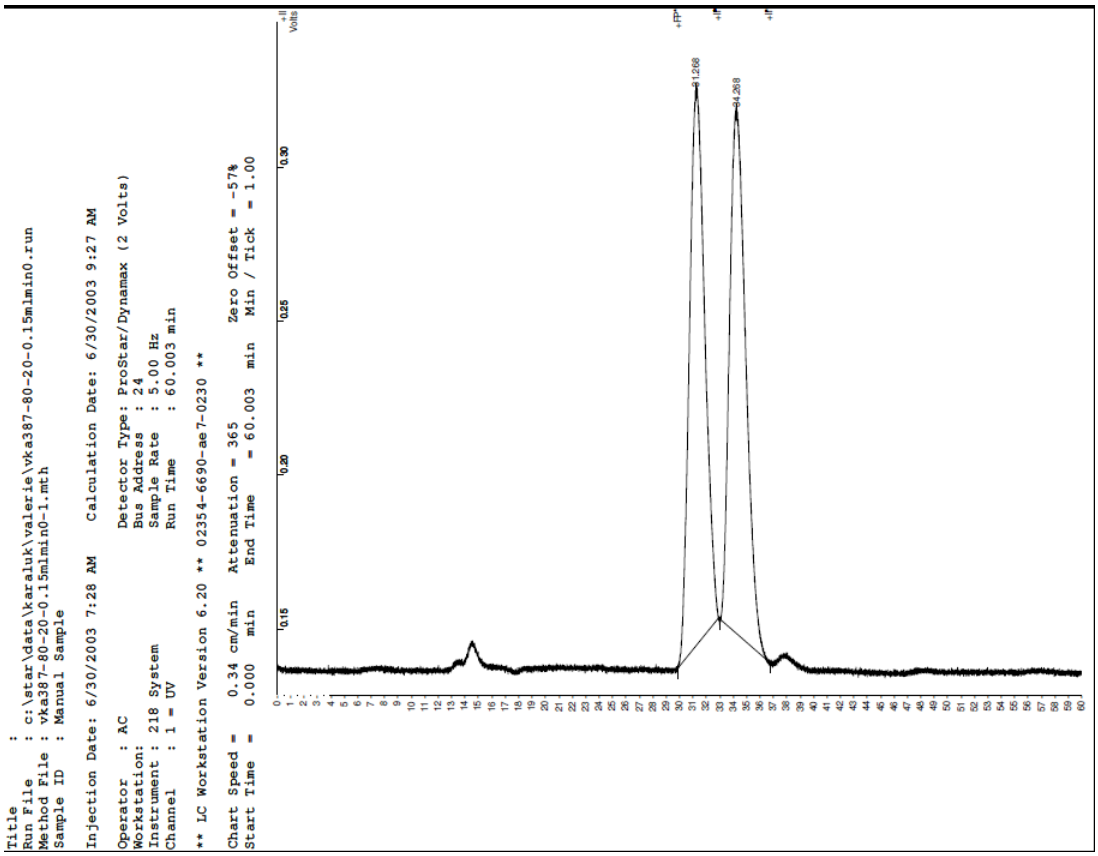
Chiralcel OD-1 was used for **63n** (^{n}Hex/^{i}PrOH; 90/10; 0.8 mL/min; 218 nm; R_t(S) = 20.72 min.

Chiralcel OD-1 was used for **98g** (^{n}Hex/^{i}PrOH; 95/5; v/v; 0.5 ml/min; 218 nm; R_t(S) = 23.58 min.

Chiralcel OD-H was used for **100b** (^{n}Hex/^{i}PrOH; 97/3, 0.5 ml/min; 254 nm; R_t(S) = 15.79 min.

Chiralcel OD-1 was used for **103i** (^{n}Hex/^{i}PrOH; 90/10, 1 ml/min; 254 nm; R_t(S) = 13.06 min.

N-Benzyl-2-hydroxy-2-phenylacetamide – rac

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Print Date: Mon Jun 30 09:27:30 2003            Page 1 of 1

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Method File : vka387-80-20-0.15mlmin0-1.mth
Sample ID   : Manual Sample

Injection Date: 6/30/2003 7:28 AM    Calculation Date: 6/30/2003 9:27 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     : 60.003 min

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

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

                                 Ret.    Time                      Width
 Peak      Peak        Result    Time   Offset      Area    Sep.   1/2    Status
  No.      Name          ()      (min)   (min)    (counts) Code  (sec)  Codes
 ---- ------------ ---------- -------- -------- ---------- ---- ------ ------
    1                 50.3938   31.268    0.000   14447830   BB   77.4
    2                 49.6062   34.268    0.000   14222052   BB   77.0
 ---- ------------ ---------- -------- -------- ---------- ---- ------ ------
      Totals:        100.0000             0.000   28669882

Total Unidentified Counts :   28669882 counts

Detected Peaks: 2           Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: 135842 microVolts          LSB:     1 microVolts

Noise (used): 2586 microVolts - monitored before this run

Manual injection
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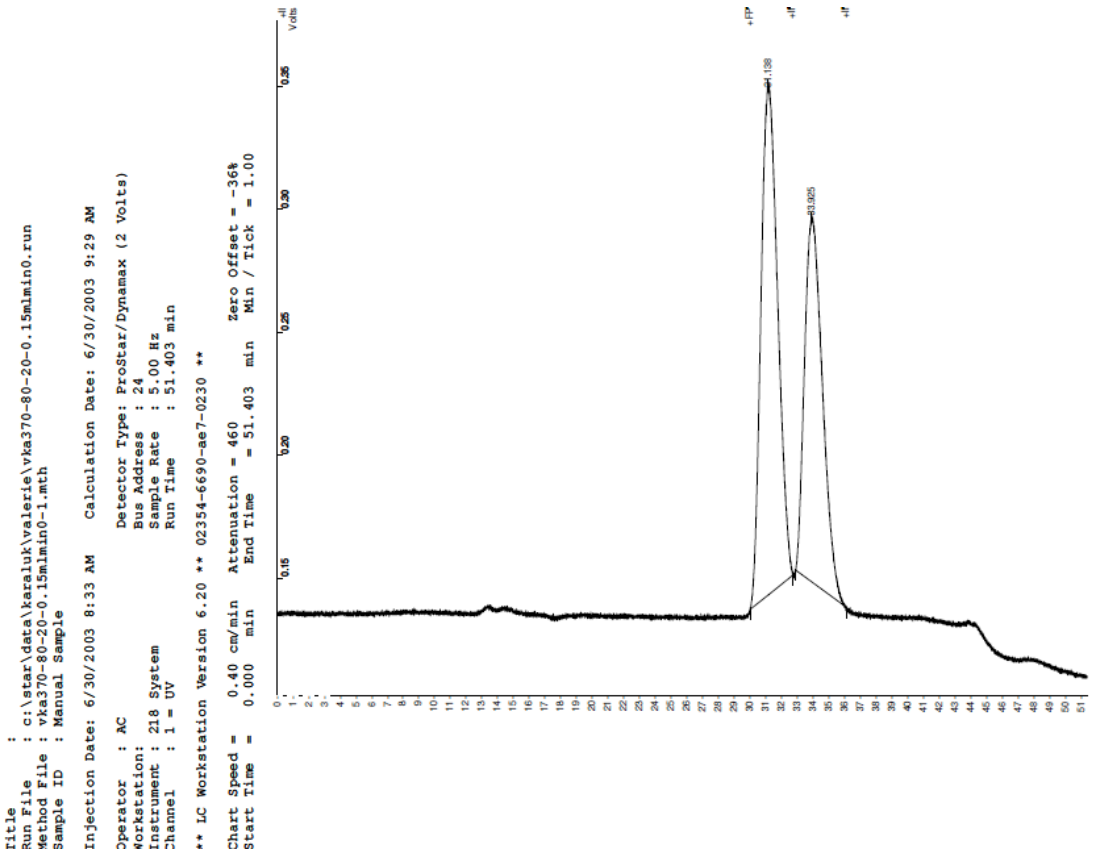
(*R*)-*N*-Benzyl-2-hydroxy-2-phenylacetamide 55n



Print Date: Mon Jun 30 09:29:35 2003 Page 1 of 1

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Injection Date: 6/30/2003 8:33 AM Calculation Date: 6/30/2003 9:29 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 : 51.403 min

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

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

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Total Unidentified Counts : 27004806 counts

Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: 135179 microVolts LSB: 1 microVolts

Noise (used): 1881 microVolts - monitored before this run

Manual injection

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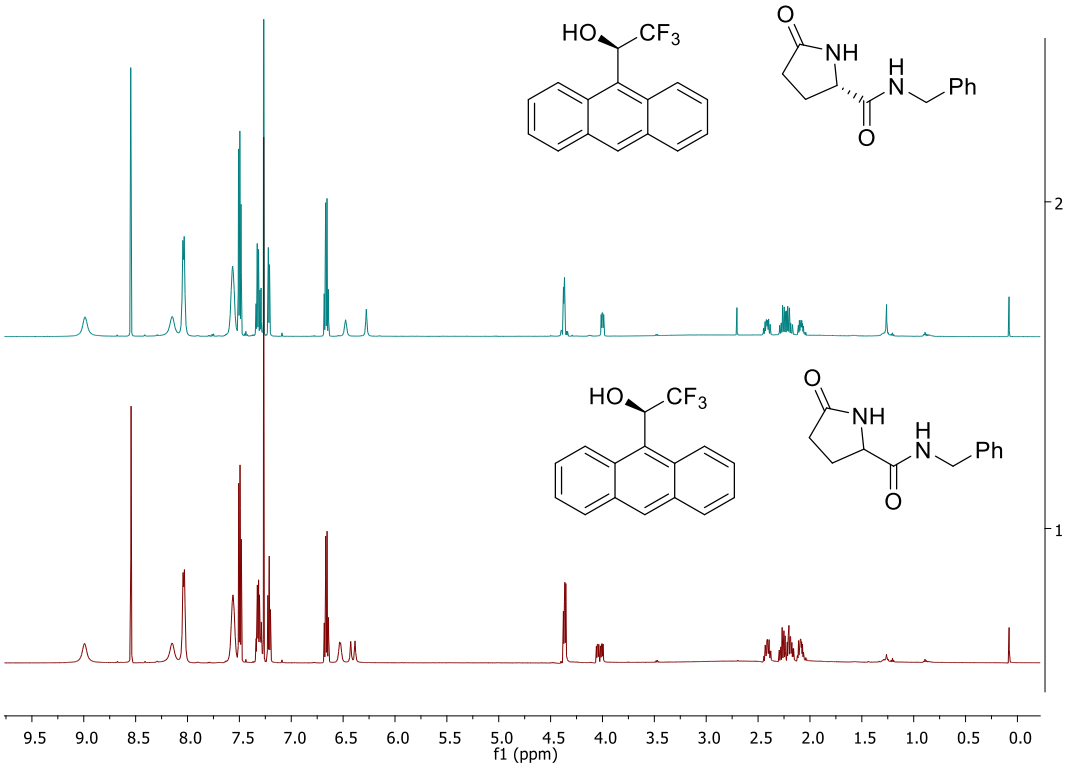
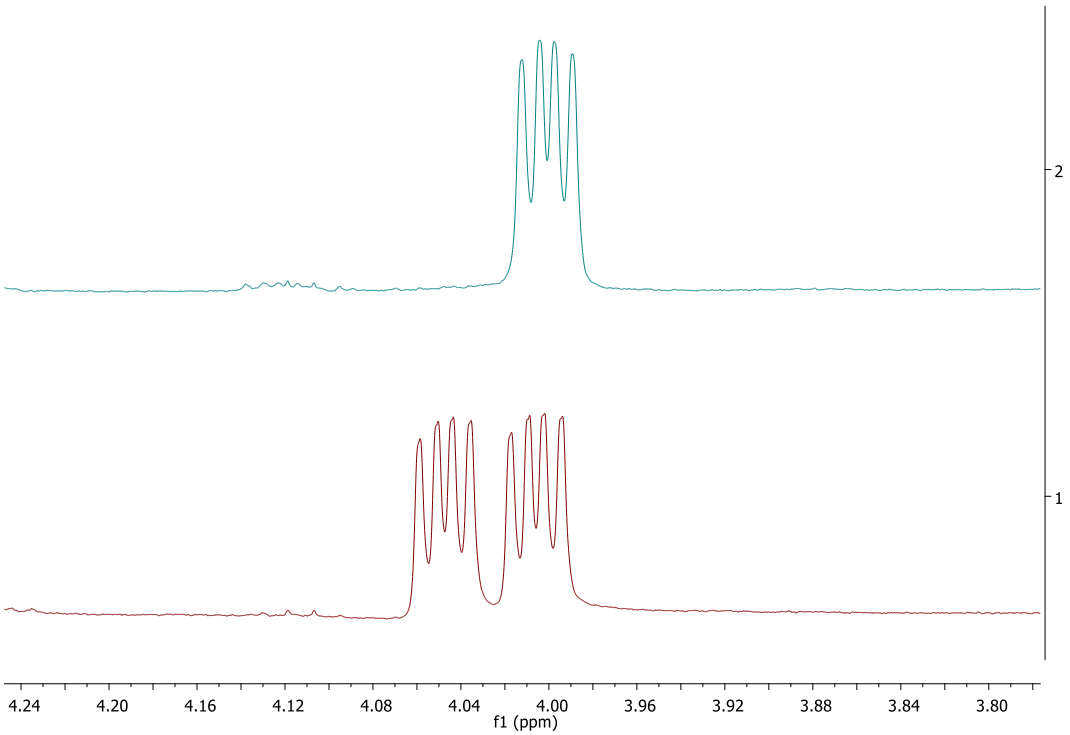
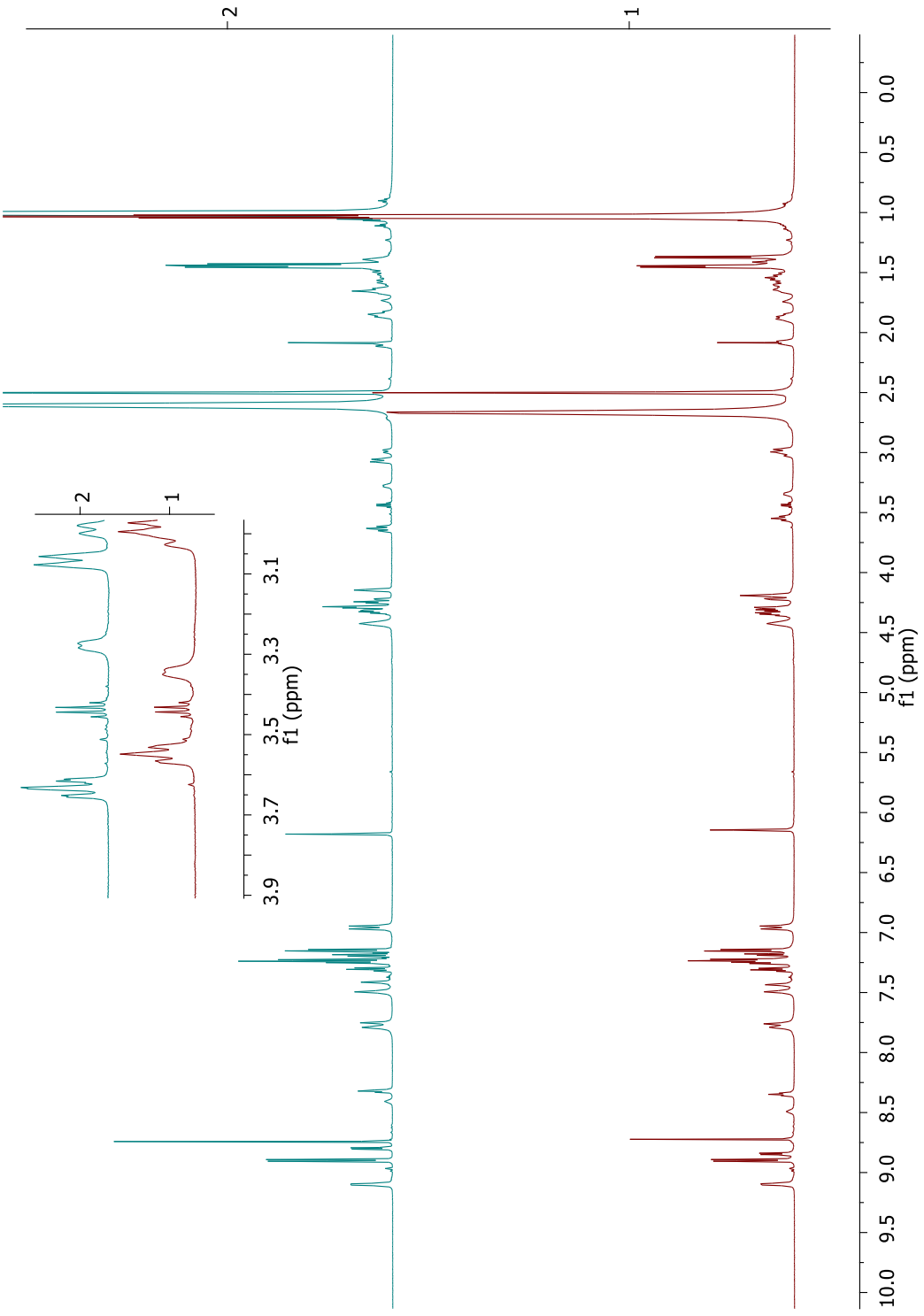
(*S*)-*N*-Benzyl-5-oxopyrrolidine-2-carboxamide 55p

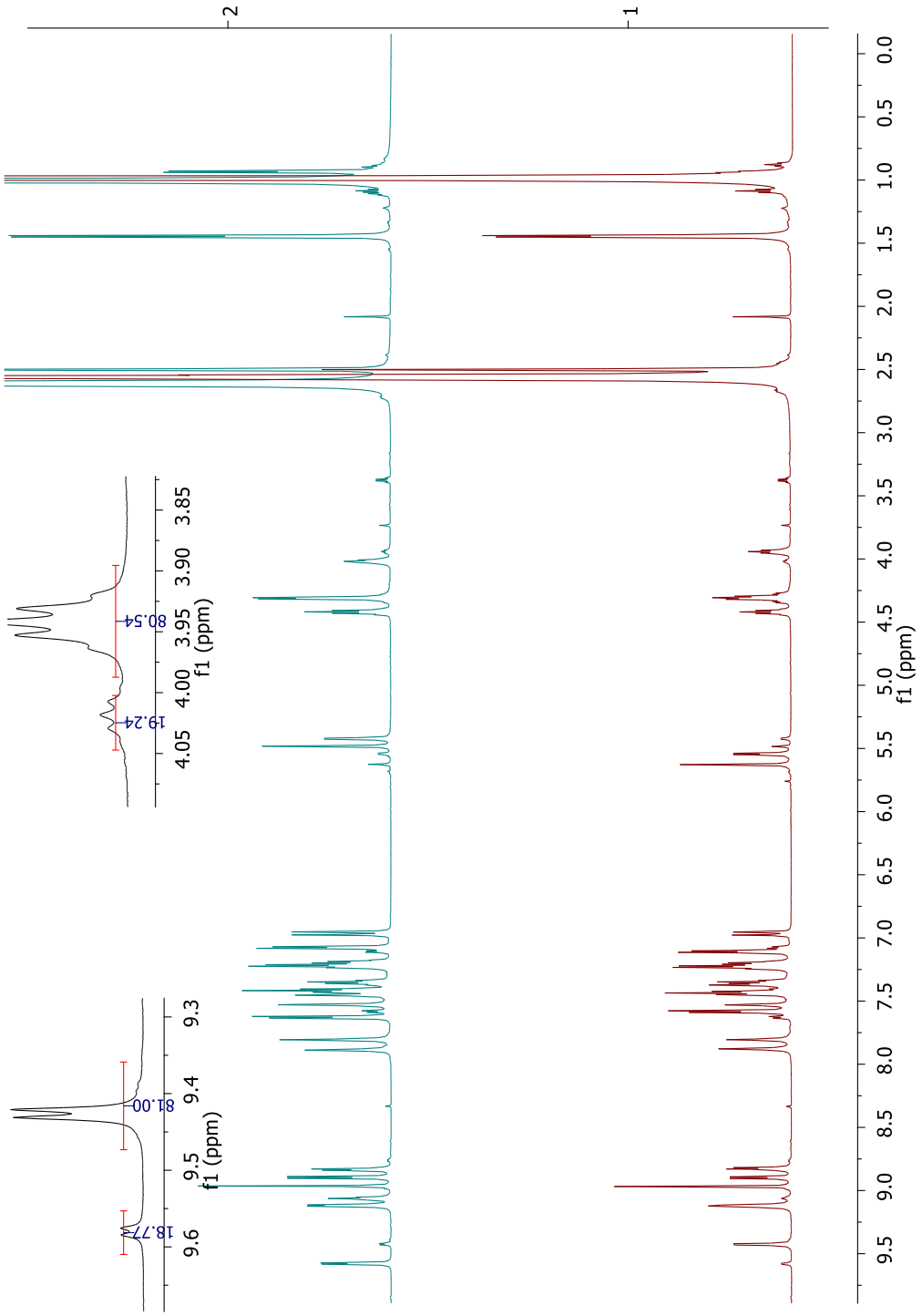




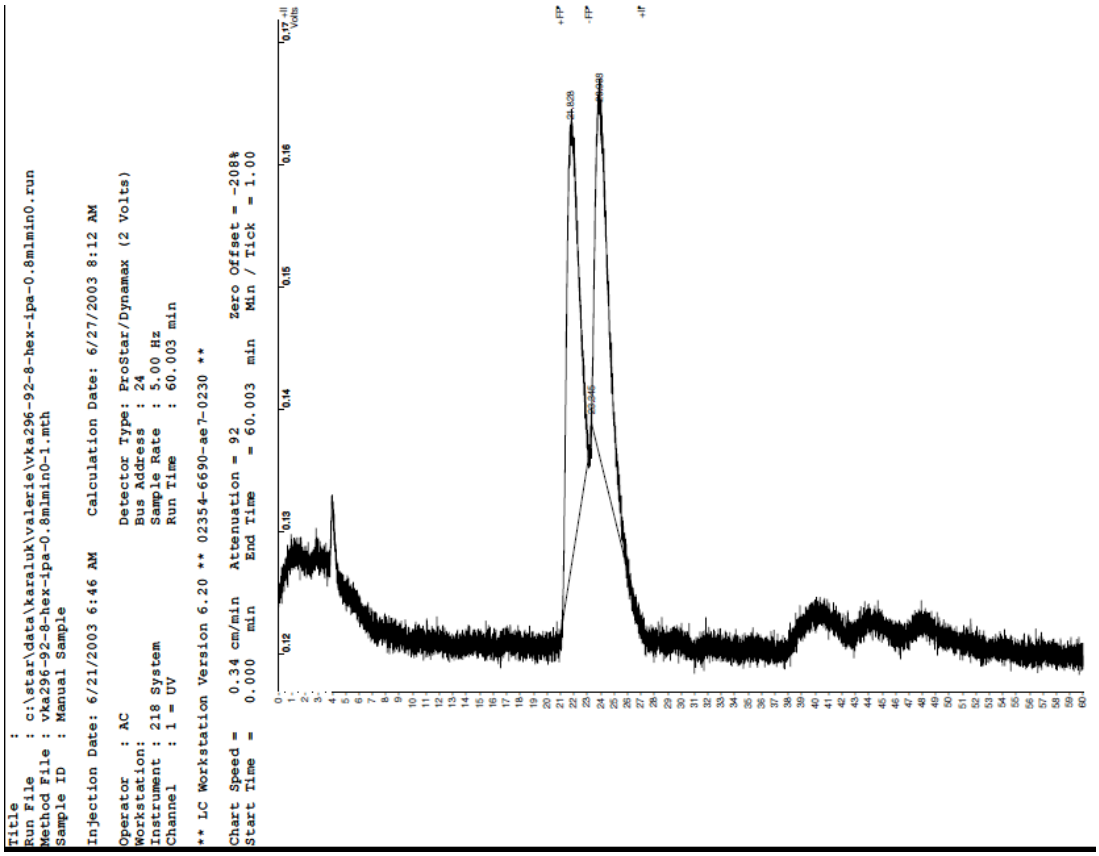
(*R*)-*Tert*-butyl 2-(benzylcarbamoyl)piperidine-1-carboxylate 55q



(*S*)-*Tert*-butyl (2-(benzylamino)-2-oxo-1-phenylethyl)carbamate 55r



2-(2-Phenylacetamido)propanamide – rac



Print Date: Fri Jun 27 08:12:26 2003 Page 1 of 1

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Injection Date: 6/21/2003 6:46 AM Calculation Date: 6/27/2003 8:12 AM

Operator : AC
Workstation:
Instrument : 218 System
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Run Time : 60.003 min

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

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Peak Measurement: Peak Area
Calculation Type: Percent

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2		0.0318	23.345	0.000	1355	BB	0.0	
3		46.7928	23.938	0.000	1992557	BB	53.6	
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Total Unidentified Counts : 4258257 counts

Detected Peaks: 3 Rejected Peaks: 0 Identified Peaks: 0

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Baseline Offset: 124431 microVolts LSB: 1 microVolts

Noise (used): 2029 microVolts - monitored before this run

Manual injection

Peak not split: event not in an existing peak

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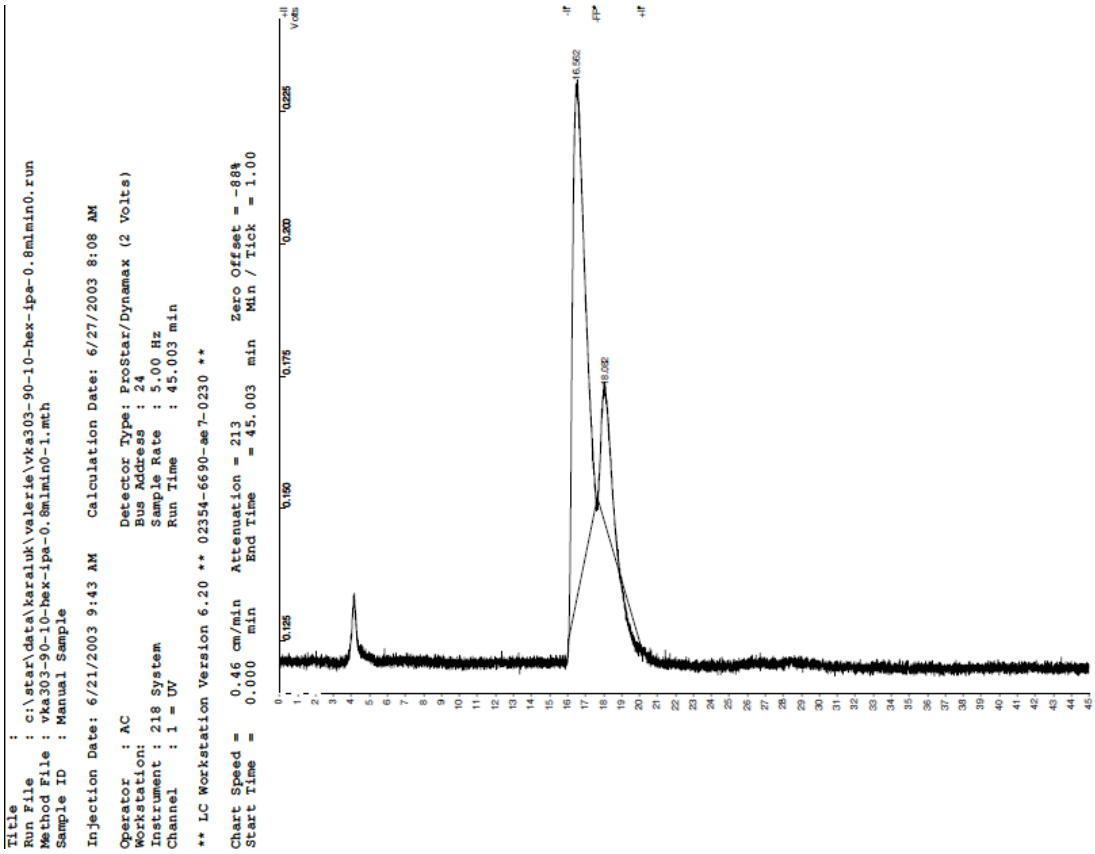
(*S*)-2-(2-Phenylacetamido)propanamide 63m



Print Date: Fri Jun 27 08:09:23 2003 Page 1 of 1

Title :
Run File : c:\star\data\karaluk\valerie\vka303-90-10-hex-ipa-0.8mlmin0.run
Method File : vka303-90-10-hex-ipa-0.8mlmin0-1.mth
Sample ID : Manual Sample

Injection Date: 6/21/2003 9:43 AM Calculation Date: 6/27/2003 8:08 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 : 45.003 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		86.1220	16.562	0.000	4589388	BB	54.0	
2		13.8780	18.082	0.000	739551	PB	26.2	
	Totals:	100.0000		0.000	5328939			

Total Unidentified Counts : 5328938 counts

Detected Peaks: 3 Rejected Peaks: 1 Identified Peaks: 0

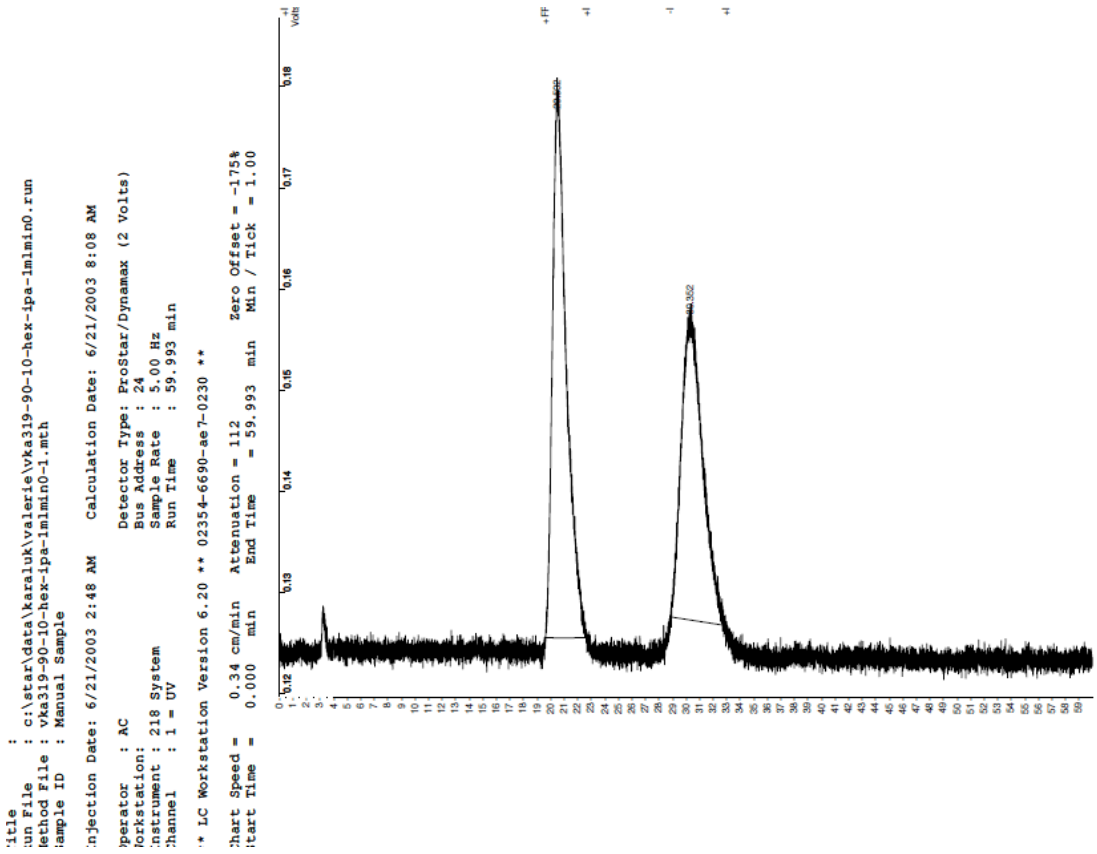
Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: 120627 microVolts LSB: 1 microVolts

Noise (used): 3757 microVolts - monitored before this run

Manual injection

Methyl-1-(2-phenylacetyl)pyrrolidine-2-carboxylate – rac



Print Date: Sat Jun 21 08:09:23 2003 Page 1 of 1

Title :
Run File : c:\star\data\karaluk\valerie\vka319-90-10-hex-ipa-1mlmin0.run
Method File : vka319-90-10-hex-ipa-1mlmin0-1.mth
Sample ID : Manual Sample

Injection Date: 6/21/2003 2:48 AM Calculation Date: 6/21/2003 8:08 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 : 59.993 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		53.9745	20.502	0.000	3827943	BB	59.7	
2		46.0255	30.352	0.000	3264192	BB	95.5	
	Totals:	100.0000		0.000	7092135			

Total Unidentified Counts : 7092134 counts

Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

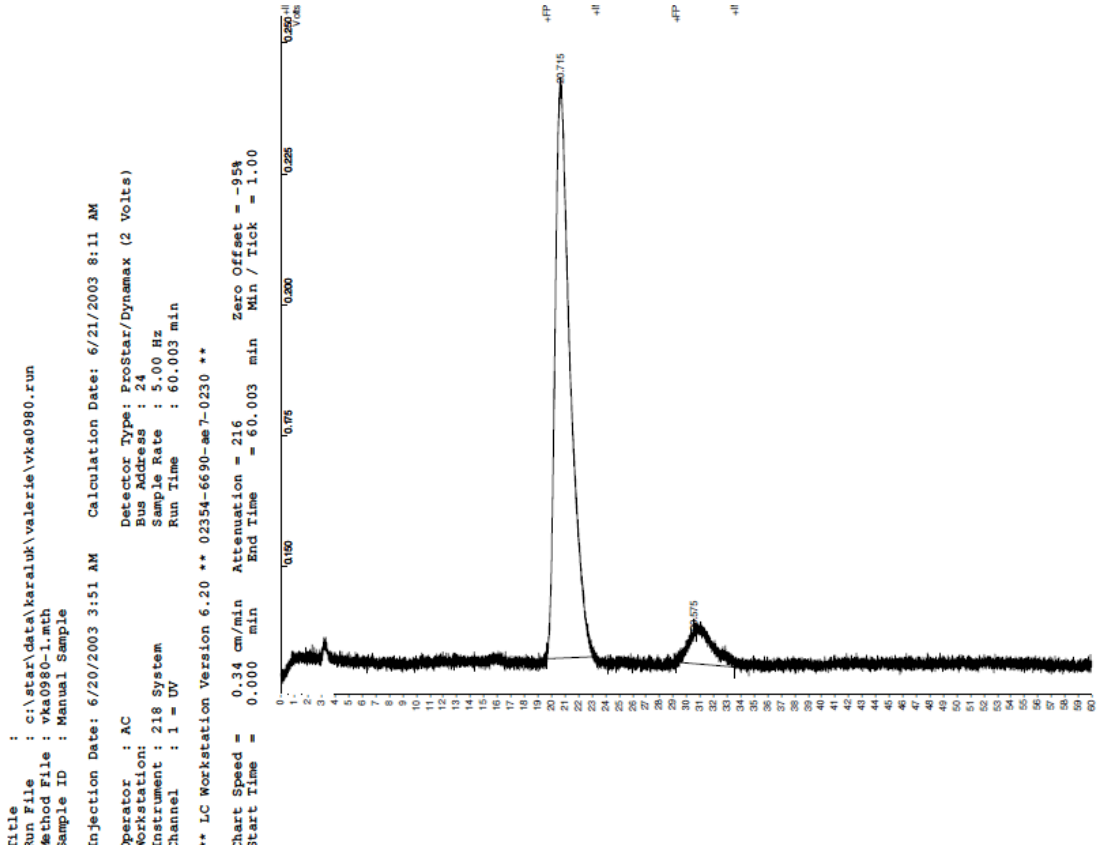
Baseline Offset: 124339 microVolts LSB: 1 microVolts

Noise (used): 2288 microVolts - monitored before this run

Manual injection

****

(*S*)-Methyl-1-(2-phenylacetyl)pyrrolidine-2-carboxylate 63n



Print Date: Sat Jun 21 08:11:59 2003 Page 1 of 1

Title :
Run File : c:\star\data\karaluk\valerie\vka0980.run
Method File : vka0980-1.mth
Sample ID : Manual Sample

Injection Date: 6/20/2003 3:51 AM Calculation Date: 6/21/2003 8:11 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 : 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		90.7876	20.715	0.000	8607774	BB	68.1	
2		9.2124	30.575	0.000	873452	BB	13.1	
	Totals:	100.0000		0.000	9481226			

Total Unidentified Counts : 9481226 counts

Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

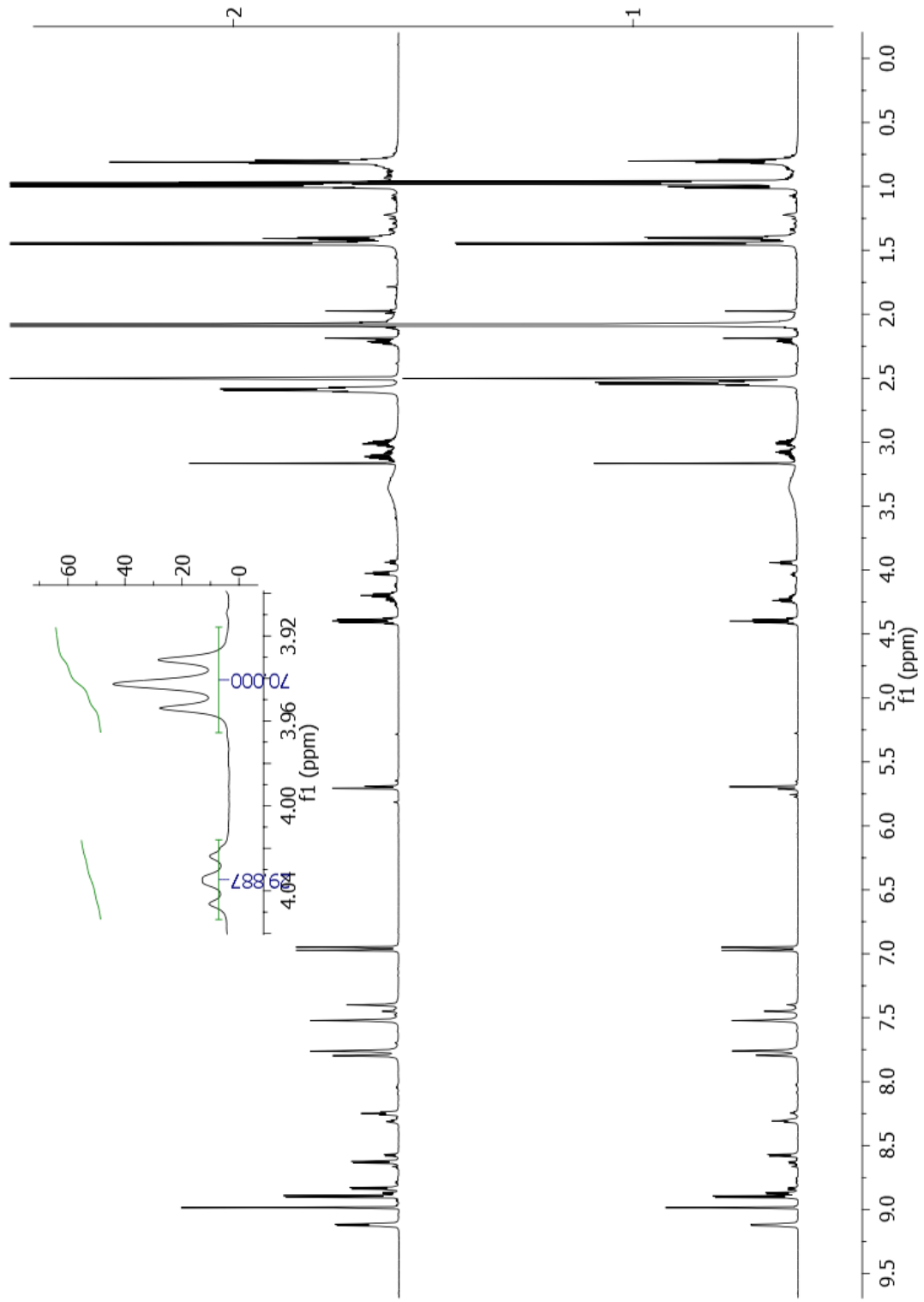
Baseline Offset: 129590 microVolts LSB: 1 microVolts

Noise (used): 3892 microVolts - monitored before this run

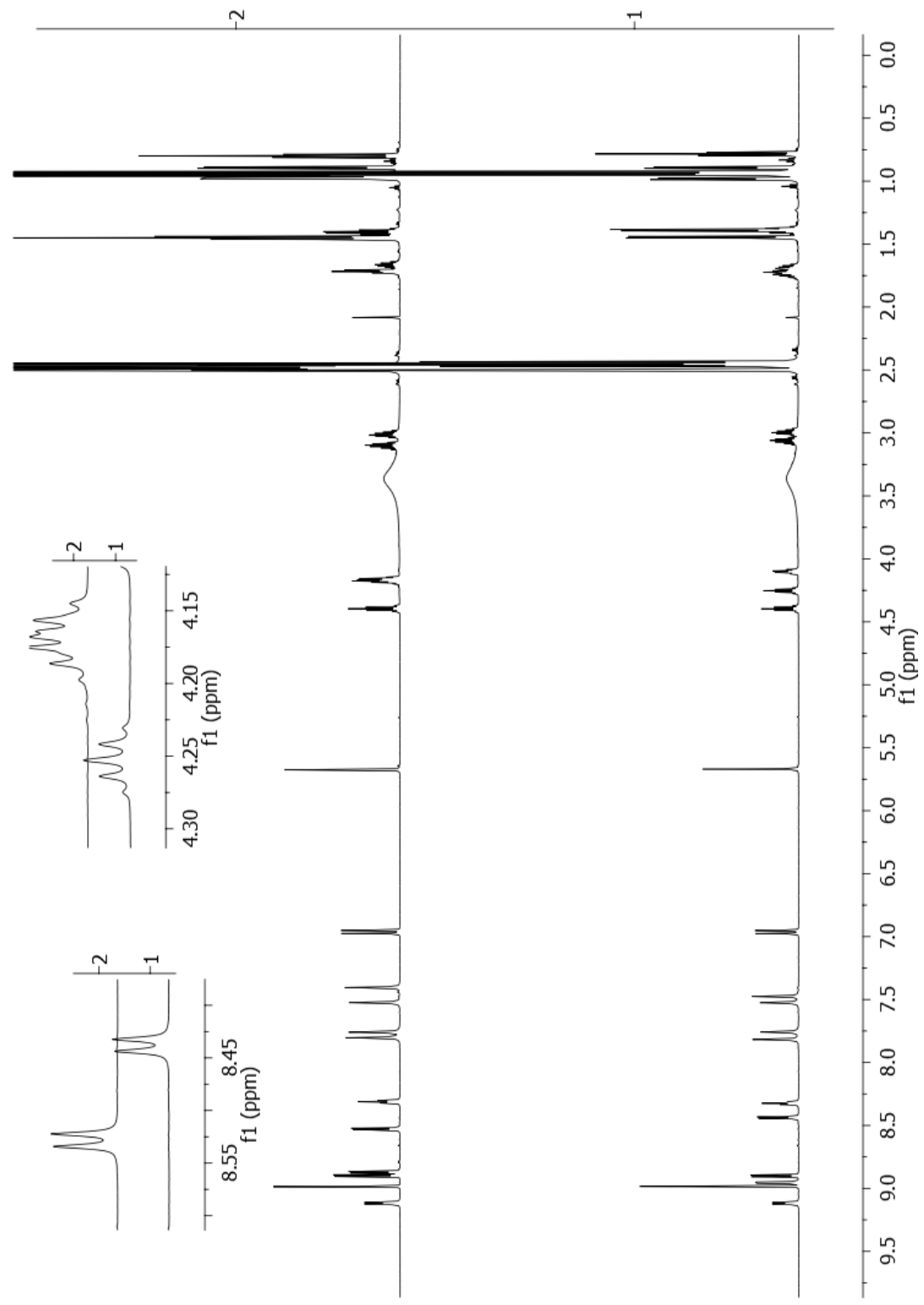
Manual injection

****

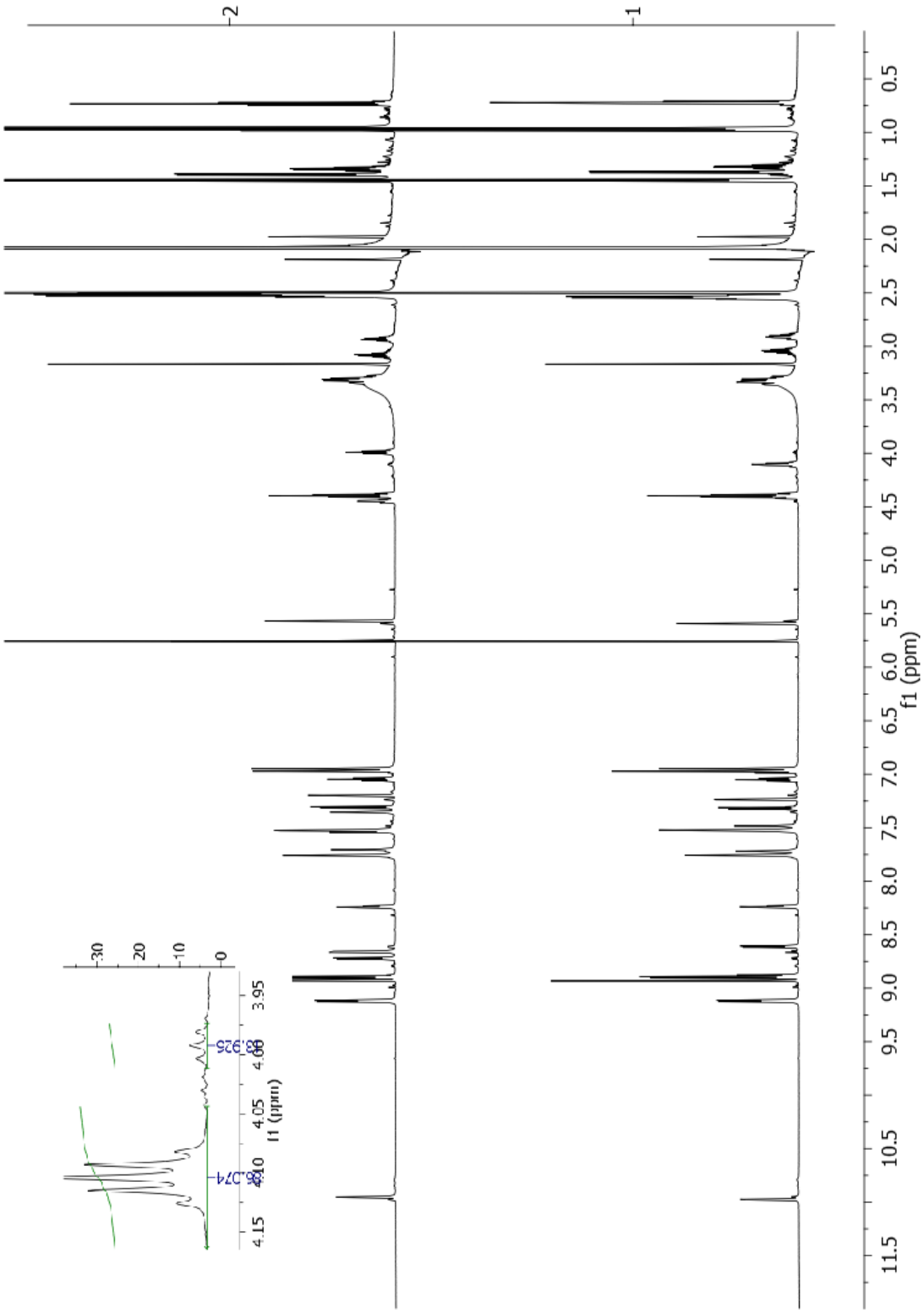
(*S*)-2-Amino-3-methyl-*N*-propylbutanamide 98b



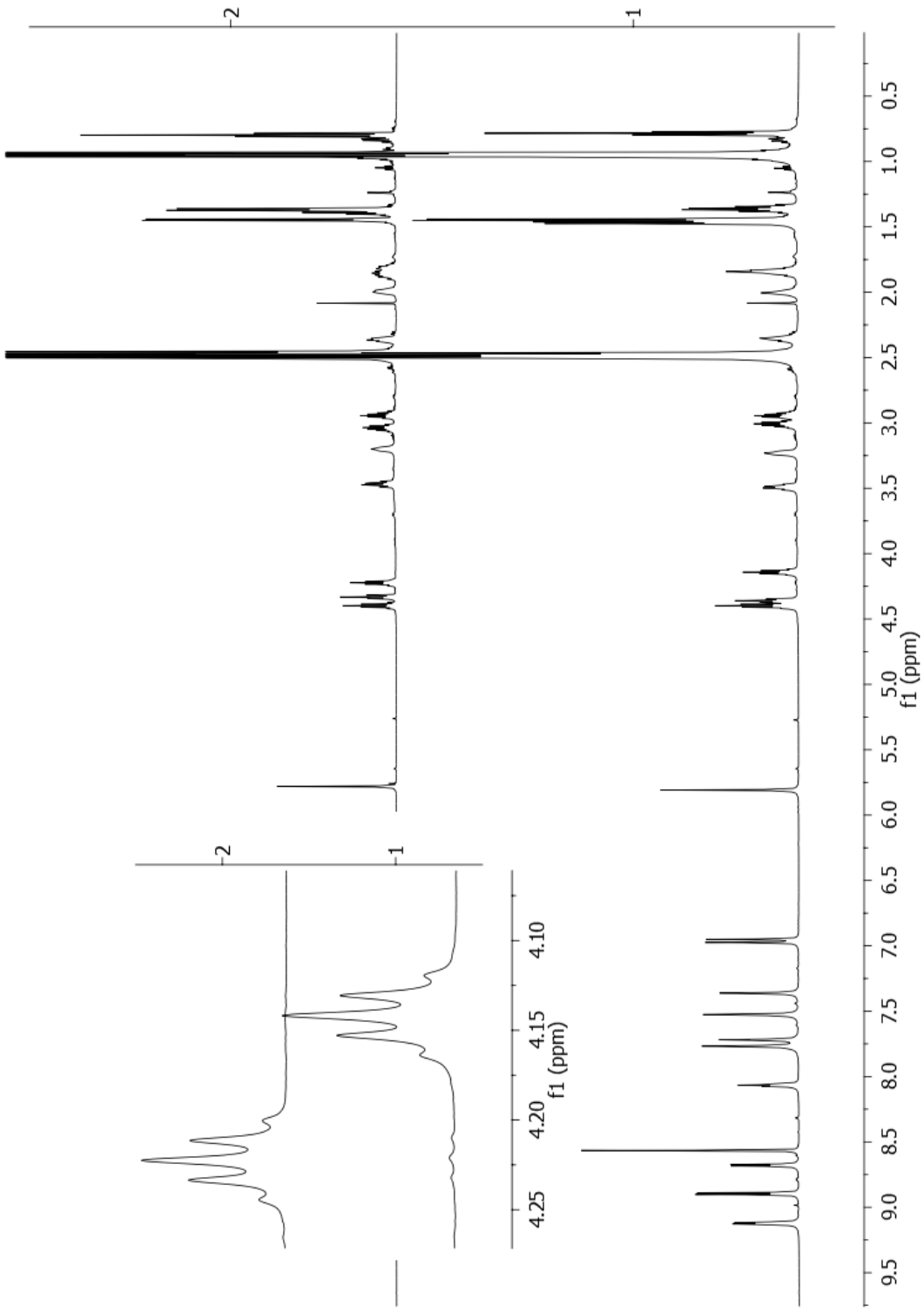
(*S*)-2-Amino-4-methyl-*N*-propylpentanamide 98c



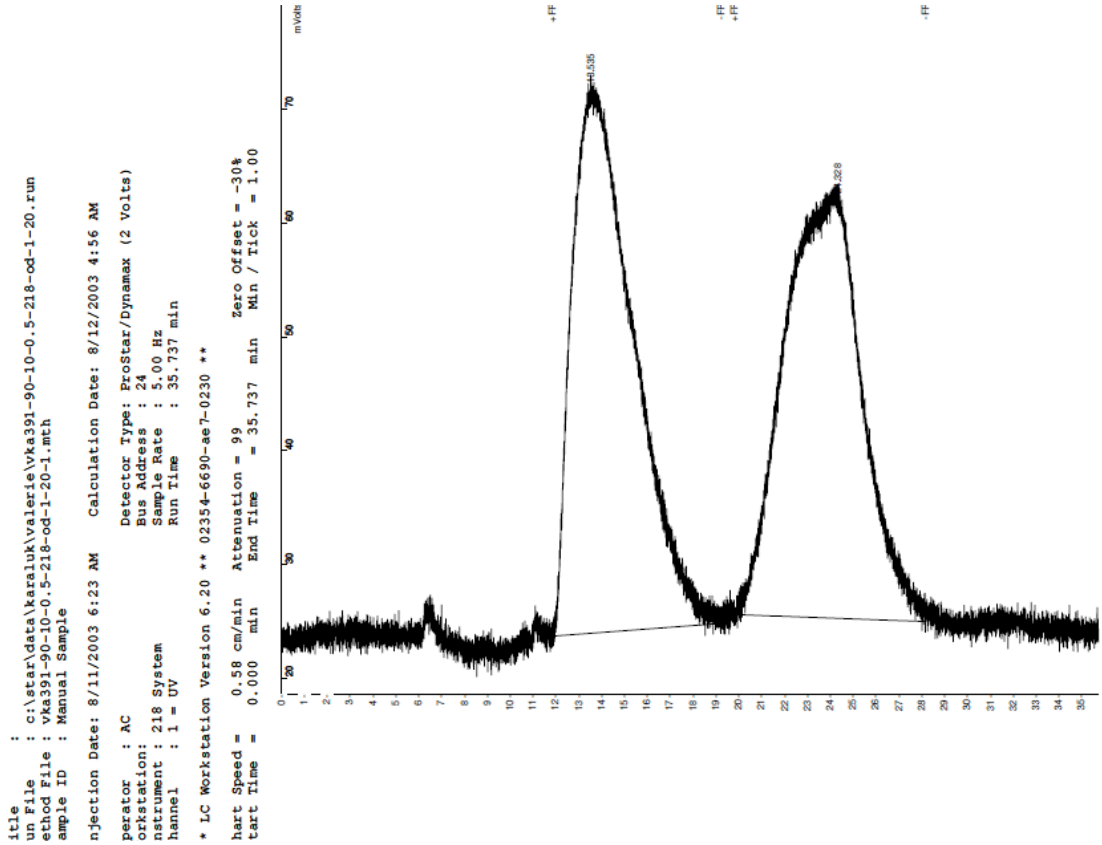
(*S*)-2-Amino-3-(1*H*-indol-3-yl)-*N*-propylpropanamide 98e



***(S)-N*-Propylpyrrolidine-2-carboxamide 98f**



(*R*,*S*)-2-Amino-3-(4-hydroxyphenyl)-*N*-propylpropanamide rac-98g



Print Date: Tue Aug 12 04:56:28 2003 Page 1 of 1

Title :
Run File : c:\star\data\karaluk\valerie\vka391-90-10-0.5-218-od-1-20.run
Method File : vka391-90-10-0.5-218-od-1-20-1.mth
Sample ID : Manual Sample

Injection Date: 8/11/2003 6:23 AM Calculation Date: 8/12/2003 4:56 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 : 35.737 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		50.0583	13.535	0.000	8942808	BB	179.0	
2		49.9417	24.328	0.000	8921987	BB	218.2	
	Totals:	100.0000		0.000	17864795			

Total Unidentified Counts : 17864796 counts

Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

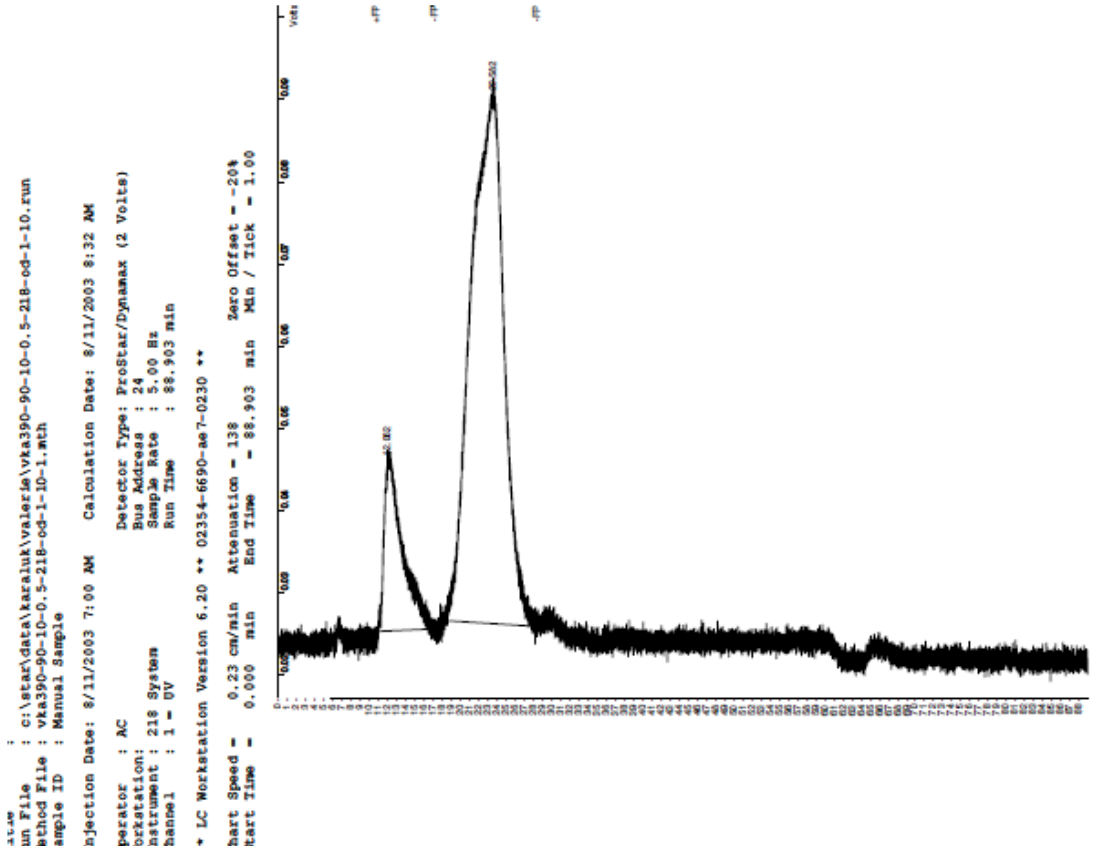
Baseline Offset: 24311 microVolts LSB: 1 microVolts

Noise (used): 3675 microVolts - monitored before this run

Manual injection

****

(*S*)-2-Amino-3-(4-hydroxyphenyl)-*N*-propylpropanamide 98g



Print Date: Tue Aug 12 04:55:18 2003 Page 1 of 1

Title :
Run File : c:\star\data\karaluk\valerie\vka390-90-10-0.5-218-od-1-10.run
Method File : vka390-90-10-0.5-218-od-1-10-1.mth
Sample ID : Manual Sample

Injection Date: 8/11/2003 7:00 AM Calculation Date: 8/11/2003 8:32 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 : 88.903 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		15.2839	12.062	0.000	2943300	BB	105.3	
2		84.7161	23.582	0.000	16314168	BB	239.3	
	Totals:	100.0000		0.000	19257468			

Total Unidentified Counts : 19257468 counts

Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

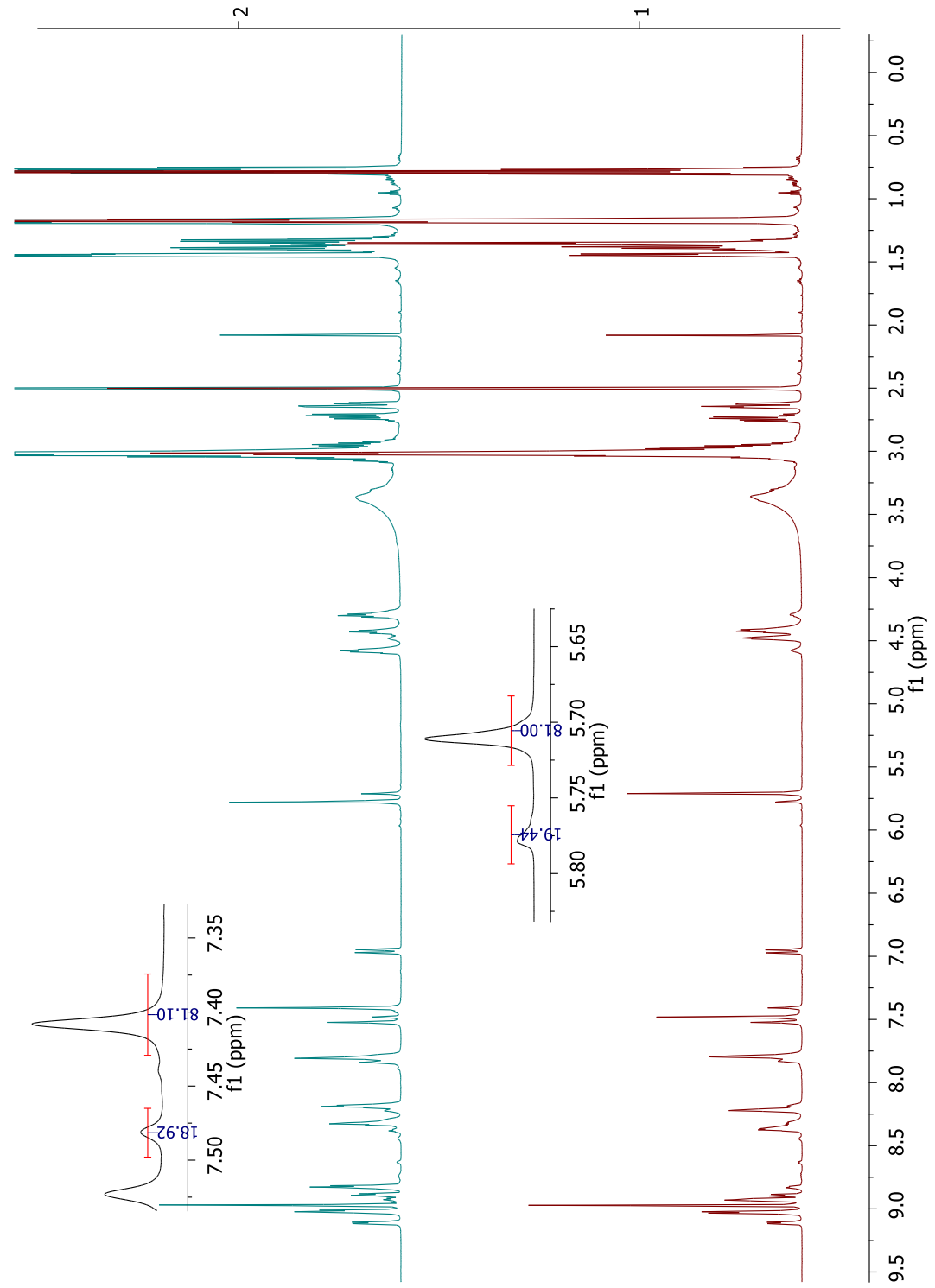
Baseline Offset: 24836 microVolts LSB: 1 microVolts

Noise (used): 4138 microVolts - monitored before this run

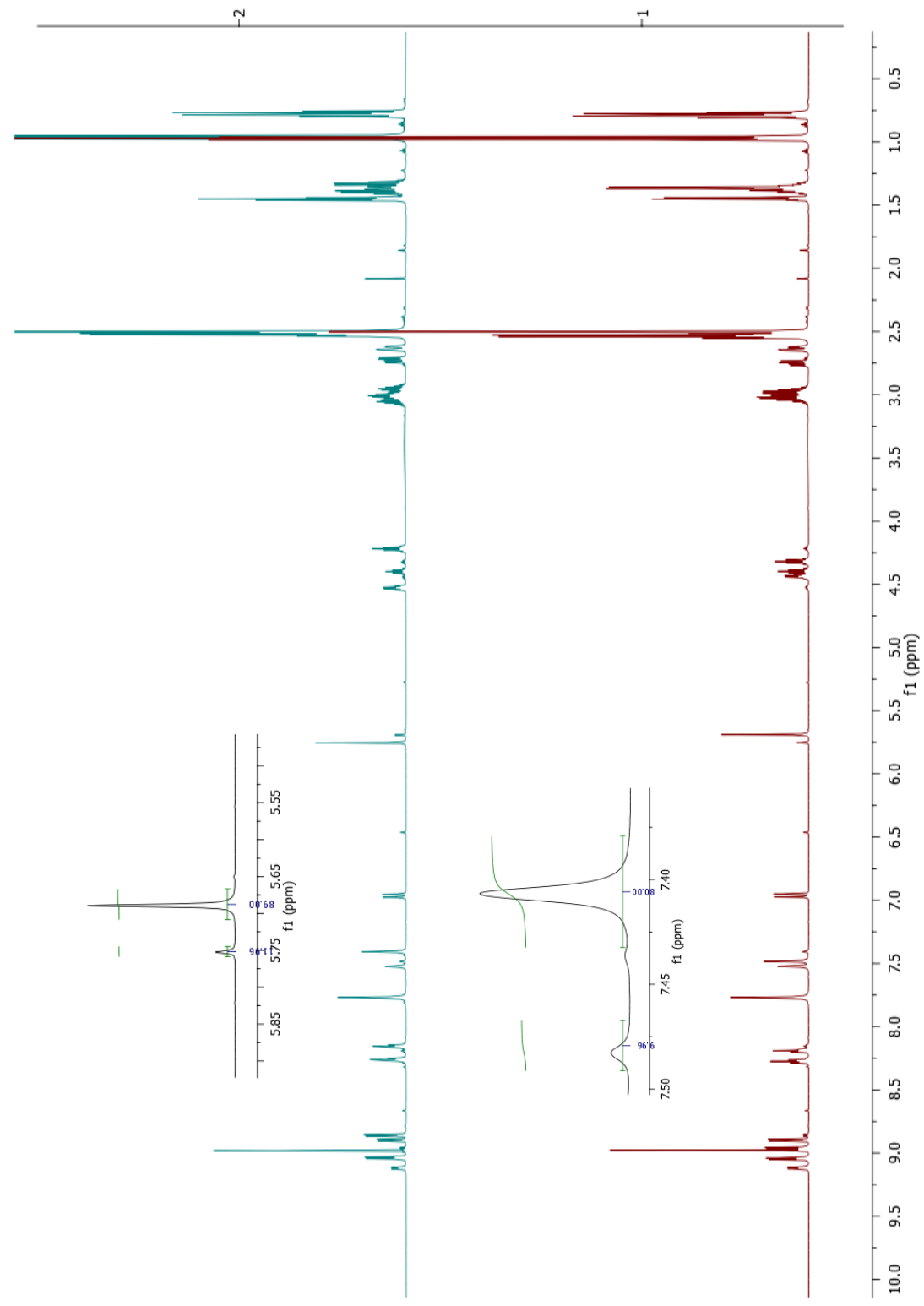
Manual injection

****

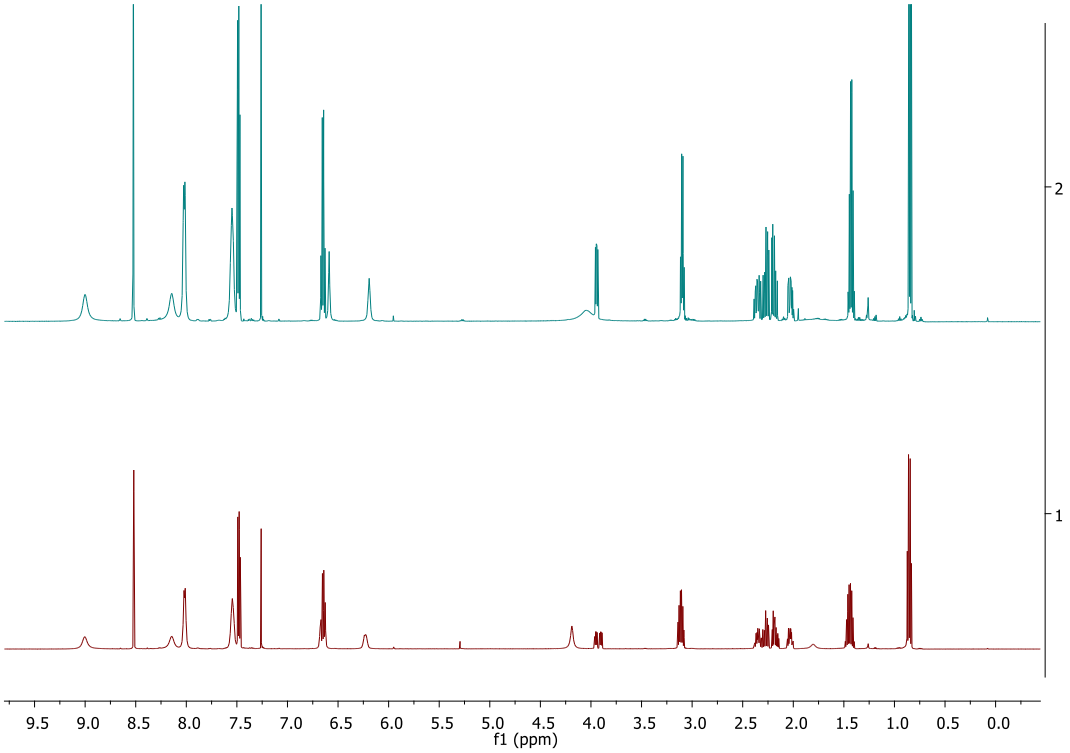
(*S*)-2-Amino-*N*^{1},*N*^{4}-dipropylsuccinamide 98k

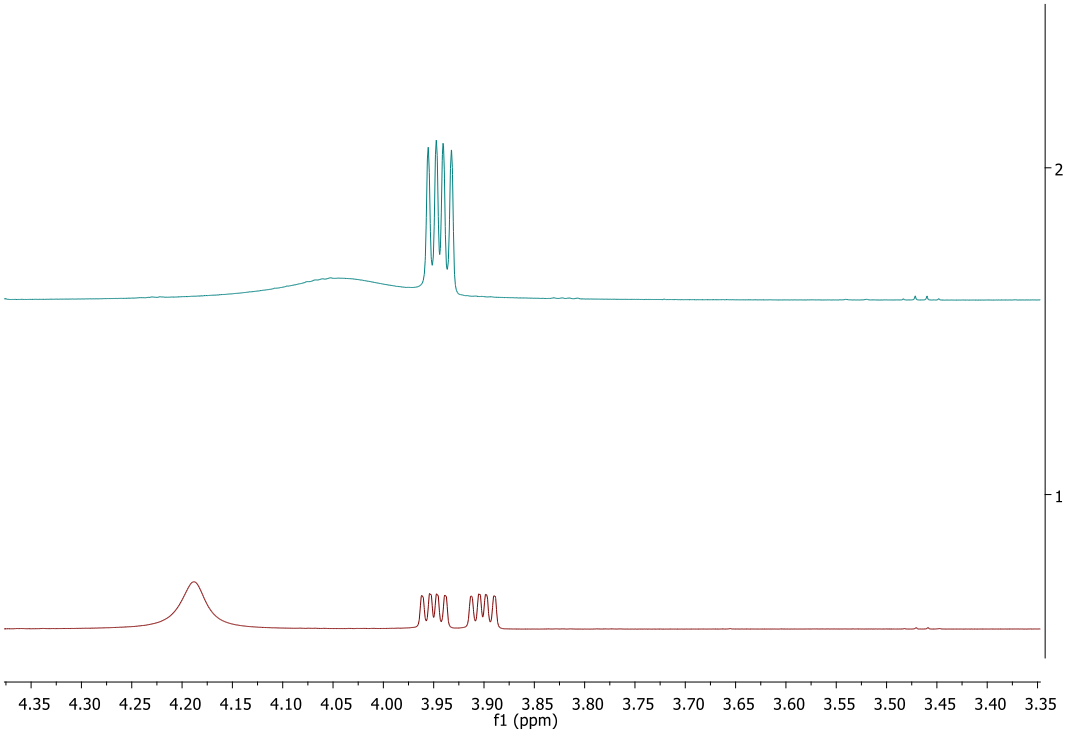


(*S*)-2-Amino-*N*^{1},*N*^{4}-dipropylsuccinamide 98k

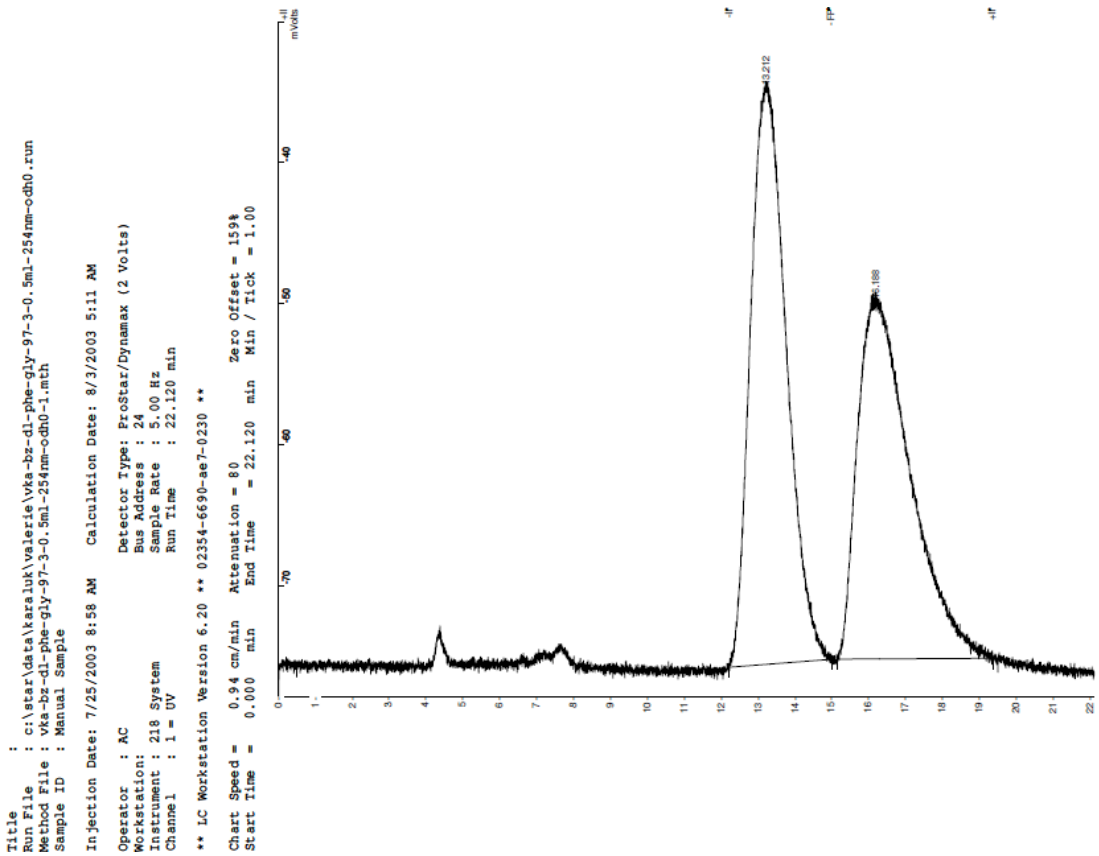


(*S*)-5-Oxo-*N*-propylpyrrolidine-2-carboxamide 98l





(*R*,*S*)-2-Amino-2-phenyl-*N*-propylacetamide rac-100b



Print Date: Sun Aug 03 05:11:28 2003 Page 1 of 1

Title :
Run File : c:\star\data\karaluk\valerie\vka-bz-dl-phe-gly-97-3-0.5ml-254nm-odh0.run
Method File : vka-bz-dl-phe-gly-97-3-0.5ml-254nm-odh0-1.mth
Sample ID : Manual Sample

Injection Date: 7/25/2003 8:58 AM Calculation Date: 8/3/2003 5:11 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 : 22.120 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		52.2138	13.212	0.000	2774281	BB	64.0	
2		47.7862	16.188	0.000	2539031	BB	89.3	
	Totals:	100.0000		0.000	5313312			

Total Unidentified Counts : 5313311 counts

Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

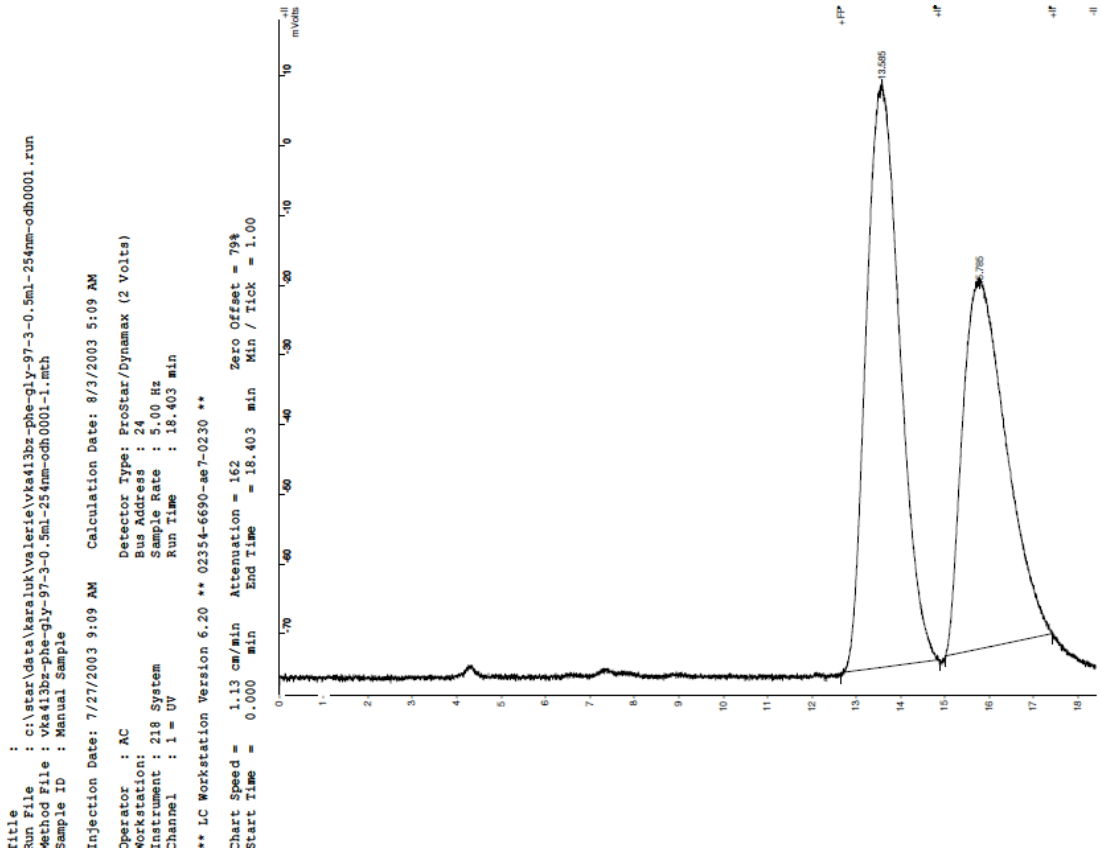
Baseline Offset: -75552 microVolts LSB: 1 microVolts

Noise (used): 1135 microVolts - monitored before this run

Manual injection

****

(*S*)-2-Amino-2-phenyl-*N*-propylacetamide 100b



Print Date: Sun Aug 03 05:10:20 2003 Page 1 of 1

Title :
Run File : c:\star\data\karaluk\valerie\vka413bz-phe-gly-97-3-0.5ml-254nm-odh0001.run
Method File : vka413bz-phe-gly-97-3-0.5ml-254nm-odh0001-1.mth
Sample ID : Manual Sample

Injection Date: 7/27/2003 9:09 AM Calculation Date: 8/3/2003 5:09 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 : 18.403 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		55.0445	13.585	0.000	4410035	BB	50.3	
2		44.9555	15.785	0.000	3601722	BB	67.2	
	Totals:	100.0000		0.000	8011757			

Total Unidentified Counts : 8011757 counts

Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

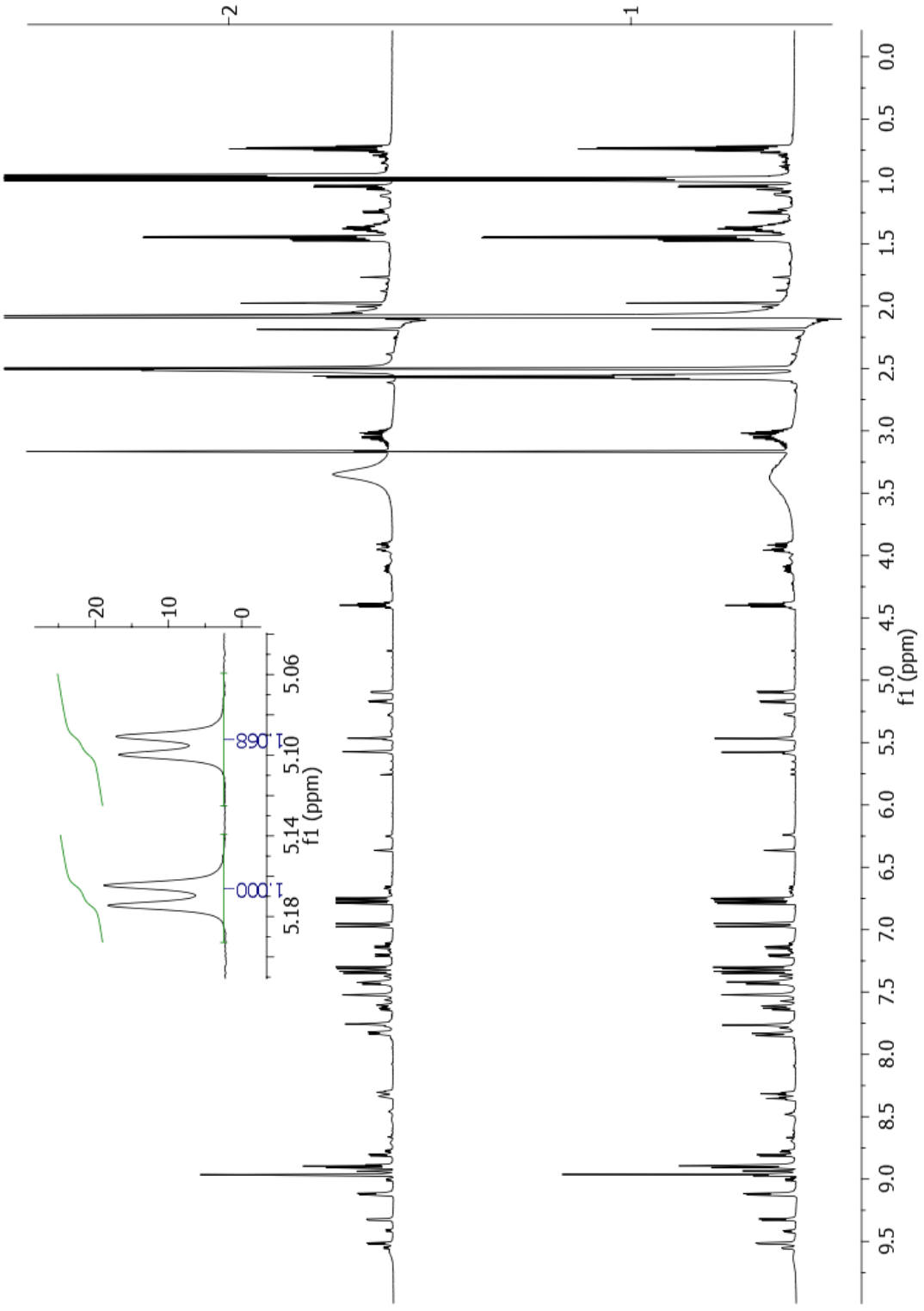
Baseline Offset: -76268 microVolts LSB: 1 microVolts

Noise (used): 1122 microVolts - monitored before this run

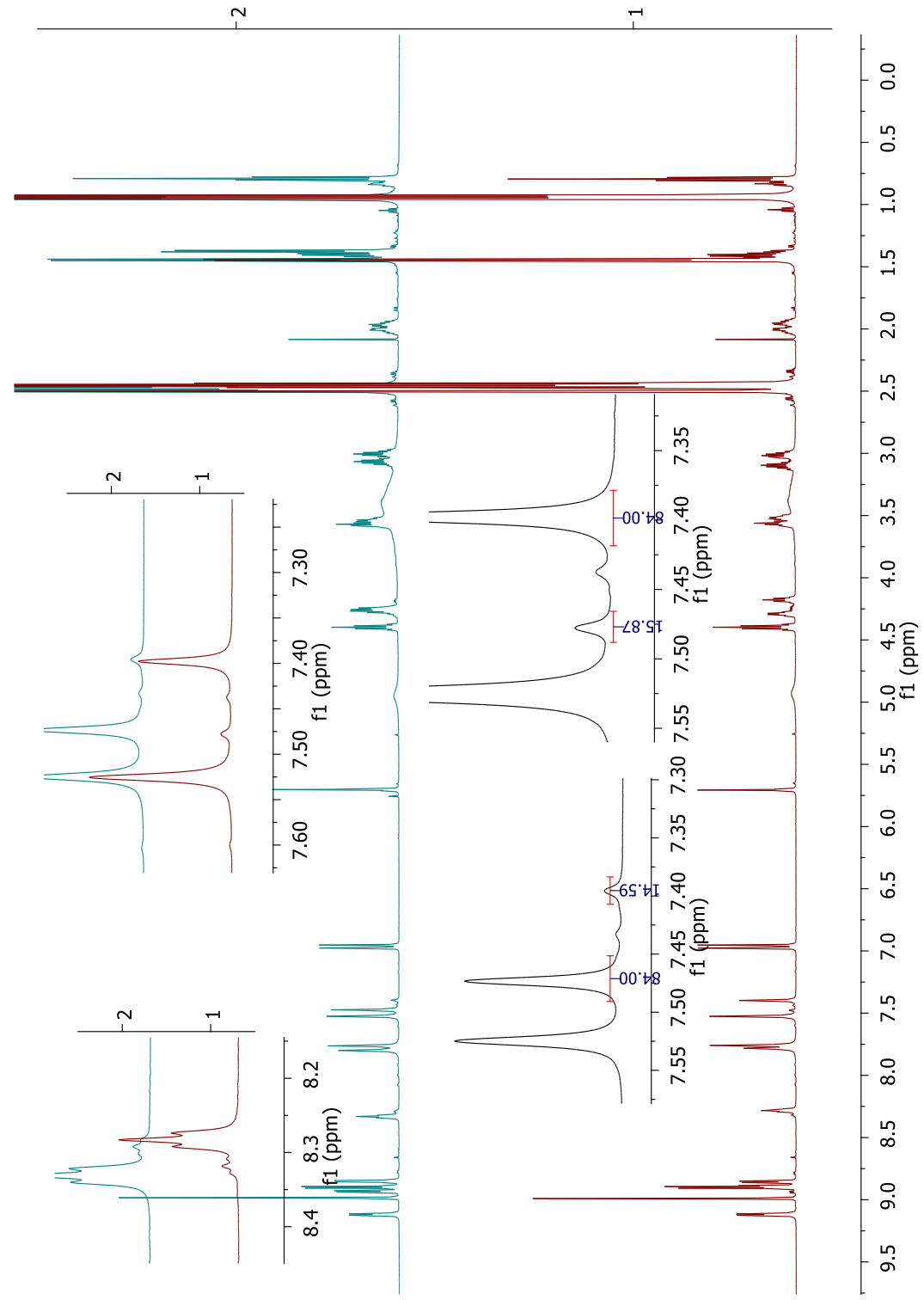
Manual injection

****

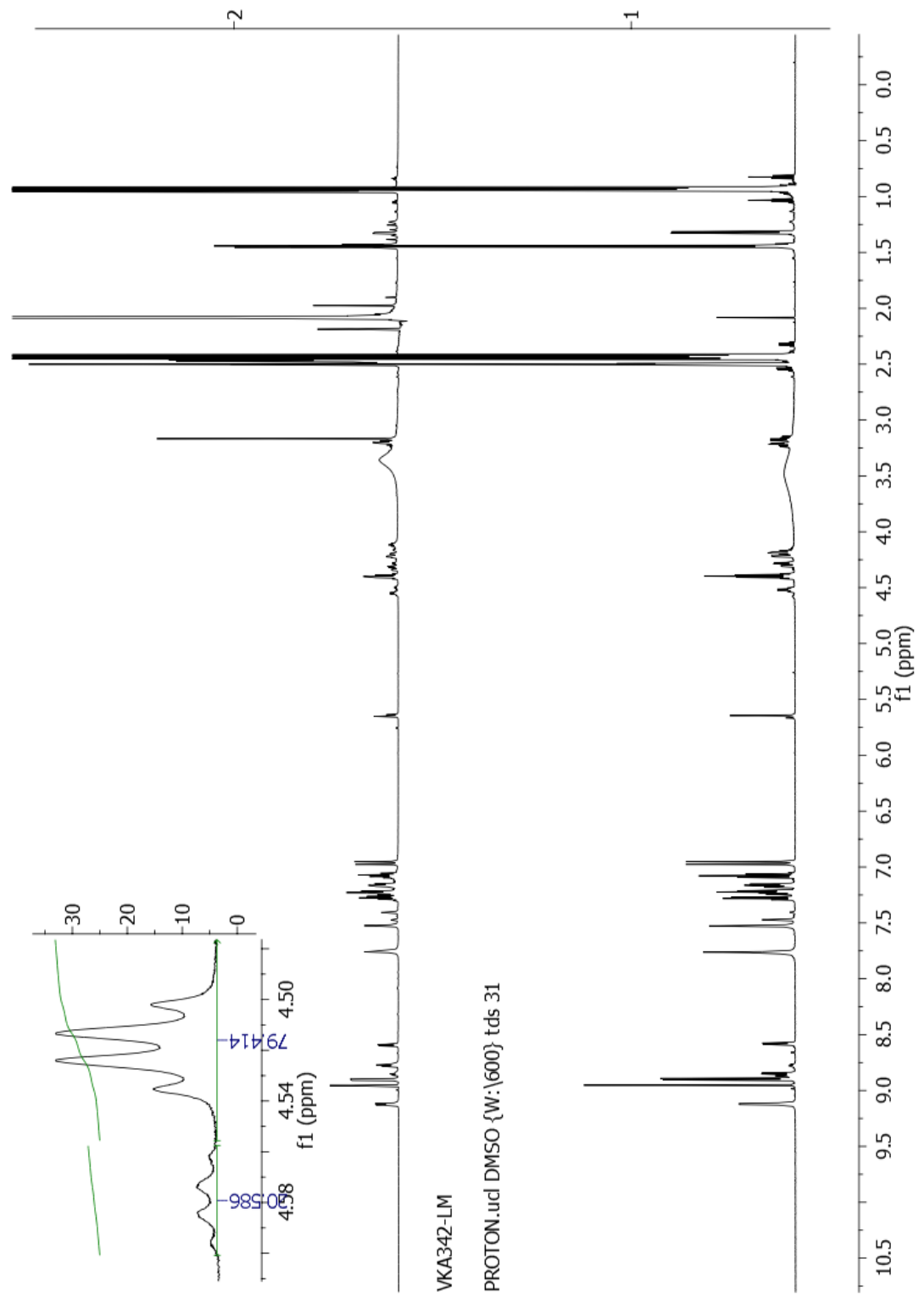
(*S*)-2-Amino-2-(4-hydroxyphenyl)-*N*-propylacetamide 100c



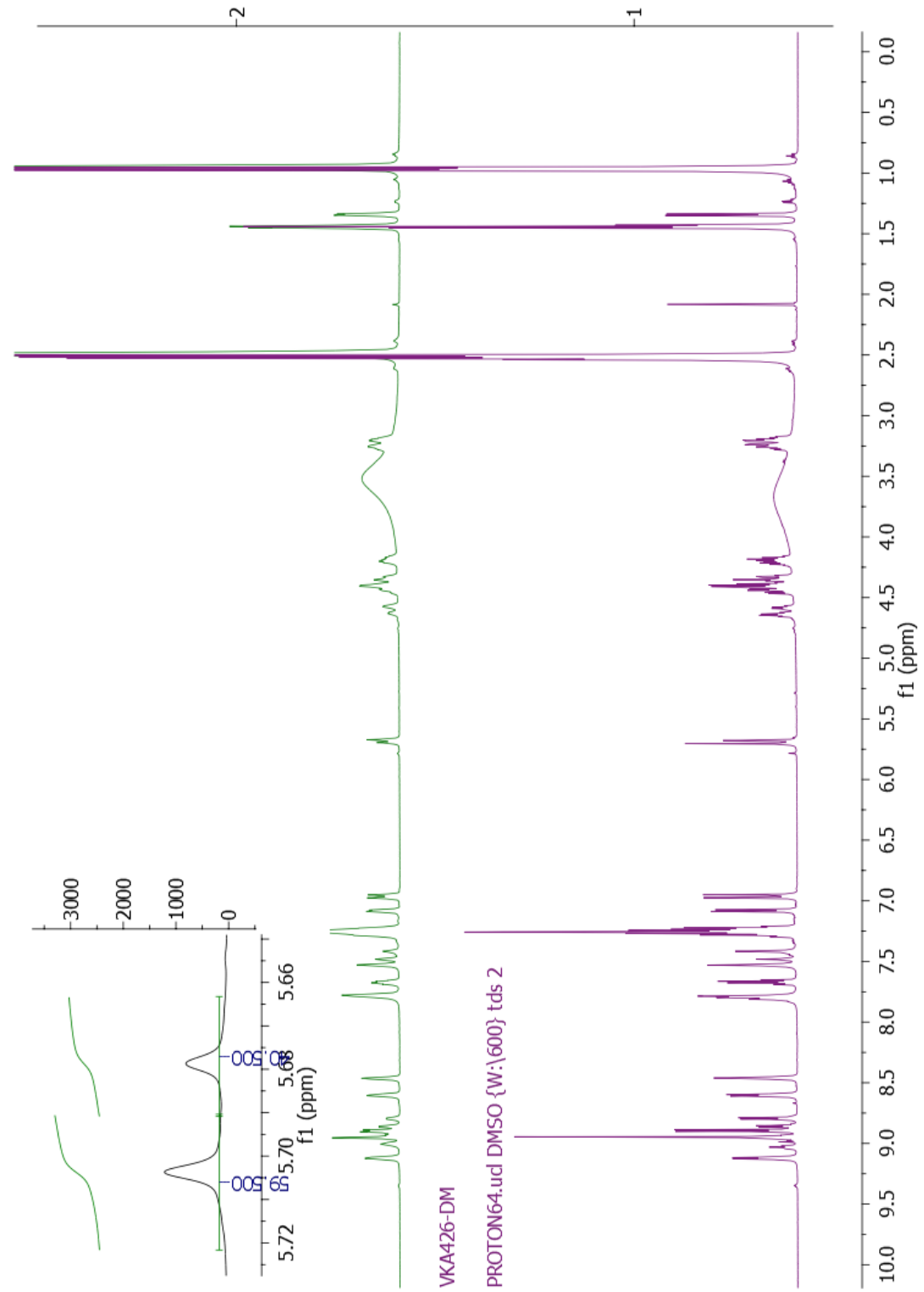
(*S*)-2-Amino-4-hydroxy-*N*-propylbutanamide 100e



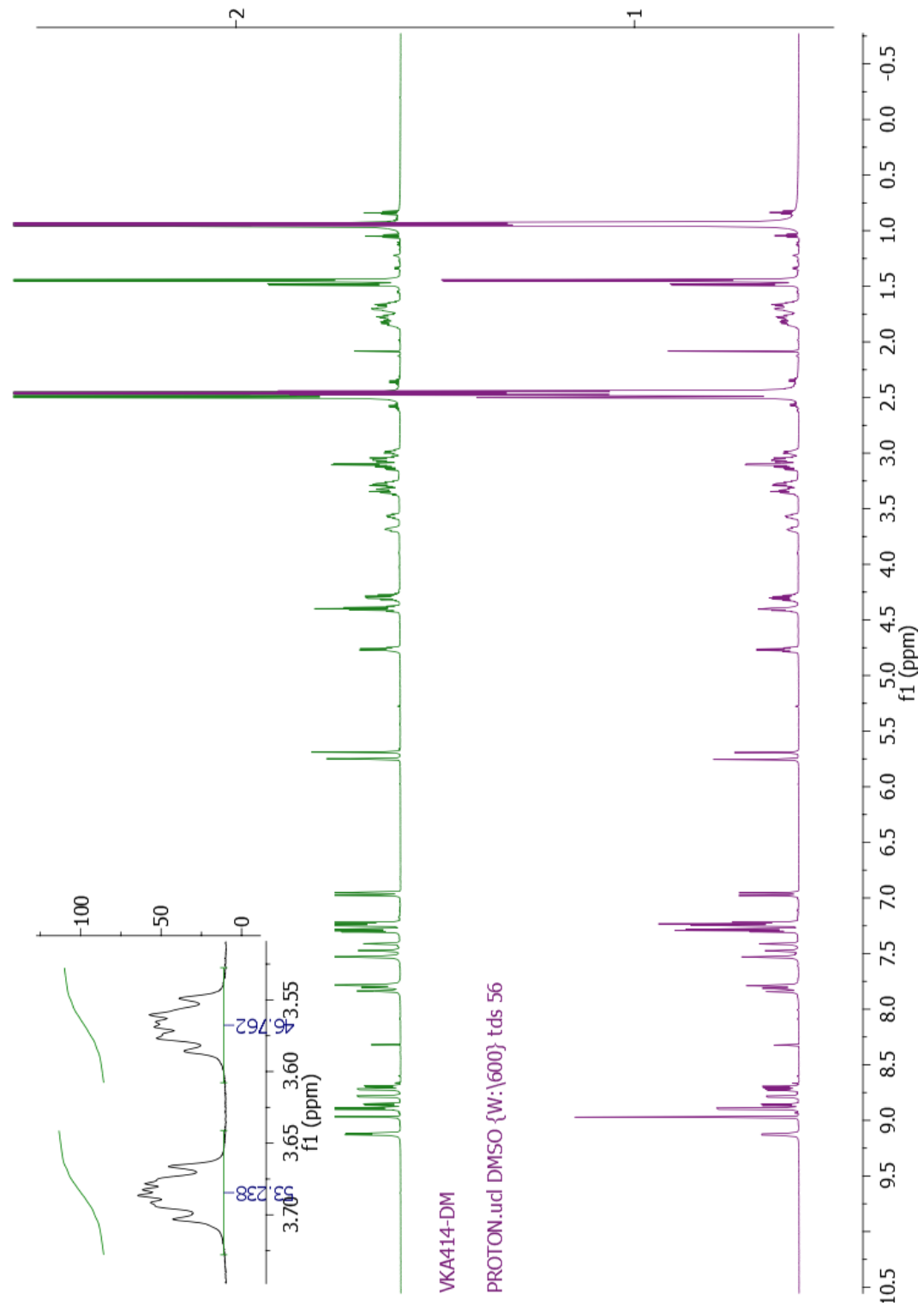
(*S*)-2-Amino-*N*-(4-fluorobenzyl)-3-phenylpropanamide 103a



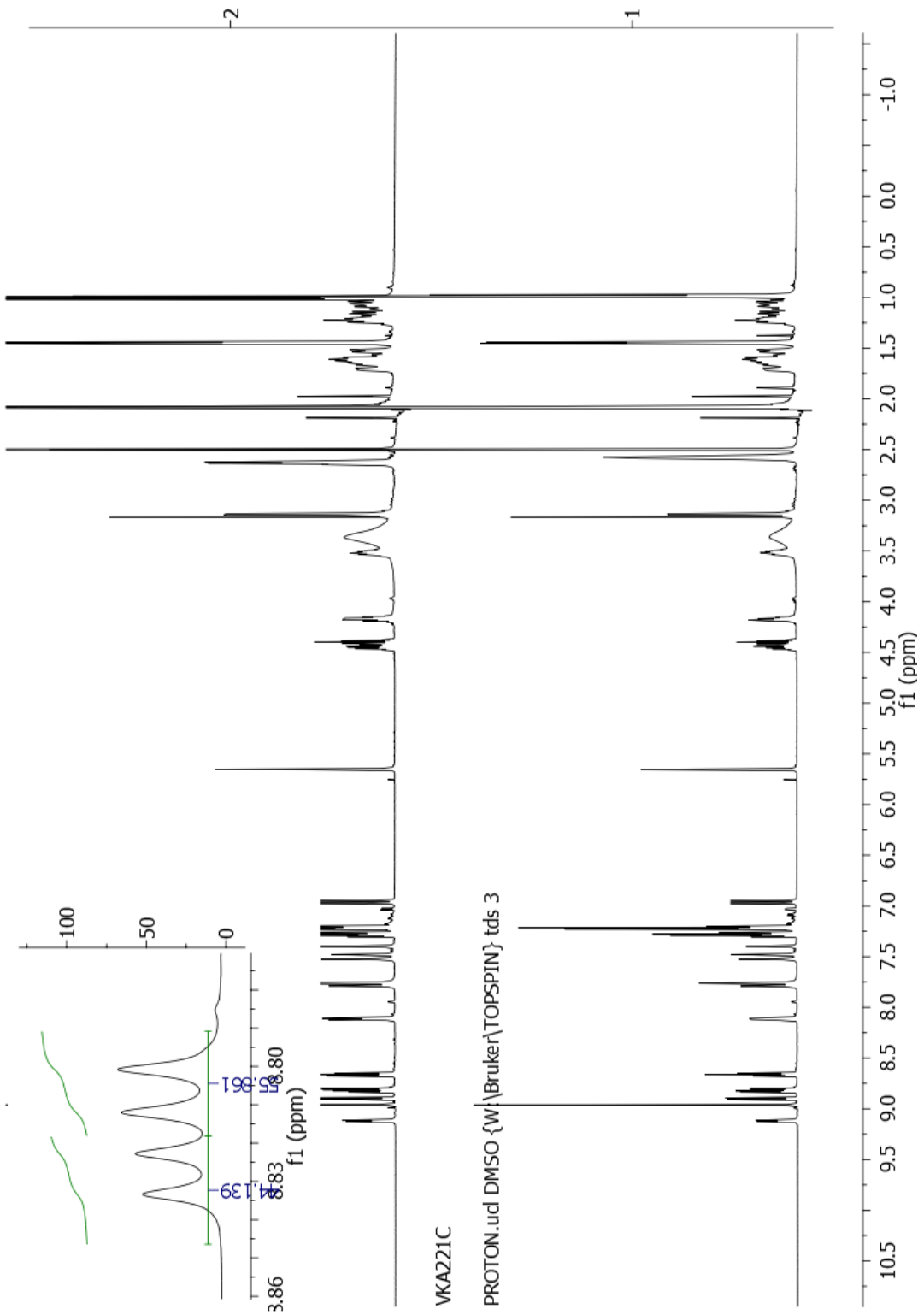
(*S*)-2-amino-3-phenyl-*N*-(pyridin-2-ylmethyl)propanamide 103b



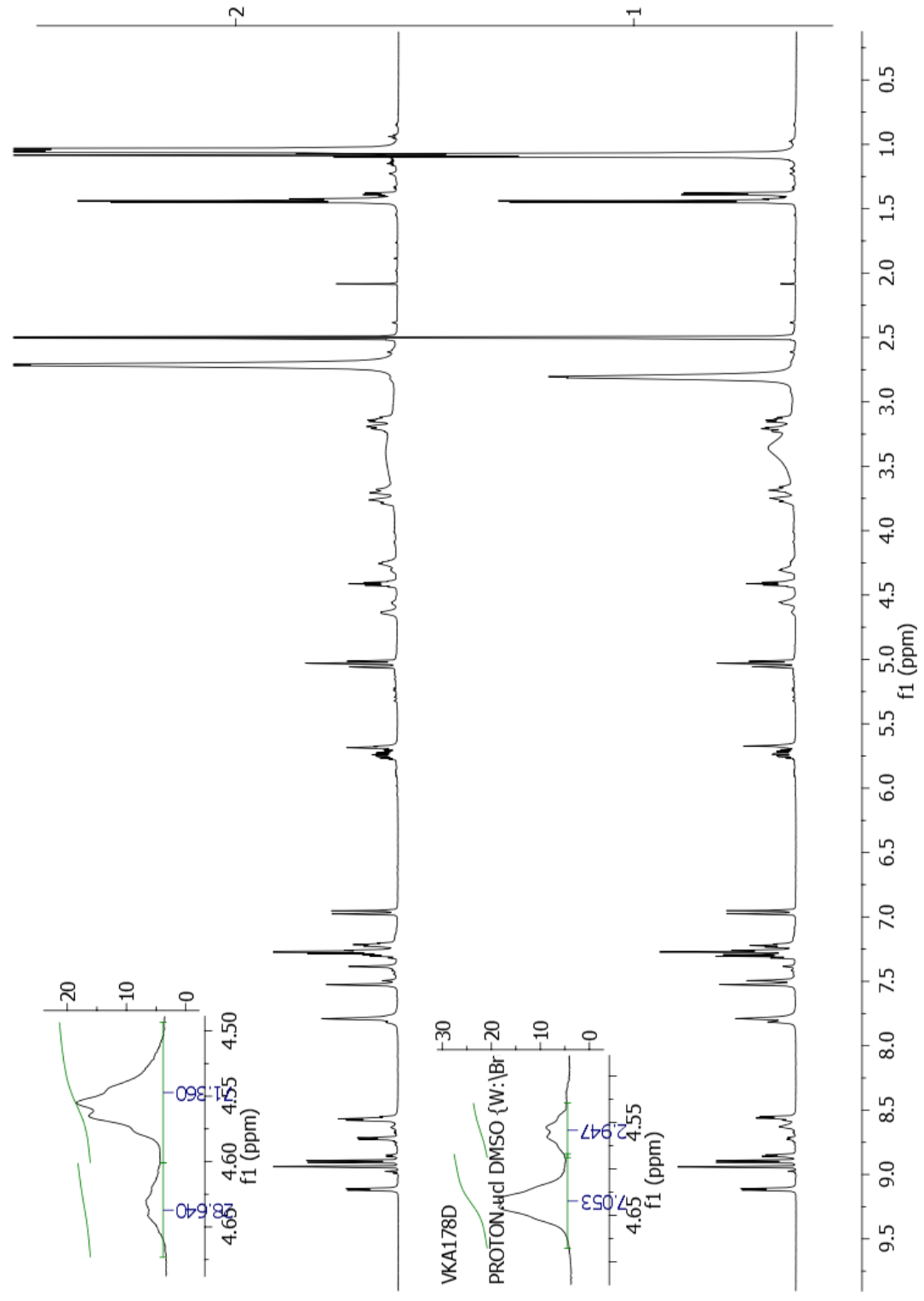
(*S*)-2-Amino-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one 103d



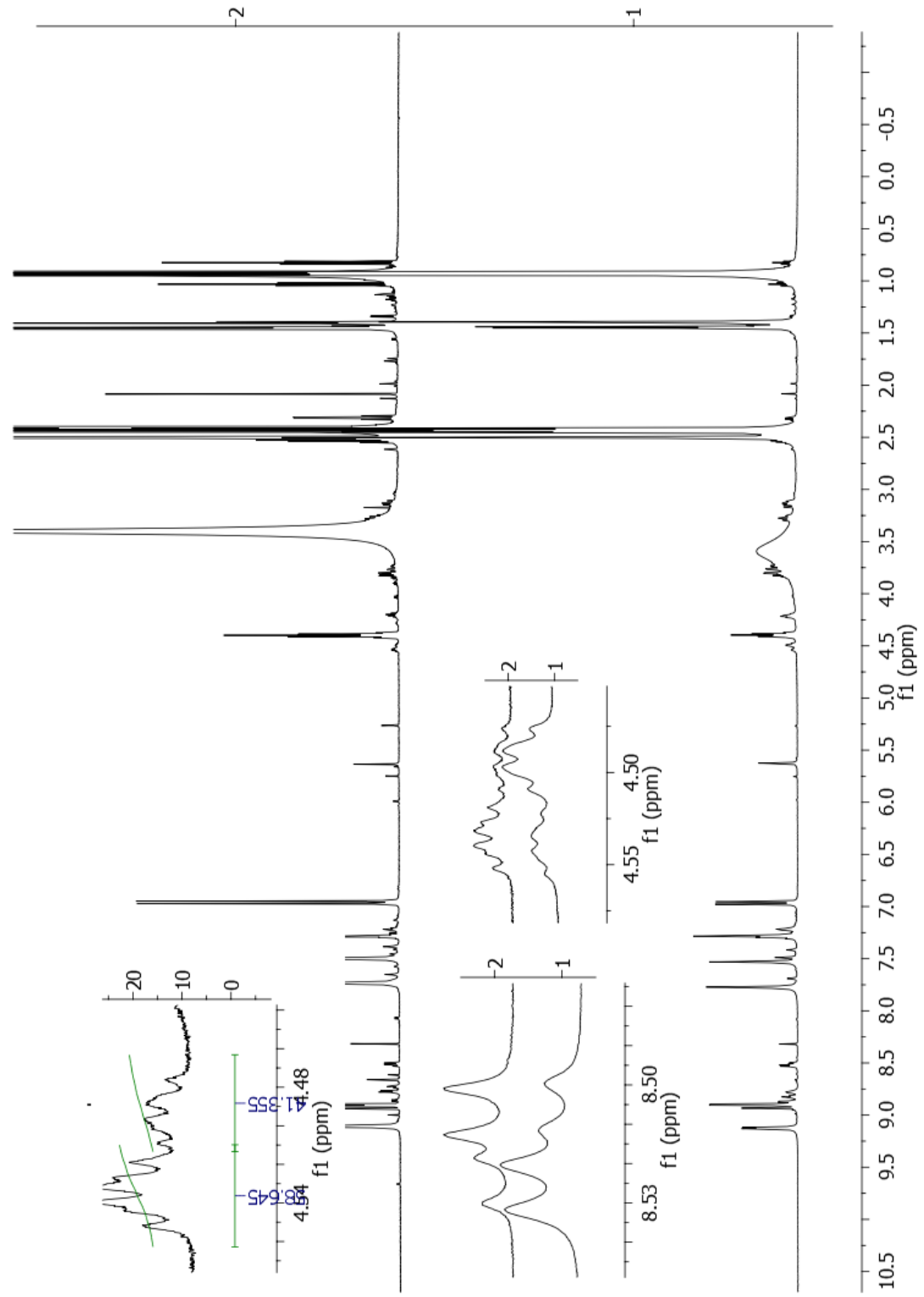
(*S*)-2-Amino-*N*-cyclohexyl-3-phenylpropanamide 103e



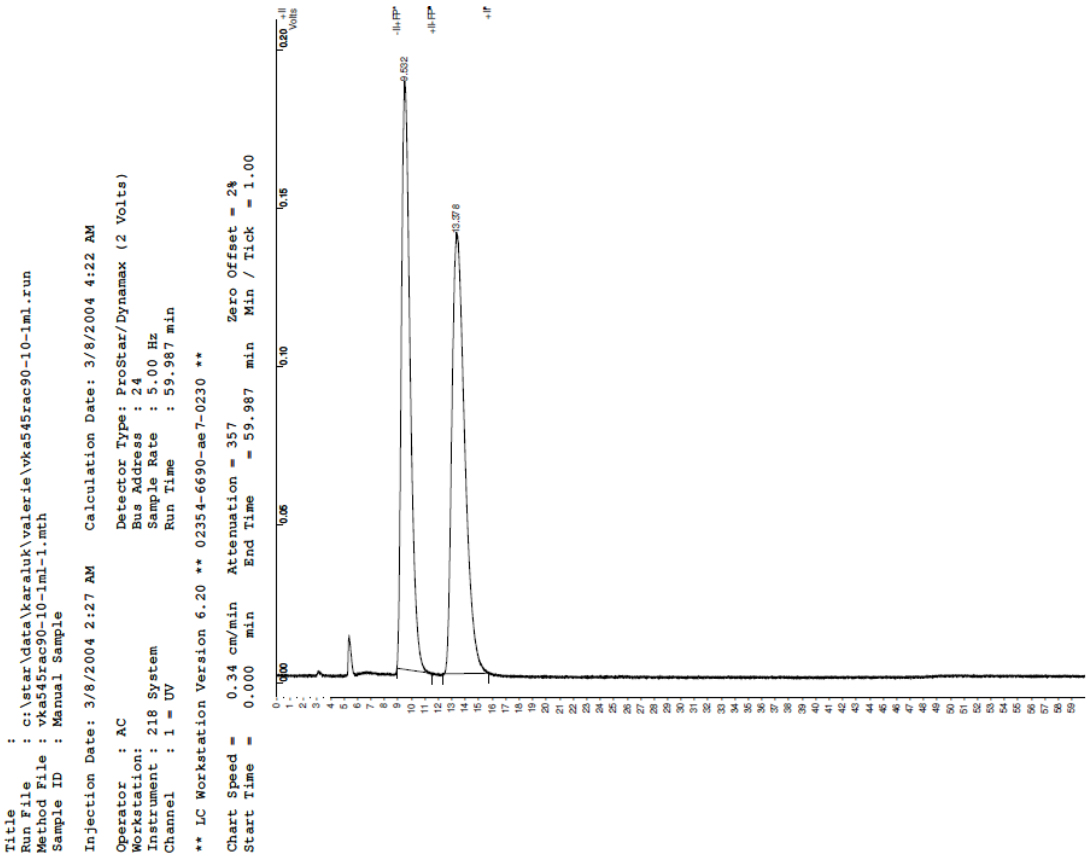
(*S*)-*N*-Allyl-2-amino-3-phenylpropanamide hydrochloride 103f



(*S*)-*Tert*-butyl 2-(2-amino-3-phenylpropanamido)acetate 103h



3-Benzyl-5-phenyl-1,3-dihydro-2*H*-benzo[e][1,4]diazepin-2-one 103i - rac

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Print Date: Mon Mar 08 04:23:24 2004            Page 1 of 1

Title       :
Run File    : c:\star\data\karaluk\valerie\vka545rac90-10-1ml.run
Method File : vka545rac90-10-1ml-1.mth
Sample ID   : Manual Sample

Injection Date: 3/8/2004 2:27 AM    Calculation Date: 3/8/2004 4:22 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     : 59.987 min

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

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

                                 Rel.    Time                        Width
 Peak      Peak       Result     Time    Offset      Area    Sep.    1/2    Status
  No.      Name         ()       (min)   (min)     (counts)  Code   (sec)   Codes
 ---- ------------ ---------- -------- -------- ---------- ---- -------  ------
    1                 47.6089    9.532    0.000    8345667   BB    41.6
    2                 52.3911   13.378    0.000    9183962   BB    61.2
 ---- ------------ ---------- -------- -------- ---------- ---- -------  ------
      Totals:        100.0000             0.000   17529629

Total Unidentified Counts :   17529628 counts

Detected Peaks: 2           Rejected Peaks: 0       Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: 3016 microVolts          LSB:     1 microVolts

Noise (used): 1092 microVolts - monitored before this run

Manual injection

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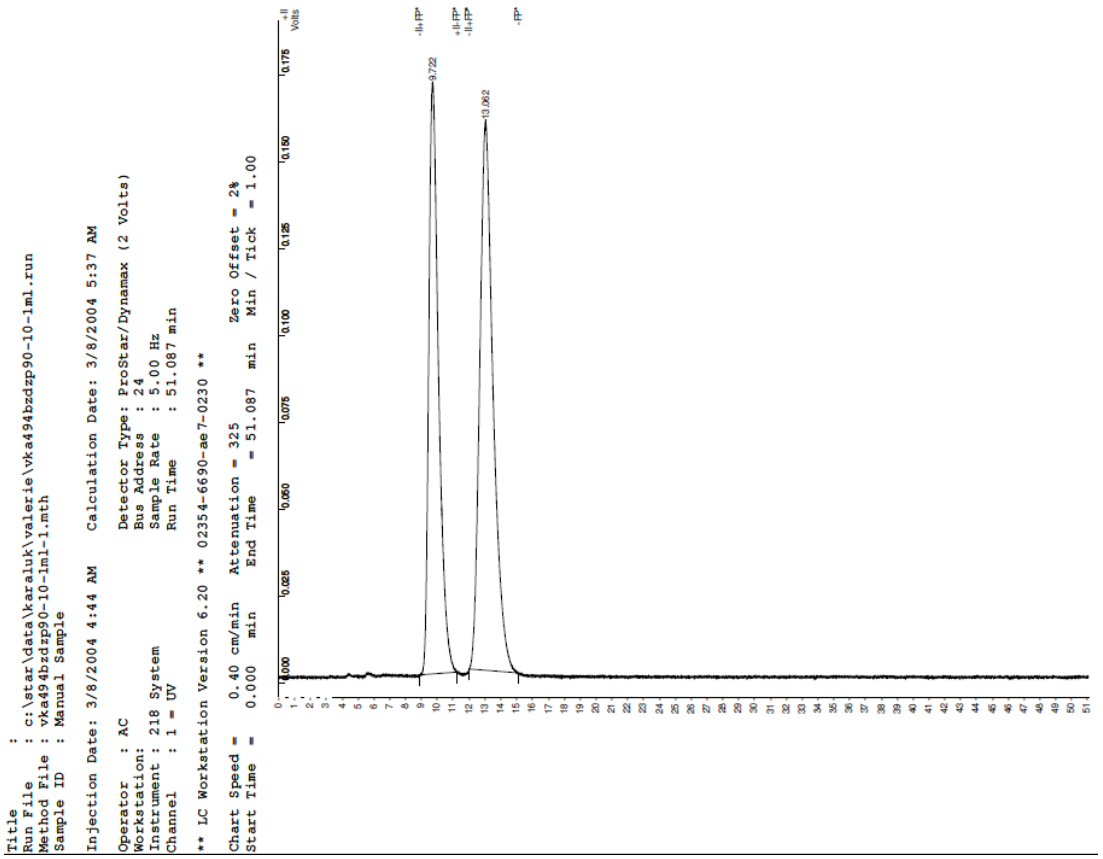
(*S*)-3-Benzyl-5-phenyl-1,3-dihydro-2*H*-benzo[e][1,4]diazepin-2-one 103i



Print Date: Mon Mar 08 05:38:11 2004 Page 1 of 1

Title :
Run File : c:\star\data\karaluk\valerie\vka494bzdzp90-10-1ml.run
Method File : vka494bzdzp90-10-1ml-1.mth
Sample ID : Manual Sample

Injection Date: 3/8/2004 4:44 AM Calculation Date: 3/8/2004 5:37 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 : 51.087 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		44.0294	9.722	0.000	7276156	BB	38.6	
2		55.9706	13.062	0.000	9249526	BB	52.5	
	Totals:	100.0000		0.000	16525682			

Total Unidentified Counts : 16525682 counts

Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

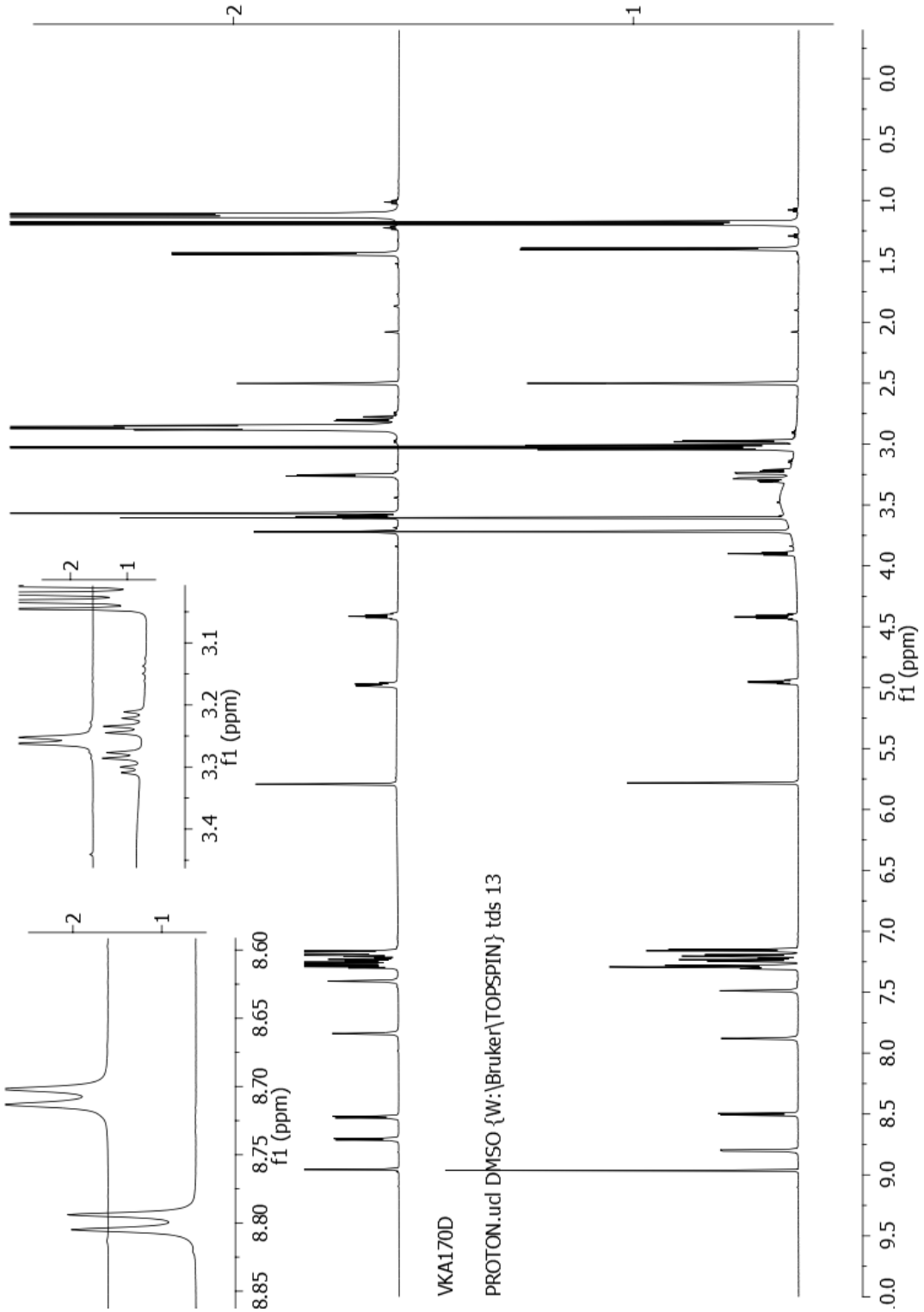
Baseline Offset: 1924 microVolts LSB: 1 microVolts

Noise (used): 1035 microVolts - monitored before this run

Manual injection

(*S*)-2-((5-Fluoro-2,4-dinitrophenyl)amino)propanamide L-91 and

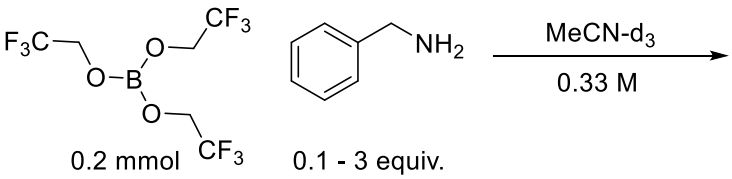
(*R*)-2-((5-Fluoro-2,4-dinitrophenyl)amino)propanamide D-91



7.2 Mechanistic Study

7.2.1 Interaction of $B(OCH_2CF_3)_3$ with amines

$B(OCH_2CF_3)_3$ + benzylamine



^{19}F NMR

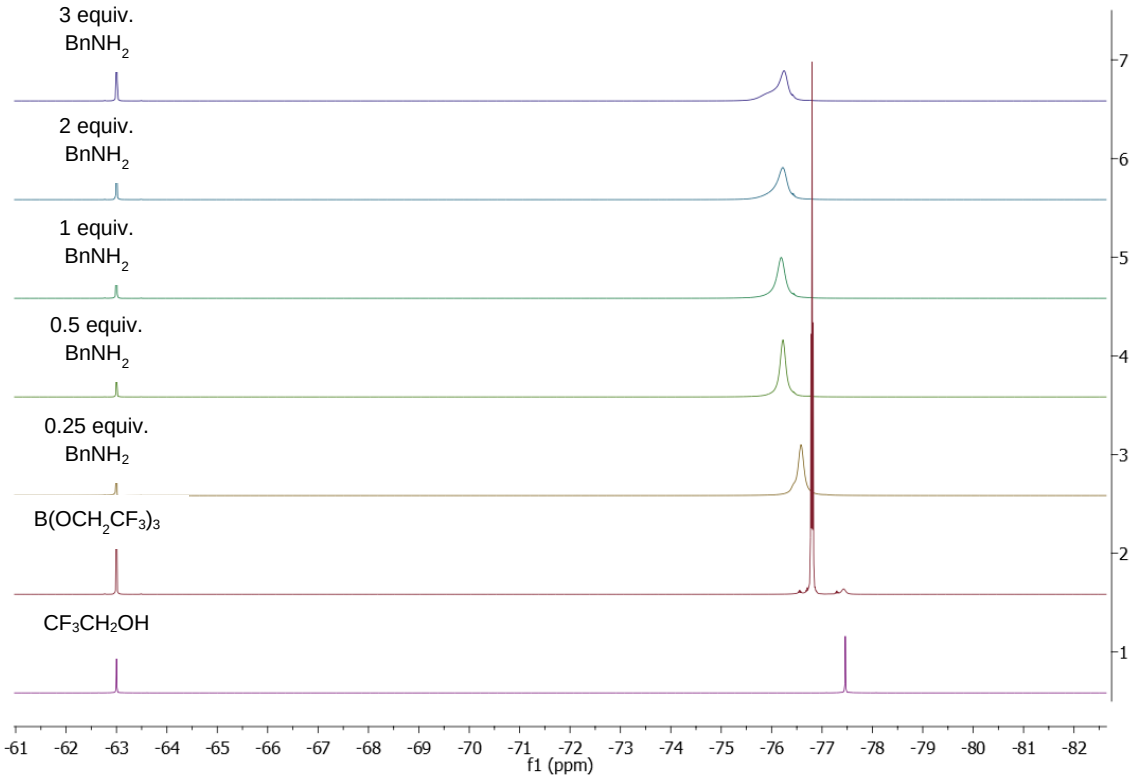


Figure 45

7.2.2 Trisaminoboranes with carboxylic acids

1:1 **170**:**53** ^{13}C NMR

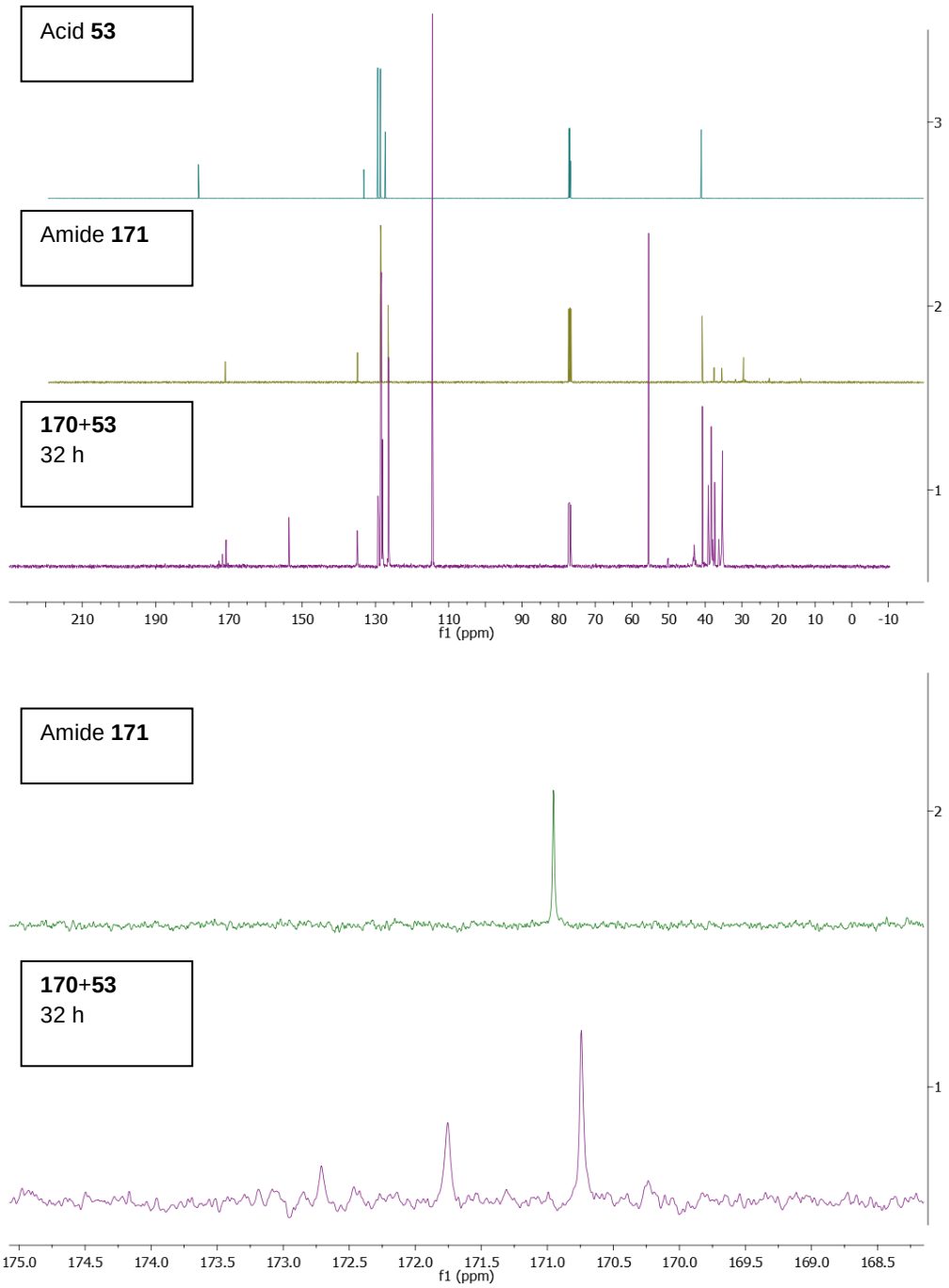


Figure 46

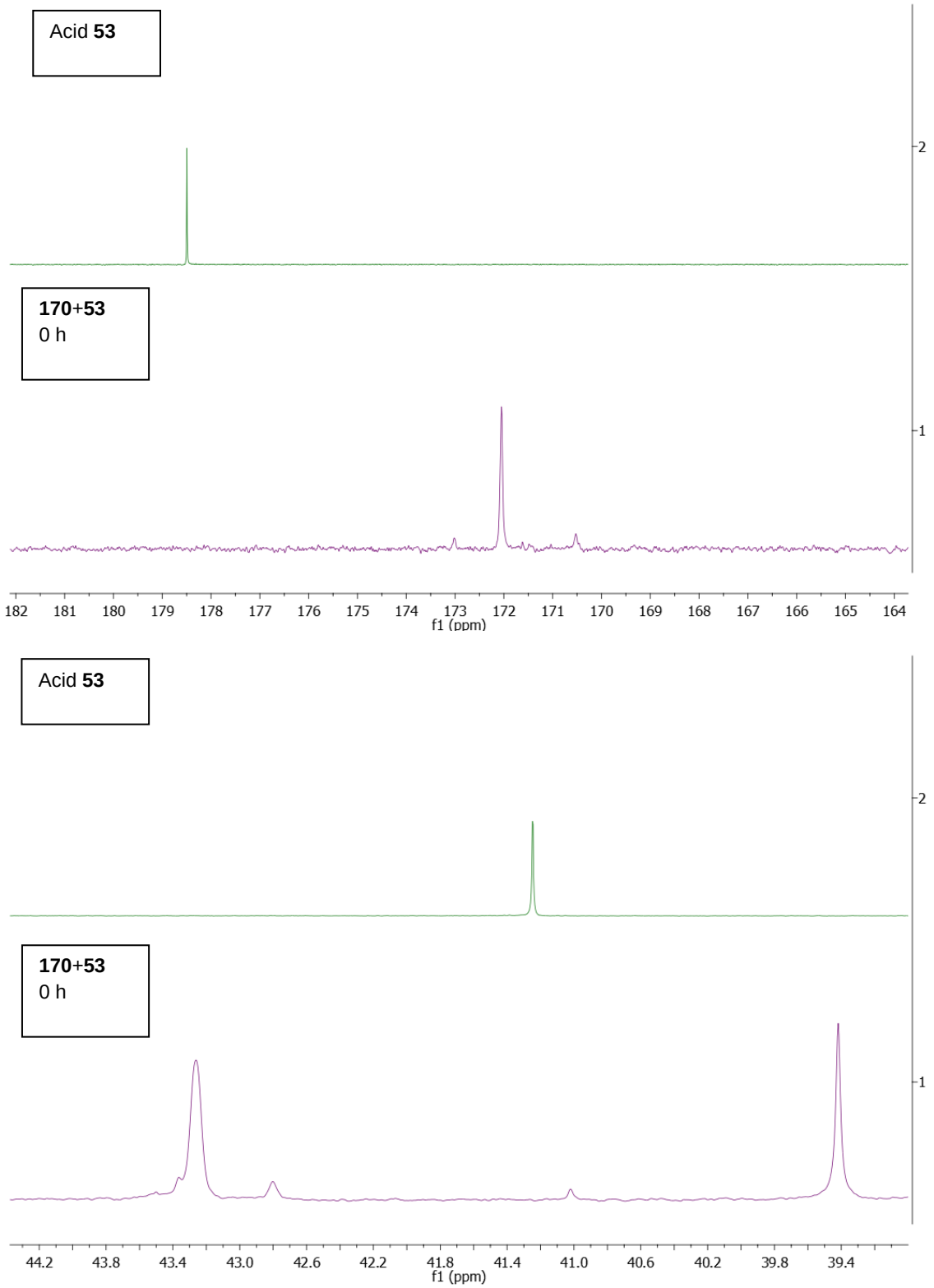

Acid 53
2
170+53
0 h
1
182 181 180 179 178 177 176 175 174 173 172 171 170 169 168 167 166 165 164
f1 (ppm)
Acid 53
2
170+53
0 h
1
44.2 43.8 43.4 43.0 42.6 42.2 41.8 41.4 41.0 40.6 40.2 39.8 39.4
f1 (ppm)

Figure 47

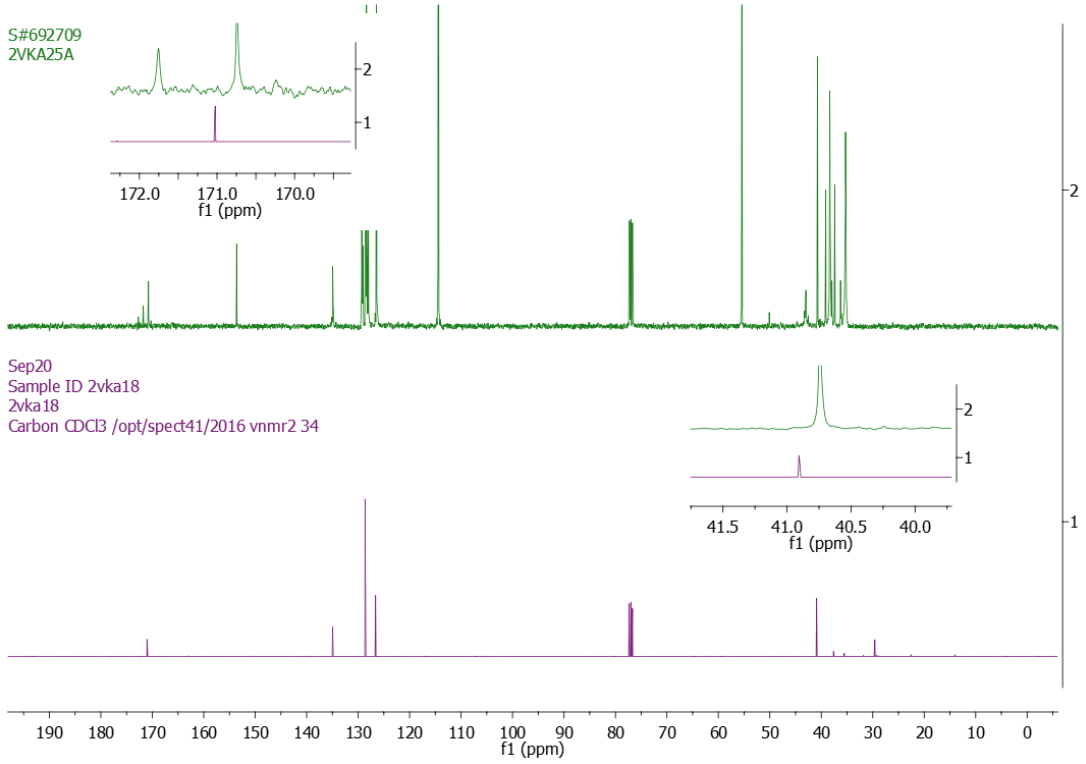
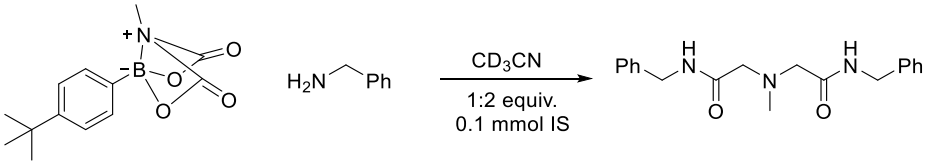
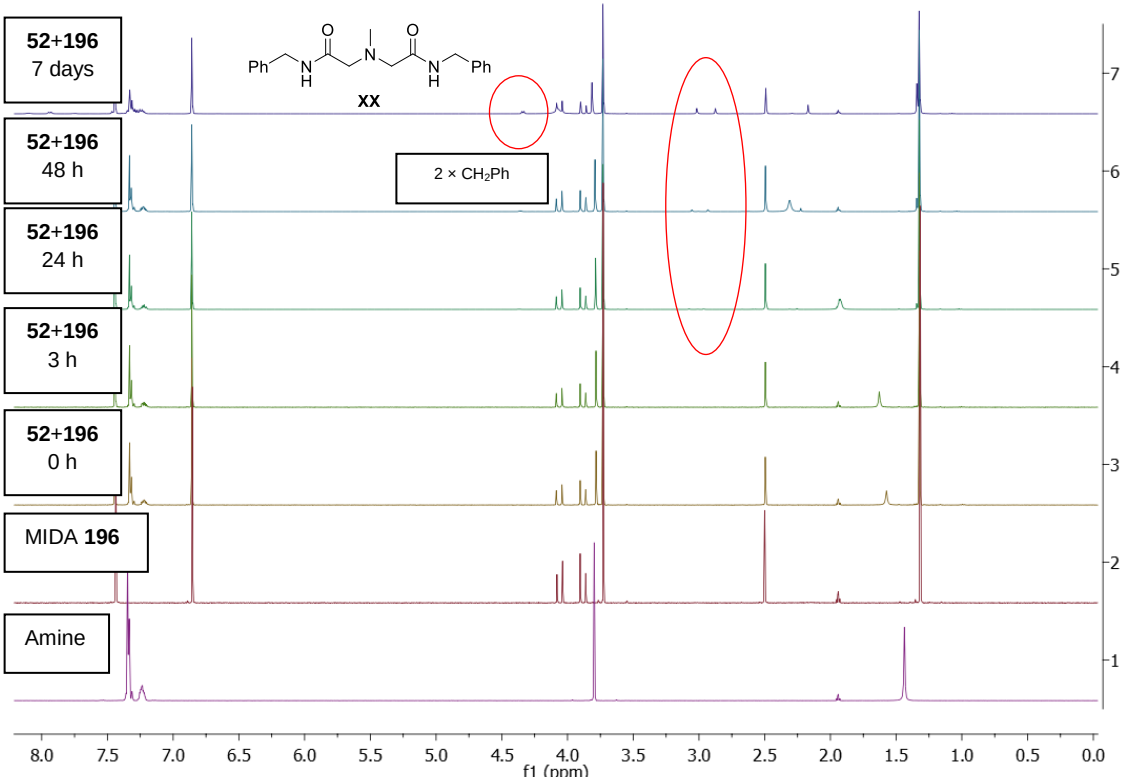


Figure 48 Comparison of ^{13}C NMR shifts (carbonyl and CH_2) of isolated amide **171** and in the reaction mixture

7.2.3 MIDA boronate experiments

Experiment A: MIDA + Benzylamine





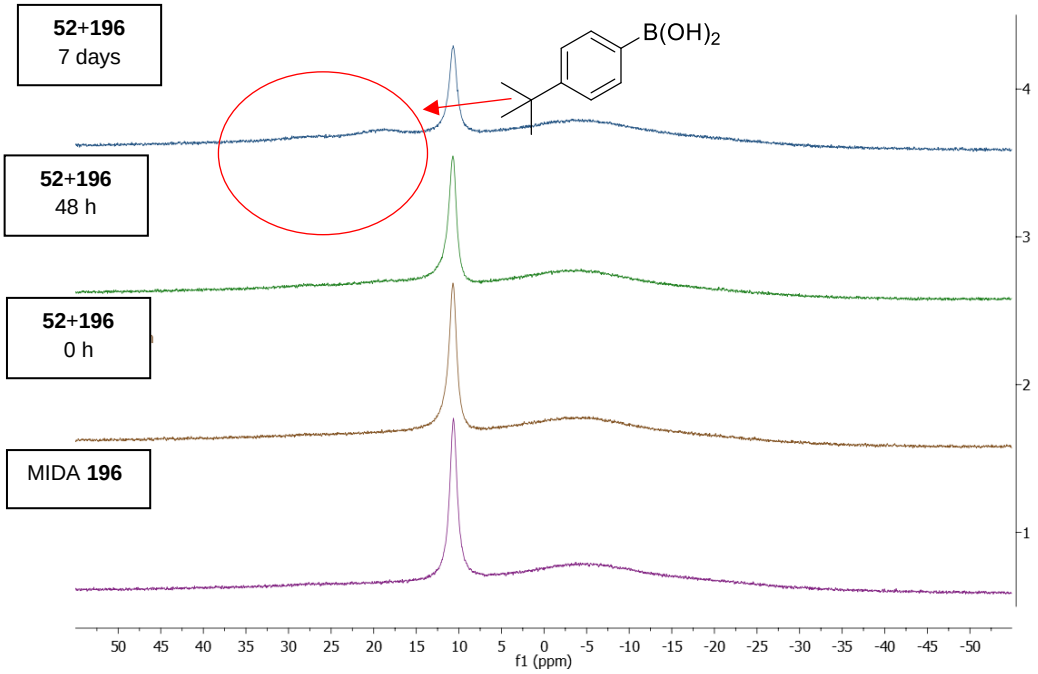


Figure 49

Experiment B: MIDA boronate + borate, then amine

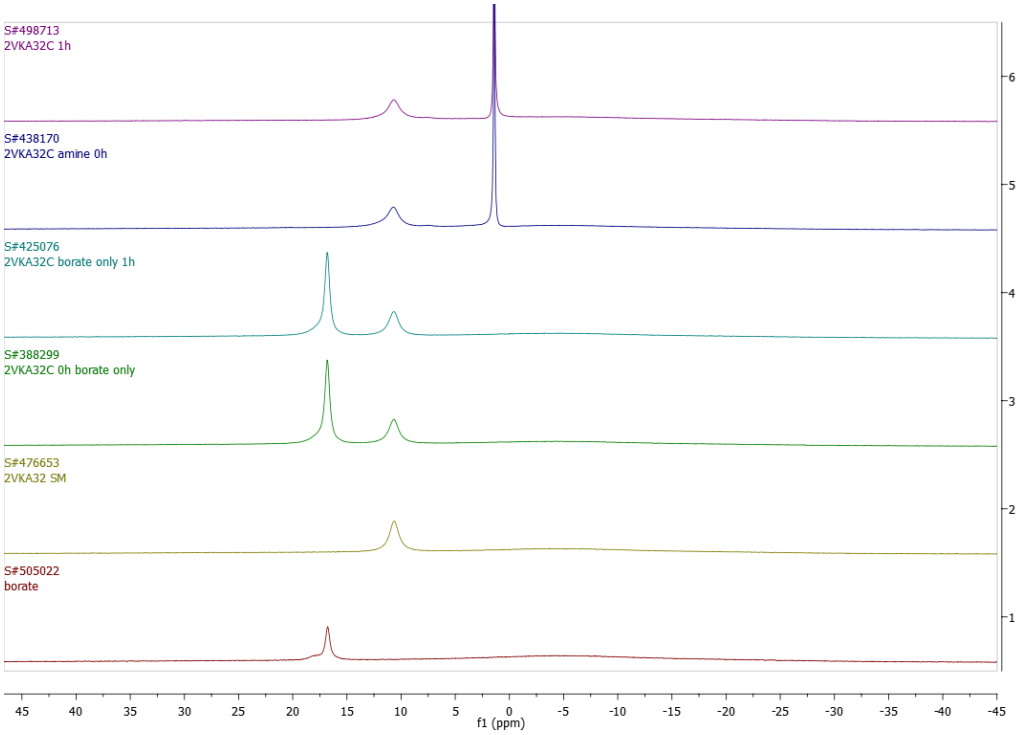
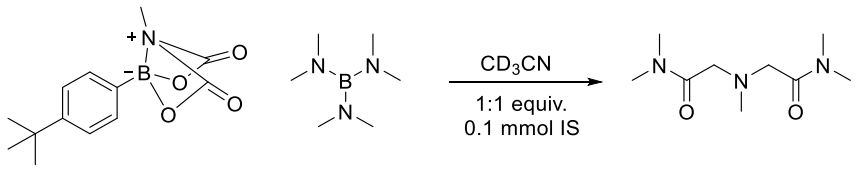


Figure 50

Experiment C: MIDA boronate + tris(dimethylamino)borane



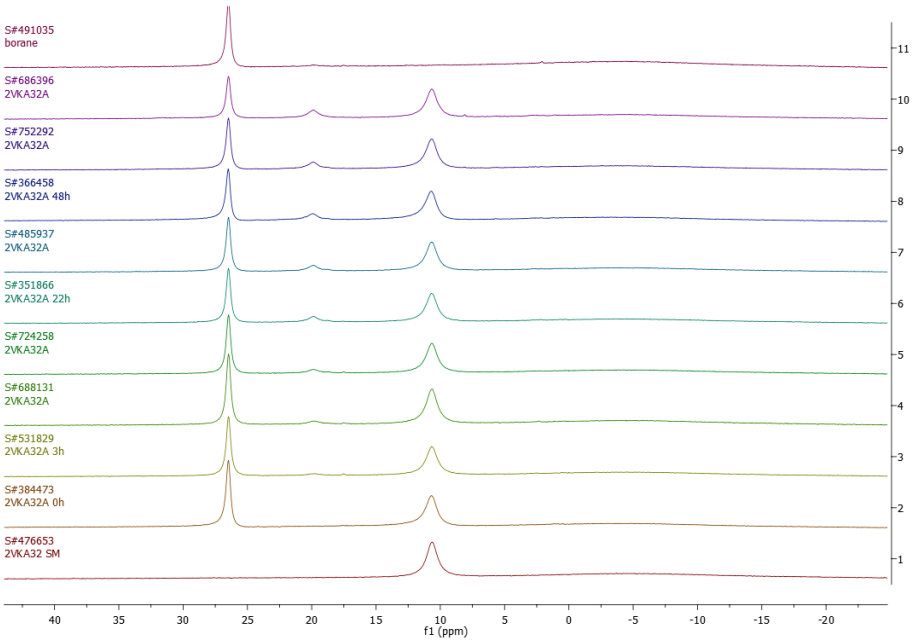
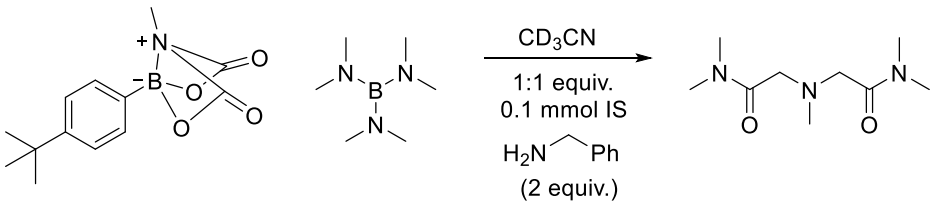


Figure 51

Experiment D: MIDA boronate + borane, then amine



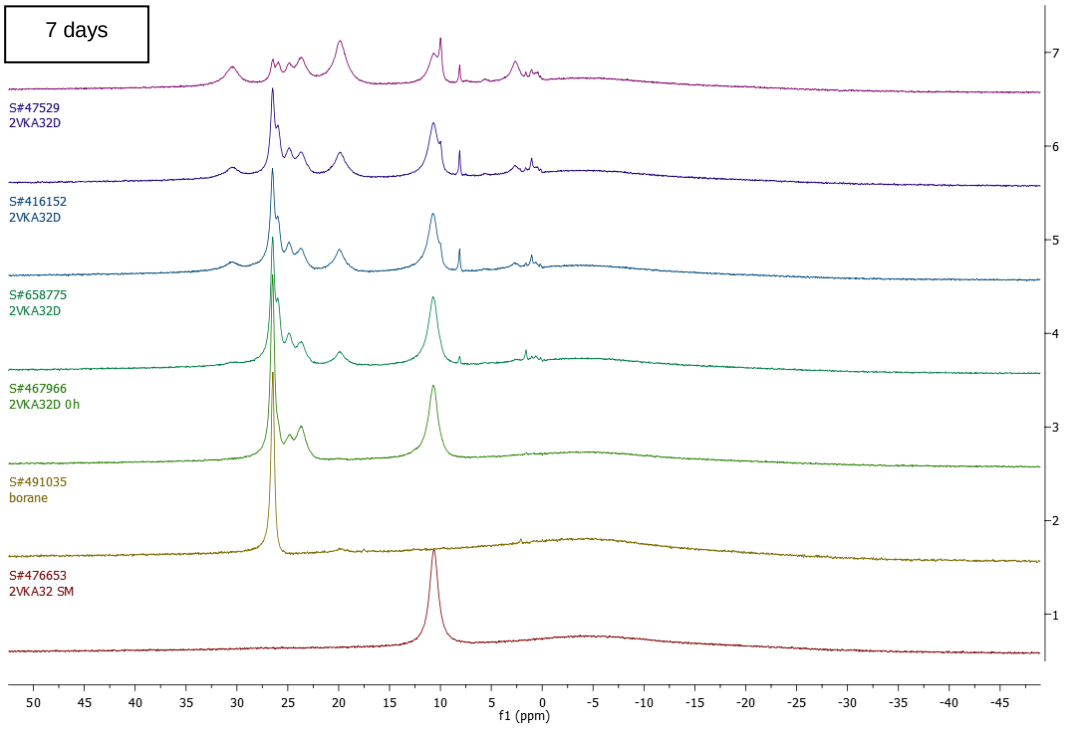
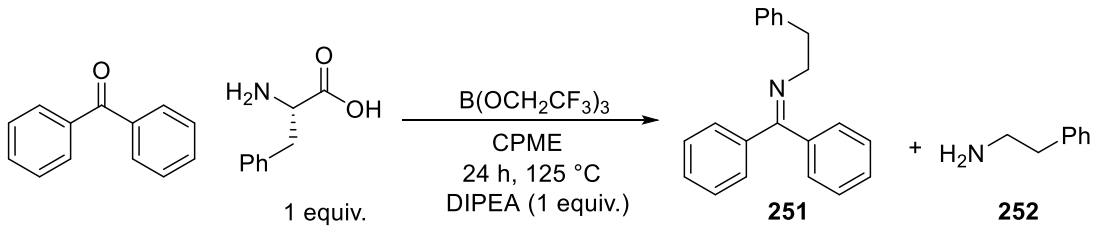


Figure 52

7.3 DoE: Decarboxylation

The experimental design was set up using MODDE 10 software to investigate the effect of the following factors:

Benzophenone: Number of equivalents of Ph_2CO; 0.2 to 2 equiv.
Borate: Number of equivalents of $B(OCH_2CF_3)_3$; 0.2 to 2 equiv.
Concentration: Volume of the solvent with respect to L-Phe (1 equiv.)
Base: Qualitative - DIPEA (1 equiv.) added to the reaction mixture when specified
General Procedure: A mixture of Ph_2CO, $B(OCH_2CF_3)_3$, and L-Phe with or without DIPEA (1 equiv.) was heated at 125 °C in CPME for 24 h. At the end of the reaction, 1 mmol of 1,4-dimethoxybenzene was added and stirred well. A sample was taken, concentrated in vacuo and dissolved in $CDCl_3$. The yield was measured by ^1H NMR against the internal standard. The results and conditions are provided below (Table 16).



Entry	Ph_2CO (equiv.)	Borate (equiv.)	[C]	DIPEA (1 equiv.)	**251** yield (%)	**252** yield (%)	TOTAL (%)
1	2	0.2	0.2	No	33	0	33
2	1.1	1.1	0.7	No	45	17	62
3	1.1	1.1	0.7	No	43	14	57
4	0.2	0.2	1.2	No	0	0	0
5	2	0.2	1.2	Yes	58	0	58
6	2	2	0.2	Yes	72	0	72
7	0.2	2	1.2	Yes	0	0	0
8	1.1	1.1	0.7	No	47	13	60
9	2	2	1.2	No	59	0	59
10	0.2	2	0.2	No	0	14	14
11	0.2	0.2	0.2	Yes	14	7	21

Table 16

A model was generated using the MODDE 10 software which provided a good fit to the data (Figure 53).

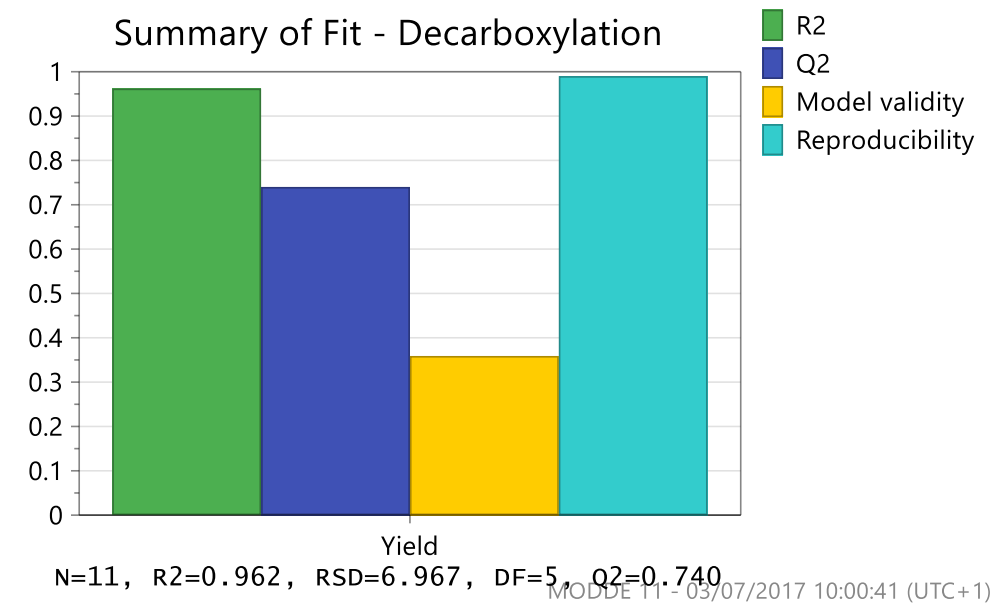


Figure 53

The most significant factor was found to be Ph_2CO equivalent (more was better). Equivalents of the borate reagent and presence of DIPEA was also favoured (Figure 54).

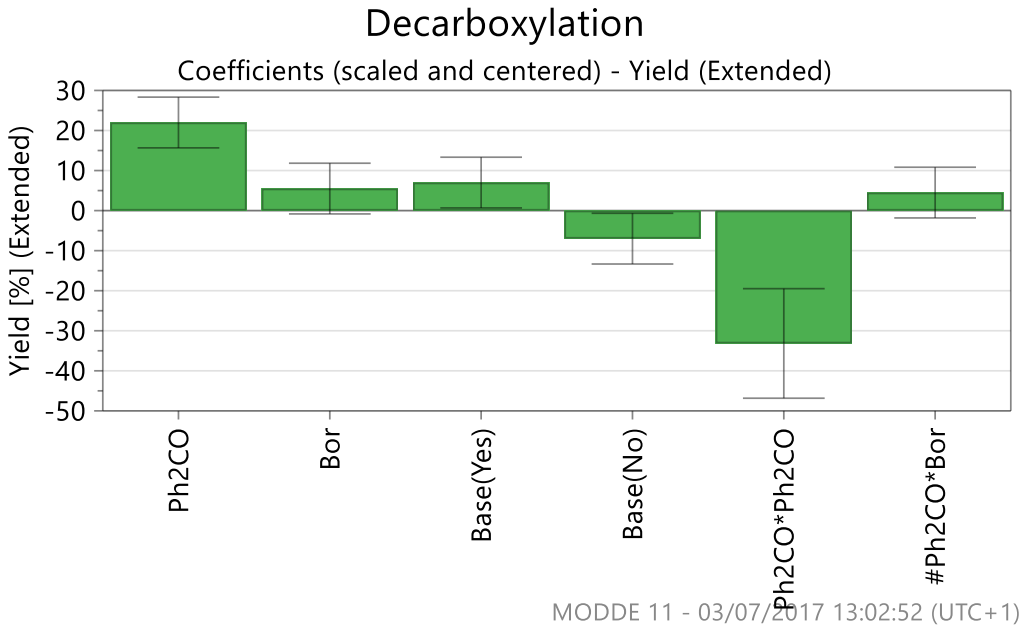


Figure 54

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