NOVEL APPROACHES FOR CATALYTIC DIRECT AMIDE FORMATION

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NOVEL APPROACHES FOR CATALYTIC DIRECT AMIDE FORMATION

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Declaration

The work described in this thesis was carried out in the Department of Chemistry, University of Durham between April 2011 and March 2015. All of this work is my own unless specifically stated otherwise. No part of this work has previously been submitted for a degree at this or any other university.

Statement of Copyright

Then which of the Blessings of your Lord will you both (jinns and men)

deny? Blessed be the Name of your Lord (Allah),

The Owner of Majesty and Honour.

Sura Ar-Rahman, Verse-77-78.

To my parents

&

Musfiq and Rayeed

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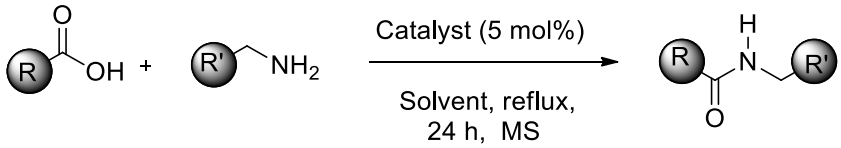
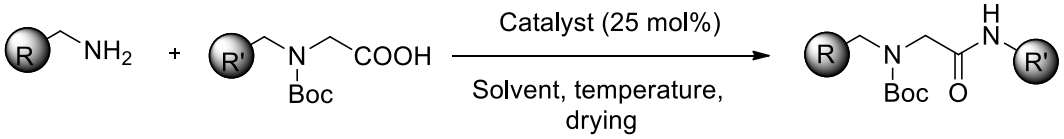
Abstract

The significance of amides as a component of biomolecules and synthetic products has triggered the development of catalytic direct amidation methods which involve reaction of a carboxylic acid and amine to form an amide with water as the only by-product. These methods evade the need for stoichiometric activation or coupling reagents and hence, are important green chemical processes.

Investigations into direct amide formation began with the development a mild reaction conditions for the direct amidation reaction with known arylboronic acid catalysts in two different model reactions and compared with both reported and potential organometallic catalysts (Zr and Fe based).

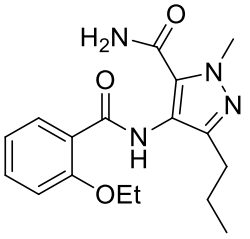


After a systematic evaluation of solvent, temperature and catalyst, ambient reaction conditions were applied in the direct amidation of amino-acid derivatives in order to exploit these more economical reagents for peptide synthesis which is both little used and little explored. Protected amino acid derivatives showed slow reactivity compared to simple amine-carboxylic acid combinations and hence high catalyst loadings were required, though did proceed at 65~68 °C generally avoiding racemisation.

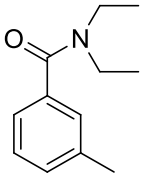


However, an interesting synergistic catalytic effect was observed during dipeptide formation using mixture of two arylboronic acid catalysts (1:1) in the direct amidation reaction at lower temperatures, although the process was particularly slow.

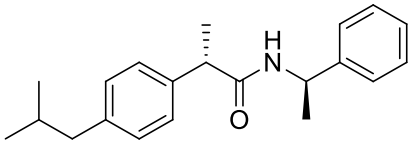
This impressive result led to explore more about the effect of '*Cooperative Catalysts',* particularly, on the less reactive acid-amine combination. As a consequence, some commercially important synthesis has been reviewed through this novel cooperative catalysis to ensure their real applicability in industries.



152
Sildenafil Precursor



119
DEET



142
(+)-Ibuprofenamide

Acceptance of the practicability and general applicability of this new approach depends upon the understanding of the mechanism of the cooperative catalysis. In order to reveal the mechanism of the cooperative catalysis the direct amide formation reactions were followed by the real time monitoring technology (React-IR) and HPLC. However, further investigations are required to understand the mechanistic intricacies of this cooperative catalysis.

Further, the role of H-bonding in the amide bond formation with significantly inert acid (pivalic acid) towards the amine to form amide has been attempted. In order to accelerate the catalytic activity the use of a potential catalyst promoter, 'ANB 209' in the direct amidation reactions was also examined. Improvements in catalysts activity or alterations in catalyst would need further study so that the direct amide formation becomes a common tool for a wide range of carboxylic acid and amine partners.

The effect of different substituents on the α-position of carboxylic acid with various amine substrates was investigated to understand the exceptional direct amide formation of the synthesis of mandipropamid, a well known fungicide. Both uncatalysed and catalysed direct amidations of mandelic acid was done with different amine substrates at different temperatures, resulting different rate of amide formation.

Finally, the application of two novel borinic acid (R_1RBOH) compounds in the direct amide formation reactions has been assessed for the first time, which displayed in some cases the

potential to act as catalysts for direct amide formation. Further research will likely to accelerate the developments of this type of catalysts in direct amidations.

Acknowledgements

Firstly, I would like to express my profound gratitude to my supervisor, Prof. Andy Whiting for his invaluable guidance, unwavering enthusiasm, encouragement, support, insightful comments and suggestions throughout this project. I really appreciate the opportunities he has offered me during this time to attend at different conferences.

Secondly, I would like to acknowledge The *Ministry of Science and Technology, Bangladesh,* for funding my studies and research work.

I am also grateful for the cooperation of the analytical services at *Durham University*, in particular: Dr. Alan Kenwright, Catherine Heffernan and Ian McKeag of the NMR service; Dr. Michael Jones, Dr. Jackie Mosely and Lara Turner of the mass spectroscopy service; and Jarika Dostal and Judith Magee for elemental analysis.

I would like to express my appreciation to my labmates, current and past members of the Whiting group for the stimulating discussions and for all the fun we have had in the last four years. All of their presence have made the lab a fascinating place to work, thanks to: Dr. Alexander Gehre, Dr. Mona al Batal, Dr. Wade Leu, Dr. Adam Daniel James Calow, Dr. Garr-Layy Zhou, Dr. Ricardo Girling, Dr Duangduan "Nim" Chaiyaveij, Dr. Hayley Charville, Dr. Irene Georgiou, Hesham Raffat Shawky Haffez, Sergey Arkhipenko, Ludovic Eberlin, David Chisholm, Enrico La Cascia, Katrina "Kate" Madden, and Alba Pujol. It has been great working with you! Special thanks must go to those who have become my true friends, thanks for making me understand, *"never give up in life"* and whom I miss seeing every day, you will be always in my mind no matter how far we are!!!

I wish to express my heartful thanks to my beloved husband, Dr. Musfiq Mannan Choudhury whose support, especially continuous guidance and understanding enabled me to make a good beginning and ending in my research work and also during the writing of this thesis, thanks for opening my eyes to new opportunities and experiences. Thanks to Rayeed, my six year old son, mummy always appreciates your patience all through these years and supporting me and I love you so much.

And last but not the least, I would not be, where I am today, and this thesis would not have been possible without the unconditional support I always have from my parents. *Abbu-Ammu*, I love you so much! You are the inspiration of everything in my life. I am also thankful to my sisters, brothers, and in-laws. Thanks for supporting me spiritually throughout writing this thesis and my life in general.

Thank you.

List of Abbreviations

Å - angstrom(s)
Ac - acetyl
aq - aqueous
Ar- aromatic
ASAP - atmospheric solids analysis probe
Bn - benzyl
b.p. - boiling point
br - broad
Bu - butyl
B_2Pin_2 - bis(pinacolato)diboron
Bz - benzoyl, -C(O)Ph
calc - calculated
$CDCl_3$ - deuterated chloroform
CDI - carbonyldiimidazole
d - doublet
dd - doublet of doublets
DCM- dichloromethane
d.e. - diastereomeric excess
DFT - density functional theory
DMAP - 4-dimethylaminopyridine
DMF - dimethylformamide
DoE - design of experiments
DMSO - dimethyl sulfoxide
DS - Dean-Stark technique
e.e. - enantiomeric excess
EI - electron ionization
ES - electrospray
Et - ethyl
Et_2O - diethyl ether
EtOAc - ethyl acetate
exp - experimental
GC-MS - gas chromatography mass spectrometry
Hz - hertz
HPLC - high performance liquid chromatography
HRMS - high resolution mass spectrometry
IPA - isopropyl alcohol
IR - infra-red
J - coupling constant-NMR
k - rate constant
M - molar (1 M = 1 mol dm-3)
m – multiplet
mol - mole(s)
Me - methyl
MeCN - acetonitrile
m.p. - melting point
M.S. – molecular sieves
MS - mass spectrometry
MTBE - methyl *tert*-butyl ether
M_w - weight-average molecular weight
NMP - *N*-methylpyrrolidinone
NMR - nuclear magnetic resonance
Ph – phenyl
PIV- pivalic acid
PPA - polyphosphoric acid
ppm - parts-per million
Pr - propyl
q - quartet
ReactIRTM - ReactIR, trademark name for Mettler-Toledo *in situ* IR spectroscopy
rt - room temperature

t - triplet TBAI - tetrabutylammonium iodide TFA - trifluoroacetic acid THF - tetrahydrofuran TLC - thin layer chromatography TMEDA - tetramethylethylenediamine TMSCl - trimethylsilyl chloride UV - ultra-violet	s - singlet

Chapter 1: General Review Of Amide Bond Formation

1.0 Introduction

The amide functionality, especially the carboxamide (-CONR-) bond is ubiquitously found in natural molecules. It links mostly amino acids to form peptides and proteins[1] which play a crucial role in all biological processes like enzymatic catalysis, transport and storage (haemoglobin), immune protection (antibodies) and mechanical support (collagen). It is also very common in the medicinal world. Some important amide containing drugs are shown Fig 1.

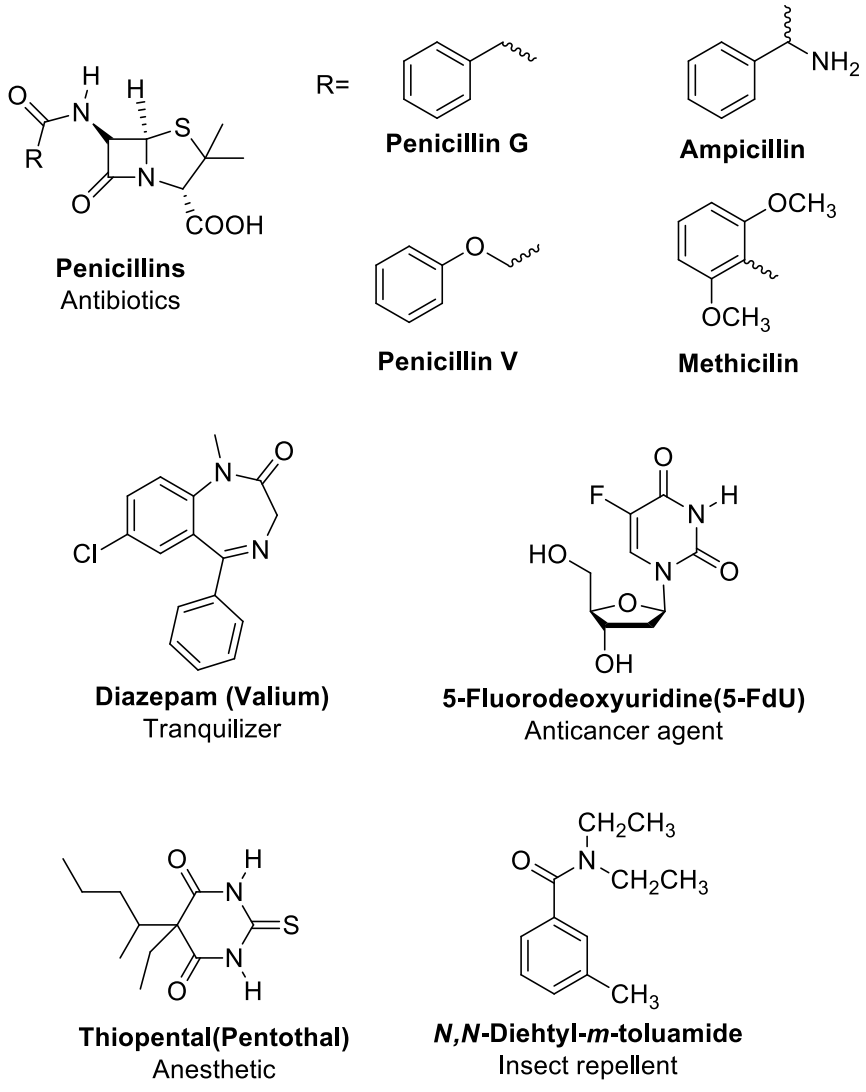


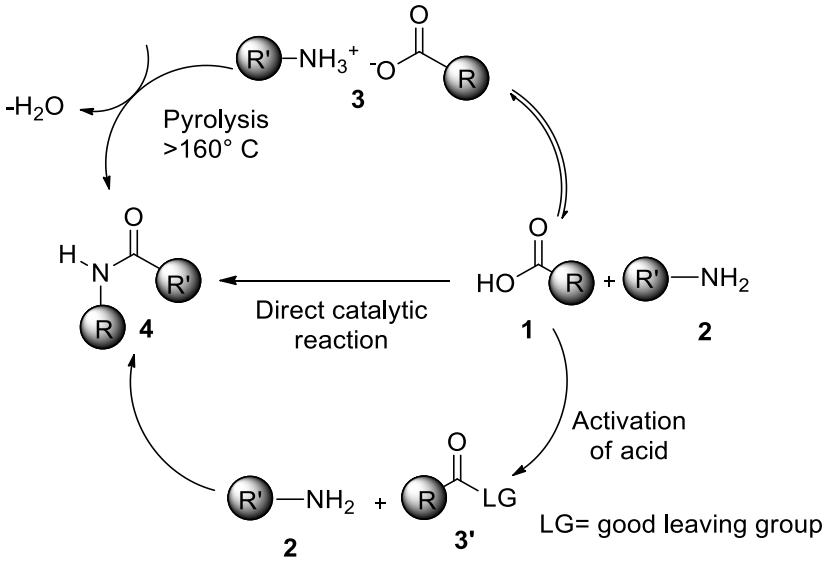
Fig 1. Some important amide containing drugs

A recent survey of the Comprehensive Medicinal database shows the presence of amide motifs in almost 25% of all the synthetic drugs.[2] As a consequence, formation of amide bonds

was considered to be a preferable research area by the American Chemical Society (ACS), Green Chemistry Institute (GCI) and several leading global pharmaceutical corporations (Pharmaceutical Roundtable).[3] Consequently, rapid and high yielding, along with high atom economy amidation methods have become a challenging scientific pursuit for the synthetic chemist. Indeed, direct amidations from carboxylic acids and amines, without using any stoichiometric and high molecular weight reagents, is the key part of developing greener direct amide formation reactions.

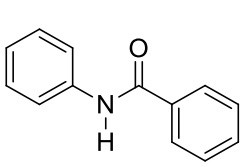
1.1 Methods for Generating Amide: (Common Means-Pyrolysis)

Amide formation was reported as early as 1858 and over the past century, there have been tremendous developments of many methods for accomplishing amide formation.[4-15] The following Scheme 1 shows typical ways of making amides.

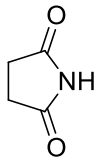


Scheme 1: Typical routes of amide formation

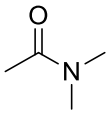
The simplest and most appealing protocol is the 'direct amidation' which involves the reaction between a carboxylic acid **1** and an amine **2** and proceeds through the elimination of water (*via* condensation) which drives the reaction towards the amide. This process is also known as the *pyrolysis* of acids and amines, and/or of carboxylate ammonium salts. The process has been known since the 19th century and the reaction has even been done under flow conditions.[16]



Benzanilide
5



Succinimide
6



Dimethylacetamide
7

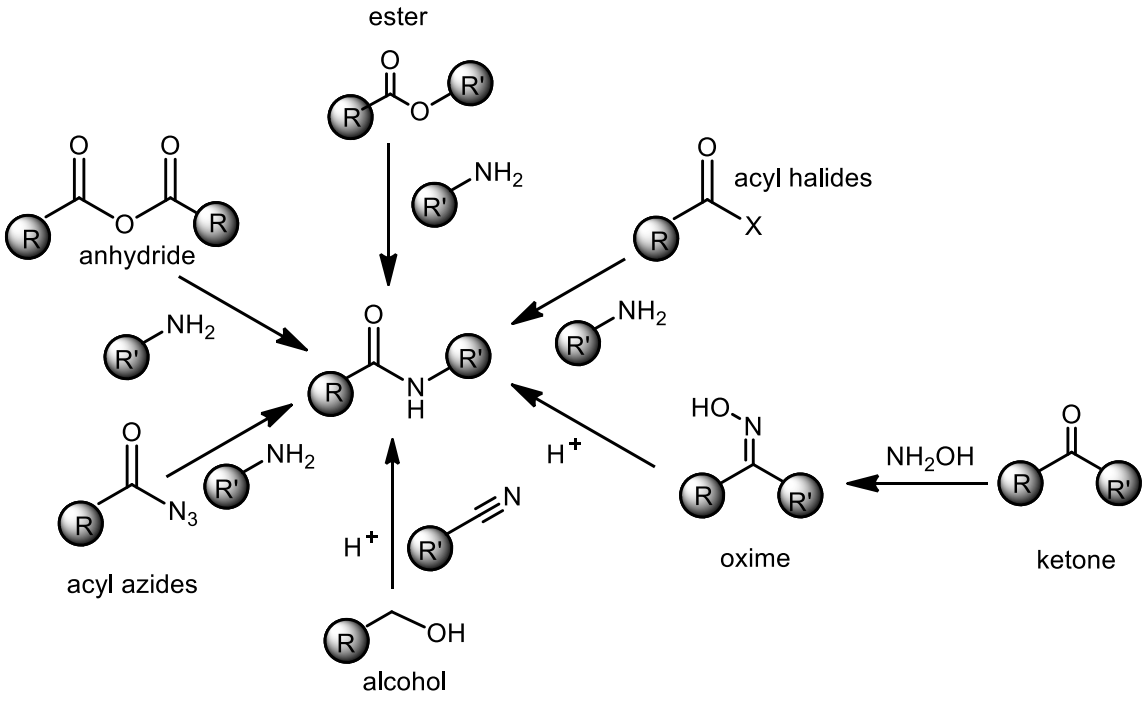
Coleman and Alvarado[17] followed the pyrolysis of carboxylic acids and amines for the direct conversion of ammonium acetate to acetamide. They carried out the amidation with hot acetic acid with continuous distillation to remove excess acetic acid and water that supports the formation of amide. The same protocol was applied for the preparation of benzanilide **5**[18] and succinimide **6.**[19] Mitchell and Reid[16] showed that aliphatic amides could be prepared easily by passing ammonia through a number of carboxylic acids at a temperature that helps continuous removal of water from the reaction mixture. By replacing ammonia with dimethylamine, dimethylamides **7** were also synthesised applying the same method. However, the major problem with this method appeared with long chain carboxylic acids. The rate of reaction decreased extensively with longer alkyl chain carboxylic acids than butyric acid, and at the temperature (at which the acid was heated) the dehydration of longer amides easily converted into nitriles. For example, there was no amide formation with hexadecanoic acid or octadecanoic acid when the reaction mixture was heated to 125 ºC or 190 ºC for a long reaction time. A similar approach has been applied for a commercial synthesis[20,21] of dimethylacetamide **7** from acetic acid and dimethylamine. Afterwards, a range of amides were prepared by heating different carboxylic acids[22] and the optimum conditions were found to be ~ 160-180 ºC over 10-30 minutes. On the contrary, Davidson and his co-worker Newman[23] showed that monocarboxylic acids undergo dehydration forming anhydrides when refluxed at 250 ºC-350 ºC, which upon the addition of amines give the amides.

The process of ‘pyrolysis’ for the amidation is environmentally benign, as water is the only waste product and no solvent or catalyst is needed. However, this process has very limited applications.[24] This is because, although amide bond formation is thermodynamically favourable, the condensation reaction (between carboxylic acid and amine) has afflicted a high activation energy,[1,25] though the mechanism is still not fully understood.[26,27] Moreover, in most cases, the ammonium carboxylate salts (which are formed due to the lower value of the pK_a of most of the carboxylic acids compared to the protonated amines) are less reactive

to this desired dehydration, resulting in high temperature reactions (more than 160 ºC) and low conversion of amide under direct thermal reaction conditions.[1,26] However, the output of the thermal amidation reaction is remarkably substrate, temperature, substrate concentration, solvent and other reaction parameters dependent. As a result, there is still a lack of a general method to approach direct amidation at ambient temperature.

1.2 Activation of the Carboxylic Acids: Adoption of Coupling Agents

In order to overcome the problems associated with the direct amidation through heating, numerous innovative methods have been investigated in the past two decades. Most are associated with the activation of carboxylic acids by different activating, condensing or coupling agents (Scheme 2), which need to be applied in stoichiometric amounts. Today, many of them are commercially available and have considerably extended the arsenal of the synthetic chemist for the construction of any type of amide bond. The major drawback of this process is the formation of considerable amounts of waste or by-products in each case.



Scheme 2. Many routes for amide synthesis

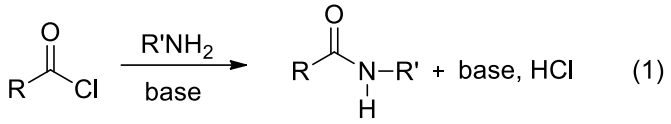
The main methods for the activation of carboxylic acids are the use of acyl halides, esters, anhydrides, acyl azides, acyl imidazoles and so on.[25] In 2005, Montalbetti and Falque[25] found three different ways of coupling the reactive carboxy derivatives with amines:

a) Formation of an intermediate acylating agent, which undergo aminolysis prior to isolation.

b) Formation of a sensible acylating agent from acid in a different step(s) followed by the addition of amine

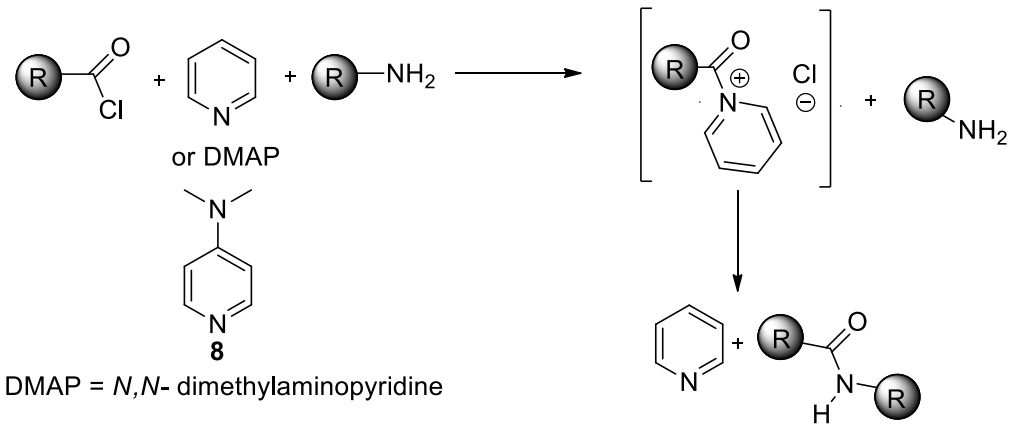
c) *In situ* formation of an acylating agent from the acid in the presence of an amine, then treating with an activating or coupling agent.

One of the easiest ways of activating an acid is acyl chlorides formation, many of which are also commercially available. The amide bond is formed by using the acyl chloride with the desired amine (Equation 1).



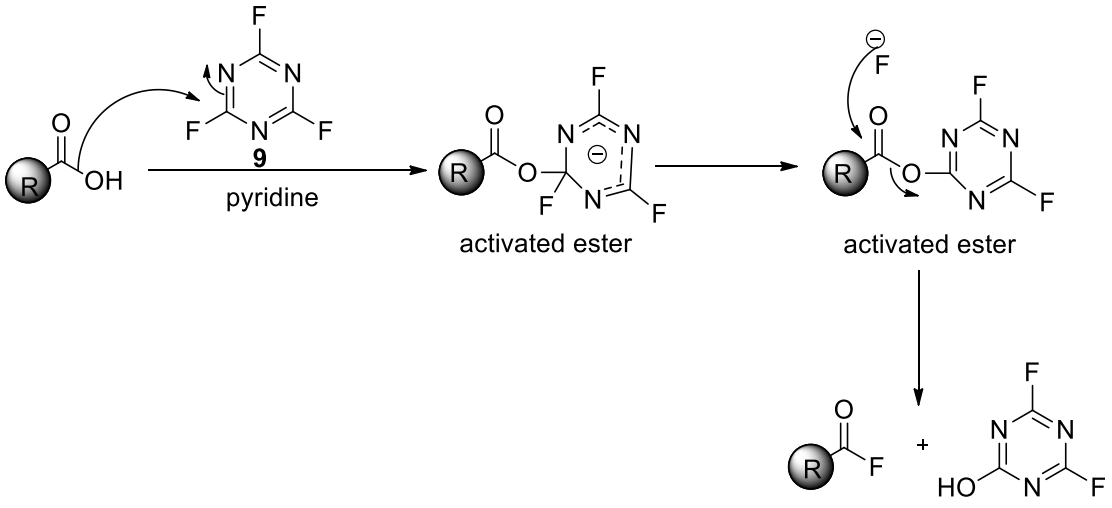
(1)

Some of the familiar reagents for the generation of acyl chlorides are: thionyl chloride ($SOCl_2$),[28] oxalyl chloride ($(COCl)_2$),[29,30] phosphorous trichloride (PCl_3),[31] phosphorous oxychloride ($POCl_3$)[32] and phosphorous pentachloride (PCl_5).[33] Phosphonium pentachloride is generally used for aromatic acids containing electron-withdrawing substituent.[34] One of the major drawbacks of the previously mentioned chlorinating agents is the formation of HCl as a side product, and sometimes substrates containing Boc-protected amines *etc*. are acid sensitive. In order to maintain basic conditions, organic bases (e.g. NEt_3, $^{i}Pr_2NEt$, *etc*.) are used,[25,35] and these reactions can be accelerated with catalysts like pyridine (Scheme 3) or dimethylaminopyridin (DMAP) **8**.[36]



Scheme 3. Catalytic role of pyridine

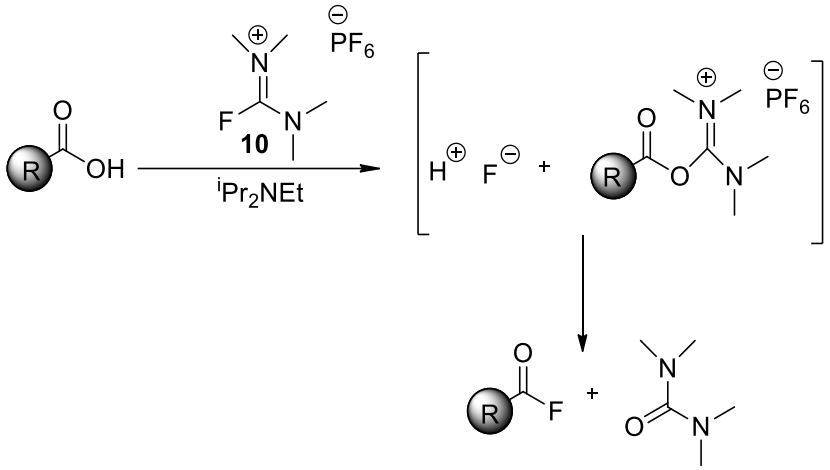
Neutral conditions have also been investigated and afforded moderate conversion of carboxylic acids into acyl chlorides, e.g, triphenylphosphine (TPP) and a source of chloride like carbon tetrachloride (CCl_4).[37-39] Because of the toxicity of CCl_4, hexachloroacetone can be used instead, reported by Villeneuve.[40] Alternatively, trichloroacetonitrile and TPP can be used for mild and efficient amidation.[41] The major limitations associated with acyl chlorides are the side reactions such as hydrolysis, racemisation, cleavage of protecting groups *etc.* which make their use limited.[25]



Scheme 4. Acyl fluoride formation using cyanuric fluoride

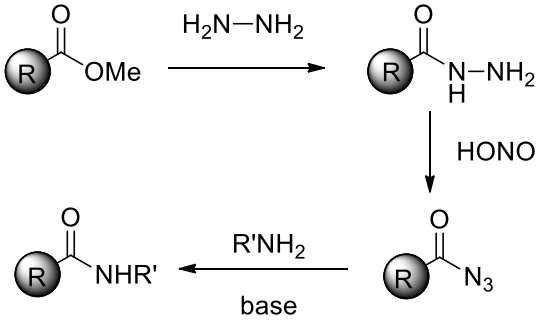
By using acyl fluorides as an active intermediate, some of the problems, such as racemisation, can be solved. Acyl fluorides are less sensitive to moisture than acyl chlorides, and also more reactive towards amines. They are generally prepared from cyanuric fluoride **9** in the presence of pyridine (Scheme 4).[42,43] Alternative fluorinating agents are *N,N*-

tetramethylfluoroformamidium hexafluorophosphate[44] (TFFH) **10** (Scheme 5), diethylaminosulphur trifluoride[45,46] (DAST) Et_2NSF_3 and deoxofluor $(MeOEt)_2NSF_3$.[47]



Scheme 5. Acyl fluoride formation using TFFH

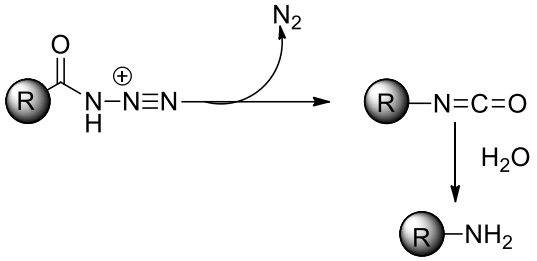
On the contrary, acyl bromides are used only occasionally to synthesise amide bonds. One of the most common agents is α-bromoacetyl bromide which can be prepared from reaction of acetic acid with phosphorous pentabromide.[48] Others reagents are PPh_3/ NBS,[49] PPh_3/ Br_2,[50] $SOBr_2$,[51] BBr_3/ Al_2O_3[52] or even $(BrCO)_2$.[53] Recently, acylbromides were prepared from 1-bromo-*N*,*N*-2-trimethyl-1-propenylamine.[54]



Scheme 6. Multistep amide synthesis via acyl azide formation

The acyl azide is another way of making amide bonds and was first developed for peptide coupling by Curtius [55] in 1905 from the corresponding methyl esters *via* a two-step synthesis with hydrazine and nitrous acid (Scheme 6).

Despite the advantage of having no racemisation, this coupling method suffers from the occasional formation of unwanted isocyanates[56] (Scheme 7).



Scheme 7. Formation of unwanted isocyanate

Later, Yamada and co-workers[57] used a more convenient one-pot process for amide formation using more convenient DPPA (diphenylphosphonic azide) **11** (Fig 2) as coupling agent, together with a nucleophile.

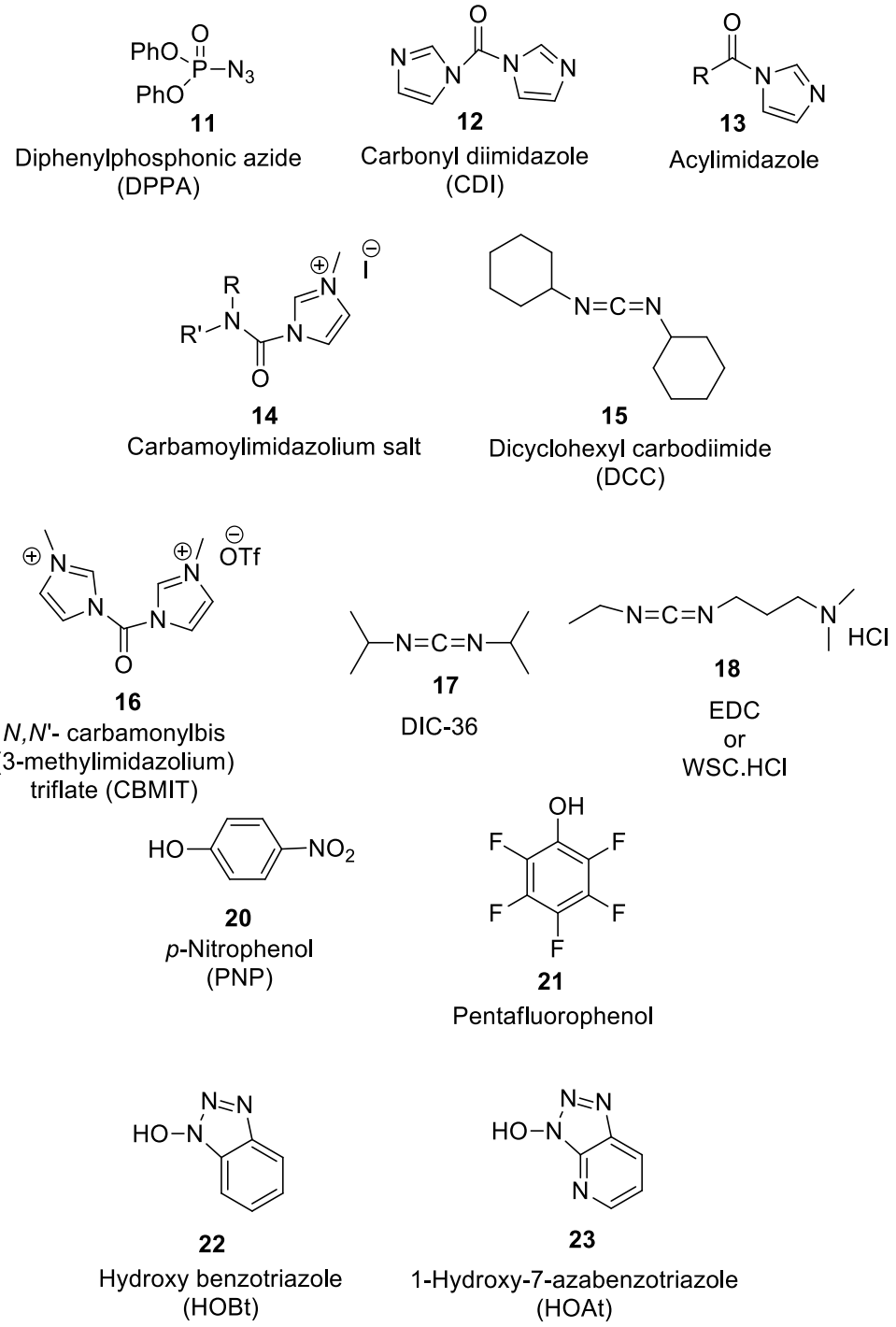
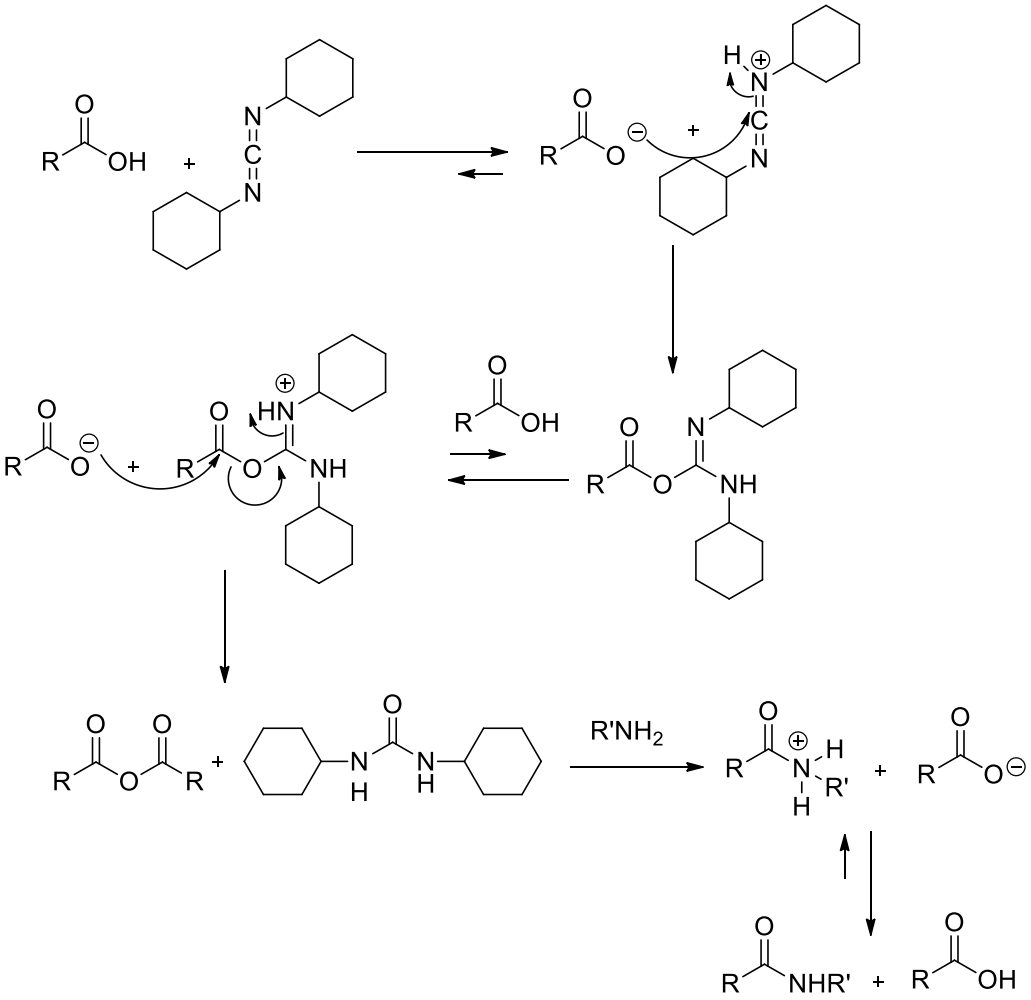


Fig 2: Some important coupling agents, additives and precursors used to activate esters and acids

With the development of the one-pot amide formation, carbonyl diimidazole (CDI) **12** (Fig 2) became a useful and familiar coupling reagent which forms an activated species, acylimidazole **13**(Fig 2), from the acyl carboxyimidazole and imidazole *in situ.*[58] This reagent appears to be more useful to the peptide chemist as it can be used on a large scale.[59]

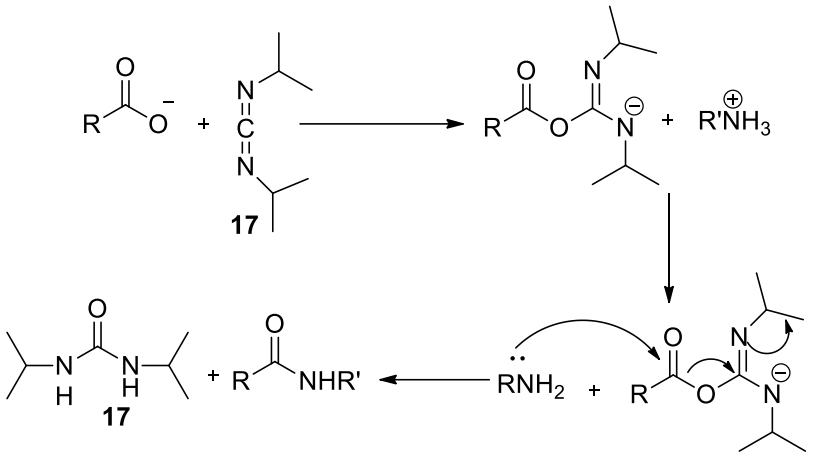
For the preparation of tertiary amides, the carbamoylimidazolium salts **14** (Fig 2) (prepared from the secondary amines and *N,N*-carbonyldiimidazole) have proven to be effective.[60]

Both symmetric and mixed anhydrides are very active intermediates for the formation of amides as these species readily undergo aminolysis to form amides. The presence of one equivalent of dicyclohexyl carbodiimide (DCC) **15** (Fig 2) with two molecules of acid generates the symmetric anhydrides (Scheme 8), which undergo further reaction with the selected amine to form an amide**.**[61] However, the problem is that acids do not completely react. Mixed anhydrides (*e.g.* mixed pivalic anhydride) methods[62] have been developed to eliminate the by-product problem where the second carboxylic group is easily coupled onto the acid.



Scheme 8. Anhydride preparation and coupling of anhydride

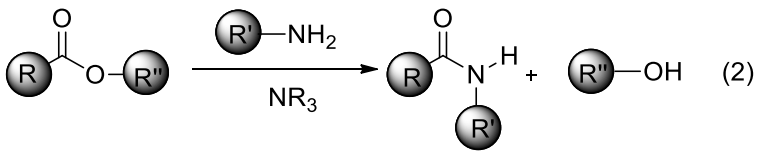
The idea of the mixed anhydride has been extended to other activated species, which are achieved, from the condensation or addition of a carboxylic acid to a phosphoric acid–derived species, boronic acid derivative, carbodiimide (Scheme 9) or ethoxyacetylene.[25]



Scheme 9. One-pot carbodiimide coupling

Despite the inertness of esters to be good activated species for amidation, alkyl esters are occasionally reacted with an amine under vigorous condition such as high temperature or the addition of a Lewis acid (e.g. $TiCl_4$).[63] Aran *et al.*[64] found that intramolecular amide formation was observed abruptly from methyl or ethyl esters after the reduction of a nitro group. In most cases, the alkyl esters were found to be quite stable under the general coupling conditions. On the contrary, aromatic esters are more prone to react with a wide range of amines under moderate conditions.[25] There is a good number of reactive alcohols used for the synthesis of amides, particularly, the electron withdrawing substituted alcohols like *p-N*itrophenol (PNP) **20**,[66] pentafluorophenol moiety **21**[67], HOBt **22**,[65] 1-hydroxy-7-azabenzotriazole (HOAt) **23** *etc.* (Fig 2) are more popular in this case.

Over the past few years, some exotic procedures were developed for the synthesis of amides *via* different active esters (Equation 2).



(2)

Activated esters are usually synthesised using standard ester-formation methods. Some of the striking active esters are shown in Fig 3. For example, succinimidyl esters **24**[68] is generated from corresponding acid and DCC **16**, triazine based ester **25** is prepared from CDMT or DMTMM,[69,70,71] whereas, ester **26** is generated from isooxazolium salts like *N*-ethyl-5-phenylisoxazolium-3′-sulfonate (also called Woodward's reagent K or NEPIS)[72].

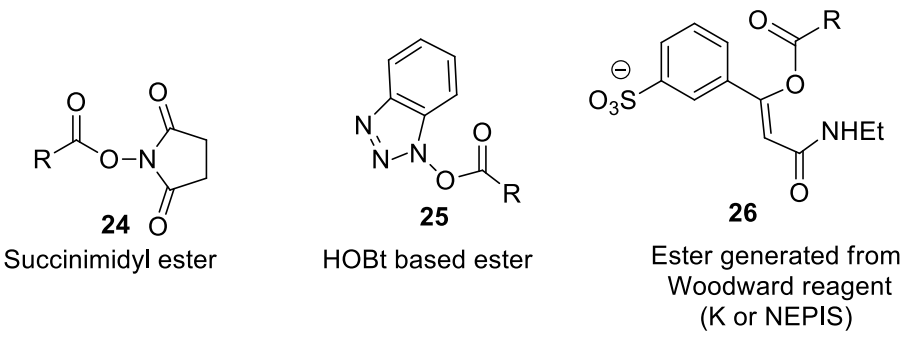


Fig 3: Some active esters used for amide bond formation

More recently, one-pot coupling conditions have been developed on the basis of the addition of a catalytic or stoichiometric amount of HOBt **22** or HOAt **23** based 'onium salts' and halogenated coupling reagents (Fig 2). Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP) or Castro's reagent is the first reported example of an HOBt **22**–based onium salt reagent.[71] This reagent has proved to be effective, but the generation of hexamethylphosphoric triamide (HMPA) **27** (Fig 4), which is highly toxic, has made its use very limited.

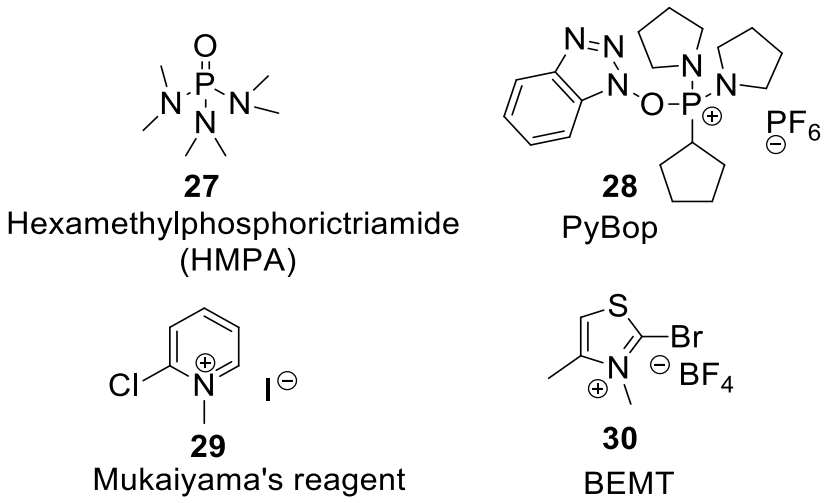


Fig 4: Some one-pot coupling procedure reagents and toxic by-products

Surprisingly, phosphonium based coupling reagents like benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate (PyBop) **28** are more capable of generating less toxic by-products (Fig 4).[72] More recently, the predominance of active ester technique has been gradually redeemed with the coupling reagents based on the so-called 'onium salts' like uronium and ammonium or immonium salts, giving a new dimension in the arena of amide synthesis. Mukaiyama's reagent **29** (Fig 4) is the most successful in the conversion of β-amino acids into β-lactams.[73] However, the poor solubility of the pyridinium iodide in the conventional solvent makes the reagent unfavourable for general application. Recently, Xu *et al*.[74] solved the problem by developing 2-bromo-3-ethyl-4-methylthaiazolium tetrafluoroborate (BEMT) **30** (Fig 4) which was very successful in the formation of oligopeptides.

1.3 Catalytic Amide Formation from Non-activated Carboxylic Acids and Amines: Research Trends in Direct Reaction

The stoichiometric use of all the condensing and activating agents mentioned above is atom uneconomic and in some cases the product purification and use of toxic reactive reagents make those methods questionable. Therefore, these reagents should ideally be altered by developing a catalytic process reduced impact on the environment and reduced reagent.[26] In recent years, several catalytic systems have been developed which led to the direct transformation of a carboxylic acid **1** and amine **2** to form the amide **3** with water as the only side product (Scheme 1). Some of the popular catalytic amide formations are described below:

1.3.1 Organo-Catalysis: Triazine Based Catalysts

Organocatalysis has become a tool for the synthesis of organic compounds.[75] With increasing attention being given to this new area, new chemical transformations are being discovered. There have been some interesting studies on the development of methods for the direct formation of an amide bond using organocatalysts to promote the condensation between carboxylic acids and amines. Triazine-based catalysts are one of those categories of organocatalysts used in the direct amidation processes.

Several papers have been published related to 1,3,5-triazine-based catalytic processes for amide synthesis. These catalysts were used as the activating reagents for carboxylic acids to effect the amide formation in high yield. The use of cyanuric chloride **31**,[76] cyanuric fluoride **32**,[42,43] CDMT **33** (2-chloro-4,6-dimethoxy-1,3,5-triazine)[70] or DMT-MM **34** (4-(4,6-dimethoxy-1,3,5-triazine-2-yl)-4-methylmorpholinium chloride)[71,77] in the amide formation is noteworthy (Fig 5).

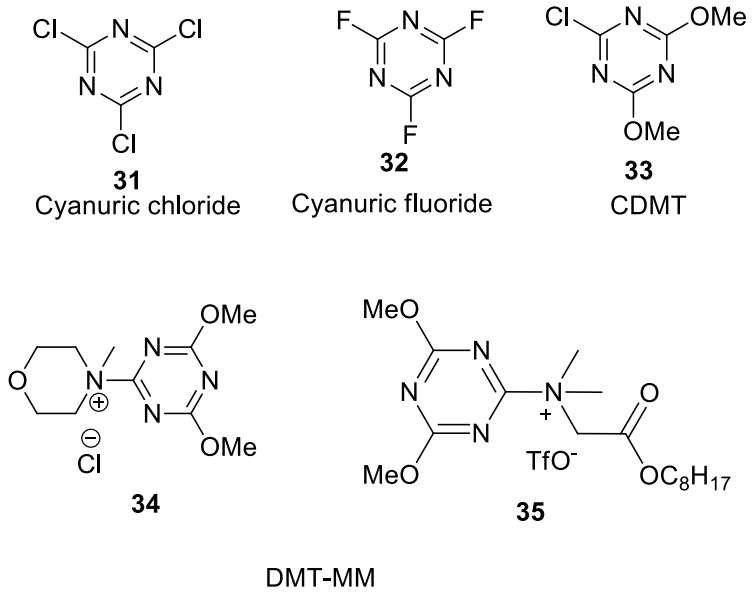
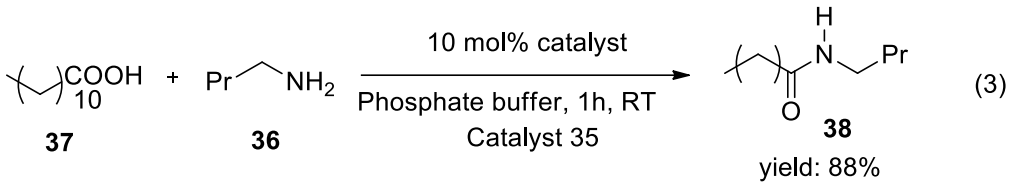


Fig 5: Triazine based catalysts used for amide formation

In 2005, Kunishima and his co-workers[78a] reported the feasibility of catalytic amide formation in micellar reaction media utilizing amphiphilic DMT-MM **35**, which acts as a dehydro-condensation agent. The DMT-MM **35** was synthesised *in situ* from the corresponding chlorotriazine and was investigated in aqueous medium with a range of substrates. In theory, the rate of the reaction should increase through dehydro-condensation in the colloidal surroundings. This is due to the formation of the micelles due to the reagent having a long hydrophobic alkyl chain. Additionally, the carboxylate salts and the triazine catalysts can align at the micellar interface in a contiguous manner as they both have polar moieties, resulting in high local concentrations, which give advantages in reorientation. This makes it easier for amines (which are also within the micellar core) to attack the activated intermediates which leads to increased reaction rates.

The idea was examined in the presence of 10 mol% of various triazine-based catalysts in a phosphate buffer at 25 ºC through the simultaneous condensation of two carboxylic acids with excess *n*-butylamine **36.** The amidation of 1-octanoic acid and 1-butanoic acid exhibited 24% conversion within 4 hours resulting in a mixed product composition which differed with catalyst. However, the mixed product did not appear to any considerable amount when one of the acids had a longer alkyl 'tail' enabling micelle formation. Further, kinetic studies revealed that reaction between 1-dodecanoic acid **37** and *n*-butylamine **36** in the presence of triazine **35** is 1700 times faster than with 1-butanoic acid due to micellar effects. This was further authenticated by use of butyl dodecanamide **38**, which reacted in just over an hour at room temperature (Equation 3) and 99.6% chemoselectivity was found for the inclusion of 1-butanoic acid in the reaction of a longer chain carboxylic acid.



(3)

Thus, triazine **35** proved to be a highly efficient catalyst under these conditions when it is applied to longer alkyl chain carboxylic acids.[78] It is thought that reaction occurs *via* an acyloxy triazine derivative *i.e. via* the displacement of the triazinyl leaving group. The amide product is formed from the activated carboxylate, which reacts like a mixed anhydride with the incoming amine. Despite the impressive yields produced by the catalyst **35**, to date, there has not been extensive use as the substrates require a large hydrophobic segment.

Later, Kunishima *et al.*[78b,78c] have also used other triazine-based reagents like 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride and got high yield. Unfortunately, these reagents are not atom economic as they work as stoichiometric form to activate carboxylic acid.

1.3.2 Transition Metal Catalysis

Organic synthesis has historically been governed by Lewis acidic *transition metal catalysis*.[79] Understanding of metal properties and the applications of their versatile reactivity in various

transformations are undoubtedly yet to be discovered.[80] Early transition metal compounds have several desirable features, especially their Lewis acidic character which make them attractive reagents for amide formation.[114] However, their ligands are often labile in water, and have a tendency toward the formation of metal-oxygen bonds.[83] Some of the early transition metal compounds that have been reported include $Mo(CO)_6$, $TiCl_4$, $Ti(O^iPr)_4$, $FeCl_2$, $Zr(O^iPr)_4$ *etc.*[115] A wide range of transition metal based compounds have been tested as effective catalysts for a long time in the amide formation.

1.3.2.1 Titanium(IV) Catalysts

In 1970, Weingarten *et al.*[81] found that direct amide formation could be effected by stoichiometric amounts of $TiCl_4$ in THF at –70 ºC. They used the ratio of catalyst:acid:amine is 1:2:6, respectively. After warming to room temperature, the reaction was left for several hours resulting in good yields of amides through direct isolation. For instance, the condensation of formic acid and ethylamine gave ethyl formamide in 82% yield after 8 hours. This technique was suitable for the synthesis of *N*-alkyl and *N*,*N*-dialkyl carboxamides, but it was less useful for weakly basic amines and sterically hindered acids.[81] More recently, Carlson *et al.*[82] proposed that stoichiometric amounts of $TiCl_4$ acted catalytically in direct amidation and that it was considerably more impressive for the condensation of secondary amines, rather than primary. They also found that the addition of a drying agent had a minute effect on yield. Using conditions involving a 1: 1: 3 stoichiometry of catalyst: acid: amine respectively in refluxing toluene. For instance, condensation of di*iso*propylamine with benzoic acid to afforded the corresponding amide 66%, and morpholine with benzoic acid gave 88% of the corrresponding amide in 10 hours.[82]

This work was further investigated in 1988 by Mader *et al.*[83a] who observed the efficacy of $Ti(O^iPr)_4$ as a catalyst for the formation of 5- and 6-membered lactams from simple primary and secondary amino acids with high yields, however, the reaction was still favoured by high titanium loadings, *i.e.* 50 mol%. Titanium dioxide was produced as the by-product with the use of 2:1 amino acid to catalyst in the reaction, which limited the reaction to essentially a stoichiometric process. Thus, ratios of 4:1 and 10:1 of amino acid to $Ti(O^iPr)_4$ were also convincing, but gave reduced conversion.[83a]

Although the metal-catalysed primary amide formation from carboxylic acids and ammonia was less explored before, in 2003, Shteinberg for the first time used $Ti(OBu)_4$ (2 mol%) in combination with PEG-400 (0.9 mol%) in the reaction of 4-nitrobenzoic acid and ammonia and the yield of amide was found 90%.[83b] However, $Ti(OBu)_4$ alone has also been proven very efficient for the formation of secondary and tertiary amides. Shteinberg *et al*.[83c] published the first successful catalytic intermolecular amidation protocol using 2 mol% of $Ti(OBu)_4$ in the amidation of aniline with different carboxylic acids under refluxing *o*-xylene. For example, in the amidation of benzoic acid and aniline, $Ti(OBu)_4$ was found superior (afforded 85% of amide) in comparison with $TiCl_4$ (39%), $SnCl_4$ (26%), Bu_2SnO (22%), and $BF_3.OEt_2$ (10%).

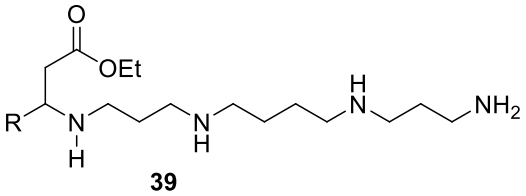
Recently, Adolfsson and co-workers[83d] used the titanium (IV) chloride (20 mol%) for the formation of nine different primary amides at 100-120 °C in the presence of molecular seives using ammonium carbamate as the source of ammonia and the amide yields ranged from 67-99%. Despite the relatively low cost of titanium(IV) compounds, these cannot be recycled which limits their application on a large scale in industry.

1.3.2.2 Antimony-Based Catalysis

The uses of antimony-based reagents for accelerating the amide formation reaction have been investigated for several years. In 1986, Nomura *et al*.[84] accomplished a series of experiments which revealed that triphenylstibine oxide could catalyze direct amidation at temperatures in excess of 100 ºC. Further, investigations by the same group revealed that a combination of triphenylstibine oxide and tetraphosphorous decasulfide could also catalyze direct amidation but at ambient temperatures.[85] The development of a combined reagent system was an obvious development since triphenylstibine oxide had been found to accelerate the direct amide formation by reaction of amines with thiocarboxylic acids and to expedite the thiolation of carboxylic acids in the presence of tetraphosphorous decasulfide.

The reaction was accomplished in the presence of 5 mol% of triphenylstibine oxide and 15 mol% of tetraphosphorous decasulfide using equimolar quantities of the carboxylic acid (for

instance, acetic acid) and amine (*e.g.* hexylamine) at 40 ºC giving hexyl acetamide in 90% yield in 5 hours. The important observation was that there was no amide formation in the absence of either catalyst, even at elevated temperatures and extended reaction times. This catalytic system was used for direct amidation of a range of simple aliphatic or aromatic amines having good yield. However, with sterically hindered substrates, more forcing reaction conditions were needed, *e.g*. the condensation of pivalic acid with *tert*-butylammine completed at 80 ºC with a large excess of amine over 12 hours afforded 88% amide formation. This was also effective at coupling *N*-protected amino acids with amino acid esters, and for the amidation of hydroxylated dipeptides.[85]

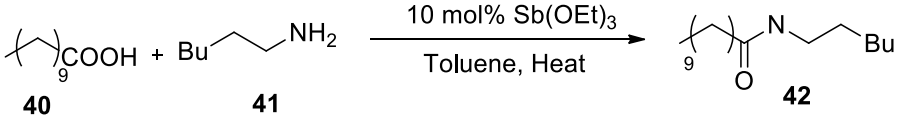


39

a: R= 4-MeOC$_6$H$_4$
b: R=Ph

This process was developed further in 1996 by Ishihara *et al*.[86] who published a series of experimental results based on the antimony(III) ethoxide as catalyst for the formation of 17-membered ring lactams from spermine-derived tetraamino esters.[86,87] The high loading (120 mol%) of antimony(III) ethoxide forced the substrate **39** to undergo intramolecular ester aminolysis in dry benzene yielding the corresponding lactam in 76% yield within 14 hours. Under the same conditions, the methoxyphenyl-substituted substrate **39a** cyclised, giving 90% yield over 9 hours. However, both catalyst loading and lack of wider substrate applicability made this process limited.

Ishihara also studied the catalytic activity of antimony(III) ethoxide, which was used as an intermolecular amidation catalyst for amide formation from carboxylic acids and esters with amines. They found that primary amines with less hindered substrates showed high chemoselectivity and effective conversions. For example, 1-dodecanoic acid **40** condensed with *n*-hexylamine **41** to give 91% yield of amide **42** after refluxing for several hours using 10 mol% antimony(III) ethoxide (Equation 4).[86,87]



40 **41** **42** (4)

1.3.2.3 Zirconium-Based Catalysis

In recent years, zirconium–based catalysts were investigated in the direct amide formation reactions by different groups. In 2012 Williams and co-workers[116] reported the increase of reaction rate by the addition of catalytic amount of zirconium-based complexes in the direct amide formation reactions of carboxylic acids and amines. The most efficient catalysts were reported as $ZrCl_4$ and $ZrCp_2Cl_2$, which resulted high conversions of amide even after 4 hours using 5 mol% of catalyst loading.In parallel the thermal amidations of the same substrates resulted much lower yield. Williams *et al.* were also successful to synthesize the pharmaceutical compounds, like paracetamol and moclobemide with full conversion employing these zirconium catalysts, whereas the thermal amidation afforded only 37% and 14% yield of these two compounds respectively. Further, the applications of $ZrCl_4$ and $ZrCp_2Cl_2$ in the direct amidation of amino-acid derivatives (like *N*-Boc-prolin) showed moderate efficiency with retained stereochemical purity at 100 °C (yield of benzyl amide of *N*-Boc-prolin was 56%).

In parallel to Williams work, Adolfsson and co-workers[117] also worked on direct amide formation reactions catalysed by $ZrCl_4$ and reported that $ZrCl_4$ was also efficient at 70 °C in THF in the presence of molecular sieves as water scavenger. The yield of 24 different secondary and tertiary amides ranged from 62-99% with a catalyst loading of 2-10 mol%. Further, in the coupling with benzylamine, the Boc-protected alanine and proline showed no racemisation. In addition, the synthesis of benzyl amide of antiflamatory drug, indomethacin was synthesised in 97% using only 2 mol% of $ZrCl_4$. Even the catalyst was found to be suitable for the larger scale synthesis.

1.3.2.4 Zinc-Based Catalysis

The use of zinc-based catalysts for the direct amide formation of carboxylic acids and amines has drawn attention in the last few years. In 2009, Shekhar *et al.* investigated the use of $ZnCl_2$ as catalyst in the *N*-formylation of amines using neat formic acid. Using 10 mol% of $ZnCl_2$ at a moderate temperature (70 °C) the formamide products were found in the range of 80-98% after 10-90 min.[83e] The electron rich aniline derivatives were found most reactive and the

electron poor aryl amines and secondary amines suffered from long reaction times (4-15 hrs) in order to afford good yields of amide. However, the thermal reactions of the same substrates resulted very low conversion of amides even in some cases did not proceed at all. Further investigations revealed that the amide formation reactions of longer chain carboxylic acids with aniline were less effective under the same conditions. For example, with acetic acid the reaction afforded only 55% of amide after 12 hrs whereas decanoic acid remained completely unreacted.

Similarly, Brahmacharia *et al.* revealed zinc acetate as efficient catalyst for the direct amidation of acetic acid with different amines under reflux conditions, although the catalyst loading was high (25-30 mol%).[83f,g] Both the primary and secondary amines (including the aromatic and aliphatic amines) were efficient in acylating with a yield of good to excellent. It was also discovered that *N*-acylation also proceeded well even with the stoichiometric amount of $Zn(OAc)_2$ in the absence of acetic acid due to the formation of ZnO which was confirmed by the the residual metal analysis and it was thought that ZnO could be used as pre-catalyst to form the metal acetate ($Zn(OAc)_2$) *in situ*.

1.3.2.5 Iron-Based Catalysis

The use of iron-based catalyst offers significant advantages in a broad range of synthetic transformations like addition reactions, substitution reactions, cycloaddition, hydrogenation, reduction, oxidation, coupling reactions, isomerizaisomerization, rearrangements, and polymerization.[164] But its use in the homogeneous catalysed direct amide formation reaction of carboxylic acids and amines is very limited.

In 2008, Terada *et al*. discovered the catalytic activity of different metal salts in the direct amidation of long chain aliphatic carboxylic acids and amines. They found that $FeCl_3.6H_2O$ was the most efficient among the others metal salts like $ZnCl_2$, $NiCl_2.6H_2O$ or $MnCl_3.6H_2O$. The reactions were highly efficient in refluxing mesitylene with the azeotropic water removal technique. The yield of the aliphatic amides ranged from 47-93% after 6 hrs using 2 mol% of $FeCl_3.6H_2O$ as catalyst.

Later, Rao and co-workers described a facile *N*-formylation of amines using Lewis acid catalysts $FeCl_3$, including $AlCl_3$, $NiCl_2$, and $ZnCl_2$.[83h] Further, Williams and co-workers[116] used $FeCl_2$ as catalyst in the direct amidation of 3-phenylpropionic acid and benzylamine in toluene under refluxing conditions and with the use of 20 mol% of $FeCl_2$, the reaction proceeded to the full conversion just after 4 hrs. Unfortunately, the yield dropped hugely (only 35% of amide was formed) with the reduction of catalyst loading (5 mol%).

Recently, Sureshbabu *et al*.[83i] reported a detailed investigation of the catalytic activity of commercially available iron salts including $FeCl_2$, $FeCl_3$, and $FeCl_3.6H_2O$ in the synthesis of amides from various carboxylic acids and amines. They found $FeCl_3$ was the most efficient catalyst in refluxing toluene to afford different amides. But, when a similar reaction was carried out using $FeCl_3$ (20 mol%) in the presence of 0.5 eq. of glacial AcOH, the product yield increased highly. A possible explanation of increasing the yield in presence of acetic acid was thought to be the increased leaving group ability of the hydroxy group of an acid in the presence of AcOH. The results were compared with the thermal reactions and the poor outcome of the uncatalyzed reactions also confirmed the catalytic efficiency of iron(III). The protocol worked efficiently for the less nucleophilic aniline and its variants which gave the best results (68-98% yield of amides), even the amidation of bromoacetic acid and sterically hindered amino acids worked effectively to afford the corresponding amides with a good yield.

A possible mechanistic explanation was thought that $FeCl_3$ catalysed the activation of the carbonyl group of the acid and the iron-coordinated carbonyl increased its electrophilicity to trigger the nucleophilic attack by an amine component, whereas AcOH serves as a source of H^+ ions which assist the protonation of the –OH group of an acid. It was also speculated that $FeCl_3$ might combine with AcOH to form $Fe(OCOCH_3)_3$ which might behave as an active catalyst species *in situ* and involve in the reaction.

1.3.3 Heterogeneous Catalysis: Development of Microwave Controlled Amide Synthesis

Over the last few years heterogeneous catalysis has become popular for amide synthesis along with the application of microwave conditions. A good number of publications and reviews have reported the success of microwave assisted amidations.[88] K-10 montmorillonite,[89] zeolite-HY,[90] $TaCl_5$- silica,[91] KF-alumina and silica[92] or mesoporous solid acid (Starbon® acid)[93] have been found to be efficient in heterogeneous catalysis for amide synthesis. These catalysts have proven to be cost-effective and efficient in some cases and sometimes can be readily recycled.[95] Some of these reactions were carried out in a domestic microwave (MW) ovens to prove that microwaves increase the rate of reaction, possibly through polarity changes during the course of the reaction due to the development of a dipolar transition state and intermediate.[88d] The disadvantage was that since domestic MW ovens do not have temperature or power control, and hence, it was difficult to make a comparison between various reactions, so further applications were not possible.

However, in 2002, Loupy *et al.*[88e] revealed a systematic comparison between thermal and microwave assisted amidations under solvent free, heterogeneous conditions mainly for the pyrolysis of carboxylate ammonium salts. This study emphasised the three observations which are general to both thermal and microwave assisted reactions: 1) aliphatic carboxylic acids were more reactive than aromatic carboxylic acids; 2) the reactivity of amines are: $PhCH_2NH_2$> *n*-$C_8H_{17}NH_2$> *p*-MeO$PhNH_2$> $PhNH_2$; 3) the reactivity was not dependent only on $pK_{a/b}$ which apparently has important mechanistic implications, though why this is the case is still unclear.[26] It was also clear that these microwave conditions were very effective only for certain acid–amine combinations resulting good yields (up to 93%) in 10-30 minutes, whereas standard thermal procedures afforded >20% less conversion.

In 2009, Clark *et al.*[94] reported a successful amidation process using pre-activated silica gel (Kieselgel 60) as a cost effective and efficient heterogeneous catalyst. The silica gel was pre-activated at 700 °C and was used in the range 10-50 wt% depending on the different substrates examined. The yield was calculated after 24 hours and was found in the moderate (38%) to high (up to 98%) range. Sterically hindered, weakly nucleophilic or strong acid and

amine combinations gave a good yield without any toxic by-products. Even the most difficult substrates such as benzoic acid and aniline gave 47% yield, which was far better than some boron-based catalysts used for amidations (see below). The pre-activated silica remained highly effective for a long time, even upon exposure to air and the E-factor (the ratio of waste to product) calculated after using for four times was found to be satisfactory.[95]

Although microwave assisted heterogeneous catalysis for amide synthesis is in some cases successful at reducing long reaction times, giving higher yields with fewer by-products, with a more flexible work-up and matching the goals of 'Green Chemistry',[22] still there is limited scope in applying the procedures, and they suffer from a lack of general applicability as well as atom economy.

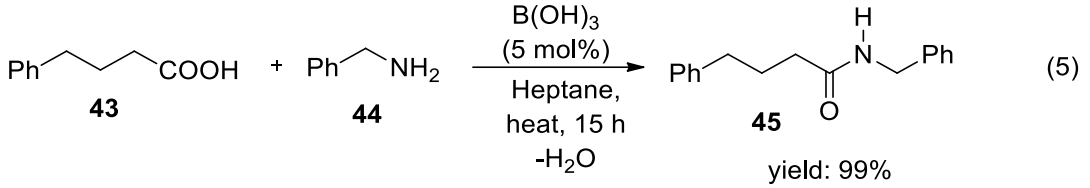
1.3.4 Homogeneous Boron Mediated Protocols for Amidation

As early as 1965, it was revealed that boron compounds could be applied for the conversion of amines and carboxylic acids into amides. Many examples were found in the literature based on boric acid and arylboronic acids (especially containing electron withdrawing substituent) for catalysing direct amidation. Perhaps this process is the most developed catalytic system for amide synthesis.

A) Boric Acid: More Accustomed Catalysis

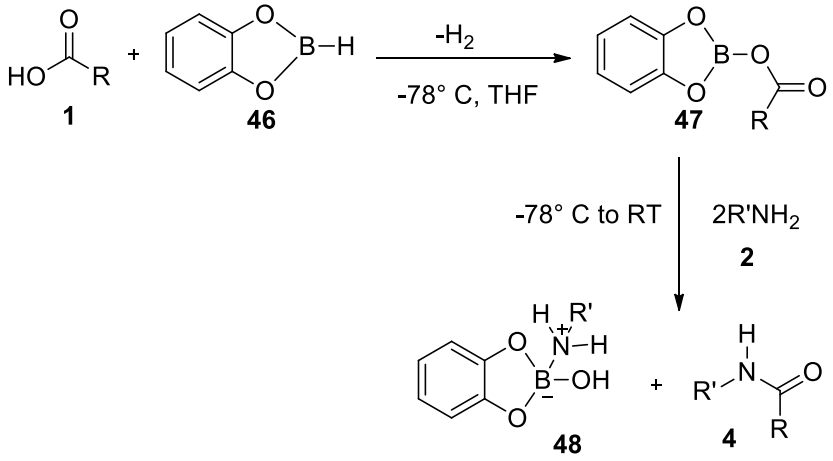
The use of inexpensive, non-toxic and environmentally neutral boric acid, $B(OH)_3$ in direct amidation has been well-received by academic and industrial researchers.[95,96] The first application of boric acid as an effective catalyst for direct amidation was revealed in 2005 by Tang.[95] The reaction was accomplished with the condensation between simple amines and carboxylic acids using 5 mol% catalysts and the water was removed azeotropically.

The process was also very effective with an electron withdrawing substituent attached to aniline, although catalyst loadings needed to be increased up to 25 mol%. For instance, reaction between 4-phenylbutyric acid **43** and benzylamine **44** gave 99% yield of amide **45** (refluxing in heptanes; b.p. ~98 °C) (Equation 5).



On the contrary, with the less nucleophilic 3,5-dimethylpiperidine, 95% (while refluxing in toluene, b.p. ~110 °C) of the corresponding amide was afforded.[94] However, it was found that the reactivity of boric acid was improved at high temperatures and decreased at lower reaction temperatures.[95, 97]

The practice of using more complex boron-based compounds has a longer history than the work of Tang.[95] Earlier, Ganem *et al.*[98] published the stoichiometric use of catecholborane **46** in the condensation of carboxylic acid and amines in THF between -78 °C and room temperature (Scheme 10). They proposed the formation of an acyloxyborane **47** reaction intermediate which further reacted with an amine **2** to provide amide **4** as shown in Scheme 14.[96] The most fascinating part of this investigation was that a second equivalent of base (amine **2**) was needed to facilitate reaction completion by forming an amino complex **48** with the Lewis acidic catechol.

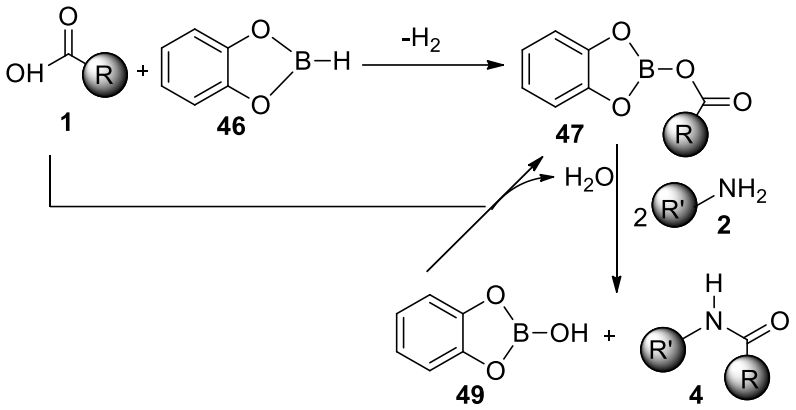


Scheme 10. Ganem's Catechol based amide condensation

Ganem concluded that catecholborane was the most potentially useful condensation agent among all the other boron compounds tested. The leaving group resulting from the intermediate **47**, *i.e.* benzo[*d*][1,3,2]dioxaborol-2-ol, **48** has a low propensity towards disproportionation forming non-nucleophilic products.

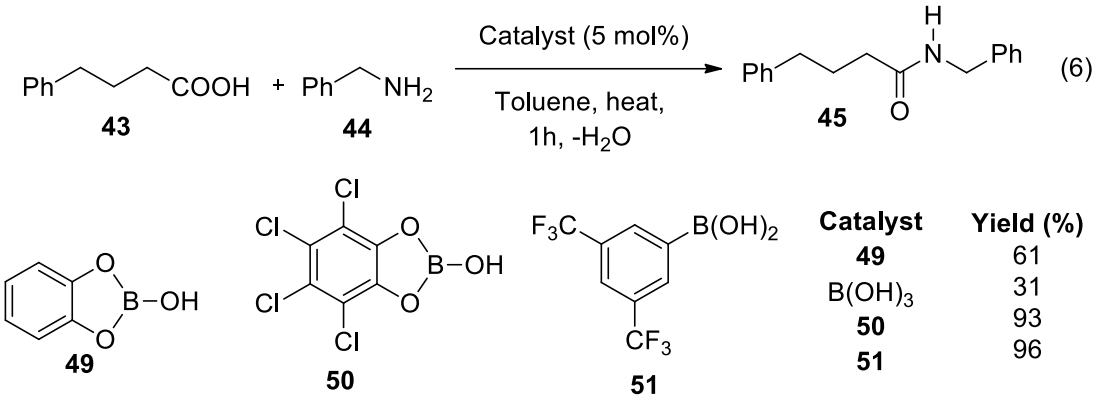
The major advantage of this process is the generation of relatively electron deficient borate intermediates having high reactivity, which resists unwanted side-reactions. The addition of suitable substituents on the catechol ring gives an opportunity for developing a catalytic application, and hence, increases the versatility of this process. However, the stoichiometric use of catecholborane and inability of the intermediate **48** to undergo dehydration to reform an acyloxycatecholate ester **47**, makes its use difficult as catalyst. Yet, it can be an effective amidation agent in condensing some chiral active amino acid derivatives like *N*-benzoyl-*L*-leucine.[98] In addition, resin bound catecholborane has been developed by Wang,[99] resulting a modest yields of amides compared to the Ganem procedure.

Although the Ganem process has been claimed to be atom uneconomic, it has become significant when the Ishihara group[100] invented a catalytic system based on the original reaction, where the catecholborate ester **49** formed reacts further with carboxylic acid **1** with the loss of water and reforms the active acylating agent **47**. The process is outlined in Scheme 11.

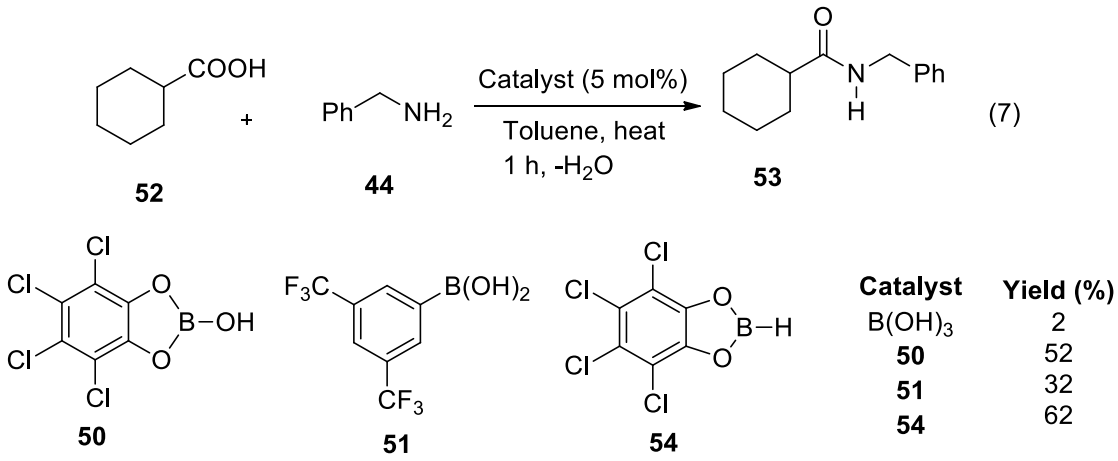


Scheme 11. The catalytic process developed by Ishihara *et al.*[100]

Furthermore, the enhancement of the Lewis acidity of boron by including chlorine or fluorine atoms in the catechol ring has been demonstrated and increases the catalytic activity. For example, chlorocatechol borate **50** or 3,5-bis(trifluoromethyl)phenylboronic acid **51** are effective amidation catalysts as shown in Equation 6.[100,101]



Using catalyst **50** is slightly less efficient than **51** which is more Lewis acidic. However, for more sterically hindered acids and amines like cyclohexanecarboxylic acid **52** and benzyl amine **44**, catalyst **50** was more efficient than **51** (conversion is 52% and 32% respectively) (Equation 7).

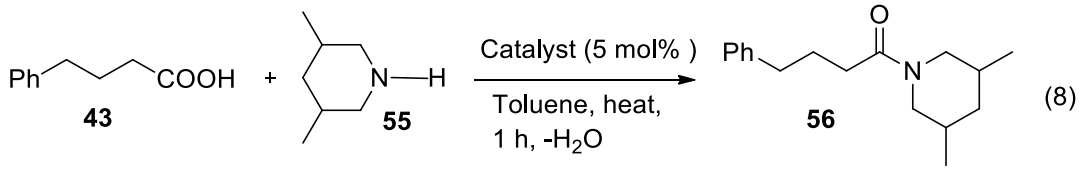


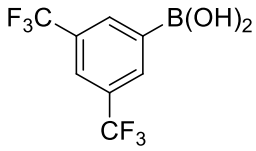
The use of 5 mol% 4,5,6,7-tetrachlorobenzo[d][1,3,2]dioxaborol **54** in this reaction afforded higher yield (62%) than other catalysts. These catalysts are also reasonably effective at condensing small aliphatic carboxylic acids, however, they are more efficient with larger and more functionalized substrates, like *N*-protected alanine (conversion is 90%) using 5 mol% catalyst for 24 hours refluxing in toluene or *o*-xylene. Moreover, since boric acid is a readily available and cost-effective, catalyst **50** can be prepared economically.

B) Boronic Acid Catalysis: Advancements in Boron Reagents

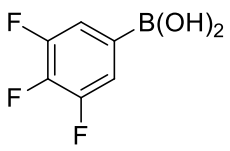
Benzeneboronic acids having electron withdrawing groups at the *meta*- or *para*-position are highly effective for the direct amide condensation in less polar solvents like toluene or

xylene**.** This was first reported by the Ishihara and Yamamoto[102] group in 1996. They found that the advantage of these types of catalyst was the low sensitivity towards water, acids or bases. They revealed that the condensation of 4-phenylbutyric acid **43** and 3,5-dimethylpiperidine **55** in refluxing toluene with 5 mol% of catalyst 3,4,5-triflurobenzeneboronic acid **57** and 4Å molecular sieves to remove water, gave yield of 74% of amide **56**, whereas with 3,5-bis(triflurомethyl)benzeneboronic acid catalyst **51**, 56% of amide **56** within one hour. This yield was dramatically reduced when unsubstituted benzene boronic acids (only 23% conversion) or in the uncatalysed reaction (< 2% conversion) (Equation 8) were used.





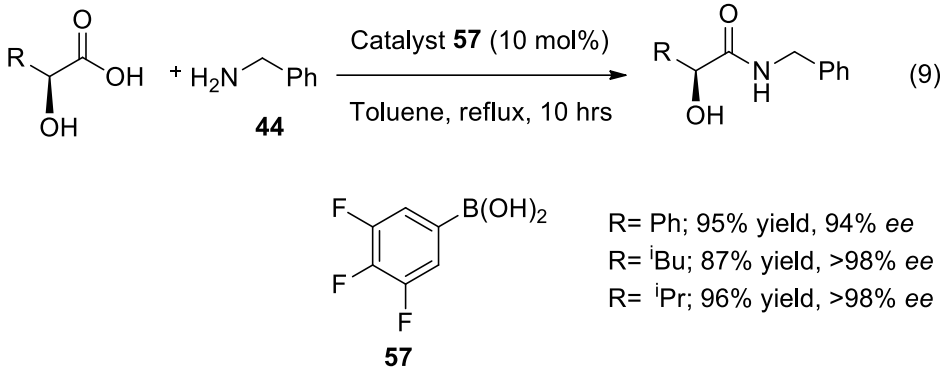
51



57

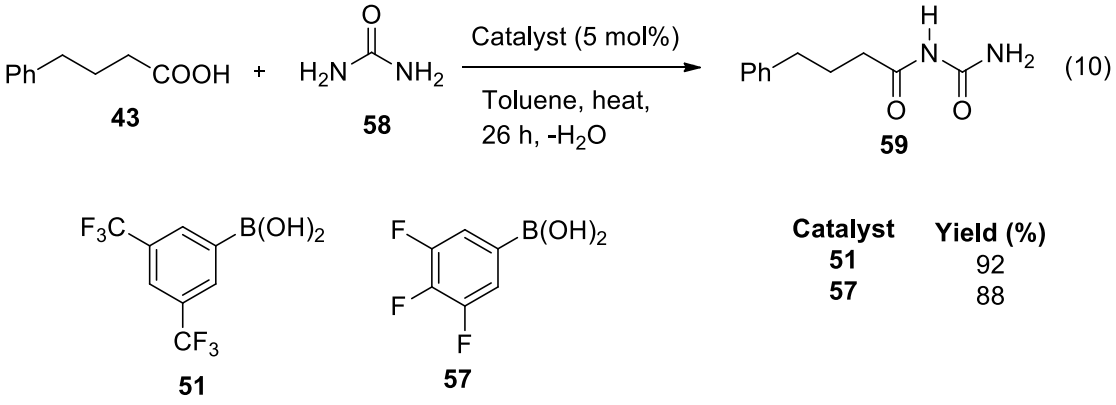
Catalyst	**Yield (%)**
51	56
57	74

Even 1 mol% catalyst **57** under the same conditions, condensed 4-phenylbutyric acid **43** and benzylamine **44**, giving a yield 96% of amide within 18 hours, and 99% amide over 16 hours, with the same acid and piperidine **55**. The catalyst **57** also proved to be effective for the reaction of secondary amines and aromatic substrates when refluxing in toluene. However, in some cases, high temperatures were needed, *e.g.* for aniline, the reaction was condensed in refluxing mesitylene (b.p. ~ 165 °C) to afford the corresponding amide in high yield with good purity. In some cases, the enantiomeric purity of products was also appreciable.[102] For example, the catalytic amidation of optically active aliphatic *α*-hydroxycarboxylic acids with benzylamine proceeded with no measurable loss (<2%) of enantiomeric purity under conditions of reflux in toluene. However, slight racemization was observed in the case of (*S*)-(+)-mandelic acid (Equation 9).



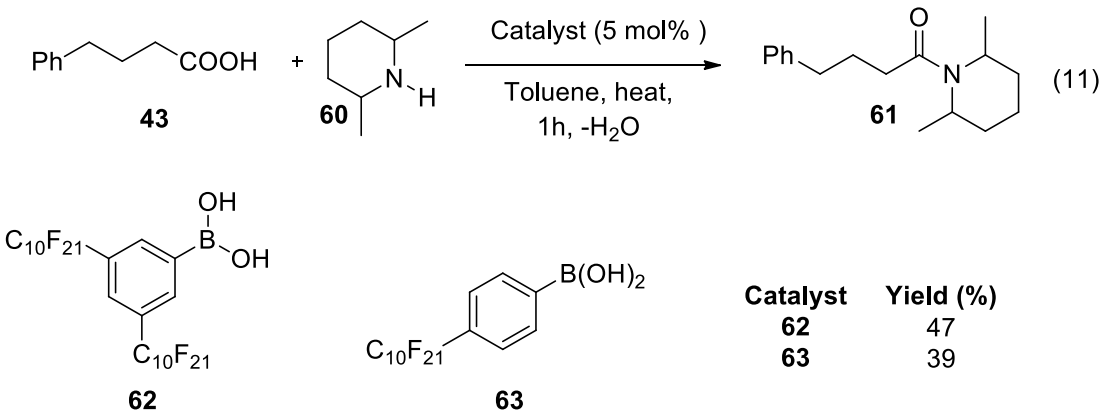
Further investigations by the same group revealed that triflurophenylboronic acid catalyst **57** also played an effective role in the direct polycondensation of carboxylic acids and amines.[103] With a loading of 10 mol% of this catalyst, the reaction between adipic acid and hexamethylenediamine yielded 89% of nylon-6,6 when refluxing in *o*-xylene (with 4Å molecular sieves). The number and weight average molecular weights of the polymer could be increased by a mixture of solvents (*m*-cresol: *o*-xylene, 1:3) while the yield was 85%.[102]

Recently Ishihara *et al.*[104] found that catalysts **51** and **57** were also effective in condensing carboxylic acids and non-nucleophile urea (Equation 10).



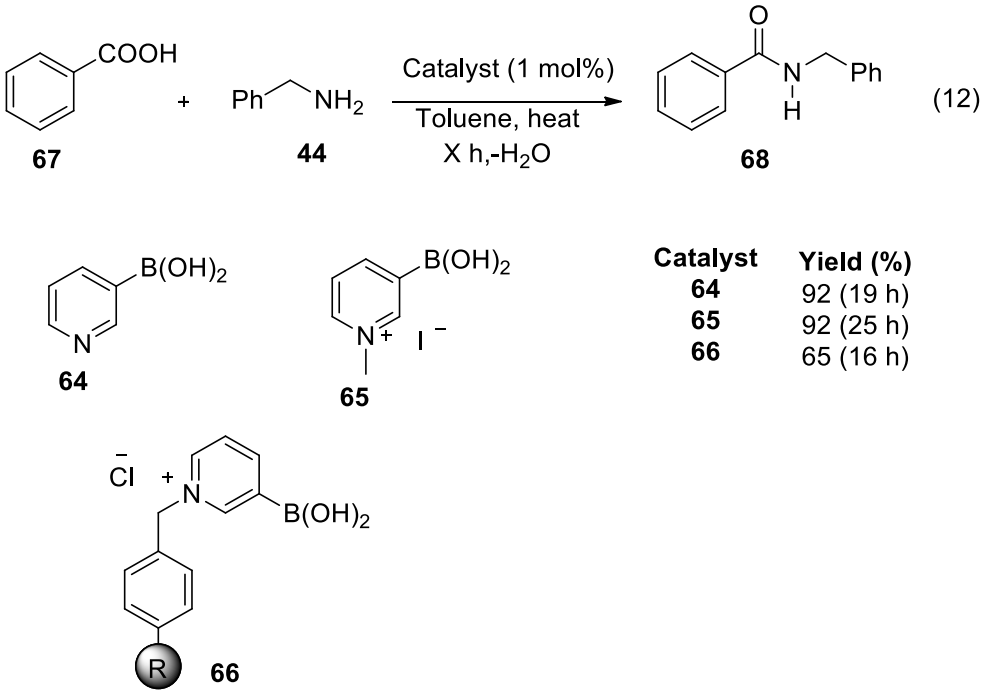
As a result of further investigation, in 2001, the Ishihara group[105] synthesised another two boronic acid catalysts 3,5-bis(perfluorodecyl)phenylboronic acid **62** and 4-(perfluorodecyl)phenylboronic acid **63**, which are less effective compared to catalysts **51** and **57**. However, they could be easily retrieved by extraction with a fluorous solvent, such as perfluoromethylcyclohexane.

The efficacy of these catalysts were compared using the reaction of 4-phenylbutyric acid **43** and 3,5-dimethylpiperidine **60** in refluxing toluene (4Å molecular sieves) with 5 mol% catalyst loading (Equation 11).

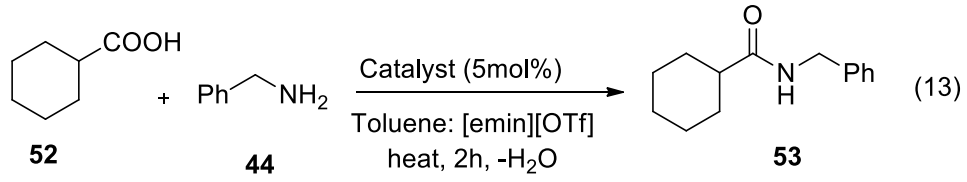


Using the more reactive benzylamine, rather than 3,5-dimethylpiperidine **60**, only 2 mol% of the catalyst **62** afforded a yield of 99% over 4 hours with 4-phenylbutyric acid **43**. Again, the efficacy of the catalyst **62** was tested in a mixture of solvents, o-xylene:xylene: perfluorodecalin (1:1:1) over 12 hours under reflux with azeotropic removal of water. It was found that only 3 mol% of the catalyst was required for the reaction of cyclohexanecarboxylic acid and benzylamine to afford >99% of the corresponding amide. An attempt to recover the catalyst from the fluorous phase was found to be successful (98% yield), even following recycle for the five times, the reactivity of the catalyst was good.[105] Hence, efficient solvent recycling is necessary for the fluorous solvent which are used to recycling the fluorinated catalysts.

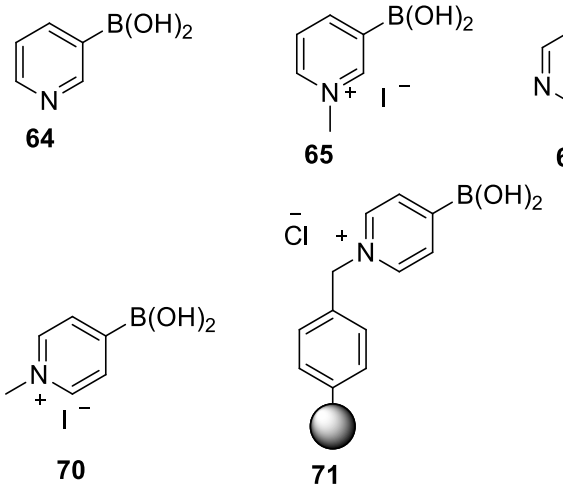
The development of fluorinated catalysts for direct amide formation has given a new dimension to direct amidation. However, more attempts at reducing the reaction temperature, along with increasing catalytic activity has led to the development of boronopyridinium salts as catalysts in direct amidation.[106] In fact, their application in direct amidation in polar solvents, like anisole, acetonitrile or *N*-methylpyrrolidinone, was anticipated.



In 2001, Wang and co-workers[107] promoted the use of two catalysts based on the pyridine ring: *i.e.* pyridine-3-boronic acid **64** and 3-borono-*N*-methylpyridinium iodide **65**. They followed the condensation of benzoic acid **67** and benzylamine **44** in toluene (Equation 12) (4Å molecular sieves) with 1 mol% of catalyst loading. The results were impressive; catalyst **64** yielded 92% of amide **68** in 19 hours, whereas the catalyst **65** afforded the same amount in 25 hours. Meanwhile, a polystyrene supported pyridinium salt-based catalyst **66** analogous to catalyst **65**, was also found to be very effective to yield 95% amide (Equation 12) **68** in 16 hours with only 1 mol% catalyst loading and 96% in 8 hours with 5 mol% loading of catalyst **66**. Moreover, the catalytic activity remained quite good after repeated use of the catalyst. This result emphasised the possibility of reduced reaction times and better yields by increasing the catalyst loading up to 5 mol%.[107]



52 44 53



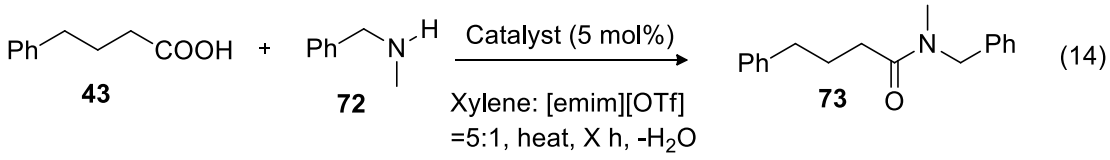
64 65 69 70 71

Catalyst	Yield (%)
64	43
65	54
69	8
70	59
71	59

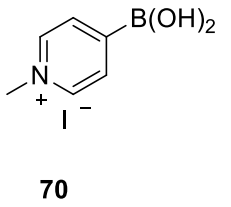
Further research on pyridine or pyridinium analogous catalysts was reported by Ishihara *et al.*[106] In 2005, they have developed catalysts **69-71** among which, **70** was found to be effective in direct amidation in polar solvent due to its greater thermal stability.[104,107] Catalyst **70** could be re-used if an ionic liquid-toluene biphasic solvent is used. A resin bound catalyst **71** was also tested as a heterogeneous alternative, which could be retrieved by simple filtration.[103] Ishihara *et al.* also proposed that catalysts **65** and **70** were more reactive than **64** and **69** due to being charged (Equation 13). The lowest yield (8%) was found (Equation 13) from the catalyst **69** due to its poor dissolution in the solvent system employed (5:1, toluene:1-ethyl-3-methylimidazoliumtrifluoromethanesulfonate). The thermal stability of the catalysts **69-71** was also investigated by heating them for several hours at 120 °C in DMF. After heating, catalyst **70** turned into a yellow precipitate of dodecameric derivative of **70** (denoted by $\mathbf{70_d}$), which was confirmed by the X-ray diffraction studies. The catalytic activity of **65** and $\mathbf{70_d}$ were also compared by applying them in the condensation reaction of 4-phenylbutyric acid **43** and benzylamine **44** in toluene and it was found that catalyst **70** was more effective than its derivative $\mathbf{70_d}$. Their activity could be improved by changing the solvent system to 5:1, toluene:1-ethyl-3-methylimidazolium trifluoromethanesulfonate,[emim][OTf]. It appeared that the change in solvent polarity facilitated the removal of water, and hence, played a significant role in improving the yield of the direct amide formation. It was also revealed that the catalyst **70** could easily be re-used

with no loss of activity from the biphasic solvent system after extracting of the product with ether, whereas this was not possible with the catalyst **62** without further extraction.

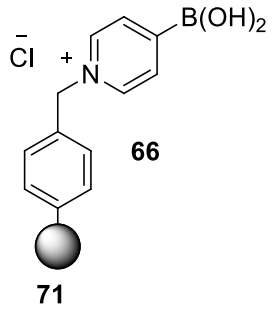
It also appeared that catalyst **70** worked well with more functionalised substrates such as conjugated carboxylic acids and aromatic substrates. This was further facilitated by changing the toluene in the biphasic solvent to *o*-xylene for more difficult amidations (Equation 14). On the other hand, through repeated use, catalyst **71** did not lose its catalytic activity, rather having a high level of activity even in the absence of biphasic solvent system since the polymeric support resisted the dodecamerization. With a 5 mol% loading, catalyst **70** and **71** gave 95% and 92% yield in the condensation of 4-phenylbutyric acid and *N*-benzylmethylamine within 18 and 20 hours (Equation 14) respectively.



(14)



70



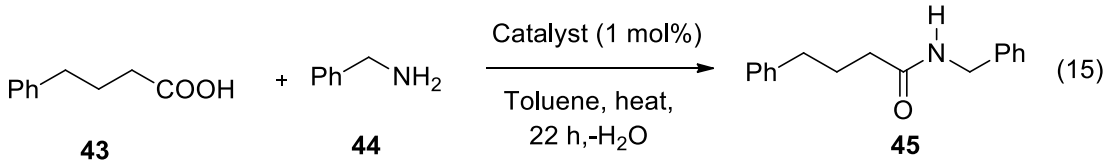
71

Catalyst	Yield (%)
70	95 (18h)
71	92 (20h)

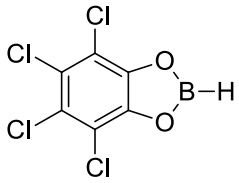
1.4 Comparative Studies of Catalysed and Uncatalysed Direct Amidation (Use of Bifunctional Catalysts)

Due to the possible formation of ammonium carboxylate salts (Scheme 1), direct uncatalysed amide formation has traditionally been viewed as an unlikely reaction. Nevertheless, there are some surprisingly easy uncatalyzed direct amide formation reactions.[108,109,110] For instance, Suzuki[110] reported the direct condensation of linoleic acid and 2-phenylhexylamine in an azeotropic xylene reaction medium giving a conversion of 86% in 55 hrs.

A systematic comparative study of the catalysed and uncatalysed direct amide formation reactions were carried out by Whiting *et al.* in 2006.[96] Using kinetic studies, they showed that some direct amidations could occur at moderate temperature, even in the absence of a catalyst, however, these reactions were extremely substrate dependent, *e.g*. the thermal or uncatalysed condensation of benzylamine **44** with 4-phenylbutyric acid **43** refluxing in toluene (3 Å sieves) afforded an yield of *ca.* 60% within 22 hours, and in presence of boric acid or catalyst **57**, **75**, or the newly developed bifunctional catalyst *ortho*-*N*,*N*-di*iso*propylbenzylaminoboronic acid **76** showed slight improvements under the same reaction condition (yield 65-80%) with 1 mol% loading (Equation 15).

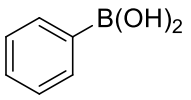


43 **44** **45**

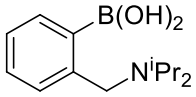


54

Catalyst	Yield (%)
no catalyst	60
$B(OH)_2$	73
54	80
75	78
76	65



75

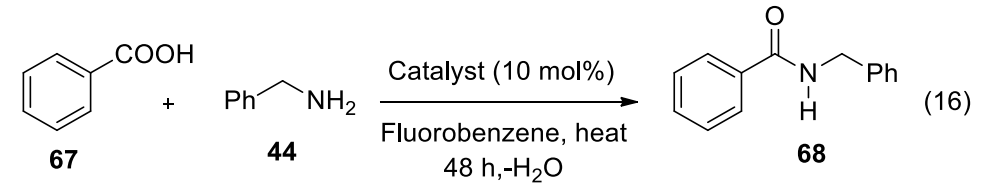


76

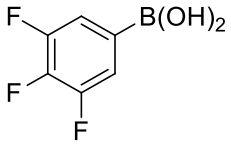
Likewise, the condensation between 4-phenylbutyric acid **43** and 4-phenylbutylamine also showed substantial thermal reaction resulting in 70% yield within 22 hours and insignificant enrichment of yield (85-100%) was found upon use of the same catalysts. This indicated that these reaction conditions were more favourable for those thermal reactions in which were substantially less aggressive. Again, it was found that under the same conditions, benzylamine **44** and benzoic acid **52** were poorly catalysed by most of the catalysts mentioned above, except for boric acid and bifunctional catalyst **76** (yield 70% and 40%, respectively) over 22 hours with a catalyst loading of 1 mol% catalyst.

The Whiting[97] group re-examined each of the condensation reactions at a reduced temperature to lower the thermal contributions to the product, in order to differentiate the catalytic effects of the uncatalysed reactions. They preferred to use fluorobenzene (b.p. ~85

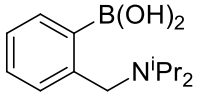
°C) instead of toluene (b.p. ~110 °C) which allowed them to evaluate the better catalyst. They found that for the highly reactive substrates, *e.g.* 4-phenylbutyric acid and benzylamine, the uncatalysed reaction achieved moderate yield (60%) within 24 hours and respectable yields (80-85%) when the same reaction was done with catalysts. Thus, catalysts had little effect on the yield as well as the reaction rate upon these highly reactive substrates. However, for intrinsically less reactive substrates, catalysts displayed a profound improvement in yield; especially the bifunctional catalysts like **76**, which showed greater effectiveness (Equation 16).



67 **44** **68**

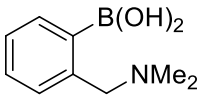


57



76

Catalyst	Yield (%)
no catalyst	0
Boric acid	40
57	65
76	80
77	58

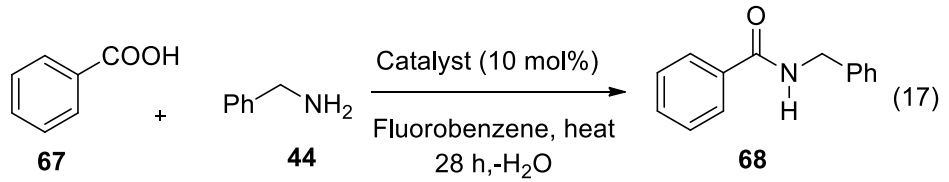


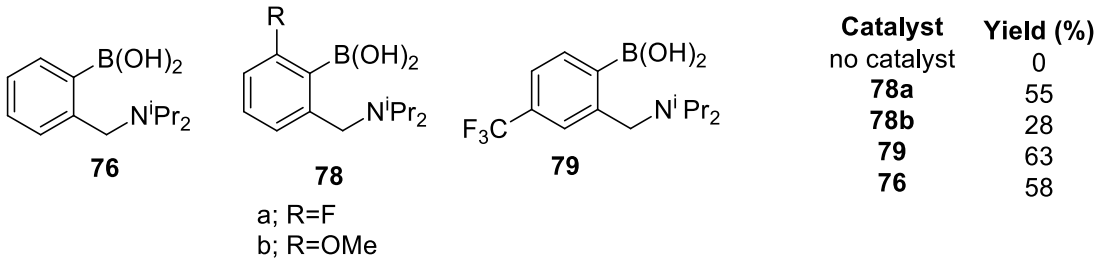
77

The final observation was that bulkier and more basic catalysts were suitable for less hindered and less reactive acid and amine amidations, whereas more Lewis acidic catalysts, like **57**, are best for the reactive substrate amidations.[97]

1.5 Effect of Aryl Substitution upon Boronic Acid Catalysts

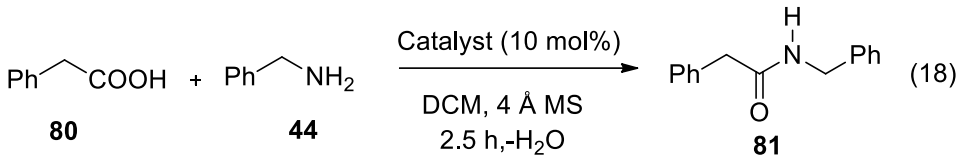
Recently, the effect of aryl substituent has been further elucidated by Whiting *et al*,[96] by studying Lewis acidity of the boronic acid catalysts for amide formation by the inclusion of electron-withdrawing and donating groups on the aryl ring. This led them to synthesise the catalysts **76** and **77**, which were examined under the following reaction conditions (Equation 17).

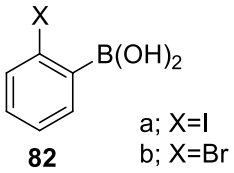




Catalyst	Yield (%)
no catalyst	0
78a	55
78b	28
79	63
76	58

It was found that the inclusion of an electron-withdrawing group in the *para*-position (**79**) increased the reaction rate relative to the unsubstituted catalyst (**76a**), whereas the *ortho*-substituted catalyst **78a** caused a reduction in rate. On the contrary, the inclusion of an electron-releasing group (**78b**) caused a large reduction in reaction rate indicating that a more Lewis acidic boronic acid was necessary to get higher reaction rates as well as better yields.





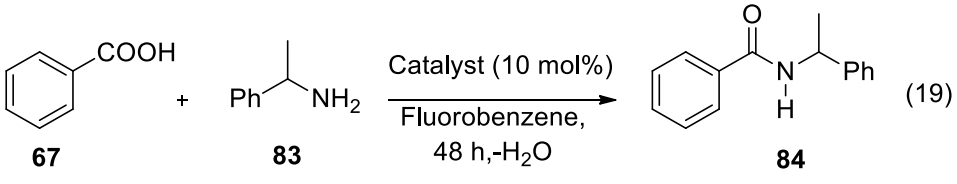
Catalyst	Yield (%)
82a	91
82b	76

In 2008, Hall *et al.* reported the direct synthesis of amides using some *ortho*-halogenated benzeneboronic acid catalysts **82.**[1] They found that an iodo-substituted catalyst **82a** was more reactive than the bromo-substituted **82b** in the direct amidation of 4-phenylacetic acid **80** and benzylamine at 25 ºC in DCM within 2.5 hours (Equation 18). Hence, these catalysts were more effective towards the more reactive carboxylic acids and primary amine condensations. The activity was still good enough with some cyclic secondary amines. The advantage of these catalysts was their recovery from the aqueous phase in high yield for re-use.

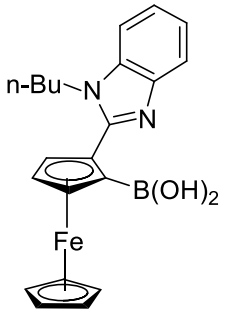
Finally, Hall and co-workers[1] revealed that *meta*- and *para*- substituted catalysts were less reactive than the *ortho*-substituted boronic acid catalysts, and they speculated that inductive effects, along with the electronic or structural effects of the halide groups played an important role in the reaction mechanism. However, recent investigation of these reactions through DFT calculations[111] have suggested the formation of H-bonding between the halogen atom and the OH group of boronic acids which gives a more complex reaction mechanism than the simple acyloxyboronate intermediate based process.

1.6 Asymmetric Direct Amidation

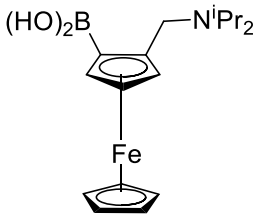
In view of direct amidation preferring elevated temperature processes, it appears almost impossible to apply this process for asymmetric systems and kinetic resolutions through amidation. The reason behind this is that at higher temperature, the energy difference between the diasteromeric transition states would be smaller and perhaps, the reagents could be degraded.[26] In spite of this, the first example of non-enzyme catalysed asymmetric direct amidation was reported by the Whiting group in 2008.[112] They synthesised a bifunctional ferroceneboronic acid derivative catalyst **85** which exhibited kinetic resolution using racemic α-substituted benzylamines through the direct amide formation with achiral carboxylic acids while refluxing in fluorobenzene. Thus, the condensation of benzoic acid **67** and α-methylbenzylamine **83** with a 10 mol% catalyst **85** afforded 21%, which was lower than other catalysts (**57** or **86**) (Equation 19).



67 **83** **84**



85



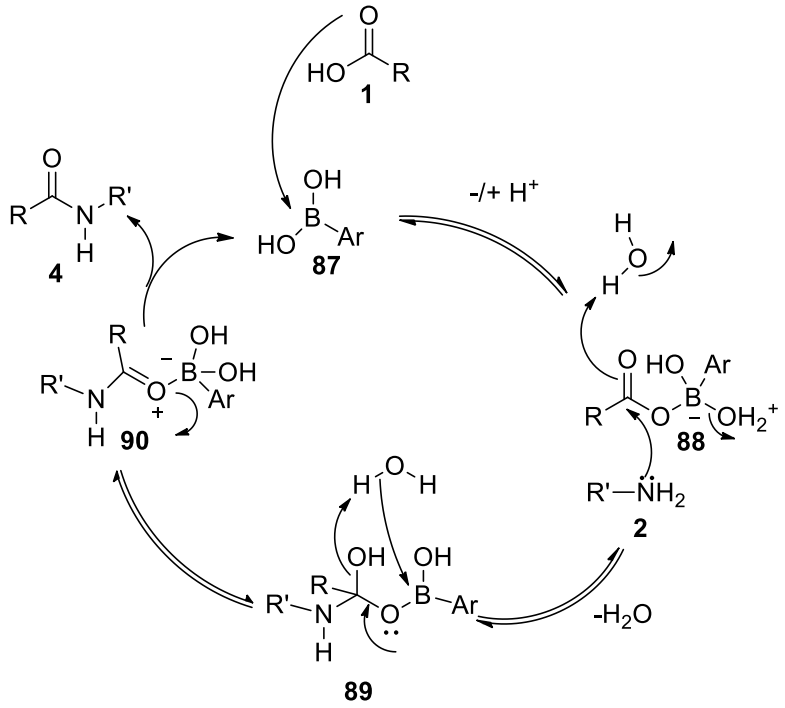
86

Catalyst	Yield (%)
no catalyst	0
57	52
85	21 (41% *ee*)
86	38 (0% *ee*)

Although the yield was low, it showed that the asymmetric induction was possible, giving the amide **84** in 41% *ee*. whereas the catalyst **86** was totally ineffective at kinetic resolution, despite a higher yield (38%). From a mechanistic point of view, it is still unclear how the catalyst **85** was effective. Again, the conversion was increased to 73% with the more reactive 4-phenylbutyric acid **43** under the same reaction conditions with catalyst **85**, however, unfortunately with a reduced 29% *ee.* This was due to competing proto-deboronation which gives boric acid catalysed direct amidation products which are racemic.[112]

1.7 Mechanism for Boronic Acid and Boric Acid Catalysis

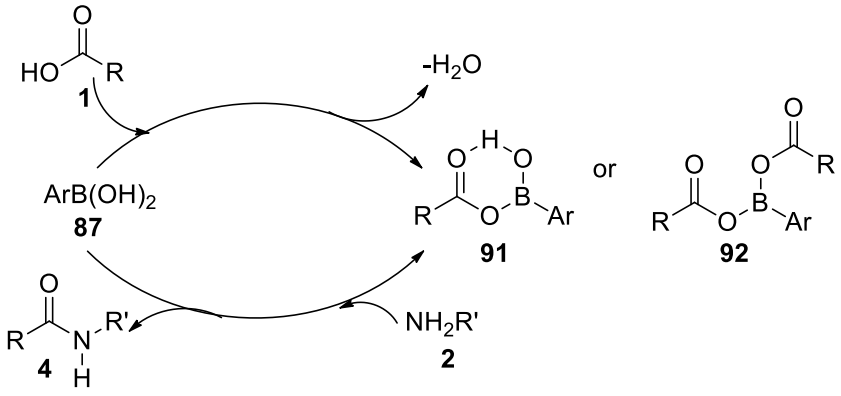
It is necessary to understand the mechanism of direct amidation for the fundamental understanding of the amide formation process. It also helps to design improved and effective catalysts. The actual mechanism of catalysis of direct amidation by boric or boronic acids is still under studied. Both the rate-determining step (RDS) and the exact nature of the acylating agent involved are far from clear. Theoretically, mono- di- or tri-acyloxyboron species are possibly formed in this step,[1,97,102,111] however, the most acceptable hypothesis to date was reported on the basis of the DFT calculations,[111] is outlined in Scheme 11.



Scheme 11. Proposed mechanism for boronic acid catalyzed direct amide formation

According to this mechanism, catalyst **87** reacts first with the carboxylic acid **1** to form an acyloxyboronate species **88** which remains closely associated with water and is accompanied by a concerted proton transfer with the formation of a good leaving group (water) attached to boron. Therefore, species **88** is the activated form of the carboxylic acid. Boron conjugation, as well as the intramolecular hydrogen bonding, extends the activation of the carboxylic acid. A tetrahedral intermediate **89** is formed by the subsequent attack of amine **2** from which the derivative **90** is generated, following a water-assisted dehydration step.[1,11] Finally, the amide is formed along with catalyst **87** by the dissociation of the species **90**. The rate-determining step is considered to be the dissociation of **89** to form the mono-acyloxyboronate complex **90**,[102] or it could be the dissociation of the ammonium salt **3**. Evidence shows that carboxylic acids having electron-rich groups (higher pKa) undergo more rapid direct amidation than their electron deficient analogues (low pK_a).[27] Hence, electron deficient carboxylic acids from less reversible ammonium salts, while electron rich carboxylic acids are more prone to form acyloxyboronate species, as they are more nucleophilic. Moreover, due to the higher Lewis acidity, the electron-deficient boronic acid catalysts are more reactive towards acylation, however, the electrophilicity of boron is not the only factor involved here.

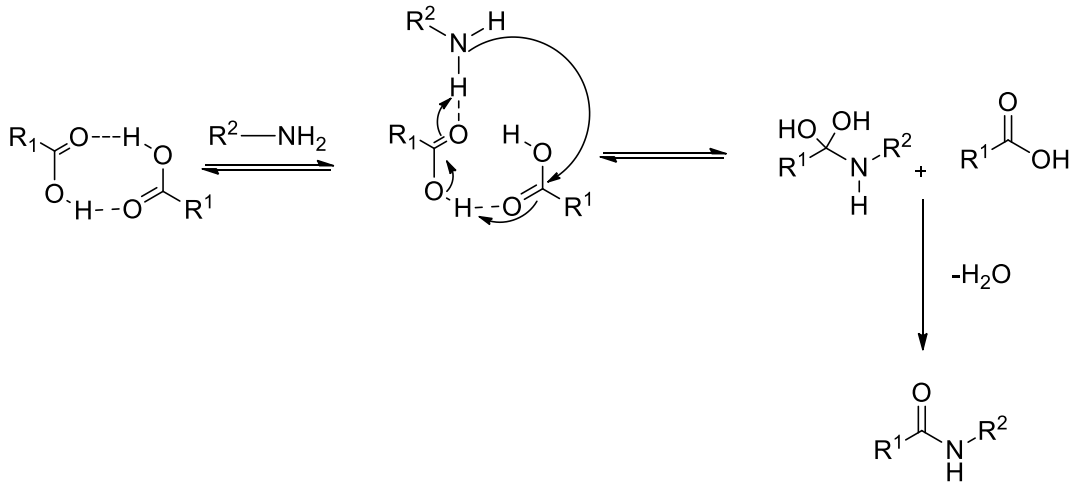
A recent theoretical study has been accomplished investigating the mechanism of this catalytic process by Wang *et al*,[113] (Scheme 12). They found that the constitution of the acyloxyboronic acid intermediates from the carboxylic acid and the arylboronic acid is kinetically able, but thermodynamically not favourable using more comprehensive calculation methods.



Scheme 12. Proposed mechanism for boronic acid catalyzed direct amide formation by Wang *et al*.[113]

Therefore, removal of water (as experimentally accomplished by using molecular sieves, for example) is imperative for overall conversion. Finally, C–N bond formation between the acyloxyboronic acid intermediates and the amine occurs immediately to generate the preferred amide product. In this process, the rate-determining step is the cleavage of the C–O bond of the tetracoordinate acyl boronate intermediates. Wang's[113] analysis indicates that the mono(acyloxy)boronic acid is the key intermediate. The high catalytic activity of *ortho*-iodophenylboronic acid is attributed to steric effects as well as the orbital interactions between the iodine atom and the boron atom.

In contrast, mechanism studies have been reported for the thermal amidation (without catalyst) at elevated temperatures and has been shown to be dependent on the acids and amines concerned (Scheme 13).[27,96] Experimental and computational studies of the mechsnism of thermal amidation reaction by the Whiting group[27] in nonpolar solvents revealed a correlation between the acidity of a carboxylic acid and reactivity.



Scheme 13: Proposed mechanism for direct thermal amidation

Stronger acids were found generally unreactive, due to the high degree of ammonium carboxylate salt formation. The reactivity of the amine component was thought to be due to a complex balance of steric and electronic effects and so the trends in the reactivity were more difficult to explain. On the basis of computational studies, they proposed that the key step of

the reaction mechanism was nucleophilic attack of the amine on a hydrogen-bonded carboxylic acid dimer (Scheme 13).[27]

1.8 Conclusions

Considering the long history of direct amide formation reaction, it is notable that to date, there have been major developments in exploring novel and more efficient amidation reagents. Yet, very few have resolved the relative reactivity of different combinations of carboxylic acids and amines. Moreover, reviewing all the published literature, it is noteworthy that there is still an incomplete understanding of the mechanisms involved for both the uncatalysed and catalysed direct amide formation reactions. This provides opportunities for the chemical community to carry out more comprehensive studies. Detailed basic kinetic and thermodynamic studies of direct amide formation are needed for catalyst design. Not only that, the discovery of these mechanistic details will surely lead to new applications, including larger scale industrial process applications. Accordingly, there still remains the need for the development of clean, sustainable processes for direct amidation, which work under ambient conditions.

Chapter 2: Objectives

2.0 Aim of the Study

From the history of amide synthesis, it can be seen that direct amide formation is still little explored[26] and current processes for direct amidation are still in need of improvement in terms of art and greenness. The major disadvantages of current processes include high reaction temperatures, scarcity in general substrate tolerence, narrow solvent compatibility and lack of high catalytic activity. Apart from these, with the growth of 'Green Chemistry' concepts, high yield with high atom efficiency, as well as reduced 'E-factor', are now desirable in this transformation. Limited solutions to this problem have been demonstrated by the adoption of boronic acids and boric acid as catalysts for the direct condensation of carboxylic acids and amines, as discussed in Chapter 1.[31,39,45,46,48,50]

The primary aspiration of this research was to design a cleaner synthetic route for direct amide formation as it has become a central goal of many chemical companies, as well as pharmaceutical industries. Investigations into this area started with the development of mild reaction conditions for the direct amidation reaction with known arylboronic acid catalysts in different model reactions, comparing their activities with both reported and potential new organometallic catalysts (Zr and Fe based). It was crucial to screen new catalysts under identical reaction conditions and this study included a systematic evaluation of solvent, temperature and catalyst, *i.e.* ambient reaction conditions. A further aim was to find the scope of this new approach in direct amidations of amino-acid derivatives and other biologically active targets, in order to develop a more economical route to bioactive amides which to date has been both little used or explored.

The second aim of this research was to examine the synergistic effect of two catalysts, *i.e.* 'Cooperative Catalysts', in direct amidations, and particularly for less reactive acid-amine combinations. The real applicability of novel cooperative catalysis in industry was explored by applying this approach in some commercially important syntheses. Further mechanistic investigations, by following the direct amidation with the real time monitoring technology (React-IR and HPLC), were also a part of the study.

The design and synthesis of new catalysts for direct amide formation, which could operate under ambient conditions, was another aim of this research and was to follow from a better

understanding of the mechanism. The role of H-bonding in amide bond formation with unreactive acids towards the amine to form amide was attempted. In order to accelerate the catalytic activity, the use of a potential catalyst promoter in the direct amidation reaction was to be examined. Improvements in catalysis activity or alterations in catalyst would need further study so that the direct amide formation could become a common tool for a wide range of carboxylic acids and amines partners.

Chapter 3: Direct Amide Formation at Reduced Reaction Temperature

3.0 Introduction

The direct thermal amidation reaction is often insufficient at lower reaction temperatures to effect reaction and hence, the direct amide formation has historically been done under higher temperature conditions.[1] However, the discovery of many stoichiometric and catalytic boron compounds have reduced reaction temperatures considerably,[26] under which the direct amide formation runs, making the reaction more environmentally friendly. Consequently, the development of improved and novel catalytic approaches based on boron continues to be a challenging pursuit for synthetic chemists.

As already described in the literature review (Chapter 1), clear steps have been followed by the scientific community in the direction of amide formation and with boron based catalysts,[1,96,97,100-106,112] a renaissance in this area has been triggered. In the last few years, the most developed and significant examples of direct amide formation have been found with boric acid or arylboronic acids, especially having electron withdrawing substituents.[26] Due to their high tolerance to water, acids and bases,[102] these types of catalysts could be considered one of the most potentially interesting areas of research in the arena of direct amidation at reduced temperature.

Later, the direct transformation of amines and carboxylic acids into amides involving bifunctional catalysts (*e.g.* with amino-boronic acid catalysts) has been demonstrated and was also proved their potential at lower temperature (85 °C) for amide formations.[94,108,109] A good number of reports have recently been published on direct amidation using aryl boronic acids including bifunctional boronic acids as catalysts.[96,97] Further investigations revealed the potential of such the amino boronic acid catalysts (*e.g.* catalyst **85**) for the asymmetric direct amide formation *via* kinetic resolution of amines.[93] However, further applications of this important class of catalyst are still underdeveloped.

The objective of this part of the project was to achieve more general, more widely applicable and useful results with these types of aryl boronic acids, especially at lower temperature. Apart from the aryl boronic acid catalysts, the efficiency of some inorganic and

organometallic catalysts (which have recently been reported as potential catalysts for direct amidation[75,79,80-87]) was also compared at low temperature, in order to expand their applicability in this area and to understand the relative reactivity of such systems. To carry out these reactions, different amidations were followed using the conventional refluxing method, as well as the Soxhlet-based water removal. In addition to these, the amide formation was also examined by React-IR in order to get a clearer idea and insight into the amide formation reaction mechanism.

3.1 Review of Catalytic Activity

In consideration of lowering the use of high temperature conditions and identifying the catalysts that would function under more ambient conditions, a systematic evaluation of the catalytic activity of known catalysts (see Table 1) was carried out, with two model reactions (Equations 20 and 21) in different solvents and at different temperatures.

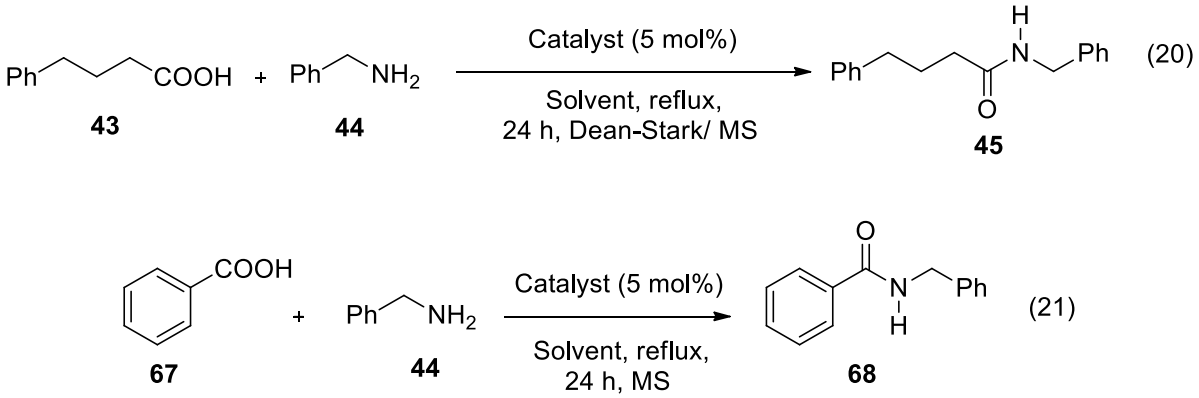


Table 1. Reaction conditions applied in model reactions

Solvents	**Temp. (°C)**	**Catalysts**
Toluene	110	*o*-Nitrophenylboronic acid
(Dipole moment 0.36 D)		*p*-Nitrophenylboronic acid
Fluorobenzene	85	Zirconium(IV) chloride ($ZrCl_4$)
(Dipole moment 1.66 D)		Iron(II) trifluoromethanesulfonate [$Fe(OTf)_2$]
THF	65	Iron(III) trifluoromethanesulfonate [$Fe(OTf)_3$]
(Dipole moment 1.63 D)		Gallium(III) trifluoromethanesulfonate [$Ga(OTf)_3$]

Evidence[1,111] shows that with an increase in the Lewis acidity of aryl boronic acids by the insertion of electron withdrawing groups, the generation of mono- or di-acyloxyboron species (intermediates) is probably favoured, in which subsequently enhances their amide formation properties. Therefore, introduction of an electron withdrawing group, like $–NO_2$, may increase the catalytic activity of different aryl boronic acids. In addition, evidence also shows the crucial importance of the *ortho*-position of the aryl ring, as the *ortho*-substituent can interact with the Lewis acidic boronate group. Hence, *o*-functionalized arylboronic acids may be more efficient than the *meta*- or *para*-substituted in amidation reactions, even at room temperature.[1,111] In pursuit of this strategy, *o*-nitrophenylboronic acid and *p*-nitrophenylboronic acids were investigated as potential catalysts in direct amidation reactions both being commercially available and cheap.

Moreover, during the last few years the use of catalysts based on first row transition metal iron in the direct amidation have drawn attention as more economical and environmentally benign protocol as discussed in Chapter 1 (Section1.3.2). So the catalyst based on iron(II/III) was chosen. Iron(II/III) trifluoromethanesulfonate ($Fe(OTf)_{2/3}$) has been well known for its catalytic activity in different organic reactions.[114] But it was not used before in the direct amidation reaction. So for the first time iron(II/III) trifluoromethanesulfonate ($Fe(OTf)_{2/3}$) was applied here in the direct amide formation. Due to have some similar properties like iron, gallium(III)trifluoromethane sulfonate was also investigated here as catalysts which has never been used before in the direct amide formations.

The solvent is an important factor in direct amidation, as reported in previous work.[1] The practice of using non-polar solvents (*e.g.* toluene, heptanes, xylene *etc.*) in amide formation reactions has a long history. Further, the use of polar solvents (like anisole, acetonitrile, *N*-methylpyrrolidinone *etc.*)[3] has given a new dimension for direct amide formation that mainly extends the use of reduced reaction temperatures and times to access better yields, but only in certain cases. Based on this idea, three solvents, including polar and non-polar solvents (with higher and lower boiling points), were examined here under the same catalyst and temperature conditions to determine the importance of solvent polarity in the direct amide formation process (See Table 1).

Different drying methods were used for the removal of water from the reaction mixtures. The high temperature (at 110 °C) amidations were carried out under azeotropic reflux conditions (Dean-Stark procedure) to dry the reactions. On the other hand, direct amidations at 85 °C were achieved by using a Soxhlet refluxing method using pre-dried molecular sieves (4 Å) which were kept out of the reaction mixture by using the Soxhlet thimble containing the molecular sieves to remove the water from the reaction under reflux conditions. Typical refluxing with the pre-dried molecular sieves (4 Å) in the reaction mixture was used for the direct amidation reactions at 65 °C.

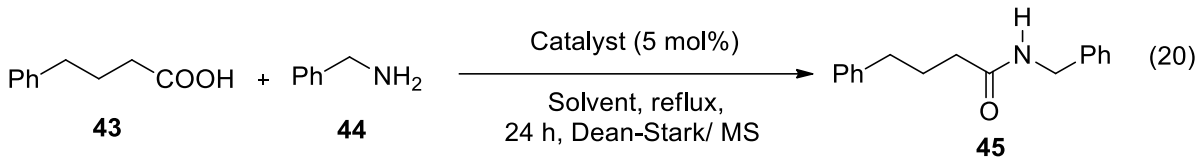
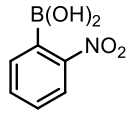
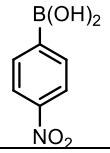


Table 2. Direct amidation[a] of 4-phenylbutyric acid **43** and benzylamine **44** to give amide **45**

Entry	Catalyst (5 mol%)	Catalyst no	Solvent	Drying method	Yield[b] of amide 45 (%)
1	No catalyst	-	Toluene	Dean-Stark	50
2			Fluorobenzene	4Å MS in the Soxhlet	65
3			THF	4Å MS in reaction	64
4		**1**	Toluene	Dean-Stark	71
5			Fluorobenzene	4Å MS in the Soxhlet	91
6			THF	4Å MS in reaction	86
7		**2**	Toluene	Dean-Stark	62
8			Fluorobenzene	4Å MS in the Soxhlet	81
9			THF	4Å MS in reaction	78
10	$ZrCl_4$	**3**	Toluene	Dean-Stark	91
11			Fluorobenzene	4Å MS in the Soxhlet	83
12			THF	4Å MS in reaction	85
13	$Fe(OTf)_2$	**4**	Toluene	Dean-Stark	96
14			Fluorobenzene	4Å MS in the Soxhlet	92
15			THF	4Å MS in reaction	88
16	$Fe(OTf)_3$	**5**	Toluene	Dean-Stark	97
17			Fluorobenzene	4Å MS in the Soxhlet	92
18			THF	4Å MS in reaction	89
19	$Ga(OTf)_3$	**6**	Toluene	Dean-Stark	59
20			Fluorobenzene	4Å MS in the Soxhlet	64
21			THF	4Å MS in reaction	75

[a]Reaction conditions: acid (2.86 mmol), benzylamine (2.86 mmol), solvent (20 mL), t = 24 h, [b]Isolated pure amide after recrystallisation.

Our initial attempts involved re-examining the effect of reduced reaction temperatures on the amidation using 4-phenylbutyric acid **43** and benzylamine **44** (Equation 20) in the presence of each of the catalysts (Table 1). The background thermal reaction (with no added catalyst) was also examined under the same conditions to compare with the catalysed reactions. The amidation protocol involved the direct reaction of amine **44** and carboxylic acid **43**, using a catalyst (5 mol%) in various dry solvents at different temperatures. Analytically pure samples of amide **45** were obtained by: 1) solvent removal after 24 hrs; and 2) acid-base extraction.

This method was slightly modified for the reactions which were carried out at 65 °C since molecular sieves (4 Å) were used in the reaction mixture as drying agent.

In order to remove the molecular sieves from the reaction mixtures, filtration was followed using a pad of Celite was followed by washing with EtOAc, before doing a conventional acid-base extractive workup. This procedure was equally efficient for the isolation of the product(**45**). Finally, pure amide product was obtained by recrystallisation from EtOAc/hexane and the results are given in Table 2. The results confirmed the high reactivity of 4-phenylbutyric acid **43** (pK_a 4.76) towards benzylamine **44** (ammonium pK_a 9.33). The relatively electron-rich carboxylic acid **44** was intrinsically more reactive towards acyloxyboronate formation, and hence, went through to amide **45** formation more readily. Also, the non-polar nature of the solvent seemed to disfavour the formation of the ammonium salt and hence, accelerated the formation of amide **45**. Under thermal conditions in anhydrous toluene over 24 hours, 50% pure amide **45** was isolated (Entry 1, Table 2) when a Dean-Stark trap was used for the removal of water from the reaction mixture. The yield rose to 64-65% (Entries 2-3, Table 2) when the refluxing temperature was dropped down to 85 °C or 65 °C using solvents like fluorobenzene or THF. This suggests that this specific direct amide condensation proceeds similarly in lower boiling solvents, but the odd increase in yield may very well be due to more efficient, and hence faster, water removal with the pre-dried molecular sieves employed directly in the reaction mixture. This idea is supported by the previous observations about the impact of water removal on reaction kinetics.[97]

The results of the purely thermal reaction were compared to reactions run with different catalysts under the same conditions. Notably, the addition of catalysts enhanced the reaction rate, and in particular, bifunctional boronic acid catalysts (*o*-nitrophenylboronic acid and *p*-nitrophenylboronic acid) were highlighted as promising catalysts for the reaction. The efficiency of these catalysts was better in refluxing solvents (*i.e.* fluorobenzene and THF) (Entry 4 to 9, Table 2), rather than in the less polar toluene. In comparison, fluorobenzene was only incrementally better than THF for amide **45** formations. However, in each case, *o*-substituted boronic acid exhibited higher activity than *p*-substituted examples, no matter which solvent was used (Entries 4-9, Table 2). This perhaps confirms the idea of the *ortho*-group participates in the amide formation reaction, as discussed by Hall and Marcelli.[1,111]

In addition to arylboronic acids, other metallic and organometallic, Lewis acidic materials (3-6, Table 2) have been employed for amidation reactions (Equation 20). More recently, Williams *et al.* and Adolfsson *et al.*[116,117] have found that zirconium tetrachloride ($ZrCl_4$) was a competent inorganic catalyst for the conversion of amides at high temperature with a high catalyst loading (20 mol%). To contrast with these reports, its catalytic activity, at reduced temperature, in other direct amidations was explored here. Hence, $ZrCl_4$ was applied in order to compare it to the standard amidation reaction of acid **43** and amine **44**. Only 5 mol% of $ZrCl_4$ significantly accelerated the reaction in toluene at high temperature (Entry 10, Table 2), which was consistent with the aforementioned reports.[116,117] At lower temperatures, the reaction was also favourable and afforded very respectable yields (83 and 85%, Entry 11 and 12, Table 2). This proves the potential of $ZrCl_4$ as a catalyst both at higher and lower temperatures. The success of this catalyst can be explained in light of several possible mechanisms related to the activation of the carboxylic acid **43** through several different co-ordination modes mentioned in the previous studies.[117] Hence, the acid **43** becomes electropositive enough for subsequent attack by the amine **44**. These features also reflect on the important compatibility of $ZrCl_4$ with both polar and non-polar solvents (Entry 10 to 12, Table 2) which opens up its utility for individual substrates. Furthermore, the toxicity of $ZrCl_4$ is low.

Recently, the increasing number of use of catalytic amounts of iron compounds in direct amidations indicates an increased interest in the use of this cheap, non-toxic metal in catalysis of direct amidation.[114] In continuation of exploring the catalytic activity of this early transition metal in direct amide formation reactions, iron(II) triflate was examined as a catalyst in direct amidation of carboxylic acid **43** and amine **44**. There was a clear indication of the yield enhancement of amide **45** (Entries 14-16, Table 2) using 5 mol% iron(II) triflate in Equation 20. Surprisingly, iron(II) triflate showed higher activity compared to both *o*-nitrophenylboronic acid and $ZrCl_4$, both at higher and lower temperature.

Since iron(III) is a stronger Lewis acid than iron(II),[114] iron(III) triflate was also tested in the same direct amidation reaction (Entries 16-18, Table 2). But the yield in this case was similar to the Fe(II) system and the differences in yields were not statistically significant, though there was a suggestion that the Fe(II) might be a superior catalyst at lower temperatures. Fig.

6 compares the yields of the two different Fe-based systems obtained from Entries 13-18, Table 2. All these results were repeated for two times.

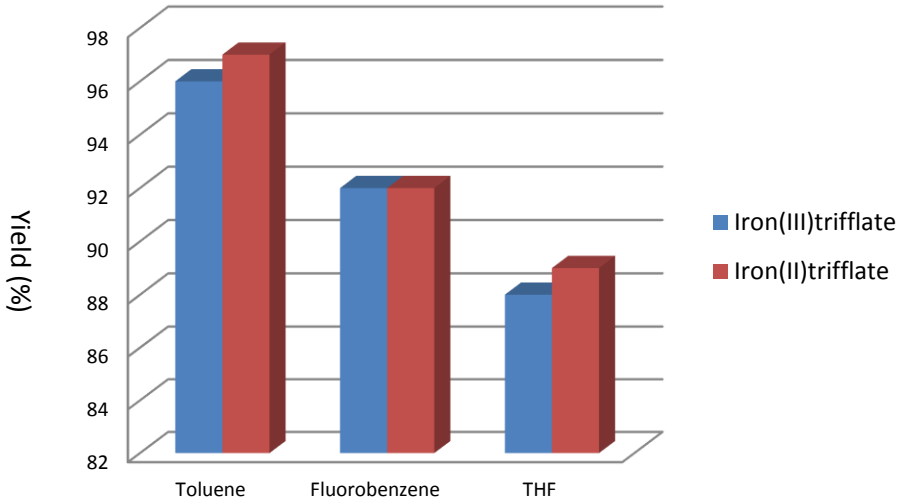


Figure 6. Comparison between iron(II) and iron(III) triflate as catalysts in Equation 2 (Entries 13-18, Table 2)

The use of $Ga(OTf)_3$ as a safe and stable, water-tolerant, Lewis acid has been exploited in many organic reactions.[118] Its remarkable catalytic properties were identified from its thermal, as well as aqueous stability and catalytic activity. Due to having similar properties like iron, $Ga(OTf)_3$ catalyst was therefore examined in the direct amidation of carboxylic acid **43** and amine **44**. The yields were quite satisfactory from 59% to 75%, though notably this catalyst was more efficient at low temperature (65 °C in THF) (Entries 19-21, Table 2). Although Ga(III) and Fe(III) salts behaved similarly in some cases,[119] in this amidation (Equation 19), their catalytic efficiency was different in different solvents. The isolated yields from Ga(III) were lower in comparison to those from the Fe(III) catalyst.

Subsequently, the same reaction conditions were applied for the direct amidation of benzoic acid **67** and benzylamine **44** in order to get a picture of the reactivity of these catalysts at reduced temperature using the inherently less reactive acid-amine combination. The results are shown in Table 3.

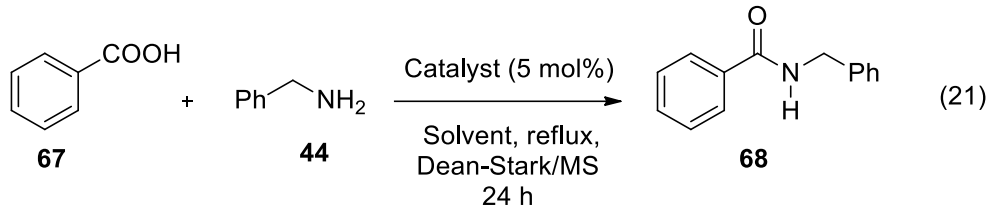
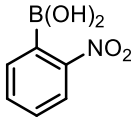
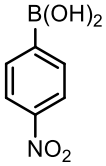


Table 3. Direct amidation[a] of benzoic acid **67** and benzylamine **44**

Entry	Catalyst (5mol%)	Catalyst no	Solvent	Drying method	Yield[b] (%)
1	No catalyst	-	Toluene	Dean-Stark	19
2			Fluorobenzene	4Å MS in Soxhlet	1
3			THF	4Å MS in reaction	No reaction
4		**1**	Toluene	Dean-Stark	89
5			Fluorobenzene	4Å MS in Soxhlet	23
6			THF	4Å MS in reaction	15
7		**2**	Toluene	Dean-Stark	19
8			Fluorobenzene	4Å MS in Soxhlet	13
9			THF	4Å MS in reaction	14
10	$ZrCl_4$	**3**	Toluene	Dean-Stark	29
11			Fluorobenzene	4Å MS in Soxhlet	7
12			THF	4Å MS in reaction	No reaction
13	$Fe(OTf)_2$	**4**	Toluene	Dean-Stark	51
14			Fluorobenzene	4Å MS in Soxhlet	30
15			THF	4Å MS in reaction	29
16	$Fe(OTf)_3$	**5**	Toluene	Dean-Stark	41
17			Fluorobenzene	4Å MS in Soxhlet	25
18			THF	4Å MS in reaction	16
19	$Ga(OTf)_3$	**6**	Toluene	Dean-Stark	36
20			Fluorobenzene	4Å MS in Soxhlet	27
21			THF	4Å MS in reaction	18

[a]Reaction conditions: acid (2.86 mmol), benzylamine (2.86 mmol), solvent (20 mL), t = 24 h, [b]Isolated pure amide after recrystallisation.

Previous calorimetric studies showed, in contrast to 4-phenylbutyric acid (pK_a 4.76), that benzoic acid was less reactive towards direct amidation with the amine **44** due to having a lower pK_a (4.19) and higher total heat output with benzylamine (60 $kJmol^{-1}$ for benzoic acid and 24 $kJmol^{-1}$ for phenylbutyric acid), which leads to the exothermic formation of the corresponding ammonim salt formation.[27] The ammonium salt was genuinely observed (a cloudy solution or white precipitate) as soon as the amine was added to the mixture of acid and catalyst, even in the room temperature. However, the salt gradually dissolved and a clear solution was observed as the reaction temperature elevated to reflux temperature.

As demonstrated by the results presented in Table 3, the background thermal reaction of benzoic acid **43** and benzylamine **44**, under the same reaction conditions, showed the same poor reactivity both at high and low temperature (Entry 1-3, Table 3). Even the solvent polarity did not affect the uncatalysed reaction rate much.

In the majority of catalytic direct amidations examined, poor yields were obtained (Table 3). Except *o*-nitrophenylboronic acid which afforded 89% isolated yield of amide **68** under toluene refluxing conditions over 24 hrs (Entry 4, Table 3). This indicates that both the higher refluxing temperature and the catalyst (*o*-nitrophenylboronic acid) have a profound effect on rate enhancement. In comparison with the *o*-substituted phenylboronic acid (Entries 4-6, Table 3), *p*-nitrophenylboronic acid(Entries 7-9, Table 3) was less reactive for the conversion to amide **68**, indicating again the importance of the *o*-position, irrespective of the solvent or temperature.

Despite the efficiency of zirconium(IV) tetrachloride in amide formation for highly reactive acid-amine combinations (Equation 21), it failed to prove efficient in forming the amide **68** both at higher and lower temperatures, and there was no solvent effect to improve the yields.

Likewise, both $Fe(OTf)_2$ and $Fe(OTf)_3$ were incapable of forming respectable yields of amide **68** under the standard conditions. Nevertheless, $Fe(OTf)_2$ afforded 51% of the corresponding amide in toluene by refluxing at an elevated temperature (Entry 13, Table 3). It did not work well also at lower temperature (Entry 14-15, Table 3). In order to raise the yield of these more challenging substrates, the amount of catalyst was increased to 10 mol% and despite the increase in the catalyst loading, the yield was only 55%. It was clear that this particular direct amidation reaction was most favourable at high temperature. Similarly, $Ga(OTf)_3$ was also

inefficient at forming any substantial amount of amide **68** under these reaction conditions, irrespective of the polar and less polar solvent system (Entry 19-21, Table 3).

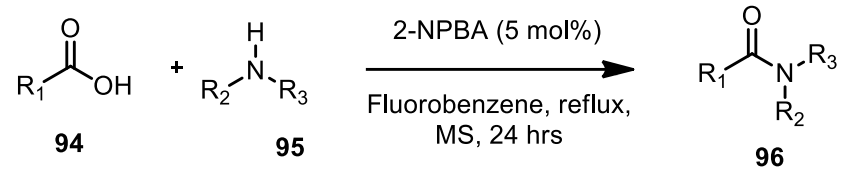
The catalyst screening at reduced temperature did uncover that *o*-nitrophenylboronic acid was one of the more promising catalysts again for direct amidations for both high and low reactivity acid-amines combinations. This extends the idea of using this particular aryl-boronic acid catalyst further in other direct amide formation reactions on more with diverse substrates, and also in wider synthetic applications.

3.2 Application of o-Nitrophenylboronic Acid

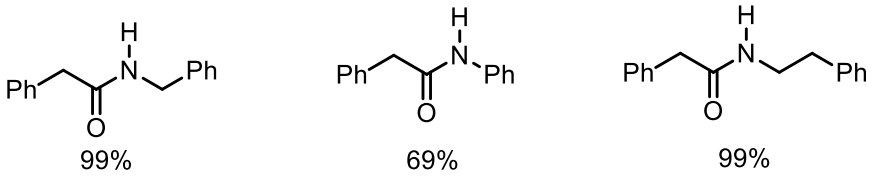
3.2.1 Direct Amidations with Diverse Acid-Amine Combinations

Having reviewed the catalyst screening and ambient reaction conditions with two model reactions of direct amidation at reduced temperature, the next stage was to investigate applications of the successful new catalyst, *o*-nitrophenylboronic acid, in diverse acid-amine direct amidations. To verify that the products are formed through 2-nitrophenylboronic acid catalysis, amidations of different substrates are shown in Table 4.

Table 4. Yields for the 2-nitrophenylboronic acid-catalysed direct amidation of different carboxylic acids and amines.[a]

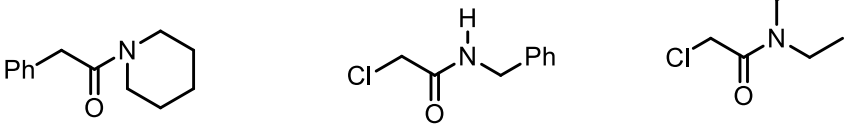


94 95 96



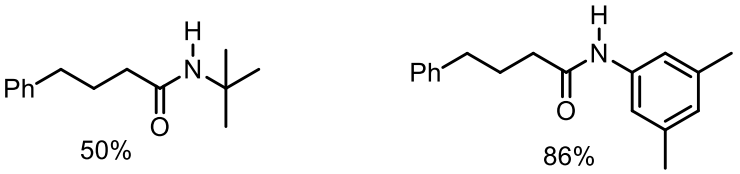
99% 69% 99%

1 2 3



90% 92% 47%

4 5 6



50% 86%

7 8

[a]Reaction conditions: acid (2.86 mmol), amine (2.86 mmol), solvent (20 mL), catalyst (5 mol%), T= 85 °C, t = 24 h, drying method: 4Å MS (in the thimble of Soxhlet extraction, [b]Isolated pure amide after recrystallisation.

The examples compiled in Table 4 demonstrate the versatility and scope of the new catalyst *o*-nitrophenylboronic acid in promoting direct amidations at fluorobenzene refluxing temperature (85 °C). The standard conditions were applied in fluorobenzene with the Soxhlet water removal containing 4 Å molecular sieves. The selection of amines and carboxylic acids used in the study included a range of different structures, both electron withdrawing or electron donating properties, a range of pK_a values in water, primary amines containing aromatic substituents, straight aliphatic chains, or branched and also secondary amines.

It was observed that carboxylic acids with low pK_as were not as efficient in the catalytic direct amidation with different amine substrates. For example, chloroacetic acid (pK_a 2.87)

was the least efficient at producing the corresponding amides (Entry 6, Table 4). On the other hand, phenylacetic acid (with a moderate pK_a value of 4.31) was highly reactive and produced the corresponding primary amides (Entries 1-3, Table 4) with different amines, including the less reactive aniline to afford a moderate yield (69%, entry 2, Table 4). Even with the cyclic amine (piperidine) it gave an excellent yield (90%) of the tertiary amide (Entry 4, Table 4). 4-phenylbutyric acid (pK_a 4.76) afforded moderate to high yield of the corresponding amides. For example, with the hindered 3,5-dimethylaniline, it produced 86% of the amide **8**.

Although primary amines were found to be suitable substrates for direct amidation with different carboxylic acids (Table 4, Entries 1-3, 5, 7, 8), cyclic and acyclic secondary amines also afforded the desired tertiary amides using 5 mol% *o*-nitrophenylboronic acid catalyst (Table 4, Entries 4 and 6). The amidation of phenylacetic acid and piperidine was efficient yielding the corresponding tertiary amide (90%, Entry 4, Table 4). Similarly, chloroacetic acid was excellent to afford the corresponding amide 92% with benzylamine (Entry 5, Table 4). However, with the chloroacetic acid and diethylamine, the yield was only 46% (Entry 6, Table 4).

These results provided clear testimony to the success of the new arylboronic acid catalyst, *o*-nitrophenylboronic acid, under low temperature conditions. Moreover, these catalytic direct amidations were operationally clean and straightforward. They employed equimolar amounts of acid and amine substrates, generating no by-products and affording pure amides after a simple acid-base extraction with the removal of any unreacted substrates or catalyst. This success led us further to investigate the efficacy of *o*-nitrophenylboronic acid in the synthesis of peptide analogous because these are particularly challenging substrates for direct amide formation.

3.2.2 Direct Amidations of Amino Acid Derivatives

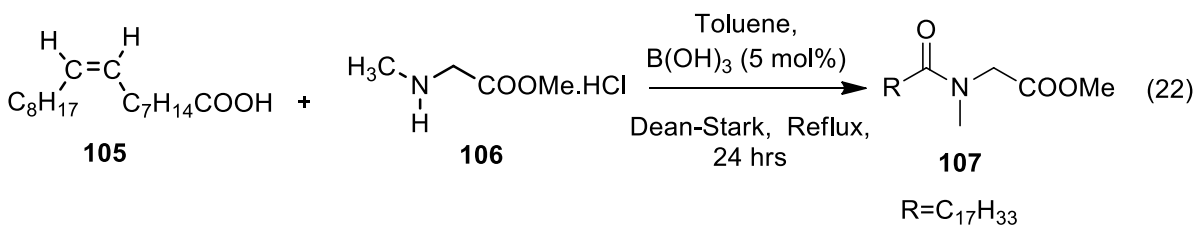
Many of the new developments and methodologies for forming amide bonds were originally aimed towards the most demanding and specialised field of peptide synthesis being an important area for biological and medicinal studies.[25] Peptides are mostly synthesized by the condensation of protected amino acid derivatives using coupling reagents of various types,

such as carbodiimides, uronium/ammonium and phosphonium salts, halo-uronium and halo-phosphonium salts.[120] These can be used in both solid or solution phase strategies, which often require the use of an excess of high-priced and atom uneconomic reagents to propel the condensation to completion. Additionally, in order to obtain clean products, and separate excess reagent waste products, large amounts of solvent are imperative to wash the resin when using solid phase synthesis systems. Hence, the development of new cleaner synthetic methods for peptide synthesis is an important goal for chemical research[26,111,121,27] and there is still a need for novel approaches and thinking,[122] especially for application on dipeptide formation, perhaps using arylboronic acid catalysts under conditions which do not cause racemisation.

Based on these general ideas, and in continuation of this interest, previously developed amidation conditions for ambient reaction conditions using aryl-boronic acid catalysts for amino acid derivatives, in order to optimize yields, reduce by-products, improve selectivity. This would allow the assessment of such methods, and to see if they were more economical and effective for the highly challenging area of peptide synthesis. Hence, the catalytic direct amidation of amino acid analogous both as amine and carboxylic acid donors were examined, reacting either with carboxylic acid or amine partners, respectively, in the first instance. Based on the preliminary results, the synthesis of dipeptide derivatives by direct amidation was then also investigated.

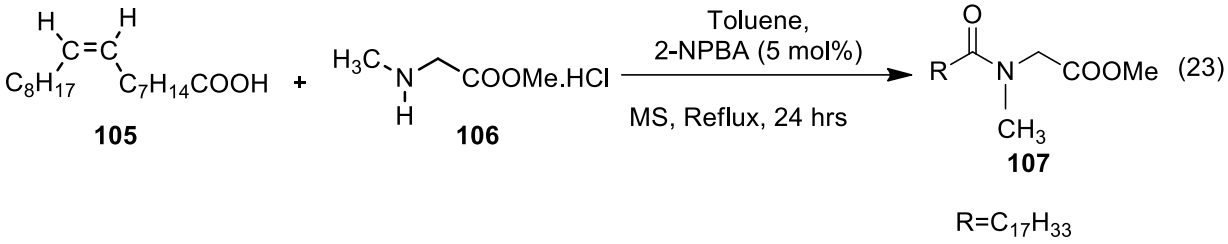
3.2.3 Direct Amidations of Oleic acid and Sarcosine Methyl Ester Hydrochloride

In order to form simple amino-acid derivatives by the direct amidation using the successful catalysts, firstly the direct amidation of sarcosine methyl ester hydrochloride **70** as an amine donor (C-protected amino acid) with an unsaturated carboxylic acid, oleic acid **69**, as in Equation 22 was chosen for investigation.



(22)

The reaction was carried out in toluene to check the higher temperature conditions in presence of the most efficient and commercially available boric acid as catalyst. The HCl salt **106** was initially neutralized using Hünig's base and then the acid **105** was added into the mixture, along with the catalyst [$B(OH)_3$, 5 mol%]. The reaction was refluxed for 24 hours at 110 °C using the Dean-Stark trap to remove water. The product formation was followed by TLC, however, after 24 hrs, there was no conversion of starting materials into amide which was confirmed by NMR. The same reaction was carried out in presence of *o*-nitrophenylboronic acid as catalyst (Equation 23), keeping the reaction conditions unchanged, but this catalyst also failed to produce the corresponding amide **107**.

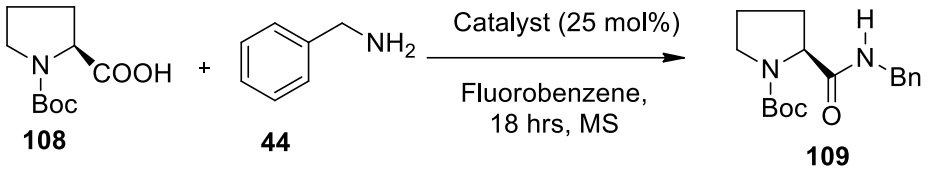


Indeed, even larger catalyst loadings (10 mol%) were ineffective for this amide **71** conversion. There was no decomposition of the starting materials during any of these reactions, therefore, these attempts to perform direct amide bond formation using the carboxylic acid **105** and amine **106** showed the lack of intrinsic reactivity of the substrates and that neither of the catalysts could play any role in enabling the direct condensation. This lack of reactivity of oleic acid **105** (the pK_a of this unsaturated fatty acid is 9.85) and amine **106** is interesting. It is notable that oleic acid **105** was used in the direct amide formation with a bio-catalyst, and was found to work well in the formation of an oleic amide.[123] Presumably, the acid **105** was not compatible with the amine **106** substrate because of the inertness of secondary amine towards direct amide formation, even at high temperature or with higher catalyst loadings. Therefore, investigations with this particular amino-acid derivative synthesis by direct amidation were suspended.

3.2.4 Direct Amide Formation of N-Boc-Proline with Benzylamine

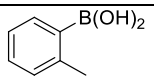
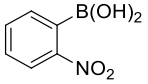
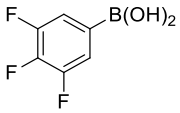
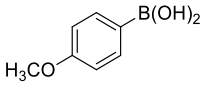
After an unsuccessful effort of amino-acid derivative synthesis by direct amidation using sarcosine and oleic acid, different reaction conditions for less reactive amino-acids in the

direct amidation process were screened. Simple amino-acids (both *C*- and *N*-terminally protected) were chosen to check the effect of different arylboronic acid catalysts at low temperature in the direct amidation process.



(24)

Table 5. Direct amidation[d] of N-Boc-proline and benzylamine (Eqn. 24).

Entry	Catalyst (25 mol%)	Temp. (°C)	Drying Method	Time (h)	Yield[a] of amide 109 (%)
1		85	A	18	70
2		65	A	18	46
4		85	A	18	75
5		65	A	18	59
6		85	A	18	91
7		85	B	12	98
8		65	A	12	89
9		85	A	18	76
10	$ZrCl_4$	85	A	18	65
11	$Fe(OTf)_2$	85	B	18	73

[a]Isolated yield of pure amide after crystallisation. Method A = Powdered 3Å molecular sieves in the reaction, Method B = Soxhlet thimble drying using powdered 3Å molecular sieves, [d]Reaction conditions: acid (2.86 mmol), amine (2.86 mmol), solvent = fluorobenzene (20 mL).

N-Protected amino acid, *N*-*tert*-butyloxycarbonyl Boc-*L*-proline **108** was selected as carboxylic acid to react with the reactive benzylamine **44**, in order to synthesize the corresponding amide **109** (Eqn. 24). Four different boronic acid catalysts (which had been applied for catalysing the direct amidation of a number of amine-carboxylic acid combinations[26,117,124,125]) including *o*-nitrophenylboronic acid, were examined. In addition to arylboronic acid catalysts, $ZrCl_4$ and $Fe(OTf)_2$ were also applied as Lewis acidic amide formation catalysts. Fluorobenzene was chosen as solvent as it was found in the previous work to be the best solvent for the lower temperature direct amidation. Two different temperatures and drying methods were employed. The results are summarised in Table 5.

These preliminary studies (Table 5) demonstrated that among the four boronic acid catalysts, 3,4,5-trifluorobenzeneboronoic acid had the highest catalytic activity under refluxing fluorobenzene (at 85 °C) conditions. With a catalyst loading of 25 mol%, 3,4,5-trifluorophenylboronic acid afforded an excellent yield of amide **11** (91%, Entry 6, Table 5). This catalyst had almost the identical effect on the reaction rate at lower temperature (65 °C), as the yield of amide **11** was also satisfactory at this temperature (89%, Entry 8, Table 5). The benefit of the latter reaction conditions were that reactions could be carried out with molecular sieves in the reaction mixture; virtually minimising any chance of racemisation on account of the lower reaction temperature. These results emphasised the consequence of electron withdrawing groups (F atoms) attached to the aromatic ring of the arylboronic acid catalysts which have been used in several previous studies on the direct amidation processes.[102,103] The electron withdrawing ability of fluorine atoms plays an important role to enhance the reaction rate by making the B-atom more Lewis acidic, which leads ultimately the carbonyl C-atom of the carboxylic acid being more electrophilic towards the nucleophilic attack of amine. Likewise, *o*-nitrophenylboronic and *p*-methoxyphenylboronic acids were also moderately effective in the amidation process (Eqn. 24). In effect, both these catalysts had the same efficiency in the preparation of amide **109** under refluxing conditions (Entry 4 and 9, Table 5).

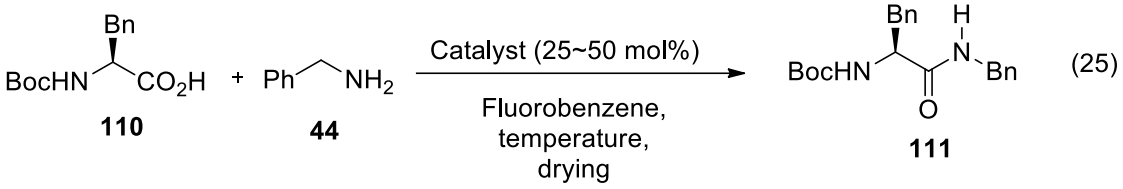
The catalyst with a mild electron releasing group ($-CH_3$), *i.e. o*-methylphenylboronic acid, was found to be less efficient than those catalysts with the electron withdrawing groups, although the conversion of amide **109** was still 70% (Entry 1, Table 5) at reflux temperature (85 °C). However, at lower temperature, the rate of reaction dropped abruptly resulting only 46% of the amide **109** (Entry 2, Table 5). This illustrates that the catalytic activity of *o*-methylphenylboronic acid was not great below the reflux temperature of fluorobenzene and seems to reinforce the idea that a less electrophilic form directly relates to a less reactive direct amide formation catalyst.

In contrast to the arylboronic acid catalysts, the two Lewis-acidic catalysts [($Fe(OTf)_2$ and $ZrCl_4$] were fairly efficient in the direct amidation of *N*-Boc-*L*-proline **108** and benzylamine **44** at the same temperature (Entry 10 and 11, Table 5), although $Fe(OTf)_2$ was better than $ZrCl_4$.

It was also noteworthy that the direct amidation of *N*-Boc-proline was more sluggish than that of many simpler carboxylic acid-amine combinations studied before under the same reaction conditions, which is why a substantially higher catalyst loading (25 *versus* 5 mol%) was required.[96,97] In addition, the reflux temperature (85 °C for fluorobenzene) was found to be another important factor in improving the reaction rate. Accordingly, the yield of the reaction was increased, especially while using the Soxhlet extraction system, which resulted in up to 98% yield of amide **109** (Entry 7, Table 5).

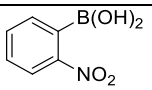
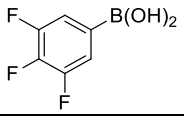
3.2.5 Direct Amide Formation of N-Boc-phenylalanine with Benzylamine

In order to confirm the scope of application of the successful catalysts and conditions from Equation 23, direct amidation of *N*-Boc-phenylalanine **110** was examined, as outlined in Eqn. 25.



(25)

Table 6. Direct amidation[d] of *N*-Boc-phenylalanine and benzylamine (Eqn. 25).

Entry	Catalyst	Temp (°C)	Drying Method	Time (h)	Catalyst loading (mol%)	Yield[a] of amide 111 (%)
1		85	A	18	25	94
2		65	B	24	50	89
3		85	A	18	25	45
4		65	B	18	25	trace

[a]Isolated yield of pure amide after recrystallisation. Method A = Soxlet thimble drying using powdered 3 Å molecular sieves. Method B = Powdered 3 Å molecular sieves in the reaction. [d]Reaction conditions: acid (2.86 mmol), amine (2.86 mmol), solvent = fluorobenzene (20 mL).

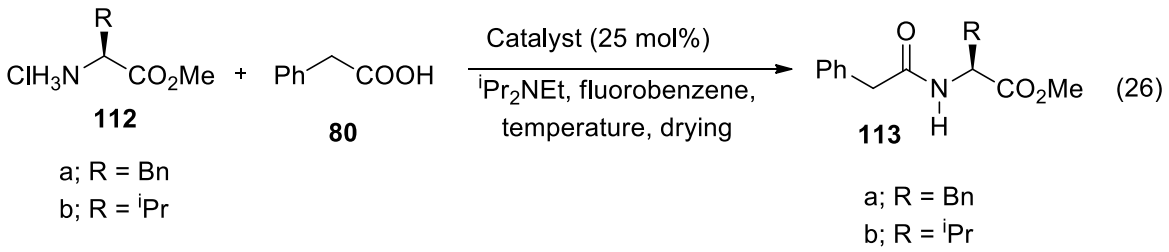
In this case, 3,4,5-trifluorophenylboronic acid was not effective enough for the amidation of the phenylalanine derivative **110**, rather *o*-nitrophenylboronic acid was remarkable, providing the benzylamide **111** in 94% yield (Entry 1, Table 6) using the Soxhlet extraction drying in refluxing fluorobenzene. Although the reaction seemed rather slow at 65 °C, with a high catalyst loading (50 mol%) and long reaction time (24 h), an isolated yield of 89% (Entry 2,

Table 6) could be obtained. The excellent activity of *o*-nitrophenylboronic acid was not surprising since its use had been reported by Hall *et al,*[1,126] Moreover, it is cheaper than 3,4,5-trifluorophenylboronic acid and readily commercially available, hence, its usage is possibly more attractive than other catalysts.

In addition, the Lewis acidic catalysts $Fe(OTf)_2$ and $ZrCl_4$ were also examined in the same reaction (Eqn. 25) to probe their reactivity. Unfortunately, these Lewis acidic catalysts were found inefficient at producing even trace amounts of amide **111** even with a catalyst loading of 25 mol% over 24 hrs and following the same reaction conditions. Further investigations carried out with a 50 mol% of these catalysts in the direct amidation of phenylalanine derivative **110** did not show any improvement in the yield.

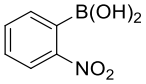
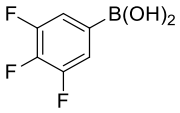
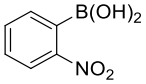
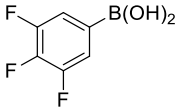
3.2.6 Direct Amide Formation of Phenylalanine and Valine Ammonium Chloride Derivatives with Benzylamine

From the above results, it appears that *N*-protected amino acids react quite efficiently with amines to form the corresponding amides using electron deficient arylboronic acids as catalysts. Therefore, the corresponding *C*-protected amino acids in the form of methyl ester HCl salts (neutralized *in situ* from the corresponding HCl salts using Hünig's base) were examined by reacting with phenylacetic acid **80**. The results are outlined in Equation 26 and Table 7, employing phenylalanine and valine ammonium chloride derivatives **14a** and **14b**.



(26)

Table 7. Effect of catalysts and temperature on the Equation 26.

Entry	Amine 112	Catalyst (25 mol%)	Temp. (°C)	Drying method	Time (h)	Yield[a] of amide 113 (%)
1	a		85	A	14	92
2	a		65	A	14	86
3	a		85	A	14	94
4	a		65	B	14	89
5	b		85	A	14	86
6	b		65	A	14	78
7	b		85	A	14	90
8	b		65	A	14	77

[a]Isolated yield of pure amide after recrystallisation. Method A = Soxlet thimble drying using powdered 3 Å molecular sieves. Method B = Powdered 3 Å molecular sieves in the reaction. [d]Reaction conditions: acid (2.86 mmol), ester (2.86 mmol), Hünig's base (2.86 mmol), solvent = fluorobenzene (20 mL).

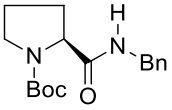
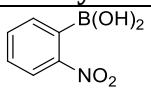
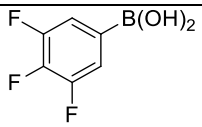
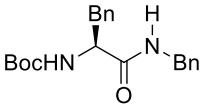
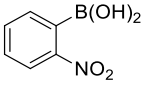
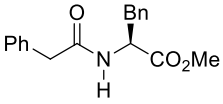
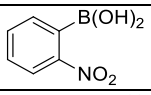
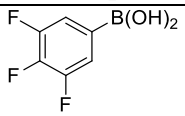
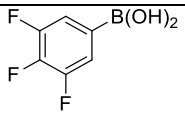
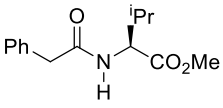
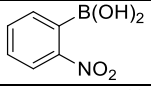
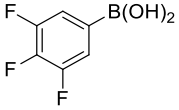
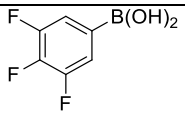
The direct amide formation was reasonably efficient using both boronic acid catalysts. 3,4,5-Trifluorobenzenboronic acid exhibited marginally higher activity. For example, for the phenylalanine analogue **113a,** amide formation at 85 °C with 3,4,5-trifluorobenzenboronic acid afforded 94% yield over 14 hrs, whereas *o*-nitrophenylboronic acid gave 92% of amide **113a** under the same reaction conditions (Entries 1 and 3, Table 7).

At 65 °C, the corresponding amides could also be isolated in respectable yields for **113a** with both the two arylboronic acid catalysts (Entries 2 and 4, Table 7). Similar trends were observed for the other analogue, **113b**, under the same reaction conditions and no major differences were observed between these two catalysts activities at the different temperatures (Entries 5-8, Table 6). However, it was noteworthy (apart from the temperature and catalysts) that, the nature of the attached group R in compound **112** (Equation 26) played an important role in controlling the formation of amide **113**.

3.2.7 Effect of Catalysts and Temperature on the Racemisation of Amides Derived from Chiral Amino Acids

The enantiopurity of the amides formed from the amino acid derivatives was tested by chiral HPLC (Column OD-H, 0.46 cm × 25 cm). The advantage of applying lower temperatures than the reflux temperature in the above amidation reactions of amino-acid derivatives being that reaction could not only be run with the molecular sieves in the reaction mixture, but potentially minimising any chance of racemisation.

Table 8. Effect of catalysts and temperature on the racemisation of amides derived from chiral amino acids

Entry	Amide	Amide structure	Catalyst	Temp(°C)	*ee* (%)
1	**109**			85	79
2				85	>99
3				65	>99
4			$Fe(OTf)_2$	85	95
5			$ZrCl_4$	85	84
6	**111**			85	>99
7				65	>99
8	**113a**			85	67
9				85	64
10				65	68
11	**113b**			85	71
12				85	>99
13				65	>99

It is noteworthy that chiral HPLC analysis of the amide **109** formed from 3,4,5-trifluorophenylboronic acid did not reveal any racemisation (*ee* more than 99%, Entries 2 and 3, Table 8). This indicates that 3,4,5-trifluorophenylboronic acid plays a leading role in keeping the enantiopurity of the amide high. However, using *o*-nitrophenylboronic acid in the same amide formation much greater racemisation was observed (*ee* 79%, Entry 1, Table 8). Notably, $Fe(OTf)_2$ afforded an excellent enantiopure amide of **109** (*ee* 95%, Entry 4, Table 8) although the yield was lower (only 76%), whereas $ZrCl_4$ afforded greater racemisation with only moderate yield (Entry 5, Table 8).

On the other hand, in case of the amide **111**, complete retention of enantiopurity was found at both temperatures (Entries 6 and 7, Table 8), while using this *o*-nitrophenylboronic acid as catalyst. Nevertheless, an appreciable amount of racemisation did occur with **113a** derivatives, although the yields were quite high. In this particular case, neither temperature nor catalysts preserved high enantiopurity (the ee are almost same, see Table 8, Entry 8, 9 and 10). It could be that the benzyl group attached to **112a** makes the products more susceptible towards racemisation. On the contrary, highly enantiomerically pure amides were formed from derivative **112b** using 3,4,5-trifluorophenylboronic acid at lower temperature (Entries 12 and 13, Table 8). It could be the *iso*-propyl group attached with **112b** helps resist any racemisation in **113b**. However, the enantiopurity was diminished while using *o*-nitrophenylboronic acid catalyst under the same reaction conditions (*ee* was 71%, Entry 11, Table 8).

In summary, the arylboronic acid catalysts used in the direct amidations of amino-acid derivatives were reasonably efficient in most cases for retaining the absolute configuration and enantiopurity of the starting amino-acid derivatives, but not completely, and catalyst loadings showed that there was further development required to find a general solution to direct amide formation in such systems.

Chapter 4: Cooperative Catalysis

4.0 Introduction

Organocatalysis has become an important and elementary tool used to synthesise organic compounds.[127] In addition to their newly identified types of sensitivity, organocatalysts also have benefits that are useful from a practical outlook, which have appeared in many scientific credentials over the last 10 years having been accorded from both academic and industrial researchers.[128] On the contrary, organic synthesis has historically been governed by transition metal catalysis.[129] Understanding of metal properties and the applications of their versatile reactivity in various transformations are undoubtedly yet to be discovered.[130]

During recent years, the speculative goal of combining pairs of distinct catalytic systems in different novelty has been examined in organic synthesis. Examples take into account combining different transition metals in one catalysis, [131] combining biocatalysis or enzyme catalysis with metal catalysis[132] and combining organocatalysis with transition metal catalysis.[133] The driving force behind these synergistic efforts is to discover more effective avenues for complex molecule synthesis. Thus, efficacy of cooperative catalysis has been perceived in organic synthesis in present years.[134] With increasing attention being given to this new area, momentous chemical transformations are being discovered. Generally, two or more catalysts are mixed in a one pot process, which allow stimulation of both reactants.

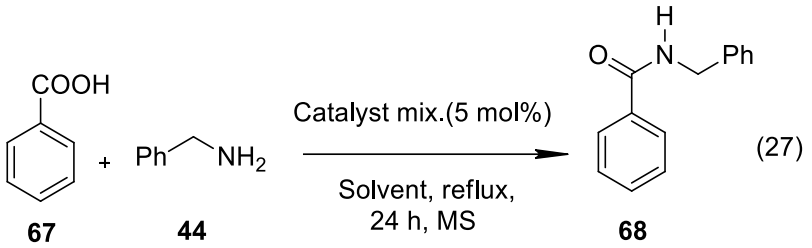
In connection with our prime interest in the generation of greener and atom-economic amide bond (-CONH-) synthesis, we were attracted by the power of cooperative catalysis was attractive for application in the direct condensation of acids and amines. Precedent for this approach was reported in our recent works[96,112] where dipeptide formation was achieved by the use of a mixture of *o*-nitrophenyl boronic acid and *o*-methylphenylboronic acid (1:1) in the direct amidation reaction of amino-acids at lower temperatures. But the dipeptide formation process was particularly slow and inefficient with a single catalyst under the identical reaction conditions.

Driven by these impressive results, in this part of the project, the potential of cooperative catalytic system were examined on the direct amidation processes, especially with the less reactive acid-amine combinations which were found to be inert at low temperature with single catalysts. In a quest for more efficient cooperative catalysts, different cooperative

catalyst combinations were tested, including arylboronic acids and metal-based catalysts in direct amidation reaction. More scope and applicability of this *de novo* synthetic approach towards some real industrial products syntheses was also explored.

4.1 Primary Screening of Different Cooperative Catalysts

At the outset, the possibility of this new catalytic protocol for amide synthesis was explored as shown in Equation 27.



Beyond question, direct amidation of benzoic acid **67** and benzylamine **44** was very sluggish both in thermal (Section 3.1, Chapter 3) and also in most of catalysed conditions due to the inherently less reactive substrate combinations.[96,97] Therefore, this reaction can be regarded as a good model reaction for testing the co-operative catalytic effect. The following seven catalysts (Fig 7) and their binary mixtures (1:1 ratio) were tested to examine their combined catalytic effect in the Equation 27.

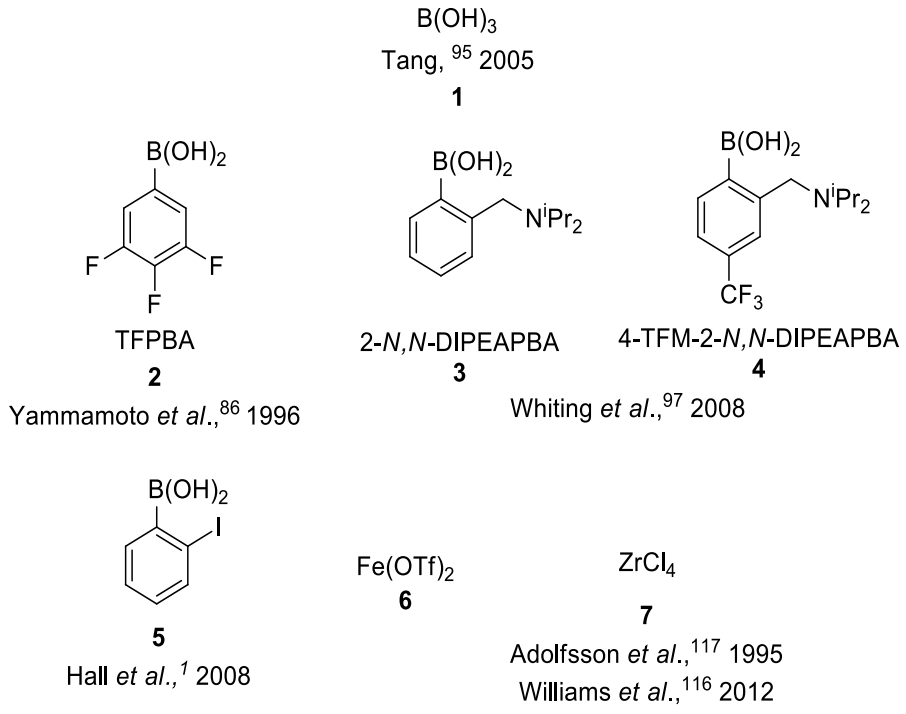


Fig 7. Catalysts chosen for developing various co-operative catalysts

The use of inexpensive, non-toxic and environmentally neutral $B(OH)_3$ in direct amidation has been well-received by academic and industrial researchers.[95,96] Likewise, arylboronic acid catalysts such as *o*-*N*,*N*-di*iso*propylbenzylaminoboronic acid (Whiting catalyst),[96,97] *o*-iodophenylboronic acid (Hall catalyst)[1,126] and trifluorophenylboronic acid (Yammamoto catalyst),[101-104] have been effectively exercised for catalyzing the direct amidation of a number of amine-carboxylic acid combinations.[26,117,124,] Aside from these attractive organic catalysts, in recent years, some inorganic and organometallic catalysts based on Fe and Zr metals have also been used due to their excellent competency in different direct amidation reactions.[116,117] The results of the reactions generalised by Equation 27 are shown in Table 9.

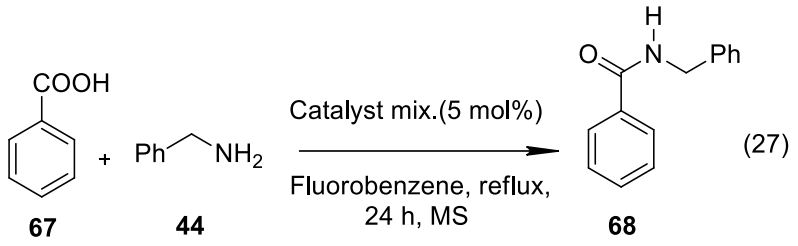
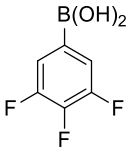
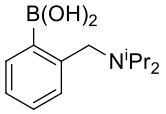
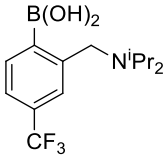
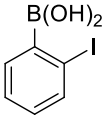


Table 9. The effect of single catalysts on the model reaction (Equation 27)[a]

Entry	Catalyst (5 mol%)		Conversion [a] of amide 68 (%)
1	**1**	$B(OH)_3$	<1
2	**2**		63
3	**3**		25
4	**4**		45
5	**5**		59
6	**6**	$Fe(OTf)_2$	32
7	**7**	$ZrCl_4$	9

[a]Reaction conditions: acid (2.86 mmol), benzylamine (2.86 mmol), solvent = fluorobenzene (20 mL), t = 24 h, drying method: 4Å MS in the Soxhlet, [b]Percent of conversion was determined by reverse phase HPLC (Gemini C18 column, 150 X 4.6 mm, 5 µ)

It was clear that with a catalyst loading of 5 mol% and under Soxhlet reflux conditions (with the pre-dried molecular sieves 4 Å) in fluorobenzene for 24 h, the majority of the single catalysts mentioned in Fig 7, failed to catalyse successfully the direct amidation of benzoic acid **67** and benzylamine **44**. Although fluorobenzene proved a suitable and practical azeotropic solvent for many of the highly reactive amidation reactions,[96, 97] in this particular direct amidation reaction, it did not affect the reaction rates.

Although catalyst **1** [$B(OH)_3$] was found to provide higher yield (70% of amide **68**) for the coupling of benzoic acid **67** and benzylamine **44** in refluxing toluene over 22 hrs,[9] at relatively lower temperature (refluxing in fluorobenzene at 85°C), it displayed negligible potential for conversion of amide **68** (Entry 1, Table 9).

Arylboronic acid catalysts with electron-withdrawing substituents on the aryl group, like catalyst **2**, possibly enhance the rate of the generation of acyloxy-boron species and their reactivity with amines due to their strong Lewis acidity.[102] Because of its remarkable catalytic potential, this catalyst was used in the direct condensation of benzoic acid **67** and benzylamine **44,** and the conversion was quite reasonable (63%, Entry 2, Table 9) under these reaction conditions (*vide supra*).

Likewise, catalysts **3** and **4** (the amine-functionalized boronic acids) proved promising catalysts (by suppressing the N-B chelation due to the sterically hindered amine substituents) both at high and moderate temperatures.[96,97] In this particular amidation reaction (Equation 27) they failed to accelerate the rate efficiently (Entry 3 and 4, Table 9) under the reaction conditions (*vide supra*). The benefit of the addition of a *p*-trifluoromethyl group in the arylboronic acid ring (catalyst **4**) was notable, in the resulting higher conversion of carboxylic acid **67** into amide **68** than catalyst **3**, though the conversion was not satisfactory (Entry 4, Table 9). Previous reports showed that catalyst **4** could afford 50% of amide **68** with a catalyst loading of 10 mol% under refluxing condition in fluorobenzene for 48 hrs,[96] whereas only 45% conversion to amide **68** was found here at lower temperature and with low catalyst loading for 24 hrs (Entry 4, Table 9).

Based on the hypothesis that an *ortho*- substituent can interact directly with the Lewis acidic boron centre or activate a bound reagent or substrate,[1] the more active amidation catalyst **5** was also examined under the same amidation process conditions and afforded a reasonable conversion of amide **68** (59%, Entry 5, Table 9). The results showed that the *o*-iodo-substituent did not affect the acceleration of the rate of the amidation much in this case. In addition to the arylboronic acid catalysts, the metallic and organo-metalic catalysts, catalysts **6** and **7** were also inefficient to form amide **68** under this reaction conditions. Beyond question, the rate of amide **68** formation proved once again quite slow with the single catalyst amidation process.

Subsequently, the sluggish nature of the overall single catalytic systems in the direct amidation reaction of benzoic acid **67** enhanced the possibility of a cooperative catalytic system in this area. In the quest for a synergistic effect of binary mixture of these catalysts at low temperature, further mixtures of two catalysts (1:1 ratio) were applied in the same model reaction. For the sake of comparison with the single catalyst mediated direct amidations, all the reaction conditions were kept unaltered. The results are shown in Table 10.

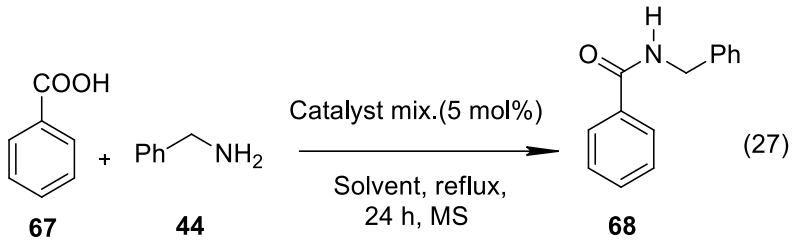


Table 10. Cooperative catalysts screening for the amidation of **67** with **44** (Eqn. 27).[a]

Entry	Co-operative Catalysts (5 mol%)	Catalyst no	Conversion (%)[b]
1	$B(OH)_3$ + 3,4,5-TFPBA	**I**	69
2	$B(OH)_3$ + 2-*N*,*N*-DIPEAPBA	**II**	30
3	$B(OH)_3$ + 4-TFM-2-*N*,*N*-DIPEAPBA	**III**	74
4	$B(OH)_3$ + 2-IPBA	**IV**	30
5	$B(OH)_3$ + $Fe(OTf)_2$	**V**	<1
6	$B(OH)_3$ + $ZrCl_4$	**VI**	8
7	3,4,5-TFPBA + $Fe(OTf)_2$	**VII**	23
8	2-*N*,*N*-DIPEAPBA + $Fe(OTf)_2$	**VIII**	62
9	4-TFM-2-*N*,*N*-DIPEAPBA + $Fe(OTf)_2$	**IX**	53
10	2-IPBA + $Fe(OTf)_2$	**X**	3
11	$Fe(OTf)_2$ + $ZrCl_4$	**XI**	8
12	3,4,5-TFPBA + $ZrCl_4$	**XII**	26
13	2-*N*,*N*-DIPEAPBA + $ZrCl_4$	**XIII**	70
14	4-TFM-2-*N*,*N*-DIPEAPBA + $ZrCl_4$	**XIV**	41
15	2-IPBA + $ZrCl_4$	**XV**	8
16	3,4,5-TFPBA+ 2-IPBA	**XVI**	10

[a]Reaction conditions: benzoic acid (2.86 mmol), benzylamine (2.86 mmol), fluorobenzene (20 mL), T = 85 °C, drying method: 4Å MS in the Soxhlet, t = 24 h; [b]Percent of conversion was determined by reverse phase HPLC (Gemini C18 column, 150 × 4.6 mm, 5 µ)

It was notable that the majority of catalysts mixtures were unsuccessful for the conversion to amide **68** under these reaction conditions. However, in some cases, there was clear advantage for the use of the cooperative catalysts compared to the corresponding single catalysts under the same reaction conditions. In those cases, the cooperative catalysts showed a genuine effect on the yield enhancement over the single catalytic amidation process, *e.g.* a positive synergistic effect was noticed in case of catalyst **1** [$B(OH)_3$], when it was used with some

arylboronic acid catalysts, like catalysts **2** (3,4,5-TFPBA), **3** (2-*N*,*N*-DIPEAPBA) or **4** (4-TFM-2-*N*,*N*-DIPEAPBA) as a mixture (1:1 ratio as a binary catalysts) in the amidation process of benzoic acid **67** and benzylamine **44** (entry 1-3, Table 10). The most impressive cooperative catalyst was catalyst **III** [$B(OH)_3$ and 4-trifluoromethyl-2-*N*,*N*-di*iso*propylethylaminophenylboronic acid mixture]. The cooperative effect of both the catalysts (**1** and **4**) increased the conversion of amide **68** at 74% (Entry 3, Table 10) whereas, the rate of the reaction was quite sluggish with each of these single catalysts (Entries 1 and 4, Table 9). The possible reason for the success of the cooperative catalysts might be due to the compatible combination of two distinct catalysts, which might play a vital role to activate the electrophile (carboxylic acid) and facilitate the attack of the nucleophile (amine) to form the product (amide).

Another successful cooperative catalyst was system **VIII** (Entry 8, Table 10). In spite of the inefficiency of the individual Lewis acidic $ZrCl_4$ (catalyst **7**) at forming the amide **68** (only 8% conversion, Entry 7, Table 9), the addition of arylboronic acid catalyst **3** (2-*N*,*N*-DIPEAPBA) enhanced the rate dramatically and the conversion rose to 70% (Entry 13, Table 10), in contrast to the catalyst **3** alone which was inefficient (Entry 3, Table 9).

Likewise, cooperative catalyst **XIII** also performed well in the less reactive direct amidation of benzoic acid **67** and benzylamine **44**. Nevertheless, catalyst **6** [$Fe(OTf)_2$] was able to afford only 32% conversion of amide **68**, but the addition of a 1:1 mixture of catalyst **3** and **6** together resulted a significant increase in the rate of reaction (Equation 26), and eventually, the conversion of amide **68** was almost doubled (62%) under the same reaction condition. Notably, this conversion was also higher than the conversion with catalyst **3** alone (Entry 3, Table 9). The cooperative catalyst **IX** also showed a moderate conversion of amide **68** (53%).

Surprisingly, in some cases negative cooperative effects were observed on the rate of direct amidation reaction of benzoic acid **67** and benzylamine **44** by two catalyst mixtures. For instance, catalyst **3** and **5**, were both efficient individually giving a reasonable conversion of carboxylic acid **67** into amide **68** (Entry 3 and 5, Table 9). In contrast, the presence of both these arylboronic acid catalysts as a mixture (catalyst **XVI**) had a deleterious effect on the rate of the reaction, which led to a lower conversion of amide **68** (Fig 8).

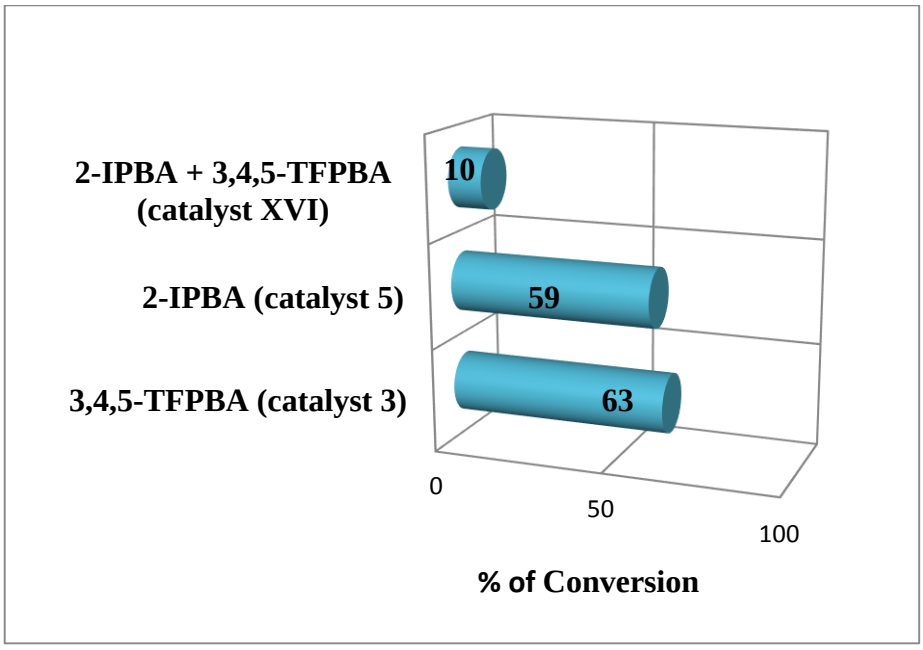


Fig 8. Negative synergistic effect of cooperative catalyst **XVI** on the percent of conversion of amide **68** (Equation 27)

Similarly, non-cooperative effects were displayed by the other combinations of cooperative catalysts based on, *e.g.* catalyst **6** [$Fe(OTf)_2$] for the formation of amide **68**. For instance, catalyst **X** was inefficient for the conversion of amide **68**, as shown in Fig 9.

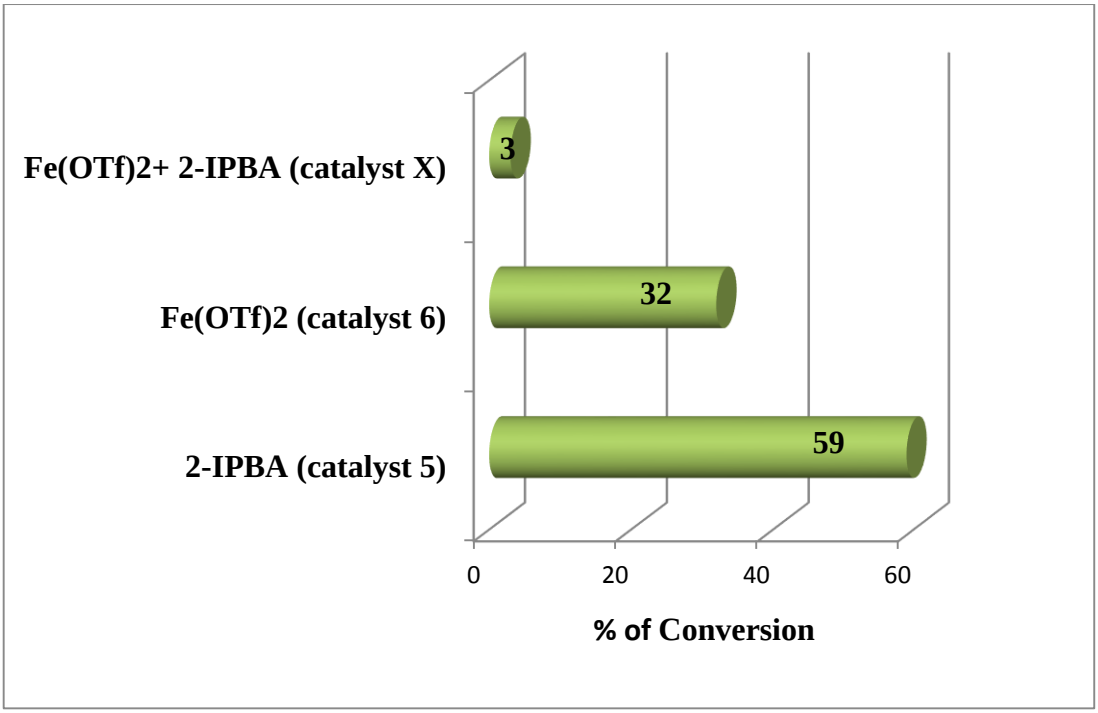


Fig 9. Negative synergistic effect of cooperative catalyst **X** on the percent of conversion of amide **68** (Equation 27)

Despite, catalyst **5** (2-IPBA) was reasonably efficient for the direct amidation of benzoic acid **67**, its catalytic efficiency dropped down significantly when it was combined with $Fe(OTf)_2$ (catalyst **6**) in the same reaction. The possible reason for this negative effect might be due to the incompatible combination of these two catalysts which result the deactivation of the electrophile (carboxylic acid) and reduced the ultimate yield of amide. Nonetheless, this negative effect attributed a big challenge to overcome in the development of the highly promising cooperative catalysis in direct amidation processes.

4.2 Reaction Progression Monitored by HPLC: Effect of Single and Cooperative Catalysts on the Direct Amidation

Further, the effect of cooperative catalysts along with the other single catalysts on the reaction progression was investigated. For this study, direct amide formation reactions (Equation 26) were carried out in refluxing fluorobenzene in the absence of a catalyst and in the presence of the single (catalyst **1** and **4**) and cooperative catalysts (catalyst **III)**, and were followed by HPLC for 24 hrs by taking samples manually in every 2 hrs. The percent of

carboxylic acid remained and amide formed were calculated beforehand to ensure that accurate amount of each species could be identified by HPLC. The data collected was processed using Clarity software and Microsoft Excel.

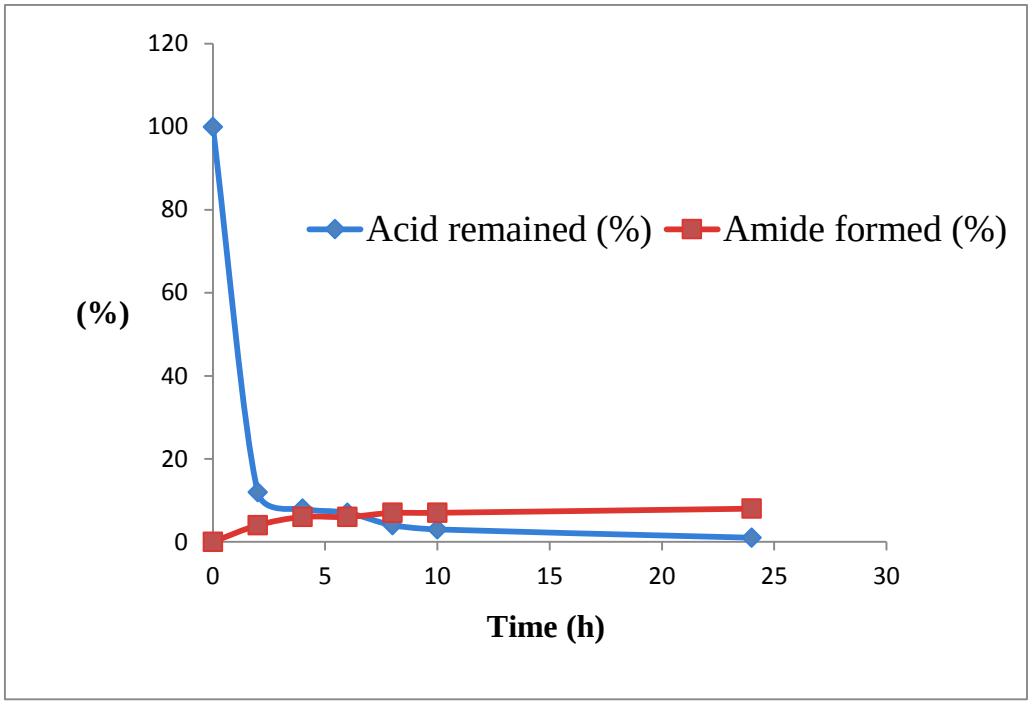


Fig10. Reaction progression of thermal (without catalyst) direct amidation of benzoic acid **67** and benzylamine **44** to form amide **68**

As expected, the thermal reaction proved to be much slower than the reaction using catalysts and this trend has been observed previously[96] (see Chapter 3). The direct thermal (uncatalysed) formation of amide **68** from the condensation of benzoic acid **67** and benzylamine **44** under these conditions was found almost non-existent. The thermal reaction progression is shown in Fig 10, where it is clear that the carboxylic acid **67** disappeared within 2 hrs and formed white precipitate of ammonium salt. After 2 hrs the percent of acid remained almost zero but very slowly decreased over the rest of the reaction period. This evidently indicated that the formation of the stable intermediate ammonium salts was fast, which was further converted into amide more slowly.

Further, the reaction progression in the presence of the cooperative catalyst **III** was also monitored along with the individual catalysts **1** and **4**. The results of this comparison are shown in Fig 11.

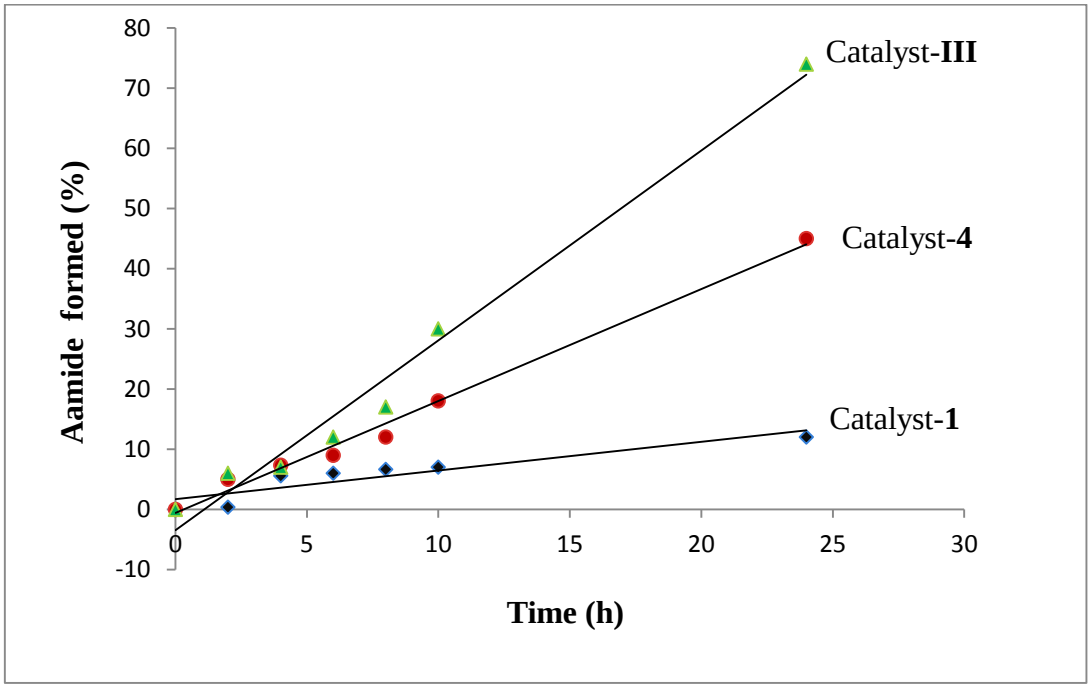


Fig11. Reaction progression of benzoic acid and benzylamine with different catalysts

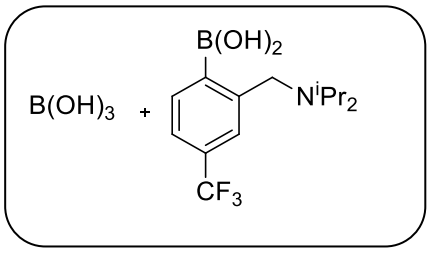
As the reaction proceeded, the amount of amide increased and also resulted some inaccuracies when sample was processed for following the amide formation by HPLC at room temperature; this can be seen in Figure 11 as the increase in scattering of the percent of amide formed. This was due to the amide product precipitating out of solution under the room temperature sampling conditions and reaching the saturation limit. Hence, the reaction progression was followed using the calculated data collected for following the amine over time.

There was a difference between the rate of formation of amide **68** with or without catalyst. Without catalyst the formation of amide looked quite sluggish (**Fig 10**) whereas with catalysts, formation was quite rapid (**Fig 11**). The addition of catalyst **1** did not change the rate of reaction much in comparison with the thermal reaction which implied an insignificant

effect of the catalyst **1** on the amide **68** formation under this condition. On the contrary, the addition of an arylboroonic acid catalyst **4** with an electron withdrawing group like *p*-trifluoromethyl methyl group showed a substantial rate enhancement. However, the incorporation of cooperative catalyst **III** appeared most beneficial for rate enhancement for the formation of amide **68** to a greater extent by the direct amidation process. This also gave evidence for the conversion of amide **68** from the stable ammonium salt which was slower than the formation of the salt from the carboxylic acid. However, the nature of the kinetic reaction behaviour showed that reaction needed to run for a further 24 hours for completion.

4.3 Scope of Co-operative Catalysis

From that primary screening of different cooperative catalysts, the following cooperative catalyst **III** (mixture of $B(OH)_3$ and 4-trifluoromethy-2-*N*,*N*-di*iso*propylethylaminophenylboronic acid[96]) was found to be the most efficient in converting the carboxylic acid to the corresponding amide wishing mild reaction conditions.



Catalyst **III**

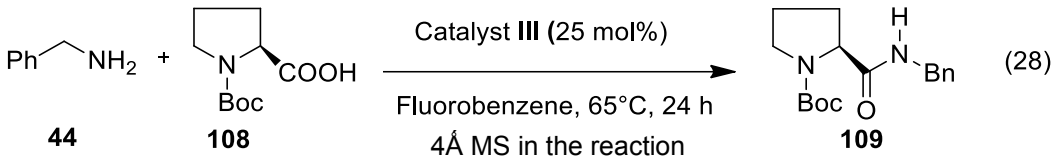
The amide bond links amino acids to form peptides and proteins which are biologically crucial,[117] despite their importance in drug design and synthesis, the catalytic synthesis of α-amino acids derivatives is very limited partly due to racemisation problems.[140] Our recent work reported that a high loading of 3,4,5-trifluorophenylboronic acid or 2-nitrophenylboronic acid (typically 25−50 mol%) improved amide synthesis using a suitably protected α-amino acid.[139] High temperatures, combined with less efficient catalysts, resulted in racemisation resulting in low *ee* (64%) for amides derived from *N*-protected (*S*)-proline or (*S*)-phenylalanine. Under previous conditions, the peptide coupling of two α-amino acids enforced stoichiometric amounts of the catalysts (100 mol% of 2-methyl and 2-nitrophenylboronic acid) to afford reasonable yields (46−62%) of different protected pure

dipeptides with excellent diastereoselectivity (Pro-Phe, Phe-Val, PheGly or Phe-Phe).[139] More recently, an efficient method has been developed *via* [2-(thiophen-2-ylmethyl)phenyl]boronic acid as a highly active bench-stable catalyst for catalytic amidation of amino-acid derivatives as well as dipeptide synthesis.[141]

In this context, we were further intrigued to apply the most successful cooperative catalyst **III** in direct amidations of both the *C*-protected and *N*-protected amino-acid derivatives. The utilisation of the best cooperative catalyst **III** in the challenging dipeptide synthesis (containing two amide bonds) for which the substoichiometric amount of reagents was unknown to date was also a goal for this project.

4.3.1 Direct Amidation of N-protected Cyclic Amino Acid

To probe the scope of cooperative catalysts, the direct amidation of L-*N*-*tert*-butyloxycarbonyl (Boc)-proline **108** and benzylamine **44** was carried out in presence of cooperative catalyst **III** to synthesise the corresponding amide **109** (Equation 28). Since the direct amidation of amino-acid derivatives proved sluggish, the catalyst loading was quite high. The reaction was stirred in flurobenzene at 65 °C with a catalyst loading of 25 mol% and 4Å molecular sieves were used in the reaction to remove water from the reaction. The mild reaction temperature potentially minimized the chance of racemisation as mentioned before (Section 3.2.4, Chapter 3). Like other direct amide formation reactions, the reaction mixture was also worked up to obtain an isolated yield of amide **109**.

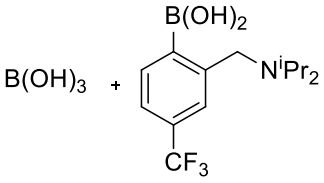
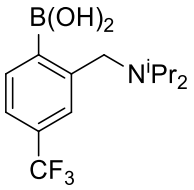


44 **108** **109** (28)

Isolated yield: 92%

After 24 hrs, the crude NMR looked almost completely clean, indicating high conversion of amino acid **108** into amide **109**. Pure amides were obtained by simple filtration of the reaction mixture through a pad of Celite (to remove the molecular sieves), washing with EtOAc, followed by the aqueous acid-base extraction. The isolated yield was found to be 92% (Entry 3, Table 11).

Table 11. Direct amidation of L-*N*-Boc-proline and benzylamine using single and cooperative catalysts

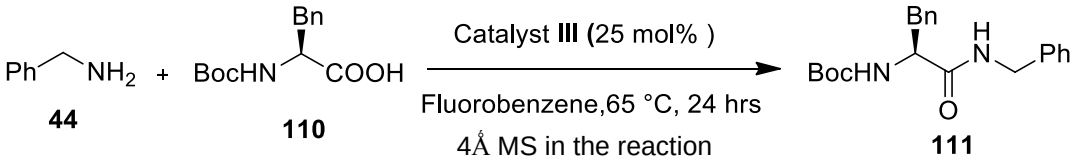
Entry	Catalyst used (25 mol%)	Yield[a] of 109 (%)
1	**III** 	92 (*ee* > 99%)
2	**1** $B(OH)_3$	14
3	**4** 	30

[a] Isolated yield of pure amide, reaction conditions: T = 65 °C, 4 Å powdered MS was used in the reaction, t = 24 h.

For comparison, the efficiency of the single and cooperative catalysts for the same reaction was carried out in the presence of catalysts **1** and **4** [$B(OH)_3$ and 4-TFM-2-*N*,*N*-DIPEAPBA] independently and under the same reaction conditions. Results for these experiments showed that the rate was reduced to a great extent with the use either of catalyst **1** or **4**, which affected the ultimate amide **129** formation (yield: only 14% and 30% respectively, Entry 1 and 2, Table 11). This indicated that the cooperative catalyst **III** was more efficient than each of the single catalysts. Further, chiral HPLC analysis revealed that the chiral enantiomerically pure *N*-protected amino-acid converted into the corresponding amide without racemisation (*ee* > 99%), emphasising again the mildness of the cooperative catalytic procedures.

4.3.2 Direct Amidation of N-protected Aromatic Amino Acid

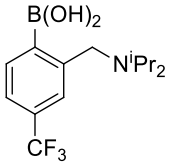
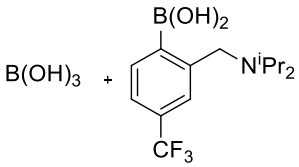
In order to check the tolerance of the reaction conditions and the use of other amino-acid reactants, *e.g. N*-protected aromatic amino-acid, L-*N*-Boc phenylalanine was further examined in the direct amidation with the cooperative catalyst **III** (as outlined in Equation 29). The results are summarised in Table 12.



(29)

Isolated yield: 89%

Table 12. Direct amidation of L-*N*-Boc-phenylalanine **110** and benzylamine **44** using single and cooperative catalysts

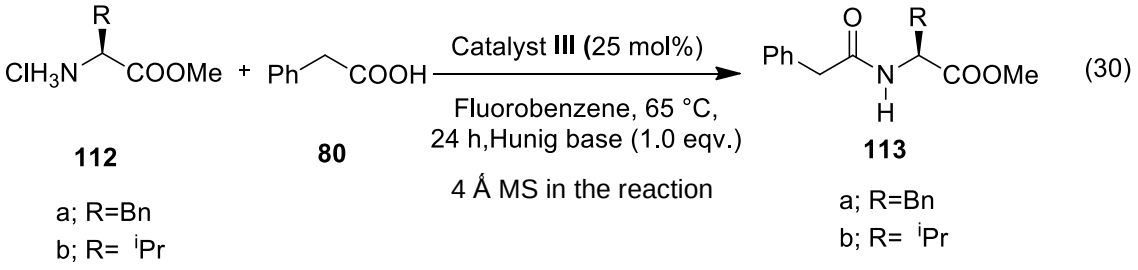
Entry	**Catalyst used (25 mol%)**		**Yield[a] of 111 (%)**
1	**1**	$B(OH)_3$	20
2	**4**		40
3	**III**		89 (*ee* > 99%)

[a] Isolated yield of pure amide, reaction condition: T = 65 °C, 4 Å powdered MS was used in the reaction, t = 24 hrs.

As expected, the direct amidation of *N*-protected aromatic amino-acid derivatives proved to be much slower than the other normal acid-amine direct amidation process and this low reactivity was observed previously (See Chapter 3). As a result of which, high catalyst loading (25 mol%) was required in each case. With the individual catalysts **1** and **4**, direct amide formation led to an extremely poor yield of amide **111**(Entry 1 and 2, Table 12). The same set of experiments were carried out with the cooperative catalyst **III** increased the yield of amide **111** increased to 89% without any racemisation (*ee* > 99%), indicating its excellent efficiency in this direct amidation reaction (Entry 3, Table 12). However, it is noteworthy that under the similar reaction conditions, the aromatic amino-acid *N*-Boc-phenylalanine **110** was a little less reactive than the cyclic amino-acid *N*-Boc-proline **108** (Entry 1, Table 11 and Entry 3, Table 12) towards the direct amidation with benzylamine **44**.

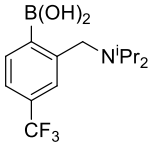
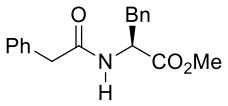
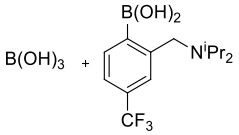
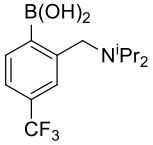
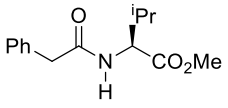
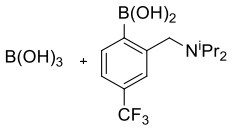
4.3.3 Direct Amidation of C-protected Aromatic Amino Acid

After the success of cooperative catalyst **III** in transforming the *N*-protected amino acids into the corresponding amides with amine through direct amidation, we endeavoured to investigate the corresponding *C*-protected amino acids. Two different *C*-protected amino acid derivatives (L-Valine ester **112a** and L-phenylalanine ester **112b**) were tested for these direct amidation reactions. The amino-acids were in the form of methyl ester HCl salts, which were neutralized *in situ* by using Hünig's base (*N*,*N*-di*iso*propylethylamine). The amino group reacted with phenylacetic acid **80**. The reactions are configured in Equation 30 and the results are summarized in Table 13.



(30)

Table 13. Direct amidation of *C*-protected amino acid derivatives (**112a** and **112b**) and phenylacetic acid **80** using single and cooperative catalysts

Entry	*C*-protected amino acids	Catalysts used (25 mol%)	Catalyst no	Amide formed	Yield[a] (%)
1		$B(OH)_3$	**1**		15
2	**112a**		**4**	 **113a**	45
3			**III**		86 (*ee* 68%)
4		$B(OH)_3$	**1**		19
5	**112b**		**4**	 **113b**	39
6			**III**		84 (*ee* > 99%)

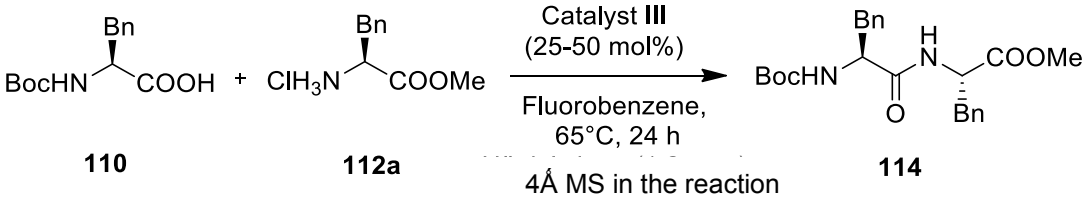
[**a**] Isolated yield of pure amide, reaction condition: T = 65 °C, 4 Å powdered MS was used in the reaction, t = 24 h.

The results showed that the cooperative catalyst **III** had a favourable effect on both of the direct amidation reactions of C-protected amino acids. Although the catalyst loading was high (25 mol%), the L-valine analogue **112a** formed 86% of amide **113a** at 65 °C in fluorobenzene after 24 h, whereas the phenylalanine derivative **112b** afforded 84% of amide **113b** under the same reaction conditions. The enantiopurity of these amide products formed was tested by chiral HPLC (Column OD-H, 0.46 cm × 25 cm). Although the low reaction temperature (65 °C) was thought to be favourable for minimizing racemisation, an appreciable amount of racemisation did occur with **113a**, although the yield was quite high (Entry 3, Table 13). Neither temperature nor catalyst **III** preserved high enantiopurity. A possible explanation for this racemisation could be the benzyl group attached to **112a** makes the products more susceptible towards racemisation. However, highly enantiomerically pure amides were formed from derivative **112b** (Entry 6, Table 13), hence, it could be for the *iso*-propyl group attached with **112b** helps to prevent racemisation in **113b**.

Notably, catalyst **1** was quite inert in the direct amidations of these C-protected amino acids under the same reaction conditions (Entry 1 and 4, Table 13). Although the reaction rate appeared to increase with catalyst **4**, the yield was not good enough for having a practical use of this catalyst towards these amidations to afford amides **113a** and **113b** (Entry 2 and 5, Table 13). It was also less efficient than the new cooperative catalyst **III**.

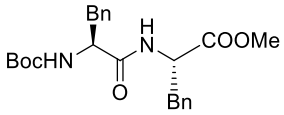
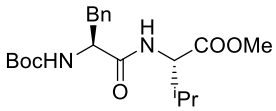
4.3.4 Challenging Dipeptide Formation

In view of the success of cooperative catalyst **III** for the direct amide bond formation of both *C*-protected and *N*-protected amino acids, it was considered whether it would be possible to apply this catalyst to couple *N*-terminal to *C*-terminal protected amino acids. Attempts to address this issue related to dipeptide synthesis began with coupling of L-phenylalanine methyl ester hydrochloride **112a** and L-*N*-Boc-phenylalanine **110** to examine the efficiency of the cooperative catalyst **III**. The reaction was studied under the same reaction conditions applied for the amino-acid derivatives synthesis as shown in Equation 31 and the results are summarised in Table 14.



(31)

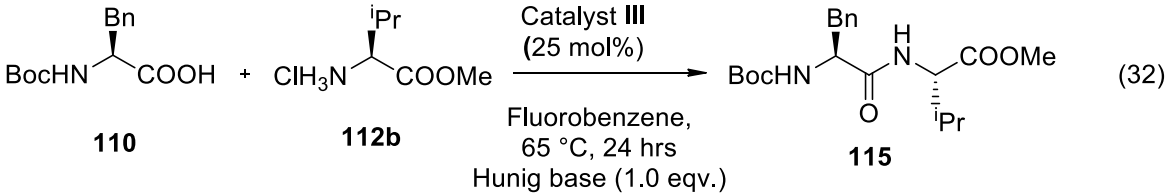
Table 14. Dipeptide synthesis by cooperative catalyst **III**

Entry	Dipeptide	Catalyst III loading (%)	Yield[a] (%)
1	 **114**	25	53
2		50	86
3	 **115**	25	89

[**a**] Isolated yield of pure amide, reaction conditions: T= 65 °C, acid (1.4 mmol), amine (1.4 mmol), solvent = fluorobenzene (20 mL), Hünig's base (1.4mmol), 4 Å powdered MS was used in the reaction, t = 24 h

As expected, the dipeptide synthesis by direct amidation process proved to be much slower than the direct amidation of amino-acid derivatives synthesis discussed in the preceding sections. Accordingly, only half of the carboxylic acid **110** reacted with **112a** in fluorobenzene at 65 °C with the use of 25 mol% of the cooperative catalyst **III** to form the corresponding dipeptide **114** in 24 h. With the increase of catalyst loading (50 mol%), there was a substantial improvement of the yield of amide **114** (86%, Entry 2, Table 14) occurred within a reasonable reaction time. Careful examination of ^{1}H NMR spectra showed excellent diastereoselectivity, *i.e.* no detectable amount of the (*R*,*S*) diastereoisomer.

Interestingly, the synthesis of dipeptide **114** was reported in our previous work synthesised by employing stoichiometric amounts of *o*-nitrophenylboronic acid (100 mol%) at the same temperature for 32 h affording an yield of only 58%.[139] Even the mixture of two arylboronic acid catalysts (*o*-nitrophenylboronic acid and *o*-methylphenylboronic acid; 1:1 ratio) provided only 62% of the dipeptide **114**.[1] However, catalyst **III** proved more efficient than *o*-nitrophenylboronic acid alone or as a mixture with *o*-methylphenylboronic acid.



(32)

Similarly, the cooperative catalyst **III** was employed for the synthesis of dipeptide **115** from the amino acid **110** and valine methyl ester **112b** under the same reaction conditions (Equation 32). It was noted that the valine derivative **112b** was more reactive than phenylalanine methyl ester **112a** to form the corresponding dipeptide **115** approaching higher yield (89%) with only 25 mol% catalyst loading (Entry 3, Table 14). It appeared that neither catalyst nor temperature played a major role in causing the low yield of the dipeptide **115**. Rather, the amino acid structure itself, particularly the presence of bulky benzyl side chain in **112b**, results in greater propensity for low yield. Importantly, it was clear that the cooperative catalyst **III** could be beneficial to synthesise different peptides, including aryl-aryl and aryl-alkyl systems.

4.3.5 Industrial Applications of Cooperative Catalysed Direct Amidation Reactions

The ubiquity of amide bonds in nature (*e.g.* peptides, antibiotics) as well as in technology for structural materials (*e.g.* nylon) is well known. In addition, amide functional groups appear in many pharmaceuticals and fine chemicals, usually with other functionalities that are not suitable with simple stoichiometric activators. Recent data from medicinal chemistry campaigns has revealed that 16% of all reactions performed for the synthesis of pharmaceuticals containing amide bonds, involve acylation of amines with activated carboxylic acids.[142] Another industry-led survey showed that among 128 drug syntheses, acylations accounted for 12% of the reactions (second only to heteroatom alkylations/arylations), of which 66% were *N*-acylations to form amides.[143]

The activation of carboxylic acids is mostly accomplished using different coupling agents. Today the peptide industry uses different coupling reagents (especially involving *N*-Boc chemistry and conventional DCC/HOBt methods) for the synthesis of the majority of peptide

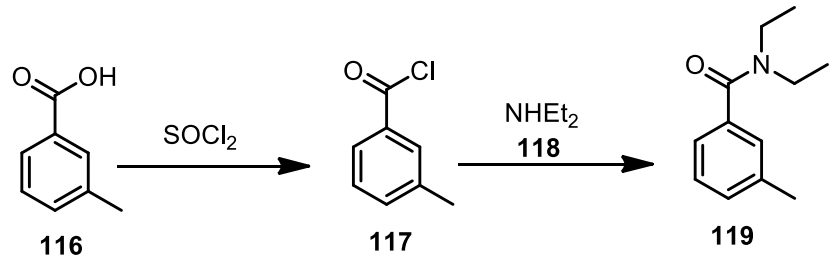
drugs.[144] Recently, the use of solid phase Fmoc chemistry has increased in industry, as modern coupling techniques involving reagent combinations such as HBTU/TBTU and HCTU/TCTU. Interestingly, despite accounting for a large proportion of the transformations, none of the *N*-acylation reactions used for amide bond formation were catalytic. All these current methods used for amide formations in industry are general, but overpriced and unrefined, which has made these methods questionable. Even the best stoichiometric reagents are usually inert towards the synthesis of sterically hindered amides,[143] and hence, have caused a rethink in direct amide formation strategies, like using new thermal catalytic processes.[145]

In contrast to acid-catalysed esterification, there have been few catalytic processes for converting carboxylic acids to amides. As discussed before (Chapter 1), direct amide formation methodology has advantages of atom economy and avoids protection/deprotection steps. Boric acid and arylboronic acid-catalysed direct amidation exploits all these advantages in a potentially green and sustainable setting. An excellent review of the academic work in this area has been discussed in previous chapters, but most of the academic work uses simple aliphatic or aromatic acids or amines as substrates such as 4-phenylbutyric acid, benzoic acid or benzylamine.

From an industrial point of view, it was of interest to know if the catalytic direct amidation methodology also worked for typical pharmaceutical intermediates or fine chemicals, which are often rich in heteroatoms. The use of $B(OH)_3$ has been explored by different pharma companies, like GSK, Pfizer and Dr. Reddy's Laboratories and they showed that the methodology has great efficacy.[146] However, it still remains in its infancy stage and in this section, the practical feasibility of the novel approaches of cooperative catalysis in some important industrial applications was explored.

4.3.5.1 Synthesis of DEET (N,N-Diethyl-meta-toluamide) by Direct Amidation

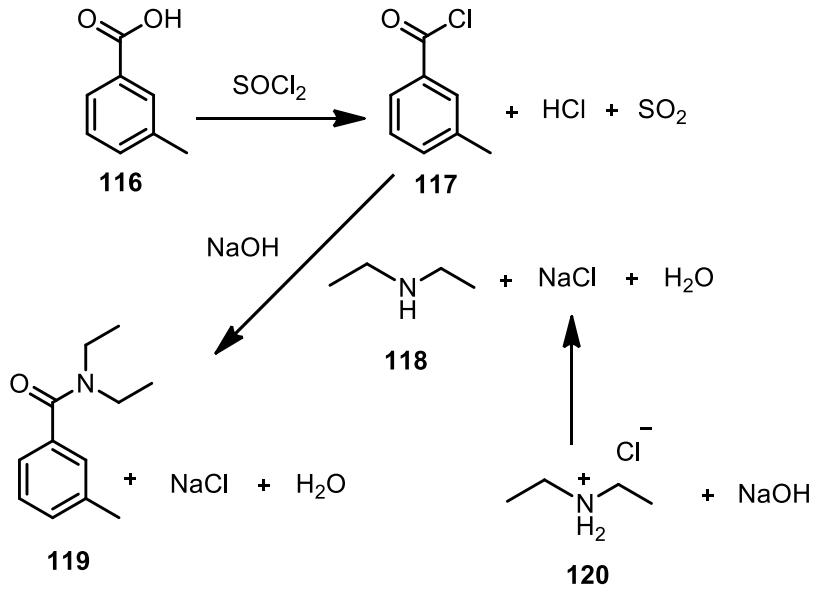
DEET (*N*,*N*-Diethyl-*meta*-toluamide) is the most familiar active ingredient (available in concentrations 5-98%) in most of the insect repellents like "OFF" from World War II. Most of the reported procedures for the formation DEET reported before[147] are based on using different coupling reagents in a two step synthesis which results in the formation of a tertiary amide. In the first step, the acid **116** is activated to an acyl chloride, which is usually done with thionyl chloride (or phosphorous trichloride (PCl_3), and then the second step involve treating the chloride with the amine **117** which leads to the formation of amide **118**. One of the drawbacks of this method is the formation of two noxious gases as by-products, (SO_2 and HCl), while using thionyl chloride ($SOCl_2$) to activate the acid.



Scheme 14: Synthesis of DEET using coupling agent (thionil chloride)

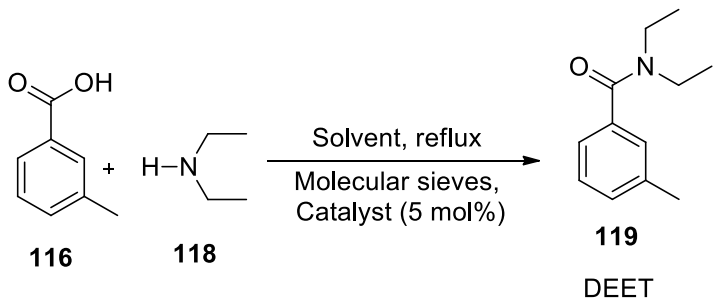
As a result of the high reactivity of acyl chlorides, the reactions are usually fast and exothermic enough that in many cases, the rate is controlled by cooling, or by using an appropriate solvent. When the reaction is carried out in an inert solvent, such as diethyl ether or toluene, at least a 100% excess of the nitrogen compound is necessary, since the reaction forms HCl which reacts with one equivalent of amine (or ammonia) to produce the amine salt.

Another disadvantage of this method is the separation of salt from the product which is usually difficult. To avoid these disadvantages, a base such as pyridine, triethylamine or sodium hydroxide can be added to react with the evolved HCl (Scheme 15). The introduction of aqueous alkali also makes it feasible to use an amine hydrochloride **120** rather than the free amine **118**, as the salt reacts with base (NaOH) to liberate the amine *in situ*.



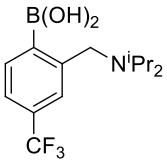
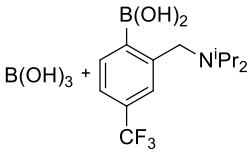
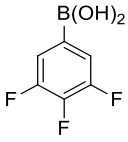
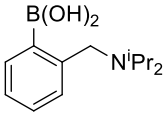
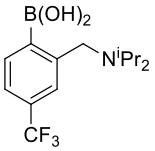
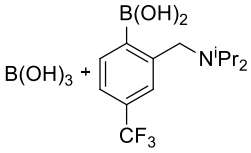
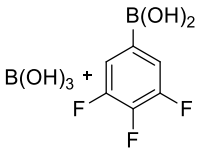
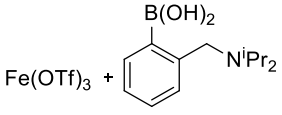
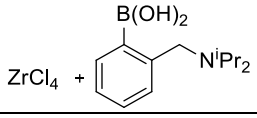
Scheme 15. Second route of Synthesis of DEET

Direct amide formation could afford a more sustainable and environmentally friendly alternative to the typical synthesis of DEET. In this part of this study, the feasibility of using catalysts, especially the cooperative catalysts, for synthesising DEET by the direct amidation of *m*-toluic benzoic acid **116** and *N*,*N*-diethylamine **117** (Equation 33) was explored.



(33)

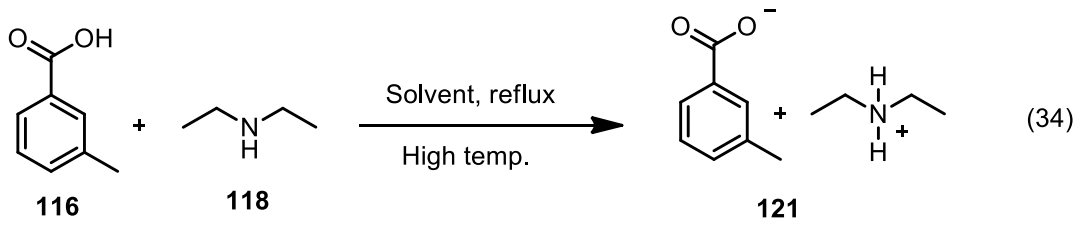
Table 15. DEET synthesis by direct amidation[b] of acid **116** and amine **118**

Entry	Catalyst (5 mol%)	Solvent & Temp(°C)	Drying method	[a]Conversion of 119 (%)
1	No catalyst	Fluorobenzene (85)	MS (4 Å)	0
2	No catalyst	Toluene (110)	DS	0
3	No catalyst	Xylene (300)	DS	0
4	**1** $B(OH)_3$	Fluorobenzene (85)	MS (4 Å)	0
5	**4** 	Fluorobenzene (85)	MS (4 Å)	0
6	**III** 	Fluorobenzene (85)	MS (4 Å)	0
7	**1** $B(OH)_3$	Toluene (110)	DS	8
8	**2** 	Toluene (110)	DS	4
9	**3** 	Toluene (110)	DS	3
10	**4** 	Toluene (110)	DS	6
11	**III** 	Toluene (110)	DS	56
12	**I** 	Toluene (110)	DS	60
13	**VIII** 	Toluene (110)	DS	41
14	**XIII** 	Toluene (110)	DS	72

[a] Percent of conversion was determined by reverse phase HPLC. [b]Reaction conditions: acid (2.86 mmol), amine (2.86 mmol), solvent (20 mL), 4 Å powdered MS was used in the Soxhlet, t = 24 h.

For a systematic comparison, the background reaction (thermal reaction) was also compared with the addition of 5 mol% of each of the catalysts, with direct monitoring of the reaction being carried out over 24 hours by HPLC. The results are given in Table 15.

The thermal reaction of *m*-toluic acid and *N*,*N*-diethylamine was carried out first at 85 °C in fluorobenzene with the Soxhlet refluxing of the acid **116** and amine **118**, using pre-dried molecular sieves (4Å) to remove water from the reaction mixture. The reaction was monitored by HPLC for 24 hours. With the moderate reaction temperature, no trace of amide **119** was observed at all and both of the reactant concentrations remained unaltered with time (Entry 1, Table 15). In order to accelerate the rate, the reaction was refluxed at high temperature (110 °C) in toluene for the same time period, using a Dean-Stark trap as the drying method (Entry 2, Table 15). Unfortunately, no product was observed at this temperature and even higher temperature (144 °C) in refluxing xylene no change in the reactants or the rate of formation of DEET (Entry 3, Table 15) was observed . So, it was presumed that the thermal reaction was not efficient; a simple acid-base reaction occurred instead, with the addition of amine **118** directly to the acid **116** to form the ammonium salt **121** which was observed to precipitate out after the reaction was stopped. The evidence of this ammonium salt formation during the amide bond formation was also proved in previous literature.[26,27]



116 **118** **121** (34)

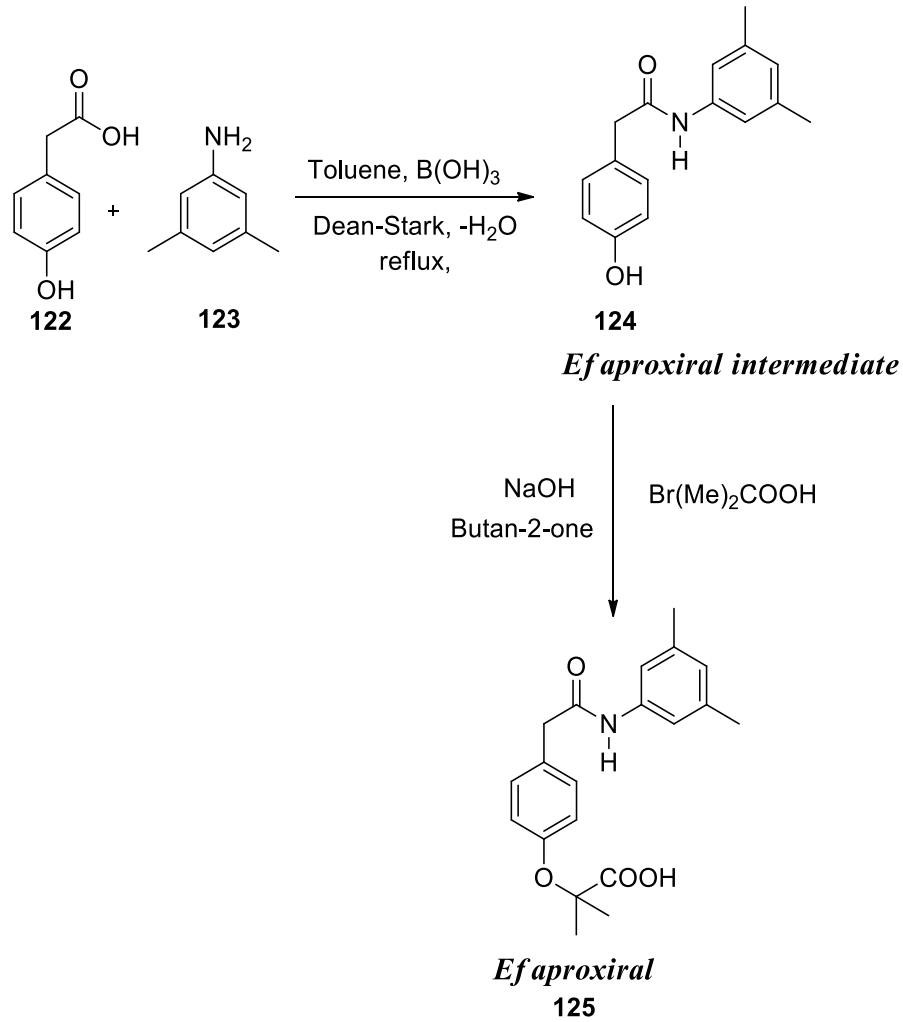
The rate of the reaction increased slightly in the presence of catalyst **1**, **2** and **4** while refluxing in toluene (Entries 4, 5 and 6, Table 15), though the conversion was very poor. However, the rate increased hugely in the presence of 5 mol% of two arylboronic acid catalysts in the reaction mixture. Cooperative catalyst **III**, which was efficient before in direct amidation processes (Section 4.2), was also found competent to afford more than 50% of amide **119** (Entry 11, Table 15). Similar trends of improvement in rate were observed with the cooperative catalyst **I** (HPLC conversion 60%, Entry 12, Table 15), although the reaction was much slower with the cooperative catalyst **VIII**, which led to only 41% conversion of

DEET within 24 hrs. Nonetheless, the catalyst **XIII** showed the best catalytic activity giving over 70% conversion within the same reaction time (Entry 14, Table 15). To minimise the contribution of the high temperature, reactions were also carried out in fluorobenzene instead of toluene at 85 °C with different single and cooperative catalysts (Entries 4, 5 and 6, Table 15). Unfortunately, no conversion was noticed at this moderate temperature. One of the reasons for the inert reactivity could be the solubility of the substrate as it hardly dissolved in fluorobenzene at lower temperature. This suggests that the direct amide formation of acid **116** and amine **118** is favourable at high temperature.

Nonetheless, the application of cooperative catalysts in the synthesis of DEET gives a new approach for its industrial production, which could be cheaper, more atom economic and environmentally safe compared to conventional coupling methods.

4.3.5.2 Synthesis of Efaproxiral Intermediates

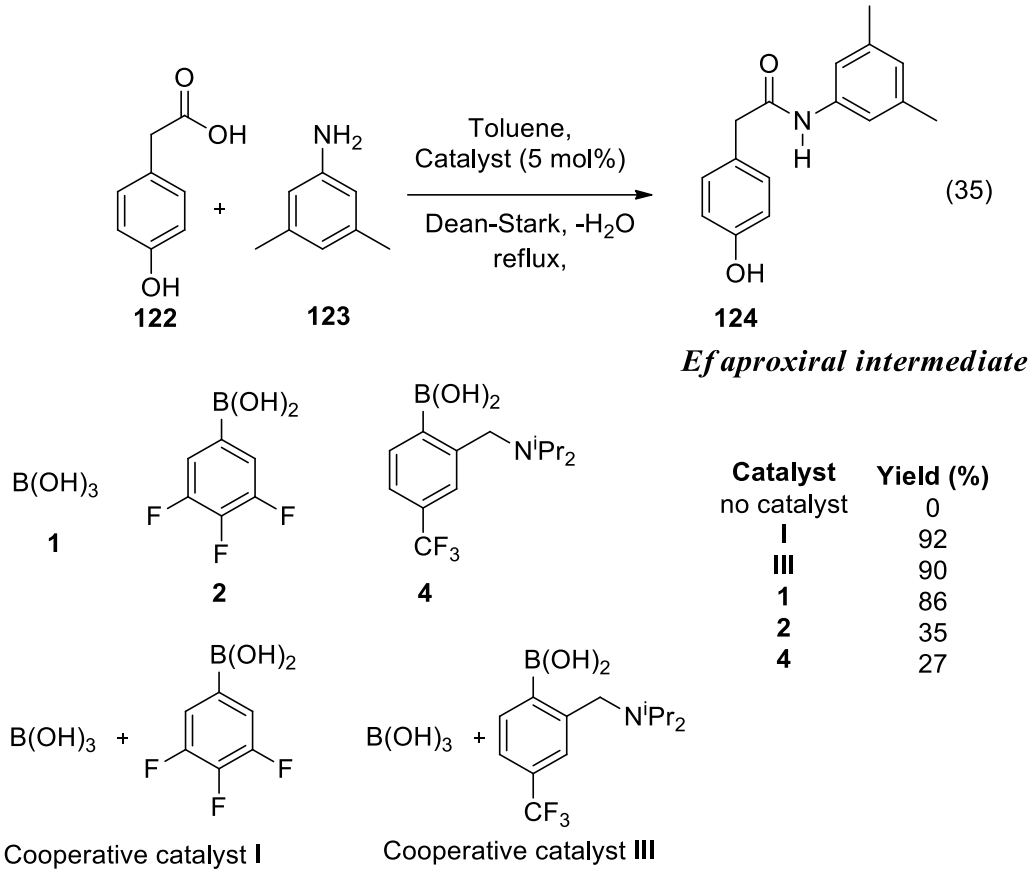
Efaproxiral **125** is mainly a metastatic drug for cancer therapy, which makes tumour cells more responsive to radiation by increasing the amount of oxygen in the cells. More recently, GSK have explored the scope and utility of low cost $B(OH)_3$ in the formation of efaproxiral drug intermediate **124** from direct amidation of 4-hydroxyphenylacetic acid **122** and 3,5-dimethylaniline **123** (Scheme 16).[146]



Scheme 16. Synthesis of Efaproxiral by boric acid catalysed direct amidation by GSK company

This research paves the way for synthesis of efaproxiral intermediate **124** using different catalysts through a direct amidation process. In order to explore the applicability of the newly developed cooperative catalysts, the cooperative catalytic approach into the synthesis of **124** was examined. For this purpose, the direct amidation of 4-hydroxyphenylacetic acid **122** was

carried out with 3,5-dimethylaniline **123** using 5 mol% of the potential cooperative catalyst **III** in toluene (Equation 35). Both the acid **122** and amine **123** are commercially available.



Due to low cost and low toxicity, toluene was used as solvent. Moreover, its ability to form azeotropes is excellent. Since, rapid mixing or efficient refluxing curtailed the reaction time in the direct amidation process, the reaction was refluxed in toluene for 24 hrs followed by the azeotropic water removal from the reaction mixture. Water removal by molecular sieves is critical from an industrial point of view, as it causes some problems, especially if the plant equipment cannot be used to a specific reaction. The presence of molecular sieves creates substantial complications in the cleaning process; hence the Dean-Stark technique was followed for this amidation.

After 24 hrs, the resulting mixture was cooled and the solid was collected by filtration. The crude yield of amide was found to be quite impressive (more than 90%). Further attempts to purify the product were followed by simple acid-base extraction. Again, cooperative catalyst **I** was applied in the same amidation process which was efficient to the same extent as catalyst **III** (yield of amide **124** found 92%).

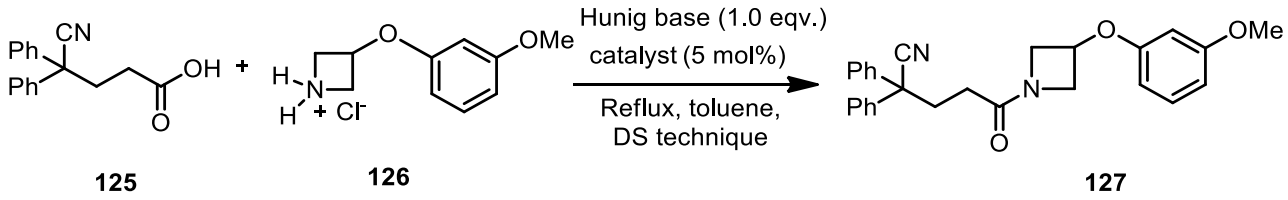
The thermal reaction was also carried out without any catalyst under the same reaction conditions. However, no product was found after 24 hrs by TLC which was further confirmed by NMR. Even a higher reaction time (further 48 hrs) did not convert the acid **122** into the amide **124**. Interestingly, GSK reported the uncatalysed water elimination reaction, requiring 3 days in refluxing xylene at 140 °C, followed by efficient mass and heat transfer to optimize water elimination.[146]

Nevertheless, the cooperative catalyst **I** and **III** were found to be very promising in the synthesis of the efaproxiral intermediate **124**. In order to probe the synergistic effect, the individual catalytic effect was also examined under the same reaction conditions. Detailed examinations showed that in the presence of 5 mol% of catalyst **1**, direct amidation of acid **122** and amine **123** proceeded at an excellent rate, affording a high yield of amide **124** (86%) within a reasonable time period. It was straightforward to fully evaluate the catalytic effect due to the zero thermal contribution at this high temperature (110 °C) in this amidation reaction. The result was also consistent with the previous outcome reported by GSK, although they operated the amidation with higher catalyst loading (7.7 mol%) and shorter reaction time (only 18 hrs).[146] Catalyst **1** seemed to be superior to catalyst **2** and **4** under these conditions, as they were notably inefficient at accelerating the rate (yield of amide **124** were 35% and 27% respectively). Moreover, there was no major synergistic effect on the reaction rate when two catalysts were used as a mixture (1:1); cooperative catalysts **I** and **III** exhibited almost similar effects on the formation of amide **124** under these conditions and the yields were similar to catalyst **1**. Since, catalyst **1**[$B(OH)_3$] is cheaper, available and less toxic, it is more advantageous than the cooperative catalytic system for synthesising the amide **124** from an industrial point of view. That is why, the reaction did not scale up beyond laboratory scale with the cooperative catalyst **I** or **III**.

4.3.5.3 Synthesis of Azetidine Derivatives

Azetidine (a saturated heterocyclic compound) and its analogues have biological importance in therapeutic applications; some azetidine-based derivatives recently have become new potent alternative tools for the treatment of breast cancer.[148] Azetidine-amides, one of the important class of biologically potent compounds, are typically prepared by standard amide formation techniques, which involves the use of toxic coupling agents like CDI. Recently, Pfizer initiated the synthesis of different azitidine-amide derivatives by catalytic direct amidation processes which are more atom-economic and environmentally friendly.[146] Due to the beneficial effects of this important class of compound, applicability of the novel cooperative catalytic amidation towards the synthesis of azetidine-amide derivatives was further examined, and hence, improve the atom efficiency of this reaction.

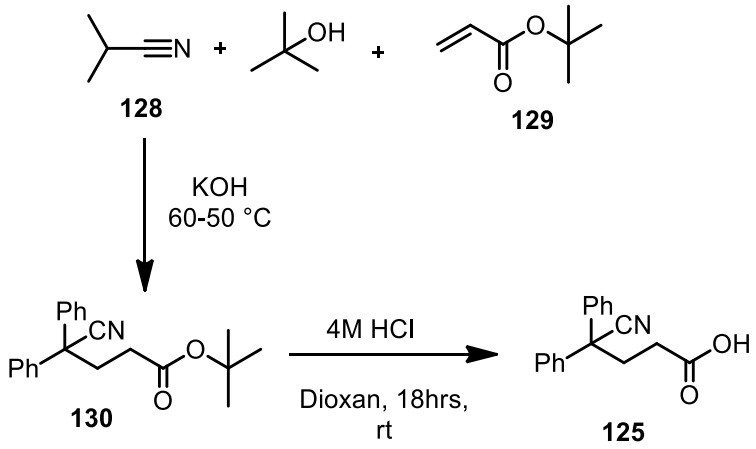
Due to the extremely basic nature compared to most secondary amines, azetidines are highly reactive towards aliphatic acids as shown in the Scheme 17. This involves direct amidation of aliphatic acid **125** with the azetidine hydrochloride salt **126** to form azetidine amide **127**.



125 **126** **127**

Scheme **17.** Synthesis of azetidine derivatives

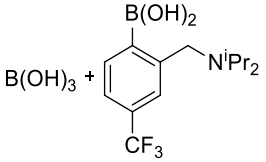
The acid **125** was not commercially available, and as such it was synthesized from diphenylacetonitrile **128** following a two step synthetic process (Scheme 18). The initial step was to convert diphenylacetonitrile **128** into the ester **130** by reacting with *t*-butanol in presence of KOH at temperature 60-50 °C followed by the addition of *tert*-butylacrylate **129** for 3 hrs, giving an yield of 99% of ester **130** as a white solid. Later, simple acid hydrolysis of ester derivative **130** in dioxane at room temperature provided the acid **127** as a white solid with yield of 41%.



Scheme **18.** Synthesis of acid **125**

The amine **126**, procured as the hydrochloride salt, was treated with the Hünig's base (1 eqv.) at room temperature before using in the direct amidation reaction. With the acid **125** in hand, direct amide formation reaction was attempted with the in *situ* amine formed from the salt **126**, the reaction mixture was refluxed in boiling toluene in presence of 5 mol% catalyst **1** [$B(OH)_3$], the azeotropic water removal afforded 70% of amide **127** within 24 hrs (Entry 2, Table 16).

Table 16. Direct amidation of acid **125** with the in *situ* amine formed from the salt **126** to form the azetidine derivative **127**

Entry	**Catalyst (5 mol%)**	**[a]Yield of 127 (%)**
1	No catalyst	No reaction
2	**1** $B(OH)_3$	70
3	**III** 	73

[**a**] Isolated yield of pure amide, reaction condition: T= 110 °C, acid (2.86 mmol), amine (2.86 mmol), solvent = toluene (20 mL), Hünig's base (2.86 mmol), drying method = Dean-Stark technique, t = 24 h

Interestingly, the trend of the reaction was not consistent with the previous outcome, [146] where the same direct amidation (Scheme 17) was carried out in the presence of 2 mol% catalyst **1** with refluxing toluene, yielding 87% of amide **127**. This anomaly could be due to the engineering dependence of the water removal from the reaction mixture; water elimination via Dean-Stark trap can be unsatisfactory. Another question might arise as to whether the Hünig's base was efficient enough at fully neutralising the hydrochloride salt of amine **126** to convert amine *in situ*. Nonetheless, the simple thermal reaction was carried out alongside to evaluate the catalytic effect in this direct amidation reaction. Following the reaction by TLC showed that even after 3 days, the reaction mixture consisted largely of starting materials. The inertness may be due to the low solubility of acid **125** and amine salt **126** in toluene even at this high temperature (110 °C). Since the reaction did proceed at a reasonable rate in presence of catalyst **1**, it was expected that cooperative catalysts might play a role in the rate enhancement. Unfortunately, no significant improvements was observed with the potential cooperative catalyst **III** (1:1 mixture of $B(OH)_3$ and 4-trifluoromethyl-2-*N*,*N*-di*iso*propylaminophenylboronic acid); like catalyst **1**, a similar trend of rate was observed with this cooperative catalyst (yield of amide **127** was 73%, entry 3, Table 16). One possible reason could be that catalyst **4** (4-trifluoromethyl-2-*N*,*N*-di*iso*propylaminophenylboronic acid) had no effect on this direct amidation, only catalyst **1** (boric acid) played the role in the formation of amide **127**.

4.3.5.4 Synthesis of Alfuzosin Intermediate

In continuation of the synthesis of different active pharmaceutical ingredients (API) by catalytic amidation process, our next attempt was to synthesise the Alfuzosin intermediate **136**, the active ingredient of Alfuzosin **131** (**Fig 12**), which has been commercialised as the hydrochloride salt and use for the treatment of prostate cancer.[149, 150]

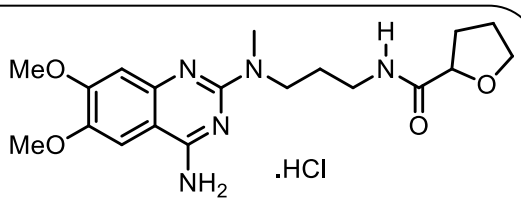
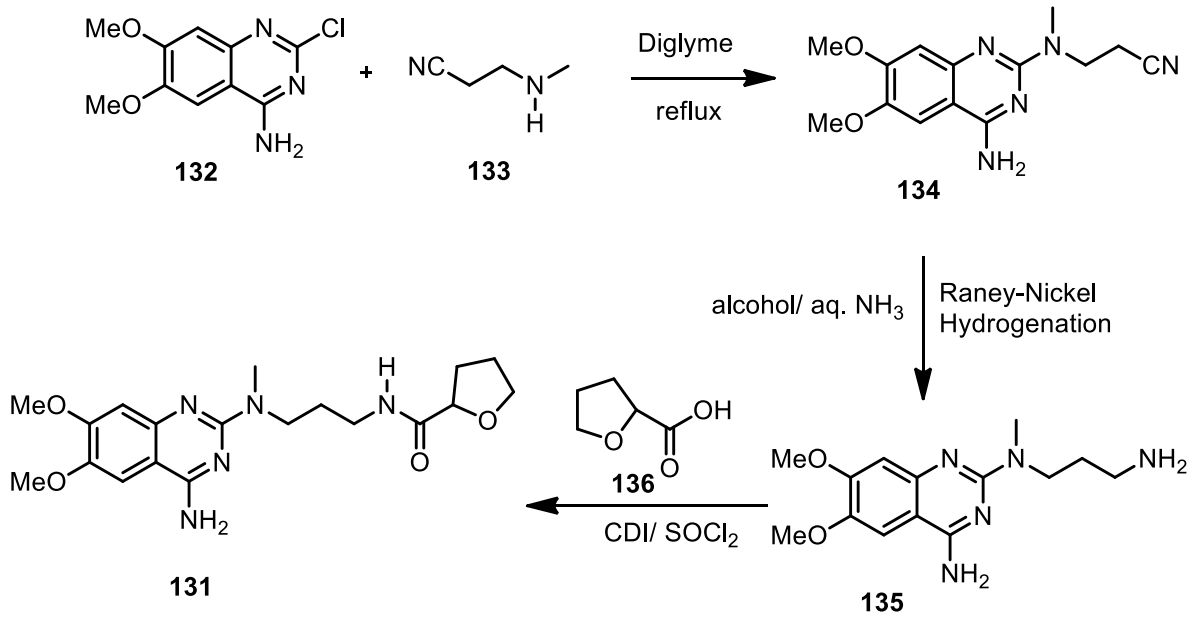


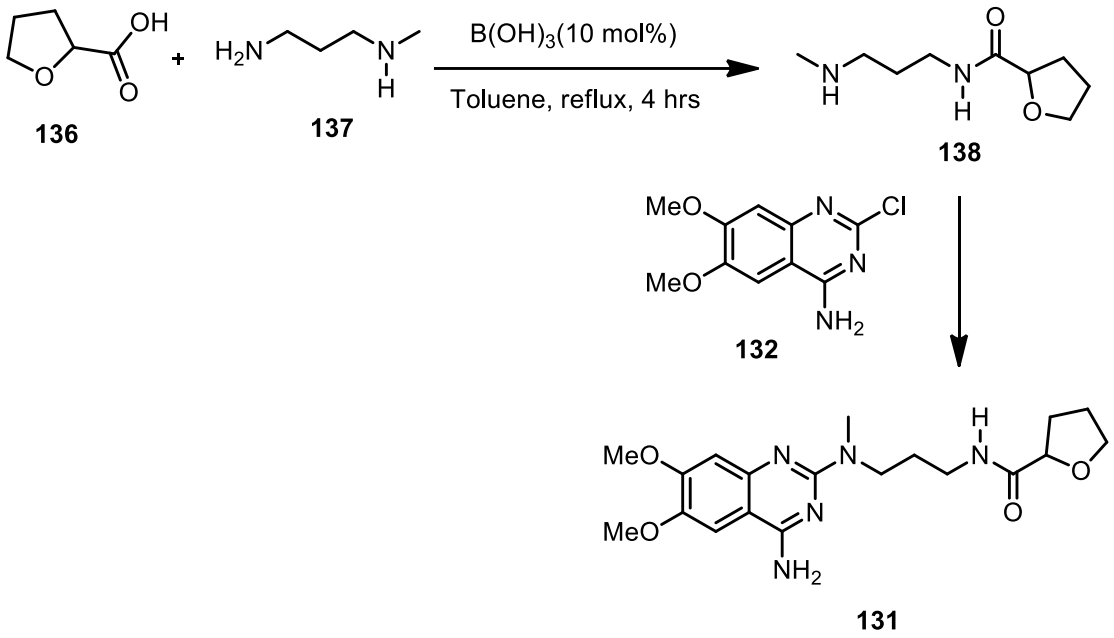
Fig 12. Alfuzosin **131**

Alfuzosin **131** can be synthesized in three steps,[151] shown in Scheme 19, which involves: a) condensation of chloroquinazoline **132** with the 3-methylaminopropionitrile **133** in the presence of a polar aprotic solvent to form cyanoethylamine compound **134**; b) hydrogenation of **134** using a hydrogenating agent like Raney-nickel to form the diamine **135**; and c) condensing the amine **135** with the acid **136** followed by the standard amide formation process (using coupling agents) to form alfuzosin base **131** or as a salt.



Scheme **19.** One route towards the synthesis of alfuzosin

In order to progress the atom efficiency of the amide formation stage of the synthesis, recently Dr. Reddy's laboratory developed a new synthetic route[152] to alfuzosin **131** (Scheme 20). Tetrahydro-2-furanoic acid (**136**) was first converted to the alfuzasin intermediate **138** successfully by direct amidation reaction with 3-(methylamino)-1-propylamine (**137**) (yield 94% by GC analysis). Both the acid **136** and amine **137** are commercially available. The alfuzasin intermediate **138** then react with chloroquinazoline **132** to form alfuzosin **131**.



Scheme **20.** Synthesis of alfuzosin by the direct amide formation

The aim of this part of the project was to investigate whether the reaction step of amide **138** from acid **136** in the new synthetic route could also be carried out favourably by cooperative catalytic direct amide formation.

Our attempts started with the re-examination of the direct amidation of tetrahydro-2-furoic acid **136** and amine **137** (Equation 36) refluxing in toluene in the presence of 5 mol% catalyst **1**[$B(OH)_3$]. Drying was carried out by the use of Dean-Stark technique and the reaction was run under argon (Equation 36) for 24 hrs affording 82% yield of amide **138** (after acid-base extraction) with an excellent regeoselectivity towards the primary amine rather to the secondary amine (Entry 1, Table 17).

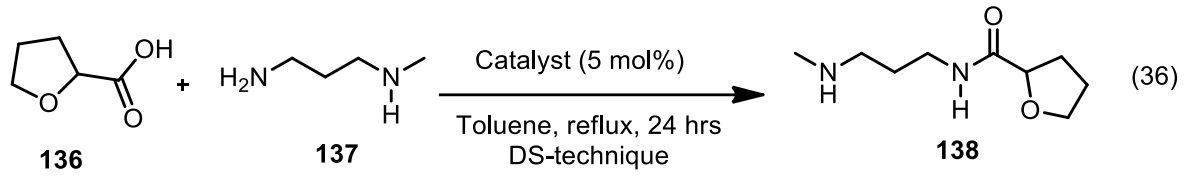
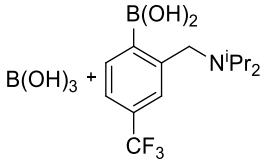
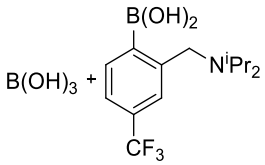
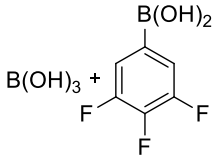


Table 17. Direct amidation of acid **136** with amine **137** to form the amide **138**

Entry	Catalyst (5 mol%)		Solvent and Temp.(°C)	Drying method	[a]Yield of amide 138 (%)
1	**1**	$B(OH)_3$	Toluene (110)	Dean-Stark	82
2	**III**		Toluene(110)	Dean-Stark	85
3	**III**		Fluorobenzene (85)	4Å MS in the Soxhlet	8
4	**I**		Toluene(110)	Dean-Stark	40

[**a**] Isolated yield of pure amide, reaction condition: T = 110 °C, acid (2.86 mmol), amine (2.86 mmol), solvent (20 mL), t = 24 h.

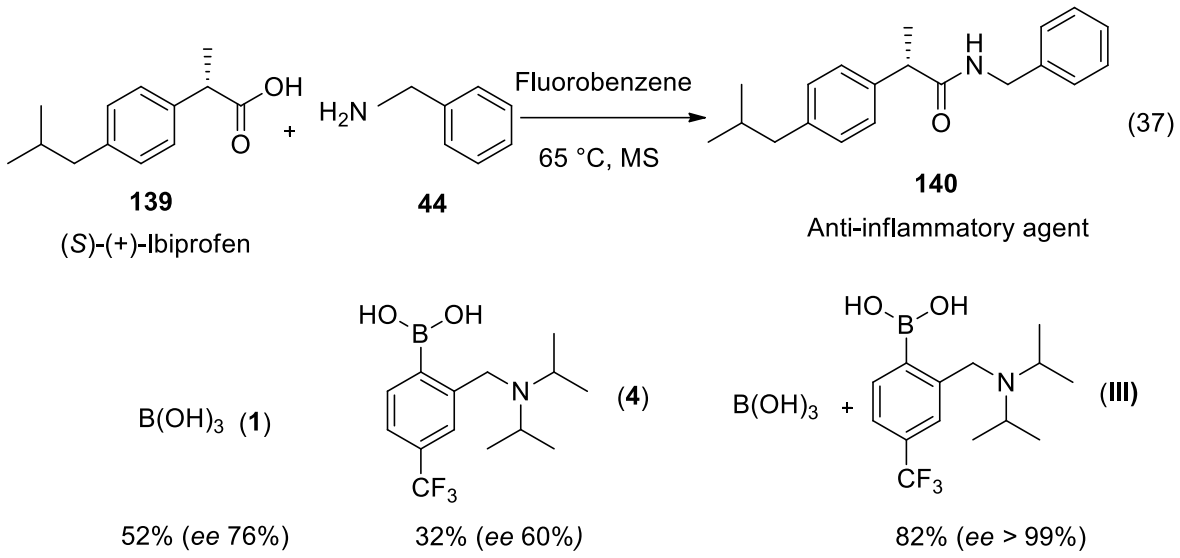
Again, the reaction was carried out in presence of 5 mol% cooperative catalyst **III** to probe the synergistic effect of cooperative catalyst on the rate of direct amidation process. However, no significant enhancement in rate was observed within these conditions (Entry 2, Table 17). Moreover, the regeoselectivity was same as with the single catalyst **1**. Therefore, in an attempt to improve the yield of amide produced, the reaction solvent was changed to more polar solvent, fluorobenzene, in order to achieve more solubility at its reflux temperature and reduce the high temperature effect. But, the result was disappointing (yield

of amide was only 8%, entry 3, Table 17), which showed no advantage over the high boiling solvent. Even changing the catalyst to another potential cooperative catalyst **I** (mixture of $B(OH)_3$ and 3,4,5-trifluorophenylaboronic acid) in this direct amidation reaction did not improve the yield, rather surprisingly, the yield was reduced substantially in presence of this cooperative catalyst (only 40% of amide **138** formed, entry 4, Table 17), indicating a negative synergistic effect of cooperative catalyst **I** in this amidation reaction.

4.3.5.5 Synthesis of Ibuprofen Amide

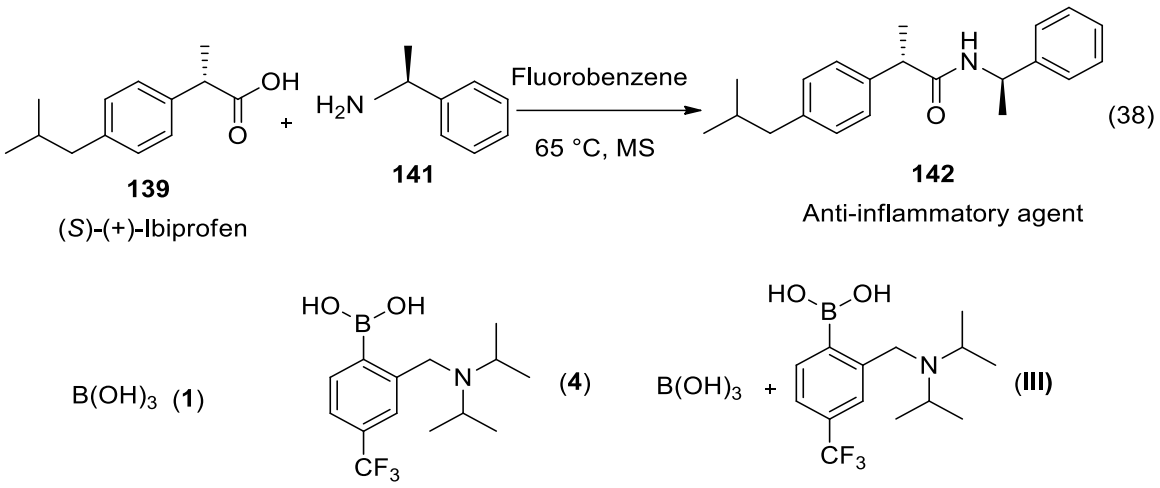
Ibuprofen (**139**), namely [2-(4-*iso*butylphenyl) propionic acid], belongs to the arylpropionic acid family and that is mostly used for anti-inflammatory and anti-pyretic properties. Ibuprofen amides have been known to display upgraded anti-inflammatory activity with lower toxicity and therefore, their syntheses have taken an important attention to the synthetic chemists. However, most of the methods for preparing various kinds of ibuprofen amides are based on the standard amide formation techniques using different coupling agents like CDI, $SOCl_2$ *etc.* where excess coupling agent and chromatographic purification is required.

In order to improve the atom efficiency during the synthesis of ibuprofen amide, a direct amidation process was thought to be preferable. Precedent for this approach was reported recently, where optically active (*S*)-ibuprofen amide (**140**) was synthesised by direct amidation of (*S*)-ibuprofen with benzylamine and also with (*R*)-(+)-α-methylbenzylamine in THF in the presence of 10-20 mol% of catalyst **5** (2-iodophenylboronic acid), with less than 5% racemisation,[1] However, the yields were not high (70-73%) even with a high catalyst loading (20 mol%). In order to improve the reaction rate and also the yield, this part of the project attended to synthesize these biologically important (*S*)-ibuprofen amides **140** and **142** by cooperative catalytic direct amidation process, and hence, ensuring a simple and highly economic process.



The reaction started with the commercially available (*S*)-ibuprofen **139** and benzylamine **44** in presence of 5 mol% cooperative catalyst **III** [1:1 mixture of $B(OH)_3$ and 4-TFM-2-*N*,*N*-DIPMAPBA] in fluorobenzene (Equation 37). In order to prevent any racemisation, high temperature (110 °C) was avoided. On the other hand, room temperature was not suitable for the rate enhancement required, as discovered in the previous study.[1] Therefore, the direct amidation was carried out at a moderate temperature (65 °C). Also, to ensure better solubility, fluorobenzene was preferred to use as solvent instead of less polar toluene. Molecular sieves (4 Åpowder form) were used to scavenge the water by-product of the reaction conveniently. Catalyst **III** enhanced the reaction rate efficiently and formed an excellent yield of the corresponding ibuprofen amide **140** (82%) within 24 hrs with less than 1% racemisation.

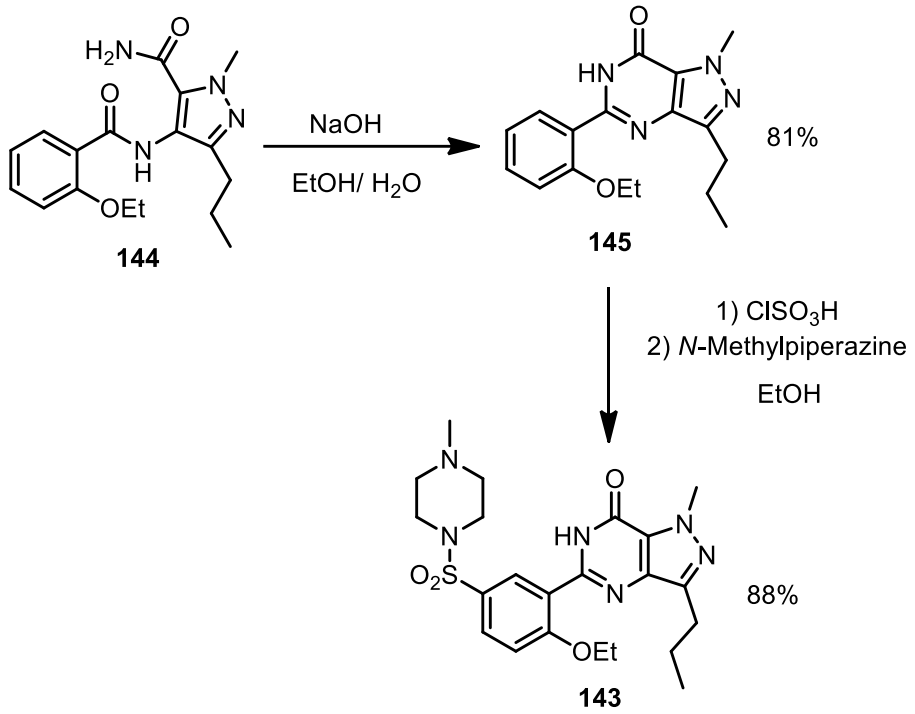
A parallel series of experiments were also carried out with catalyst **1** and **4** under the same reaction conditions, although the rates were much lower compare to the cooperative catalyst **III**. Similar rate enhancement was observed with another potential cooperative catalyst **XIII** (1:1 mixture of $ZrCl_4$ and 2-*N*,*N*-DIPEAPBA), although the yield was less than the catalyst **III** (afforded 64% of the ibuprofen amide **140**). The uncatalysed thermal reaction did not display any trace amount of amide **140**.



The contribution of single catalysts were notably higher in the other direct amidation of (*S*)-ibuprofen **139** with the optically active (*R*)-(+)-α-methylbenzylamine **141** to form ibuprofen amide **142** (Equation 38), although the cooperative effect increased the yield much higher than the individual catalysts. The chiral HPLC analysis revealed less than 5% racemisation in the amide **142**. It is remarkable that both of the ibuprofen amides can be made with such ease using the novel approach of cooperative catalysts.

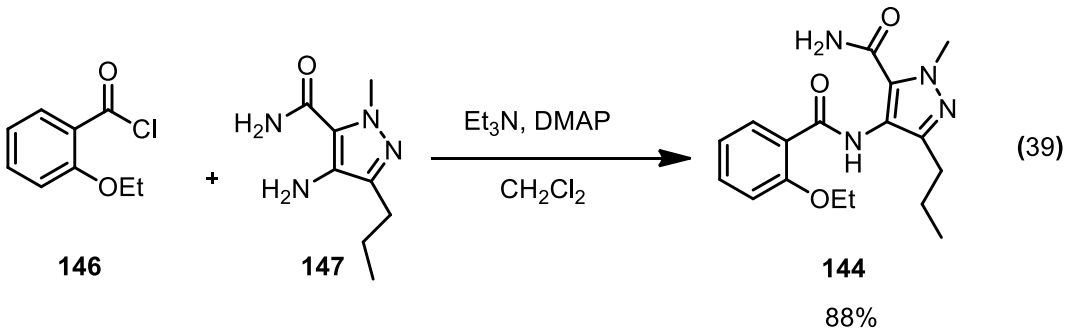
4.3.5.6 Synthesis of Sildenafil Precursor

'Sildenafil' (**143**) has been commercialised since 1998 as Viagra®, Revatio® and under different other trade names. It has been the prime medication of erectic dysfunction and pulmonary arterial hypertension (PAH).[153,154] Sildenafil **143** can be synthesised from the cyclisation of the amide precursor **144**, which is followed by sulfonation to give the chlorosulfonylderivative. At the end, the derivative is condensed with 1-methylpiperazine to afford Sildenafil **143** (Scheme 21).[155-157]

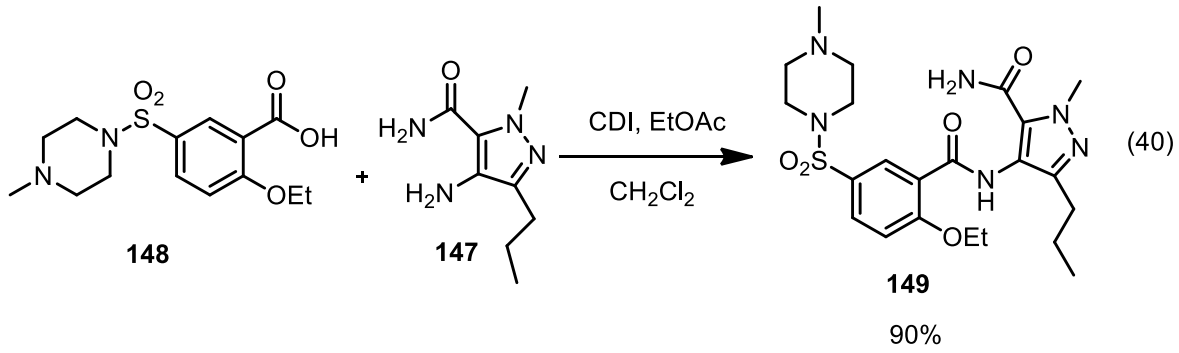


Scheme 21. Synthesis of Sildenafil **143** (one of the routes)

The amide precursor **144** can be formed by the typical amide formation procedure using the acid chloride **146** as displayed in Equation 39.[8,11]



A second route of the synthesis of **143** (Equation 40) demonstrated the chlorosulfonation reaction is accomplished before the amidation and the successive cyclisation. Likewise, the synthesis of the key intermediate associates an amide formation reaction which is performed using the coupling agent carbonyldiimidazole (CDI). Then, the amide **149** can undergo cyclisation in order to produce Sildenafil **143**.



148 + **147** → **149** (40)

90%

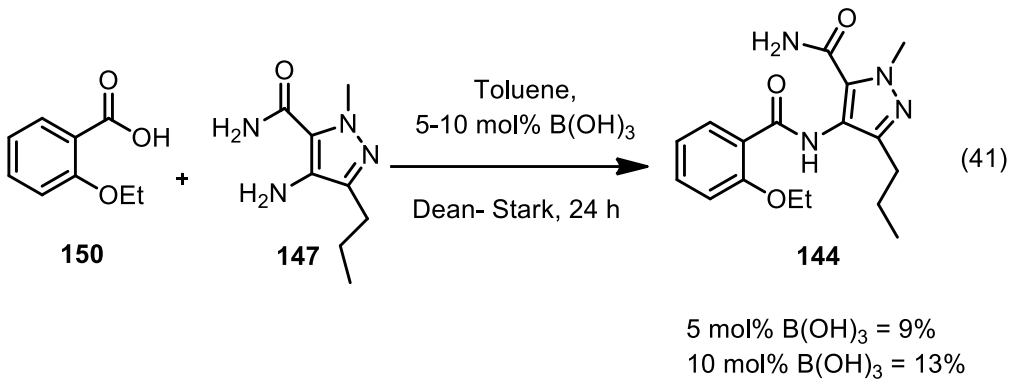
The most unfavourable feature of these two routes towards the syntheses of the two Sildenafil precursors (**144** and **149**) is the use of relatively expensive and toxic activation reagent (like CDI) or catalyst (like DMAP), as well as expensive and tedious purification steps to separate the by-products associated with these reagents.

In an effort to improve the synthesis of Sildenafil precursor (**144** and **149**) and apply direct amide formation as a more convenient technique, Equation 39 and 40 were attempted to carry out by catalytic direct amide formation leading to an overall atom efficiency of this stage. Similar efforts were taken before in our group, but were not successful with the potential $B(OH)_3$ catalysed direct amidation process. Therefore, the novel cooperative catalysis was deemed to be effective in the synthesis of the Sildenafil precursors **144** and **149**.

2-Ethoxybenzoic acid **150** is commercially available, and the amine **147** was kindly provided (as a form of HCl salt) by Pfizer. The HCl salt was treated with 20% NaOH to make the solution slightly basic (pH~9) and then extracted with $CHCl_3$ to afford a pale white solid of amine **5** (yield 98%).

With the amine in hand, the direct amide formation reactions were investigated. Initially the carboxylic acid **150** and amine **147** were refluxed in toluene for 24 hours without any catalyst. Drying was carried out by the means of a Dean-Stark condenser and the reaction was

done under argon (Equation 36). After 24 hours, the thermal conversion of amide **144** was only 3% (determined by ^{1}H NMR).



5 mol% $B(OH)_3$ = 9%
10 mol% $B(OH)_3$ = 13%

The reaction was re-examine in presence of 5 mol% $B(OH)_3$ [12,13] (catalyst **1**) for 24 h and was followed by TLC. Even after 5 days the reaction mixture comprised of large starting materials. Accordingly, the reaction was worked up affording very low (only 9%) amide product **144** as a pale white solid. Further addition of 10 mol% boric acid barely increased the yield to 13% of amide under the same reaction conditions (Equation 41).

Although, the direct amide formation reactions worked, these reactions were slow and did not provide good yields. Therefore, in an attempt to raise the yield, the reaction solvent was altered to xylene to attain a higher reflux temperature (140 °C). After 5 days with 10 mol% boric acid the yield of amide was unsatisfying (9%), which showed no development over the reactions accomplished in the lower boiling solvent toluene (b.p. 110 °C). These results support the previous study in our group.[165] However, since there was no decomposition of starting materials during any of these reactions, it was thought to be due to a certain reactivity issue under the reaction conditions and not for the stability of the starting materials.

Potential arylboronic acid catalysts were chosen in order to investigate further in the synthesis of the precursor **144**, as shown in Table 18, especially employing the novel cooperative catalytic systems.

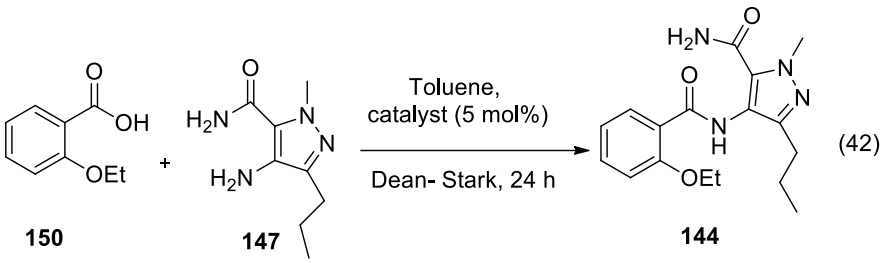
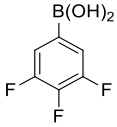
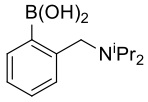
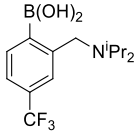
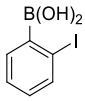
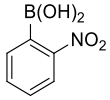
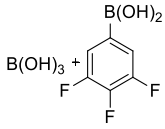
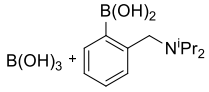
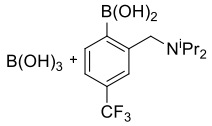
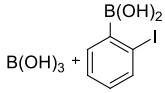
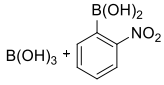
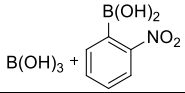


Table 18: Effect of different arylboronic acid catalysts on the synthesis of Sildenafil precursor **144** (Equation 42).

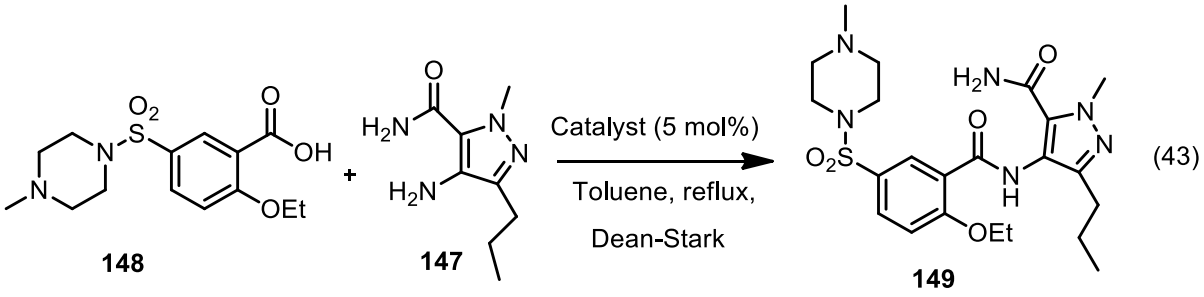
Entry	Catalyst	[a]Conversion (%)
1	**2** 	4
2	**3** 	1
3	**4** 	8
4	**5** 	1
5	**7** $ZrCl_4$	6
6	**8** 	9
7	**I** 	8
8	**II** 	8
9	**III** 	15
10	**IV** 	2
11	**V** $B(OH)_2$ + $Fe(OTf)_2$	30
12	**VI** $ZrCl_4$+ $B(OH)_3$	8
13	**XVII** 	93
14	**XVII** 	88[b]

Reaction conditions: acid (2.86 mmol), amine (2.86 mmol), toluene (20 mL), catalyst loading (5 mol%), T=110 °C, t= 24 h; [a]Percent of conversion was determined by ^1H NMR. [b] Reflux in fluorobenzene (85 °C).

With a catalyst loading of 5 mol%, the rate of the amide **144** formation was quite slow with all the single arylboronic acid catalysts as in most cases the percent of conversion was poor (Entry 1-6, Table 18) and little enhanced catalytic activity was displayed by the different cooperative catalysts; the percent of conversion was still low in most cases. Only the cooperative catalyst **XVII** [$B(OH)_3$ and 2-nitrophenylboronic acid mixture] showed a significant contribution to covert the acid **150** into the amide **144** (92% conversion, Entry 13, Table 18) under the same conditions. Even at lower temperature (85 °C) refluxing in fluorobenzene, the conversion of amide **144** was more than 80% (Entry 14, Table 18) with this cooperative catalyst; whereas, the rate of the reaction was quite sluggish with the individual 2-nitrophenylboronic acid alone to afford very low conversion of precursor **144** (Entry 6, Table 18). Precedent of this interesting synergistic catalytic effect has been reported in the previous sections. However, further investigations were carried out regarding scaling up the reaction for finding the real industrial applicability.

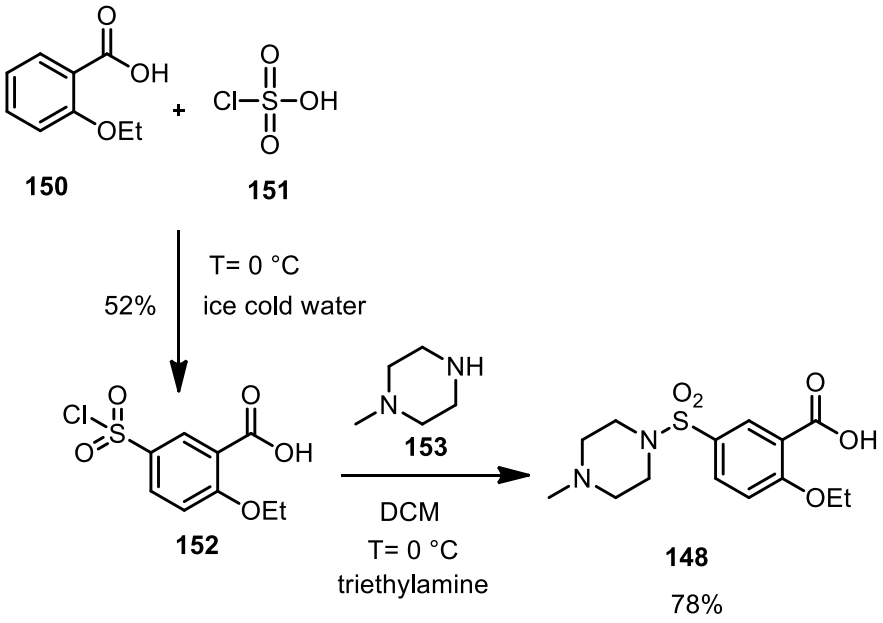
The effect of Fe(II) based cooperative catalyst (cooperative catalyst **V**) was noticeable in this direct amidation process. The conversion of amide **144** was 30% under identical conditions (Entry 11, Table 18). Therefore, the reaction was run for a further 48 hrs and more than 60% conversion was achieved. It was noteworthy that the crude ^1H NMR consisted of broad peaks in presence of Fe-catalyst (due to its paramagnetism property), a small column of Celite and silica followed by the washing of hexane and EtOAc (1:1) separated the catalysts from the reaction mixture, and solved the problems of screaning NMR spectra. Having the same kind of group properties like, Fe(II), $Yb(OTf)_3$ and $Sc(OTf)_3$ (along with their mixture with $B(OH)_3$) were also employed in the Equation 37, however, they were not efficient as $Fe(OTf)_2$ to form the amide **144** by the direct amidation.

Furthermore, the Sildenafil precursor **149** was also synthesised by the direct amidation procedure with the successful cooperative catalyst **XVII** which is shown in Equation 43.



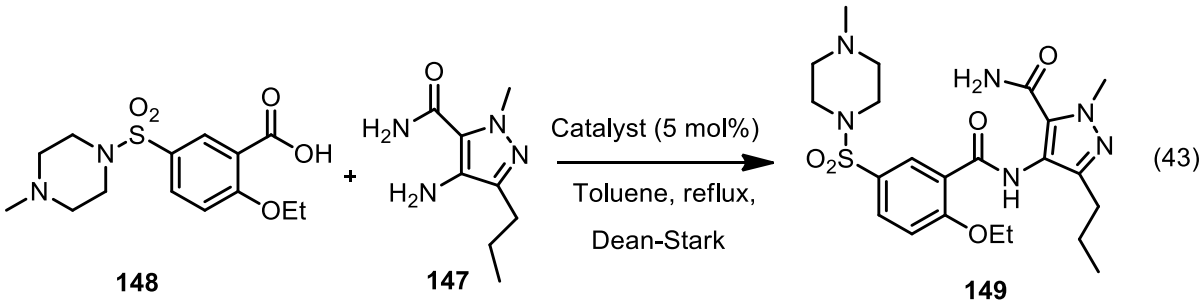
(43)

Before the amidation reaction, the acid **149** was synthesized from the compound **150** followed by a two step routes as shown in Scheme 22.



Scheme **22.** Synthesis of acid **148**

2-Ethoxybenzoic acid **150** was treated carefully with chlorosulfonic acid **151** at 0 °C followed by the addition of ice-cold water followed by the extraction with DCM forming the sulfonated derivative **153** with a yield of 52% as white solid. The derivative **152** then went through the nucleophilic substitiution with 1-methylpiperazine **153** in DCM at 0 °C in presence of triethylamine yielding compound **148** within 2 hrs. The yield of compound **148** was 78% and afforded as white solid.



148 147 149 (43)

With the acid in hand, the direct amidation of acid **148** and amine **147** was carried out in presence of 5 mol% of cooperative catalyst **XVII** (Equation 43). For comparison, the reaction conditions were kept unaltered. After 24 hrs, the crude ^{1}H NMR showed very low conversion of amide **149** compared to the other form of Sildenafil precursor **144**. Presumably, this was due to the hindrance of both the acid and amine functionality. Hence, the investigation of the synthesis of Sildenafil precursor in this route was suspended.

4.3.6 Conclusion

In this chapter, the scope of the newly developed cooperative catalysts were revealed by applying them in less reactive amino acid derivatives syntheses, as well as in more desirable dipeptide synthesis. Overall, the use of combined catalysts in the direct amidation displayed some potential over single catalytic approaches.

Table 19. Use of Cooperative catalysts in different direct amide bond formation reactions

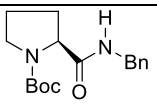
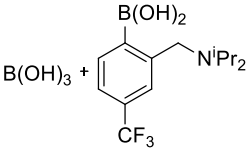
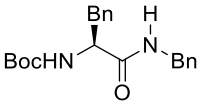
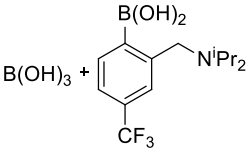
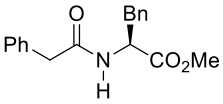
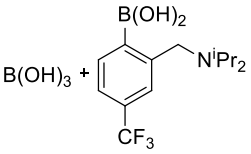
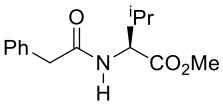
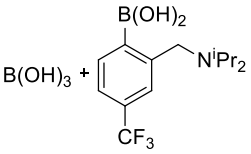
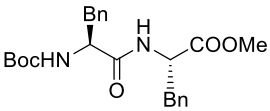
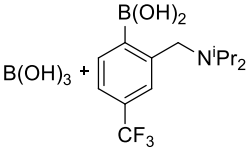
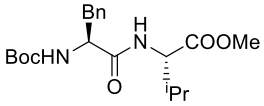
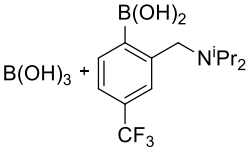
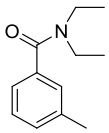
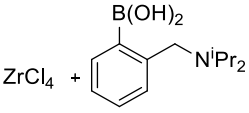
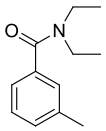
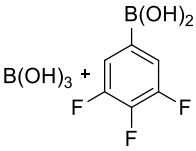
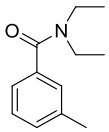
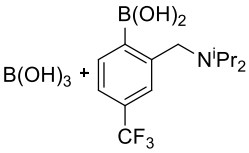
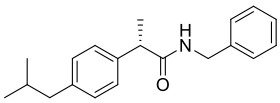
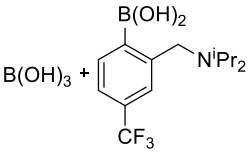
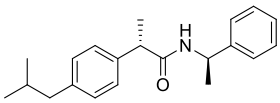
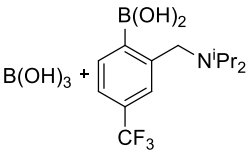
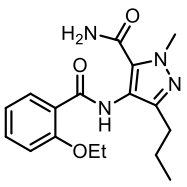
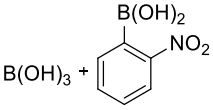
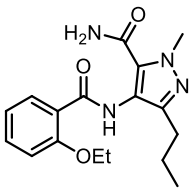
Entry	Amides formed	Structure of amide	Catalysts used	Catalyst number	Temp (°C)	Isolated Yield (%)
1	amide **109**			**III**	65	92
2	amide **111**			**III**	65	89
3	amide **113a**			**III**	65	86
4	amide **113b**			**III**	65	84
5	amide **114**			**III**	65	86

Table 19 continued

Entry	Amides formed	Structure of amide	Catalysts used	Catalyst number	Tempe. (°C)	Isolated Yield (%)
6	amide **115**			**III**	65	89
7	DEET **119**			**XIII**	110	72[a]
8	DEET **119**			**I**	110	60[a]
9	DEET **119**			**III**	110	56[a]
10	(*S*)-Ibuprofen amide **140**			**III**	65	82
11	(*S*)-Ibuprofen amide **142**			**III**	65	93
12	Sildenafil precursor **144**			**XVII**	110	88[b]
13	Sildenafil precursor **144**		$B(OH)_2$ + $Fe(OTf)_2$	**V**	110	60[c]

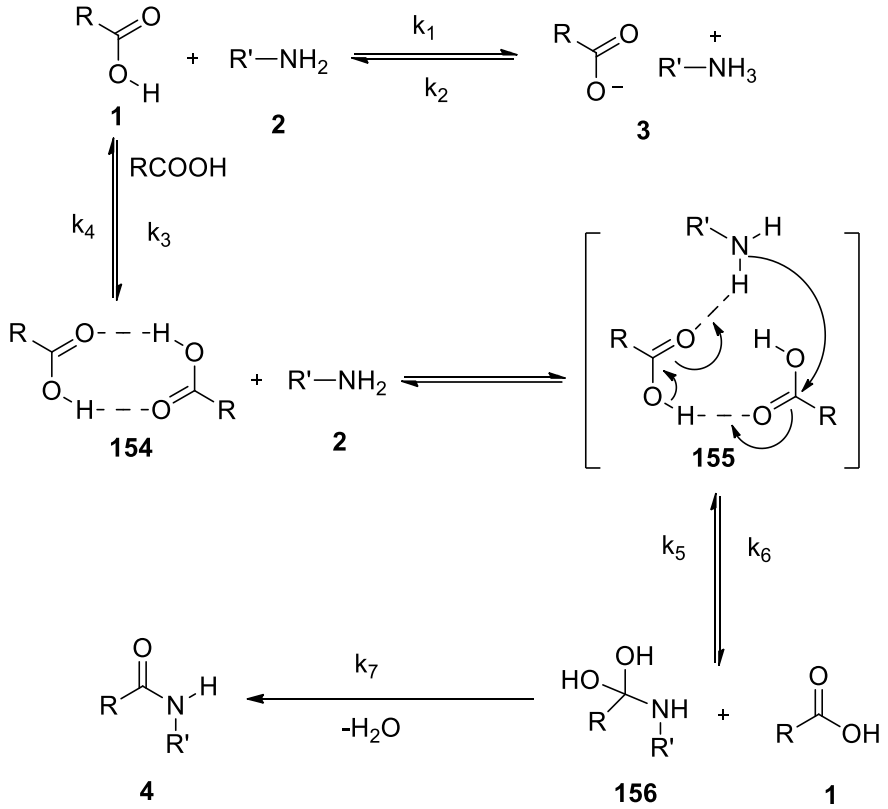
The results also suggest that cooperative catalysis can be beneficial in direct amide bond formation even at low temperature. Indeed, the novel approach of cooperative catalysis also introduces a new era in the direct amidation process for the real industrial application (like the Sildenafil precursor **144** synthesis, DEET *etc*.). This direct catalytic amidation is operationally very simple. It employed equimolar amounts of acid and amine substrate; generated no toxic by-product and it afforded pure amide products after a simple acid-base extraction to remove any unreacted acid or amine and the catalyst. The boronic acid catalyst can be recovered efficiently from the basic aqueous phase.[1] Considering the reported method for the synthesis of the industrially important compounds (using excess coupling reagents and chromatographic purification), it is remarkable that amide bond can be made with such ease using the new catalytic approach. It is important to continue the research in this cooperative catalytic area to get a universal acceptance in the direct amide formation.

Chapter 5: Mechanism Studies and Development of Novel Catalysts

5.1 Acid Catalysed Direct Amide Bond Formation

5.1.1 Introduction

The role of H-bonding in amide bond formation has been conceived for some years. A previous kinetic study[27] showed that H-bonding with the carbonyl oxygen by protonation increased the electrophilicity of carboxylic acid which ultimately facilitates the attack of amine leading to amide bond formation. Kinetic evidence showed that direct amide formation was not amenable to either general acid or base catalysis as only a minor effect was observed on the rate of amide formation from the addition of excess acid or amine.



Scheme 23. Mechanism for direct amide formation supported by DFT[27]

Further, DFT calculations suggested that amide bond formation proceeds through an intermolecular carboxylic acid hydrogen bonded dimer **154**, which plays an important role to activate carboxylic acid **1** towards the neucleophilic attack by the amine **2** (Scheme 23). Not only that, the H-bonded dimer **154** also helps the reaction to proceed through to a neutral intermediate **156** (*via* the transition state **155**) which is energetically accessible.[27] It is

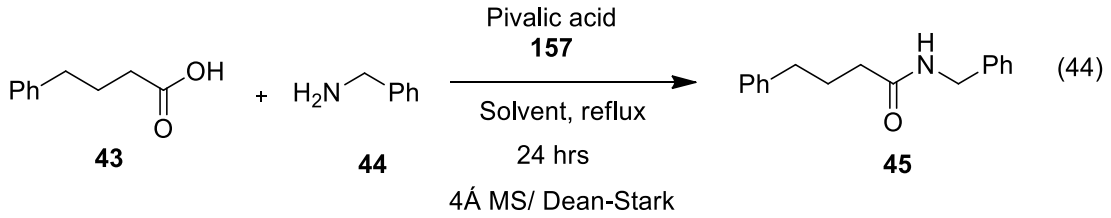
noteworthy that such H-bonded carboxylic acid dimers **154** persist not only at high temperature but are also highly favourable in non-polar solvents.

In order to examine in more detail of the role of H-bonding in direct amide formation, investigations into direct amide bond formation in the presence of a carboxylic acid, which will be unreactive towards the amidation process was undertaken. The idea was to see if an external carboxylic acid could be efficient at forming strong H-bonded dimers with carboxylic acid substrates, and hence, facilitate amide bond formation.

5.1.2. Direct Amide Formation Using Pivalic Acid

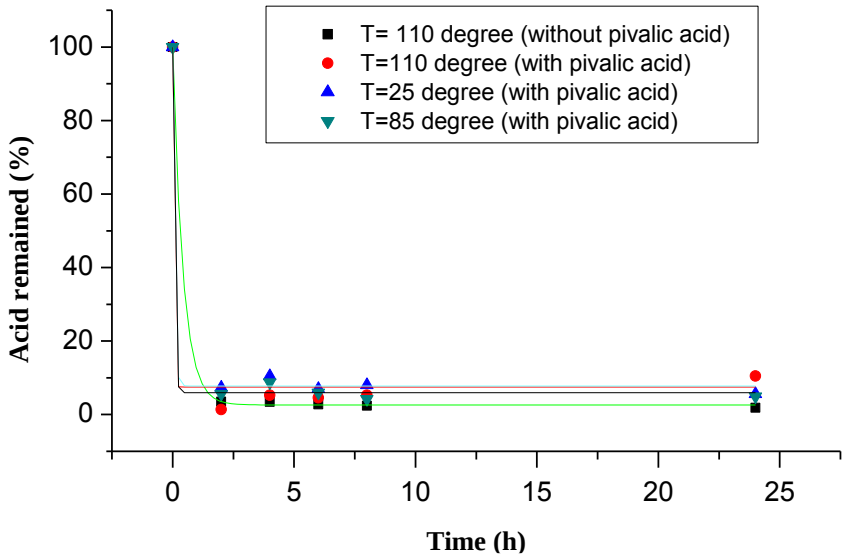
5.1.2.1 Reaction Progression Followed by HPLC

To start, the direct amide formation reaction of 4-phenylbutyric acid **43** and benzylamine **44** in presence of pivalic acid **157** was investigated (Equation 44). Pivalic acid (trimethylacetic acid), is inert towards amine reaction to form the corresponding amide (pK_a of pivalic acid is 4.83 at 20 °C). So, it was deemed that this acid **158** might be suitable to form the H-bonds with the carboxylic acid **43** to make the carbonyl group (C=O) more electrophilic towards amine **44** attack, and hence, possibly enhance the rate of amide **45** formation.

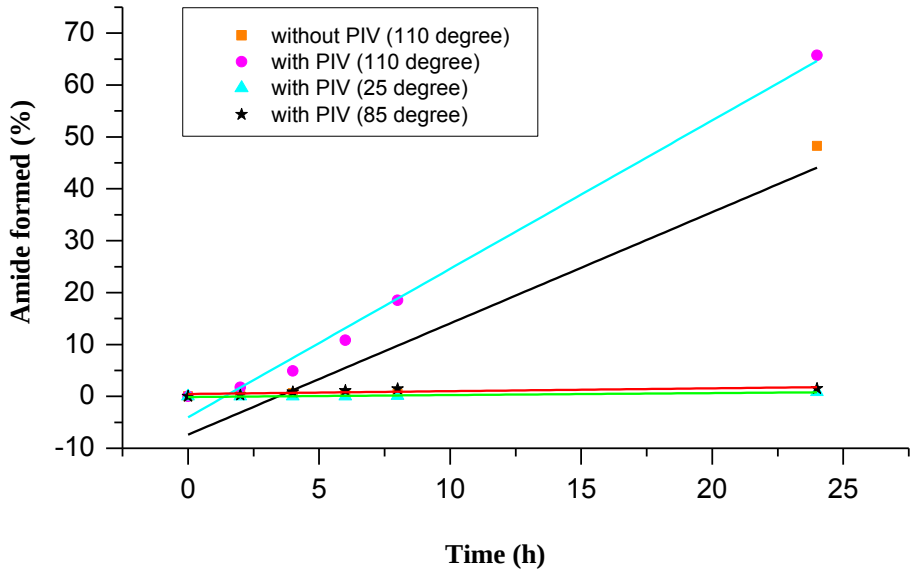


(44)

According to the previous study, the carboxylic acid dimer **155** formation was particularly efficient in non-polar solvents and even at high temperatures,[17] therefore, the direct amidation of acid **43** and amine **44** was carried out in refluxing toluene at 110 °C. The reaction progression was followed by reverse phase HPLC.



(a)



(b)

Without pivalic acid at T= 110 °C, isolated yield: 50%,

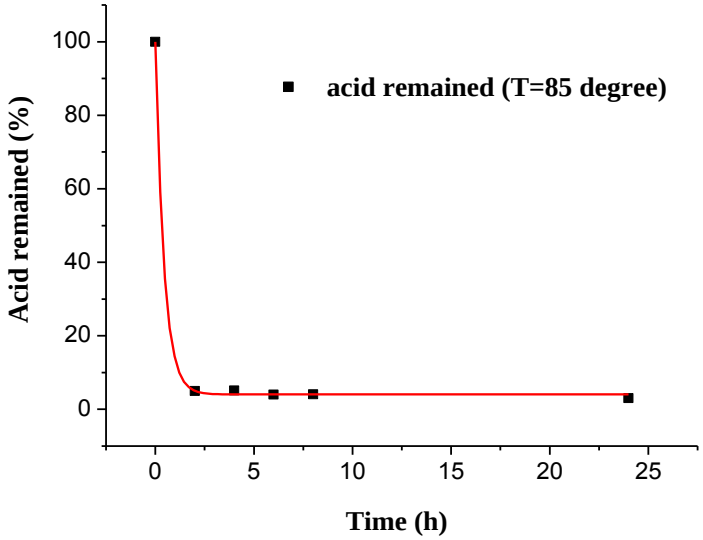
with pivalic acid at T= 110 °C, isolated yield: 55%, at T= 25 °C amide conversion < 1% and at T= 85 °C amide conversion < 2%

Fig 13. Reaction progression of 4-phenylbuyric acid and benzylamine in toluene at different temperatures with or without pivalic acid: a) acid consumption, b) amide formation

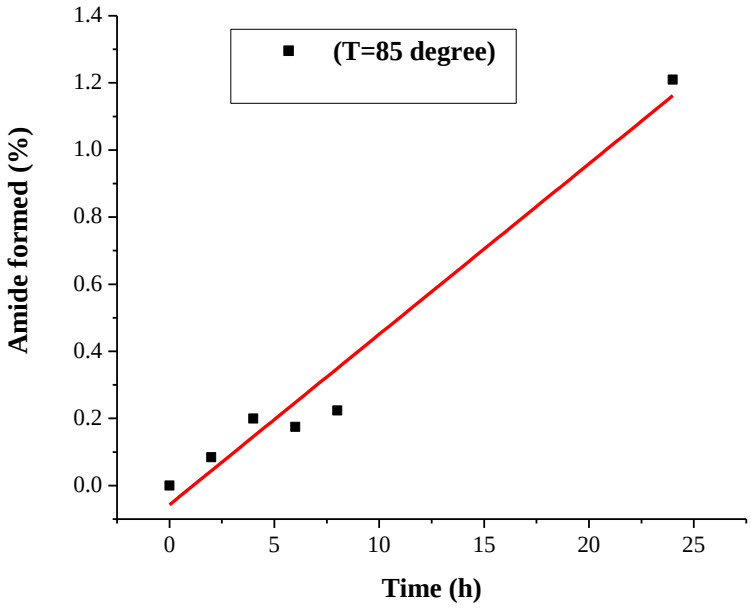
From the Fig 13a, it is clear that the acid **43** consumption was so fast at different temperatures, presumably forming a salt, and on the contrary, the amide **45** formation was slow to form and in a linear manner (Fig 13b). The thermal reaction was quite significant to produce 50% of amide **45** using the standard conditions. Although the total amount of acid was close to zero after 24 hrs(Fig 13a), the conversion of acid **43** into amide **45** was not 100% (Fig 13b)., indicating the formation of some sort of other species, most likely ammonium salt along with the desired amide. With the addition of pivalic acid **158** in this direct amidation, a slight rate enhancement as well as higher yield of amide **45** (55%) was observed in comparison to the thermal reaction(Fig 13b), although the trend of acid **43** consumption was similar in both cases (Fig 13a). This rate enhancement might be due to the formation of the theorised H-bonded dimer **154** with the added pivalic acid **157**. Indeed, the rate enhancement was very close to the calculated ranges, but this difference may be a real effect. Hence, if amidation is truly amenable to such catalysis of pivalic acid **157**, a more significant rate enhancement would have been expected to be observed.

The reaction was examined further at room temperature (25 °C) and at 85 °C in toluene to compare the lower temperature effects, as outlined in Fig 13a and 13b. The trends of acid consumption at these temperatures were almost similar to the high temperature (Fig 13a). But the formation of amide **45** was negligible at these temperatures (Fig 13b). This might be due to the lower formation of the theorised H-bonded dimer **154** at these temperatures with the added pivalic acid **157**; this again supports the previous observation that the H-bonded dimer formation is not much favourable at lower temperature.[27]

It was presumed that changing of non-polar solvent (toluene) might enhance the formation of amide in presence of pivalic acid. That is why, the reaction was examined further in more polar solvent, fluorobenzene (T = 85 °C), instead of toluene.



(a)



(b)

Fig 14. Reaction progression of 4-phenylbuyric acid and benzylamine in fluorobenzene with pivalic acid at 85 °C: a) acid consumption, b) amide formed

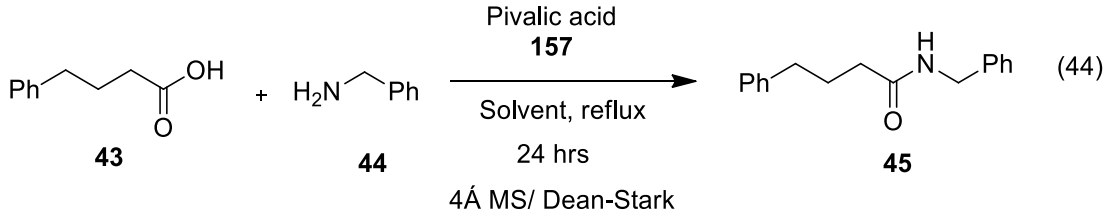
The reaction progression in case of acid **43** cosumption in fluorobenzene was similar to that in toluene (Fig 14a). But there was no sign of increase in amide **45** formation due to the addition of pivalic acid **158** in refluxing fluorobenzene as shown in Fig 14b. The amide

conversion was only 1.2% after 24 hrs, which was similar to toluene (the amide **45** conversion was 1.5%) at the same temperature (T = 85 °C). This examination again supported the previous observation[27] that the H-bonded dimer formation is favourable in non-polar solvent than in polar solvent.

5.1.2.2 Reaction Progression Followed by React-IR

In most gaseous compounds, the stretching of the free O-H group absorbs infrared radiation at a frequency close to 3700 cm^{-1}. But in the liquid or solid states, or in relatively concentrated solutions, absorption is shifted to lower frequencies by hundreds of wave numbers in many compounds, resulting in a broad band for the O-H group. This is because the O-H group is no longer free, due to the association through hydrogen bonding to form dimers and higher polymers. It is easy to measure this change of frequency of a few wavenumbers and hence, it is evident that this method is sensitive for detecting hydrogen bonds. The lowering of the frequency is due to the weakening of free O-H bond when it forms the O-H…O bond.

Based on this idea, having examined the reaction progression of carboxylic acid **43** and amine **44** (Equation 44) in the presence of pivalic acid by HPLC, the next stage was to employ the *in situ* FTIR technique (React-IR) to have a better understanding of the mechanism of formation of amide through H-bonding dimmers (like **154**) in presence of pivalic acid **157**. The formation of amide **45** was followed with this technique under uncatalysed conditions for 24 hours. The nature of reaction progression was found to be similar to the HPLC analysis.



(44)

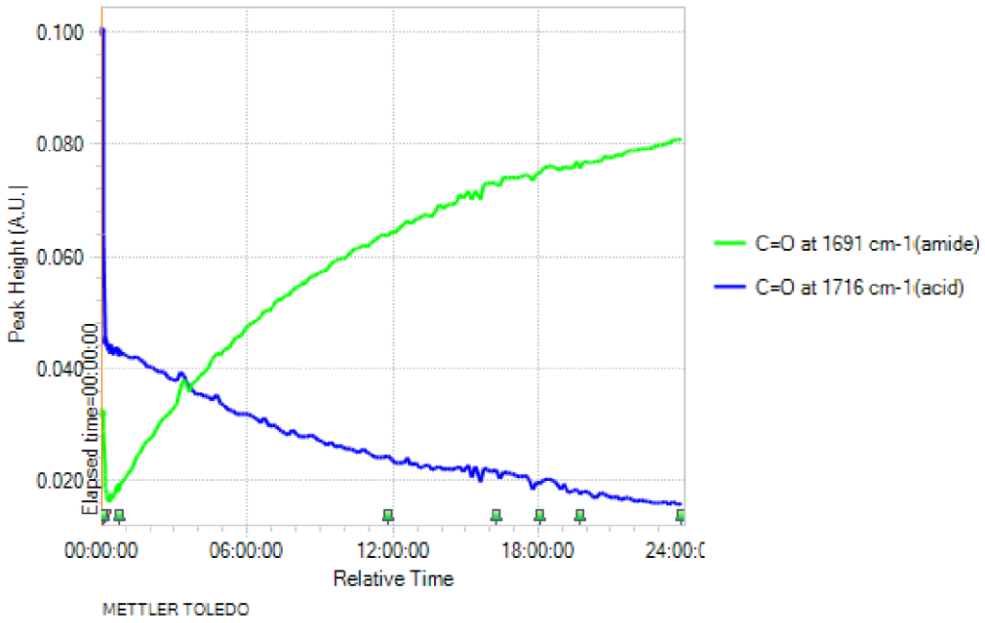


Fig 15. Reaction (Equation 44) progression in thermal condition in toluene

The IR analysis in refluxing toluene at 110 °C without any catalyst (**Fig 15**) showed the peak of –COOH acid disappeared quickly, as soon as the amine was added to the reaction mixture, indicating that the rate of loss of carboxylic acid **43** was fast. It was difficult to measure the O-H…O bond shifting by React-IR during the reaction under refluxing conditions. So the shifting of -COOH peak of carboxylic acid **43** was followed. The carboxylic acid **43** peak shifting was noticd from 1750 cm^{-1} to 1737 cm^{-1} (**Fig 16**), suggesting the formation of the corresponding carboxylate ammonium salt. The shifting towards lower frequency might also be due to the formation of H-bonds between ammonium and carboxylate, the existence of which was proved in the previous study.[27]

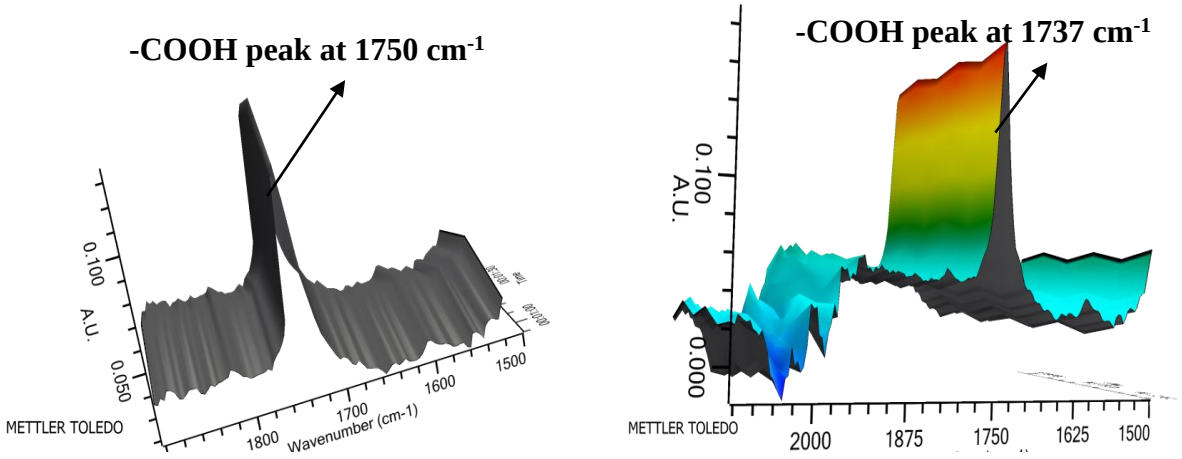


Fig 16. Shifting of –COOH peak of acid **43** (Equation 44) from 1750 to 1737 cm^{-1}.

However, without any catalyst, after 4 min 30 sec, the –CONH amide peak started to appear at 1689 cm^{-1} with an intensity which gradually increased, and after 24 hours the intensity was the highest (**Fig 17**), although the reaction seemed incomplete (**Fig 18**). The isolated yield of amide **45** was 50%, which was similar to the previous HPLC result (see Section 5.2.1, Chapter 5).

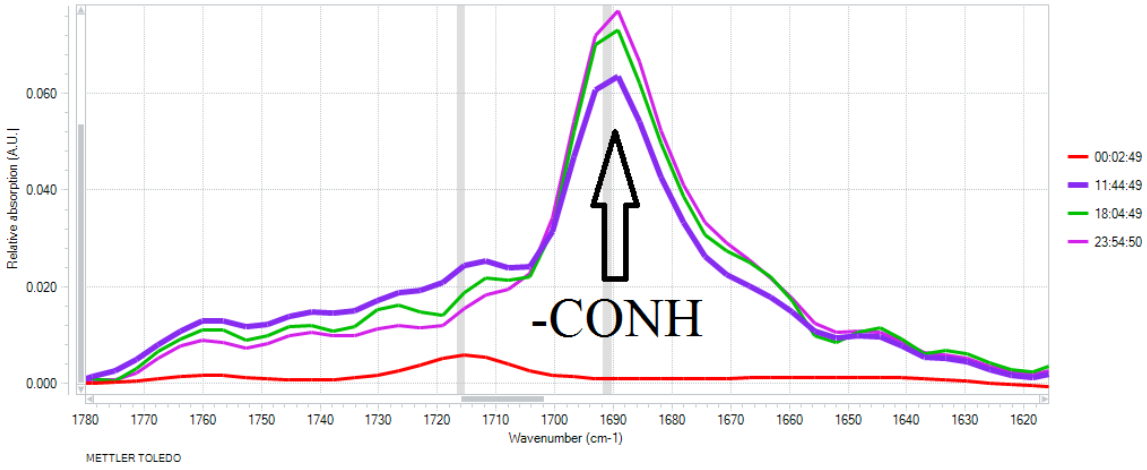


Fig 17. Superimposed IR spectra of amide **45** peak formation with time in thermal condition in toluene

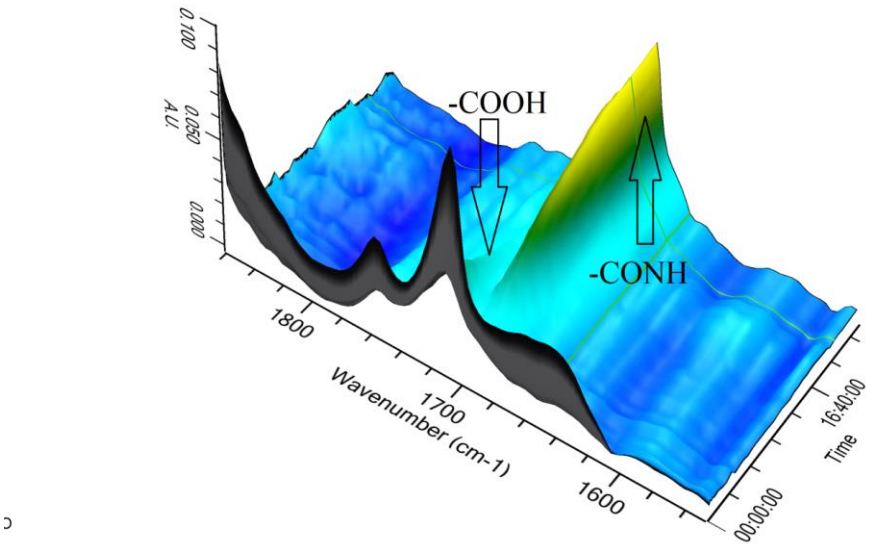
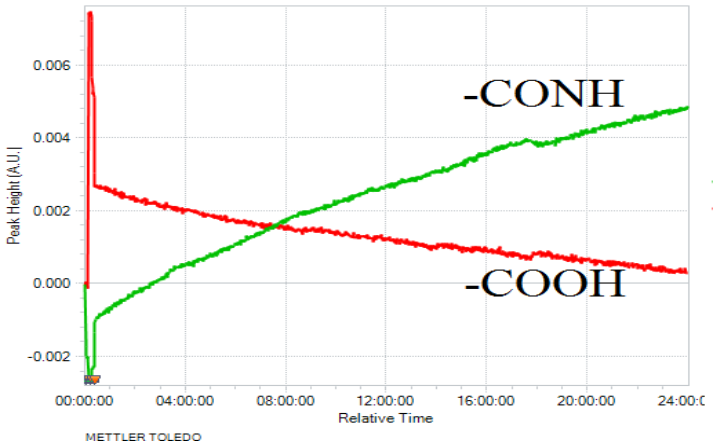
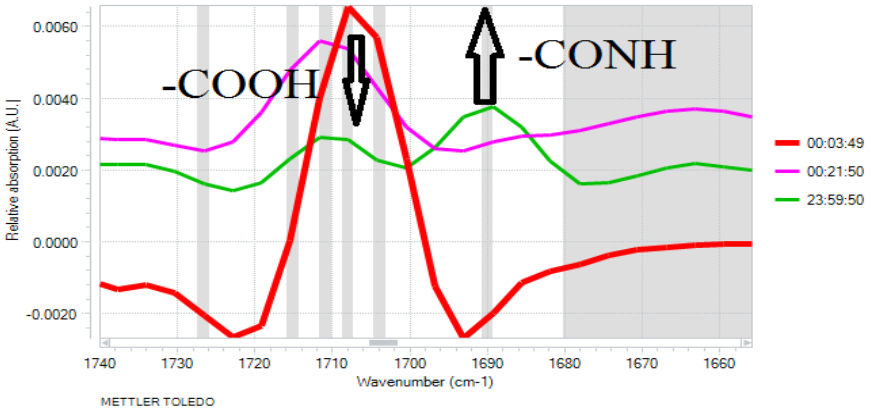


Fig 18. Graphical output of slow formation of thermal amide **45**. Processing - 2nd derivative base-line function was applied.

The next step was to follow the reaction *in situ* in the presence of 1.0 equivalent of pivalic acid **157**. In this case, the loss of the –COOH peak was not rapid (**Fig 19a**), unlike in thermal reaction.



(a)



(b)

Fig 19. a) Reaction progression in toluene with pivalic acid; b) Superimposed IR spectra of amide **45** peak formation with time in presence of pivalic acid **158** in toluene

Although due to the addition of pivalic acid, the intensity of the acid peak at 1725 cm^{-1} increased initially, but it decreased very slowly with the addition of benzylamine **43** over the whole reaction period (24 hrs). In comparison with the thermal IR spectrum, the –COOH peak shifting was smaller in presence of pivalic acid than without pivalic acid. The –COOH

peak shifted from 1725 cm^{-1} to 1715 cm^{-1}, indicating the formation of less weak, or no H-bonds between carboxylic acid **43** and pivalic acid **157** (**Fig 19b**).

The IR spectrum **21** showed slow formation of amide peak at 1690 cm^{-1} in presence of pivalic acid. This indicates a slight positive effect of pivalic acid at this high temperature (T= 110°C) for the amide **45** formation reaction. However, the isolated yield found after 24 hours did not support this, particularly, as the yield (isolated yield: 55%) was almost similar to thermal isolated yield (50%) obtained without using any acid **157** catalyst.

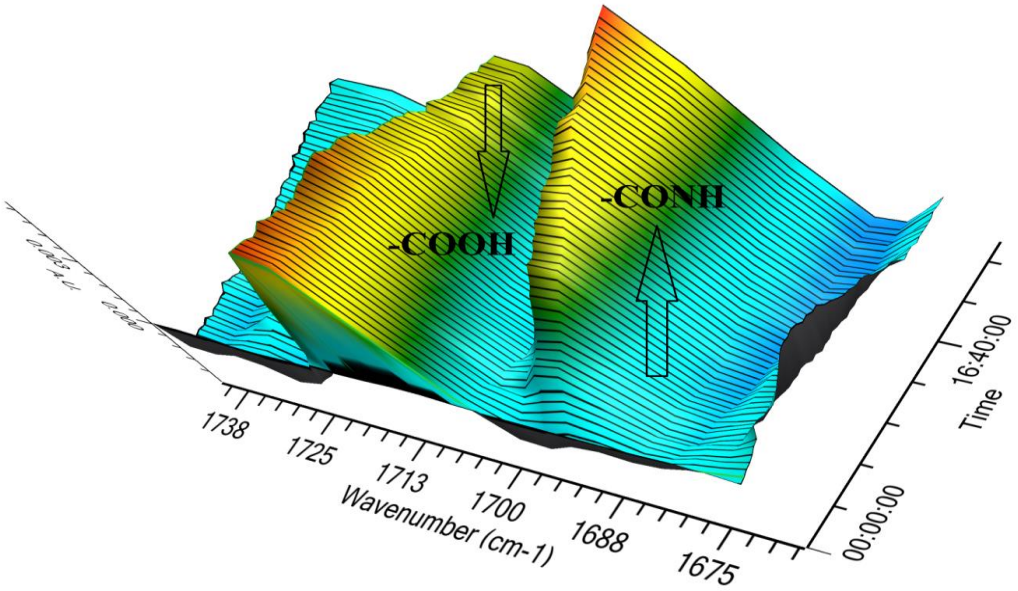


Fig 21. Graphical output of slow formation of amide in presence of pivalic acid. Processing - 2nd derivative base-line functions was applied.

The effect of lower temperature (T = 85 °C) and more polar solvent (fluorobenzene) on the reaction progression in presence of pivalic acid **157** was also examined *in situ* IR spectrum. Unlike the HPLC result, similar sluggish reaction progression of Equation 44 was observed at these conditions (**Fig 22**). In this case, the amide peak started to form at 1686 cm^{-1} very slowly yielding after 24 hours only 30%. Surprisingly, this yield was much lower than the thermal yield (isolated yield 65% without pivalic acid **157**) in fluorobenzene. Evidently, this slow loss of carboxylic acid **43** and the formation of amide **45** in fluorobenzene suggested that the pivalic acid might play a negative role in this case.

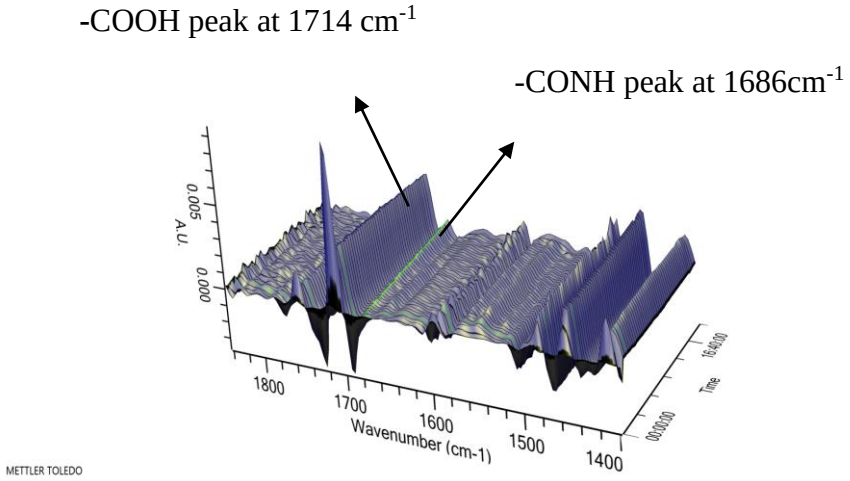


Fig 22. React-IR study of direct amidation of 4-phenylbutyric acid in presence of pivalic acid fluorobenzene

Based on all these evidences, it can be concluded that although it was expected that pivalic acid **157** might increase the rate of amide **45** formation by participating in the H-bond formation, there was no clear or definitive evidence of any major catalytic effect from the use of pivalic acid **157** as a H-bond-based activator for direct amide formation reaction. However, further investigations in the future may assist in the development of acid catalysed direct amide formation reactions.

5.2 Direct Amidations Using Pollen of 'Lycopodium Clavatum'

5.2.1 Introduction

As well as examine the effect of catalysts, we also evaluated the effect of a potential catalyst promoter in the direct amidation reactions at reduced temperature. The idea was based on the fact that a 'promoter' may help to accelerate the catalytic activity of those boronic acid catalysts or other catalysts, at lower temperatures by assisting with localised water removal. Based on this, 'ANB 209', a chemically modified pollen was employed in a hydrophobic reaction chamber which is a fine powder of '*Lycopodium clavatum'*- the most extensive species in the genus *Lycopodium* of the club moss family Lycopodiaceae. The pollen grains have been processed to be reasonably chemically inert and hydrophobic. *i.e. Lycopodium clavatum* crude pollen was heated in acetone and treated with base (heating in KOH for 12 hours), then added acid (80% H_3PO_4 for five days) to convert the entire cellulosic component into –OH groups, which were further converted into ethers (-OMe groups) with Me_2SO_4. Finally, the mixture was reacted with benzylamine for 24 hours in xylene to form amides on any residual carboxylic acids to render the internal surface hydrophobic.

5.2.2 Results

The chemically modified pollen 'ANB 209' was then applied in the direct amidation of 4-phenylbutyric acid **43** and benzylamine **44** (Equation 45) in THF at 65 °C for 24 hrs. For comparison, the reaction was also carried out in refluxing toluene (110 °C). The results are summarized in Table 20.

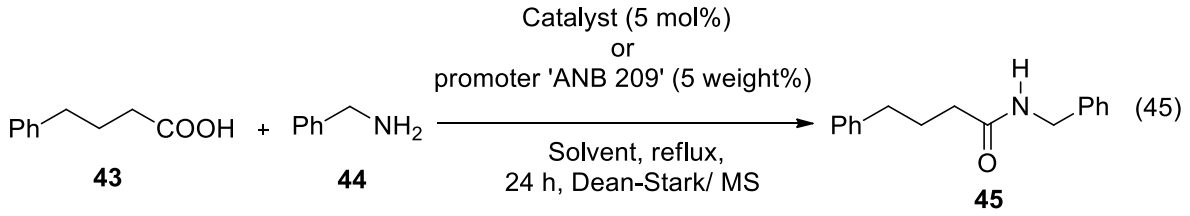
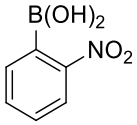
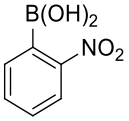
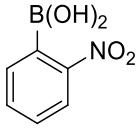
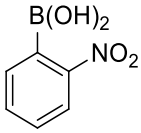


Table 20. Effect of catalyst promoter (ANB 209) in the direct amidation of 4-phenylbutyric acid **43** and benzylamine **44**

Entry	Solvent	Catalyst (5 mol%)	Promoter (5 weight%)	Temp. (° C)	Time (hrs)	Drying Method	[c]Yield of 45 (%)
1	THF	no catalyst	no promoter	65	24	a	64
2	THF		no promoter	65	24	a	86
3	THF		ANB209	65	24	a	74
4	THF	no catalyst	ANB209	65	24	a	44
5	Toluene	no catalyst	no promoter	110	24	b	50
6	Toluene		no promoter	110	24	b	71
7	Toluene		ANB209	110	24	b	62
8	Toluene	no catalyst	ANB209	110	24	b	47

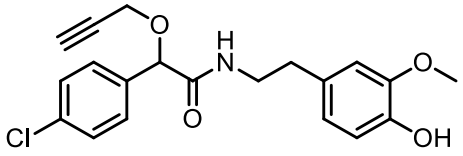
a: 3Å MS in the reaction. b: Dean-Stark technique, **c**: Isolated pure amide after recrystallisation

The direct amidation of acid **43** and amine **44** was reactive enough to afford a significant yield of amide **45** both at high and low temperature without any catalyst (Entry 1 and 5, Table 20). The rate was enhanced further to a good extent in the presence of one of the most efficient *o*-nitrophenylboronic acid catalyst at these temperatures (Entry 2 and 6, Table 20). It was deemed that the reaction would proceed to completion with the addition of a promoter 'ANB 209', but unfortunately, it appeared that the promoter had no positive effect on the enhancement of catalytic activity for the amide **44** formation. Indeed, rather it seemed to impede the rate of reaction to a great extent, as a result the yield dropped off remarkably (Entries 3 and 7, Table 20). Even, the promoter itself reduced the yield profoundly in comparison with the thermal reactions (Entry 4 and 8, Table 20). Hence, the examination of the use of the catalyst promoter 'ANB 209' in the direct amidation was not taken further.

5.3 Synthesis of 'Mandipropamid Analogues' by Direct Amidations: Effect of α-Activating Group on the Carboxylic Acid

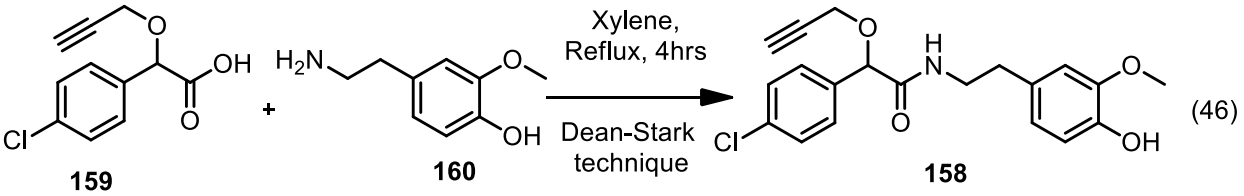
5.3.1 Introduction

Mandipropamid **158** is an important target for the agrochemical industry because of its highly efficient fungicidal properties towards most water mould pathogens. It was found as one of the active ingredient of the commercial fungicides Revus® and Pergado®[77].



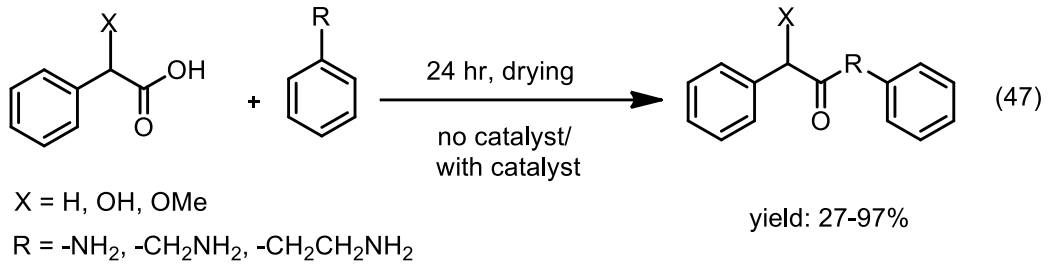
158

Mandipropamid **158** can be synthesised by both catalysed and uncatalysed direct amide formation processes (Equation 46), which are high yielding, as well as atom efficient with favourable E-factors.



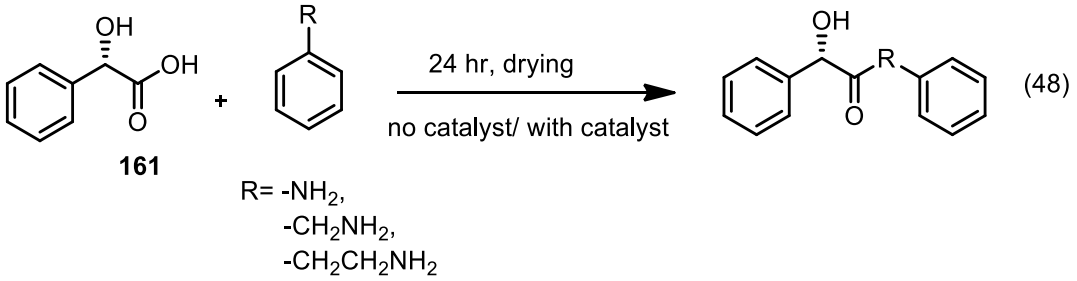
159 + **160** → **158** (46)

The success of this particular direct amide formation (Equation 46) is thought to be mostly governed by the α-activating group of the carboxylic acid **159**. However, previously in our group,[166] the uncatalysed direct amidations of different structural analogues of **158** (like methoxyphenylacetic acid, phenylacetic acid and mandelic acid) were studied by following the Equation 47 using three different amine substrates. The results showed the trend of carboxylic acid reactivity was: (racemic) methoxyphenylacetic acid (α = OMe) > phenylacetic acid (α = H) > (racemic) mandelic acid (α = OH), though reactivity differences were minor.



Unfortunately, mandelic acid **161** when reacted with different amines showed the lowest reactivity due to the formation of an insoluble salts on mixing the carboxylic acid with amines. These salts did not go in solution even at high temperature. Thus, sampling from such a heterogeneous reaction mixture meant results determined by HPLC were erroneous. In fact, this raised the questions of the effect of the carboxylic acid possessing an –OH group in the α-position, whether it hindered the reactions or not, in comparison to an α–H or –OMe group under the uncatalysed conditions.

To answer this question, in this part of the project the effect of the -OH group in the α-position of (*S*)-(+)-mandelic acid **161** through catalytic direct amide formation reactions (Equation 48) with different amine substrates (benzylamine, phenylethyl amine and aniline) was examined. Alongside, for comparison, the standard reactions (without any catalyst) were also carried out. The temperature effect was assessed to see if there was any significant effect on these direct amidations.



5.3.2 Results

The reactions were carried out in various refluxing solvents (toluene, fluorobenzene or THF) for 24 hrs and isolated yields were then calculated. Although the reactions led to the formation of insoluble salts in some cases, it did not create major inconveniences to measure correctly the ultimate yield of the reactions. The results are reported in Table 21.

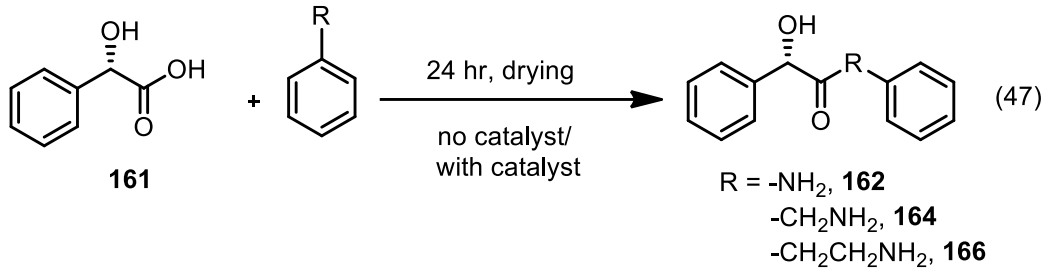


Table 21: Direct amidation[a] of (*S*)-(+)-mandelic acid **161** with different amines at different temperatures and in different solvents

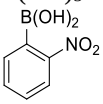
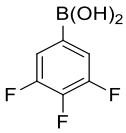
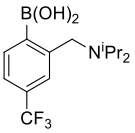
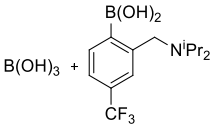
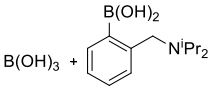
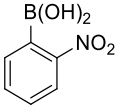
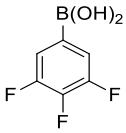
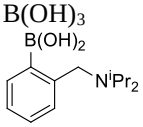
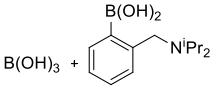
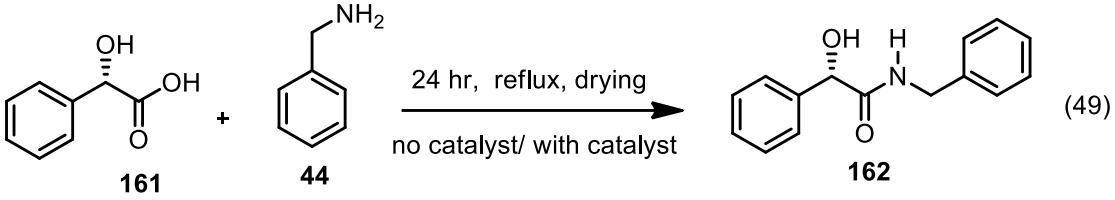
Entry	Amine Group	Solvent	Catalyst (5 mol%)	Temp (°C)	Amide	Yield[b] of amide (%)
1	$PhCH_2NH_2$	Toluene	no	110	**162**	56 (*ee*: 40%)
2	$PhCH_2NH_2$	Fluorobenzene	no	85		89 (*ee* > 98%)
3	$PhCH_2NH_2$	Fluorobenzene	no	65		no product
4	$PhCH_2NH_2$	THF	no	65		6
5	$PhCH_2NH_2$	Toluene	$B(OH)_3$	110		68
6	$PhCH_2NH_2$	Toluene		110		92 (*ee*: 20%)
7	$PhCH_2NH_2$	Toluene		110		95 (*ee* : 98%)
8	$PhCH_2NH_2$	Toluene		110		67
9	$PhCH_2NH_2$	Toluene		110		80
10	$PhCH_2NH_2$	Toluene		110		26
11	$PhCH_2CH_2NH_2$	Toluene	no	110	**164**	78
12	$PhCH_2CH_2NH_2$	Toluene	$B(OH)_3$	110		76
13	$PhCH_2CH_2NH_2$	Toluene		110		90 (*ee* > 99%)
14	$PhCH_2CH_2NH_2$	Toluene		110		94 (*ee* > 99%)
15	$PhCH_2CH_2NH_2$	Fluorobenzene	no	85		5
16	$PhCH_2CH_2NH_2$	Fluorobenzene	$B(OH)_3$	85		negligible
17	$PhCH_2CH_2NH_2$	Fluorobenzene		85		12
18	$PhCH_2CH_2NH_2$	Fluorobenzene		85		3

Table 21 continued

Entry	Amine Group	Solvent	Catalyst (5 mol%)	Temp (°C)	Amide	Yield[b] (%)
19	$PhCH_2CH_2NH_2$	THF	no	65	**164**	5
20	$PhNH_2$	Toluene	no	110	**166**	97 (*ee*: 90%)
21	$PhNH_2$	Fluorobenzene	no	85		89 (*ee*: 98%)
22	$PhNH_2$	THF	no	65		4

[a]Reaction conditions: acid (2.86 mmol), amine (2.86 mmol), solvent (20 mL), drying method: Dean-Stark or 4Å MS, t = 24 h; [b] Isolated yield.

The uncatalysed reaction of (*S*)-(+)-mandelic acid **161** and benzylamine **44** (Equation 49) in refluxing toluene was not high yielding, only 56% of the corresponding amide being formed after 24 hrs (Entry 1, Table 21).



(49)

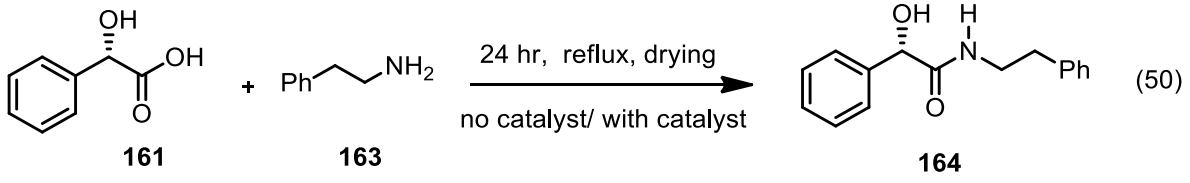
Chiral HPLC analysis showed substantial racemisation (*ee* was 40%) within this conditions. The yield of the reaction stepped up hugely when refluxing in fluorobenzene (yield 89% of amide **162**, Entry 2, Table 21) with very low racemisation (*ee* > 98%). This could be due to the more efficient water removal from the reaction mixture with 4 Å molecular sieves using the Soxhlet extraction technique rather than the Dean-Stark technique, and/ or the solvent polarity could play a key role to enhance the reaction rate. Moreover, the lower temperature might reduce the racemisation, as low temperatures are more favourable for producing pure enantomers.

In order to reduce the high temperature effect, the same reaction was carried out at 65 °C in fluorobenzene, but unfortunately no conversion of (*S*)-(+)-mandelic acid **161** was observed at this temperature (Entry 3, Table 21). The TLC and NMR of the crude reaction mixture showed only the starting materials. This indicated that below the solvent refluxing temperature, this particular reaction seemed to be inert. Use of more polar solvents like THF also failed to produce any satisfactory amount of amide **162**, even in refluxing conditions (Entry 4, Table 21). In this case the mass recovery was 100% and most of this was starting materials as observed in the crude NMR.

Since the yield was not satisfactory in the uncatalysed conditions at high temperature, there was scope to check for catalytic activity in order to raise the yield by using different known catalysts, including the cooperative catalytic systems (Equation 44). Based on this idea, the reaction was carried out with $B(OH)_3$ (5 mol%) and the yield increased from 56% to 68% (Entry 5, Table 21). Furthermore, 2-nitrophenylboronic acid and 3,4,5-triflurophenylboronic acid catalysts were excellent at forming the amide **162** under the same conditions (yields of amide **162** were 92% and 95%, respectively). Chiral HPLC revealed considerable racemisation by the 2-nitrophenylboronic acid catalyst (*ee* 20%), but minor racemisation occurred with 3,4,5-triflurophenylboronic acid catalyst (the *ee* was > 98%, Entries 6 and 7, Table 21) at this high temperature. The efficiency of 4-trifluoro-2-*N*,*N*-di*iso*propylethylaminophenylboronic acid was also good, and was similar to $B(OH)_3$ (Entry 8, Table 21).

In order to check the cooperative effect for enhancing the rate of reaction further, $B(OH)_3$ and 4-trifluoro-2-*N*,*N*-di*iso*propylethylaminophenylboronic acid, were used (1:1 ratio) in the same reaction. As expected, after 24 hrs the reaction afforded an excellent yield of amide **162** (80%, Entry 9, Table 21). On the contrary, a negative cooperative effect was observed while using the combination of $B(OH)_3$ and 2-*N*,*N*-di*iso*propylethylaminophenylboronic acid catalysts, the yield was greatly reduced using this cooperative catalyst and only 26% of amide was formed (Entry 10, Table 21).

Similar kinds of experiments were carried out with (*S*)-(+)-mandelic acid **161** and phenylethylamine **163** (Equation 50), in order to compare the reactivities of different amine substrates.

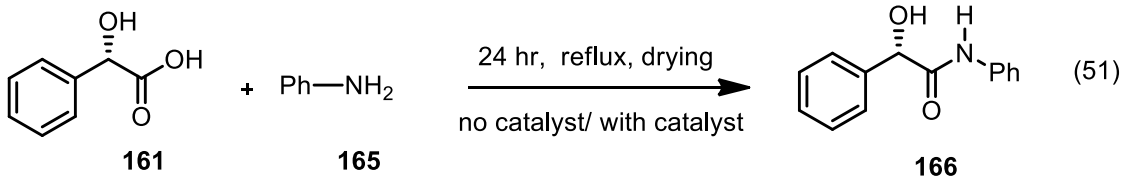


161 **163** **164** (50)

The thermal reaction with phenylethylamine **163** was more efficient than benzylamine at high temperature (Entry 11, Table 21). The yield reduced slightly in the presence of $B(OH)_3$, however, 2-nitrophenylboronic acid and 3,4,5-triflurophenylboronic acid showed outstanding

capacity for converting to amide **164** from the acid **161** and without any racemisation (Entries 13 and 14, Table 21). Further investigations at lower temperature and in more polar solvents revealed that this reaction was not favourable, neither in a more polar solvent nor at lower temperature, *e.g.* at 85 °C (Entries 15-19, Table 21).

Finally, the condensation reaction of (*S*)-(+)-mandelic acid **161** with aniline **165** was carried out under the same reaction conditions (Equation 51).



161 **165** **166** (51)

Interestingly, the amine was found most reactive compared to the other amine substrates (benzylamine and phenylethylamine) under the uncatalysed conditions. It was equally efficient in toluene and fluorobenzene forming the amide **166** at both high and low temperatures with a large enantiomeric excess (Entries 20-21, Table 21). However, the rate of formation reduced significantly in THF. Since there was a major thermal effect on this direct amide formation reaction, there was little scope for catalysts to be used for the rate enhancement.

5.3.3 Conclusion

To summarize, (*S*)-(+)-mandelic acid **161** reacted efficiently under uncatalysed direct amidations conditions with benzylamine, phenethylamine and aniline at different temperatures, resulting in different rates of amide formation. Examining the three amine reactivities was intriguing. The results showed that the reactivity of the different amines was not only influenced by basicity, but that steric and electronic effects might also play a role. Although, with aniline, the rate of amide formation was as expected to be reduced due to its lower nucleophilicity, it was actually observed that it showed the highest thermal reactivity for amide formation with mandelic acid compared to benzylamine and phenethylamine. However, the catalysed direct amide formations were also efficient with different potent and known catalysts, especially with the (*S*)-(+)-mandelic acid **161** and benzylamine **44**

combination. Even the cooperative catalytic system worked well in this case. Nonetheless, the low temperature reaction was still more favourable for avoiding racemisation.

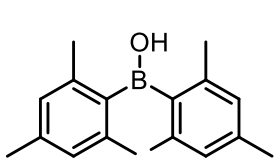
Further detailed experiments need to be run to screen a broader range of substrates to fully understand the effect of substituents at the α-position of the carboxylic acid with various amine substrates, which may ultimately lead to a better understanding of direct amide formation for the synthesis of mandipropamid **158**.

5.4 Direct Amide Formation Catalysed by Borinic Acids

5.4.1 Introduction

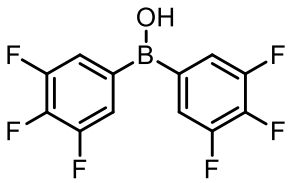
The diverse applications of borinic acid as Lewis acid has been well known for decades.[159] Examples include aldol reactions, acylation of alcohols, dehydration, sulfonylation, cycloaddition *etc*. However, there have been no reports of borinic acids applied in direct amide bond formation, although the use of boronic acids and other organoboron derivatives has been well documented. In this part of the project, investigations into the use of borinic acids for direct amidation processes was carried out.

Two different borinic acids, namely dimesitylborinic acid **167** and bis-(3,4,5-trifluorophenyl)borinic acid **168**, were synthesised in the Whiting group and these borinic acids were chosen to examine their catalytic activities in the direct amide formation of the following two model reactions (Equation 52 and 53).



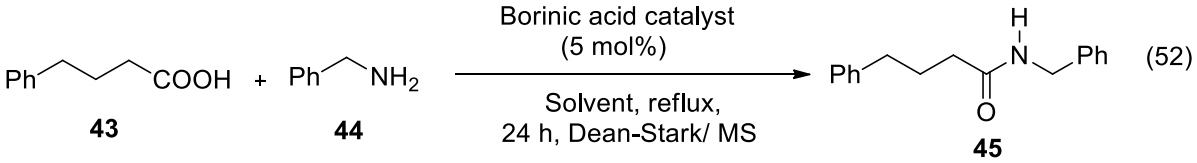
Mes_2BOH

167

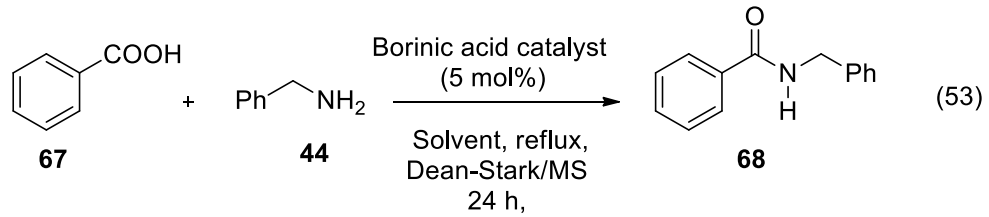


$(C_6F_3H_2)_2BOH$

168



43 **44** **45** (52)



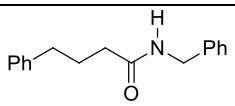
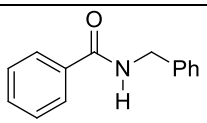
67 **44** **68** (53)

5.4.2 Results

The reactions were carried out with benzylamine **44** and either 4-phenylbutyric acid **43** (4-PBA) or benzoic acid **67** (BA) in two different solvents (toluene and fluorobenzene) and

temperatures (110 °C and 85 °C) for 24 hrs. For comparison, the thermal standard reactions were also performed. The results are given in Table 22.

Table 22: Direct amidations with two different borinic acids **167** and **168**.

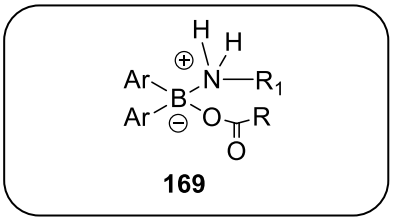
Entry	Carboxylic acid	Borinic acid catalyst (5 mol%)	Solvent	Amide	[b]Yield (%)
1	4-PBA	**167**	Toluene	 **45**	79
2		**168**	Toluene		80
3		No catalyst	Toluene		50
4		**167**	Fluorobenzene		45
5		**168**	Fluorobenzene		50
6		No catalyst	Fluorobenzene		65
7	BA	**167**	Toluene	 **68**	negligible
8		**168**	Toluene		negligible
9		No catalyst	Toluene		22
10		**167**	Fluorobenzene		negligible
11		**168**	Fluorobenzene		negligible
12		No catalyst	Fluorobenzene		19

[a]Reaction conditions: acid (2.86 mmol), amine (2.86 mmol), solvent (20 mL), drying method: Dean-Stark or 4Å molecular sieves, t = 24 h; [b] isolated yield

Some intriguing results were observed with the two different borinic acids (**167** and **168**), although there was no major difference in their reactivity towards the amide formation reactions with either of the carboxylic acids. Both the catalysts were effective at high temperature in forming the amide **45** from the acid **43** (Entry 1-2, Table 22). However, their catalytic activities reduced a great deal while refluxing in fluorobenzene at lower temperature, in comparison with the thermal results. The success of both the borinic acid catalysts only at high temperature indicates only limited catalytic activities in the direct amide bond formation reactions.

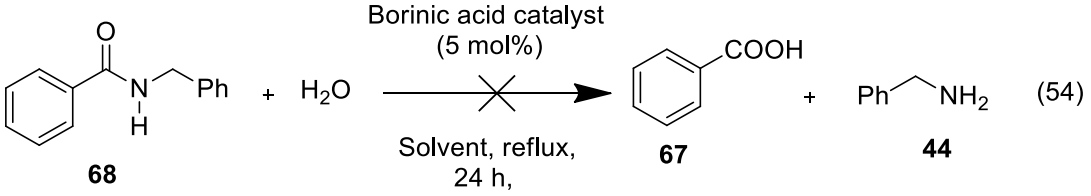
A surprising 'inhibition' effect seemed to be observed with benzoic acid **67** and in different solvents at temperatures which make the result difficult to explain until the reactions were

further investigated. The crude NMR clearly showed two broad –CONH peaks at 6.3 ppm (strong) and 6.52 ppm (weak), but there was only a very weak signal for the benzylic $–CH_2$ peak (doublet) at 4.56 ppm, indicating the probability of a different amide formation, apart from N-benzylbenzamide **68**. In addition, the ^{11}B NMR of the crude reaction mixture showed a peak at 0 ppm indicating the presence of some sort of tetrahedral boron-complex. Separate work within the Whiting group later revealed[167] that borinic acids form amino-carboxylate structures of type **169**.



169

It was initially thought that this boron-complex formation might be due to the hydrolysis of the amide product **68** in presence of the borinic acid catalysts. To test this idea, further investigations of the hydrolysis reaction of the amide **68** in presence of two borinic acid catalysts (Equation 54) were carried out.



68 **67** **44**

After 24 hrs, the crude ^1H NMR showed no hydrolysis of the amide; the mass recovery of **68** was 100%. This showed that amide hydrolysis was not occurring in the presence of borinic acids, but other mechanistic implications might be involved in these observations, though it is not clear what these are at present. Further investigations related to borinic acid catalysed direct amide formation are underway by others in the Whiting group. For the time constraints, these investigations did not continued further here.

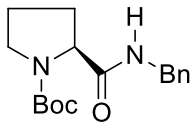
Chapter 6: Conclusions and Future Work

6.0 Conclusions

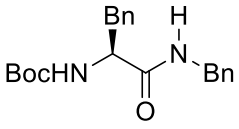
On account of the increasing importance of the direct amide formation reaction and its role for the synthesis of some pharmaceuticals, there have been many new developments in the past decades. It can be seen from the review of the previously published literature that both the uncatalysed and catalysed direct amide formation reactions were still a long way to go for over complete understanding of the mechanisms.

In addition, most of the ongoing research efforts are leading to improvements in the direct amidation reactions, providing new reagents, catalysts and protocols, which are increasingly environmentally friendly. This research project focused on these investigations into alternatives to the traditional approaches towards amide formation.

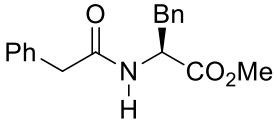
In a quest for new environmentally conscious methodologies and catalysts, catalyst screening at reduced temperature uncovered the efficiency of some known, potent boron-based and metal-based catalysts which have been used as Lewis acid previouslyin other reactions only at high temperature. *o*-Nitrophenylboronic acid was one of the most promising catalysts for direct amidations for both high and low reactivity acid-amine combinations. Being one of the cheaper catalysts, *o*-nitrophenylboronic acid extended the number of diversified applications with diverse substrates, and also in wider synthetic applications, especially in the more demanding and specialised field of peptide synthesis.



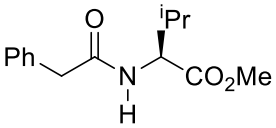
Amide **109**



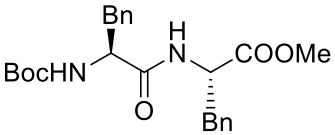
Amide **111**



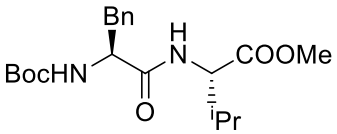
Amide **113a**



Amide **113b**



Amide **114**

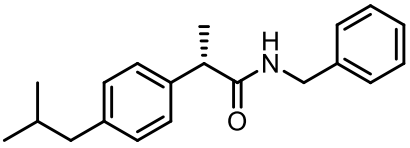


Amide **115**

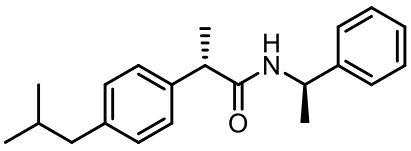
The catalytic direct amidations were investigated with amino acid analogues reacting either with carboxylic acids or amine partners. These amidations were successful with *o*-nitrophenylboronic and 3,4,5-trifluorophenylboronic acids as catalysts with a reasonable enantiopurity in most cases. However, high catalyst loadings (25-50 mol%) showed that there is further development required to find a general solution to direct amide formation in such systems.

The *de novo* synthetic approach of cooperative catalysis revealed an improved solution over the more sluggish nature of the single catalytic systems for mediating the direct amidation reactions of less reactive substrates, and those containing more delicate functionality like peptide bonds. Screening of different cooperative catalysts, such as cooperative catalyst **III** (mixture of $B(OH)_3$ and 4-trifluoromethy-2-*N*,*N*-di*iso*propylethylaminophenylboronic acid[96]) was found to be the most efficient at converting carboxylic acids to the corresponding amides even under mild reaction conditions. The reaction progression was readily monitored by HPLC and React-IR which gave evidence for the rate enhancement for the formation of the amides by these cooperative catalysts over the single catalysts. However, the mechanism of cooperative catalysis system is not understood at this point.

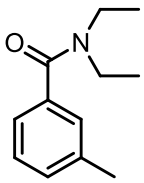
Having proposed a new method for the catalysed direct amide formation reaction, attention was directed to the synthesis of some real industrial products, like DEET **119**, (*S*)-ibuprofen amides **140** and **142**, Sildenafil precursor **144** *etc*.



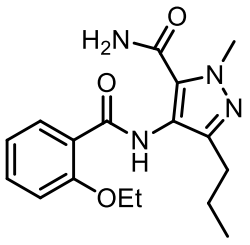
(S)-Ibuprofen amide **140**



(S)-Ibuprofen amide **142**



DEET **119**

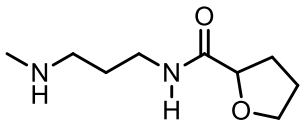


Sildenafil precursor **144**

The prime advantages of the cooperative process includes simple operation, equimolar amounts of acid and amine substrate, cheaper catalysts, more atom economic and environmentally safe compared to conventional coupling methods.

The synthesis of DEET **119** by the direct amidation reaction in the presence of cooperative catalyst **XIII** [$ZrCl_4$ and 2-*N*,*N*-di*iso*proppylethylaminophenylboronic acid mixture] found satisfactory, although the reaction seemed more favourable at high temperature. The cooperative catalyst **III** and **I** were also efficient for converting DEET **119** under the same reaction conditions.

No significant synergistic effect of cooperative catalysts was observed in the synthesis of alfuzosin intermediate **138**, but the regioselectivity was the same as with the single catalyst.



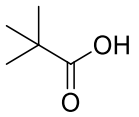
138

However, a surprising negative effect was observed during this amidation process with the cooperative catalyst **I**, although the reason was not understood. The cooperative catalytic systems similarly failed to enhance the rate of the reaction of efaproxiral intermediate **124** synthesis by the direct amide formation, although the single catalyst $B(OH)_3$ was excellent under the same conditions. Alike, no significant rate enhancement was observed with the potential cooperative catalyst **III** in the synthesis of azetidin derivative **127**.

The contribution of the cooperative catalyst **III** was notably higher in the synthesis of the (*S*)-ibuprofen amide **140** and **142** by direct amidation reactions at a moderate temperature with low racemisation.

The cooperative catalyst **XVII** [$B(OH)_3$ and 2-nitropphenylboronic acid mixture] was highly successful in converting the Sildenafil precursor **144** both at low and high temperature, although the effect of Fe-based cooperative catalyst **V** [$B(OH)_3$ and $Fe(OTf)_3$ mixture] in the same amidation process was also noticeable.

Previous DFT calculations suggested that thermal amide bond formation proceeds through the intermolecular carboxylic acid hydrogen bonded dimers **154**, which play an important role to activate a carboxylic acid towards the nucleophilic attack by the amine. Therefore, the role of H-bonding in the direct amide formation was investigated in the presence of pivalic acid **157**, which was expected to be unreactive towards the amidation process.

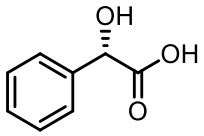


Pivalic acid
157

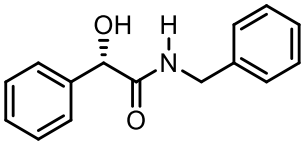
Based on all the evidence achieved from the isolated yield of the reaction (at different temperature and solvents), reaction progression by HPLC and the real time monitoring technique (React-IR), it was concluded that there was little or no effect as a catalyst in the direct amide formation reaction. In fact, it seemed there was a negative impact on the rate of the reaction. However, further investigations may assist the development of new acid catalysed direct amide formation using different systems in future.

As well as examining the effect of novel catalysts, the effect of a potential catalyst promoter in the direct amidation reactions at reduced temperature was also evaluated. This was in fact based on the idea that a promoter might help to accelerate the catalytic activity of those boronic acid catalysts or other catalysts at lower temperatures by assisting with localised water removal. *Lycopodium clavatum* crude pollen, 'ANB 209' was employed in the direct amidation reactions. Rather it impeded the rate of reaction to a great extent, and as a result the yield dropped off remarkably in comparison with the thermal reactions. An interesting area of research would understand the necessity of any form of water removal for continuous flow reactions which would allow the examination of the use of the continuous flow systems in direct amidation as a potential new way of producing amides directly.

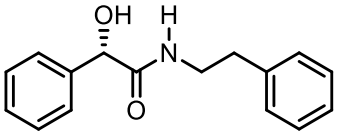
Further, the effect of different substituents on the α-position of carboxylic acid with various amine substrates was investigated in order to understand this effect on direct amide formation of the synthesis of mandipropamid **158**.



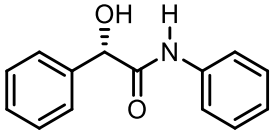
161



162



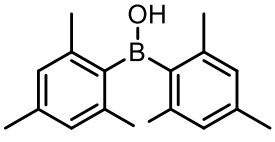
164



166

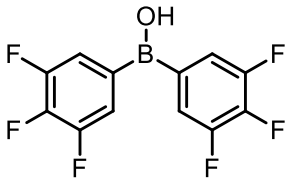
Uncatalysed direct amidations of mandelic acid **161** occurred with benzylamine **44**, phenethylamine **163** and aniline **165** at different temperatures, resulting different rates of different amides (**162**, **164** and **166**) formation. Examining the three amine reactivities showed that the reactivity of different amines was not only influenced by basicity, but also the steric and electronic effect might have played a role. It was found that aniline had the higher thermal reactivity for amide bond formation with mandelic acid compared to both benzylamine (pK_a = 9.34) and phenethylamine **163** (pK_a = 9.83). However, the catalysed direct amide formations were also remarkable with different catalysts, like $B(OH)_3$, *o*-nitrophenylboronic acid and 3,4,5-trifluorophenylboronic acid. The cooperative catalytic system of $B(OH)_3$ and 4-trifluoro-2-*N*,*N*-di*iso*propylethylaminophenylboronic acid (1:1 ratio) was found to be promising at enhancing reaction conversion. More experiments with a wider range of substrates are required to understand which substitution patterns and functional groups enhance or hinder direct amide formation in particular cases.

Finally, borinic acid catalysed direct amidation processes were investigated. Dimesitylborinic acid **167** and bis-(3,4,5-trifluorophenyl)borinic acid **168** were employed in the direct amide formation of 4-phenylbutyric acid and benzoic acid with benzylamine in two different solvents (toluene and fluorobenzene) and temperatures (110 °C and 85 °C).



Mes_2BOH

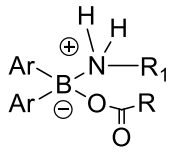
167



$(C_6F_3H_2)_2BOH$

168

Although both the catalysts were reactive to the same extent towards the amide formation reactions at high temperature, an inhibition effect was observed with benzoic acid **67**. Investigations of the crude ^{1}H and ^{11}B NMR revealed the formation of a boron-complex **169** which was not catalytically active according to recent work in the group.



169

6.1 Future Work

From the point of view of future work, cooperative catalysed direct amidations are worthy of future studies to investigate in more detail their applications in direct amidation reactions. Indeed, mechanistic studies of this cooperative effect are required in order to design improved coopearative systems for less reactive substrates, although some attempts have been taken here by following the reactions through the React-IR to understand this synergistic effects of two catalysts *in situ*. More detailed investigations into these mechanistic studies have already started within our research group with some success by following the rate of the individual direct amidation reaction through '*Continuous Flow Reactions*'. One other interesting area of research would understand the necessity of any form of water removal for continuous flow reactions. This would allow examining the use of the continuous flow systems in direct amidation as a potential new way of producing amides directly. Continuation of this research and further optimisation of this process potentially could explore how two arylboronic acids or other catalysts play the role of increasing the rate of the direct amide formation reactions.

Another interesting future research could be the complexations between boron-containing catalysts and the amine or carboxylic acids. This will lead to the better understanding of the mechanism of the borinic acid catalysed direct amide formations as well as assist ultimate understanding of the mechanism of other boron-based catalysts like arylboronic acids or even the new cooperative catalysis. This will also provide insights to further advanced catalyst design, synthesis and applications.

Chapter 7: Experimental

7.1 General Experimental

Glassware was dried in an oven (130 °C) as required and cooled under a positive pressure of argon. All chemicals and reagents were analytical grade and were procured from Aldrich, Across Organics and Fisher Scientific. Dry THF was freshly distilled from benzophenone and sodium, under argon, immediately prior to use and other solvents (toluene, DMF and Et_2O) were dried before use following the conventional SPSS procedures. Fluorobenzene was dried over 4Å molecular sieves. Molecular sieves were activated by heating at 200 ^oC overnight.

The NMR spectra (^1H, ^{13}C and ^{11}B) were measured on a Bruker 400 spectrometer. The ^1H NMR was recorded at 400 MHz, whereas the ^{13}C and ^{11}B were measured at 100 MHz and 128 MHz respectively. Chemical shifts were recorded in parts per million (ppm) using an internal standard tetramethylsilane (TMS) on the δ scale and coupling constants (J) are expressed in Hz. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Column chromatography was performed on Davisil Silica gel (60 mesh). The TLC was done on Merck pre-coated TLC plates (silica gel 60 GF_{254} 0.25 mm) with visualisation achieved using a UV lamp or staining with basic $KMnO_4$.

Mass spectral analysis was performed using the Durham University Mass Spectrometry suit using a Waters LCT or a Waters TQD spectrometer. Accurate masses were obtained on a Thermo LTQ-FT spectrometer and elemental analysis was done on an Exeter CE-440 Elemental Analyser. Melting points were determined using an Electrothermal melting point apparatus or Gallenkamp Variable Heater and are reported uncorrected.

HPLC analysis was carried out on an Agilent 1100 Series system with a UV Diode Array Detector, Gilson 322 Pump, Gilson 402 Syringe Pump fitted with a Perkin Elmer series 200 degasser. Percent conversion was determined by reversed phase HPLC (Phenomenex Gemini C18 column, 150 × 4.6 mm, 5 µm). Enantiomeric excesses were determined by normal phase HPLC using a Chiralpak OD-H column (Column OD-H, 0.46 cm × 25 cm) using n-hexane and isopropanol mixtures.

Data for reactions followed by IR was obtained using a Mettler Toledo ReactIR4000 instrument using React-IR (version 3.0) software; ReactIR 15 with MCT detector; ConcIRT window = 1900-900 cm^{-1}. Apodization = Happ General. Probe: Prob A DiComp (Diamond)

connected *via* KAgX 9.5 mm x 2 m fiber (silver halide); Sampling 2500-650 at 8 cm^{-1} resolution; Scan option: auto select, gain 1X.

7.2 General Procedure for the Preparation of Amides at 110 °C

The appropriate carboxylic acid (2.86 mmol), catalyst (5 mol%), toluene (20 mL) and amine (2.86 mmol) were added respectively to the reaction vessel, followed by azeotropic water removal at 120 °C for 24 hrs using a Dean-Stark condenser. After the reaction completed, the mixture was cooled at room temperature and the solvent was evaporated using a rotary evaporator. The crude product was re-dissolved in DCM (40 mL) and washed with 5 % (*w/v*) HCl (3 × 20 mL), sat. $NaHCO_3$ (3 × 20 mL), brine (3 × 20 mL) and water (1 × 20 mL) respectively. The organic solution was dried over $MgSO_4$, filtered and concentrated in *vacuo* to give the amide. The crude amide was recrystallised from hexane and EtOAc.

7.3 General Procedure for the Preparation of Amides at 85 °C

The appropriate carboxylic acid (2.86 mmol) and catalyst (5 mol%) were dissolved in fluorobenzene (20 mL), and amine (2.86 mmol) was added. The reaction mixture was refluxed at 85 °C using Soxhlet extraction with activated 4 Å molecular sieves in the thimble. The reaction was allowed to stir for 24 h before cooling and concentrating *in vacuo*. The residue was re-dissolved in DCM (40 mL), washed with 5 % (w/v) HCl (3 × 20 mL), sat. $NaHCO_3$ (3 × 20 mL), brine (3 × 20 mL) and water (1 × 20 mL) respectively. The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the amide. The crude amide was recrystallised from hexane and EtOAc.

7.4 General Procedure for the Preparation of Amides at 65 °C

The appropriate carboxylic acid (2.86 mmol) and catalyst (5 mol%) was dissolved in solvent (20 mL), and amine (2.86 mmol) was added. The reaction mixture was refluxed at 65 °C followed by water removal using activated 4 Å molecular sieves in the reaction mixture. The reaction was allowed to stir for 24 h before cooling and filtering through Celite. The

remaining solid mass on the Celite was washed with EtOAc (40 mL). The combined solvent was concentrated under reduced pressure. The residue was re-dissolved in DCM (40 mL), washed with 5 % (w/v) HCl (3 × 20 mL), sat. $NaHCO_3$ (3 × 20 mL), brine (3 × 20 mL) and water (1 × 20 mL) respectively. The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the amide. The crude amide was recrystallised from hexane and EtOAc.

7.5 General Procedure for Following Reactions over Time by HPLC

The appropriate carboxylic acid (2.86 mmol) was weighed into the reaction vessel, dry solvent (20 mL), catalyst (5 mol%) and amine (2.86 mmol) were added respectively. The reaction was heated to the desired temperature for 24 hrs followed by different drying methods under argon. Reactions were sampled (1 mL) at 1 h intervals. Samples were passed through Celite and extracted with EtOAc (2 mL) if molecular sieves (4 Å) were used for drying at 65 °C. The solvents were dried off and the residue was re-dissolved and diluted with acetonitrile (5 mL) to give the stock solution for HPLC analysis. The samples were rediluted once (50 μL in 950 μL MeCN) and analysed by HPLC (gradient MeCN (0.05% TFA) / water (0.05% TFA). Column temperature was 30 °C. Before running any sample, standard calibration curve was prepared (Please see appendix 4 for graphs and equations) for each type of compound from the data found from the different standard solutions of that particular compound. Standard solutions of different compounds (with different concentrations *e.g.* from 0.05 mM to 3.0 mM) were prepared by the dilution of relevant stock solution (100 mM), which was prepared by dissolving the appropriate amount of the relevant compound in acetonitrile.

7.6 General Procedure for the Direct Amidation of N-protected Amino Acids

To the catalyst (25~50 mol %), solvent (20 mL), the amine (1.4 mmol), *N*-protected amino acid (1.4 mmol) and activated 4 Å molecular sieves (if the reaction was carried out at reflux temperature or 65 °C, or if a Soxhlet apparatus was used, a thimble was loaded with the activated 4 Å molecular sieves. The mixture was heated under Ar (time indicated in the Tables above). After the reaction finished, the solution was filtered through Celite and the

remaining solid mass was washed with EtOAc (40 mL). The combined solvent was concentrated under reduced pressure, diluted with $CHCl_3$ (40 mL) and the solution was washed with sat. $NaHCO_3$ (3 × 10 mL), 1 M HCl (2 × 5 mL), H_2O (2 × 10 mL) and brine (10 mL). After drying with $MgSO_4$, filtration and concentrated *in vacuo*, the crude product was re-crystallized from a mixture of acetone and pet ether to give pure product.

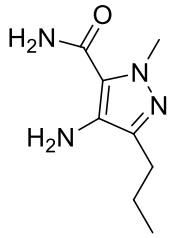
7.7 General Procedure for Direct Amidation of C-protected Amino Acids

To the catalyst (25 mol %), C_6H_5F (20 mL), phenylacetic aicd (1.4 mmol), amino acid methyl ester hydrochloride (1.4 mmol), di*iso*propylethylamine (1.4 mmol), and activated 4 Å molecular sieves (if the reaction was carried out at reflux temperature or 65 °C, or if a Soxhlet apparatus was used, a thimble was loaded with the activated 4 Å molecular sieves. After the reaction finished, the solution was filtered through Celite and the precipitate was washed with EtOAc (40mL), concentrated under reduced pressure. Then $CHCl_3$ (40 mL) was added to the residues and the solution was washed with sat. $NaHCO_3$ (3 × 10 mL), 1 M HCl (2 × 5 mL), H_2O (2 × 10 mL) and brine (10 mL) respectively. The solution was dried over $MgSO_4$, filtered and concentrated to provide the product, which was re-crystallized from a mixed solvent of acetone and petroleum to give pure product.

7.8 General Procedure for Dipeptide Synthesis by Direct Amidation

The amino acid methyl ester hydrochloride (1.4 mmol) was neutralized using di*iso*propylethylamine (1.4 mmol, 246 µL) in fluorobenzene (5 mL). After 2 h, the catalyst (25-50 mol %), fluorobenzene (15 mL), *N*-protected amino acid (1.4 mmol) and activated 4 Å molecular sieves were added. The mixture was heated at 65 °C for 24 h with stirring. After the reaction finished, the mixture was filtered through Celite. The solution was concentrated and the crude solid was dissolved in $CHCl_3$ (40 mL). The solution was washed with 0.5 M K_2CO_3 (4 × 10 mL), 1 M HCl (2 × 5 mL), H_2O (2 × 10 mL) and brine (10 mL) respectively. The solution was dried over $MgSO_4$, filtered and concentrated to get the product which was re-crystallized from a mixture of acetone and petroleum to give pure product.

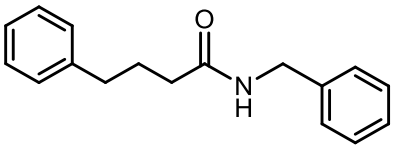
7.9 Preparation of 4-Amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide



For the synthesis of the Sildenafil precursor **152**, the amine 4-Amino-1-methyl-3-propyl-1-H-pyrazole-5-carboxamide was kindly provided by Pfizer in the form of its hydrochloride salt. The salt (2.0 g) was dissolved in H_2O (60 mL) and the solution was treated with 20% NaOH dropwise to make it slightly basic (pH~ 9).The solution was then extracted with $CHCl_3$ (40 mL). The organic phase was separated and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuuo* and the amine, 4-Amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide was found as pale yellow colored oil. ν_{max} (ATR): 3447, 3291, 2955, 2870, 1645, 1560, 1447, 1417 and 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.73 (sextet, *J* = 6.3 Hz, 2H, C*H*$_2$), 2.54 (t, *J* = 7.2 Hz, 2H, C*H*$_2$), 2.89 (s, br, 2*H*, N*H*), 4.09 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 (*C*H_3), 24.3, 28.5, 66.2, 113.5, 115.5, 119.9, 169.8 (*C*ONH_2). All spectroscopic and analytical properties were identical to that reported in the literature. [160]

7.10 Synthetic Procedures

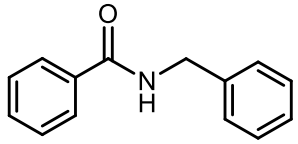
N-Benzyl-4-phenylbutyramide 45



The general procedure for the preparation of amides was followed to attain the product as a white solid. M.p. 78-81 °C (*n*-hexane/ethyl acetate) (lit mp = 81-83 °C). ν_{max} (ATR): 3283 (N-H), 1689 (s) (C=O), 1540, 1494, 1451, 1411, 1267, 1213, 1077, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.97-2.05 (m, 2H, C*H*$_2$), 2.22 (t, 2H, *J* = 6.8, ArC*H*$_2$), 2.67 (t, 2H, *J* = 7.6, C*H*$_2$), 4.43 (d, 2H, *J* = 6.0, C*H*$_2$N), 5.63 (s, br, 1H, N*H*), 7.15-7.35 (m, 10H, Ar*H*). ^{13}C NMR

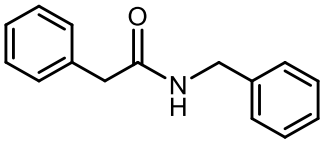
(100 MHz, $CDCl_3$): δ 27.1 (*C*H_2), 35.2 (*C*H_2), 35.9 (*C*H_2), 43.7 (*C*H_2), 126.0 (Ar*C*), 127.6 (Ar*C*), 127.9 (Ar*C*), 128.4 (Ar*C*), 128.5 (Ar*C*), 128.7 (Ar*C*), 138.2 (Ar*C*), 141.4 (Ar*C*), 172.4 (*C*=O). *m/z* (ES^+): 254.2 [$M+H^+$]. All spectroscopic and analytical properties were identical to that reported in the literature.[100, 102]

N-Benzylbenzamide 68



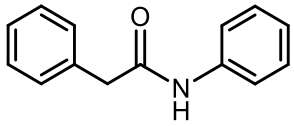
The general procedure for the preparation of amides was followed to attain the product as a white solid. M.p. 104-106 °C (*n*-hexane/ethyl acetate) (lit mp = 104-106 °C). ν_{max} (ATR): 3296 (N-H), 3080, 1635(s) (C=O), 1545s, 1416, 692s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.56 (d, 2H, *J* = 6.0, C*H*$_2$), 6.30 (s, br, 1H, N*H*), 7.19-7.42 (m, 8H, Ar*H*), 7.67 (d, 2H, *J* = 6.0, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.2 (*C*H_2), 126.9 (Ar*C*), 127.7 (Ar*C*), 127.9 (Ar*C*), 128.6 (Ar*C*), 128.8 (Ar*C*), 131.6 (Ar*C*), 134.4 (Ar*C*), 138.1 (Ar*C*), 167.3 (*C*ONH). *m/z* (ES^+): 212.2 [$M+H^+$]. All spectroscopic and analytical properties were identical to that reported in the literature.[100]

N-Benzyl-2-phenylacetamide 1(Table 4)



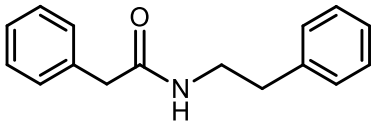
The general procedure for the preparation of amides was followed to provide the title compound as a white solid. M. p. 118-120 °C (*n*-hexane/ethyl acetate) (lit. 118-120 °C); ν_{max} (ATR): 3289 (N-H), 3080, 3062, 3030, 2917, 1638 (C=O), 1551, 1493, 1453, 1028, 771, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 2H, C*H*$_2$CO), 4.42 (d, 2H, *J* = 5.6 Hz, C*H*$_2$NH), 6.06 (br, 1H, N*H*), 7.17-7.19 (m, 2H, Ar*H*), 7.23-7.25 (m, 1H, Ar*H*), 7.28-7.37 (m, 7H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.9 (*C*H_2CO), 43.9 (*C*H_2NH), 126.7 (Ar*C*), 127.3 (Ar*C*), 128.8 (Ar*C*), 128.9 (Ar*C*), 129.6 (Ar*C*), 129.6 (Ar*C*), 135.0 (Ar*C*), 137.5 (Ar*C*), 170.6 (*C*ONH). Elemental Analysis (%) for $C_{15}H_{15}NO$. Calcd: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.85; H, 6.65; N, 6.29. All spectroscopic and analytical properties were identical to that reported in the literature.[135]

N-2-Diphenylacetamide 2(Table 4)



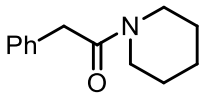
The general procedure for the preparation of amides was followed to provide the title compound as a white solid; M. p. 110–114 °C (*n*-hexane/ethyl acetate) (lit. 110-112 °C). ν_{max} (ATR): 3290 (N-H), 3080, 3062, 3027, 2930, 1639 (C=O), 1538, 1498, 1026, 771, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 2H, C*H*$_2$), 7.08 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.28-7.35 (m, 5H, Ar*H*), Ar*H*), 7.39-7.43 (m, 3H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 44.8 (*C*H_2CO), 119.8, 124.6 (Ar*C*), 127.8 (Ar*C*), 129.1 (Ar*C*), 129.4 (Ar*C*), 129.7 (Ar*C*), 134.6 (Ar*C*), 137.7 (Ar*C*), 169.0 (*C*ONH); HRMS (ESI^+): calcd. for $C_{14}H_{13}NO$ $[M+Na]^+$ 234.0889; found 234.0884. All spectroscopic and analytical properties were identical to that reported in the literature.[136]

N-Phenethyl-2-phenylacetamide 3(Table 4)



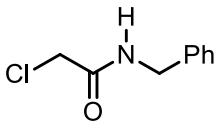
The general procedure for the preparation of amides was followed to provide the title compound as a white solid. M. p. 110–113 °C (*n*-hexane/ethyl acetate) (lit. 110-112 °C); ν_{max} (ATR): 3291 (N-H), 3080, 3063, 3027, 2930, 1639 (C=O), 1538, 1498, 1026, 763, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.62 (t, 2H, *J* = 6.6 Hz, C*H*$_2$), 3.34-3.37 (m, 2H, C*H*$_2$N*H*), 3.43 (s, 2H, C*H*$_2$CO), 5.25 (br, s, 1H, N*H*), 6.92 (d, 2H, *J* = 7.8 Hz, Ar*H*), 7.06-7.23 (m, 8H, Ar*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 34.3 (*C*H_2), 39.4 (*C*H_2), 42.7 (*C*H_2CO), 125.2 (Ar*C*), 126.1 (Ar*C*), 127.4 (Ar*C*), 127.5 (Ar*C*), 127.8 (Ar*C*), 128.2 (Ar*C*), 133.6 (Ar*C*), 137.5(Ar*C*), 169.6 (*C*ONH). HRMS (ESI^+): calculated for $C_{16}H_{18}NO$ $[M+H]^+$ 240.1388, found 240.1397. All spectroscopic and analytical properties were identical to that reported in the literature.[136ii,137]

1-(2-Phenylacetyl)piperidine 4 (Table 4)



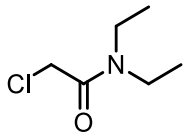
The general procedure for the preparation of amides was followed to provide the title compound as a white solid. M. p. 116-117 °C (lit. 118-120 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45-1.43 (m, 2H, CH_2), 1.64 (q, *J* = 6.0 Hz, 4*H*, C*H*$_2$), 2.85 (t, *J* = 6.4 Hz, 4H, C*H*$_2$N), 3.72 (s, 2H, C*H*$_2$CO), 7.37-46 (m, 2H, Ar*H*), 7.30-7.10 (m, 3H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.0 (*C*ONH), 137.6 (Ar*C*), 134.4 (Ar*C*), 129.5 (Ar*C*) , 129.2 (Ar*C*), 128.9 (Ar*C*), 127.7 (Ar*C*), 124.4 (Ar*C*), 119.8, 44.8 (*C*H$_2$CO); HRMS (ESI$^+$): calcd. for $C_{14}H_{13}NO$ $[M+Na]^+$ 234.0889; found 234.0884. All spectroscopic and analytical properties were identical to that reported in the literature.[137]

N-Benzyl-2-chloroacetamide 5(Table 4)



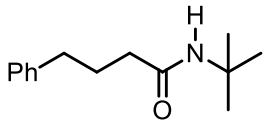
It was obtained by following the general procedure for the preparation of amides and was found in white crystalline form. M.p. 91-93 °C; ν_{max} (ATR): 3275 (N-H), 1624 (C=O), 1543 (N-H), 1438.94 (C-N), 785-540 (C-Cl), 567 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 2H, C*H*$_2$Cl), 4.42 (d, *J* = 6.1 Hz, 2H, C*H*$_2$), 6.81 (br, s, 1H, N*H*), 7.31-7.16 (m, 5H, Ar*H*),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.6 (*C*H$_2$), 43.9 (*C*H$_2$), 127.8 (Ar*C*), 127.9 (Ar*C*), 128.8(Ar*C*), 137.3 (Ar*C*), 165.9 (C=O); Elemental Analysis (%) for $C_9H_{10}ClNO$. Calcd: C, 58.86; H, 5.49; N, 7.63. Found: C, 58.61; H, 5.65; N, 7.84; *m/z* (ES$^+$): [M+1] 183.37, [M+2] 148.06. All spectroscopic and analytical properties were identical to that reported in the literature.[138]

N,N-Diethyl-2-chloroacetamide 6(Table 4)



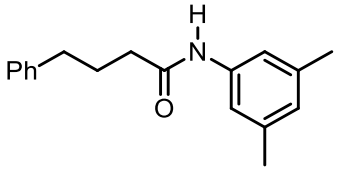
It was obtained by following the general procedure for the preparation of amides and was found in off-white powdered form. M.p. 92-95 °C (lit. 92-97 °C); ν_{max} (ATR): 3288 (N-H), 1652 (C=O), 1564 (N-H), 1433 (C-N), 791 (C-Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (s, 2H, C*H*$_2$Cl), 3.38 (q, *J* = 6.1 Hz, 4H, C*H*$_2$N), 1.13 (t, *J* = 6.4 Hz, 2H, C*H*$_3$), 1.03 (t, *J* = 6.4 Hz, 2H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (C=O), 43.0 (*C*H_2), 42.6 (*C*H_2), 43.0 (*C*H_2Cl), 14.6 (*C*H_3), 14.3 (*C*H_3); Elemental Analysis (%) for $C_6H_{12}ClNO$. Calcd: C, 48.17; H, 8.08; N, 9.36. Found: C, 48.25; H, 8.05; N, 9.44; *m/z* (ES^+): [M+1] 150.62, [M+2] 152.06. All spectroscopic and analytical properties were identical to that reported in the literature.[159]

N-(tert-Butyl)-4-phenylbutanamide 7 (Table 4)



The general procedure for the preparation of amides was followed to yield the compound as yellow oil. ν_{max} (ATR): 3301, 2927, 1644vs(C=O), 1543s (N-H), 1494, 1451, 1411, 1221, 741, 696vs, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H, 3C*H*$_3$, 1.95-1.99 (m, 2H, C*H*$_2$), 2.11 (m, 2H, C*H*$_2$), 2.63-2.68 (m, 2H, C*H*$_2$), 5.19 (br, s, 1H, N*H*), 7.17-7.21 (m, 3H, 3Ar*H*), 7.26-7.30 (m, 2H, 2Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0 (*C*H_2), 28.8 (3*C*H_3), 34.6 (*C*H_2CO), 35.6 (*C*H_2Ar), 125.3 (Ar*C*), 128.4 (2Ar*C*), 128.7 (2Ar*C*), 129.1 (Ar*C*), 142.2 (Ar*C*), 170.1 (*C*=O). *m/z* (ES^+): 220.1 [M+H^+]. All spectroscopic and analytical properties were identical to that reported in the literature.

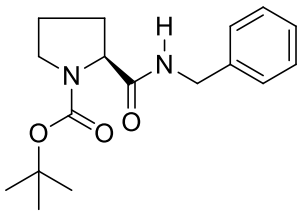
N-(3,5,-Dimethylanilin)-4-phenylbutyramide 8(Table 4)



The general procedure for the preparation of amides was followed to yield the compound as off white solid. M.p. 145-148 °C. ν_{max} (ATR): 31056 (C-H), 696vs, 3301 (N-H), 2927 (C-H), 1645vs (C=O), 1544s (N-H), 1494, 1451, 1411, 1221, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):

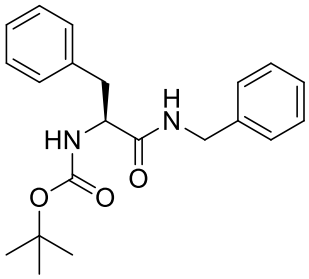
δ 1.96-2.23 (quintet, 2H, CH_2), 2.29 (s, 6H, CH_3), 2.32 (t, *J* = 7.3 Hz, CH_2CO), 2.56-2.90 (m, 2H, CH_2), 5.32 (bs,1H, N*H*), 6.48 (s, 1H, C*H*), 6.52 (s, 1H, C*H*), 6.82 (s, 1H, C*H*), 7.10-7.14 (m, 2H, Ar*H*), 7.16-7.20 (m, 1H, Ar*H*), 7.26-7.36 (m, 2H, Ar*H*),. ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4 (2CH_3), 26.0 (CH_2), 34.1 (CH_2CO), 35.4 (CH_2Ar), 117.3 (2Ar*C*), 118.3 (Ar*C*), 128.5 (2Ar*C*), 128.7 (2Ar*C*), 129.3 (Ar*C*), 138.6 (Ar*C*), 139.1 (Ar*C*), 139.3 (Ar*C*), 142.0 (Ar*C*), 171.1 (*C*=O); Elemental Analysis (%) for $C_{18}H_{21}NO$. Calcd: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.79; H, 7.98; N, 5.30; *m/z* (ES^+): 268.37 [$M+H^+$]. All spectroscopic and analytical properties were identical to that reported in the literature.

N-Boc-Prolinbenzylamide 109



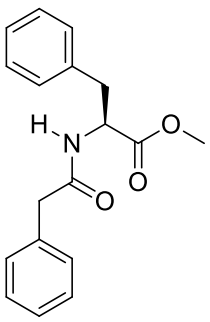
The general procedure for the preparation of amides was followed (Section 7.6) and recrystalisation was done in a mixture of toluene and petroleum ether. Different yields were found in the different reaction conditions which were reported in Table 5 and 11. The different enantiomeric excess (*ee*) found using different catalysts were reported in Table 8. 96% hexane and 4% IPA as eluent, 1 mL/ min, Ï = 254 nm, 14.69 min and 24.08 min, column OD-H (0.46 cm × 25 cm). M. p. 133-135 °C (lit. 132-136 °C); ν_{max} (ATR): 3294, 2978, 2872, 1682vs (C=O), 1656, 1527, 1453, 1393 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (s, 9H), 1.72–1.81 (m, 1H), 1.82–1.87 (m, 2 H), 2.05–2.16 (m, 1H), 3.29–3.37 (m, 1H), 3.38–3.44 (m, 1 H), 4.09–4.15 (m, 1H), 4.20–2.26 (m, 1 H), 4.34 (dd, *J* = 15.1, 6.2 Hz, 1 H), 7.18–7.33 (m, 5 H), 8.05–8.08 (br, s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.4 (CH_2), 28.3 (3*C*), 28.6 (CH_2), 42.8 (CH_2Ar), 43.4 (CH_2NCO), 56.1 (*C*HCO), 80.2 (*C*-OCO), 127.6 (2Ar*C*), 128.6 (2Ar*C*), 128.7 (Ar*C*), 137.7 (Ar*C*), 155.4 (*C*O), 171.1 (*C*ONH). MS (ES): *m/z* = 305.81 [M+ H]$^+$. All spectroscopic and analytical properties were identical to that reported in the literature.[23]

N-Boc-Phenylalanine benzylamide 111



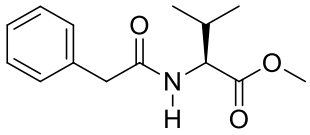
The general procedure for the preparation of amides was followed (Section 7.6) and single crystals were grown from mixture of toluene and petroleum ether. Different yields were found in different reaction conditions which were reported in Table 6 and 12. The different enantiomeric excess (*ee*) found using different catalysts were reported in Table 8. 97% hexane and 3% IPA as eluent, 1 mL/ min, Ï = 254 nm, 11.66 min and 22.94 min, column OD-H (0.46 cm × 25 cm). M. p. 144-147 °C. ν_{max} (ATR): 3332, 3296, 3064, 2982, 1680vs (C=O), 1656, 1522, 1453, 1367 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (s, 9H, 3CH_3), 2.98 (d, *J* = 6.6 Hz, 2H, CH_2), 4.24-4.30 (m, 2H, CH_2), 4.34-4.38 (m, 1H, C*H*), 5.16 (br, s, 1H, N*H*), 6.31 (s, 1H, N*H*COO), 7.00 (s, 2H, Ar*H*), 7.05-7.21 (m, 8H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.3 (3*C*H_3), 38.6 (*C*H_2), 43.4 (*C*H_2NH), 56.1 (*C*HNH), 80.2 (*C*OC=O), 126.9 (Ar*C*), 127.4 (Ar*C*), 127.6 (Ar*C*), 128.6 (2Ar*C*), 128.7 (2Ar*C*), 129.4 (2Ar*C*), 136.7 (Ar*C*), 137.7 (Ar*C*), 155.4 (*C*OO), 171.1 (*C*ONH), 172.6 (NH*C*OO). MS (ES): *m/z* = 355.21 [M+ H]$^{+}$. All spectroscopic and analytical properties were identical to that reported in the literature.[24]

N-Phenylacetyl-phenylalanine methyl ester 113a



The general procedure for the preparation of amides was followed (Section 7.7). Recrystalisation was carried out in a mixed solvent of acetone and petroleum ether. Different yields were found in different reaction conditions which were mentioned in the Table 7 and 13. 95% hexane and 5% IPA as eluent, 1 mL/ min, Ï = 254 nm, 29.07 min and 31.91 min, column OD-H (0.46 cm × 25 cm). The different enantiomeric excess (*ee*) found using different catalysts were reported in Table 8. M. p. 142-146 °C. ν_{max} (ATR): 3253, 2971, 2951, 1744vs (C=O), 1639, 1550, 1436, 1252, 1154, 773 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.95 (ddd, J = 13.8, 13.7, 5.8 Hz, 2H, C*H*$_2$), 3.48 (s, 2H, C*H*$_2$), 3.63 (s, 3H, C*H*$_3$), 4.77 (dt, *J* = 7.8, 5.8 Hz, 1H, C*H*), 5.79 (s, 1H, N*H*), 6.75-6.85 (m, 2H, Ar*H*), 7.06-7.17 (m, 4H, Ar*H*), 7.21-7.28 (m, 4H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_{ppm} 37.6 (*C*H_2), 43.6 (*C*H_2CO), 52.2 (*C*HN), 52.9 (*C*H_3O), 127.0 (Ar*C*), 127.3 (Ar*C*), 128.5 (2Ar*C*), 128.9 (2Ar*C*), 129.1 (2 Ar*C*), 129.39 (2Ar*C*), 134.4 (Ar*C*), 135.6 (Ar*C*), 170.3 (*C*ONH), 171.7 (*C*OO). MS (ES): *m/z* = 298.21 $[M+ H]^+$. All spectroscopic and analytical properties were identical to that reported in the literature.[25]

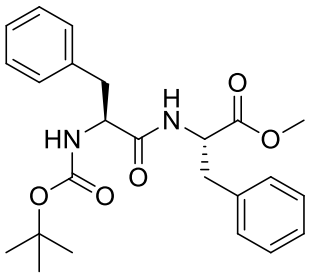
N-Phenylacetyl-valine methyl ester 113b



The general procedure for the preparation of amides was followed (Section 7.7) and the single crystal was grown in a mixed solvent of acetone and petroleum ether. Different yields were found in different reaction conditions which were mentioned in the Table 7 and 13. 95% hexane and 5% IPA as eluent, 1 mL/ min, Ï = 254 nm, 16.54 min and 22.98 min, column OD-H (0.46 cm × 25 cm). The *ee* values found using different catalysts were reported in Table 8. M. p. 138-141 °C. ν_{max} (ATR): 3253, 2970, 2951, 1742vs (C=O), 1638, 1549, 1436, 734 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.68 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 0.77 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 1.96-2.05 (m, 1H, C*H*), 3.53(s, 2H, C*H*$_2$), 3.60 (s, 3H, CH_3O), 4.46 (dd, *J* = 8.8, 4.9 Hz, 1H, C*H*CO), 5.97-6.05 (d, *J* = 8.2 Hz, 1H, N*H*), 7.18-7.32 (m, 5H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.6 (CH_3), 17.9 (CH_3), 30.1 (*C*H(CH_3)$_2$), 42.6 (CH_2), 51.0 (*C*HNH), 56.1 (CH_3O), 126.3 (Ar*C*), 127.9 (2Ar*C*), 128.3 (2Ar*C*), 133.8, 169.9 (*C*ONH), 171.3 (*C*OO). MS (ES)

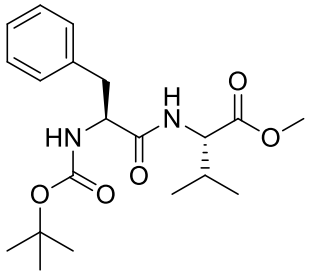
m/z: 350.14 $[M+H]^+$. All spectroscopic and analytical properties were identical to that reported in the literature.[25]

N-Boc-Phe-Phe methyl ester 114



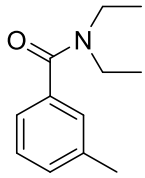
The general procedure for the preparation of amides was followed (Section 7.8). Recrystalisation was carried out in a mixed solvent of acetone and petroleum ether. Different yields were found in different reaction conditions which were mentioned in the Table 14. M. p. 152-156 °C. ν_{max} (ATR): 3315, 2970, 2951, 1745vs (C=O), 1663, 1638, 1549, 1436, 734 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 9H, 3C*H*$_3$), 2.91-3.03 (m, 4H, 2CH_2), 3.59 (s, 3H), 4.26 (br, 1H, CH_2C*H*NH), 4.71 (br, 1H, N*H*CH), 4.86 (br, 1H, N*H*CO), 6.19 (d, *J* = 6.6 Hz, 1H, C*H*CO), 6.91 (dd, *J* = 7.2, 2.1 Hz, 2H, Ar*H*), 7.10-7.23 (m, 8H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.2 (3*C*H_3), 38.0 (CH_2), 38.3 (*C*H_2CO), 52.3 (*C*HNH), 53.3 (*C*HOCO), 55.7 (*C*H_2CO), 80.21 (*C*H_3O), 127.0 (Ar*C*), 127.1(Ar*C*), 128.6 (2Ar*C*), 128.7 (2Ar*C*), 129.2 (2Ar*C*), 129.4 (2Ar*C*), 135.6, 136.5, 155.2, 170.8 (*C*ONH), 171.4 (*C*OONH), 172.2 (*C*OO). MS (ES) *m/z*: 427.22 $[M+H]^+$. All spectroscopic and analytical properties were identical to that reported in the literature.[26]

N-Boc-Phe-Val methyl ester 115



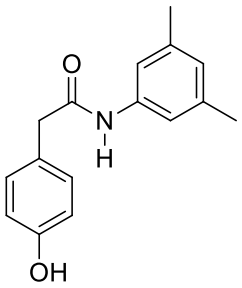
The general procedure for the preparation of amides was followed (Section 7.8) and re-crystalsation were done in a mixed solvent of acetone and petroleum ether. Different yields were found in different reaction conditions which were mentioned in the Table 14. ν_{max} (ATR): 3253, 2970, 2951, 1745νs (C=O), 1648, 1639, 1549, 1468, 773 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.77 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 0.80 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.35 (s, 9H, 3C*H*$_3$), 2.03 (dd, *J* = 7.1 and 6.9 Hz, 1H, C*H*), 3.00 (d, *J* = 6.8 Hz, 2H, CH_2), 3.62 (s, 3H, CH_3O), 4.28 (br, 1H), 4.39 (d, *J* = 6.7Hz, 1H), 4.96 (br, 1H, N*H*), 6.31 (d, *J* = 8.5 Hz,1H, N*H*), 7.11-7.24 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 18.8, 28.3 (3C), 31.3, 38.0, 52.1, 55.9, 57.2, 80.2, 126.9, 128.7 (2Ar*C*), 129.3 (2Ar*C*), 136.6 (Ar*C*), 155.4, 171.1 (*C*ONH), 171.8 (OCONH). MS (ES) *m/z*: 393.32 $[M+H]^+$. All spectroscopic and analytical properties were identical to that reported in the literature.[26]

N,N-Diethyl-meta-toluamide 119



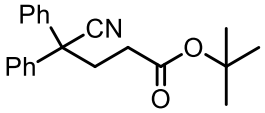
The title compound was prepared following the general procedure for the catalytic direct amide formation using *m*-toluic acid (2.86 mmol, 1.11g) and benzylamine (2.86 mmol, 0.30 mL) refluxed in different solvent (20 mL) to afford the amide as colorless oil. ν_{max} (ATR): 1641νs (C=O), 800, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (t, *J* = 7.3 Hz, 6H, 2C*H*$_3$), 2.40 (s, 3H, C*H*$_3$), 3.15 (q, *J* = 7.4 Hz, 4H, 2CH_2), 7.30-7.36 (m, 2H, Ar*H*), 7.91-7.94 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7 (CH_3), 14.0 (CH_3), 21.1 (CH_3), 38.9 (CH_2), 43.0 (CH_2), 122.9 (Ar*C*), 126.6 (Ar*C*), 128.0 (Ar*C*), 129.5 (Ar*C*), 137.6 (Ar*C*), 137.9 (Ar*C*), 171.4 (C=O); Elemental Analysis (%) for $C_{12}H_{17}NO$. Calcd: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.30; H, 8.93; N, 7.30. All spectroscopic and analytical properties were identical to that reported in the literature.[162]

4-[[(3,5-Dimethylanilino)carbonyl]methylphenol 124



General procedure for the preparation of amides was followed, a mixture of 4-hydroxyphenylacetic acid (2.86 mmol, 0.43 g) and 3,5-dimethylaniline (2.86 mmol, 0.36 mL) were refluxed in toluene (20 mL) at 110 °C using different catalysts to yield the compound as pale yellow solid. M. p. 184-186 °C (lit. 183-185 °C); ν_{max} (ATR): 1641νs (C=O), 800, 750 cm^{-1}.^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 6H, 2C*H*$_3$), 3.74 (s, 2H, C*H*$_2$), 6.35(s, 2H, Ar*H*), 6.44(s, 1H, N*H*), 7.13-7.20 (m, br, 4H, Ar*H*), 7.28-7.29 (m, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (2*C*H$_3$), 42.8(*C*H$_2$), 115.4 (2Ar*C*), 117.2 (2Ar*C*), 118.2 (Ar*C*), 127.8 (2Ar*C*), 131.5 (Ar*C*), 138.6 (Ar*C*), 139.2 (2Ar*C*), 157.21 (Ar*C*), 173.1(*C*ONH). All spectroscopic and analytical properties were identical to that reported in the literature.[163]

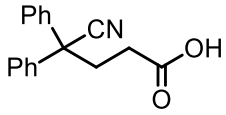
tert-Butyl-4-cyano-4,4-diphenylbutanoate 130



Diphenylacetonitrile (19.3 g, 100 mmol) was added in *tert*-butanol (100 mL) and warmed to 60 °C for 30 min. The resulting reaction mixture was cooled to 50°C and treated with a KOH solution (600 mg, 10.7 mmol) in methanol (2 mL). *tert*-Butyl acrylate (30 mL, 200 mmol) was the added dropwise and the mixture was stirred at 50°C for 2 h, then at room temperature for 18 h. A further portion of KOH (600mg, 10.7 mmol) was added and the resulting mixture was heated at 50 °C for 3 h. The mixture was cooled, and concentrated *in vacuo*. The residue was extracted by Et_2O (300 mL) and water (200mL). The organic layer was dried and concentrated *in vacuo* to afford the compound as a white solid (48.7g, 75% yield). M. p. 178-179 °C. ν_{max} (ATR): 2979, 2245, 1751νs (C=O), 1596, 1443, 1315, 756 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz) δ 1.41 (s, 9H, 3C*H*$_3$), 2.28 (distorted triplet, *J* = 8.0 Hz, 2H, C*H*$_2$), 2.71 (triplet, *J* = 8.0 Hz, 2H, C*H*$_2$), 7.29-7.33 (m, 2H, Ar*H*), 7.36-7.42 (m, 8H, Ar*H*); ^{13}C NMR

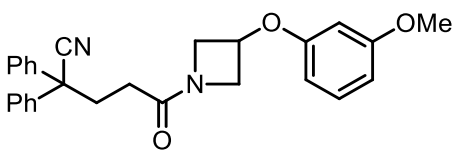
(100 MHz, DMSO-d6) δ 31.5 (*C*(Ar_2CN)), 31.9 (*C*($(CH_3)_3O$)), 35.3 (*C*H_2), 52.4 (*C*H_2), 69.5 (3*C*H_3) 122.9 (Ar*C*), 127.8 (Ar*C*), 129.3 (Ar*C*), 130.1 (Ar*C*), 141.4, 172.8 (*C*OOH). Elemental Analysis (%) for $C_{21}H_{23}NO_2$. Calcd: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.42; H, 7.21; N, 4.33.All spectroscopic and analytical properties were identical to that reported in the literature.[164]

4-Cyano-4,4-diphenylbutanoic acid 125



tert-Butyl-4-cyano-4,4-diphenylbutanoate (8.95 mmol, 2.87 g) and 4M HCl was added in dioxane (25 mL) and the mixture was stirred at room temperature for 18 h. The mixture was concentrated *in vacuo*, the residue was treated with warm di*iso*propyl ether (7.5 mL) and then cooled to room temperature resulting in a white solid. The solid was collected by filtration dried under vacuum to afford the acid as white solid (0.99 g, 41% yield). M. p. 154-159 °C ν_{max} (ATR): 2982, 2236, 1712*v*s (C=O), 1447, 1315, 1228, cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz) δ 2.36-2.40 (m, 2H, C*H*$_2$), 2.60-2.64 (m, 2H, C*H*$_2$), 7.13 (s, 1H, Ar*H*), 7.16-7.26 (m, 8H, Ar*H*), 7.27-7.28 (m, 1H, Ar*H*); ^{13}C NMR (100 MHz, DMSO-d6) δ 31.5 (*C*H_2), 35.3 (*C*H_2), 52.4, 68.1, 122.9 (Ar*C*), 127.8 (Ar*C*), 129.3 (Ar*C*), 130.1 (Ar*C*), 139.4, 172.8 (*C*OOH). Elemental Analysis (%) for $C_{17}H_{15}NO_2$. Calcd: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.89; H, 5.66; N, 5.21. All spectroscopic and analytical properties were identical to that reported in the literature.[164]

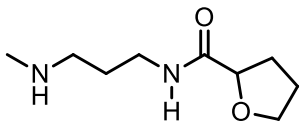
5-[3-(3-Methoxyphenoxy)azetidin-1-yl]- 5-oxo-2,2-diphenylpentanenitrile 127



The general procedure for the preparation of amides was followed, a mixture of 4-Cyano-4,4-diphenylbutanoic acid (2.86 mmol, 0.80 g) and 3-(3-methoxyphenoxy)azetidine (2.86 mmol,

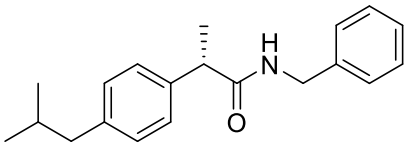
0.51g) was refluxed in toluene (10 mL) at 110 °C using different catalysts (5 mol%) to yield the compound as white solid. M. p. 187- 190 °C. ^{1}H NMR (DMSO, 400 MHz) δ 2.12-2.24 (m, 2H), 2.68-2.83 (m, 2H), 3.12 (m, 3H), 3.54-3.79 (m, 1H), 3.92-4.01 (m, 1H), 4.21-4.32 (m, 1H), 4.38−4.48 (m, 1H), 4.90-5.01 (m, 1H), 6.34-6.44 (m, 2H), 6.52- 6.62 (m, 1H), 7.16-7.24 (m, 1H, Ar*H*), 7.31-7.37 (m, 2H, Ar*H*), 7.38-7.49 (m, 8H, Ar*H*); ^{13}C NMR (100 MHz, DMSO-d6) δ 27.6, 33.4, 51.0, 54.5, 55.1, 56.5, 65.2, 101.0, 106.6, 107.1, 121.9 (Ar*C*), 126.4 (Ar*C*), 128.0 (Ar*C*), 128.4 (Ar*C*), 128.6 (Ar*C*), 129.1 (Ar*C*), 130.2 (Ar*C*), 139.5 (Ar*C*), 139.6 (CN), 157.4, 160.6 (Ar*C*OMe), 170.4 (*C*ON). Elemental Analysis (%) for $C_{27}H_{26}N_2O_3$. Calcd: C, 76.03; H, 6.14; N, 6.57. Found: C, 76.09; H, 6.17; N, 6.51. All spectroscopic and analytical properties were identical to that reported in the literature.[164]

N-[3-(Methylamino)propyl]tetrahydrofuran-2-carboxamide 138



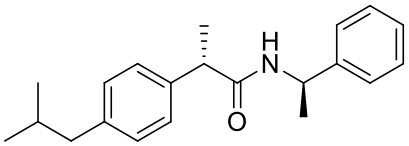
The general procedure for the preparation of amides was followed, a mixture of Tetrahydro-2-furoic acid (2.86 mmol, 0.27 mL) and 3-(methylamino)propylamine (2.86 mmol, 0.30 mL) was refluxed in different solvents and temperature using different catalysts to yield the compound as yellow oil. TLC (EtOAc/ hexane, 4:1) R_f 0.16; ν_{max} (ATR): 3416 (N-H), 1658 (C=O), 1529 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63 (quintet, *J* = 6.4 Hz, 2H, C*H*$_2$), 1.73-1.90 (m, 2H, C*H*$_2$), 1.93-2.01 (m, 1H), 2.17-2.26 (m, 1H), 2.35 (s, 3H, C*H*$_3$), 2.55-2.63 (m, 2*H*, CH_2), 2.80 (s, br, 1H, N*H*CH_3), 3.22-3.32 (m, 2H, C*H*$_2$), 3.78-3.90 (m, 2H, C*H*$_2$), 4.52-4.29 (m, 1H, C*H*), 7.22 (s, br, 1H, N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6 (*C*H_3), 28.3 (*C*H_2), 30.3 (*C*H_2), 36.0 (CH_2), 37.3 (*C*H_2), 49.9 (*C*H_2), 69.5 (*C*H_2), 78.3 (*C*H), 173.1 (*C*O). All spectroscopic and analytical properties were identical to that reported in the literature.[161]

(S)-N-Benzyl-2-(4-isobutylphenyl)propionamide 140



The title compound was prepared following the general procedure for the catalytic direct amide formation using (S)-2-(4-isobutylphenyl)propionic acid (1.44 mmol, 0.29g) and benzylamine (1.44 mmol, 0.15 mL) refluxed in fluorobenzene (20 mL) to afford the amide as a pale yellow oil. TLC (EtOAc/ hexane, 4:1) R_f =0.35; The enantiomeric excess was determined by chiral HPLC using Chiralcel OD column (250 × 4.6 mm), 25 °C, 1 mL/min, UV detection at 230 nm, hexane: IPA (9:1), t_R (*S*-ibuprofen amide product) = 11.65 min; t_R (*R*- ibuprofen amide product) = 23.0 min. ν_{max} (ATR): 3287 (s, N-H), 1649 (s, C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, *J* = 6.8 Hz, 6H, 2C*H*$_3$CH), 1.27 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 1.79 (septet, *J* = 6.8 Hz, 1H, C*H*), 2.38 (d, *J* = 7.2 Hz, 2H, C*H*$_2$CH), 3.98 (q, *J* = 6.4 Hz, 2*H*, C*H*CO), 4.50 (s, 2H, CH_2Ar), 4.89 (s, br, 1H, N*H*CO), 6.97(d, *J* = 7.6 Hz, 2H, Ar*H*), 7.11 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.28-7.32 (m, 5H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3 (2*C*H_3), 22.3 (*C*H_3), 31.3 (*C*H), 36.0 (CH_2), 37.3(*C*H), 49.9 (*C*H_2), 126.8 (2Ar*C*), 127.3 (2Ar*C*), 127.4 (2Ar*C*), 128.5 (2Ar*C*), 138.5 (Ar*C*), 140.6 (Ar*C*), 174.1 (*C*ONH). Elemental Analysis (%) for $C_{20}H_{25}NO$.Calcd: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.37; H, 8.50; N, 4.79. All spectroscopic and analytical properties were identical to that reported in the literature.[1]

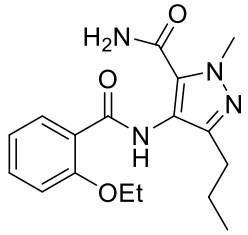
(S,R)-2-(4-isoButyl-phenyl)-N-(1-phenyl-ethyl)-propionamide 142



The title compound was prepared following the general procedure for the catalytic direct amide formation using (*S*)-2-(4-*iso*butylphenyl)propionic acid (1.44 mmol, 0.29 g) and (R)-(+)-α-methylbenzylamine (1.44 mmol, 0.15 mL) refluxed in fluorobenzene (20 mL) to afford the amide as a yellow oil. TLC (EtOAc/ hexane, 4:1) R_f =0.28; ν_{max} (ATR): 3287 (s, N-H), 1649 (s, C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (d, *J* = 6.4 Hz, 6H, 2C*H*$_3$CH), 1.27 (doublet, *J* = 8.0 Hz, 3H, C*H*$_3$ CHCO), 1.31 (doublet, *J* = 8.4 Hz, 3H, C*H*$_3$CHAr), 1.80

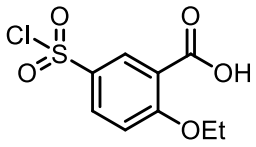
(septet, *J* = 6.8 Hz, 1H, C*H*(CH_3)$_2$), 2.40 (d, *J* = 7.2 Hz, 2H, CH_2CH), 3.45 (d, *J* = 6.0 Hz, 1H, C*H*Ar), 3.94 (q, *J* = 6.4 Hz, 1*H*, C*H*CH_3CO), 6.44 (s, br, 1H, N*H*CO), 7.0 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.13(d, *J* = 8.0 Hz, 2H, Ar*H*) 7.20-7.25 (m, 3H, Ar*H*), 7.28-7.30 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3 (2*C*H_3), 22.3(*C*H_3), 31.3 (*C*H), 36.0 (CH_2), 37.3(*C*H), 49.9 (*C*H_2), 69.5 (*C*H_2), 78.3 (d, *C*H), 125.6 (Ar*C*), 127.27 (Ar*C*), 127.4 (Ar*C*), 127.43 (Ar*C*), 128.5 (Ar*C*), 129.4 (Ar*C*), 138.5 (Ar*C*), 140.6 (Ar*C*), 174.1 (*C*ONH). Elemental Analysis (%) for $C_{21}H_{27}NO$.Calcd: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.52; H, 8.70; N, 4.50. All spectroscopic and analytical properties were identical to that reported in the literature.[1]

4-(2-Ethoxybenzamido)-1-methyl-3-propyl-1H-pyrazole-5-carboxamide 144



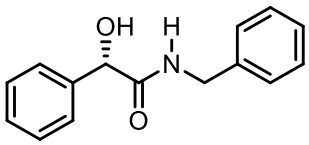
2-Ethoxybenzoic acid (0.43 mL, 2.86 mmol) and 4-Amino-1-methyl-3-propyl-1Hpyrazole-5-carboxamide (0.5208 g, 2.86mmol) were dissolved in toluene (20 mL). The reaction was carried out under both uncatalysed and catalysed (5 mol%) conditions. The reaction mixture was heated to reflux temperature under argon for 24 hrs. Water removal was carried out by the use of a Dean-Stark condenser. After 24 hrs the toluene was evaporated and the crude NMR was carried out to find the NMR conversion. The residue was re-dissolved in ethyl acetate (25 mL). This was washed with 5% (*w/v*) HCl (20 mL), brine (20 mL), 5% (*w/v*) NaOH (20 mL), brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title compound as a pale white solid. M.p. 153-156 °C (lit mp = 153-154 °C). ν_{max} (ATR): 3447, 3291, 3172, 2955, 2870, 1679, 1645, 1557, 1447, 1417 and 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, *J* = 6.9 Hz, 3H), 1.65 (t, *J* = 8.0 Hz, 3H), 1.73 (sextet, *J* = 6.3 Hz, 2H), 2.54 (t, *J* = 6.9 Hz, 2H), 4.06 (s, 3H), 4.31 (q, *J* = 6.3 Hz, 2H), 5.62 (s, br, 1H), 7.05 (d, *J* = 8.5 Hz,1H), 7.15 (t, 1H *J* = 8.0 Hz,), 7.55 (m, 1H), 7.91 (s, br, 1H), 8.30 (dd, *J* = 8.0 Hz,1H), 9.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 (*C*H_3), 18.8 (*C*H_3), 24.3, 28.5, 39.0, 66.2, 113.5, 115.5, 119.9, 122.7 (Ar*C*), 134.3 (Ar*C*), 136.6, 147.4, 158.9, 161.1 (CONH), 169.8 ($CONH_2$). All spectroscopic and analytical properties were identical to that reported in the literature. [160]

2-Ethoxy-5-(chlorosulfonyl) benzoic acid 152



To a well stirred flask containing chlorosulfonic acid (8 mL) cooled at 0 °C, 2-ethoxybenzoic acid was added dropwise over 20 min. Then ice cold water (150 mL) was added very cautiously to the mixture and the mixture was then stirred for 1 h. The reaction mixture was then extracted with DCM (200 mL). The organic layer was separated, dried over $MgSO_4$, and the solvent was dried off to afford a white solid. M.p. 268-270 °C. ν_{max} (ATR): 3069, 2897, 2845, 1693, 1645, 1455, 1235, 852 and 614 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49-1.56 (m, 3H, C*H*$_3$), 4.26-4.39 (m, 2H, C*H*$_2$), 7.04-7.07 (m, 1H, Ar*H*), 7.20-7.23 (m, 1H, Ar*H*), 7.20-7.23 (m, 1H, Ar*H*), 7.20-7.23 (m, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.5 (*C*H_2), 74.4 (*C*HOH), 127.7 (Ar*C*), 128.4 (Ar*C*), 129.3 (2Ar*C*), 137.6 (Ar*C*), 139.8 (Ar*C*), 173.7 (*C*ONH). All spectroscopic and analytical properties were identical to that reported in the literature.[167]

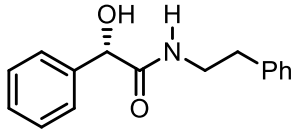
(S)-N-Benzyl-2-hydroxy-2-phenylacetamide 162



The general procedure for amide formation was followed to provide the title compound as colorless solid with different yields. The enantiomeric excess (entries 1, 2, 6 and 7, Table 21) was determined by chiral HPLC using Chiralcel OD-H column (250 × 4.6 mm), 25 °C, 1 mL/min, UV detection at 230 nm, hexane: IPA (95:4), t_R (*R*-product) = 7.18 min; t_R (*S*-product) = 8.74 min. M.p. 132-133 °C (lit mp = 133-135 °C). R_f = 0.32 (hexane: EtOAc, 80:20); ν_{max} (ATR): 3407, 3173, 1652, 1586, 1533, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.67-3.68 (d, 1H, *J* = 3.2 Hz, O*H*), 4.37-4.48 (m, 2H, C*H*$_2$), 5.05-5.06 (d, *J* = 3.6 Hz, 1H, C*H*OH), 6.53 (s, br, 1H, N*H*), 7.17-7.19 (m, 2H, Ar*H*), 7.27-7.41 (m, 8H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.5 (*C*H_2), 74.4 (*C*HOH), 126.9 (Ar*C*), 127.7 (Ar*C*), 127.9 (Ar*C*),

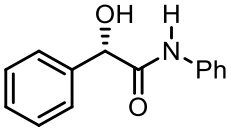
128.4 (Ar*C*), 128.7 (Ar*C*), 129.3 (Ar*C*), 137.6 (Ar*C*), 139.8 (Ar*C*), 173.7 (*C*ONH). All spectroscopic and analytical properties were identical to that reported in the literature.[90,169]

2-Hydroxy-N-phenethyl-2-phenylacetamide 164



The general procedure for amide formation was followed to provide the title compound as a white solid with different yields. R_f = 0.46 (hexane: EtOAc, 90:10); The enantiomeric excess (entries 13 and 14, Table 21) was determined by chiral HPLC using Chiralcel OD-H column (250 × 4.6 mm), 25 °C, 1 mL/min, UV detection at 230 nm, hexane: IPA (95:4), t_R (*R*-product) = 7.18 min; t_R (*S*- product) = 8.75 min. M.p. 101-103 °C (Lit[170] mp = 100-103 °C). ν_{max} (ATR): 3386, 2982, 1656, 1524, 1533, 1077 cm^{-}1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.68-2.81 (m, 2H, CH_2), 3.41-3.49 (m, 1H), 3.51-3.59 (m, 1H), 3.79 (d, *J* = 3.6 Hz, 1H, OH), 4.94 (d, *J* = 3.6 Hz, 1H, CH), 6.14 (s, br, 1H, NH), 7.01-7.04 (m, 2H, Ar*H*), 7.20-7.25 (m, 3H, Ar*H*), 7.30-7.36 (m, 5H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3 (*C*H_2), 41.7 *C*H_2), 75.7 (*C*HOH), 126.9 (Ar*C*), 127.4 (Ar*C*), 127.9 (Ar*C*), 128.7 (Ar*C*), 128.4 (Ar*C*), 129.3 (2(Ar*C*), 138.6 (Ar*C*), 141.4 (Ar*C*), 177.1 (*C*ONH). All spectroscopic and analytical properties were identical to that reported in the literature.[170]

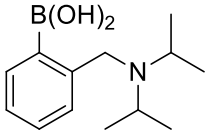
2-Hydroxy-N-2-diphenylacetamide 166



The general procedure for amide formation was followed in different solvents to provide the title compound as a white solid with different yields. M.p. 150-152 °C (Lit[168] mp = 15-151°C). R_f = 0.52 (hexane: EtOAc, 80:20); The enantiomeric excess (entries 20 and 21, Table 21) was determined by chiral HPLC using Chiralcel OD-H column (250 × 4.6 mm), 25 °C, 1 mL/min, UV detection at 230 nm, hexane: IPA (90:10), t_R (*S*-product) = 8.09 min; t_R (*R*-product) = 10.15 min; ν_{max} (ATR): 3265, 3062, 2982, 1658, 1599, 1531, 1177 cm^{-1}; ^{1}H NMR

($CDCl_3$, 400 MHz) δ 3.61 (s, br, 1H, O*H*), 5.14 (s, br, 1H, N*H*), 7.10-7.14 (m, 1H, Ar*H*), 7.29-7.33 (m, 2H, Ar*H*), 7.35-7.40 (m, 3H, Ar*H*), 7.46-7.52 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.7 (*C*HOH), 126.9 (Ar*C*), 127.4 (Ar*C*), 127.9 (Ar*C*), 128.7 (Ar*C*), 128.4 (Ar*C*), 129.3 (2(Ar*C*), 138.6 (Ar*C*), 141.4 (Ar*C*), 179.1 (*C*ONH). All spectroscopic and analytical properties were identical to that reported in the literature.[168]

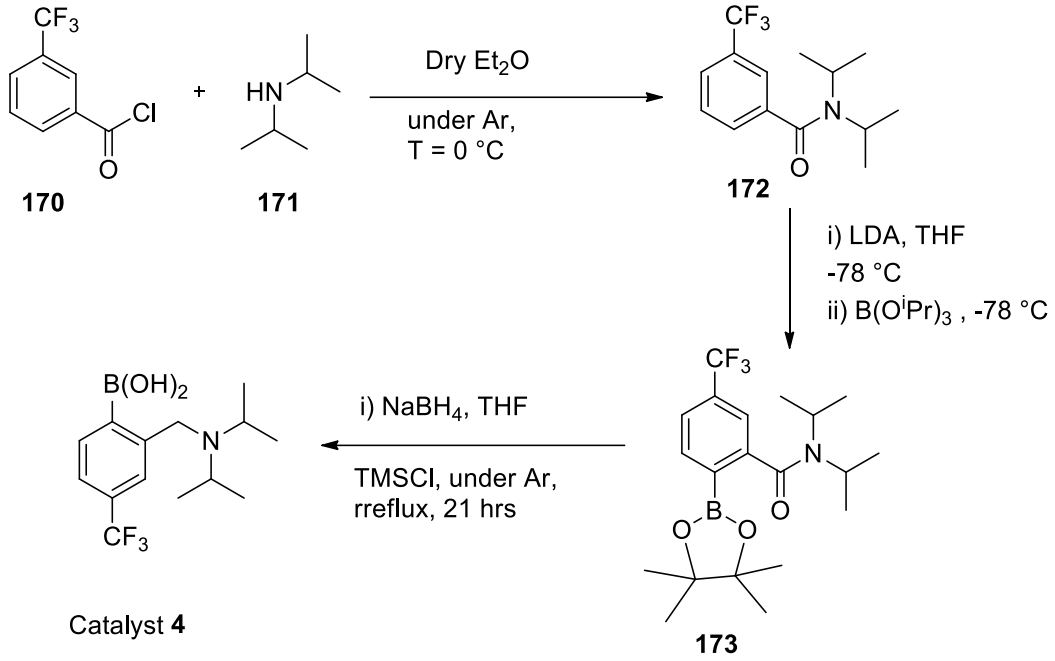
N,N-Diisopropylbenzylamine-2-boronic acid (catalyst 3)



2-Formylbenzeneboronic acid (0.91 g, 6 mmol) and di*iso*propylamine (0.85 mL, 6 mmol) were added to THF (20 mL) and 3 Å activated molecular sieves (4.0 g). After stirring for 24 h sodium triacetoxyborohydride (8.0 g, 36 mmol) was added, the reaction was then stirred for a another 24 h. Then 5% (*w/v*) HCl (10 mL) was added slowly. After 20 minutes, the resulting suspension was filtered through a sinter and washed with water (50 mL). THF was removed from the filtrate *in vacuo* and the aqueous mixture was then neutralised by slow addition of sat. $NaHCO_3$(aq). The filtrate mixture was allowed to stand for 72 h for the product crystallization. The product was extracted into DCM (50 mL) and washed with brine (50 mL), the organic layer was dried ($MgSO_4$) and solvents evaporated to afford a white solid. This was re-dissolved in 5% (*w/v*) HCl (5 mL) and washed with DCM (5 mL). To the aqueous phase was added 20% (*w/v*) NaOH (2 mL) and the precipitated product was extracted with DCM (5 × 20 mL). The solvent was removed *in vacuo* resulting a white solid (0.45 g, 50%). M.p. 140-142 °C. ν_{max} (ATR): 2930, 1625, 1527, 1438, 1334 and 1153 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, 12H, *J* = 6.7 Hz, C*H*$_3$), 3.13 (septet, 2H, *J* = 6.8 Hz, 2(C*H*(CH_3)$_2$), 3.84 (s, 2H, C*H*$_2$), 7.22-7.26 (m, 1H, Ar*H*), 7.30-7.38 (m, 2H, Ar*H*), 7.96-7.99 (m, 1H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.5 (*C*H$_3$), 47.3 (*C*H), 51.6 (*C*H$_2$), 53.2 (*C*H$_2$), 126.8 (Ar*C*), 129.9 (Ar*C*), 130.5 (Ar*C*), 136.5 (Ar*C*), 142.1 (Ar*C*). ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.14. Elemental Analysis (%) for $C_{13}H_{22}BNO_2$.calculated: C 66.41, H 9.43, N 5.96, found: C 66.28, H 9.41, N 5.96. All spectroscopic and analytical properties were identical to that reported in the literature.[112]

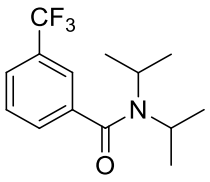
Synthesis of N,N-Diisopropyl-5-trifluoromethylbenzylamine-2-boronic acid (catalyst 4):

The catalyst *N*,*N*-di*iso*propyl-5-trifluoromethylbenzylamine-2-boronic acid (catalyst **4**) was synthesised by the following reaction scheme:



Synthetic procedure

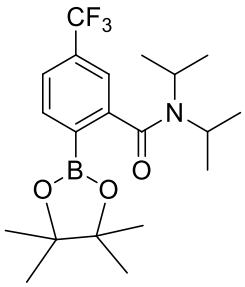
N,N-Diisopropyl-3-trifluoromethylbenzamide 172



3-(trifluoromethyl)benzoyl chloride **170** (1.78 mL, 12 mmol) was dissolved in dry Et_2O (30 mL) under argon at 0 °C, then dry diisopropylamine **171** (4.24 mL, 30 mmol) was added dropwise. The reaction was allowed to warm to rt, stirred for 2 h and then quenched with 5% (*w/v*) HCL (25 mL). The organic layer was separated and washed with 5% (*w/v*) HCl (25 mL), then brine (1× 25 mL), 5% (*w/v*) NaOH (3 × 25 mL), brine (1× 25 mL), dried over

$MgSO_4$, and concentrated *in vacuo* to yield the amide **172** (3.26 g, 99%) as a white solid. Mp 57-60 °C; ν_{max} (ATR): 2968, 1630s, 1375, 1316s, 1152 and 1123 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.13 (d, 6H, 2CH_3), 1.43 (d, 6H, 2CH_3), 3.53 (m, lH, C*H*), 3.72 (m, 1H, C*H*), 7.48-7.54 (m, 2H, Ar*H*), 7.58 (s, 1H, Ar*H*) and 7.62-7.64 (m, lH, Ar*H*); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ 21.3 (2*C*H_3), 46.3 (2*C*H_3), 51.3 (*C*H), 123.1 (q, $^3J_{FC}$ = 3.9, Ar*C*), 123.7 (q, $^1J_{FC}$ = 273, *C*F_3), 124.8 (q, $^3J_{FC}$ = 3.9, Ar*C*), 129.4 (Ar*C*), 129.2 (Ar*C*), 131.1 (q, $^2J_{FC}$ 33, Ar*C*CF_3), 139.6 (Ar*C*-CON^{i}Pr_2), 169.5 (*C*ON^{i}Pr_2); ^{19}F (376.47 MHz; $CDCl_3$) δ -63.5; Elemental Analysis (%) for $C_{14}H_{18}F_3NO$.calculated: C, 61.53; H, 6.64; N, 5.13; Found: C, 61.23; H, 6.44; N, 4.83. All spectroscopic and analytical properties were identical to that reported in the literature.[96]

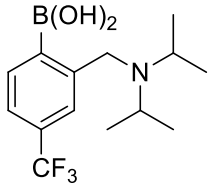
N,N-Diisopropyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzamide 173



To a stirred solution of *N,N*-di*iso*propyl-3-trifluoromethylbenzamide **172** (1.0 g, 3. 70 mmol) in dry THF (20 mL) under argon at -78°C, was added LDA (5 mL, 1.8 M, 4.44 mmol) dropwise over 15 min. The mixture was left to stir for 60 min and then tri*iso*propyl borate (0.94 mL, 4.07 mmol) was added rapidly. The mixture was allowed to reach rt overnight (24 hrs) and then quenched with 20% (*w/v*) HCl (6 mL), followed by addition of pinacol (0.48 g, 4.07 mmol). The mixture was allowed to stir for 30 min before being extracted into ether (3 x 20 mL) and the organic extracts washed with sat. aq. $NaHCO_3$ (3 × 10 mL), and brine (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography on silica gel (hexane: EtOAc, 4:1) afforded pinacol boronate **173** (1.23 g, 83%) as a white solid. M.p. 130-134 °C; ν_{max} (ATR): 2963, 1627s, 1312vs, and 1138vs cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.13 (d, 6H, *J* = 6.3 Hz, 2*C*H_3), 1.32 (s, 12H, 4C*H*$_3$), 1.61 (d, 6H, *J* = 6.8 Hz, 2*CH*$_3$), 3.53 (m, 1H, C*H*), 3.64 (m, 1H, C*H*), 7.39 (s, l H, Ar*H*), 7.56 (d, 1H, *J* = 8.5 Hz, Ar*H*) and 7.91 (d, l H, *J* = 7.5, Ar*H*); ^{13}C NMR (100.6 MHz;

$CDCl_3$) δ 20.6 (2*C*H_3), 20.5 (2*C*H_3), 25.5 (pinacol *C*H_3), 46.6 (*C*H), 51.7 (*C*H), 84.1 (pinacol C-O), 121.4 (q, $^3J_{FC}$ = 3.4, Ar*C*), 123.6 (q, $^1J_{FC}$ =273, *C*F_3), 124.1 (q, $^3J_{FC}$ = 4, Ar*C*), 132.5 (q, $^2J_{FC}$ = 33, Ar*C*-CF_3), 136.6 (Ar*C*), 145.6 (Ar*C*-CON^{i}Pr_2), 169.7 (*C*ON); ^{11}B(128.4 MHz; $CDCl_3$) δ 28.6; ^{19}F (376.6 MHz; $CDCl_3$) δ -63.3 (s); Elemental Analysis (%) for $C_{20}H_{31}BF_3NO_2$, Found: C, 60.27; H, 7.38; N, 3.28. calculated: C, 60.17; H, 7.32; N, 3.51). All spectroscopic and analytical properties were identical to that reported in the literature.[96]

N,N-Diisopropyl-5-trifluoromethylbenzylamine-2-boronic acid (catalyst 4)



To a stirred solution of *N,N*-di*iso*propyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzamide **173** (1.00 g, 2.50 mmol) and $NaBH_4$ (0.95 g, 25.0 mmol) in dry THF (50 mL) under argon was added TMSCl (6.35 mL, 50.0 mmol). The mixture was refluxed for 24 h. The reaction was quenched by the slow addition of 5% (*w/v*) HCl (7 mL) followed by the removal of THF *in vacuo*. Further 5% (*w/v*) HCl (5 mL) was added (aqueous layer to pH ~1) and washed with Et_2O (3 x 15 mL). The combined Et_2O extracts were extracted into 5% (*w/v*) HCl (5 mL) and the combined aqueous phase washed with Et_2O (3 x 10 mL). The combined aqueous phase was neutralised to pH~ 7 with NaOH (s) then 20% (*w/v*) NaOH, and extracted into DCM (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a white solid (0.45 g, 50%). M.p. 115-117 °C (Lit[96] mp = 115-116°C); ν_{max} (ATR): 3328, 2968, 1318s, 1168s, and 1120vs cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.14 (d, *J* = 6.8 Hz, 12H, 4C*H*$_3$), 3.13 (septet, 2H, *J* = 6.8 Hz, 2C*H*), 3.90 (s, 2H, C*H*$_2$), 7.47 (s, 1H, Ar*H*), 7.55 (d, l H, J = 7.6 Hz, Ar*H*), 8.10 (d, l H, J= 7.6 Hz, Ar*H*) and 10.16 (s, br, 2H, B(OH)$_2$); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ 19.8 (4*C*H_3), 47.9 (2*C*H), 51.9 (*C*H_2), 123.8 (q, $^3J_{FC}$ = 4 Hz, Ar*C*), 124.2 (q, $^1J_{FC}$ = 272 Hz, *C*F_3), 127.0 (q, $^3J_{FC}$ = 4 Hz, Ar*C*), 132.0 (q, $^2J_{FC}$ = 32 Hz, ArC-CF_3), 137.3 (Ar*C*) and 143.2 (Ar*C*); ^{11}B (128.4 132 MHz; $CDCl_3$) δ 28.5; ^{19}F (376.3 MHz; $CDCl_3$) δ -63.3 (s); Elemental Analysis (%) for $C_{14}H_{21}BF_3NO_2$. Found: C, 55.29; H, 6.87; N, 4.46.

Calculated: C, 55.47; H, 6.98; N, 4.62). All spectroscopic and analytical properties were identical to that reported in the literature.[96]

Chapter 8: References

1. R. M. Al-Zoubi, O. Marion and D. G. Hall, *Angew. Chem. Int. Ed*., 2008, **47**, 2876-2879.

2. A. K. Ghose, V. N. Viswanadhan and J. J. Wendoloski, *J. Comb. Chem*., 1999, **1**, 55-68.

3. D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Jr. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411-420.

4. A. L. J. Beckwith, In *The Chemistry of Amides*, ed. J. Zabicky, Interscience: London, 1970, p.73

5. Y. S. Klausner and M. Bodansky, *Synthesis*, 1972, 453-463.

6. B. C. Challis and J. A. Challis, In *Comprehensive Organic Chemistry*, ed. D. H. R. Barton, W. D. Ollis, Pergamon: Oxford, 1979, **vol. 2**, p. 957.

7. S. R. Sandler and W. Karo, In *Organic Functional Group Preparations*, ed. H. H. Wasserman, Academic, New York, 2nd edn. 1983, **vol. 1**, p. 315.

8. G. Benz, In *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon: Oxford, 1991, **vol. 6**, p. 381.

9. P. D. Bailley, I. D. Collier and K. M. Morgan, In *Comprehensive Organic Functional Groups Transformations*, ed. A. L. Katrizky, O. Meth-Cphn and C. W. Rees, Pergamon: New York, 1995, **vol. 5,** p. 257.

10. M. North, *Contemp. Org. Synth*., 1994, **1**, 475-494.

11. M. North, *Contemp. Org. Synth*., 1995, **2**, 269-287.

12. M. North, *Contemp. Org. Synth*., 1997, **4**, 326-351.

13. J. M. Humphrey and A.R. Chamberlin, *Chem. Rev*., 1997, **97**, 2243-2266.

14. M. J. North, *Chem. Soc., Perkin Trans. 1*, 1998, 2959-2972.

15. M. J. North, *Chem. Soc., Perkin Trans. 1*, 1999, 2209-2229.

16. J. A. Mitchell and E. E. Reid, *J. Am. Chem. Soc*., 1931, **53**, 1879-1883.

17. G. H. Coleman and A. M. Alvarado, *Org. Synth*., 1923, **3**, 3-5.

18. C. N. Webb, *Org. Synth.*, 1927, **7**, 6-7.

19. H. T. Clarke and L. D. Behr, *Org. Synth.*, 1936, **16**, 75-76.

20. C. Downing (Chemstrand Corp.), *U.S. Patent*, 2667511, 1954.

21. A. W. Campbell (Commercial Solvents Corp.), *U. S. Patent*, 3006956, 1961.

22. B. S. Jursic and Z. Zdravkovski, *Synth. Commun*., 1993, **23**, 2761-2770.

23. D. Davidson and P. Newman, *J. Am. Chem. Soc*., 1952, **74**, 1515-1516.

24. M. B. Smith and J. March, *March's Advanced Organic Chemistry*, 6th edition, Willey- Interscience, New Jersey, USA, 2007.

25. C. A. G. N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827-10852.

26. H. Charville, D. Jackson, G. Hodges and A. Whiting, *Chem. Commun*., 2010, **46**, 1813-1823.

27. H. Charville, D. Jackson, G. Hodges and A. Whiting, M. R. Wilson, *Eur. J. Org. Chem*., 2011, 5981-5990.

28. a) *Synthetic Reagents*, ed. J. S. Pizey, Wiley: New York, 1974, **vol.1**, p. 321-357. b) *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*, ed. A. J. Pearson and W. R. Roush, Wiley: New York, 1999, p. 370-373. c) W. Chu, Z. Tu, E. McElveen, J. Xu, M. Taylor, R. R. Luedtke and R. H. Mach, *Bioorg. Med. Chem*., 2005, **13**, 77-87.

29. a) R. Adams and L. H. Ulrich, *J. Chem. Soc.* 1920, **42**, 599-611. b) I. Kuwajima, H. Urabe, In *Organic syntheses*, Wiley: New York, 1993, Collect. **Vol. VIII,** p. 486-489.

30. S. Knnap and F. S. Gibson, In *Organic Syntheses*, Wiley: New York, 1998, Collect. **Vol. IX**, p-516-521.

31. *Handbook of Reagents for Organic Syntheses: Activating Agents and Protecting Groups*, ed. A. J. Pearson, W. R. Roush, Wiley: New York, 1999, p-333.

32. J. J. Klosa and J. Prakt. *Chem. (Leipzig)*, 1962, **19** (No. 1-2), 45-55.

33. a) M. F. Antell, In the Chemistry of Acyl Halides, ed., S. Patai, Interscience: London, 1972, p. 40-44. b) *Handbook of Reagents for Organic Syntheses: Activating Agents and Protecting Groups*, ed. A. J. Pearson and W. R. Roush, Wiley: New York, 1999, p-335-338.

34. A. I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannadford and P. W. G. Smith, Vogel's Text of Practical Organic Chemistry, 5th edn., Prentice Hall: Harlow, 1996, p-1073.

35. K. Venkataraman and D. R. Wagle, *Tetrahedron Lett*., 1979, **32**, 3037-3040.

36. U. Ragnarsson and L. Grehn, *Acc. Chem. Res*., 1998, **31**, 494-501.

37. J. B. Lee, *J. Am. Chem.Soc*., 1966, **88**, 3440.

38. P. C. Crofts and I. M. Downie, *J. Chem. Soc. Abstr*., 1963, 2559-2560.

39. I. M. Downie, J. B. Lee and M. F. S. Matough, *Chem. Commun*., 1968, 1350-1351.

40. G. B. Villeneuve and T. H. Chan, *Tetrahedron Lett*., 1997, **38**, 6489-6492.

41. D.O. Jang, D. J. Park and J. Kim, *Tetrahedron Lett*., 1999, **40**, 5323-5326.

42. G. A. Olah, M. Nojima and I. Kerekes, *Synthesis*, 1973, 487.

43. J. Savrda, L. Chertanova and M. Wakeselman, *Tetrahedron*, 1994, **50,** 5309-5322.

44. L. A. Carpino and A. El-Faham, *J. Am. Chem Soc*., 1995, **117**, 5401-5402.

45. S. V. V. Badu, H. N. Gopi and K. Ananda, *Indian J. Chem., Sect. B*, 2000, **39**, 384-386.

46. G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic and H. Cheng, *J. Org. Chem*., 1999, **64**, 7048-7054.

47. G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic and H. Cheng, *Chem. Commun*., 1999, 215-216.

48. K. E. Pryor, G. W. Shipps Jr., D. A. Skyler and J. Rebek Jr. *Tetrahedron*, 1998, **54**, 4107–4124.

49. P. Froeyen, *Synth. Commun*., 1995, **25**, 959–968.

50. H. J. Bestmann, R. Kunstmann and H. Schulz, *Justus Liebigs Ann. Chem*., 1966, **699**, 33–39.

51. S. D. Saraf, M. Zaki, *Synthesis*, 1973, 612.

52. S. Bains, J. Green, L. C. Tan, R. M. Pagni, G. W. Kabalka, *Tetrahedron Lett*., 1992, **33**, 7475–7476.

53. L. E. Overman and A. L. Tomasi, *J. Am. Chem. Soc*., 1998, **120**, 4039–4040.

54. A. DalPozzo, M. Ni, L. Muzi, A. Caporale, R. de Castiglione, B. Kaptein, Q. B. Broxterman and F. Formaggio, *J. Org. Chem*., 2002, **67**, 6372–6375.

55. T. Curtius, *Berichte der Deutschen Chemischen Gesellschaft*, 1902, **35**, 3226–3228.

56. a) T. Curtius, *Ber.* 1890, **23**, 3023; b) T. Curtius, *J. Prakt. Chem. [2]*, 1894, **50**, 275; c) P. A. S. Smith, *Org. React*., 1946, **3**, 337–449.

57. T. Shioiri, K. Ninomiya and S. Y. Yamada, *J. Am. Chem. Soc*., 1972, **94**, 6203–6205.

58. R. Paul and W. Anderson, *J. Am. Chem. Soc*., 1960, **82**, 4596–4600.

59. D. J. Dale, J. Draper, P. J. Dunn, M. L. Hughes, F. Hussain, P. C. Levett, G. B. Ward and A. S. Wood, *Org. Process Res. Dev*., 2002, **6**, 767–772.

60. J. A. Grzyb and R. A. Batey, *Tetrahedron Lett*., 2003, **44**, 7485–7488.

61. M. Mikolajczyk and P. Kielbasinski, *Tetrahedron*, 1981, **37**, 233–284.

62. S. J. Wittenberger and M. A. McLaughlin, *Tetrahedron Lett*., 1999, **40**, 7175–7178.

63. J. K. Chakrabarti, T. M. Hotten, I. A. Pullar and N. C. Tye, *J. Med. Chem*., 1989, **32**, 2573–2582.

64. R. Chicharro, S. Castro, J. L. Reino and V. J. Aran, *Eur. J. Org. Chem*., 2003, **12**, 2314–2326.

65. L. A. Carpino, *J. Am. Chem. Soc*., 1993, **115**, 4397–4398.

66. G. M. Gangwar, T. Pauletti, J. Siahaan, V. J. Stella and R. T. Borchardt, *J. Org. Chem.*, 1997, **67**, 1356–1362.

67. L. Kisfaludy, I. Schón, T. Szirtes, O. Nyéki and M. Lów, *Tetrahedron Lett.*, 1974, **19**, 1785–1786.

68. H. Ogura, T. Kobayashi, K. Shimizu, K. Kawabe and K. Takeda, *Tetrahedron Lett*., 1979, **20**, 4745–4746.

69. M. Jaoudai, J. Martinez, B. Castro, G. Barcelo, G. Sennyey and J. P. Senet, *J. Org. Chem*., 1987, **52**, 2364–2367.

70. a) Z. J. Kaminski, *Teterahedron Lett.* 1985, 26, 2901-2904; b) Z. J. Kaminski, *Synthesis*, 1987, 917-920.

71. a) C. Kunishima, C. Kawashi, J. Morita, K. Terao, F. Iwasaki and S. Tani, *Tetrahedron*, 1999, **b**, 13159–13170.

72. R. Woodward, R. A. Olofson and M. Mayer, *J. Am. Chem. Soc*., 1961, **83**, 1010–1012.

73. a) E. Bald, K. Saigo and T. Mukaiyama, *Chem. Lett.* 1975, 1163–1164; b) T. Mukaiyama, *Angew. Chem. Int. Ed. Engl*., 1979, **18**, 707–721; c) H. Huang, N. Iwasawa and T. Mukaiyama, *Chem. Lett*., 1984, 1465–1466.

74. J. C. Xu and P. Li, *Tetrahedron Lett*., 1999, **40**, 8301–8304.

75. a) A. Berkessel and H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Application in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; b) P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, 2004, **43**, 5138–5175; c) M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, *Drug Discovery Today*, 2007, **12**, 8–27; d) H. Pellissier, *Tetrahedron*, 2007, **63**, 9267– 9331; e) A. Dondoni and A. Massi, *Angew. Chem. Int. Ed*., 2008, **47**, 4638–4660.

76. H. L. Rayle and L. Fellmeth, *Org. Process Res. Dev*., 1999, **3**, 172–176.

77. M. Kunishima, C. Kawachi, K. Hioki, K. Terao and S. Tani, *Tetrahedron*, 2001, **57**, 1551-1558.

78. a) M. Kunishima, H. Imada, K. Kikuchi, K. Hioki, J. Nishida and S. Tani, *Angew. Chem. Int. Ed*., 2005, **44**, 7254-7257; b) M. Kunishima, C, Kawachi, J. Morita, K. Terao, F. Iwasaki and S. Tani, *Tetrahedron*, 1999, **55**, 13159-13170; c) b) M. Kunishima, C, Kawachi, K. Terao and S. Tani, *Tetrahedron*, 2001, **57**, 1551-1558.

79. *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, 2nd ed., 2004, **vol. 1 and 2**.

80. For reviews of recent advancements in transition metal catalysis, see: a) D. M. D'Souza and T. J. J. Müller, *Chem. Soc. Rev*., 2007, **36**, 1095–1108; b) S. Dez-Gonzlez, N. Marion and S. P. Nolan, *Chem. Rev*., 2009, **109**, 3612–3676; c) S. Das, G. W. Brudvig and R. H. Crabtree, *Chem.Commun*., 2008, 413–424.

81. J. D. Wilson and H. Weingarten, *Can. J. Chem*., 1970, **48**, 983.

82. R. Carlson and A. Nordhal, *Acta. Chem. Scand. Ser. B*., 1988, **42**, 28-34.

83. a) M. Mader, P. Helquist, *Tetrahedron Lett*., 1988, **29**, 3049-3052. b) L.Y. Shteinberg, *Russ. J. Org. Chem*., 2003, **39**, 972-974. c) L.Y. Shteinberg, S. A. Kondratov and S. M. Shein, *Zh. Org. Khim.*, 1988, **24**, 1968-1972. d) F. Tinnis, H. Lundberg and H. Adolfsson, *Adv. Synth. Catal*., 2012, **354**, 2531-2536. e) A.C. Shekhar, A.R.Kumar,G. Sathaiah, V. L. Paul,M. Sridhar and P. S. Rao, *Tetrahedron Lett*., 2009, **50**, 7099–7101. f) G. Brahmachari, S. Laskar and S. Sarkar, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2010, **49**, 1274–1281. g) G. Brahmachari, S. Laskar and S. Sarkar, *J. Chem. Res*., 2010, 288–295. h) A. Chandra Shekhar, A. Ravi Kumar, G. Sathaiah, V. Luke Paul, M. Sridhar and P. Shantha Rao, *Tetrahedron Lett*., 2009, **50**, 7099. i) Basavaprabhu, K. Muniyappa, N. R. Panguluri, P. Veladi and V. V. Sureshbabu, *NewJ.Chem.*, 2015, **39**, 7746-7749.

84. R. Nomura, T. Wada, Y. Yamada and H. Matsuda, *Chem. Lett*., 1986, **15**, 1901-1904.

85. R. Nomura, T. Nakano, Y. Yamada and H. Matsuda, *J. Org. Chem*., 1991, **56**, 4076-4078.

86. K. Ishihara, Y. Kuroki, N. Hanaki, S. Ohara and H. Yamamoto, *J. Am. Chem. Soc*., 1996, **118**, 1569-1570.

87. K. Ishihara, Y. Kuroki, N. Hanaki, S. Ohara and H. Yamamoto, *Bull. Chem. Soc. Japn*., 1998, **71**, 1221-1230.

88. a) M. Vazquez-Tato, *Synlett*, 1993, 556; b) B. Baldwin, T. Hirose and Z. Wang, *Chem. Commun*., 1996, 2269-2670; c) R. Varma and K. Naicker, *Tetrahedron Lett.*, 1999, **40**, 6177-6180; d) L. Perreux and A. Loupy, *Tetrahedron*, 2001, **57**, 9199-9223; e) L. Perreux, A. Loupy and F. Volatron, *Tetrahedron*, 2002, **58**, 2155-2162; f) D. Sauer, D. Kalvin and K. Phelan, *Org. Lett.*, 2003, **5**, 4721-4724; g) A. Khalafi-Nezhad, B. Mokhtari and M. N. S. Rad, *Tetrahedron Lett*., 2003, **44**, 7325-7328; h) E. Gelens, L. Sliedregt, B. Van Steen, C. Kruse, R. Leurs and R. V. Orru, *Tetrahedron Lett*., 2005, **46**, 3751-3754; i) F. Massicot, R. Plantier-Royon, C. Portella, D. Saleur and A. Sudha, *Synthesis*, 2001, **16**, 2441-2444; j) L. Perreux, A. Loupy and M. Delmotte, *Tetrahedron*, 2003, **59**, 2185-2189; k) A. de la Hoz, A. Diaz-Ortiz and A. Moreno, *Chem. Soc. Rev*., 2005, **34**, 164-178; l) N. Karis, W. Loughlin and I. Jenkins, *Tetrahedron*, 2007, **63**, 12303-12309.

89. P. Ruault, J. F. Pilard, B. Touaux, F. Texier-Boullet and J. Hamelin, *Synlett*, 1994, 935-936.

90. S. Gadhwal, M. P. Dutta, A. Boruah, D. Prajapati and J. S. Shandu, *Indian J. Chem*., 1998, **37B**, 725-727.

91. S. Chandrasekhar, M. Takhi and G. Uma, *Tetrahedron Lett.*, 1997, **38**, 8089-8092.

92. H. Marquez, A. Plutin, Y. Rodriguez, E. Perez and A. Loupy, *Synth. Commun*., 2000, **30**, 1067-1073.

93. R. Louque, V. Budarin, J. H. Clark and D. J. Macqarrie, *Green Chem.*, 2009, **11**, 459-461.

94. J. W. Comerford, J. H. Clark, D. J. Macquarrie and S. W. Breeden, *Chem. Commun*., 2009, 2562-2564.

95. P. Tang, *Org. Synth.*, 2005, **81**, 262-272.

96. K. Arnold, B. Davies, R. Giles, C. Grosjean, G. Smith and A. Whiting, *Adv. Synth. Catal*., 2006, **348**, 813-820.

97. K. Arnold, A. S. Batsanov, B. Davies and A. Whiting, *Green. Chem*., 2008, **10**, 124-134.

98. D. B. Collum, B. Ganem and S. C. Chen, *J. Org. Chem.*, 1978, **43**, 5291-5300.

99. W. Q. Yang, X. M. Gao, G. Springsteen and B. H. Wang, *Tetrahedron*, 2002, **58** (26), 5291-5300.

100. T. Maki, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2006, **8**, 1431-1434.

101. K. Ishihara, T. Maki and H. Yamamoto, *Tetrahedron*, 2007, **63**, 8645-8657.

102. K. Ishihara, S. Ohara and H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4196-4197.

103. K. Ishihara, S. Ohara and H. Yamamoto, *Macromol*, 2000, **33**, 3511-3513.

104. T. Maki, K. Ishihara and H. Yamamoto, *Synlett*, 2004, **8**, 1355-1358.

105. K. Ishihara, S. Kondo and H. Yamamoto, *Synlett*, 2001, **9**, 1371-1374.

106. T. Maki, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2005, **7**, 5043-5046.

107. R. Latta, G. Springsteen and B. H. Wang, *Synthesis*, 2001, **11**, 1611-1613.

108. J. Cossy and C. Pale-Grosdemange, *Tetrahedron Lett.*, 1989, **30** (21), 2771-2774.

109. B. S. Jursic and Z. Zadravkovski, *Synth. Commun.*, 1993, **23**, 2761.

110. H. Fukushima, H. Nakatani, Y. Nawashiro, T. Seki, Y. Suzuki and K. Toki, US3551462, 1970, Smitomo Chemical Co.

111. T. Marcelli, Angew. *Chem. Int. Ed.*, 2010, **49**, 6840-6843.

112. K. Arnold, B. Davies, D. Hérault and A. Whiting, *Angew. Chem. Int. Ed.*, 2008, **47**, 2673-2676.

113. C. Wang, H. Z. Yu, Y. Fu and Q. X. Guo, *Org. and Biomol. Chem*., 2013, **11**, 2140.

114. I. Bauer and H. J. Kn€olker, *Iron Complexes in Organic Chemistry*, Wiley-VCH, Weinheim, 2008.

115. P. A. Sutton and D. A. Buckingham, *Acc. Chem. Res.*, 1987, **20**, 357.

116. C. Liana Allen, A. R. Chhatwal and J. M. J. Williams, *Chem. Commun.*., 2012, **48**, 666-668.

117. H. Lundberg, F. Tinnis and H. Adolfsson, *Chem. Eur. J.*, 2012, **18**, 3822-3826.

118. M. Smith, (2007-03-16). "Gallium May Have Antibiotic-Like Properties". Med Page Today. Retrieved 2008-11-20.

119. "A Trojan-horse strategy selected to fight bacteria". INFOniac.com. 2007-03-16. Retrieved 2008-11-20.

120. E. Valeur and M. Bradley, *Chem. Soc. Rev*., 2009, **38**, 606–631.

121. a) V. Declerck, P. Nun, J. Martinez and F. Lamaty, *Angew. Chem. Int. Ed*., 2009, **48**, 9318–9321; b) I. W. James, *Tetrahedron*, 1999, **55**, 4855–4946; c) F. Guillier, D. Orain and M. Bradley, *Chem. Rev.*, 2000, **100**, 2091–2157.

122. V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471–479.

123. M. J. J. Litjens, A. J. J. Straathof, J. A. Jongejan and J. J. Heijnen, *Tetrahedron*, 1999, **55**, 12411–12418.

124. K. Ishihara, *Tetrahedron*, 2009, **65**, 1085-1109.

125. E. Cherbuliez and F. Landolt, *Helv. Chim. Acta*, 1946, **29**, 1315-1315.

126. N. Gernigon, R. M. Al-Zoubi, D. G. Hall, *J. Org. Chem.* 2012, **77**, 8386−8400.

127. a) A. Berkessel, H. Gröger, in: *Asymmetric Organocatalysis: From Biomimetic Concepts to Application in Asymmetric Synthesis*, Wiley-VCH, Weinheim, 2005; b) P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, 2004, **43**, 5138–5175; c) M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, *Drug Discovery Today*, 2007, **12**, 8–27; d) H. Pellissier, *Tetrahedron*, 2007, **63**, 9267– 9331; e) A. Dondoni and A. Massi, *Angew. Chem. Int. Ed.*, 2008, **47**, 4638–4660.

128. In more than 3100 article topics based on a *Scifinder* survey, up to 20th December, 2009.

129. *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, 2nd ed. 2004, **vol. 1** and **2**.

130. For reviews of recent advancements in transition metal catalysis, see: a) D. M. D'Souza and T. J. J. Müller, *Chem. Soc. Rev.*, 2007, **36**, 1095–1108; b) S. Dez-Gonzlez, N. Marion and S. P. Nolan, *Chem. Rev.*, 2009, **109**, 3612–3676; c) S. Das, G. W. Brudvig and R. H. Crabtree, *Chem.Commun.*, 2008, 413–424.

131. For recent examples, see: a) G. M. Sammis, H. Danjo and E. N.Jacobsen, *J. Am. Chem. Soc*., 2004, **126**, 9928–9929; b) Y. Shi, S. M. Peterson, W. W. Haberaecker III and S. A. Blum, *J. Am. Chem. Soc.*, 2008, **130**, 2168–2169; c)

A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Rudolph, T. D. Ramamurthi and F. Rominger, *Angew. Chem. Int. Ed.*, 2009, **48**, 8243–8246. For a review of Sonogashira coupling, see: R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874–922.

132. For reviews, see: a) F. F. Huerta, A. B. E. Minidis and J. E. Bäckvall, *Chem. Soc. Rev.*, 2001, **30**, 321–331; b) O. Pàmies and J.-E. Bäckvall, *Chem. Rev.*, 2003, **103**, 3247–3262. For recent examples, see: c) O. Iranzo, A. Y. Kovalevsky, J. R. Morrow and J. P. Richard, *J. Am. Chem. Soc.*, 2003, **125**, 1988–1993; d) C. A. Kruithof, M. A. Casado, G. Guillena, M. R. Egmond, A. van der Kerk-van Hoof, A. J. R. Heck, R. J. M. Klein Gebbink and G. van Koten, *Chem. Eur. J.*, 2005, **11**, 6869–6877; e) M. Gottschaldt, U. S. Schubert, *Chem. Eur. J.*, 2009, **15**, 1548–1557.

133. Z. Shao and H. Zhang, *Chem. Soc. Rev.*, 2009, **38**, 2745–2755.

134. For selected recent reviews on cooperative catalysts, see: a) A. Ajamian and J. L. Gleason, *Angew. Chem.*, 2004, **116**, 3842-3848; *Angew. Chem. Int. Ed.*, 2004, **43**, 3754-3760; b) J. M. Lee, Y. Na, H. Han and S. Chang, *Chem. Soc. Rev.*, 2004, **33**, 302-312; c) J. C. Wasilke, O. S. J. Brey, R. T. Baker and G. C. Bazan, *Chem. Rev*., 2005, **105**, 1001-1020; d) D. Enders, C. Grondal and M. R. Huttl, *Angew. Chem.*, 2007, **119**, 1590-1601; *Angew. Chem. Int. Ed.*, 2007, **46**, 1570-1581; e) C. J. Chapman and C. G. Frost, *Synthesis*, 2007, 1-21; f) A. M. Walji and D. W. C. MacMillan, *Synlett*, 2007, 1477-1489; g) C. Wang and Z. Xi, *Chem. Soc. Rev.*, 2007, **36**, 1395-1406; h) Z. Shao and H. Zhang, Chem. *Soc. Rev.*, 2009, **38**, 2745-2755; i) C. Zhong and X. Shi, *Eur. J. Org. Chem.*, 2010, 2999-3025.

135. P. Starkov and T. D. Sheppard, *Org. Biomol. Chem*., 2011, **9**, 1320-1323.

136. i) J. H. Dam, G. Osztrovszky, L. U. Nordstrom, R. Madsen, *Chem. Eur. J*., 2010, **16**, 6820-6827; ii) R. Fu, Y. Yang, Z. Chen, W. Lai, Yongfeng Ma and Q. Wang, *Tetrahedron*, 2014, **70**, 9492-9499.

137. J. W. Bode, R. M. Fox and K. D. Baucom, *Angew. Chem. Int. Ed*., 2006, **45**, 1248-1252.

138. V. Pace, L. Castoldi and W. Holzer, *Chem. Comm.*, 2013, **49**, 8383.

139. S. Liu,Y. Yang, X. Liu, F. K. Ferdousi, A. S. Batsanov and A. Whiting, *Eur. J. Org. Chem.*, 2013, **25**, 5692-5700.

140. For protease catalyzed peptide synthesis, see: (a) V. Schellenberger and H. D. Jakubke, *Angew. Chem. Int. Ed*., 1991, **30**, 1437-1449. (b) C. Lombard, J. Saulnier and J. M. Wallach, *Protein Pept. Lett.*, 2005, **7**, 621-629. (c) Xu. Qin, A. C. Khuong, Z. W. Yu, Du, J. Decatur and R. A. Gross, *Chem. Commun.*, 2013, **49**, 385−387. (d) M. Schustera, A. Aaviksaarb and H. D. Jakubke, *Tetrahedron*, 1990, **46**, 8093-8102. (e) A comprehensive handbook: D. Karlheinz and H. Grö ger, May, *O. Enzyme Catalysis in Organic Synthesis*, 2012, **Vol. 1.** (f) R. V. Ulijn, B. Baragan, P. J. Halling and S. L. J. Flitsch, *Am. Chem. So*c., 2002, **124**, 10988−10989.

141. T. M. E. Dine, W. Erb, Y. Berhault, J. Rouden and J. Blanchet, *J. Org. Chem.*, 2015, **80**, 4532-4544.

142. S. D. Roughley, A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451-3479.

143. V. R. Pattabiraman1 and J. W. Bode, *Nature*, 2011, **480**, 471-479.

144. O. Marder and F. Alberico, *Chemica OGGI - Chemistry Today*, 2003.

145. J. W. Comerford, T. J. Farmer, D. J. Macquarrie, S. W. Breeden and J. H. Clark, *ARKIVOC*, 2012, **VII**, 282-293.

146. J. E. Anderson, J.Cobb, R. Davis, P. J. Dunn, R. N. Fitzgerald and A. J. Pettman, *Industrial applications of boric acid boronic acid-catalyzed direct amidation reactions.* Published by Wiley and Sons, Inc., Hoboken, New Jersy. 2013, pp.111-120.

147. a) B. J-S Wang, *J. Chem. Ed.*, 1974, **51 (10)**, 631; b) M. Li, C. Wang, P. Fang and H. Ge, *Chem. Commun.*, 2011, **47**, 6587-6589; c) A. N. Rao, K. Ganesan and R. Vijayaraghavan, WO2013/65059 A1, 2013.

148. A. Chimento, M. Sala, I. M. Gomez-Monterrey, S. Musella , A. Bertamino, A. Caruso, M. S. Sinicropi, R. Sirianni , F. Puoci , O. I. Parisi, C. Campana, E. Martire, E. Novellino , C. Saturnino, P. Campiglia and V. Pezzi, *Biorg. Med. Chem. Lett.*, 2013, **23(23)**, 6401-5.

149. S. A. Doggrell, *Drugs Future*, 2002, **27**, 973.

150. A. E. Lacreda, Y. A. Kuryeshev, Y. Chen, M. Renganathan, H. Eng, S. J. DanthiJ. W. Kramer, T. Yang and A. M. Brown, *J. Pharmacol. Exp. Ther*., 2008, **324**, 427-433.

151. R. N. Kankan, D. R. Rao and D. Birari, *U.S. Patent*, US20100256370 A1, 2010.

152. R. K. Mylavarapu, G. C. M. Kondaiah, N. Kolla, R. Veeramalla, P. Koilkonda, A. Bhattacharya and R. Bandichhor, *Org. Process Res. Dev*., 2007, **11**, 1065-1068.

153. A. S. Bell, D. Brown and N. K. Terrett, *USA Patent*, 5250534 A, 1993.

154. M. Boolell, M. J. Allen, S. A. Ballard, S. Gepi-Attee, G. J. Muirhead, A. M. Naylor, I. H. Osterloh and C. Gingell, *Int. J. Impot. Res*., 1996, 8 (2), 47-52.

155. N. K. Terrett, A. S. Bell, D. Brown and P. Ellis, *Bioorg. Med. Chem.Lett*., 1996, **6**, 1819-1824.

156. T. G. Gant and S. Sarshar, *USA Patent*, 0194529, 2008.

157. D. J. Dale, P. J. Dunn, C. Golightly, M. L. Hughes, P. C. Levett, A. K. Pearce, P. M. Searle, G. Ward and A. S. Wood, *Org. Process Res. Dev*., 2000, **4**, 17-22.

158. E. Dimitrijević and M. S. Taylor, *ACS Catal.*, 2013, **3**, 945-62.

159. S. T. Hilton, W. B. Motherwell, P. Potier, C. Pradeta and D. L. Selwood, *Bioorg & Med Chem. Lett*., 2005, 15, 2239–2242.

160. G. Tian, Y. Zhu, Z. Liu and Z. Wang, J. Shen, *USA Patent*, 0048897, 2010.

161. W. C. Chou, C. W. Tan, S. F. Chen and H. Ku, *J. Org. Chem.*, 1998, **63**, 10015-10017.

162. H. Mei, J. Hu, S. Xiao, Y. Lei and G. Li, *Applied Catalysis A: General*, 2014, **475**, 40–47.

163. M. P. Grella, R. D. Danquah, M. K. Safo, G. S. Joshi, J. Kister, M. Marden, S. J. Hoffman and D. J. Abraham, *J. Med. Chem.*, 2000, **43**, 4726-4737.

164. B. R. Dillon, D. F. Roberts, D. A. Entwistle, A. P. Glossop, C. J. Knight, D. A. Laity, K. James, C. F. Praquin, R. S. Strang and C. A. L. Watson, *Org. Process Res. Dev.*, 2012, **16**, 195-203.

165. H. Charville, PhD studies, unpublished results.

166. S.Y. Arkhipenko, PhD studies, unpublished results.

167. (a) C. L. Sun, B. J. Li and Z. J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (b) A. Correa, O. G. Mancheno and C. Bolm, *Chem. Soc. Rev*., 2008, **37**, 1108; (c) B. D. Sherry and A. Furstner, *Acc. Chem. Res*., 2008, **41**, 1500; (d) S. Enthaler, K. Junge and M. Beller, *Angew. Chem., Int. Ed*., 2008, **47**, 3317; (e) C. Bolm, J. Legros, J. Le Paih and L. Zani, *Chem. Rev*., 2004, **104**, 6217.

168. R. H. Baker and L. E. Linn, *J. Am. Chem. Soc.*, 1948, **70**, 3721-3723.

169. A. Westerbeek, W. Szymanski, B. L. Feringa and D. B. Janssen, *ACS Catal*., 2011, **1**, 1654-1660.

170. A. R. Katritzky, S. K. Singh, C. Cai, and Sergey Bobrov, *J. Org. Chem.*, 2006, **71**, 3364-3374.

Chapter 9: Appendix

Appendix 1

List of Publications

1. S. Liu,Y. Yang, X. Liu, F. K. Ferdousi, A. S. Batsanov and A. Whiting, *Eur. J. Org. Chem*, 2013, **25**, 5692-5700.

Appendix 2

Durham lectures and seminars – attended

- 'Boronate complexes: old dogs with new tricks', Dr Amadeu Bonet, *The University of Bristol* (23rd of September 2014).
- 'Medicinal Inorganic Chemistry of Biomedical Imaging Probes', Prof Peter Caravan, *Harvard Medical School and Massachusetts General Hospital* (11th of September).
- 'Organo-Lanthanide molecular nanomagnets', Dr Richard A. Layfield, *The University of Manchester* (2nd of September 2014).
- 'Controlled polymer synthesis with olefin metathesis reaction', Prof Robert Grubbs (Nobel Prize 2005), *The California Institute of Technology* (16th May 2014).
- 'Glycopolymers and glyconanoparticles', Prof Neil Cameron, *Durham University* (16th May 2014).
- 'Cats and dogma', Prof Guy. C. Lloyd-Jones, *The University of Edinburgh* (12th February 2014).
- 'Automated oligosaccharide synthesis as a basis for chemical glycomics' – Prof Peter M. Seeberger, *Max-Planck Institute* (15th of May 2013).
- 'Preventing and curing infectious disease: carbohydrates and continuous flow synthesis' – Prof Peter M. Seeberger, *Max-Planck Institute* (14th of May 2013).
- 'Enzymatic dynamic kinetic resolution and directed evolution techniques for the synthesis of chiral intermediates' – Prof Jan E. Bäckvall, *Stockholm University* (U.RiV-October 2012)

- ‘Diamines are forever: Asymmetric synthesis of nitrogen heterocycles’ – Prof Peter O’Brien, *The University of York* (22nd May 2012).
- ‘Phosphate trimester hydrolysis’ – Prof Tony Kirby, *The University of Cambridge* (10th of September 2012.
- ‘Making Sense of Copper-Catalyzed Coupling Reactions’ - Prof John Hartwig, *University of California, Berkley* (16th May 2012).
- ‘Selective Functionalization of Aryl and Alkyl C-H Bonds’ - Prof John Hartwig, *University of California, Berkley* (15th May 2012).
- ‘Catalysts by Design. A Case Study of Arylamine Synthesis’ - Prof John Hartwig, *University of California, Berkley* (14th May 2012).
- ‘Functionalising hydrocarbons using Fe Catalysts’ - Dr Peter Rutledge, *The University of Sydney* (8th May 2012).
- ‘New copper catalysed reactions’ - Dr Matthew Gaunt, *University of Cambridge* (1st February 2012).
- ‘Chemistry and business a rollercoaster’ - Dr Tony Flinn, *Industry* (13th March 2012).
- ‘Green Chemistry and biorefinery - from waste to wealth’ - Prof James Clark, *The University of York* (19th October 2011).
- ‘Getting a chemical handle on protein modification’ Dr Ed Tate, *Imperial College London*, (26th October 2011).
- ‘Hetero(arenes) as activating groups in asymmetric catalysis’ - Dr Hon Wai Lam, *The University of Edinburgh* (8th November 2011).

Appendix 3

Conferences presentations

- **The 247th ACS National Meeting Dallas, TX, March 16-20, 2014**. (Ustinov College Travel Award) Gave an oral presentation with the title *Novel approaches towards green catalytic direct amide bond formation*

- **Northern Sustainable Chemistry Meeting (NORSC), The University of Hull, 04/14.** Gave a poster presentation with the title *'Single' and 'Synergistic' Catalytic Effect in the Direct Amide Formation at Reduced Reaction Temperature*

- **Durham Gala Postgraduate Symposium Durham University, 06/14.** Gave an oral presentation with the title *Novel approaches towards green catalytic direct amide bond formation*

- **Northern Sustainable Chemistry Meeting (NORSC), The University of Huddersfield, 10/14.** Gave a poster presentation with the title *Co-operative Catalysis in Direct Amide Formation: Scope at Reduced Temperatures.*

- **RSC Organic Section North East Regional Meeting, The University of York, 03/13.** Gave a poster presentation with the title *Development and Application of New Direct Amidation Catalysts.*

Conferences attended but not presented—

- RSC Organic Division North East Regional Meeting – (16th April 2011, Northumbria).
- NORSC Network Seminar Day (25th October 2011, York).
- Stereochemistry at Sheffield 'Modern Aspects of Stereochemistry' (10th January, 2012, Sheffield).
- RSC Organic Section North East Regional Meeting (28th March 2012, York).
- NEPIC - NORSC (24th April 2012, Durham).
- North West Organic Chemistry (3rd July, 2012, Liverpool).

Appendix 4

Fig 4.1 Calibration curve used for the 4-phenylbutyric acid (43) remained in the reaction outlined in Eqn 44, Section 5.1.2.1

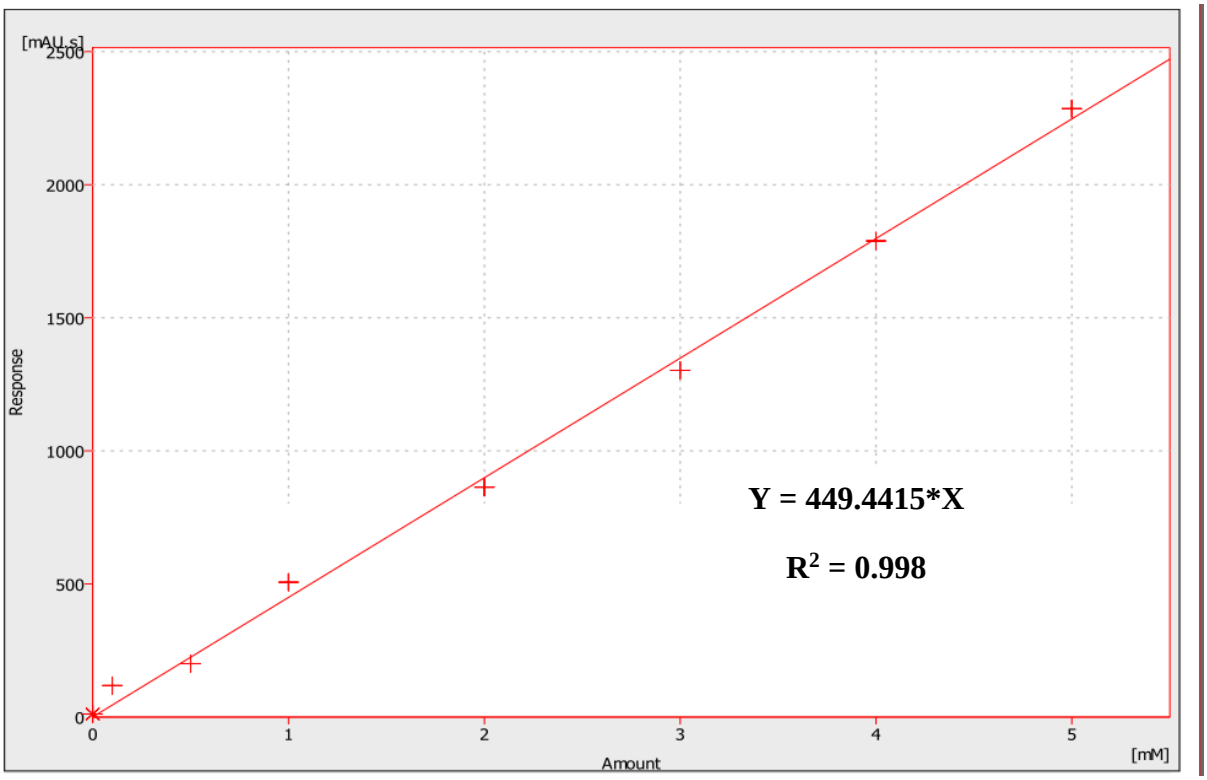


Fig 4.2 Calibration curve used for the *N*-benzyl-4-phenylbutyramide (45) formed in the reaction outlined in Eqn 44, Section 5.1.2.1

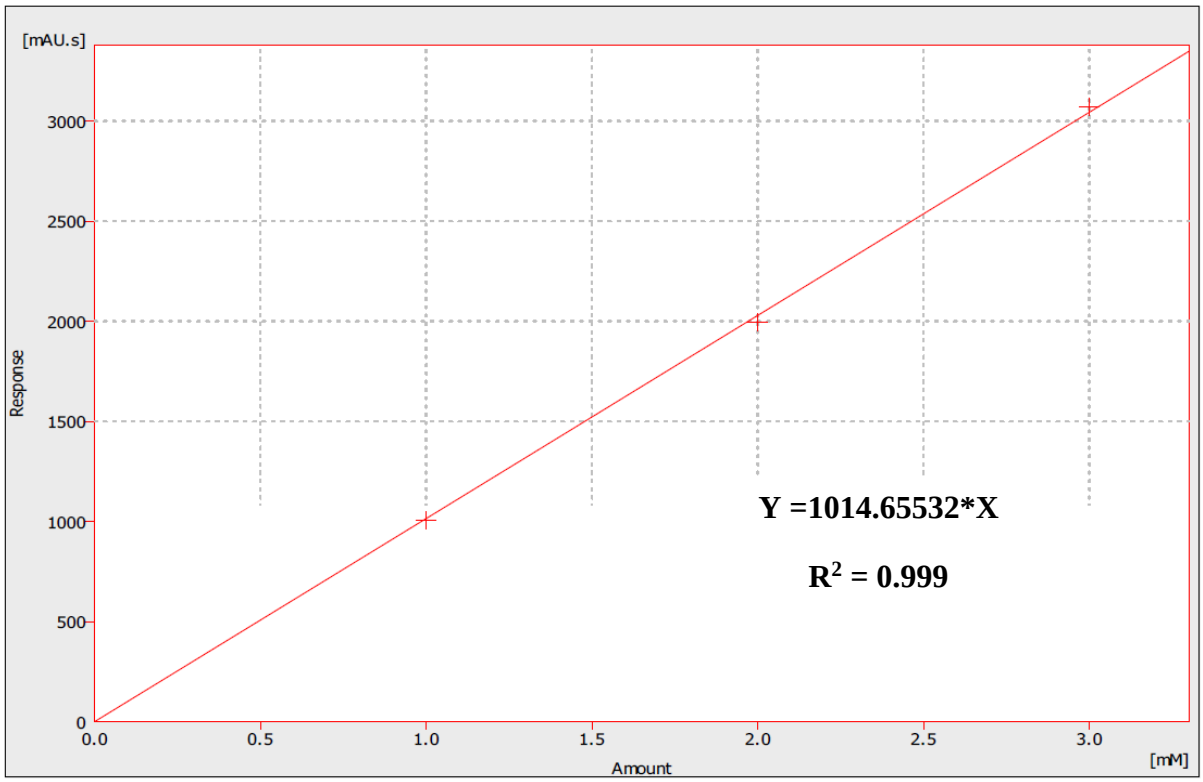


Fig 4.3 Calibration curve used for benzoic acid (67) remained in the reaction outlined in Eqn 27, Section 4.1 and 4.2

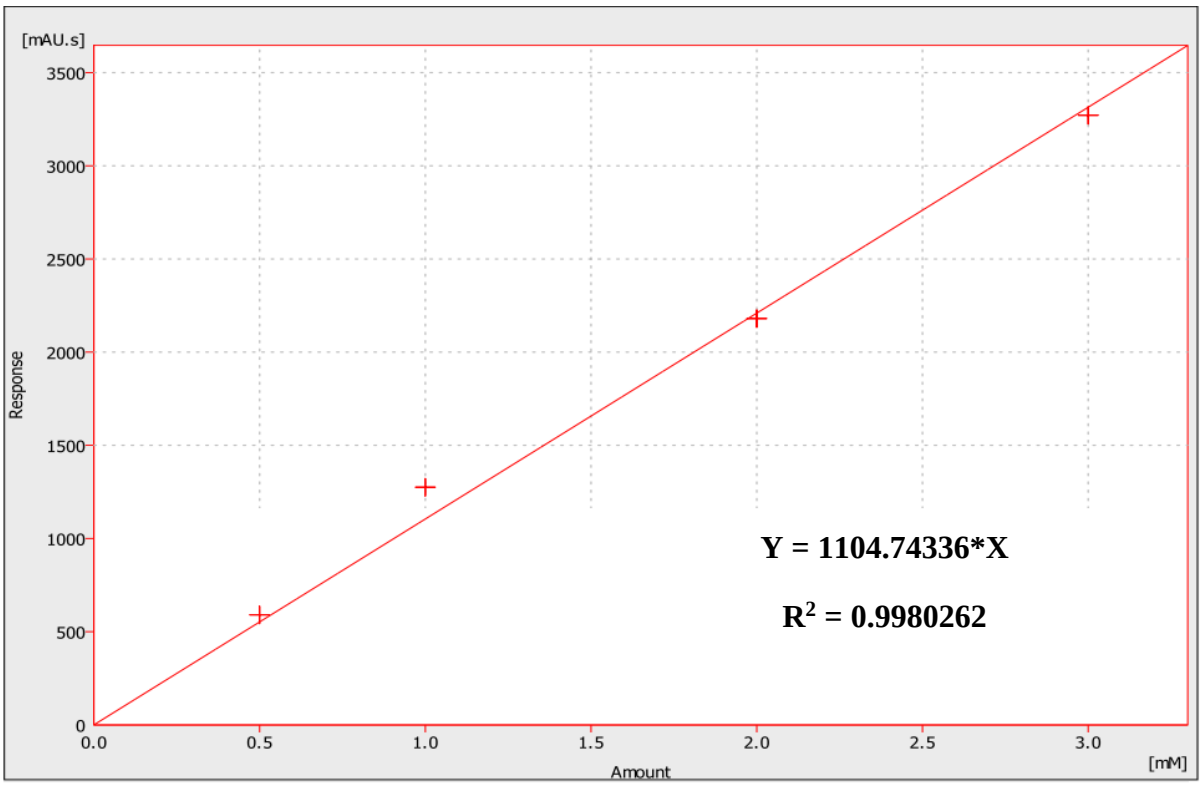


Fig 4.4 Calibration curve used for *N*-benzylbenzamide (68) formed in the reaction outlined in Eqn 27, Section 4.1 and 4.2

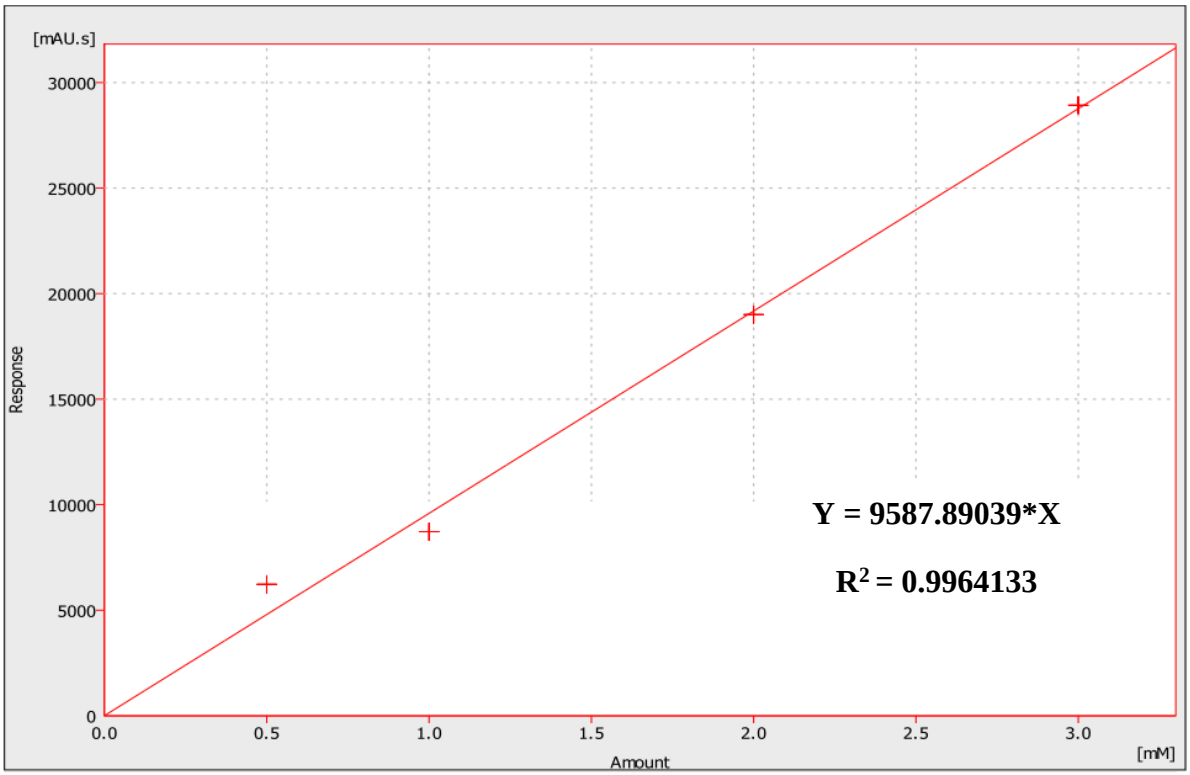


Fig 4.5 Calibration curve used for *N,N*-diethyl-meta-toluamide (119) formed in the reaction outlined in Eqn 33, Section 4.3.5.1

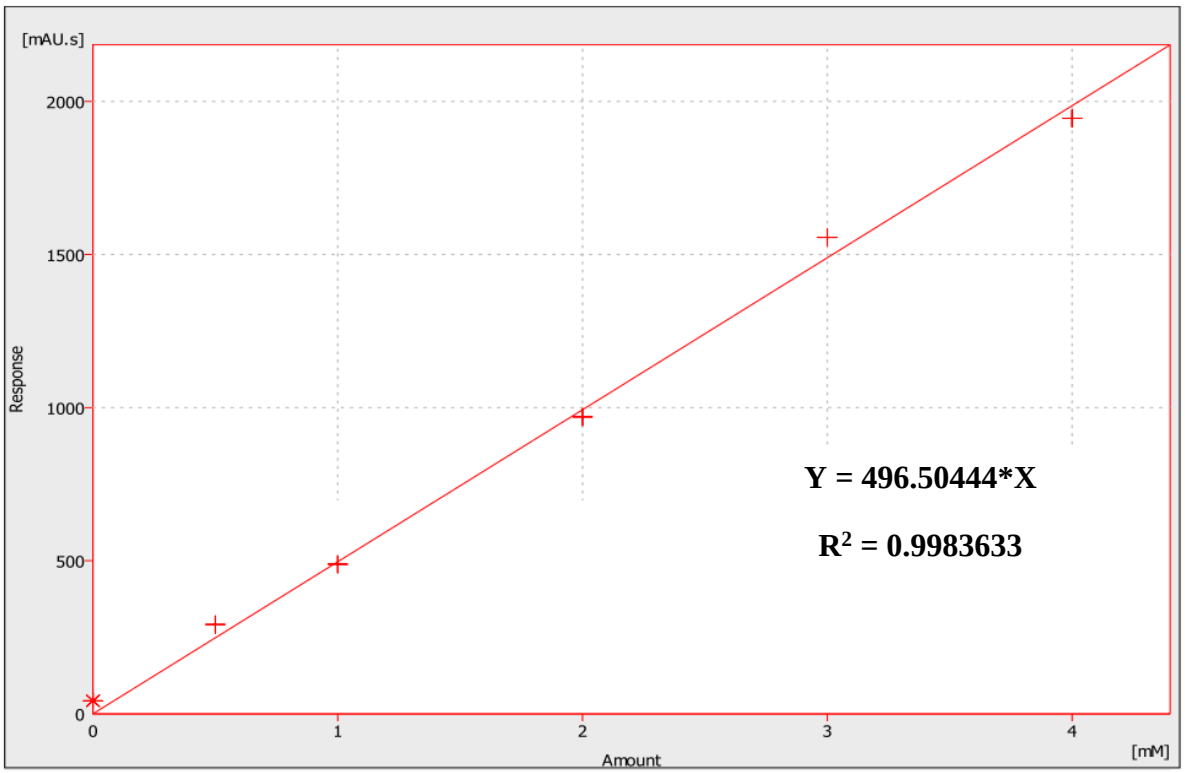
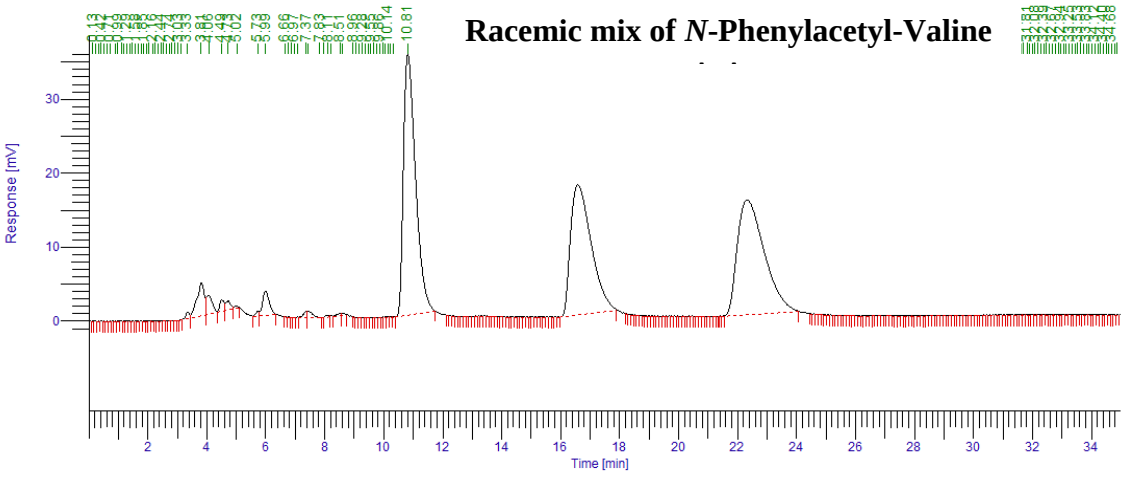


Fig 4.6 HPLC trace of racemic mix of *N*-Phenylacetyl-Valine (113b)

Software Version	: 6.3.1.0504	Date	: 23/01/2013 14:53:35
Sample Name	: racemicmix-1	Data Acquisition Time	: 17/01/2013 14:18:46
Instrument Name	: HPLC2	Channel	: A
Rack/Vial	: 0/2	Operator	: Adam
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : E:\data\AW group\FKF\17_01_2013_racemicmix-1_001.rst
Sequence File : E:\data\AW group\FKF\17Jan13_2.seq

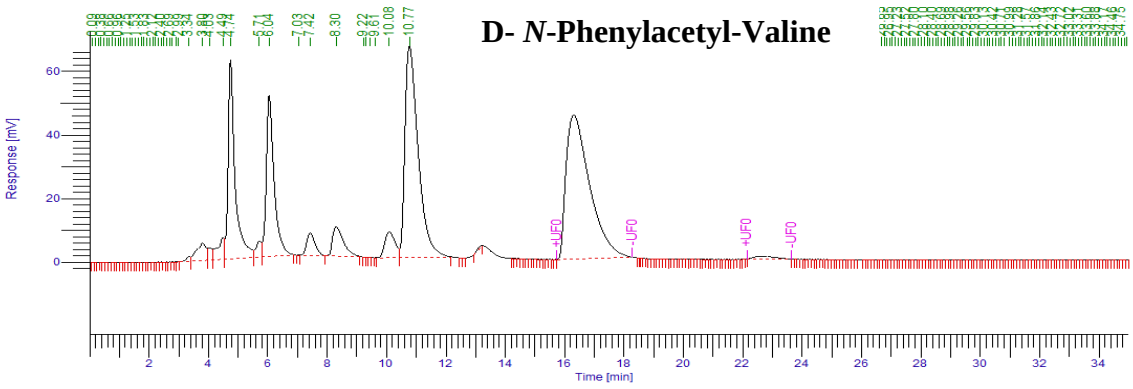


Peak #	Time [min]	Area [µV·s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
68	10.813	1003638.10	35287.47	35.27	35.27	BB	28.4418
104	16.584	854746.04	17614.96	30.04	30.04	BB	48.5239
139	22.341	986874.83	15536.30	34.68	34.68	VB	63.5206
		2845258.97	68438.73	100.00	100.00		

Fig 4.7 HPLC trace of D-*N*-Phenylacetyl-Valine (113b)

Software Version	: 6.3.1.0504	Date	: 11/02/2013 12:59:37
Sample Name	: D-Valineester-b	Data Acquisition Time	: 17/01/2013 14:55:17
Instrument Name	: HPLC2	Channel	: A
Rack/Vial	: 0/3	Operator	: Adam
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 2		

Result File : E:\data\AW group\AdamCalow\17_01_2013_D-Valineester-b_002.rst
Sequence File : E:\data\AW group\FKF\17Jan13_2.seq

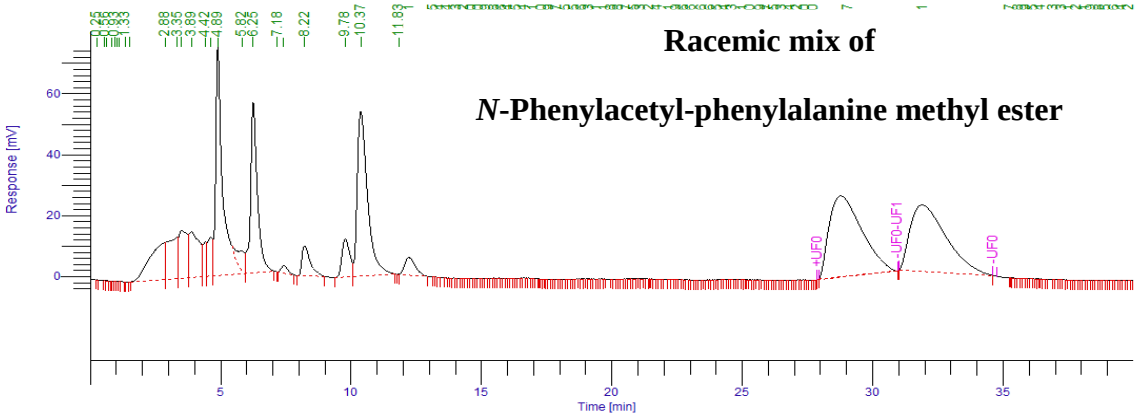


Peak #	Time [min]	Area [µV·s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
33	3.801	126769.80	5411.89	1.74	1.74	VV	23.4243
35	4.491	109769.07	6825.98	1.51	1.51	VV	16.0811
36	4.739	1004195.34	62581.96	13.77	13.77	VV	16.0461
38	6.044	926395.52	50619.65	12.70	12.70	VB	18.3011
40	7.422	139997.65	7114.59	1.92	1.92	VB	19.6775
41	8.295	236175.92	9247.26	3.24	3.24	BB	25.5401
46	10.085	195786.94	8166.23	2.68	2.68	VV	23.9752
47	10.767	2058107.06	66395.17	28.22	28.22	VB	30.9978
66	16.295	2495428.35	45272.94	34.22	34.22	MM	55.1196
		7292625.66	261635.66	100.00	100.00		

Fig 4.8 HPLC trace of racemic mix of *N*-Phenylacetyl-phenylalanine methyl ester (113a)

Software Version	: 6.3.1.0504	Date	: 11/02/2013 12:33:25
Sample Name	: racemic mix-2	Data Acquisition Time	: 21/01/2013 15:49:45
Instrument Name	: HPLC2	Channel	: A
Rack/Vial	: 0/2	Operator	: Adam
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : E:\data\AW group\AdamCalow\21_01_2013_racemic mix-2_001.rst
Sequence File : E:\data\AW group\FKF\21Jan13_3.seq



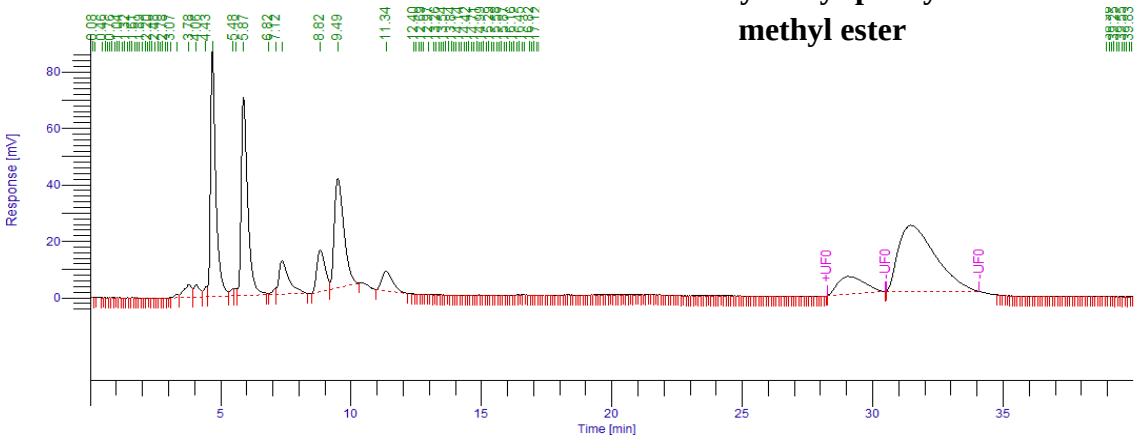
Peak #	Time [min]	Area [µV·s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
10	2.883	508363.03	12206.42	4.61	4.61	BV	41.6472
11	3.347	366005.02	13612.53	3.32	3.32	VV	26.8874
12	3.502	349804.43	15574.91	3.17	3.17	VV	22.4595
13	3.890	416437.91	15061.25	3.78	3.78	VV	27.6496
14	4.418	112663.46	11342.86	1.02	1.02	VV	9.9325
15	4.616	175603.89	12784.13	1.59	1.59	VV	13.7361
16	4.889	1402105.75	75083.91	12.72	12.72	VE	18.6739
17	5.818	131669.22	6678.73	1.19	1.19	EV	19.7147
18	6.247	1018436.08	55904.47	9.24	9.24	VB	18.2174
21	8.221	220431.07	9855.41	2.00	2.00	BB	22.3665
22	9.776	261977.04	12544.46	2.38	2.38	BV	20.8839
23	10.371	1488786.25	54146.66	13.51	13.51	VB	27.4954
25	12.211	164587.28	5886.13	1.49	1.49	VB	27.9619
162	29.070	2305085.11	26578.57	20.92	20.92	MM	86.7272
163	31.907	2097970.46	21911.38	19.04	19.04	MM	95.7480
		11019926.01	349171.80	100.00	100.00		

Fig 4.9 HPLC trace of L- *N*-Phenylacetyl-phenylalanine methyl ester (113a)

Software Version	: 6.3.1.0504	Date	: 11/02/2013 12:48:20
Sample Name	: L-Phenylalanine ester	Data Acquisition Time	: 21/01/2013 17:59:34
Instrument Name	: HPLC2	Channel	: A
Rack/Vial	: 0/4	Operator	: tcprocess
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : E:\data\AW group\AdamCalow\21_01_2013_L-Phenylalanine ester_001.rst
Sequence File : E:\data\AW group\FKF\21Jan13_3.seq

L- *N*-Phenylacetyl-phenylalanine methyl ester



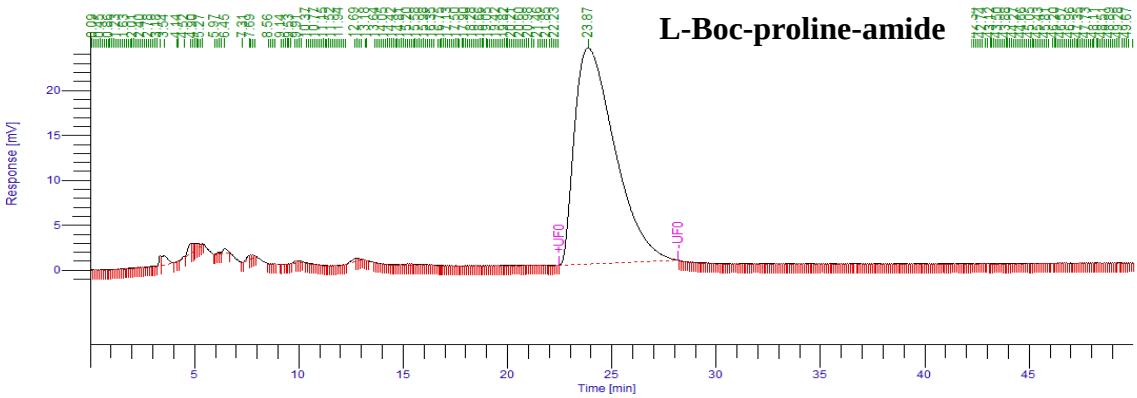
HPLC 2

Peak #	Time [min]	Area [µV·s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
35	4.679	1229838.04	86789.37	17.55	17.55	VV	14.1704
38	5.874	1207411.00	70042.22	17.23	17.23	VV	17.2383
41	7.357	307948.00	11702.16	4.40	4.40	VB	26.3155
42	8.817	322408.52	14778.72	4.60	4.60	BV	21.8157
43	9.493	993536.12	38581.53	14.18	14.18	VB	25.7516
44	11.341	201190.75	6920.39	2.87	2.87	BB	29.0722
204	29.033	437292.40	6245.19	6.24	6.24	MM	70.0206
205	31.460	2306041.76	23325.67	32.92	32.92	MM	98.8628
		7005666.58	258385.25	100.00	100.00		

Fig 4.10 HPLC trace of L-Boc-proline-amide (109)

Software Version	: 6.3.1.0504	Date	: 11/02/2013 10:40:22
Sample Name	: ex-79-a-old	Data Acquisition Time	: 07/02/2013 13:37:29
Instrument Name	: HPLC2	Channel	: A
Rack/Vial	: 0/3	Operator	: Adam
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 3		

Result File : E:\data\AW group\AdamCalow\07_02_2013_ex-79-a-old_003.rst
Sequence File : E:\data\AW group\FKF\7Feb13_1.seq

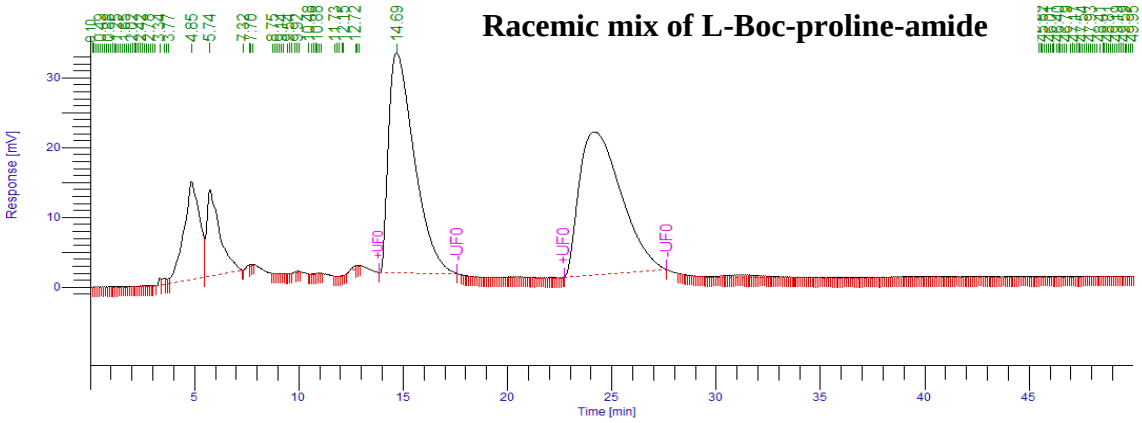


Peak #	Time [min]	Area [µV·s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
184	23.870	3221908.41	24080.18	100.00	100.00	MM	133.7992
		3221908.41	24080.18	100.00	100.00		

Fig 4.11 HPLC trace of racemic mix of L-Boc-proline-amide (109)

Software Version	: 6.3.1.0504	Date	: 13/02/2013 14:11:30
Sample Name	: Racemic-7	Data Acquisition Time	: 07/02/2013 12:45:58
Instrument Name	: HPLC2	Channel	: A
Rack/Vial	: 0/2	Operator	: Adam
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 2		

Result File : E:\data\AW group\AdamCalow\07_02_2013_Racemic-7_002.rst
Sequence File : E:\data\AW group\FKF\7Feb13_1.seq



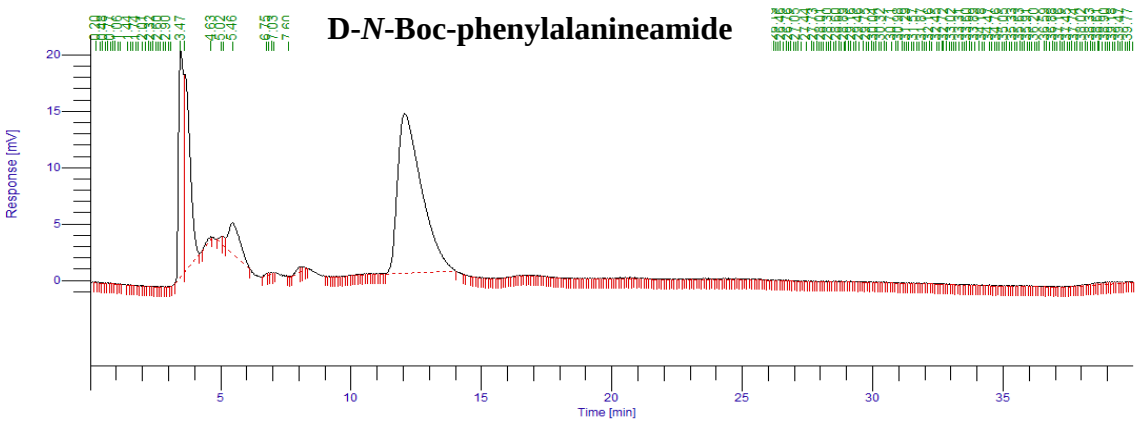
HPLC 2

Peak #	Time [min]	Area [µV·s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
37	4.853	737186.88	14015.00	10.79	10.79	VV	52.5999
38	5.739	533278.54	12392.25	7.80	7.80	VV	43.0332
70	14.689	2696563.48	31530.46	39.45	39.45	MM	85.5225
118	24.163	2867712.55	20479.71	41.96	41.96	MM	140.0270
		6834741.45	78417.41	100.00	100.00		

Fig 4.12 HPLC trace of D-*N*-Boc-phenylalanineamide (111)

Software Version	: 6.3.1.0504	Date	: 13/02/2013 13:36:23
Sample Name	: D-phenylalanine amide	Data Acquisition Time	: 01/02/2013 15:09:44
Instrument Name	: HPLC2	Channel	: A
Rack/Vial	: 0/5	Operator	: Adam
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 5		

Result File : E:\data\AW group\AdamCalow\01_02_2013_D-phenylalanine amide_005.rst
Sequence File : E:\data\AW group\FKF\1Feb13_1.seq

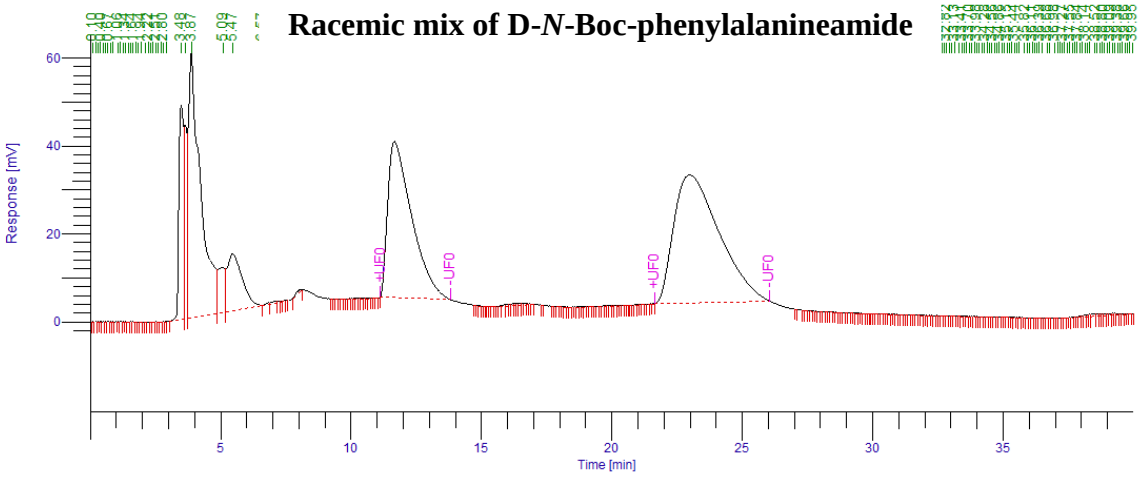


Peak #	Time [min]	Area [µV·s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
28	3.469	255254.14	20023.75	17.71	17.71	BV	12.7476
29	3.624	277675.99	17557.26	19.26	19.26	VB	15.8154
65	12.052	908475.32	14196.99	63.03	63.03	VB	63.9907
		1441405.45	51778.01	100.00	100.00		

Fig 4.13 HPLC trace of racemic mix of *N*-Boc-phenylalanineamide (111)

Software Version	: 6.3.1.0504	Date	: 11/02/2013 12:12:39
Sample Name	: racemicmix-6	Data Acquisition Time	: 01/02/2013 16:49:06
Instrument Name	: HPLC2	Channel	: A
Rack/Vial	: 0/2	Operator	: Adam
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : E:\data\AW group\AdamCalow\01_02_2013_racemicmix-6_001.rst
Sequence File : E:\data\AW group\FKF\1Feb13_3.seq



HPLC 2

Peak #	Time [min]	Area [µV·s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
29	3.483	604990.96	48746.19	6.43	6.43	BV	12.4110
30	3.642	319787.49	44107.64	3.40	3.40	VV	7.2502
31	3.874	1976260.33	60152.96	21.00	21.00	VV	32.8539
32	5.088	182903.17	10203.38	1.94	1.94	VV	17.9257
33	5.466	523033.40	12923.64	5.56	5.56	VE	40.4711
61	11.660	2268977.71	35471.78	24.11	24.11	MM	63.9657
124	23.005	3533620.91	29148.29	37.55	37.55	MM	121.2291
		9409573.96	240753.89	100.00	100.00		

Fig 4.14 HPLC trace of racemic *N*-Benzyl-2-(4-isobutylphenyl)propionamide (140)

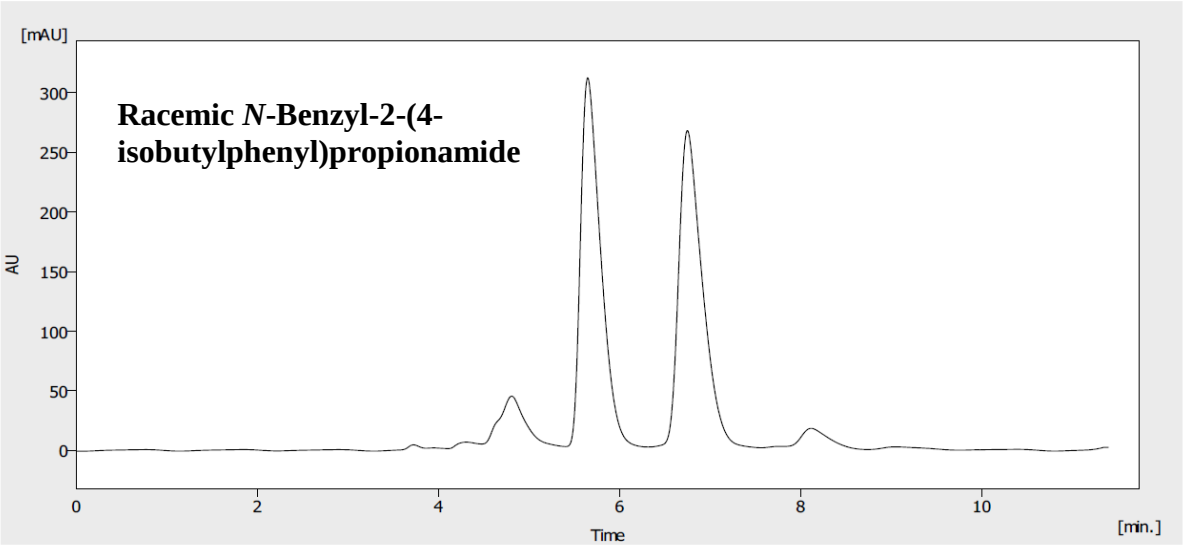


Fig 4.15 HPLC trace of chiral *N*-Benzyl-2-(4-isobutylphenyl)propionamide (140)

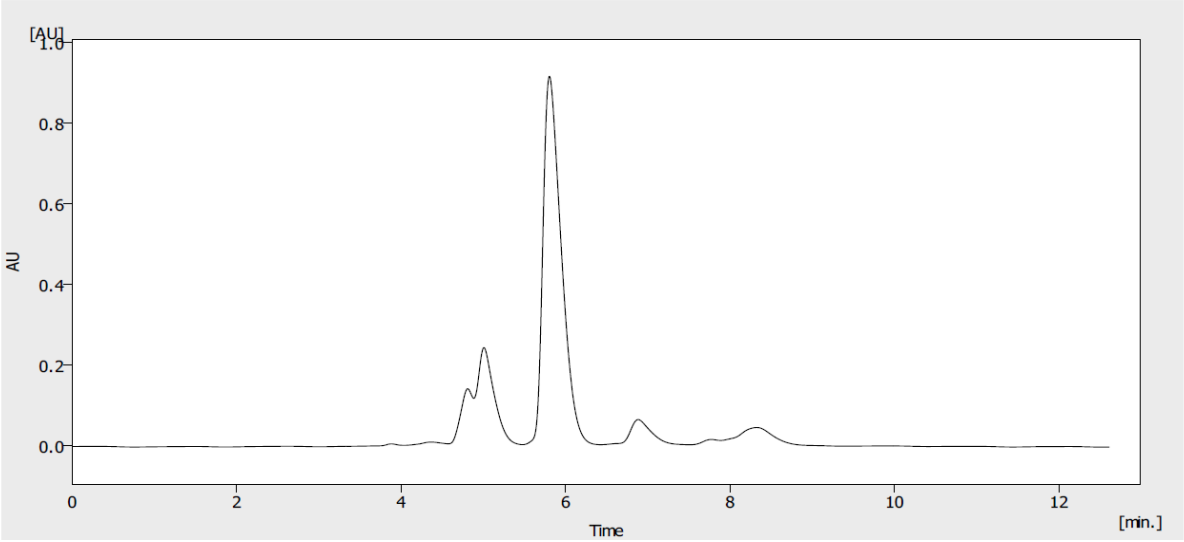


Fig 4.16 HPLC trace of 2-Hydroxy-*N*-2-diphenylacetamide (166)

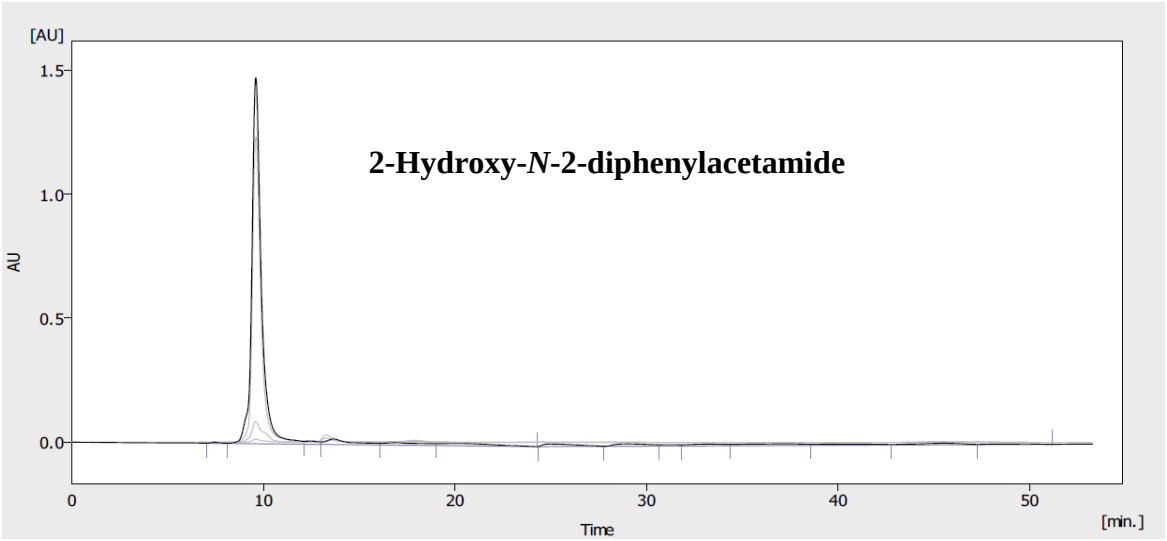


Fig 4.17 HPLC trace of racemic mix of 2-Hydroxy-*N*-2-diphenylacetamide (166)

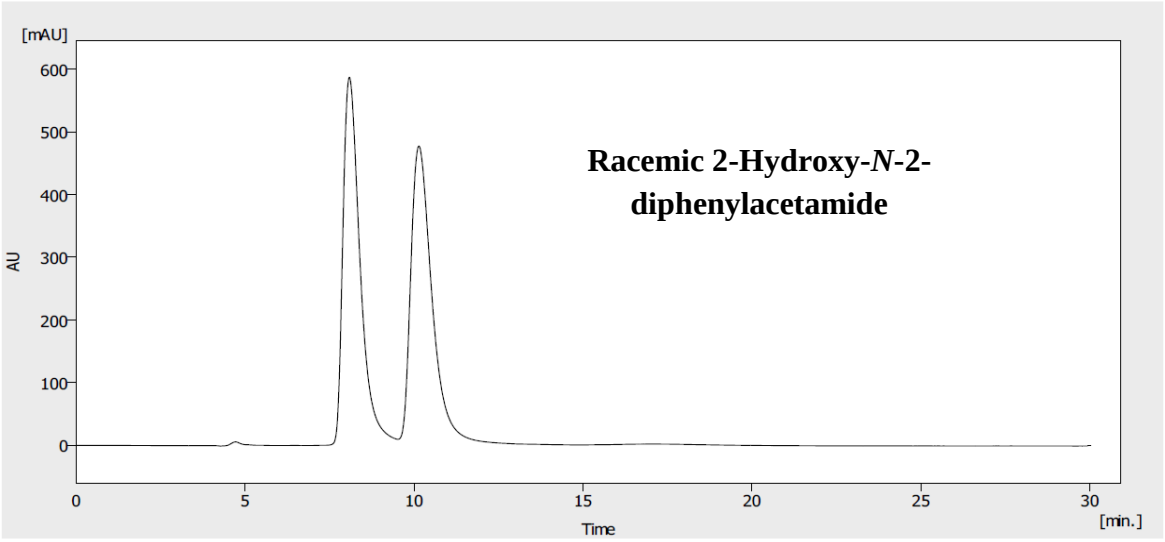


Fig 4.18 HPLC trace of *N*-Benzyl-2-hydroxy-2-phenylacetamide (162)

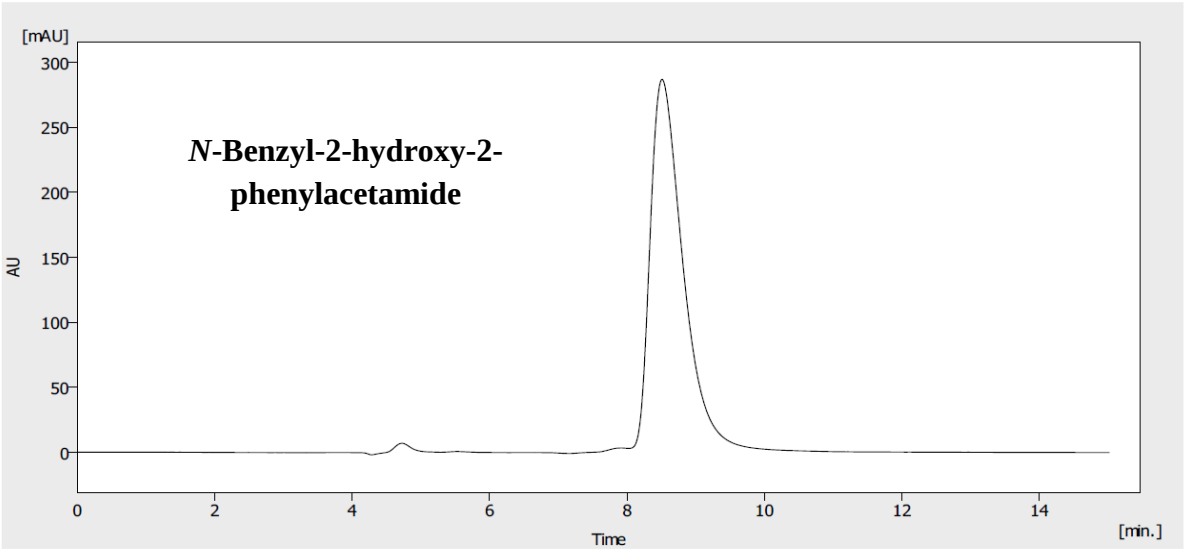


Fig 4.19 HPLC trace of racemic *N*-Benzyl-2-hydroxy-2-phenylacetamide (162)

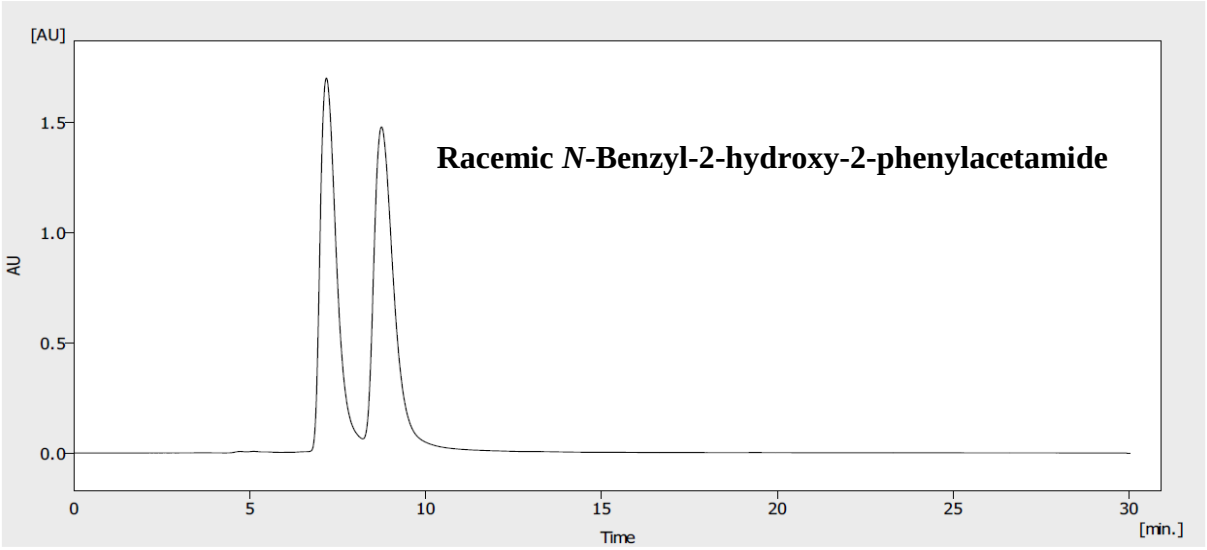


Fig 4.20 HPLC trace of 2-Hydroxy-*N*-phenethyl-2-phenylacetamide (164)

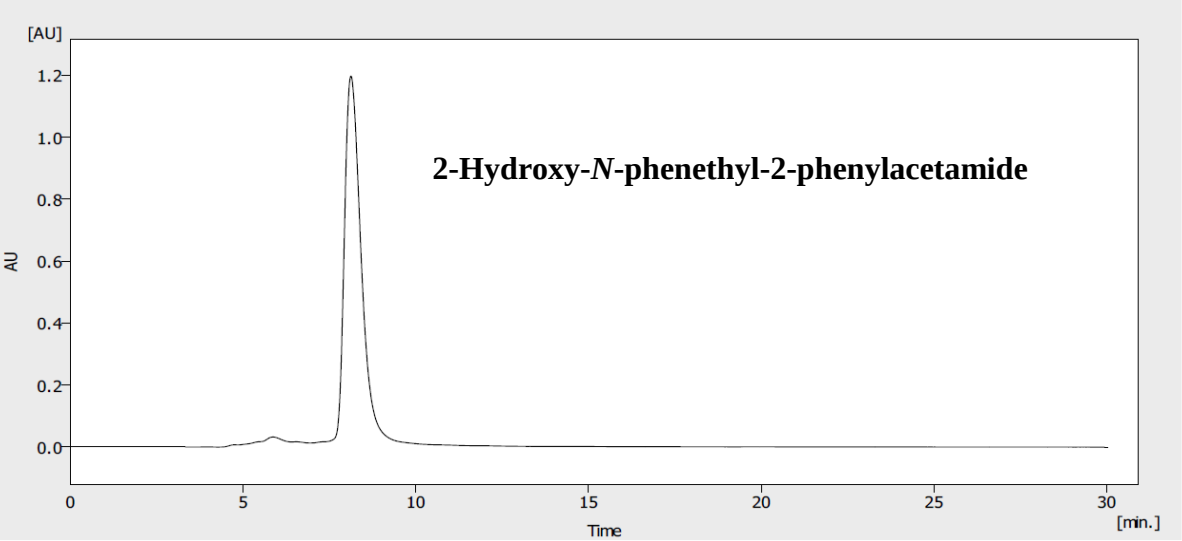


Fig 4.21 HPLC trace of racemic *2*-Hydroxy-*N*-phenethyl-2-phenylacetamide (164)