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# Beyond aldehydes and ketones
# Novel methodology for catalytic reductive amination

BACHELOR'S THESIS

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## Abstract

### English

The synthesis of amines is crucial for drug development due to their biological and pharmacological activity. Several transformations have been established for their synthesis, with reductive amination being one of the most used. A novel method to access the products of reductive amination has been developed using esters, in place of the aldehydes typically used, and sustainable catalysis. Lewis acid catalysts were found for the direct amidation and a reductive amination of esters with amines in a one-pot transformation using HBpin as the terminal reductant. The optimal Lewis acids were found to be $BBr_3$ and $Sc(OTf)_3$.

### Catalan

La síntesi d'amines és crucial pel desenvolupament de fàrmacs gràcies a la seva activitat biològica i farmacològica. Diverses transformacions s'han establert per la seva síntesi, essent l'aminació reductiva una de les més usades. S'ha desenvolupat un nou mètode per obtenir els productes de l'aminació reductiva emprant èsters, en lloc d'aldehids que s'utilitzen habitualment, i catàlisi sostenible. Es van trobar àcids de Lewis per l'amidació directa i aminació reducora d'èsters amb amines en una transformació *one-pot* emprant HBpin com a reductor terminal. Els àcids de Lewis òptims van ser $BBr_3$ i $Sc(OTf)_3$.

## Table of Contents

## Abbreviations and Acronyms

| | |
|---|---|
| Ac | acetyl |
| API | atmospheric pressure interphase |
| Ar | aryl |
| BArF | tetrakis[3,5-bis(trifluoromethyl)phenyl]borate |
| 9-BBN | borabicyclo[3.3.1]nonane |
| Bn | benzyl |
| COD | 1,5-cyclooctadiene |
| DI | deionised |
| equiv. | equivalent |
| ESI | electron spray ionisation |
| HRMS | high resolution mass spectrometry |
| HT | hydride-transfer |
| LA | Lewis acid |
| LB | Lewis base |
| LC-MS | liquid chromatography – mass spectrometry |
| NMR | nuclear magnetic resonance |
| n.p. | not performed |
| obs | observed |
| pin | pinacolato |
| SM | starting material |
| t | time |
| temp | temperature |
| TMB | 1,3,5-trimethoxybenzene |
| TLC | thin layer chromatography |
| tol | toluene |
| TOF | time-of-flight |
| UR | unreacted |

# 1 Introduction

This research project has been developed in the Thomas Group within the Section of Organic Chemistry of the School of Chemistry at The University of Edinburgh (https://chem.ed.ac.uk/thomas-group).

Amines are a ubiquitous functional group present in pharmaceuticals, bioactive compounds, natural products, agrochemicals and dyes.[1]Amines are important building blocks in organic chemistry to produce larger, more complex, molecules and polymers. Developing new, versatile methods for their synthesis has therefore become an important goal in modern synthetic chemistry.

For the 23rd time, in 2023, the World Health Organisation (WHO) published the WHO Model List of Essential Medicines, where they present a list of the minimum medication requirements for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions.[2] From the many pharmaceuticals containing an amine group, five were selected **(Figure 1.1)**, emphasizing the fundamental importance of this functionality in medicine.

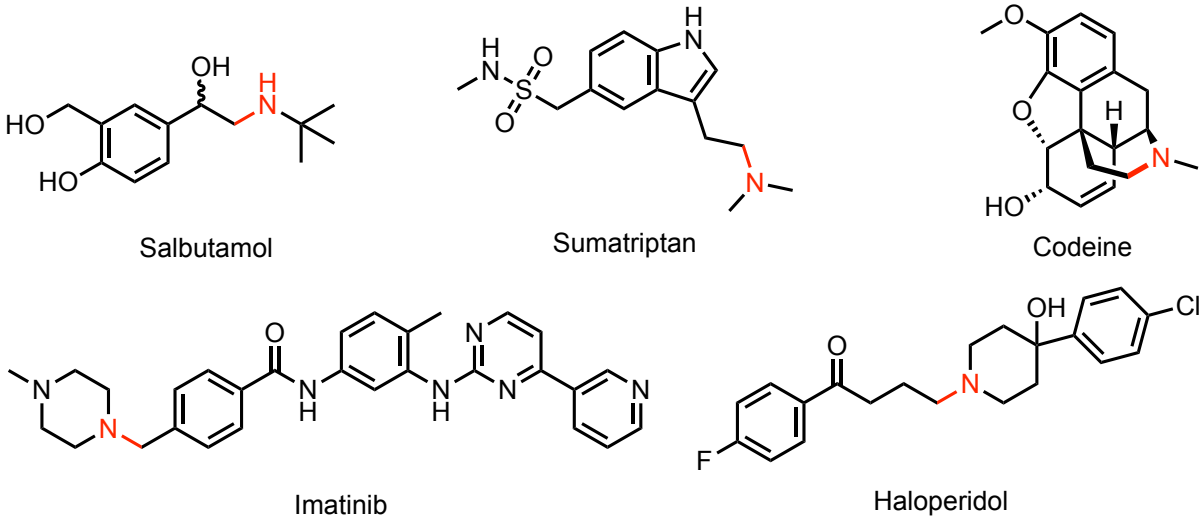
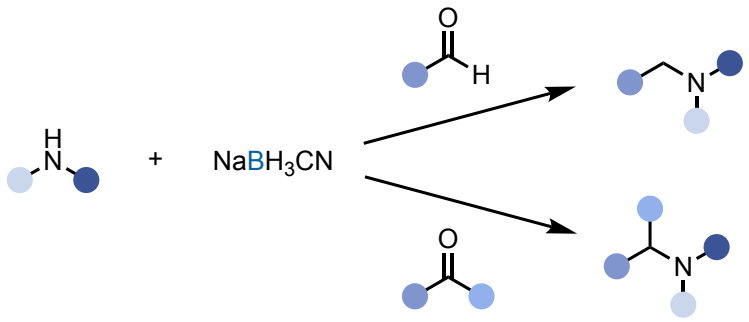



*Figure 1.1 Selection of pharmaceuticals containing amino groups from the WHO Model List of Essential Medicines synthetized by reductive amination.[3]*

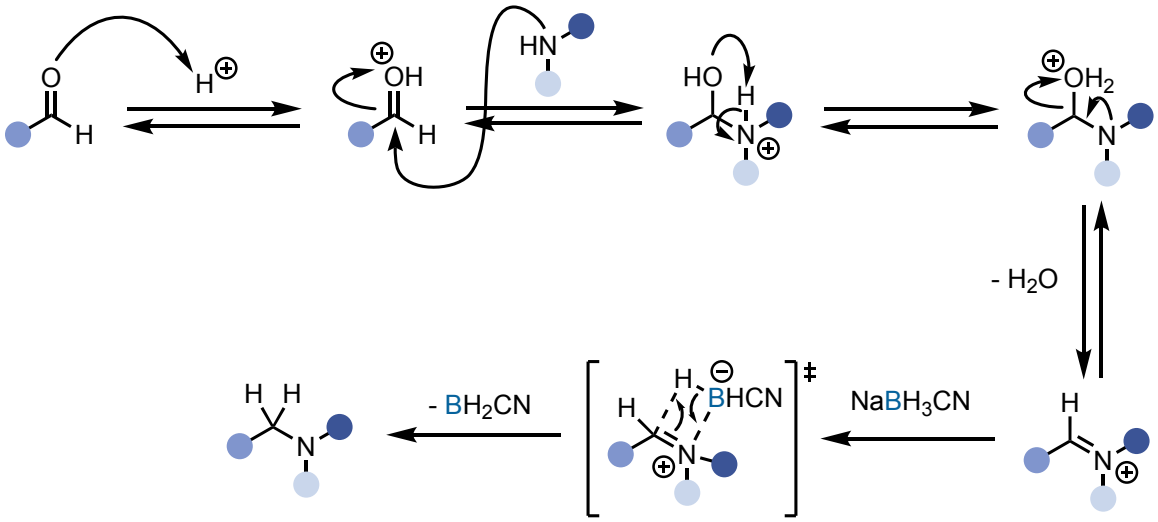
The most common nitrogen feedstock is ammonia; over 150 million metric tonnes are produced annually.[4] However, converting ammonia to biologically-relevant chemicals is a challenging process. The strength of the N-H bond is 103 kcal/mol,[5] and as a result, can only be activated by some precious metal catalysts limiting industrial applications. However, reactions derived from unsaturated substrates provide an alternative route to N-H activation. A common pathway for the synthesis of amines involves the coupling reaction between an aldehyde or ketone with an amine in the presence of a reducing agent, such as a hydride-transfer (HT) agent or catalytic hydrogenation **(Scheme 1.1)**.[6] This reaction is known as reductive amination or reductive alkylation, and it accounts for one fourth of the syntheses of carbon-nitrogen bonds in drug candidates.[7] The reaction proceeds by the formation of an iminium ion, via a hemiaminal intermediate in a weakly acidic environment, and its subsequent reduction **(Scheme 1.2)**.

Reductive amination has been developed across ammonia, primary and secondary amines, for coupling to aldehydes and unhindered ketones.[8]




*Scheme 1.1 General scheme for the reductive amination of aldehydes and ketones using sodium cyanoborohydride as a reducing agent.*

Sodium cyanoborohydride is one of the most established HT agents used in reductive amination reactions. However, the generation of hydrogen cyanide during reaction workup is a significant health risk, and thus, the switch to the non-toxic alternative sodium triacetoxyborohydride was commonly implemented.[9]

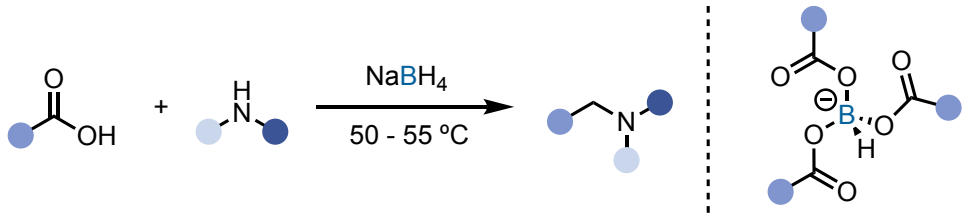



*Scheme 1.2 Mechanism for amine formation by reductive amination reaction of an aldehyde using cyanoborohydride as a HT agent.*

Although reductive amination is used extensively in drug discovery, this method has several drawbacks. Notably, the use of superstoichiometric reducing agents which are also often highly toxic. Moreover, the industrial synthesis of aldehydes, essential coupling partners in this reaction, utilizes superstoichiometric amounts of hazardous and toxic oxidants.[10] Thus, methods that reduce chemical waste, use safer reagents and rely on easily accessible chemical feedstocks were developed.

Reductive amination can also be conducted using carboxylic acids as coupling partners. First introduced in 1974, and further developed in 1978, Gribble et al. developed a method for the *N*-alkylation of

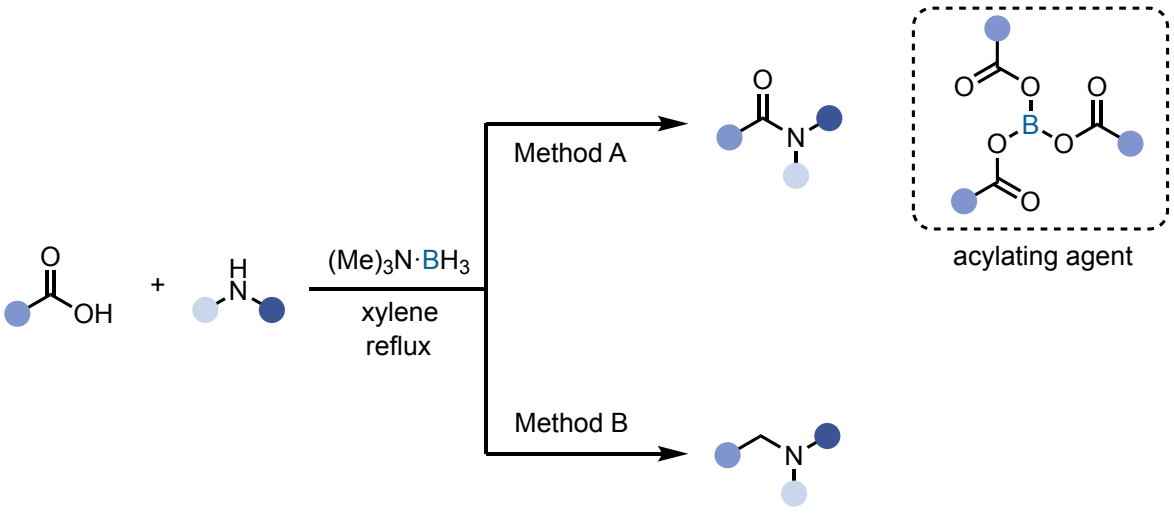
aromatic and secondary aliphatic amines with liquid carboxylic acids using sodium borohydride as a reducing agent in acidic media **(Scheme 1.3)**.[11,12]




*Scheme 1.3 Synthesis of amines reported by Gribble et al. using carboxylic acids as substrates and solvent and sodium borohydride.*

The mechanism involves the formation of an acyloxyborohydride, presumably though *in situ* formation of $BH_3$ when reacting sodium borohydride with the carboxylic acid (used as solvent), which was proposed to reduce the (same) carboxylic acid to an aldehyde.[13,14] The aldehyde reacted with the amine to form an iminium ion. As reduction of an iminium ion is much faster than the aldehyde,[8] the reductive amination proceeds selectively to produce an amine instead of an alcohol. Thereby, behaving in a similar manner as the classical reductive amination **(Scheme 1.2)**.

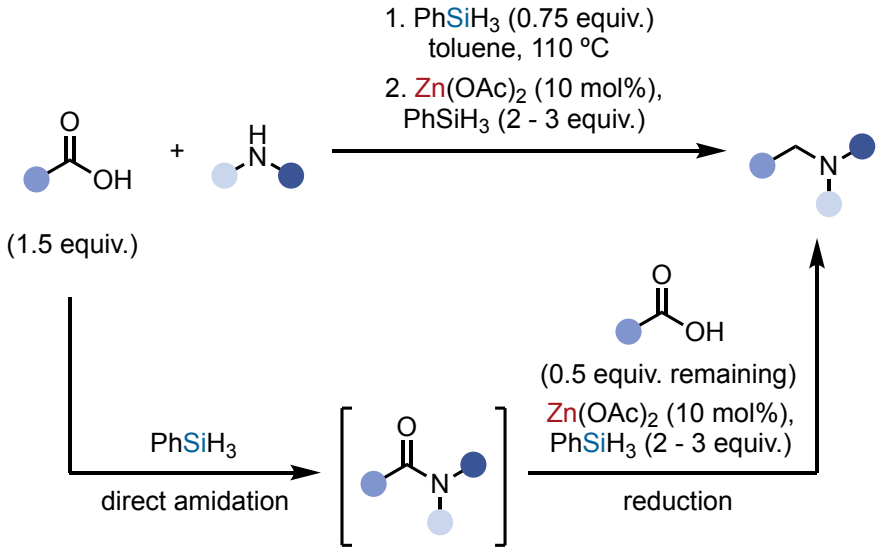
A similar approach was developed in 1983 by Trapani et al. by using trimethylamine-borane as a reducing reagent. This method enabled the synthesis of both amides and amines from carboxylic acids, which can be selectively targeted through the borane:acid ratio **(Scheme 1.4)**. It was proposed that the *N*-alkylation reaction may proceed by either an amide reduction or a reductive alkylation of the amine. Moreover, it is suggested that the reaction between the carboxylic acid and trimethylamine-borane in a 3:1 molar ratio may involve a triacyloxyborane, as an acylating agent.[15]




*Scheme 1.4 N-acylation and N-alkylation of carboxylic acids using trimethylamine-borane. Acid:amine:trimethyamine-borane in method A is 3:1:1 and in method B is 2:1:2.*

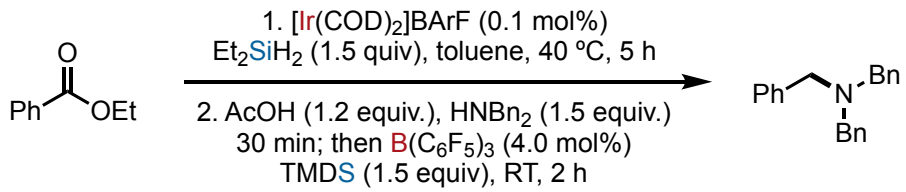
Recently, research into the use of carboxylic acids as coupling partners has gained significant interest. In 2020, Denton *et al.* reported a protocol using zinc acetate and phenylsilane for reductive amination from carboxylic acids and amines. It consisted in a two-step reaction, first, a silane-mediated amidation

followed by a $Zn(OAc)_2$-catalysed amide reduction with the silane acting as the terminal reductant **(Scheme 1.5)**.[16] Denton and co-workers suggested that the addition of a carboxylic acid improved the reduction of tertiary amides when using zinc acetate and phenylsilane. Low reactivity for tertiary amines was also reported by Beller *et al*. when using zinc triflate together with phenylsilane for reductive amination in 2011.[17]




*Scheme 1.5 Denton et al. reductive amination of carboxylic acids via an amide intermediate using phenylsilane and sub-stoichiometric $Zn(OAc)_2$.*

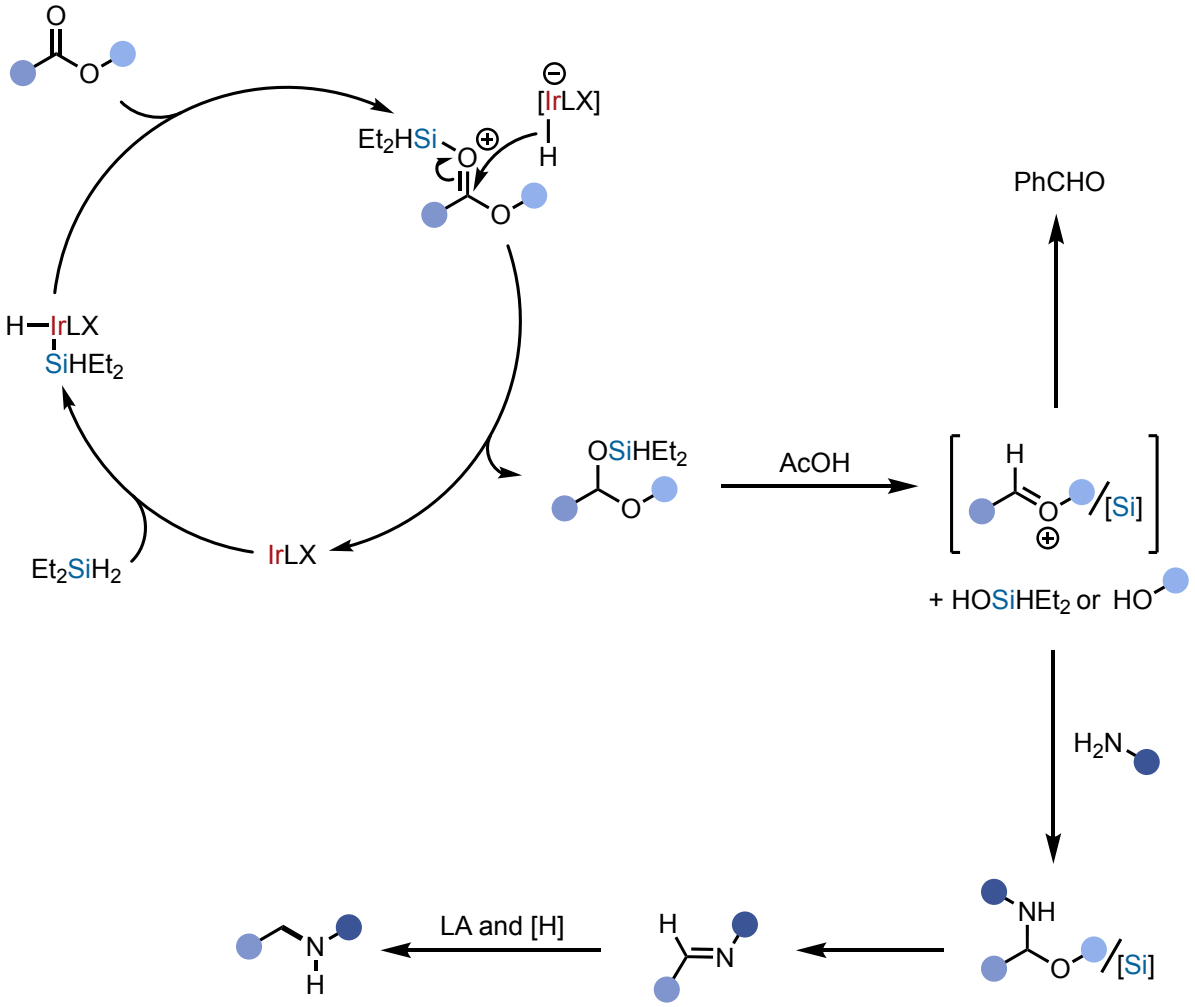
While carboxylic acids may offer a slight improvement from aldehydes, which are readily susceptible to oxidation and other forms of degradation, reductive amination using carboxylic acids has a lower functional group tolerance for groups sensitive to low pH. Furthermore, the requirement for forcing reaction conditions and metal-based reagents is also undesirable. In contrast, the use of esters, which are bench-stable and non-toxic, would be a novel, safer reagent for reductive amination. In addition, the switch from stoichiometric reactivity to catalytic activity would further reduce chemical waste. However, the reactivity of esters is lower than that of aldehydes and ketones, and thus, may require an alternative approach to achieve reductive amination.




*Scheme 1.6 Reductive amination of esters via an aldehyde formation through hydrosylilation and posterior N-alkylation.*

In late 2024, Pei-Qiang Huang and co-workers established a catalytic reductive amination of esters using a cationic iridium complex **(Scheme 1.6)**.[18] The reaction was proposed to be a chemoselective hydrosilylation of the ester generating an *O,O*-silyl acetal, followed by the formation of a highly electrophilic oxo-carbenium ion. Nucleophilic attack by the amine to the carbon of the oxo-carbenium

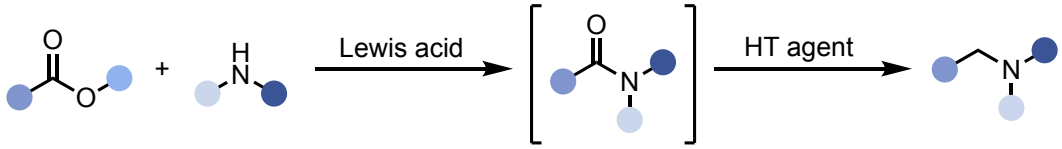
ion formed an *N,O*-acetal that collapsed into an imine or an iminium ion, if the amine was primary or secondary, respectively. The reaction proceeds to the reduction of these species by the addition of a sub-stoichiometric amount of a Lewis acid and a HT agent; in this case tris-pentafluorophenyl borane (BCF) and tetramethyldisiloxane (TMDS), respectively **(Scheme 1.7)**. Studies into the mechanism of the reaction revealed that the role of the iridium catalyst was the formation of an (isolable) aldehyde during the ester hydrosilylation reaction. The advantages of this method are low catalyst loading, mild conditions and air insensitivity, together with an excellent versatility of substrates, making the reaction useful and functional.




*Scheme 1.7 Proposed reaction mechanism for the catalytic reductive amination of esters according to Pei-Qiang Huang and co-workers.*

## 2 Aims and Objectives

This project aimed to develop a new methodology for the reductive amination of esters. Investigations into Lewis acid promoted amide formation were performed. Reduction of the amine was then explored using a Lewis acid and HT agent. Both reactions were examined individually, and then, a one-pot method for amide synthesis and reduction was explored **(Scheme 2.1)**.




*Scheme 2.1 General reductive amination of esters assuming an amide intermediate.*

From the general goal, several individual objectives were set to achieve such:

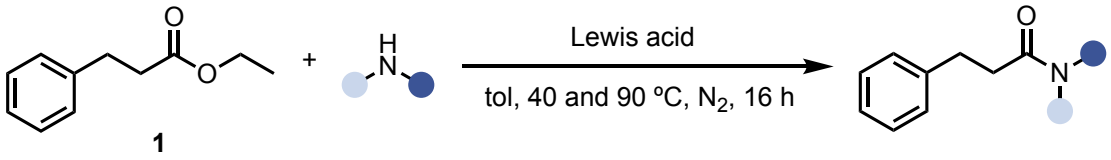
- Investigate catalytic amide formation using a Lewis acid catalyst.
- Investigate amide reduction using a Lewis acid catalyst.
- Investigate amide reduction using transborylation catalysis.
- Optimise one-pot synthesis of tertiary amines from esters and secondary amines.

# 3 Results and Discussion

## 3.1 Lewis-Acid-Assisted Direct Amidation

While direct amidation can be achieved by acyl halides, this transformation is not observed at the less reactive ester carbonyl group. A series of Lewis acids were selected with varying degrees of Lewis acidity. It was presumed that the LA would coordinate to the oxygen of the ester and remove electron density form the carbonyl, allowing it to become more electrophilic, and thus susceptible to attack by the amine. However, the amine present in the reaction is a stronger Lewis base than the ester,[19] so possibly deactivating it for nucleophilic substitution due to a strong Lewis acid-Lewis base adduct formation. Depending on the strength of the Lewis acid, it was believed that coordination to one of the LBs in the reaction would be preferential, or reviersible.[20] These results would provide insight into the Lewis acidity required to facilitate the reaction.

The ester selected for amidation **(Scheme 3.1)** and amination reactions was ethyl 3-phenylpropanoate, which is representative of an alkyl tethered to an aryl group, a common pharmaceutical motif **(Figure 1.1)**, whereas the amines were selected to examine steric and electronic parameters of the reaction (**Figure 3.1**). Heterocyclic and aryl amines are of great importance for pharmaceutical development as well for production of agrochemicals and other products.[7,21] Alky amines, 1-butylamine **5** and tert-butylamine **6**, were tested for steric concerns and evaluation of the reaction.




*Scheme 3.1 Amidation reaction of ethyl 3-phenylpropanoate using different Lewis acids and amines.*

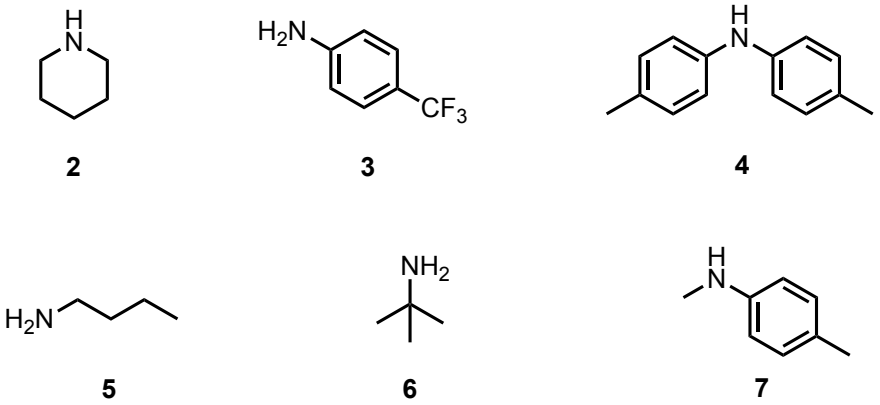
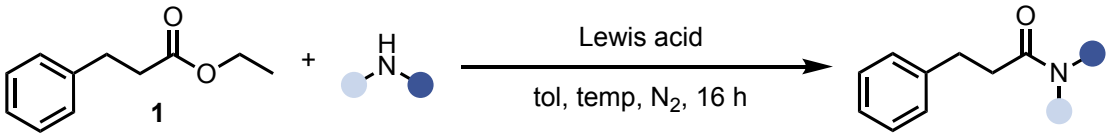



*Figure 3.1 Amine scope for the amidation reaction.*

*Table 3.1 Lewis-acid-assisted amidation reaction with ethyl 3-propanoate and several amines at 40 and 90 °C.*



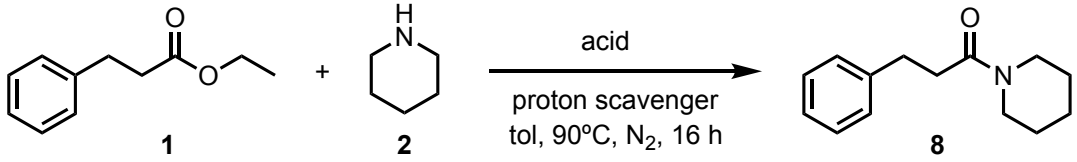

| Entry | Lewis Acid | Temperature (°C) | Amine 2 | Amine 3 | Amine 4 | Amine 5 | Amine 6 |
|---|---|---|---|---|---|---|---|
| **1** | $BF_3{\cdot}OEt_2$ | 40 | not obs | not obs | not obs | n.p. | n.p. |
| **2** | $BCl_3$ | 40 | not obs | not obs | not obs | n.p. | n.p. |
| **3** | $BBr_3$ | 40 | not obs | not obs | not obs | n.p. | n.p. |
| **4** | $BI_3$ | 40 | not obs | not obs | not obs | n.p. | n.p. |
| **5** | $BEt_3$ | 40 | not obs | not obs | not obs | n.p. | n.p. |
| **6** | $BI_3$ | 90 | obs | not obs | not obs | obs | not obs |
| **7** | $BEt_3$ | 90 | not obs | not obs | not obs | n.p. | n.p. |
| **8** | $FeCl_3$ | 90 | not obs | not obs | not obs | n.p. | n.p. |
| **9** | $TiCl_4$ | 90 | not obs | not obs | not obs | n.p. | n.p. |
| **10** | $SnCl_4$ | 90 | not obs | not obs | not obs | n.p. | n.p. |

Using boron trihalide Lewis acids and piperidine **2**, 4-(trifluoromethyl)aniline **3** and 4-methyl-*N*-(4-methylphenyl)aniline **4**, no evidence of amide formation was observed by multinuclear NMR spectroscopy **(Table 3.1, entries 1-5)**. The lack of reactivity to give the amides was confirmed by unmatched chemical shifts with respect to reported data for the products. Nevertheless, in some reactions, the starting material chemical shifts changed. It was thought to be a change due to coordination of the Lewis acid with the amine and/or the ester.[22]For this reason, 4-(trifluoromethyl)aniline **3** and ethyl 3-phenylpropanoate **1** were mixed with boron trichloride to observe any change by NMR spectroscopy. Both ethyl 3-phenylpropanoate **1** and 4-(trifluoromethyl)aniline **3** showed a downfield change in the chemical shift in the corresponding signals of the $^1$H NMR spectra **(Experimental Details, Figures 4.4-4.7)**. This successful outcome encouraged new tests at higher temperatures to break the adduct formation between the amine and the Lewis acid **(Table 3.1, entries 6-10)**. As the donor number of an amine is greater than that of an ester,[19] it was anticipated that preferential coordination of the amine to the LA would occur, hindering reactivity. Thus, the reaction temperature was elevated to break-up the LA-LB, as previously demonstrated in other systems.[23]

Only in one instance was amidation observed and occurred using $BI_3$. As boron triiodide is amongst the strongest known LAs, a highly Lewis acidic species was thought to be essential for the amidation reaction. Thus, further studies with $BI_3$ were conducted shown in **Table 3.1, entry 6**. The results demonstrate that bulky substrates such *tert*-butyl amine **6** are unlikely to undergo a favourable nucleophilic attack to form an amide. However, 1-butylamine **5** did form an amide. The distinctive reactivity of $BI_3$ prompted the hypothesis that the observed transformation may be attributed to the involvement of a Brønsted acid, such as the strong acid, hydrogen iodide. Thus, control reactions were

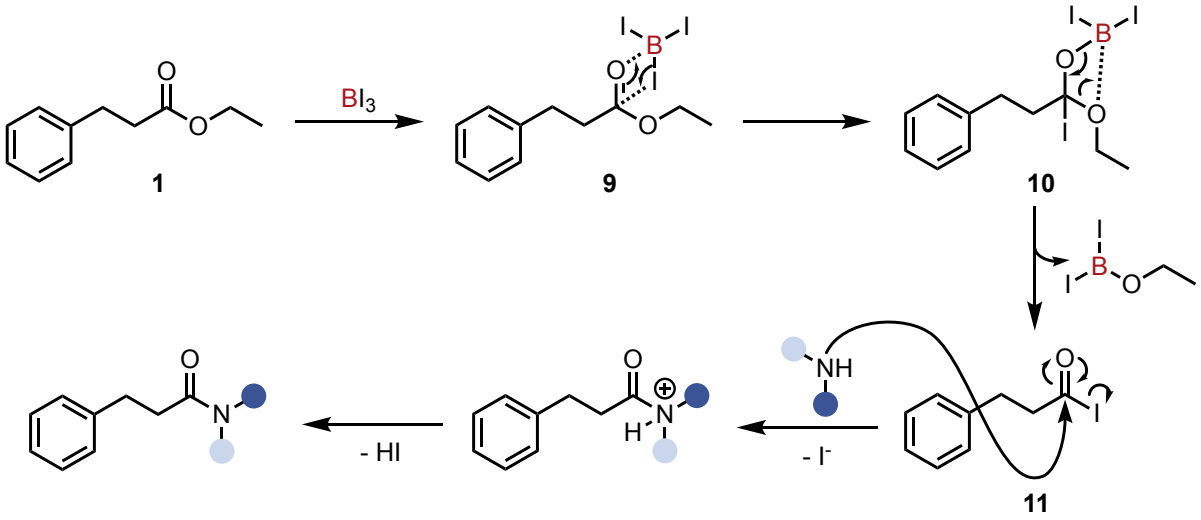
undertaken to investigate any background reaction by acid **(Table 3.2)** and elucidate the intrinsic reactivity of $BI_3$.

*Table 3.2 Control experiments for $BI_3$.*




| Entry | Acid | Equiv. | Proton Scavenger | Outcome 8 |
|---|---|---|---|---|
| **1** | HCl (conc.) | 1 | - | not obs |
| **2** | $BI_3$ | 1 | - | obs |
| **3** | $BI_3$ | 1 | 2,6-ditertbutylpyridine | obs |

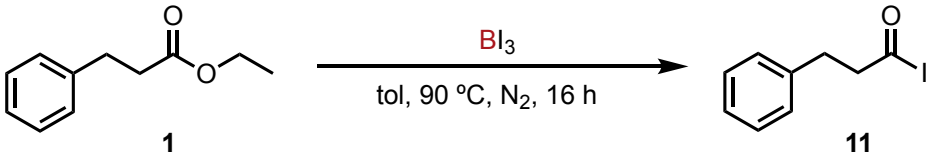
In the presence of a strong acid, HCl, no amide formation was observed. These results suggest that boron triiodide functions as a Lewis acid independently, without the involvement of a Brønsted acid. In the presence of 2,6-ditertbutylpyridine, reactivity was still observed which would normally rule out Brønsted acid-catalysis. This led to hypothesise the formation of an acyl iodide intermediate may be a plausible step in the reaction mechanism. As proposed in **Scheme 3.2**, the ester carbonyl undergoes haloboration **(9)** via a σ-bond metathesis mechanism following coordination to boron triiodide. This process leads to reformation of the carbonyl group **(10)**, resulting in the generation of an acyl iodide intermediate and the consequent elimination of ethoxydiiodoborane. The formation of a highly electrophilic carbonyl centre **(11)** facilitates subsequent nucleophilic acyl substitution, yielding the desired amide product along with hydrogen iodide as a by-product.




*Scheme 3.2 Proposed mechanism for the synthesis of an amide using $BI_3$, ethyl 3-phenylpropanoate and an amine as substrates.*

The cleavage of the B-I bond significantly alters the Lewis acidity of the reagent. This imposes a limitation on the use of boron triiodide to a stoichiometric reagent, its transformation into triethyl borate over the course of the reaction results in the lack of active Lewis acidic species. Consequently, the

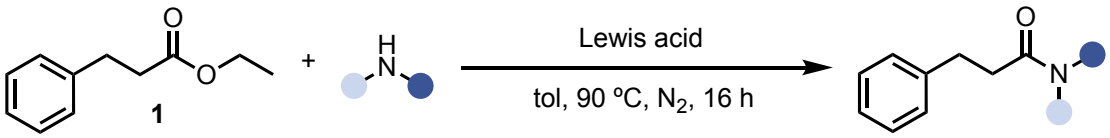
effective quantity of $BI_3$ that can be employed may be reduced to a minimum of 1/3 equivalents, only if the by-products – ethoxydiiodoborane and diethoxyiodoborane – retain sufficient Lewis acidity to sustain haloboration. Some tests were done to prove the existence of compound **11 (Scheme 3.3)**, the most relevant through a test reaction where the ester **1** was mixed with $BI_3$ under the same reaction conditions and the analysis of the reaction outcome. The assignment of the chemical shift by $^{13}C$ NMR spectroscopy consistent with an acyl iodide allowed the identification of 3-phenylpropanoyl iodide. No additional investigations were done due to the inability of using $BI_3$ as a sub-stoichiometric reagent.




*Scheme 3.3 Test reaction to investigate the formation of acyl iodide.*

The Lewis acid scope was then expanded to other main-group Lewis acids and transition metal Lewis acids to screen for the same amidation reaction **(Table 3.3)**. Evidence of amide formation was observed by LC-MS using piperidine **2** and butylamine **5**, so these amines were also screened in reactions with other Lewis acids. No amide formation was observed for 4-(trifluormethyl)aniline **3** and 4-methyl-*N*-(4-methylphenyl)aniline **4**. This suggests the reaction requires an amine of high nucleophilicity and low steric hinderance to promote nucleophilic acyl substitution. Therefore, aiming to maintain an aromatic amine due to their importance in pharmaceutical and agronomical chemistry, 4-(trifluormethyl)aniline **3** and 4-methyl-*N*-(4-methylphenyl)aniline **4** were replaced to *N*,4-dimethylaniline **7**. *N*,4-dimethylaniline **7** has higher nucleophilicity than **3** and **4**,[24] and less steric hinderance than **4**.

*Table 3.3 Amplification of the Lewis acid scope for the amidation reaction using different Lewis acids and amines.*

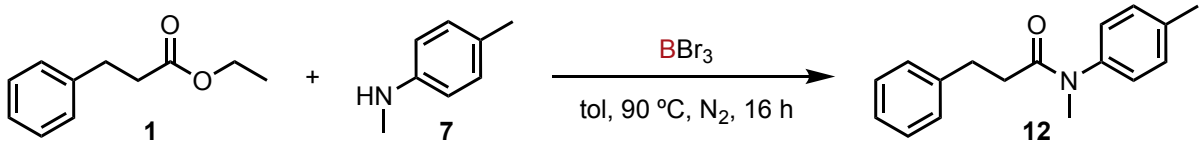



| Entry | Lewis Acid | Amine 2 | Amine 5 | Amine 7 |
|---|---|---|---|---|
| **1** | $BBr_3$ | obs | obs | obs |
| **2** | $BMes_3$ | not obs | not obs | not obs |
| **3** | $InBr_3$ | not obs | not obs | not obs |
| **4** | $AlI_3$ | obs | obs | obs |
| **5** | $Sc(OTf)_3$ | obs | obs | not obs |
| **6** | $Ti(O^iPr)_4$ | obs | obs | not obs |
| **7** | MeO-*B*-9-BBN | not obs | not obs | not obs |
| **8** | I-*B*-9-BBN | obs | obs | obs |

Amongst the Lewis acids evaluated, boron tribromide, I-*B*-9-BBN, and aluminium triiodide exhibited the most consistent reactivity across all amines tested. Boron tribromide and I-*B*-9-BBN were therefore

selected for further studies, given their potential applicability in transborylation[25] and reductive amination.

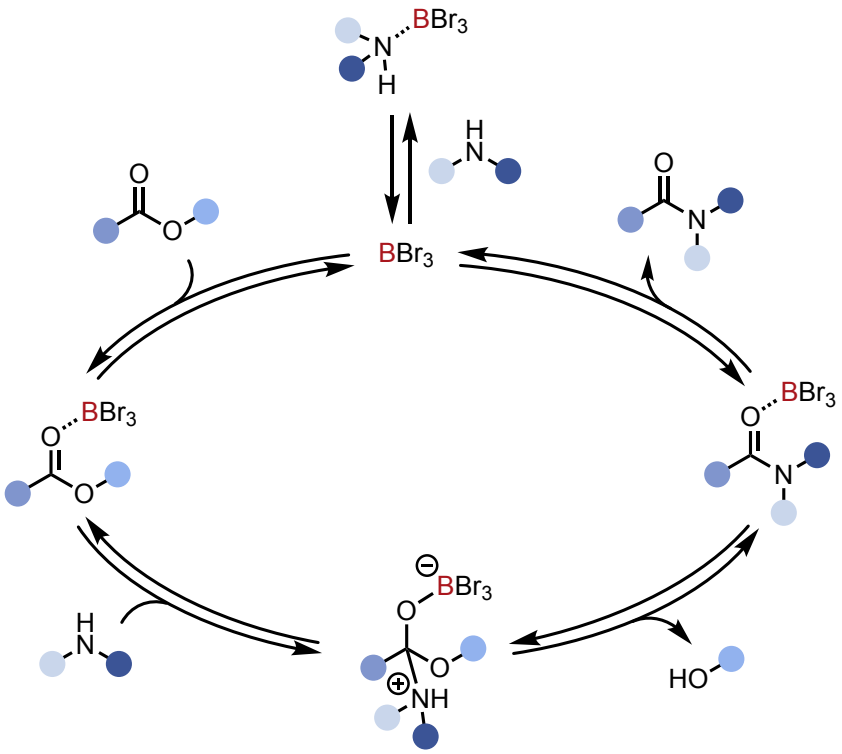
*Table 3.4 Comparison of the outcomes of the reactions using different amounts of $BBr_3$.*




| Entry | Ester | Amine | $BBr_3$ | Amide | UR SM 1 |
|---|---|---|---|---|---|
| **1** | 1 equiv. | 1 equiv. | 1 equiv. | 73% | 27% |
| **3** | 1 equiv. | 1 equiv. | 50 mol% | 62% | 38% |

The synthesis of amide **12** was achieved in 73% yield, using ester **1** by $^{1}$H NMR spectrum by comparison with the starting material ester. The 27% was ethyl 3-phenylpropanoate **1** remaining unreacted **(Table 3.4, entry 1)**. The $^{11}$B NMR spectrum revealed the formation of an adduct between $BBr_3$ and the amide at −6.81 ppm. No evidence of B-Br cleavage was observed, which may enable this species to facilitate this reaction in a catalytic manner. The Lewis acid is proposed to reversibly form an adduct with the amine at 90 °C to allow coordination of the $BBr_3$ to the ester and increase the electrophilicity of the carbon centre, making it susceptible to nucleophilic attack by the amine. Alcohol elimination and decoordination of the $BBr_3$ from the amide will release the amide product. While the Lewis acidic $BBr_3$ may interact with both the carbonyl of the ester and of the amide, only the $BBr_3$·ester interaction is productive. Elevated temperatures ensure reversibility to any $BBr_3$·amide interaction. The proposed mechanism for the rection is shown in **Scheme 3.4**. A reaction using 50 mol% of boron tribromide was performed to assess the effectiveness of using the Lewis acid as a sub-stoichiometric reagent **(Table 3.4, entry 2)**. The amide was formed in a 62% yield; the remaining 38% was determined to be unreacted ester **1**. The comparative results demonstrated that boron tribromide can be employed in sub-stoichiometric amounts while still affording yields comparable to those obtained under stoichiometric conditions.

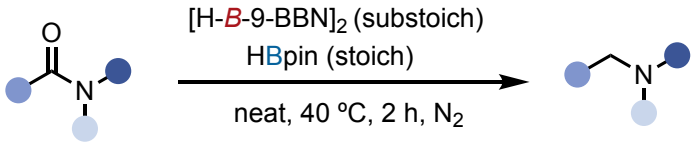
To evaluate the viability of scaling the reaction up, as would be required for industrial application, the reaction was performed using 3.57 grams of ester. Obtaining 3.04 grams of amide, the yield of the reaction was 60%, comparative to those obtained in test reactions. These data highlight the potential for this reaction to be implemented in large-scale amidation reactions.



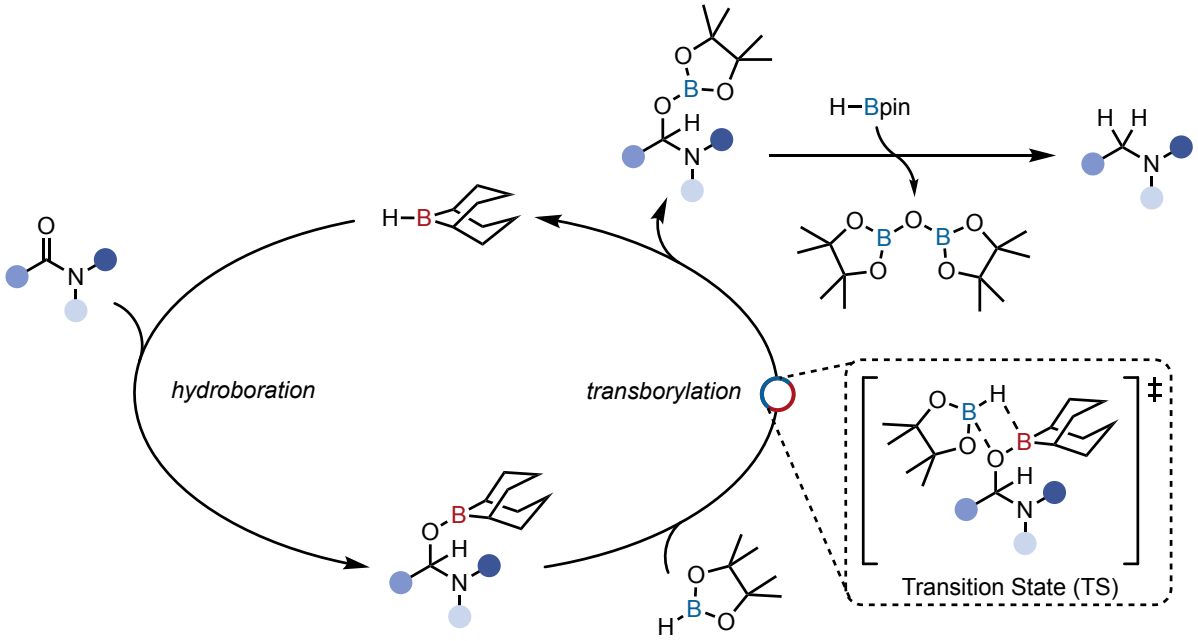

*Scheme 3.4 Proposed mechanism for the amide formation as a nucleophilic acyl substitution reaction of an ester using $BBr_3$.*

### 3.2 Reductive amination of esters

As soon as successful amide formation had been achieved, the reduction of an amide through transborylation was investigated **(Scheme 3.5)**. Illustrated in **Scheme 3.6**, it was expected that sub-stoichiometric amounts of H-*B*-9-BBN would add across the C-O bond by hydroboration, as previously reported for other carbonylic compounds,[25] and turnover achieved by transborylation (B-O/B-H metathesis) with HBpin with concurrent regeneration of the H-*B*-9-BBN.

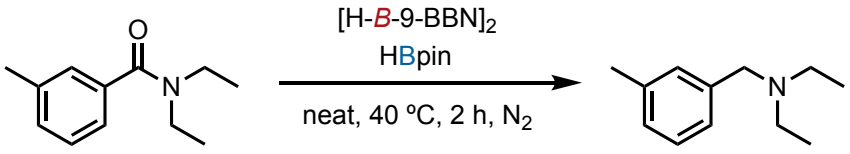



*Scheme 3.5 General reaction for the synthesis of amines by amide reduction using a borane as a sub-stoichiometric specie and a borohydride as a turnover reagent.*




*Scheme 3.6 Proposed catalytic cycle of how the reaction was expected to work for the amide hydroboration and transborylation to obtain the amine as a* product.

*Table 3.5 Reduction of N,N-diethyl-3-methylbenzamide to N-ethyl-N-(3-methylbenzyl)ethanamine using different amounts of [H-B-9-BBN]2 and HBpin.*

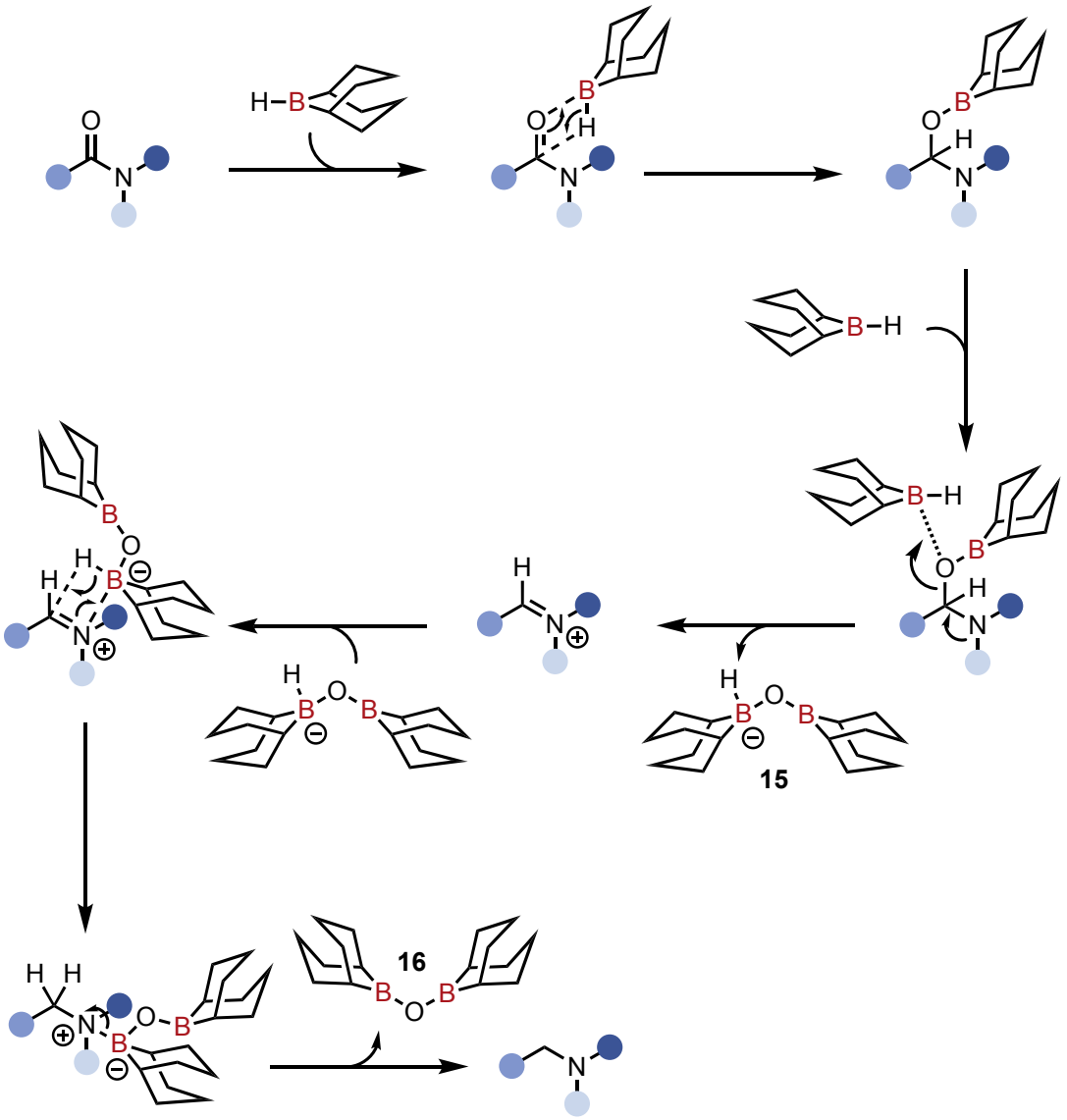



**13** **14**

| Entry | Amide 13 | [H-*B*-9-BBN]$_2$ | HBpin | Amine 14 |
|---|---|---|---|---|
| **1** | 1.0 equiv. | 10 mol% | 2.0 equiv. | none |
| **2** | 1.0 equiv. | 1.1 equiv. | none | obs |
| **3** | 1.0 equiv. | none | 2.2 equiv. | none |

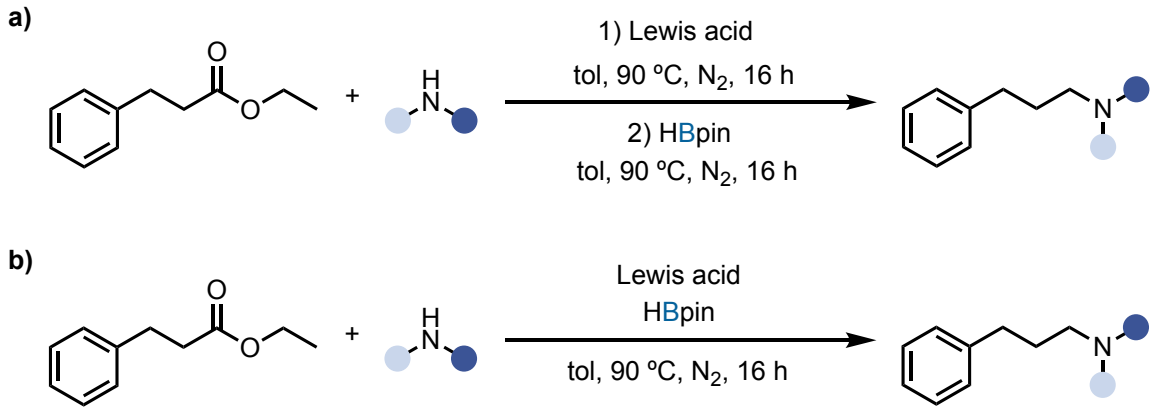
Amide **13** was reacted neat with [H-*B*-9-BBN]$_2$ and HBpin for 2 hours at 40 °C under nitrogen atmosphere **(Table 3.5)**. *N*-ethyl-*N*-(3-methylbenzyl)ethanamine **14** was only observed in the $^1$H NMR spectrum when a stoichiometric amount of [H-*B*-9-BBN]$_2$ was added to the reaction. HBpin itself cannot reduce the amide. Therefore, the transborylation step was not favoured under these reaction conditions.

A feasible mechanism for this transformation was envisaged where the amide undergoes a hydroboration by H-*B*-9-BBN across the carbonyl bond. A second H-*B*-9-BBN enables formation of an iminium ion by acting as a Lewis acid, and expelling borohydride **15,** hydroboration or hydride addition (from borohydride **15)** of the iminium ion would then give the amine, and B-O-B compound **16 (Scheme 3.7)**.



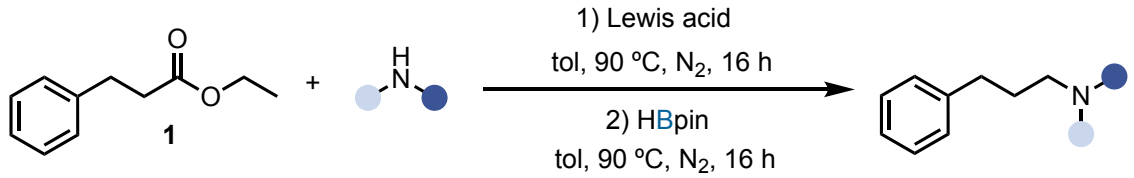

*Scheme 3.7 Proposed mechanism for the amide deoxygenation using [H-B-9-BBN]$_2$ as a stoichiometric reagent.*

The desired results for amine reduction were not achieved, therefore future investigation was focused on the reduction of amides using the combination of a Lewis acid able to form an amide and HBpin. For that, two types of reactions were performed **(Scheme 3.8)**: a) A direct amidation and sequential reduction with HBpin; b) A one-pot addition of a Lewis acid and the HBpin to compare the outcome of the reaction.




*Scheme 3.8 General reaction for amine formation a) stepwise and b) one-pot.*

*Table 3.6 Reductive amination using two different boron-based Lewis acids.*



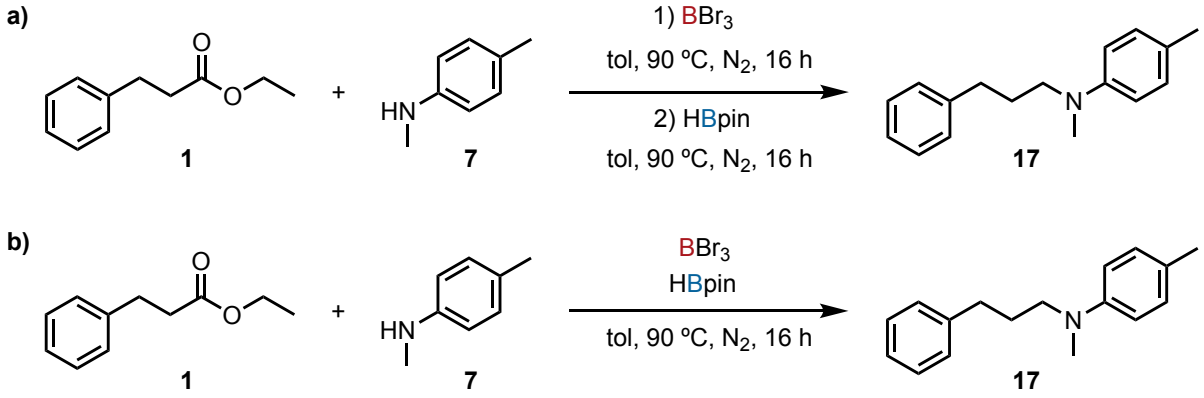

| Entry | LA | LA equiv. | HBpin | Amine 2 | Amine 5 | Amine 7 |
|---|---|---|---|---|---|---|
| **1** | I-*B*-9-BBN | 1 equiv. | 1.1 equiv. | obs | obs | obs |
| **2** | I-*B*-9-BBN | 1 equiv. | 4.0 equiv. | n.p. | n.p. | obs |
| **3** | $BBr_3$ | 1 equiv. | 1.1 equiv. | obs | obs | obs |
| **4** | $BBr_3$ | 1 equiv. | 2.0 equiv. | obs | obs | obs |
| **5** | $BBr_3$ | 0.2 equiv. | 2.0 equiv. | obs | obs | obs |

The research was focused on $BBr_3$ as well as I-*B*-9-BBN due to the achievement of the synthesis of amides. Both Lewis acids were tested under the same stepwise conditions with piperidine **2**, 1-butylamine **5** and N,4-dimethylaniline **7** and qualified by NMR and LC-MS **(Table 3.6)**. In both cases, the reactions performed with 1.1 equivalents of HBpin the amines were detected in the chromatogram as well as the amides from the first amidation reaction, being the peaks of the latter of equal or higher intensity. It is reasonable that both the amine and the amide were observed in the chromatogram since the minimum amount required of HBpin for the reduction is 2 equivalents, to form the methylene unit alpha to the nitrogen. The same behaviour was observed when 20 mol% of $BBr_3$ was used. For this reason, and for future reactions, the amount of HBpin was increased to 5 equivelants. Since successful results were obtained, both I-*B*-9-BBN and $BBr_3$ were reacted equimolarly with HBpin under identical

conditions. In both cases the reaction outcome was confirmed by analysis of the $^{11}B$ NMR spectrum **(Experimental Details, Figures 4.10 and 4.11)**, indicating the formation of new boron-containing species. These results suggest that HBpin could activate both I-*B*-9-BBN and $BBr_3$ to generate compounds competent in amide reduction. Further reactions and quantification of the products were studied only with $BBr_3$ due to more economical availability than I-*B*-9-BBN.

Due to importance of aryl amines,[21] further investigations were focused on improving the reaction conditions with *N*,4-dimethylaniline rather than exploring the substrate scope. **Table 3.7** illustrates the stepwise and one-pot reactions between ethyl 3-phenylpropanoate **1** and *N*,4-dimethylaniline **7**. The outcome of the reaction indicates the stepwise reaction is more selective towards C-O bond cleavage and obtention of an amine rather than an untargeted alcohol. However, from the perspective of operational simplicity and time efficiency, a one-pot synthesis would be more advantageous, as the stepwise approach requires twice the reaction time. A higher ratio of product amine **17** was achieved when using boron tribromide as a stoichiometric reagent, leading to less by-products and a total conversion of the starting material ester. Apart from the alcohol 3-phenylpropan-1-ol **18**, other by-products can be obtained **(Figure 3.2)** such the ester deoxygenation product, ether **20**, as well as a supposed borylated alcohol **19**, together with other minor products.

*Table 3.7 Outcome ratios of the reductive amination using $BBr_3$ and HBpin*




| Entry | $BBr_3$ | Amine 17 | Alcohol 18 | Borylated compound 19 | Ether 20 | UR SM 1 |
|---|---|---|---|---|---|---|
| **1a** | 1 equiv. | 83% | 0% | 4% | 0% | 0% |
| **1b** | 1 equiv. | 34% | 15% | 6% | 6% | 35% |
| **2a** | 50 mol% | 53% | 6% | 15% | 6% | 15% |
| **2b** | 50 mol% | 11% | 12% | 12% | 4% | 56% |

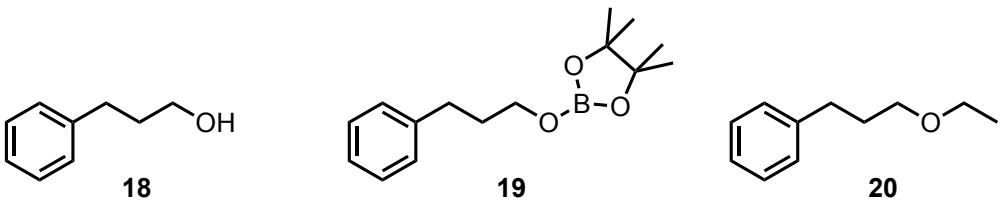
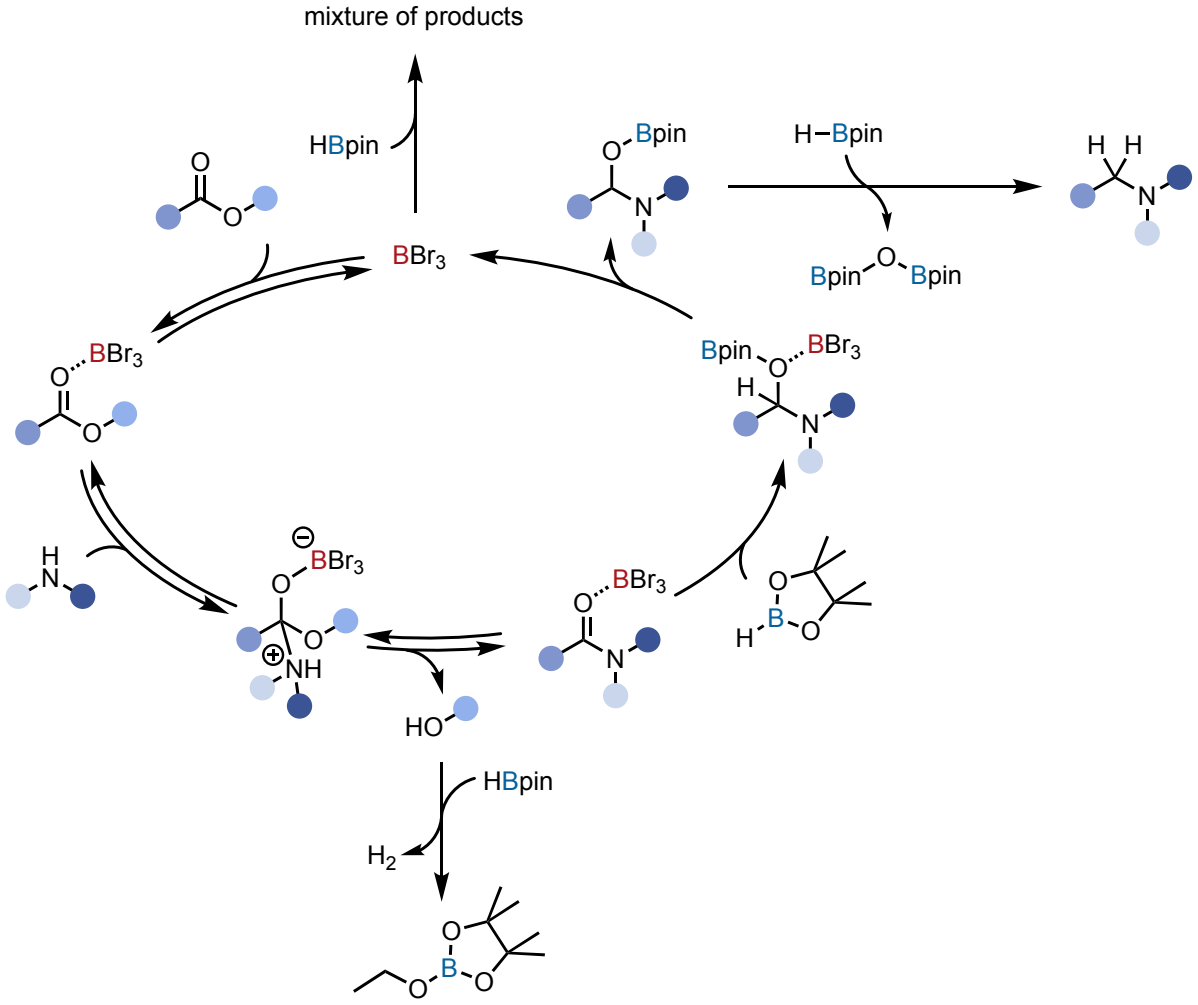


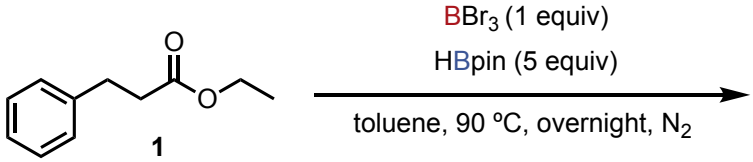

*Figure 3.2 Untargeted products of the reaction.*

These results demonstrate that the formation of an amide intermediate in a first step is crucial to suppress unwanted side reactions, thereby enhancing the yield of target amine. **Scheme 3.9** exemplifies the mechanism for the formation of the amine of the performed reaction.




*Scheme 3.9 Proposed mechanism for the formation of the amine in reductive amination of esters using $BBr_3$ and HBpin.*

Studies for the formation of by-products in the one-pot reaction were done reacting ester **1** in the same conditions and 1 equiv. of $BBr_3$ with no amine present **(Scheme 3.10)**. The reduced carbonyl produced several methylene units shown as a green circle in **Figure 3.3** corresponding to the reduction of the ester. NMR spectroscopy also demonstrated that the ester was reduced majorly to an alcohol, 3-phenylpropan-1-ol **18** together with the formation of many other by-products such 4,4,5,5-tetramethyl-2-(3-phenylpropoxy)-1,3,2-dioxaborolane **19** and (3-ethoxypropyl)benzene **20**. This supports the results in **Table 3.7** where the reaction is more efficient if performed stepwise.




*Scheme 3.10 Test reaction for the formation of by-products.*

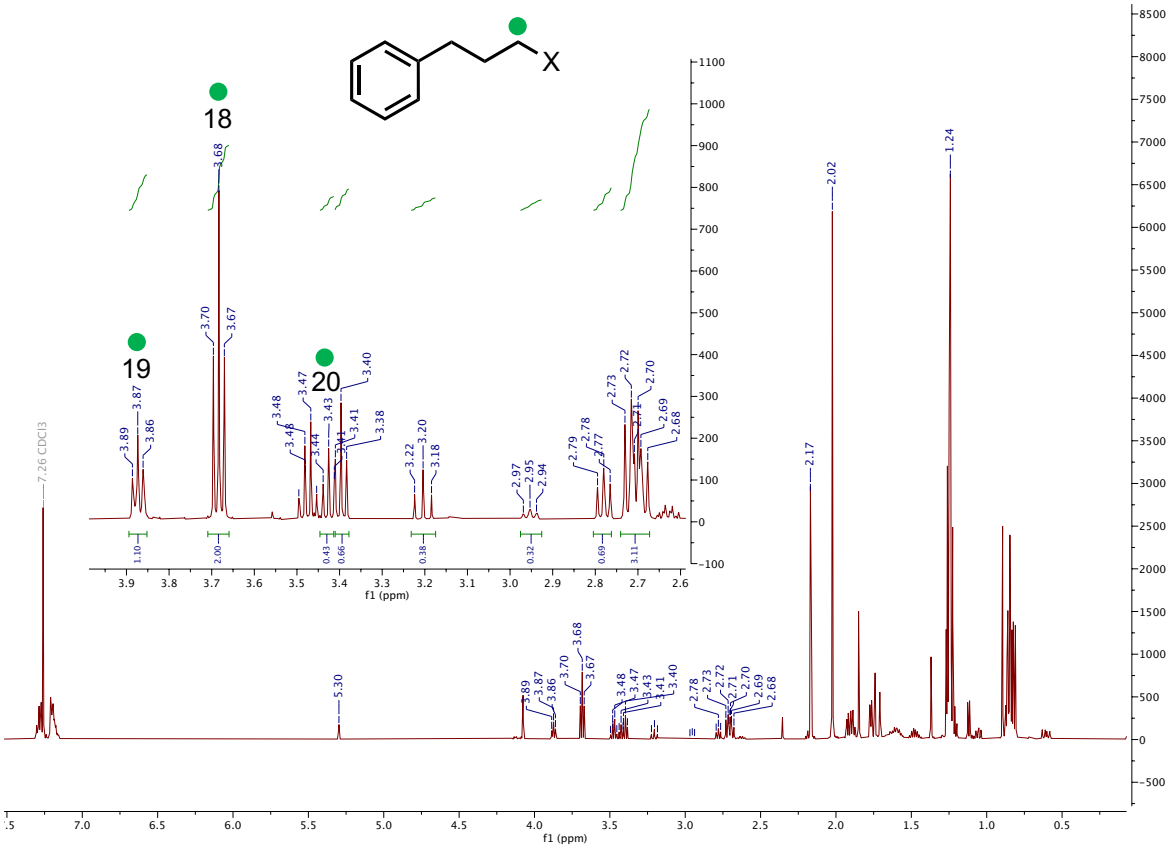
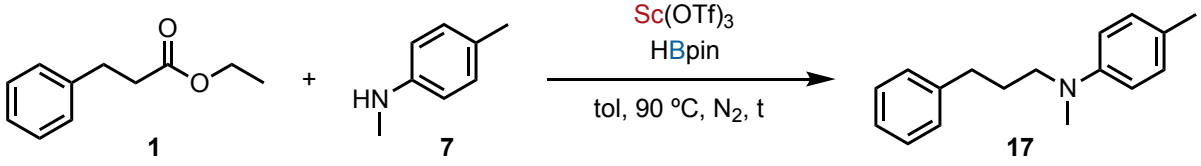



*Figure 3.3 $^1$H NMR (500 MHz, $CDCl_3$) spectrum of the reaction between ester 1, $BBr_3$ and HBpin. The chemical shift for compounds 18, 19 and 20 corresponds to the methylene unit alpha to the oxygen represented as a green circle.*

Scandium triflate is commonly used as a Lewis acid catalyst for several organic transformations such aldol additions of silyl enol ethers with aldehydes, known as the Mukaiyama aldol addition.[26] Therefore, it was decided to implement $Sc(OTf)_3$ as a LA for the reductive amination of esters. A one-pot reaction in **Table 3.8** was performed using scandium triflate and HBpin using two different reaction times. The stepwise reaction was also performed but as previously mentioned, $Sc(OTf)_3$ does not produce an amide using ethyl 3-phenylpropanoate **1** and *N*,4-dimethylaniline **7**, focusing on the one-pot reaction.

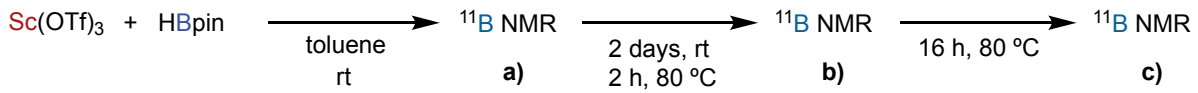
*Table 3.8 Outcome NMR yields of the reductive amination using $Sc(OTf)_3$ and using TMB as an internal standard.*




| Entry | $Sc(OTf)_3$ | time | Amine 17 | Alcohol 18 | Borylated compound 19 | Ether 20 | UR SM 1 |
|---|---|---|---|---|---|---|---|
| **1** | 1 equiv. | 16 h | 16% | 16% | 3.7% | trace | 54% |
| **2** | 2 equiv. | 16 h | 0% | 0% | 0% | 6% | 90% |
| **3** | 10 mol% | 16 h | 25% | 23% | 5% | 4% | 42% |
| **4** | 10 mol% | 3 days | 44% | 32% | 13% | 8% | 3% |

The results demonstrate that a sub-stoichiometric amount of scandium triflate was capable to reductively aminate an ester without an amide intermediate, suggesting that the reaction mechanism is significantly different from that uses $BBr_3$. As the reaction could not be performed stepwise, side-reactions must be avoided using a different approach. Superstoichiometric and stoichiometric amounts of $Sc(OTf)_3$ were less productive than 10 mol%. A violet solution was obtained when using one or two equivalents of $Sc(OTf)_3$ indicating an unconventional behaviour of scandium, because no d-d transitions can occur due to the lack of electrons in the d orbitals. Longer reaction times favoured the conversion of the starting materials mainly to *N*,4-dimethyl-*N*-(3-phenylpropyl)aniline **17** and 3-phenylpropan-1-ol **18**.

A study of the mechanism was approached by reacting $Sc(OTf)_3$ and HBpin in toluene at different temperatures in NMR tubes to check the progress of the reaction **(Scheme 3.11)**. First the reaction was analysed at room temperature, then after 2 days and 2h at 80 °C, and finally after 16 hours at 80 °C. A control reaction was run in parallel in the NMR with only HBpin in toluene. **Figure 3.4** shows the NMRs of the reactions.




*Scheme 3.11 Study of the reaction between $Sc(OTf)_3$ and HBpin in toluene at different temperatures and over time.*

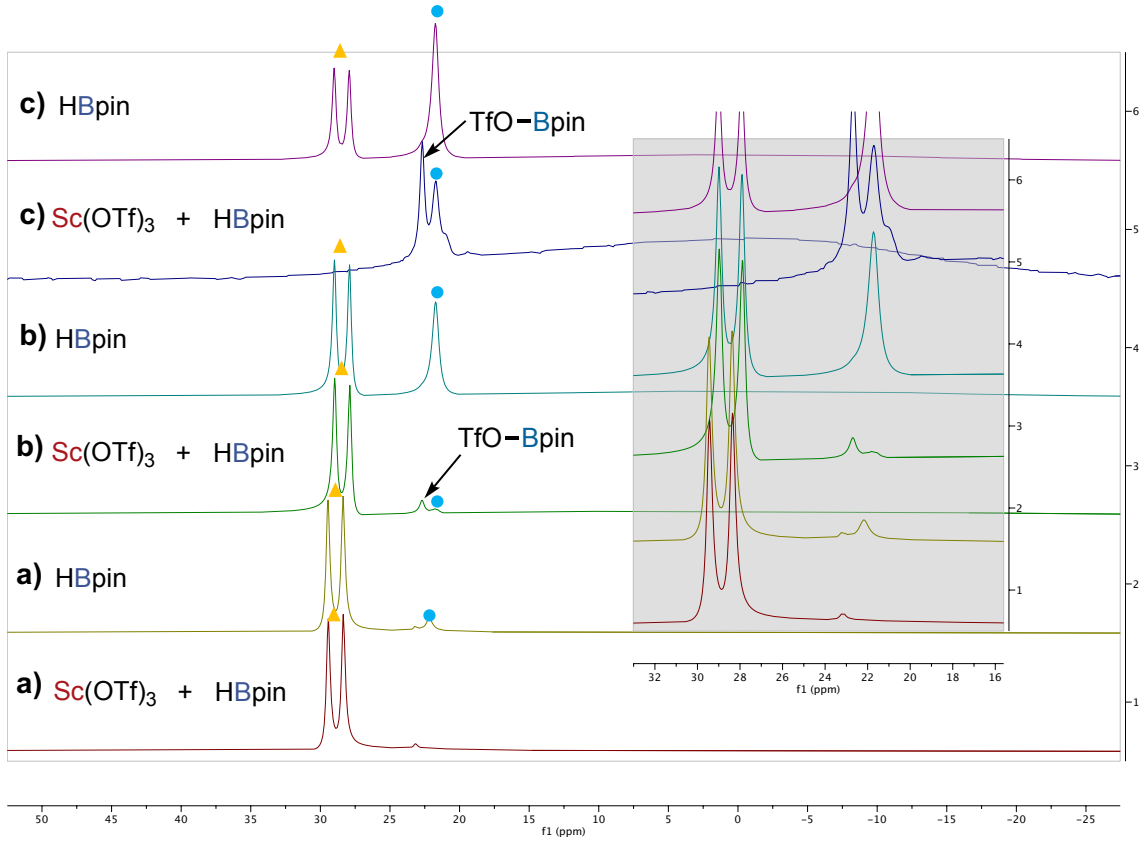



*Figure 3.4 $^{11}B$ NMR spectrum of the reaction between $Sc(OTf)_3$ and HBpin and control reaction with HBpin in toluene at different temperatures and over time: a) rt, b) 2 days at rt and 2 h at 80 °C, c) 16 h at 80 °C.*

The only observable change was when performing the NMR analysis of the reaction. Therefore, results were inconclusive, and further investigations must be done to prove the existence of a scandium hydride and a TfOBpin species. TfOBpin is reported to have a chemical shift of 21.77 ppm in $^{11}B$ NMR,[27] which may correspond to the indicated peaks in **Figure 3.4**. In any case, this species may not be the responsible for amination but for untargeted reactivity. An up-field change in the HBpin doublet **(yellow triangle, Figure 3.4)** chemical shift was observed, as well as decomposition of HBpin into $B_2pin_3$ **(blue circle, Figure 3.4)** at room temperature when using $Sc(OTf)_3$.

A study regarding the reduction of amide **12 (Table 3.9)** was conducted to explore if scandium triflate was a suitable Lewis acid for the transformation. The amide was mixed with the LA and HBpin in toluene at 90 °C under nitrogen for 16 hours. The outcome of the reaction was *N*,4-dimethyl-*N*-(3-phenylpropyl)aniline **17**, 3-phenylpropan-1-ol **18** and 4,4,5,5-tetramethyl-2-(3-phenylpropoxy)-1,3,2-dioxaborolane **19** in the case of sub-stoichiometric $Sc(OTf)_3$ whereas using stoichiometric scandium triflate, no amine was observed. In both cases the conversion of amide was low. This supports the idea that scandium triflate differs to $BBr_3$ in the reaction mechanism but, in case an amide was formed in the reaction, sub-stoichiometric $Sc(OTf)_3$ and HBpin would be able to reduce it to an amine with low formation of by-products. As a general trend, in most of the reactions, no dehydrocoupling[28] between an amine and HBpin, forming a B-N bond, was observed either using $BBr_3$ or $Sc(OTf)_3$.

*Table 3.9 Outcome ratios for the reduction of N-methyl-3-phenyl-N-(p-tolyl)propanamide using $Sc(OTf)_3$ and HBpin.*


| Entry | $Sc(OTf)_3$ | Amine 17 | Alcohol 18 | Borylated compound 19 | UR SM 12 |
|---|---|---|---|---|---|
| **1** | 1 equiv. | 0% | 0% | 0% | 82% |
| **2** | 10 mol% | 16% | 2% | 2% | 80% |

Both the use of $BBr_3$ and $Sc(OTf)_3$ have demonstrated capability of being applied for reductive amination of esters **(Table 3.10)**. The advantages of using $BBr_3$ is that, when used stoichiometrically, it can afford an amine up to an 83%, nearly as twice as using $Sc(OTf)_3$ as well as the ability to form amides when used without HBpin. On the other hand, scandium triflate is easy to handle, non-toxic and can as well afford the amine. The fact that it can be used in a lower amount counters the cost of the reagent.

*Table 3.10 Comparison between $BBr_3$ and $Sc(OTf)_3$ for the reductive amination of esters.*

| | **$BBr_3$** | **$Sc(OTf)_3$** |
|---|---|---|
| **Amidation of esters** | yes | no |
| **Reductive amination of esters** | yes | yes |
| **Toxicity** | high | none |
| **Lowest amount tested** | 50 mol% | 10 mol% |
| **Yield*** | 83% | 44% |
| **Lewis acidity** | high[20] | moderate[29] |
| **Air/moisture sensitivity** | yes | no |
| **Handling requirements** | glovebox or Schlenk | benchtop |
| **Cost** | low | high |

*Under best conditions

# 4 Experimental Details

## 4.1 General Experimental Information

### 4.1.1 Reagents

All reagents were purchased from Sigma Aldrich, Acros Organics, FluoroChem, Fischer Scientific UK or Alfa Aesar, or were synthesised in the laboratory according to literature preparations.

All the compounds used were handled using the appropriate personal protective equipment (PPE), safety spectacles, laboratory coat and nitrile gloves.

- **Ethyl 3-phenylpropanoate** (not a hazardous substance).
- **Piperidine** (flammable liquid, acute toxicity if swallowed, inhaled or in contact with skin; skin corrosion and serious eye damage).
- **4-(Trifluormethyl)aniline** (acute toxicity if swallowed, serious eye damage, short-term and long-term aquatic hazard).
- **4-Methyl-*N*-(4-methylphenyl)aniline** (causes skin irritation, causes serious eye irritation and may cause respiratory irritation).
- **1-Butylamine** (flammable liquid, corrosive to metals, acute toxicity if swallowed, inhaled or in contact with skin; skin corrosion, serious eye damage and specific target organ toxicity – single exposure, respiratory system).
- ***tert*-Butylamine** (flammable liquid, acute toxicity if swallowed or inhaled; skin corrosion, serious eye damage and long-term aquatic hazard).
- ***N*,4-Dimethylaniline** (acute toxicity if swallowed, inhaled or in contact with skin and specific target organ toxicity – repeated exposure and long-term aquatic hazard)
- **Boron tribromide (99%)** (acute toxicity, skin corrosion and serious eye damage).
- **Boron tribromide (1.0 M in heptane)** (flammable liquid, acute toxicity if swallowed or inhaled; skin corrosion, serious eye damage, specific target organ toxicity – single exposure, central nervous system, aspiration hazard, short-term and long-term aquatic hazard).
- **Scandium triflate (99%)** (not a hazardous substance).
- **I-*B*-9-BBN (1.0 M in hexanes)** (flammable liquid, skin irritation, reproductive toxicity, specific target organ toxicity – single exposure, central nervous system, specific target organ toxicity – repeated exposure, nervous system, aspiration hazard and long-term aquatic hazard).

All reagents synthetised from hazardous compounds were considered and handled as toxic.

### 4.1.2 Reaction Setup

All reactions were carried out in oven dried glassware (185 °C), which has been cleansed using base ($KOH/^{i}PrOH$) and acid ($H_2O/HNO_3$) baths. All air- and moisture-sensitive manipulations were carried out in either an inert atmosphere glovebox (Ar) or on a Schlenk line ($N_2$). Room temperature was

approximated to be 20 °C. All amidation, reductive amination and test reactions were carried out in round bottom screw thread vials (13 x 100 mm) sealed with a 13 mm vial screw thread cap in an aluminium heating block with holes drilled to fit the vials for a consistent temperature. A large-scale amidation reaction was carried out in a 100 mL three-neck round bottomed flask in an aluminium heating block.

### 4.1.3 NMR Spectroscopy

$^{1}H$, $^{13}C\{^{1}H\}$, and $^{11}B$ NMR spectra were conducted in Bruker AVA 400, 500, and 600 MHz, and Bruker PRO 500 MHz spectrometers. Chemical shifts were recorded in parts per million (ppm). Spectra were referenced to residual (proteo)solvent peaks; for $^{1}H$ spectra ($CHCl_3$: 7.26 ppm; $C_6D_5H$: 7.16 ppm) and deuterated solvent peaks for $^{13}C$ spectra ($CDCl_3$: 77.16 ppm; $C_6D_6$: 128.26 ppm) and $^{11}B$ NMR spectra were referenced to external $BF_3{\cdot}OEt_2$ (0.00 ppm). Integrations, assignments and coupling constants are given and multiplicities are specified by singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br).

### 4.1.4 Mass Spectrometry

High-resolution electrospray ionization time-of-flight mass spectrometry (ESI-TOF MS) was performed on an Agilent G1969A API-TOF instrument operating in positive ion mode. Samples were analysed via direct infusion at a flow rate of 0.05 mL/min. The instrument was operated under the following conditions: capillary voltage of –4.0 kV, fragmentor voltage of 150 V, nebulizer gas pressure of 20 psig, drying gas flow of 6 L/min at 300 °C, and flight tube voltage of –6.5 kV. Data were acquired across an m/z range of 50–3200 with 10,000 transients per spectrum. Mass calibration was performed using the Agilent API-TOF Reference Mass Solution Kit (Part No. G1969-85001), composed of two 2.2 mL ampoules each of the following compounds dissolved in 95:5 $CH_3CN$:DI $H_2O$. Hexakis(1H,1H,3H-tetrafluoropropoxy)phosphazine (2.5 mM, m/z 922.0098), Purine (5.0 mM, m/z 121.0509), and Ammonium trifluoroacetate (100.0 mM, m/z 112.9856). Samples were prepared using 10 $\mu$L and dissolving them in 1 mL 1:1 $CH_3CN$:DI $H_2O$ and filtered with 0.22 $\mu$m pore size.

### 4.1.5 Solvents

All solvents for air- and moisture-sensitive techniques were obtained from an anhydrous solvent system (Innovative Technology). Toluene (ACS grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant (supported copper catalyst for scavenging oxygen) under a positive pressure of argon. Deuterated chloroform, $CDCl_3$, (Sigma Aldrich) was dried over molecular sieves. Dichloromethane, $CH_2Cl_2$, (Sigma Aldrich) was used as received.

- **Toluene** (highly flammable liquid and vapor, may be fatal if swallowed and enters airways, causes skin irritation and serious eye irritation; may cause drowsiness or dizziness, suspected

of damaging the unborn child and may cause damage to organs through prolonged or repeated exposure).

- **Dichloromethane** (skin irritation, eye irritation, carcinogenicity and specific target organ toxicity – single exposure, central nervous system).

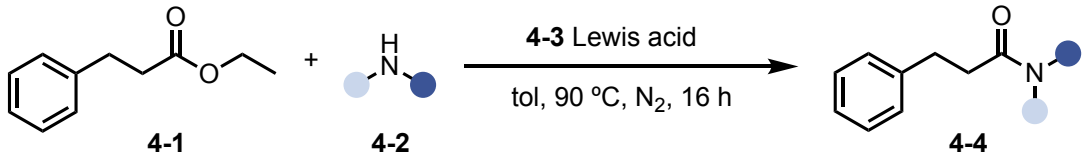
### 4.1.6 Column Chromatography

Flash Column Chromatography was run on a Teledyne Isco Combiflash NextGen 300+ machine on silica gel (Gerudan Si60). Thin layer chromatography was conducted on aluminium back silica TLC plated (Silica Gel 60 F254). $KMnO_4$ was used as a stain when necessary to elucidate an amide or amine structure.

## 4.2 Lewis-acid-assisted direct amidation of esters

### 4.2.1 Lewis Acid Screening

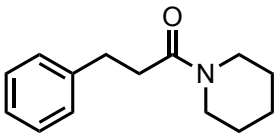
General Procedure A




*Scheme 4.1 Amine screening for Lewis-acid-assisted direct amidation.*

In a catalytic vial, **4-3** (0.10 mmol, 1.0 equiv.), ethyl 3-phenylpropanoate (17.6 $\mu$L, 0.10 mmol, 1.0 equiv.) and **4-2** (0.10 mmol, 1.0 equiv.) were added respectively in anhydrous toluene (0.5 M, 0.2 mL) under nitrogen inert atmosphere. The reaction was heated up to 90 °C and stirred at 600 rpm for 16 hours; and analysed by LC-MS.

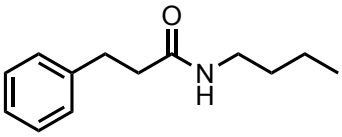
3-Phenyl-1-(piperidin-1-yl)propan-1-one **4-4a**



According to general procedure A, ethyl 3-phenylpropanoate (17.6 $\mu$L, 0.10 mmol), piperidine (9.88 $\mu$L, 0.10 mmol) and LA (0.10 mmol) were reacted. Once the reaction was done, a 10 $\mu$L aliquot was extracted and dissolved in a 1 mL 1:1 $CH_3CN$:DI $H_2O$ solution. Then the solution was filtered with a micropore filter of 0.22 $\mu$m. The reaction was analysed by LC-MS.

**HRMS** (ESI) for $C_{14}H_{20}NO^+$ $[M+H]^+$, (m/z) – calculated: 218.154; found: 218.159

*N*-Butyl-3-phenylpropanamide **4-4b**

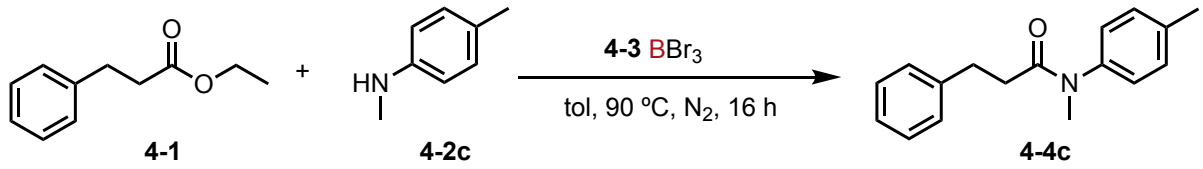


According to general procedure A, ethyl 3-phenylpropanoate (17.6 $\mu$L, 0.10 mmol), 1-butylamine (9.92 $\mu$L, 0.10 mmol) and LA (0.10 mmol) were reacted. Once the reaction was done, a 10 $\mu$L aliquot was extracted and dissolved in a 1 mL 1:1 $CH_3CN$:DI $H_2O$ solution. Then the solution was filtered with a micropore filter of 0.22 $\mu$m. The reaction was analysed by LC-MS.

**HRMS** (ESI) for $C_{13}H_{20}NO^+$ $[M+H]^+$, (m/z) – calculated: 206.154; found: 206.157

### 4.2.2 Synthesis of *N*-methyl-3-phenyl-*N*-(*p*-tolyl)propenamide

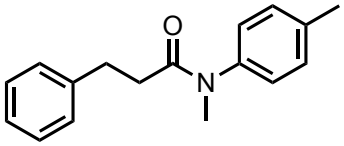
Procedure B




*Scheme 4.2 $BBr_3$-assisted direct amidation.*

In a catalytic vial, $BBr_3$ 1.0 M solution in heptane (2.0 mL, 2 mmol, 1.0 equiv.), ethyl 3-phenylpropanoate (0.35 mL, 2 mmol, 1.0 equiv.) and *N*,4-dimethylaniline (0.25 mL, 2 mmol, 1.0 equiv.) were added respectively in anhydrous toluene (0.5 M, 4 mL) under nitrogen inert atmosphere. The reaction was heated up to 90 °C and stirred at 600 rpm for 16 hours. After completion, a saturated solution of $NaHCO_3$ (10 mL) was added slowly to quench the reaction. Once no more bubbles were seen, a pipette of saturated $NaHCO_3$ was added to assure the reaction was quenched. The product was washed with $CH_2Cl_2$ (3 × 10 mL). The organic layer was collected, dried with anhydrous $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash column chromatography ($SiO_2$).

*N*-Methyl-3-phenyl-*N*-(*p*-tolyl)propenamide **4-4c**




According to procedure B, ethyl 3-phenylpropanoate (0.353 mL, 2 mmol), *N*,4-dimethylaniline (0.253 mL, 2 mmol) and $BBr_3$ 1.0 M solution in heptane (2 mL, 2 mmol) were reacted. The product was purified by flash column chromatography (80 g $SiO_2$, 50 mm Ø, hexane/ethyl acetate 4:1) to give *N*-methyl-3-phenyl-*N*-(*p*-tolyl)propanamide, **4-4c**, (0.304 g, 1.2 mmol, 60%) as a yellow oil.

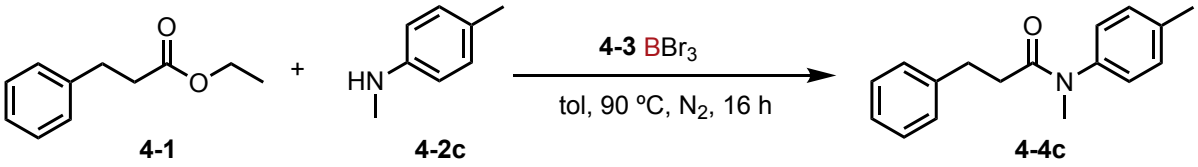
**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 7.24-7.21 (m, 2H), 7.17-7.14 (m, 3H), 7.07-7.06 (m, 2H), 6.91-6.90 (m, 2H), 3.23 (s, 3H), 2.90 (t, $J$ = 7.9 Hz, 1H), 2.37-2.35 (m, 5H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$): $\delta$ 172.48, 141.58, 141.52, 137.80, 130.46, 128.59, 128.46 127.17, 126.11, 37.51, 36.07, 31.91, 21.19.

**HRMS** (ESI) for $C_{17}H_{20}NO^+$ $[M+H]^+$, (m/z) – calculated: 254.154; found: 254.154

Data were in accordance with those previously reported.[30]

### 4.2.3 Large-Scale Synthesis of Amides




*Scheme 4.3 Large-scale synthesis of N-methyl-3-phenyl-N-(p-tolyl)propenamide.*

Procedure C

In a 100 mL three-neck round bottomed flask, neat $BBr_3$ (1.93 mL, 20.0 mmol, 1 equiv.), **4-1** (3.53 mL, 20.0 mmol, 1 equiv.) and **4-2c** (2.53 mL, 20.0 mmol, 1 equiv.) were added respectively in anhydrous toluene (0.5 M, 40 mL) under nitrogen inert atmosphere. The reaction was heated up to 90 °C and stirred at 600 rpm for 16 hours. After completion, the reaction mixture was allowed to warm to room temperature over 1 hour. A saturated solution of $NaHCO_3$ (25 mL) was added slowly to quench the reaction under inert atmosphere. Once no more bubbles were seen, saturated $NaHCO_3$ (1 mL) was added to assure the reaction was quenched. The product was washed with $CH_2Cl_2$ (3 × 25 mL). The organic layer was collected, dried with anhydrous $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash column chromatography ($SiO_2$).

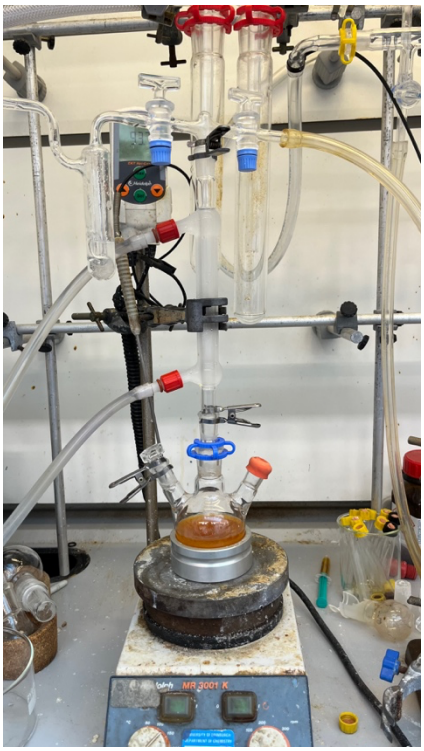
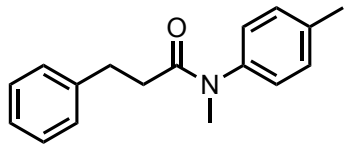


*Figure 4.1 Set-up for the scale-up reaction for the direct amidation of esters using $BBr_3$*

*N*-Methyl-3-phenyl-*N*-(*p*-tolyl)propenamide **4-4c**



According to procedure C, ethyl 3-phenylpropanoate (3.53 mL, 20.0 mmol), *N*,4-dimethylaniline (2.53 mL, 20.0 mmol), $BBr_3$ (1.93 mL, 20.0 mmol) were reacted. The product was purified by flash column chromatography (80 g $SiO_2$, 50 mm Ø, hexane/ethyl acetate 4:1) to give *N*-methyl-3-phenyl-*N*-(*p*-tolyl)propanamide, **4-4c**, (3.04 g, 12.01 mmol, 60%) as a yellow oil.

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 7.24-7.21 (m, 2H), 7.17-7.14 (m, 3H), 7.07-7.06 (m, 2H), 6.91-6.90 (m, 2H), 3.23 (s, 3H), 2.90 (t, $J$ = 7.9 Hz, 2H), 2.37-2.35 (m, 5H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$): $\delta$ 172.48, 141.58, 141.52, 137.80, 130.46, 128.59, 128.46 127.17, 126.11, 37.51, 36.07, 31.91, 21.19.

**HRMS** (ESI) for $C_{17}H_{20}NO^+$ $[M+H]^+$, (m/z) – calculated: 254.154; found: 254.154

Data were in accordance with those previously reported.[30]

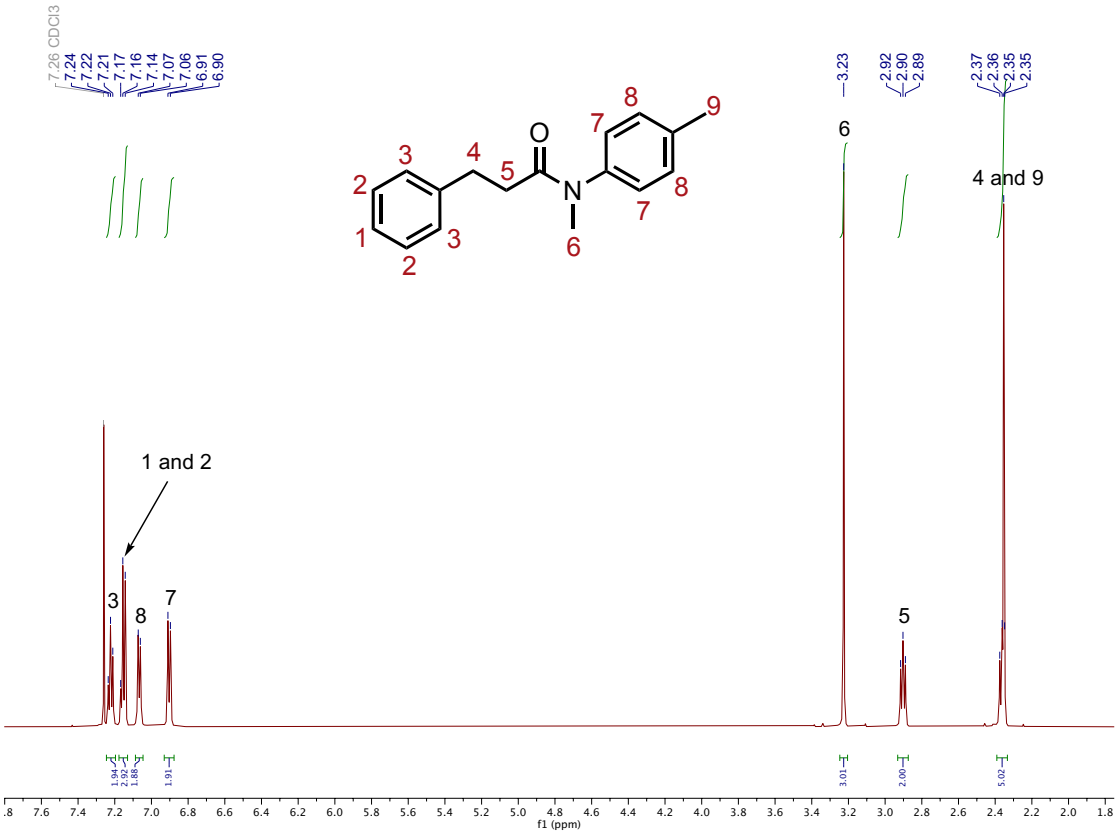



*Figure 4.2 $^1$H NMR (500 MHz, $CDCl_3$) spectrum of N-methyl-3-phenyl-N-(p-tolyl)propenamide*

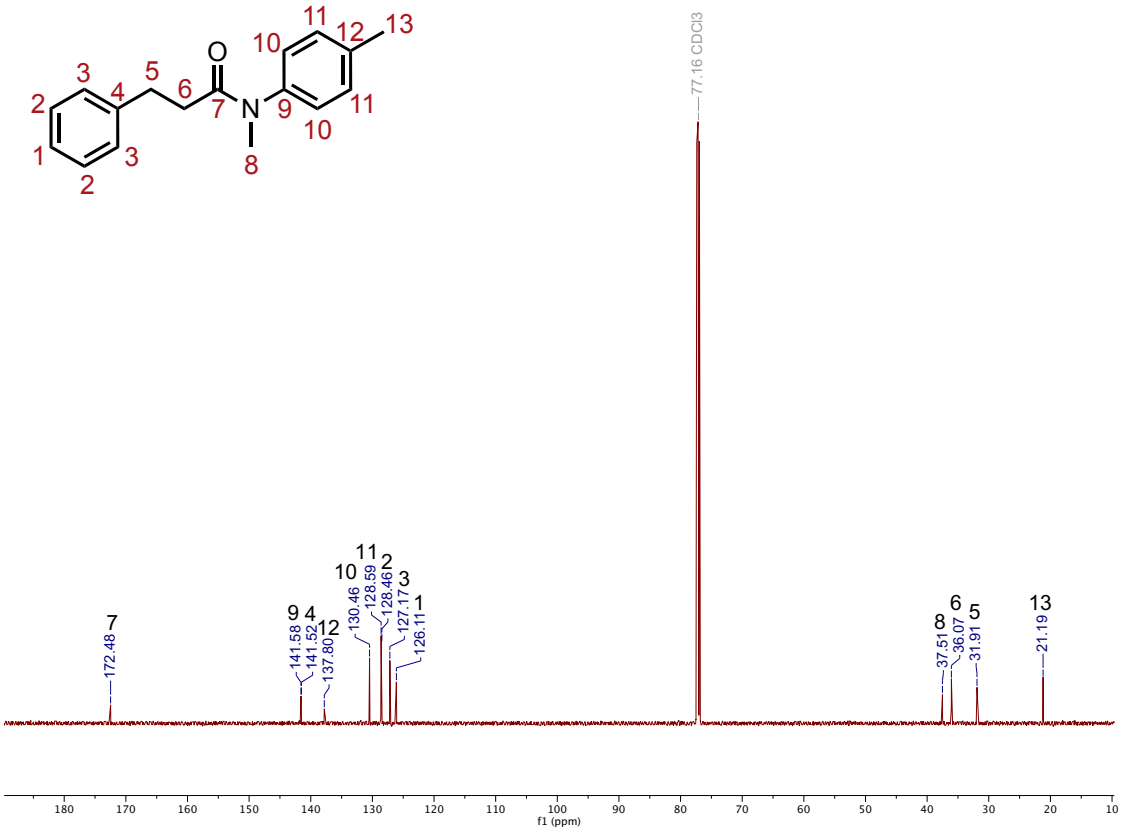
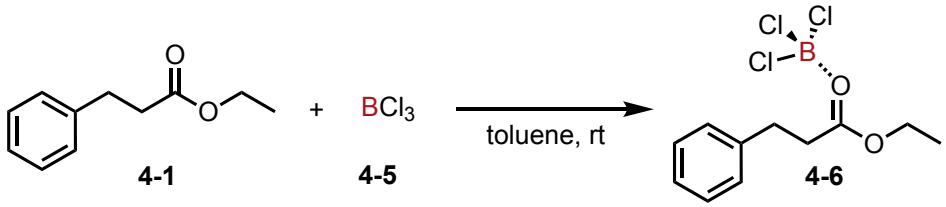
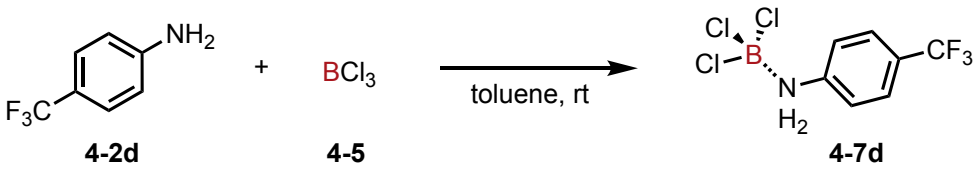



*Figure 4.3 $^{13}C$ NMR (126 MHz, $CDCl_3$) spectrum of N-methyl-3-phenyl-N-(p-tolyl)propenamide*

### 4.2.4 Lewis Acid – Lewis Base Reactivity




*Scheme 4.4 Adduct formation between ethyl 3-phenylpropanoate and $BCl_3$*




*Scheme 4.5 Adduct formation between 4-(trifluoromethyl)aniline and $BCl_3$*

In a catalytic vial, **4-1** (17.6 $\mu$L, 0.10 mmol, 1 equiv.) and **4-5** 1.0 M in heptane (0.1 mL, 0.1 mmol, 1 equiv.), were added respectively in anhydrous toluene (0.4 mL) under nitrogen inert atmosphere. In a second catalytic vial, **4-2d** (16.1 mg, 1 mmol, 1 equiv.) and **4-5** 1.0 M in heptane (0.1 mL, 0.1 mmol, 1 equiv.), were added respectively in anhydrous toluene (0.4 mL) under nitrogen inert atmosphere. The reactions were analysed by $^{1}H$ and $^{11}B$ NMR.

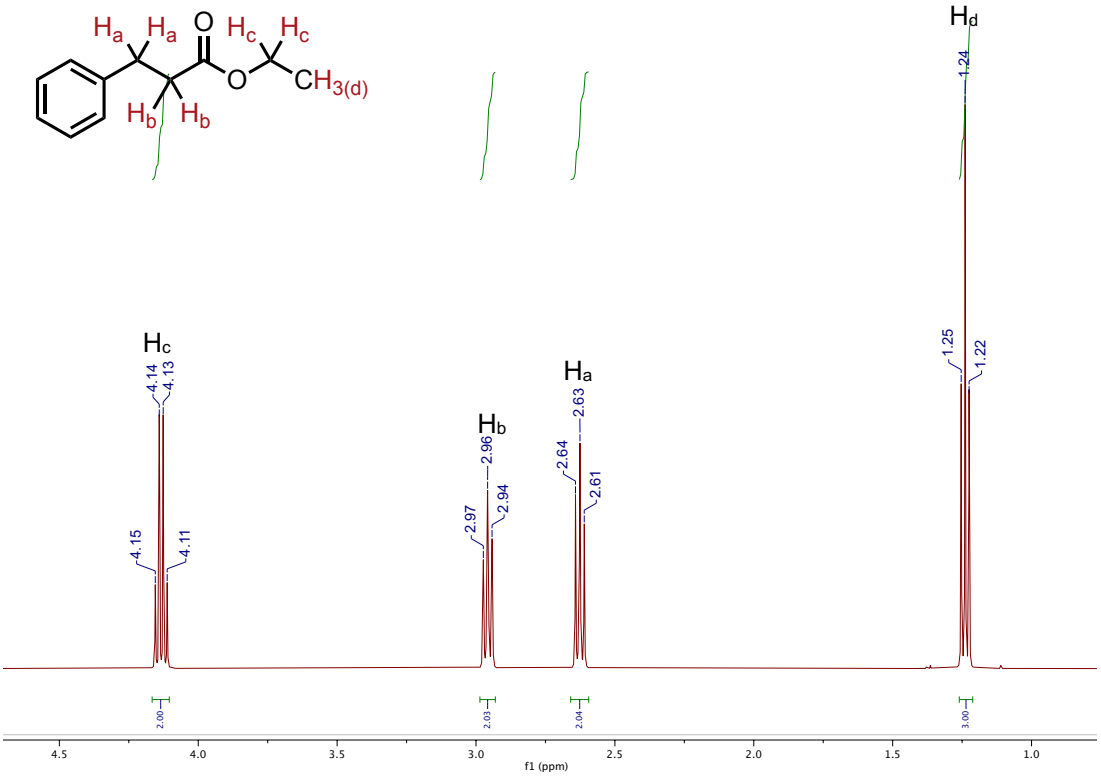



*Figure 4.4 $^{1}H$ NMR (500 MHz, $CDCl_3$) of ethyl 3-phenylpropanoate*

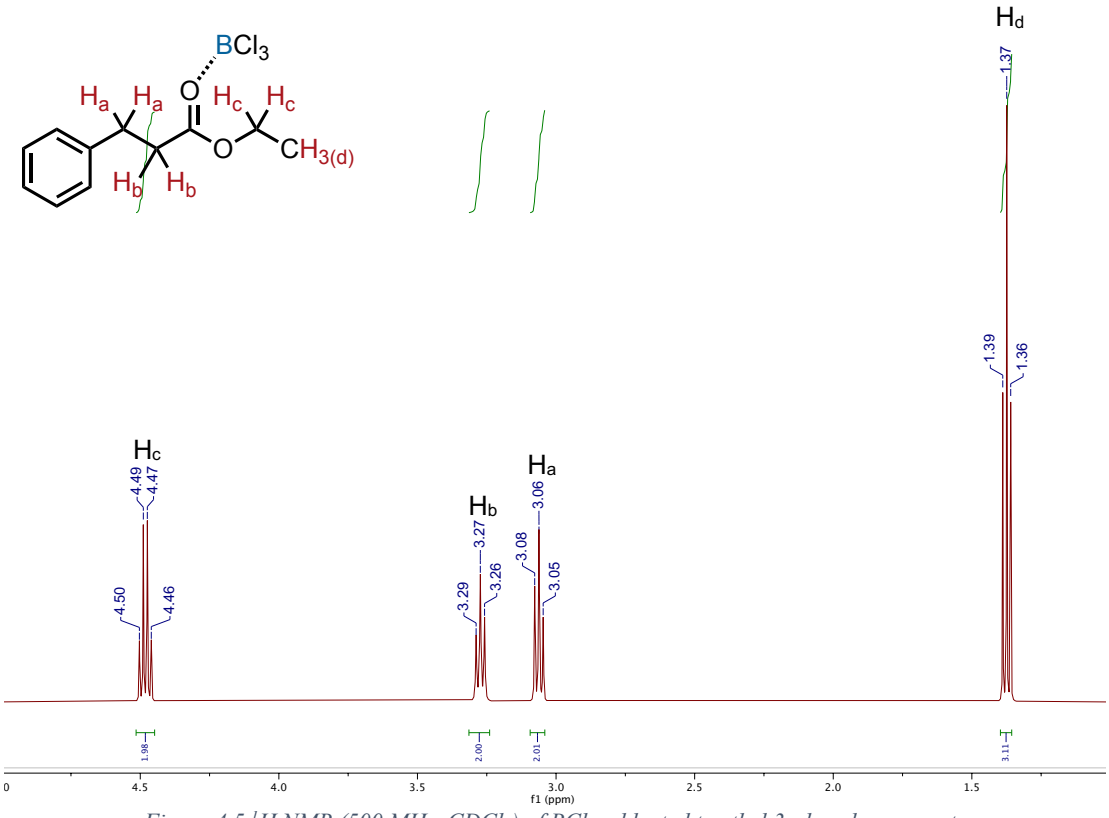



*Figure 4.5 $^{1}H$ NMR (500 MHz, $CDCl_3$) of $BCl_3$ adducted to ethyl 3-phenylpropanoate*

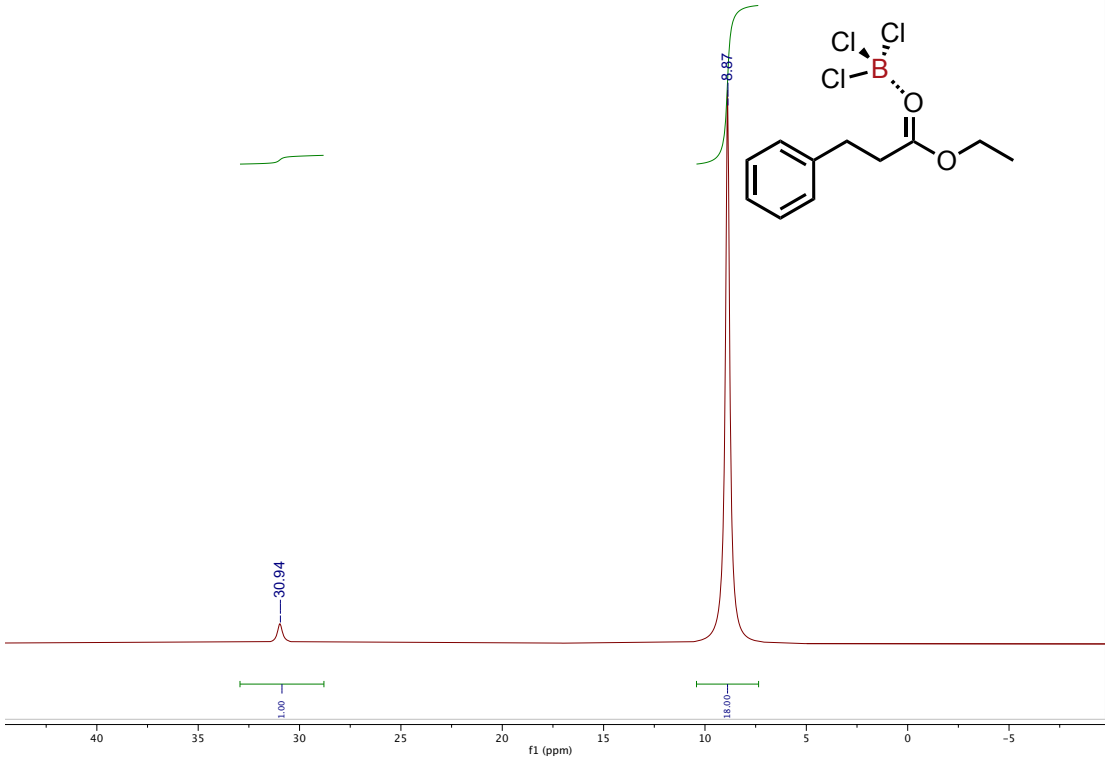



*Figure 4.6 $^{11}B$ NMR (128 MHz, $CDCl_3$) of $BCl_3$ adducted to ethyl 3-phenylpropanoate.*

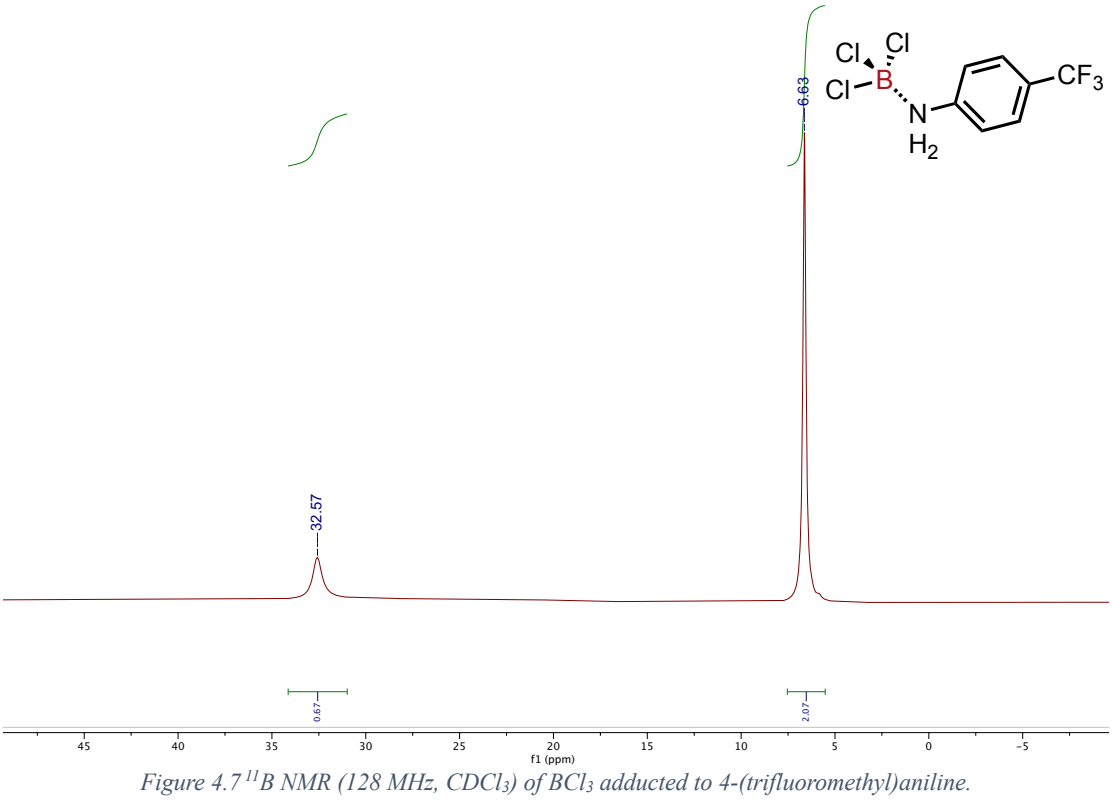
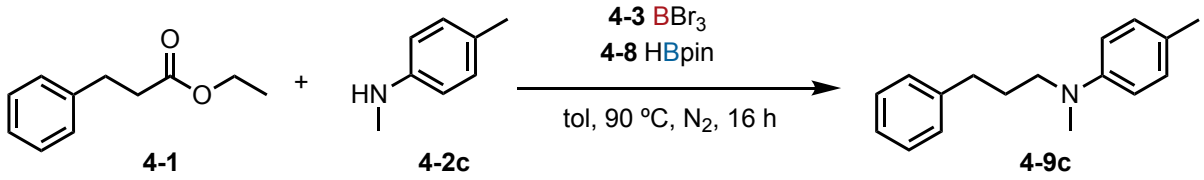



*Figure 4.7 $^{11}B$ NMR (128 MHz, $CDCl_3$) of $BCl_3$ adducted to 4-(trifluoromethyl)aniline.*

## 4.3 Reductive amination of esters

### 4.3.1 One-Pot Synthesis of Amines using $BBr_3$

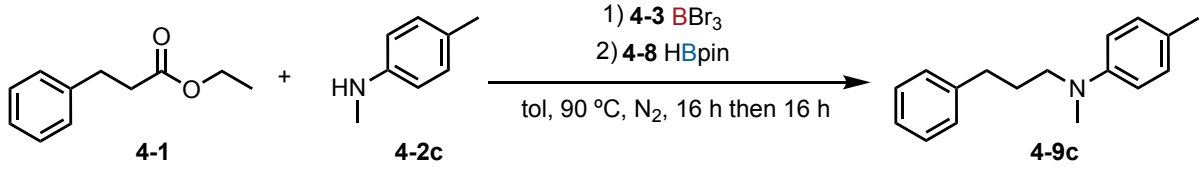



*Scheme 4.6 One-pot synthesis of N,4-dimethyl-N-(3-phenylpropyl)aniline using $BBr_3$*

Procedure D

In a catalytic vial, $BBr_3$ 1.0 M solution in heptane (2 mL, 2 mmol, 1.0 equiv.), **4-1** (0.35 mL, 2 mmol, 1.0 equiv.), **4-2c** (0.25 mL, 0.1 mmol, 1.0 equiv.) and **4-8** (1.45 mL, 10 mmol, 5 equiv.) were added respectively in anhydrous toluene (0.5 M, 1 mL) under nitrogen inert atmosphere. The reaction was heated up to 90 °C and stirred at 600 rpm for 16 hours. After completion, a saturated solution of $NaHCO_3$ (10 mL) was added slowly to quench the reaction. Once no more bubbles were seen, a pipette of saturated $NaHCO_3$ was added to assure the reaction was quenched. The product was washed with $CH_2Cl_2$ (3 × 10 mL). The organic layer was collected, dried with anhydrous $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash column chromatography ($SiO_2$).

### 4.3.2 Stepwise Synthesis of Amines using $BBr_3$

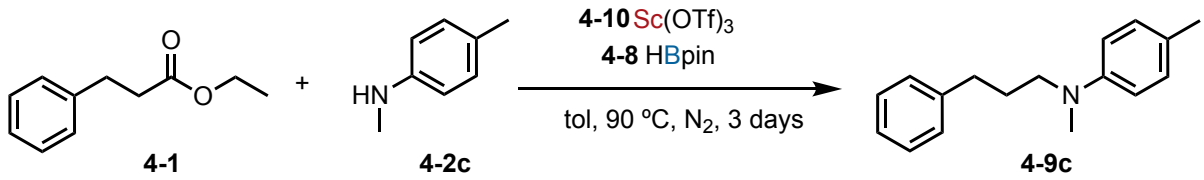



*Scheme 4.7 Stepwise synthesis of N,4-dimethyl-N-(3-phenylpropyl)aniline using $BBr_3$*

Procedure E

In a catalytic vial, $BBr_3$ 1.0 M solution in toluene (2 mL, 2 mmol, 1.0 equiv.), **4-1** (0.35 mL, 2 mmol, 1.0 equiv.), **4-2c** (0.25 mL, 0.1 mmol, 1.0 equiv.) were added respectively in anhydrous toluene (0.5 M, 1 mL) under nitrogen inert atmosphere. After 16 hours, **4-8** (1.45 mL, 10 mmol, 5 equiv.) was added under inert nitrogen atmosphere. The reaction was heated up to 90 °C and stirred at 600 rpm for 16 hours. After completion, a saturated solution of $NaHCO_3$ (10 mL) was added slowly to quench the reaction. Once no more bubbles were seen, a pipette of saturated $NaHCO_3$ was added to assure the reaction was quenched. The product was washed with $CH_2Cl_2$ (3 × 10 mL). The organic layer was collected, dried with anhydrous $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash column chromatography ($SiO_2$).

### 4.3.3 One-Pot Synthesis of Amines using $Sc(OTf)_3$

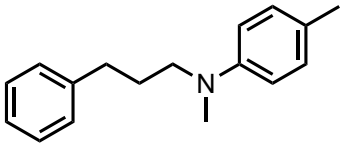



*Scheme 4.8 One-pot synthesis of N,4-dimethyl-N-(3-phenylpropyl)aniline using $Sc(OTf)_3$*

Procedure F

In a catalytic vial, $Sc(OTf)_3$ (24.6 mg 0.05 mmol, 0.1 equiv.), **4-1** (88.2 $\mu$L, 0.5 mmol, 1.0 equiv.), **4-2** (63.2 $\mu$L, 0.1 mmol, 1.0 equiv.) and **4-8** (0.363 mL, 2.5 mmol, 5 equiv.) were added respectively in anhydrous toluene (0.5 M, 1 mL) under nitrogen inert atmosphere. The reaction was heated up to 90 °C and stirred at 600 rpm for 16 hours. After completion, a saturated solution of $NaHCO_3$ (10 mL) was added slowly to quench the reaction. Once no more bubbles were seen, a pipette of saturated $NaHCO_3$ was added to assure the reaction was quenched. The product was washed with $CH_2Cl_2$ (3 × 10 mL). The organic layer was collected, dried with anhydrous $MgSO_4$ and the solvent was evaporated.

*N*,4-Dimethyl-*N*-(3-phenylpropyl)aniline **4-9c**



According to procedure E, ethyl 3-phenylpropanoate (88.2 $\mu$L, 0.5 mmol), *N*,4-dimethylaniline (63.2 $\mu$L, 0.1 mmol), $Sc(OTf)_3$ (24.6 mg , 0.5 mmol) and HBpin (0.363 mL, 2.5 mmol) were reacted. The workup of the reaction was performed and the crude analysed by NMR and LC-MS.

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 7.30-7.27 (m, 2H), 7.21-7.18 (m, 3H), 7.03-7.02 (m, 2H), 6.61-6.60 (m, 2H), 3.31 (t, $J$ = 7.4 Hz, 2H), 2.89 (s, 3H), 2.65 (t, $J$ = 7.8 Hz, 2H), 2.25 (s, 3H), 1.93-1.87 (m, 2H).

**HRMS** (ESI) for $C_{17}H_{22}N^+$ $[M+H]^+$, (m/z) – calculated: 240.175; found: 240.176

Data were in accordance with those previously reported.[31]

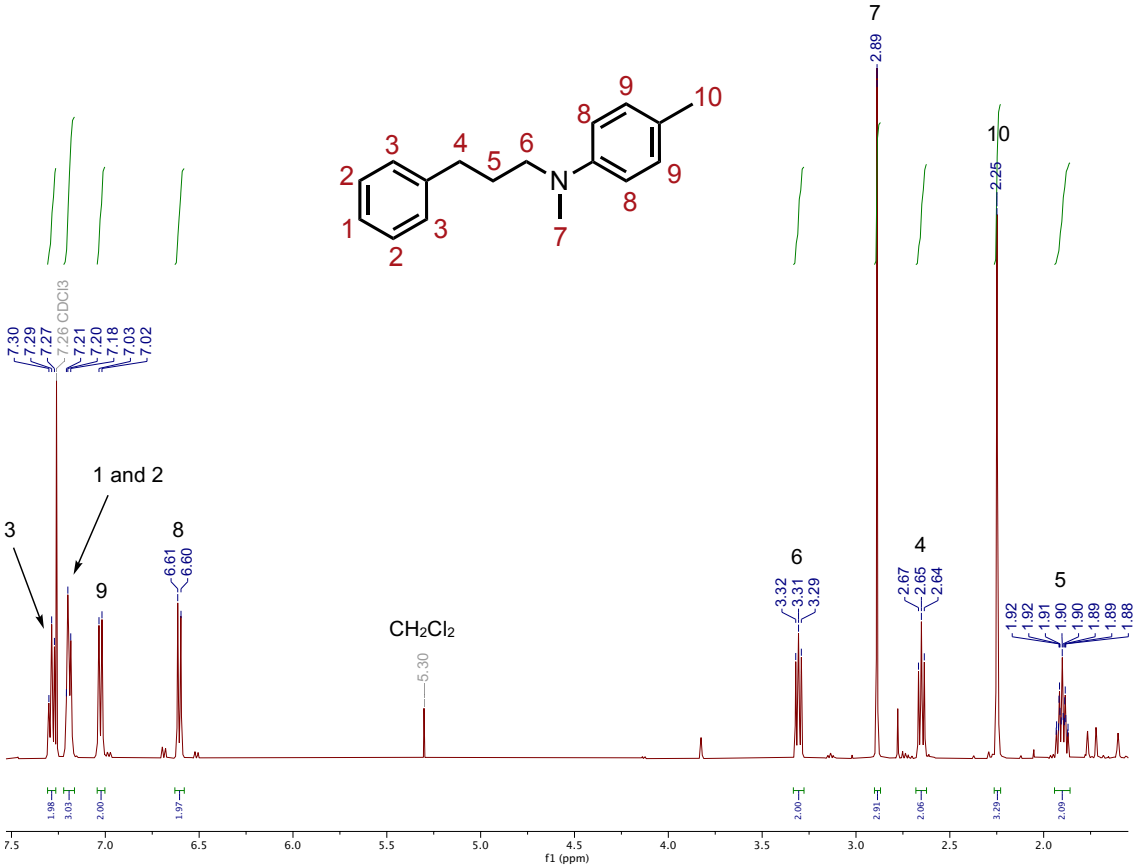
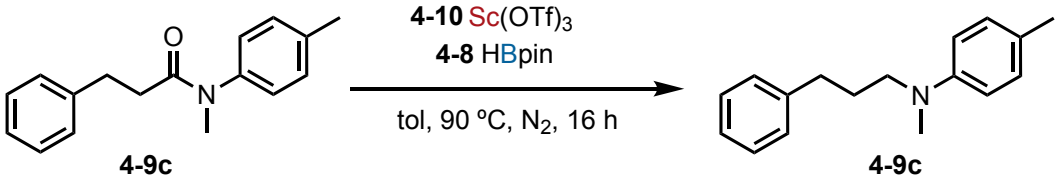



*Figure 4.8 $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of N,4-dimethyl-N-(3-phenylpropyl)aniline*

### 4.3.4 Amide Reduction using $Sc(OTf)_3$




*Scheme 4.9 Reduction of N-methyl-3-phenyl-N-(p-tolyl)propenamide using $Sc(OTf)_3$*

In a catalytic vial, $Sc(OTf)_3$ (24.6 mg , 0.05 mmol, 0.1 equiv.), **4-4c** (127 mg, 0.5 mmol, 1.0 equiv.), **4-8** (0.363 mL, 2.5 mmol, 5 equiv.) were added respectively in anhydrous toluene (0.5 M, 1 mL) under nitrogen inert atmosphere. The reaction was heated up to 90 °C and stirred at 600 rpm for 16 hours. After completion, a saturated solution of $NaHCO_3$ (10 mL) was added slowly to quench the reaction. Once no more bubbles were seen, a pipette of saturated $NaHCO_3$ was added to assure the reaction was quenched. The product was washed with $CH_2Cl_2$ (3 × 10 mL). The organic layer was collected, dried with anhydrous $MgSO_4$ and the solvent was evaporated. The crude product was analysed by NMR.

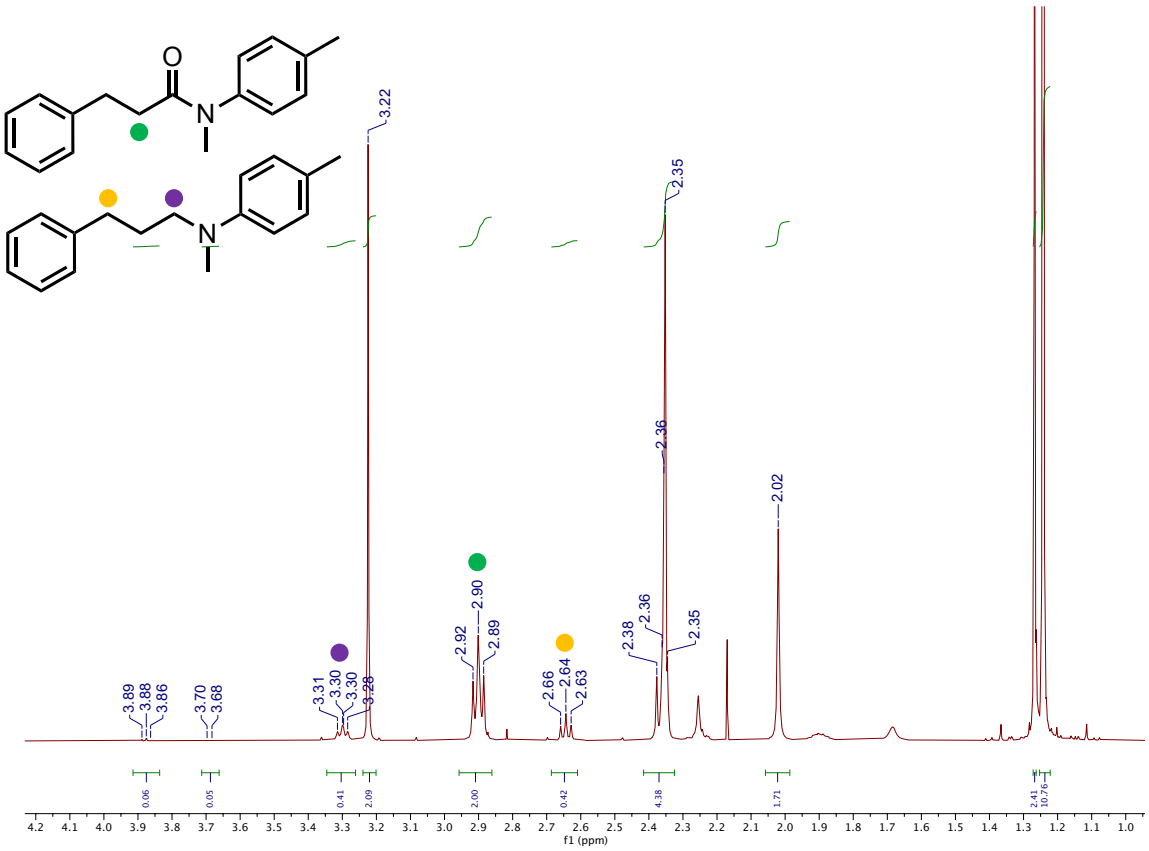
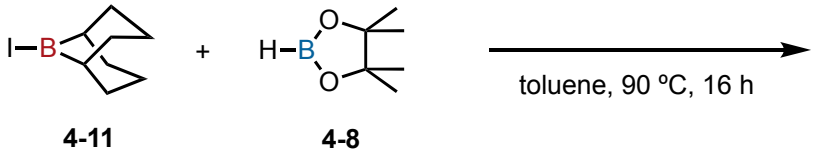



*Figure 4.9 $^1H$ NMR (500 MHz, CDCl3) of the crude of the reaction in Scheme 4.9*

### 4.3.5 Mechanistic Studies




*Scheme 4.10 Mechanistic studies for the reaction between I-B-9-BBN and HBpin.*

In a catalytic vial, **4-11** 1.0 M in hexane (0.1 mL, 0.1 mmol, 1.0 equiv.) and **4-8** (14.5 $\mu$L, 0.1 mmol, 1.0 equiv.), were added respectively in anhydrous toluene (0.25 M, 0.4 mL) under nitrogen inert atmosphere. The mixture was heated up to 90 °C and stirred at 600 rpm for 16 hours. The reaction was analysed by $^{11}$B NMR.

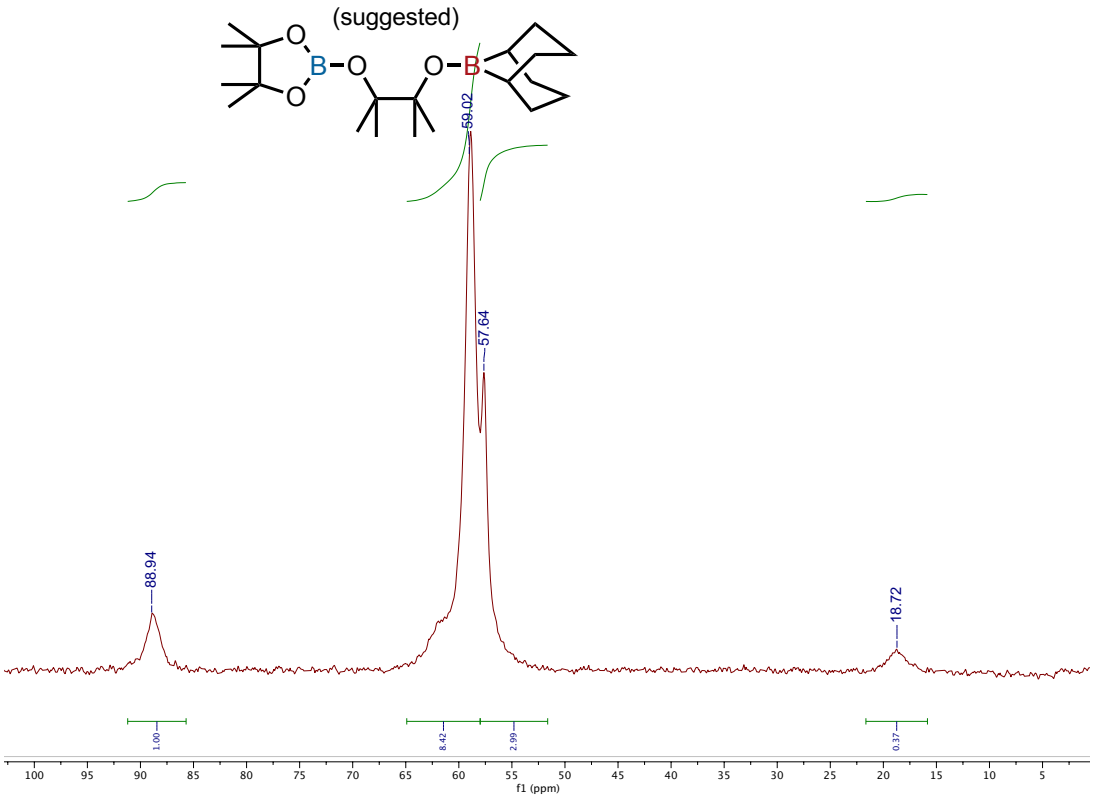
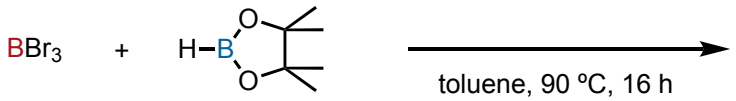



*Figure 4.10 $^{11}$B NMR (128 MHz, $C_6D_6$) of reaction in Scheme 4.10.*




**4-3** **4-8**

*Scheme 4.11 Mechanistic studies for the reaction between $BBr_3$ and HBpin.*

In a catalytic vial, **4-3** 1.0 M in heptane (0.1 mL, 0.1 mmol, 0.1 equiv.) and **4-8** (14.5 $\mu$L, 0.1 mmol, 1.0 equiv.), were added respectively in anhydrous toluene (0.25 M, 0.4 mL) under nitrogen inert atmosphere. The mixture was heated up to 90 °C and stirred at 600 rpm for 16 hours. The reaction was analysed by $^{11}$B NMR.

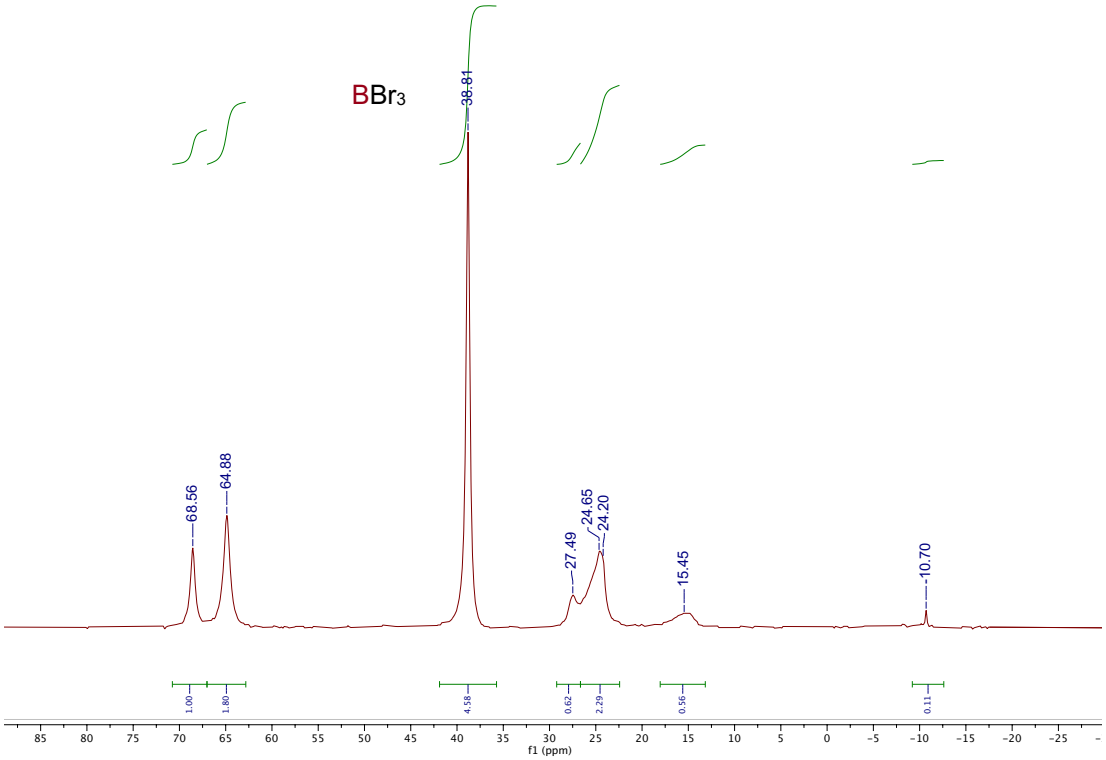
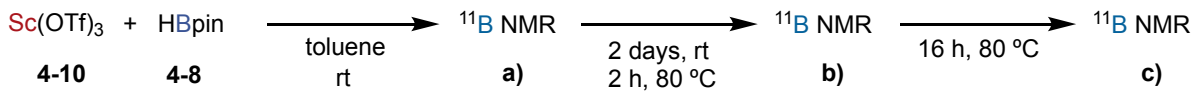



*Figure 4.11 $^{11}$B NMR (128 MHz, $C_6D_6$) of reaction in Scheme 4.11, mixture of products.*




*Scheme 4.12 Study of the reaction between $Sc(OTf)_3$ and HBpin in toluene at different temperatures and over time.*

In an NMR tube, **4-10** (20 mg, 0.04 mmol, 1.0 equiv.) and **4-8** (6.0 $\mu$L, 0.04 mmol, 1.0 equiv.), were added respectively in anhydrous toluene (1 mL) under nitrogen inert atmosphere. Alternatively, in a different NMR tube, **4-8** (6 $\mu$L, 0.04 mmol, 1.0 equiv.) was added in anhydrous toluene (1 mL). Both tubes were analysed by $^{11}$B NMR at room temperature. Then the tubes were left for two days at rt and then heated up to 80 °C for 2 h and analysed again. Finally, the tubes were heated to 80 °C for 16 h and analysed by $^{11}$B NMR. The outcome of the reaction is shown in **Figures 4.12-4.18**.

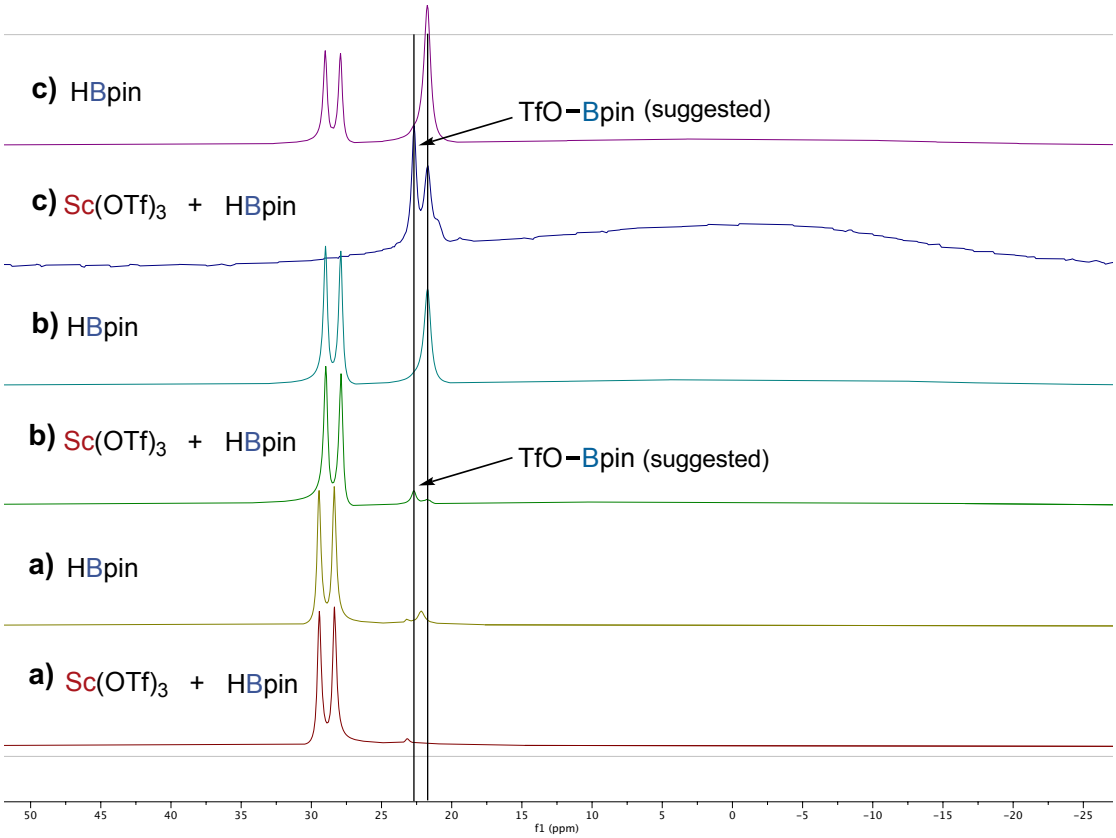



*Figure 4.12 $^{11}$B NMR (128 MHz, none) spectrum for the reactions in Scheme 4.12.*

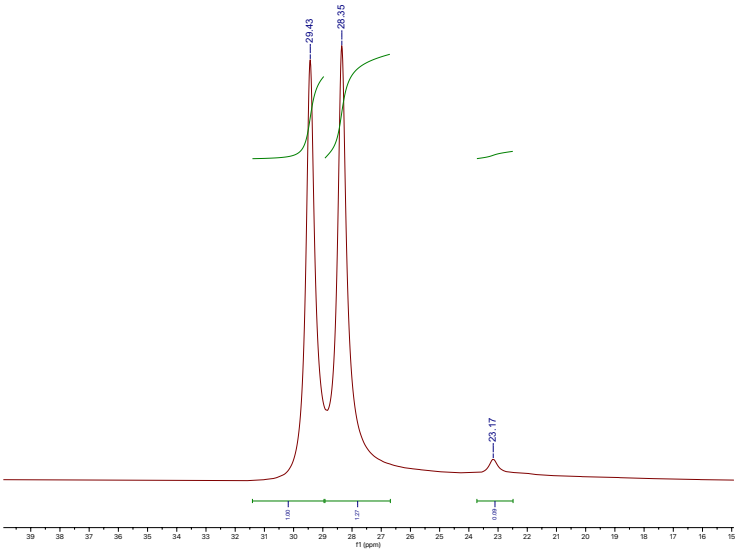



*Figure 4.13 $^{11}$B NMR (128 MHz, none) spectrum for the reaction a) bottom in Scheme 4.12.*

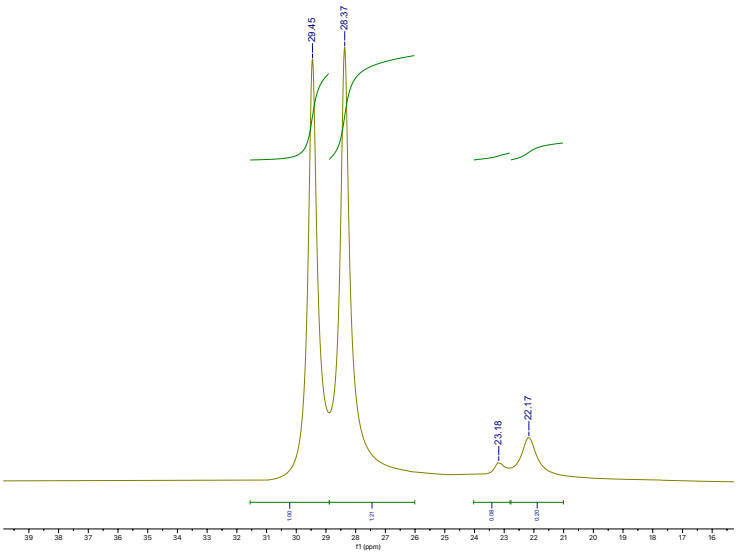



*Figure 4.14 $^{11}$B NMR (128 MHz, none) spectrum for the reaction a) top in Scheme 4.12.*

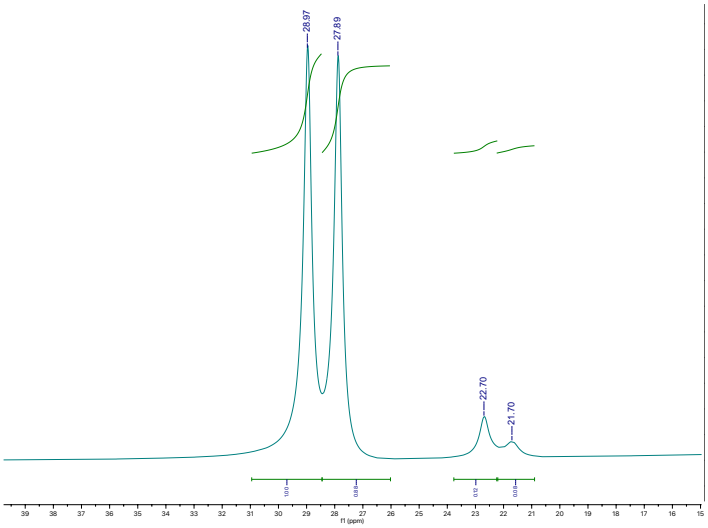



*Figure 4.15 $^{11}$B NMR (128 MHz, none) spectrum for the reaction b) bottom in Scheme 4.12.*

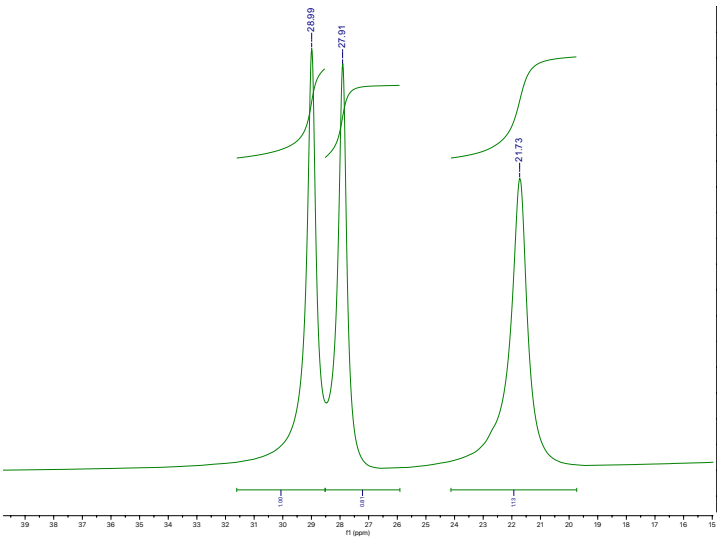



*Figure 4.16 $^{11}B$ NMR (128 MHz, none) spectrum for the reaction b) top in Scheme 4.12.*

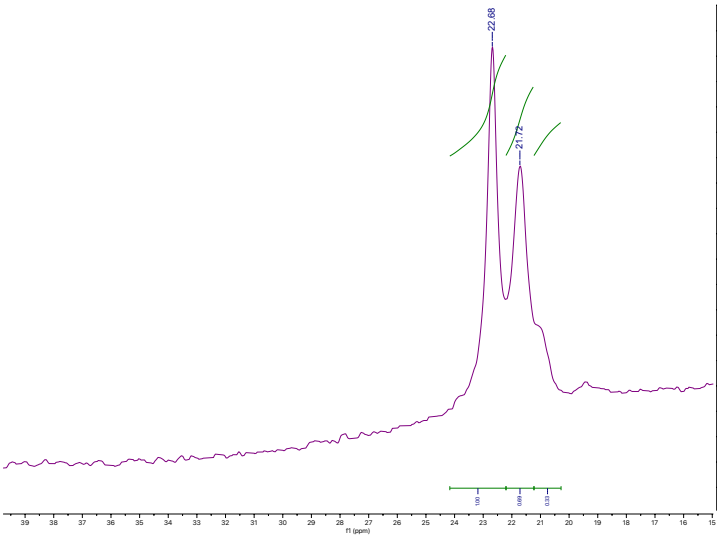



*Figure 4.17 $^{11}B$ NMR (128 MHz, none) spectrum for the reaction c) bottom in Scheme 4.12.*

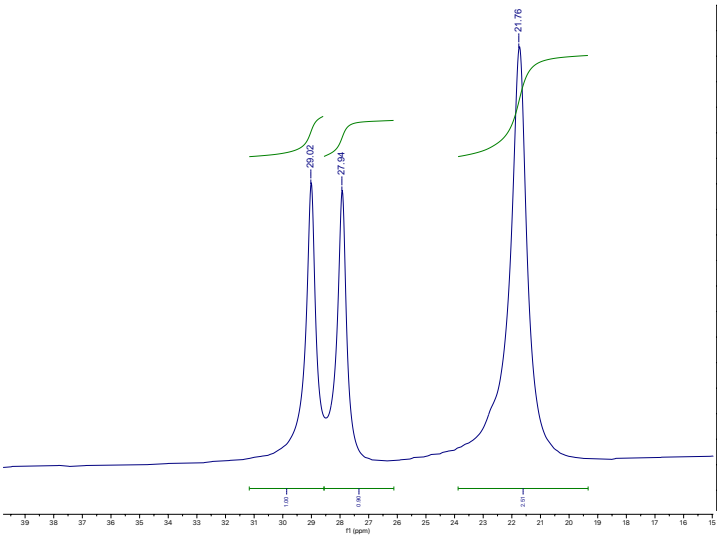



*Figure 4.18 $^{11}B$ NMR (128 MHz, none) spectrum for the reaction c) top in Scheme 4.12.*

# 5 Conclusion

**English**

The main goal for this thesis was to develop a methodology for the reductive amination of esters, either by the formation of an amide intermediate or directly the amine transformation. It was observed that both $BBr_3$ and $Sc(OTf)_3$ can reductively aminate respectively as previously mentioned. Also, other Lewis acids favoured the formation of an amide, as well as an amine, such I-*B*-9-BBN. This complex transformation has been achieved through the screening of several Lewis acids and amines, as well as several test reactions to predict plausible mechanisms. Both successful and unsuccessful results provided relevant data to follow a line of research. Not only the amine was synthetised but also the use of sub-stoichiometric reagents allowed the synthesis of the target product in significant amounts. Comparing to state-of-the-art methods such the one used by Pei-Qiang Huang and co-workers, this system is much simpler yet effective, and less expensive as opposed to the cationic iridium complex, which has a much higher cost per gram of catalyst and uses a variety of reagents to achieve the transformation. However, they obtained a higher yield for the amine and less by-product formation, implementing a stepwise transformation.

Given that the overview of this area of study is in an early stage, further research must be done to understand the mechanisms and intermediates involved in the reaction. Therefore, the ideal future work would be the plan of test reactions to find out if scandium triflate is forming an aldehyde in situ as a classical reductive amination or if TfOBpin specie is involved. Also, the addition of some protic acid to promote the formation of an iminium ion would be a test to try. On the other hand, for boron tribromide as for $Sc(OTf)_3$, some reactions adding both an organic and an inorganic base to improve reactivity could be another reaction to try. Moreover, an important transformation to test would be the formation of borane ($BH_3$) in both reactions since it could promote hidden catalysis. Ultimately, the catalyst loading, the reaction time and temperature could be lowered, as well as the widening of the scope of amines and esters would give an insight on the major trend for this method.

This novel reductive amination may open a new approach for the sustainable synthesis of amines using non-toxic and available substrates for the reaction. Moreover, scale-up projects would allow the industrial applicability of the reaction to produce some of the pharmaceuticals already in the market and the ones to be developed.

**Catalan**

L'objectiu principal d'aquesta tesi ha estat el desenvolupament d'un nou mètode per l'aminació reductora d'èsters, tant formant una amida com a intermedi o bé la transformació a amina directament. Es va observar que tant $BBr_3$ com $Sc(OTf)_3$ poden aminar respectivament com s'ha mencionat anteriorment. A més, altres àcids de Lewis han estat capaços de formar una amida, com també una amina, com I-*B*-9-BBN. Aquesta transformació complexa ha estat assolida mitjançant el *screening* de diversos àcids de Lewis i amines, com també varies proves per predir un mecanisme plausible per la reacció. Tant els resultats favorables com els desfavorables han proporcionat dades rellevants per seguir la línia de recerca. No només s'ha assolit sintetitzat una amina sinó que també s'ha aconseguit mitjançant l'ús de reactius subestequiomètrics en quantitats significatives. Comparant amb mètodes d'estat de l'art com l'emprat per Pei-Qiang Huang i col·laboradors, aquest mètode és més senzill tot i que efectiu. És menys costós econòmicament al contrari que el complex d'iridi catiònic, el qual té un elevat cost per gram de catalitzador i utilitza una varietat de reactius per assolir la transformació. Tot i així, obtenen un rendiment d'amina alt implementant un mètode per passos.

Donat que la visió general d'aquesta àrea d'estudi es troba en una fase inicial, cal dur a terme més investigacions per entendre els mecanismes i intermedis de reacció. Per tant, el treball futur ideal seria el plantejament d'unes reaccions prova per esbrinar si el triflat d'escandi forma un aldehid in situ com una aminació reductora clàssica o si hi ha l'espècie TfOBpin implicada. A més l'addició d'un àcid pròtic per afavorir la formació d'un ió imini seria una bona prova per dur a terme. D'altra banda, tan pel tribromur de bor com pel $Sc(OTf)_3$, l'adició d'una base tant orgànica com inorgànica per millorar la reactivitat pot esser una altra prova. Per altra part, una transformació rellevant a provar és la formació de borà en ambdues reaccions ja que podria promoure catàlisi amagada. Finalment, la càrrega de catalitzador, el temps i la temperatura de reacció podrien ser disminuïts, l'expansió d'amines i èsters com a substrats donaria una visió de la tendència global del mètode.

Aquesta aminació reductora recent pot obrir un nou enfocament per a la síntesi sostenible d'amines usant substrats no tòxics i disponibles per a la reacció. A més, l'enfoc a gran escala permetria l'aplicabilitat industrial de la reacció per produir alguns dels productes farmacèutics del mercat i els encara en fase de desenvolupament.

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