CHAN-LAM AMINATION STUDIES: SOLVING THE CHEMOTYPE REACTIVITY ISSUE

Julien Vantourout

March 2018

CHAN-LAM AMINATION STUDIES: SOLVING THE CHEMOTYPE REACTIVITY ISSUE

Thesis submitted to the University of Strathclyde in fulfilment of the requirements for the degree of Doctor of Philosophy

By

Julien Vantourout

March 2018

Declaration of Copyright

Signed:

Date: 15th of March 2018

Publication List

5. J. C. Vantourout, A. Isidro-Llobet, and A. J. B. Watson. **Conventional and bio-inspired syntheses of monoterpene indole alkaloids** in *Studies in Natural Products Chemistry,* vol. 55: Atta-ur-Rahman, Ed., Elsevier, Chapter 1.

4. C. Li, Y. Kawamata, H. Nakamura, J. C. Vantourout, Z. Liu, Q. Hou, D. Bao, J. T. Starr, J. Chen, M. Yan, and P. S. Baran. **Electrochemically enabled, Ni-catalyzed amination.** *Angew. Chem. Int. Ed.* 2017, **42**, 13088–13093.
Highlighted by Derek Lowe in In The Pipeline.

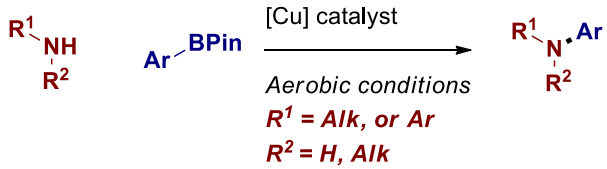
3. J. C. Vantourout, H. N. Miras, A. Isidro-Llobet, S. Sproules, and A. J. B. Watson. **Spectroscopic studies of the Chan-Lam amination: A mechanism-inspired solution to boronic ester reactivity.** *J. Am. Chem. Soc.* 2017, **139**, 4769–4779.
Highlighted by Derek Lowe in In The Pipeline.

2. J. C. Vantourout, R. P. Law, A. Isidro-Llobet, S. J. Atkinson, and A. J. B. Watson. **Chan-Evans-Lam amination of boronic acid pinacol (BPin) esters: Overcoming the aryl amine problem.** *J. Org. Chem*. 2016, **81**, 3942–3950.
Highlighted in OPRD and ACS Most Read articles of 2016.

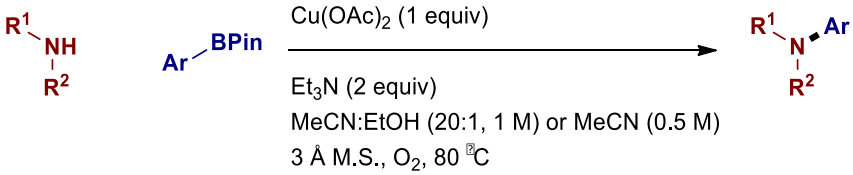
1. C. W. Muir, J. C. Vantourout, A. Isidro-Llobet, S. J. F. Macdonald and A. J. B. Watson. **One-pot homologation of boronic acids: A platform for diversity-oriented synthesis.** *Org. Lett.* 2015, **17**, 6030–6033.

Abstract

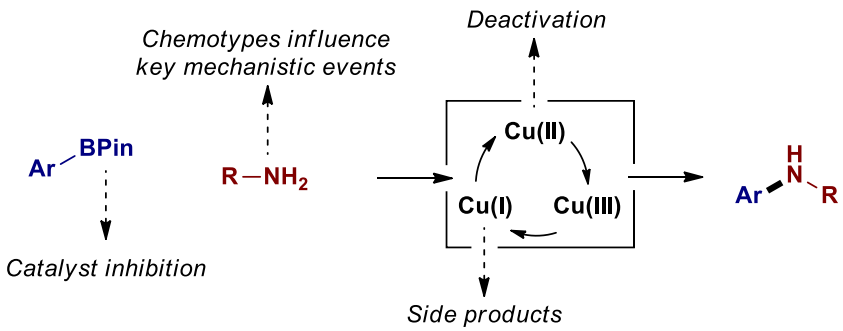
The work presented in this thesis describes the study of the Chan-Lam reaction between aryl boronic acid pinacol esters (BPin) and alkyl and aryl amines.



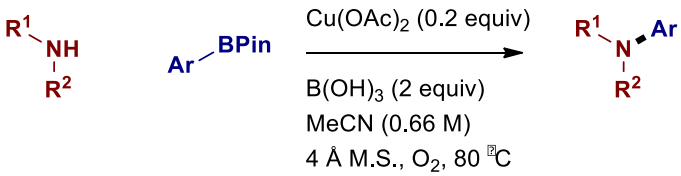
Firstly, we developed an effective stoichiometric set of reaction conditions for the Chan-Lam amination of aryl BPin with alkyl and aryl amines. A mixed MeCN/EtOH solvent system was found to enable effective C−N bond formation using aryl amines while EtOH is not required for the coupling of alkyl amines.



Secondly, we investigated the Chan–Lam amination reaction using a combination of spectroscopy, computational modeling, and crystallography techniques. We provided a full mechanistic description including the source of the boronic acid pinacol ester reactivity issue, determining the origin of amine chemotype reactivity and side reaction issues, identifying key reactive intermediates, and demonstrating the pivotal role of boron-based by-products.



Finally, manipulating Cu(I) → Cu(II) reoxidation and exploiting three synergistic roles of boric acid has allowed the development of a general catalytic Chan–Lam amination, overcoming long-standing and unsolved amine and organoboron limitations of this valuable transformation.



Acknowledgements

My utmost thanks are expressed to my industrial supervisor Dr Albert Isidro-Llobet and to my university supervisor Dr Allan Watson whose supervisions during my PhD have been consistently excellent. Their guidance has allowed me to understand the project deeply and to progress in a day to day basis. For this I am truly thankful.

I would also like to thank Prof Harry Kelly (Le patron) and Prof Billy Kerr for giving me the opportunity to join the industrial PhD program and for their constant support.

Kind thanks must go to Dr Graham Simpson, Mr Tony Dean, Dr Alan Nadin and Mr Andy Mason for their support, infectious enthusiasm and help in several projects. Collaborating with you has been an amazing experience.

I would like to thank Dr Robert Law for his help with the first Chan-Lam project; Prof Stephen Sproules (University of Glasgow) for his assistance with EPR and calculations; Dr Haralampos Miras (University of Glasgow) for X-ray analysis; and Enrique Bendito Moll for his help with different ongoing Chan-Lam projects.

Thank you to Andrea Malley (Mother GSK) for her administrative support and kindness. You make our life easier and your help is precious.

Thank you to all the people I worked with at GSK: the Peptide CPU group (Gail, Praew, Adele, Simon, Sam and Hector); the NCE group (Tony, Alan, Ian, Martin, Guy, Mythily, Abby, Paul, Vanessa, Ross, Rob, Jane, Graham, Saphia, Washio); Lisa for your constant help and support; and Katherine for your guidance.

Thank you to Krista, Alan, Tony, Harry, Albert and Allan for supporting my application for my secondment in the laboratory of Prof Phil Baran, and for financial support.

Thank you to Prof Phil Baran for his guidance and support during my 3 months' placement in his group.

Thank you to all the PhD students (especially Sam, Jason, Hannah, James, Julia, Marie-Pierre, Rob and Johnny, JT, Nick, Tom, Storm, Enrique, Blake, Simon, Rob,

Aymeric, and Ben). It was nice to have you with me during the past three years. Good luck for the future!

Thank you to the French Mafia at GSK (Eric, Seb, Sophie, Damien, Nathalie, Julien, Sandrine, Aurelie, Aymeric) for the all the good times we had together.

Thanks to the Boron Boys Club (Ciaran, Jamie and John) and all Watson group members: past (Mairi, Diana, Lisa, Calum), and present (Chao, Kirsty, Eilidh, Matt) for making my placement at Strathclyde enjoyable. I will miss you all! Keep in touch!

A massive thank you to my friends: Thibaut, Quentin, Thomas, Didier, Mathilde, Claire, Melanie, Nicolas, MJ, Fanny, Dorel, Marine, and all those I have forgotten…

I would like to thank my family who have been present with me throughout these 4 years: especially my Mom, my Dad, my brothers, and my sister for their support and without who my thesis would never be finished.

Finally, a special thank you to Camille, my wonderful wife. Your support has been incredible and I feel lucky to have you in my life in the last 7 years. You are the best and I love you!

Abbreviations

A	Ampere
Å	Angstrom
Ac	Acetyl
acac	Acetylacetone
AIM	Atoms In Molecule
AMU	Atomic Mass Unit
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bu	Butyl
*t*Bu	*tert*-Butyl
˚C	Degrees Celsius
COD	1,5-Cyclooctadiene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPF	1,1′-Bis(diphenylphosphino)ferrocene
EPR	Electron Paramagnetic Resonance
equiv	Equivalent
Et	Ethyl
fac	*facial*

FAP	(2S)-1-[4-({6-[(2,6-difluorophenynl)amino]pyrimidin-4-yl}amino)phenoxy]-3-(dimethylamino)propan-2-ol
GSK	GlaxoSmithKline
h	Hour
HEPES	4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid
HMDS	Bis(trimethylsilyl)amine
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
*I*Pr	*iso*-Propyl
IR	Infrared
L	Litre
LCMS	Liquid Chromatography – Mass Spectrometry
LED	Light-Emitting Diode
M	Molar Concentration
m	Meter or Milli (depending on usage, m as prefix is milli)
Me	Methyl
min	Minute
n	Nano
nr	No reaction
mol	Mole
M.S.	Molecular Sieves
W	Molecular Weight
NMP	*N*-Methyl-2-pyrrolidinone
NMR	Nuclear Magnetic Resonance Spectroscopy
pH	Hydrogen Potential
Pin	Pinacolate
Piv	Pivalyl

ppy	2-Phenylpyridinato-C2,*N*
R	R Group (depending on context)
RCV	Repetitive Cyclic Voltammetry
rt	Room Temperature
SPS	Bis-(sodium sulfopropyl)-disulfide
S_NAr	Nucleophilic aromatic substitution
TBAF	Tetra-*n*-butylammonium fluoride
TBME	Methyl *tert*-butyl ether
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
Tf	Triflate
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TOF	Time-of-Flight
uM	Micro molar
UV	Ultraviolet
vol	Volume
ZORA	Zeroth-Order regular approximation

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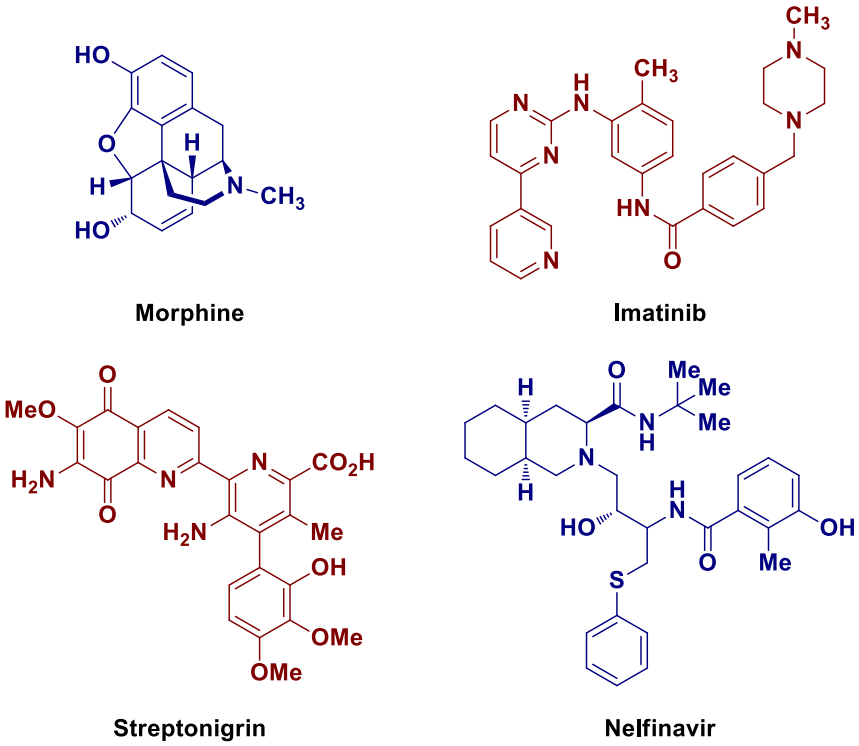
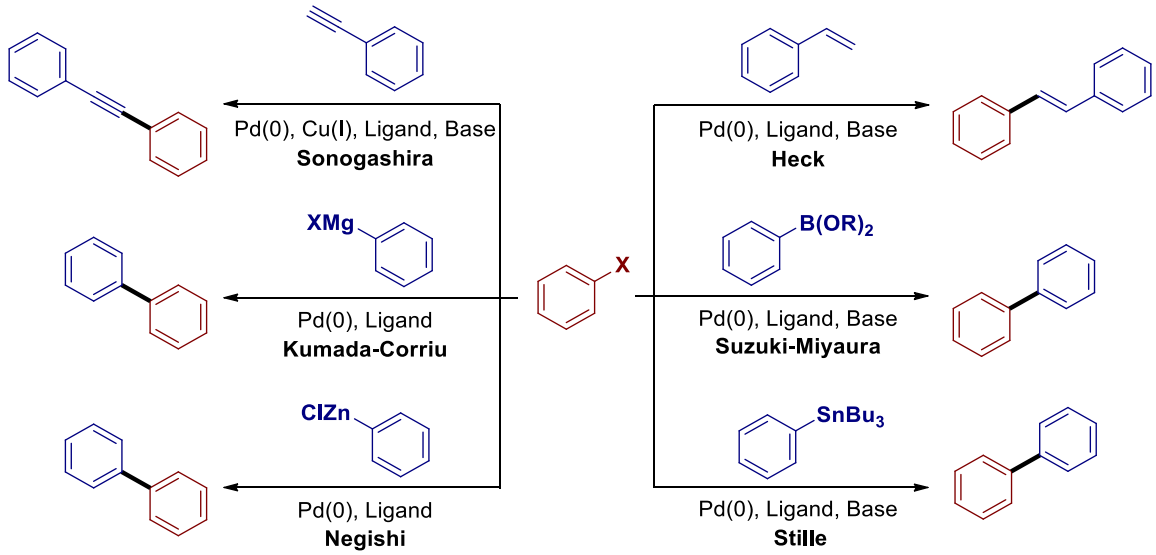
Introduction

Compounds containing nitrogen atoms, are highly important due to their abundance in both natural products and synthetic compounds with biological activity (**Scheme 1**).[1]



Scheme 1: Examples of nitrogen containing compounds.

Constructing these compounds in an efficient and economical manner is of interest for both medicinal and process chemistry. Consequently, time and effort have been dedicated to access skeletons of heterocyclic molecules, and to introduce new functionalities onto those mainly through transition metal-catalysed reactions.[2] In this regard, carbon-carbon bond formation reactions such as Heck, Kumada, Negishi, Stille, Suzuki–Miyaura, and Sonogashira have been widely studied, utilised, and are in incessant development to access more challenging structures (**Scheme 2**).[3-9] Alongside these C-C bond formation reactions, methodologies affording new carbon-nitrogen bonds also play a significant role in the synthesis of organic molecules.[1,2]

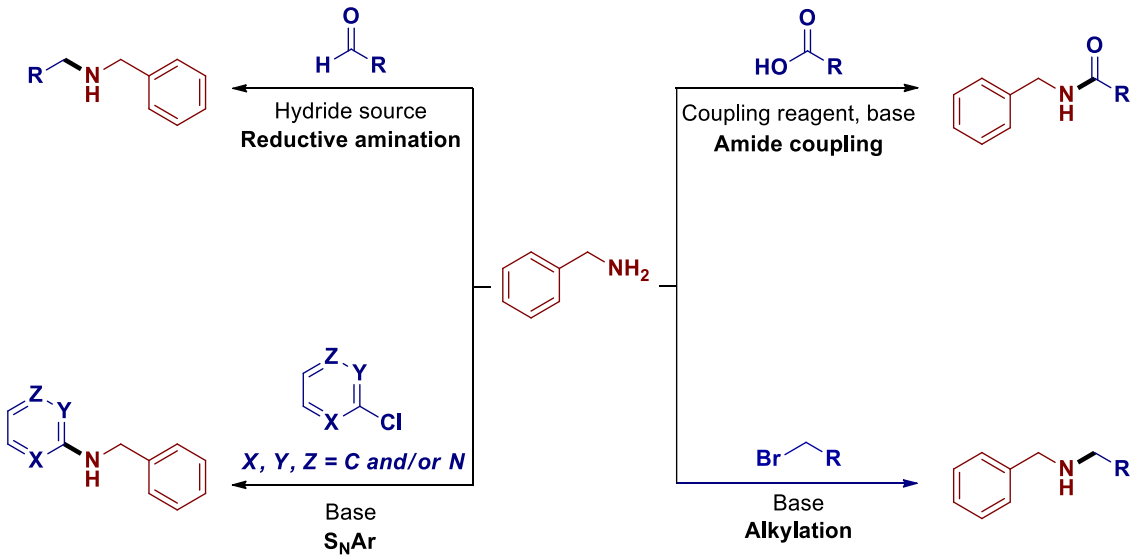


Scheme 2: Metal catalysed C-C bond formation reaction.

1. C–N bond formation reactions

1.1. Generalities

The formation of the C–N bond is significant as it opens avenues for the introduction of nitrogen into organic molecules. Amide couplings, alkylations, reductive aminations and S_NAr are part of the most practiced organic chemistry transformations to construct complex and diverse chemical entities (**Scheme 3, Figure 1**).[10] The S_NAr reaction which allows the formation of C–N bonds of aromatic compounds is of importance and proved to be challenging to medicinal chemists as it requires the use of specific substrates bearing electron-withdrawing groups, and is sometimes not suitable for late stage functionalisation. Therefore, cross-coupling reactions have emerged and have been considerably studied by chemists, as they allow the incorporation of amino groups in a direct cost-effective manner.[2]



Scheme 3: Examples of C-N bond formation reaction.

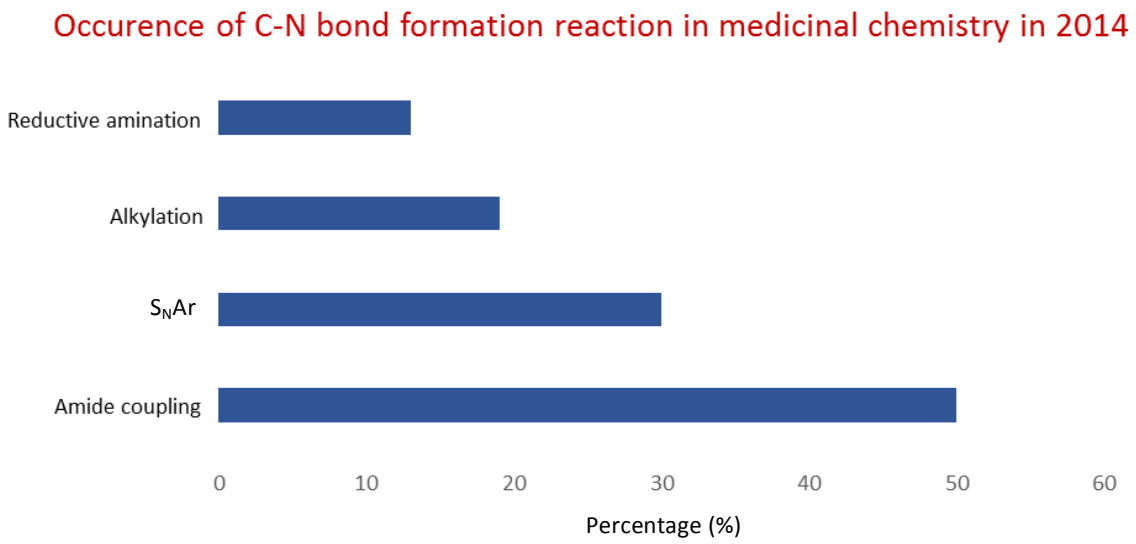


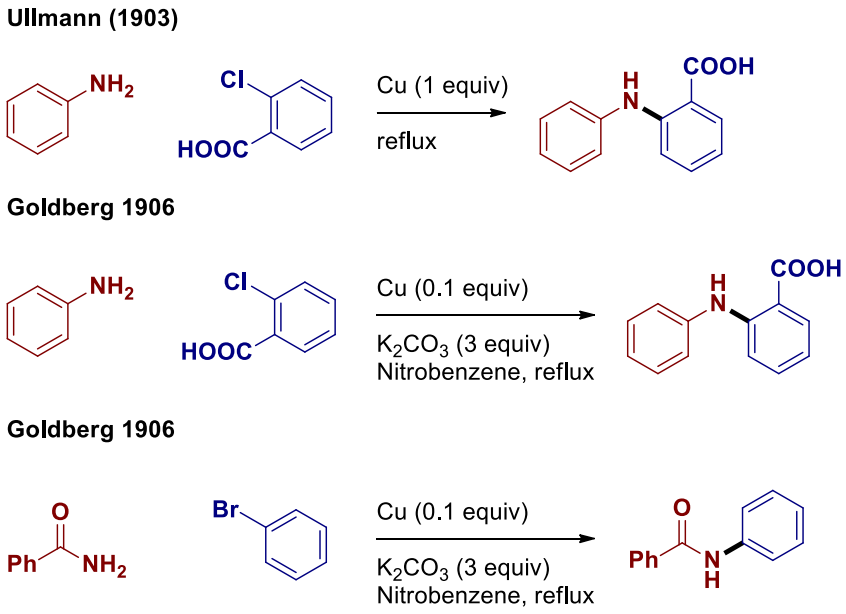
Figure 1: Percentage of occurrence of C-N bond formation reactions used in medicinal chemistry.

1.2. C-N bond formation *via* cross-coupling reactions

There is an increasing demand for the development of new methodologies to facilitate the synthesis of diarylamines, dialkylamines, and alkylaryl amines owing to their importance as structural skeletons in a broad range of molecules with numerous and significant applications.[1,2] Therefore, cross-coupling reactions have been developed to form C-N bond. These couplings can occur either *via* electrophilic-nucleophilic or *via* nucleophilic-nucleophilic cross-coupling reactions.[1,2]

1.2.1. C-N bond formation *via* electrophilic-nucleophilic cross-couplings

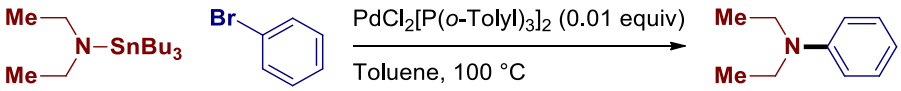
More than a hundred years ago, Ullmann and Goldberg reported for the first time that activated electrophilic aryl halides (1 equiv) react with amine or amide nucleophiles (1.5 equiv) using stoichiometric or catalytic amounts of copper catalyst (1 or 0.1 equiv), base (3 equiv) and very high temperatures (**Scheme 4**).[11,12] However, the low yields obtained, and the harsh conditions utilised, lowered the impact and development of this useful transformation.



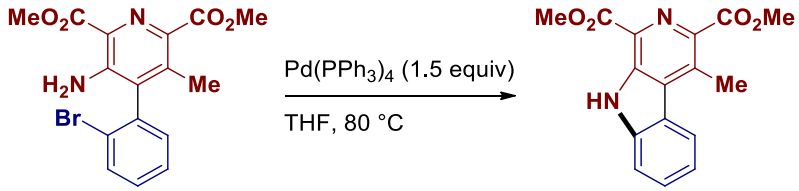
Scheme 4: Ullmann and Goldberg reactions.

Pd-catalysed C-N couplings between aryl halides (1 equiv) and aminostannanes (1.5 equiv) or amines (1 equiv) were reported as early as 1983 by Migita and co-workers, and in 1984 by Boger and Panek (**Scheme 5**).[13,14]

Migita 1983

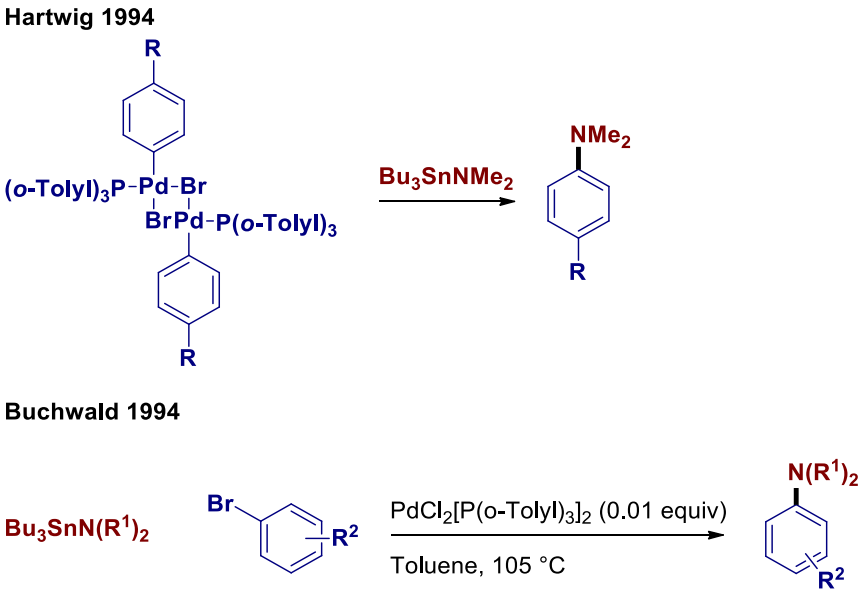


Boger 1984



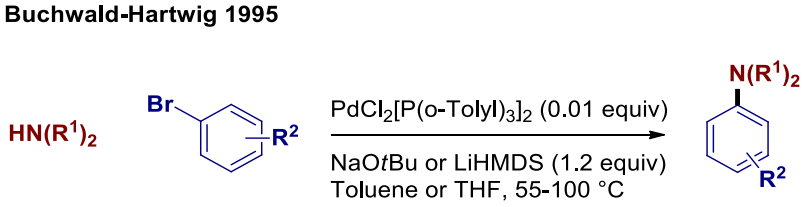
Scheme 5: First examples of Pd-catalysed C-N bond formation reactions using aminostannanes or amines.

However, these reactions did not attract the attention of the broad scientific community. Therefore, no major contribution was added to the field until 1994, when Hartwig and Buchwald independently published complementary studies to the work of Migita and co-workers. (**Scheme 6**).[15,16] Hartwig and co-workers demonstrated that the Pd[P(*o*-Tolyl)$_3$]$_2$ was the active catalyst of the Pd-catalysed reaction reported by Migita. In addition, they proposed a catalytic cycle involving oxidative addition of the aryl bromide. Buchwald *et al.* reported two major improvements over Migita's original paper. Firstly, they highlighted that transamination of Bu_3SnNEt_2 followed by argon purge to remove the volatile diethylamine affords the successful coupling of secondary amines and primary anilines. Secondly, they optimised the existing reaction conditions to improve the yield of electron-rich and electron-poor aryl compounds.



Scheme 6: Hartwig and Buchwald reports on C-N bond formation reaction.

The following year, both groups demonstrated that the couplings could be achieved with free amines (1.5 equiv) in the presence of a bulky base (1.2 equiv) and in the absence of organotin (**Scheme 7**).[17,18]

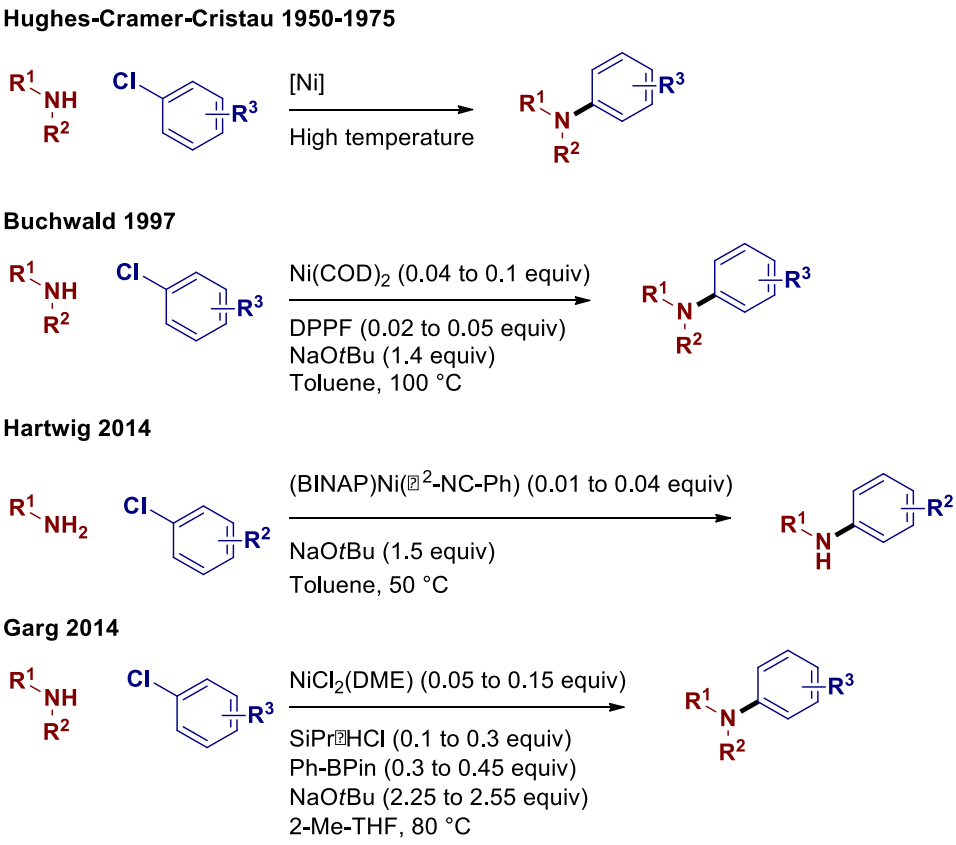


Scheme 7: First examples of Pd-catalysed C-N bond formation reactions using free amines.

Since these conditions were reported, the elaboration of designed ligands or catalysts allowed chemists to access a wide diversity of functionalised products in an efficient and practical manner. However, the requirement of high temperatures, strong bases and expensive palladium catalysts still are a few unsolved limitations.

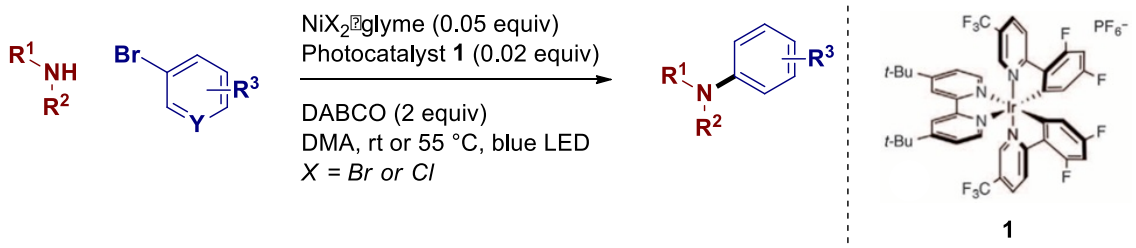
Along with Pd- and Cu-catalysed reactions, the nickel catalysed C-N cross-coupling was investigated as nickel catalysts are inexpensive, and exhibit high turnover toward less reactive electrophiles such as aryl chlorides. The first report was published in 1950

by Hughes and was further developed by the groups of Cramer and Cristau (**Scheme 8**).[19-21] However, the harsh reaction conditions limited its general adoption. Over the years, efficient protocols using designed catalysts and ligands have been developed by the groups of Buchwald, Hartwig, Garg, and others (**Scheme 8**).[22-32] Nevertheless, these efforts suffer from several constraints, including the use of air-sensitive Ni(0) catalysts, high temperatures, and alkoxide bases.



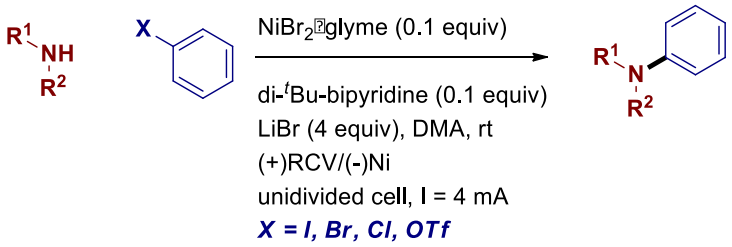
Scheme 8: Evolution of Ni-catalysed C-N bond formation reactions.

In 2016, the groups of MacMillan and Buchwald published an elegant *N*-arylation methodology using nickel catalysis.[33] Wherein the photoinduced electron transfer between an iridium complex **1** and an intermediate Ni(II) complex allows readily available Ni(II) salts to serve as catalysts under milder C-N bond formation reaction conditions (**Scheme 9**).



Scheme 9: Photoredox Ni-catalysed amination.

Last year, Baran and co-workers reported an efficient set of conditions using electrochemistry to achieve the cross-coupling between aryl halides (1 equiv) and alkyl amines (3 equiv) using a Ni(II) catalyst (0.1 equiv) in the absence of an external base at room temperature (**Scheme 10**).[34]



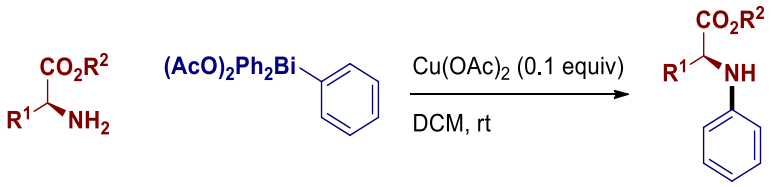
Scheme 10: Electrochemistry Ni-catalysed amination.

Despite several improvements, all previously described reactions still require the use of expensive catalysts, ligands and equipment, as well as high temperatures, strong bases, and inert atmosphere. Consequently, C–N bond formation *via* nucleophilic-nucleophilic cross-couplings have also been investigated.

1.2.2. C-N bond formation *via* nucleophilic-nucleophilic cross-couplings

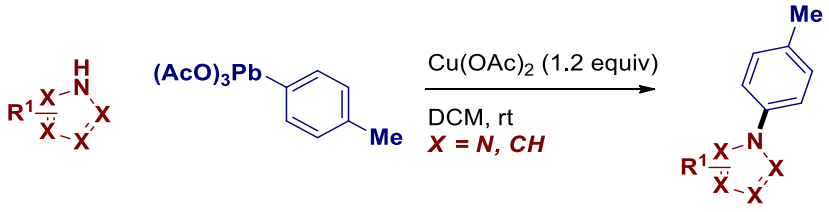
In 1989, the Barton's group reported the first C–N bond formation *via* nucleophilic-nucleophilic cross-coupling of triarylbismuth diacylates (1 equiv) with *α*-amino esters (1 equiv) using $Cu(OAc)_2$ (0.1 equiv) as the catalyst (**Scheme 11**).[35] The *N*-arylated product was obtained in good to excellent yields. In addition, no racemisation was observed, offering a serious advantage over the corresponding palladium- and nickel-

catalysed transformation in which full racemisation of the desired products was reported.



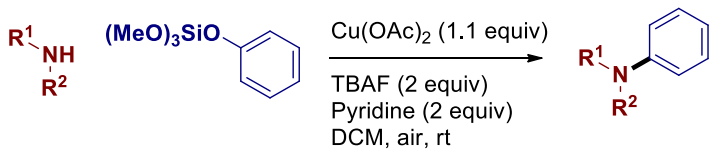
Scheme 11: Cu-catalysed C-N bond formation between triarylbismuth diacylates and *α*-amino esters.

A few years later, Avendano and co-workers showed that various NH-heterocycles (1 equiv) were suitable substrates for *N*-arylation with *p*-tolyllead diacetate (1.1-1.5 equiv) as the aryl donor using stoichiometric amounts of $Cu(OAc)_2$ (1.2 equiv) (**Scheme 12**).[36]



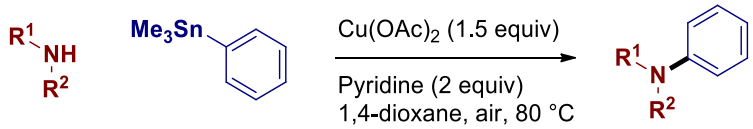
Scheme 12: Cu-catalysed C-N bond formation reaction between p-tolyllead triacetate and NH-heterocycles.

Subsequently, Lam *et al.* demonstrated that hypervalent siloxanes (2 equiv), generated *in situ* from aryl iodide, were suitable reagents for the arylation of various nitrogen-based nucleophiles (1 equiv) using $Cu(OAc)_2$ (1.1 equiv) in the absence of strong base at room temperature (**Scheme 13**).[37]



Scheme 13: Cu-catalysed C-N bond formation reaction between hypervalent siloxanes and amines.

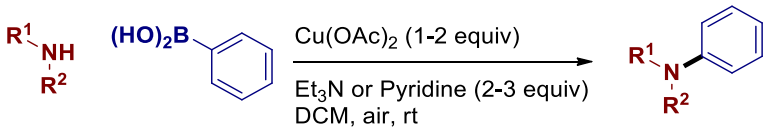
Later, the same group used aryl stannanes as alternative coupling partners (**Scheme 14**).[38] The *N*-arylation reaction occurs in presence of $Cu(OAc)_2$ (1.5 equiv) and pyridine (2 equiv) in 1,4-dioxane at 80 ºC. However, homocoupling was the favoured reaction, affording the desired product in low yields. Interestingly, using CuCl (5 equiv) instead of $Cu(OAc)_2$ allowed the reaction to be run at room temperature, but did not improve the yields.



Scheme 14: Cu-catalysed C-N bond formation reaction between aryl stannanes and amines.

All previously described nucleophilic-nucleophilic cross-couplings offer several advantages. However, the use of expensive or toxic alkylating reagents, the lack of availability of the staring materials, and the absence of a general set of conditions limited the practice of these reactions.

A breakthrough in the field of C-N bond formation reactions was the discovery of the copper-promoted Chan–Lam coupling reaction with boronic acids almost twenty years ago (**Scheme 15**).[39-41]



Scheme 15: Cu-catalysed Chan-Lam reaction between arylboronic acid and amines.

One reason for its popularity is the mild reaction conditions required: room temperature, weak base, and ambient atmosphere. This approach also takes advantage of the readily availability of boronic acid starting materials. Since its discovery, many studies have been conducted and many relevant improvements have been achieved.

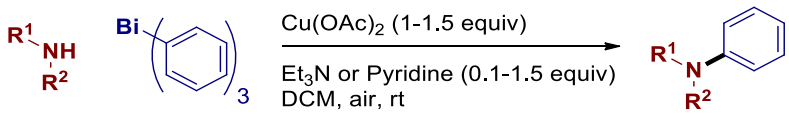
2. Chan-Lam reaction

2.1. Generalities

In 1998, the groups of Chan, Lam, and Evans reported three back-to-back publications for the copper-mediated cross-coupling of aryl boronic acids with diverse heteroatom based nucleophiles (**Scheme 15**).[39-41] Over the years, several research teams made significant progress in expanding this methodology which has proven to be mild, versatile, and robust. These progresses involve the optimisation of the reaction conditions with various catalyst sources, solvents, bases, additives, ligands and alternative boron reagents; the expansion of the substrate scope and mechanistic studies.

2.2. State of the art

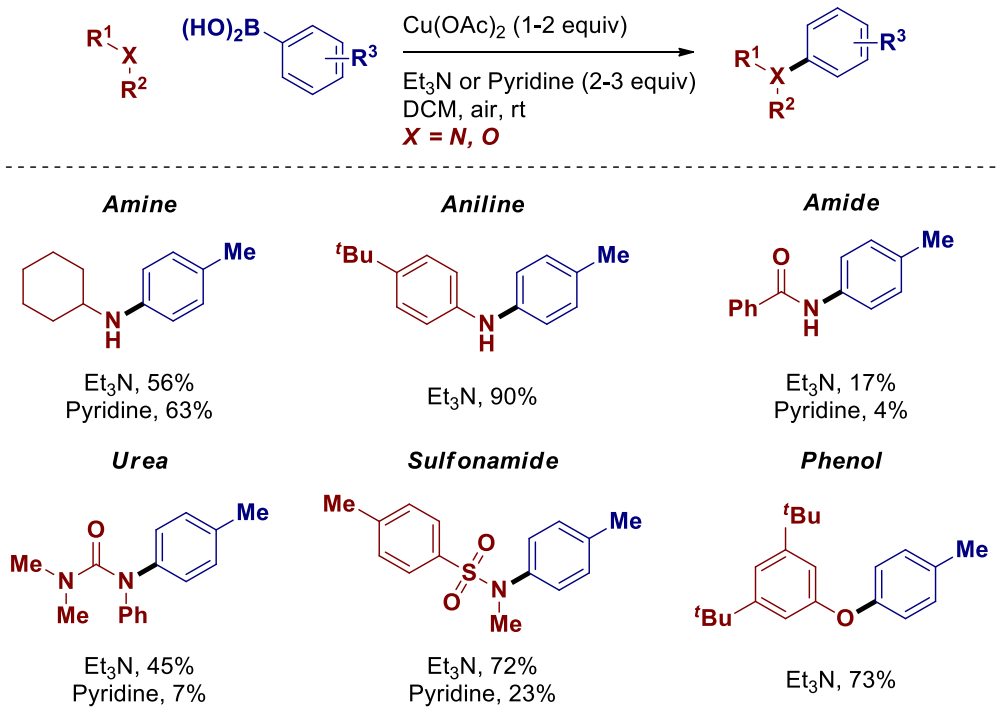
The discovery of the Chan-Lam reaction originates from the work conducted by Chan to introduce new aryl reagents as the electrophilic partner in the Ullmann reaction. His group at DuPont first noticed that stoichiometric amounts of copper acetate (1-1.5 equiv) promote the coupling of triarylbismuth reagents (1 equiv) with N-H containing compounds (1 equiv) in presence of an external base (0.1 to 1.5 equiv) like triethylamine or pyridine (**Scheme 16**).[42]



Scheme 16: Cu-catalysed C-N bond formation reaction between triarylbismuth and amines.

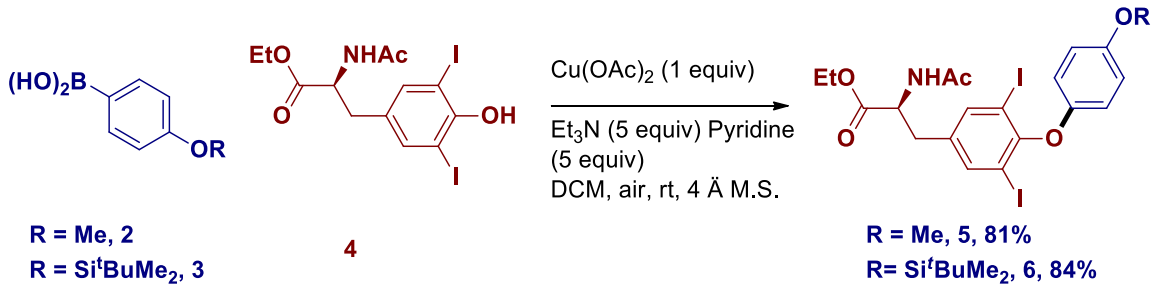
Replacing triarylbismuth reagents by boronic acid compounds allowed the achievement of an attractive, and unprecedented Ullmann type reaction, since boron reagents are directly accessible commercially or *via* synthesis. These outstanding results were disclosed in a first publication, and proved this method, using a boronic acid as the aryl donor (2 equiv), to be applicable to a wide range of nucleophilic coupling partners (1

equiv), including alkyl amines, anilines, amides, ureas, sulfonamides, and phenols (**Scheme 17**).[39]



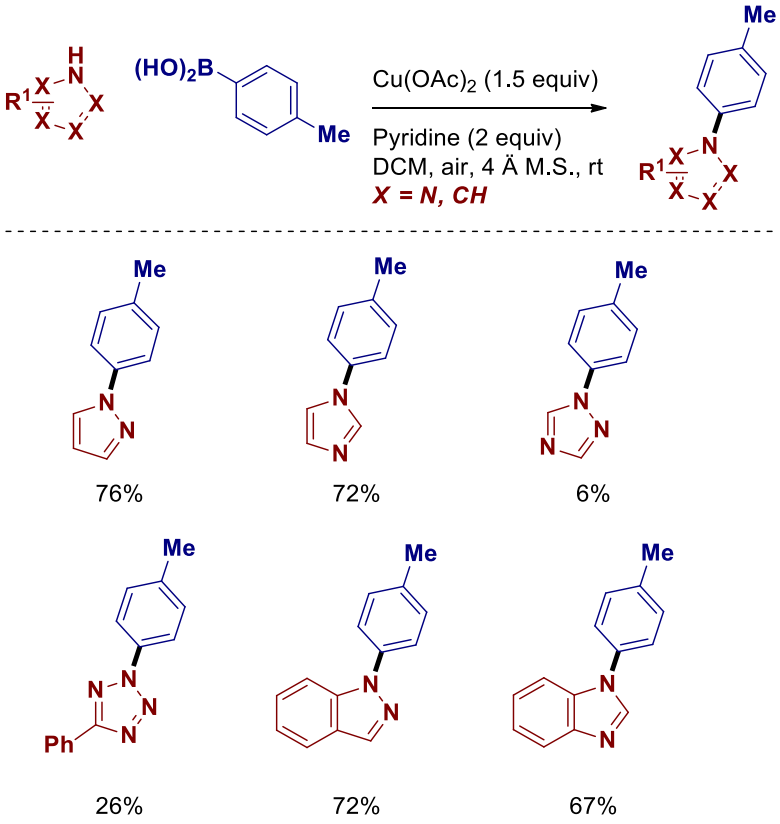
Scheme 17: First report of Cu-catalysed C-N bond formation between aryl boronic acids and amines by Chan *et al.*

This methodology was further applied by Evans and co-workers in the formal synthesis of *L*-throxine (**Scheme 18**).[40] The optimised copper-catalysed reaction between either phenylboronic acid **2** or **3** (2 equiv) and (*S*)-ethyl 2-acetamido-3-(4-hydroxy-3,5-diiodophenyl)propanoate **4** (1 equiv) using a mixture of triethylamine (5 equiv) and pyridine (5 equiv) afforded *L*-throxine intermediates **5** and **6** in 81% and 84% yield, respectively.



Scheme 18: Formal synthesis of *L*-throxine using the Chan-Lam coupling as a key step.

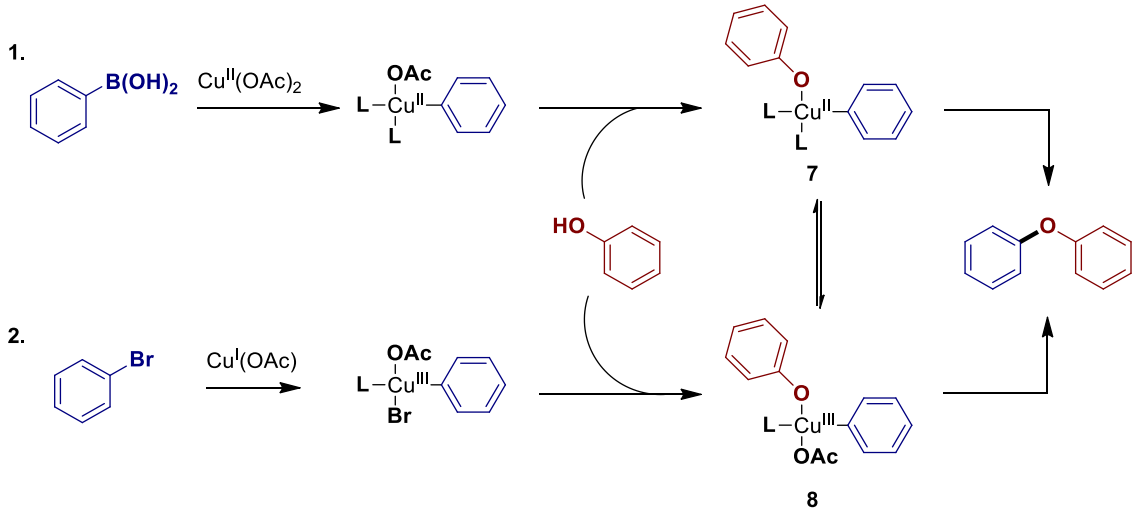
Finally, Lam, Chan, and co-workers also reported that aromatic heterocycles (imidazoles, pyrazoles, triazoles, tetrazoles, benzimidazoles, and indazoles) are suitable coupling partners in this copper-catalysed reaction (**Scheme 19**).[41]



Scheme 19: Chan-Lam reaction between aryl boronic acids and aromatic heterocycles.

Regarding the mechanism, Evans *et al.* were the first to speculate a plausible pathway of the Chan-Lam reaction in their *O*-arylation paper.[40] They mentioned that the Chan-Lam reaction (**Scheme 20, 1**) and the Ullmann reaction (**Scheme 20, 2**) certainly

overlapped at the arylcopper phenoxide intermediates **7** or **8**, which then could undergo reductive elimination to the diaryl ether. The only uncertainty was the oxidation state of this copper-based intermediate, either (II) or (III), prior to the reductive elimination event. Later, it was observed that oxygen atmosphere improved the yield of the reaction.[43] This reinforced the possibility that **7** could be oxidized to **8** before reductive elimination.

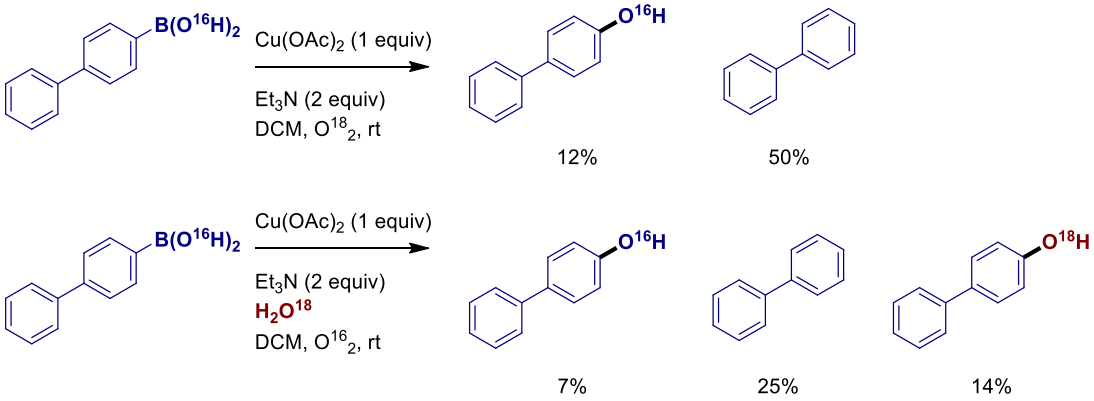


Scheme 20: Mechanistic study of the Chan-Lam reaction by Evans *et al.*

Later, Lam and co-workers reported more in-depth analysis of the Chan-Lam reaction. They first highlighted that the reaction did not proceed *via* a free radical pathway.[44] The addition of the radical trap TEMPO did not impact on the yield of the *N*-arylation reaction. Then, they justified the use of excess arylboronic acid (1.5-2.0 equiv) by the formation of two by-products arising from protodeboronation and oxidation. In the absence of amine substrate, 4-biphenylboronic acid was quickly consumed, with protodeboronation being the major side reaction.[44]

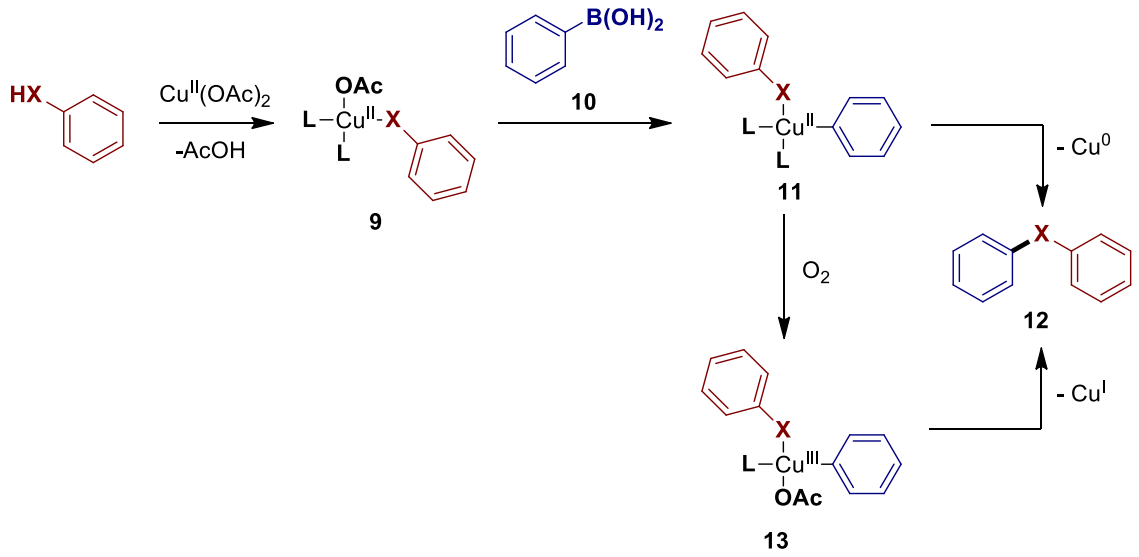
Regarding the phenol formation, Evans *et al.* first mentioned that it could arise from *O*-arylation of water.[40] In addition, Lam and co-workers hypothesised that arylboronic acids could be oxidised to phenols *via* a Cu(III) intermediate or by H_2O_2 formed by reduction of O_2. To support one of these two pathways, they studied the oxygen

incorporation with labelled O_2 and H_2O in the absence of substrates (**Scheme 21**).[45] When $O^{18}{}_2$ was used, no isotope incorporation was observed. However, when H_2O^{18} was added to the reaction, O^{18} was incorporated into biphenylphenol. Therefore, the source of phenol formation is the *O*-arylation of water. This confirmed the hypothesis of Evans and co-workers and established the use of molecular sieves to sequester water and increase the yield.



Scheme 21: Study of the oxygen incorporation in the Chan-Lam reaction with labelled O_2 and H_2O.

Based on these observations, Lam *et al.* reported a general mechanism for the Chan-Lam amination (**Scheme 22**).[45] The first step consisted in the rapid coordination of $Cu(OAc)_2$ by the nucleophile to form the soluble Cu(II) complex **9**. Then, transmetalation of the boronic acid **10** with **9** afforded the Cu(II) complex **11**. At this stage, complex **11** could undergo reductive elimination to give **12**, or could be oxidised to give the Cu(III) species **13** which could then reductively eliminate to afford the desired product **12**. Quantitative analysis of the reaction was conducted, and revealed only trace amounts of Cu(0) at the end of the reaction. This suggested that reductive elimination from a Cu(II) intermediate was not the major pathway.



Scheme 22: Proposed general mechanism for the Chan-Lam reaction by Lam *et al.*

These papers settled the ground of the Chan-Lam amination reaction. The main advantage of these new copper-catalysed cross-coupling was the high functional group tolerance due to the mild reaction conditions employed. The wide diversity of nitrogen-containing substrates was also striking. However, low yields were obtained for some coupling partners like amides, sulfonamides, and aromatic heterocycles. In addition, the reaction required stoichiometric amounts of copper catalyst and excess of boronic acid starting material. Therefore, extensive work was conducted to develop better conditions and to expand the scope of this useful reaction.

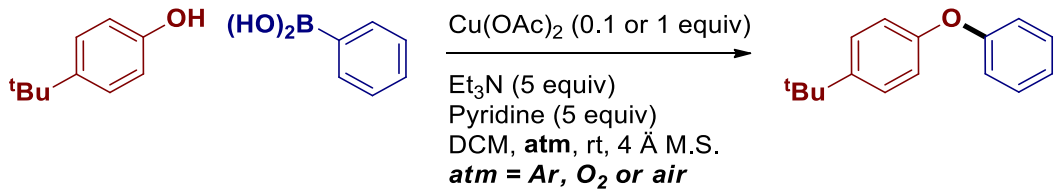
2.3. Development of the reaction conditions

Since 1997, more than 100,000 papers or patents highlighted the use of the Chan-Lam reaction. This process has been extensively studied. Many groups directed their efforts to the optimisation of the reaction conditions investigating the catalyst sources, the solvents, the bases, the ligands, and the additives, to afford an efficient cross-coupling of aryl boronic acids with various heteroatom-based nucleophiles.

2.3.1. Catalyst sources

The first three publications by the groups of Chan, Evans and Lam sparked the interest of synthetic chemists as they highlighted remarkably simple conditions for an incredibly useful transformation. A mixture of the amine (1 equiv), aryl boronic acid (2-3 equiv), anhydrous $Cu(OAc)_2$ (1-2 equiv), and Et_3N or pyridine (2-3 equiv) in dichloromethane was stirred at room temperature for 1-2 days under air and afforded the desired product after purification (**Schemes 17** to **19**).[39-41]

Evans ad co-workers studied the reaction in more detail using 4-*tert*-butylphenol (1 equiv) and phenylboronic acid (1 equiv) as coupling partners.[40] They demonstrated that stoichiometric amounts of copper acetate and aerobic conditions were required for the reaction to proceed in good yield (**Table 1**).

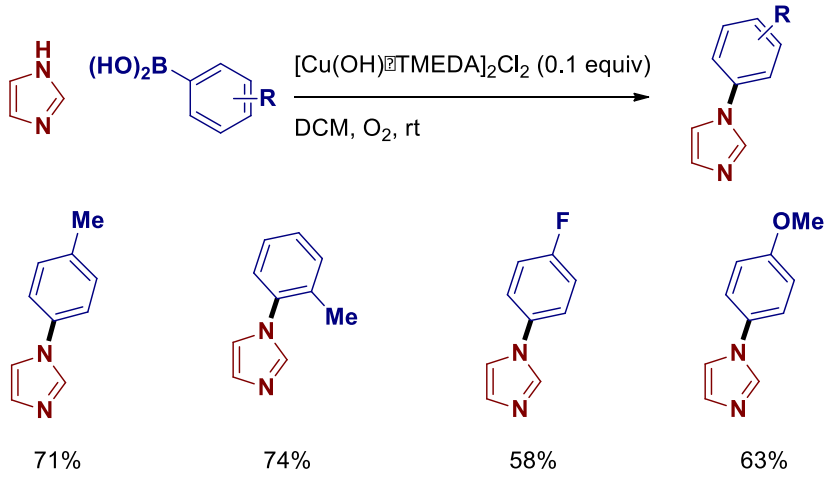


Entry	Equiv $Cu(OAc)_2$	Atmosphere	Equiv base	Isolated yield
1	1	Argon	5	34%
2	1	Air	5	71%
3	1	Oxygen	5	71%
4	0.1	Oxygen	5	30%

Table 1: Influence of catalyst loading and atmosphere.

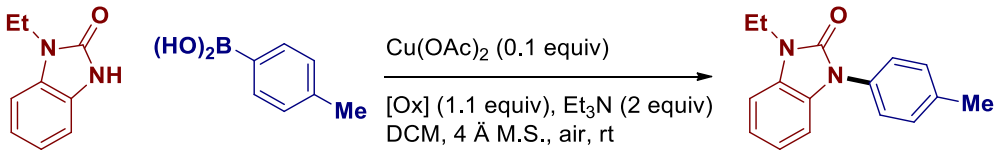
In addition, they showed that the use of $Cu(OAc)_2$ was optimal. Other copper sources such as $Cu(OPiv)_2$, $Cu(acac)_2$, $Cu(CO_2CF_3)_2$, $CuCl_2$, or $CuSO_4$ did not lead to the desired arylated products or resulted in significant C-C bond formation.

In 2000, Collman and Zhong reported the first high-yielding catalytic Chan-Lam reaction using an unprecedented diamine-copper complex (0.1 equiv) to catalyse the intermolecular cross-coupling of arylboronic acids (2 equiv) with imidazoles (1 equiv) under oxygen atmosphere (**Scheme 23**).[46]



Scheme 23: First example of a catalytic Chan-Lam reaction between aryl boronic acids and imidazoles.

Soon after this report, Lam and co-workers studied the effect of stoichiometric oxidants in the presence of catalytic amounts of $Cu(OAc)_2$ (0.1 equiv), and realised that the use of pyridine *N*-oxide, 2,2,6,6-tetramethyl-1-piperidinyloxyl, or *N*-methylmorpholine-*N*-oxide (1.1 equiv) afforded good reaction yields (**Scheme 24**).[43]

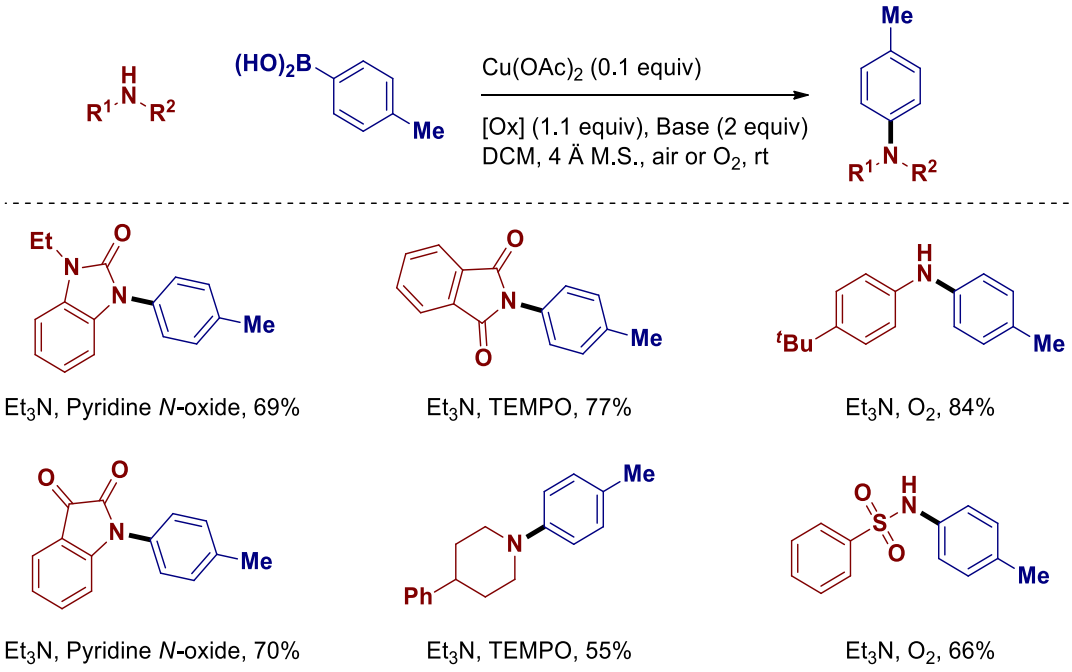


Pyridine *N*-oxide > TEMPO > NMO > di-*t*-butyl nitroxide > $NaB(OH)_3$ > mCPBA

69% 64% 62% 55% 31% 6%

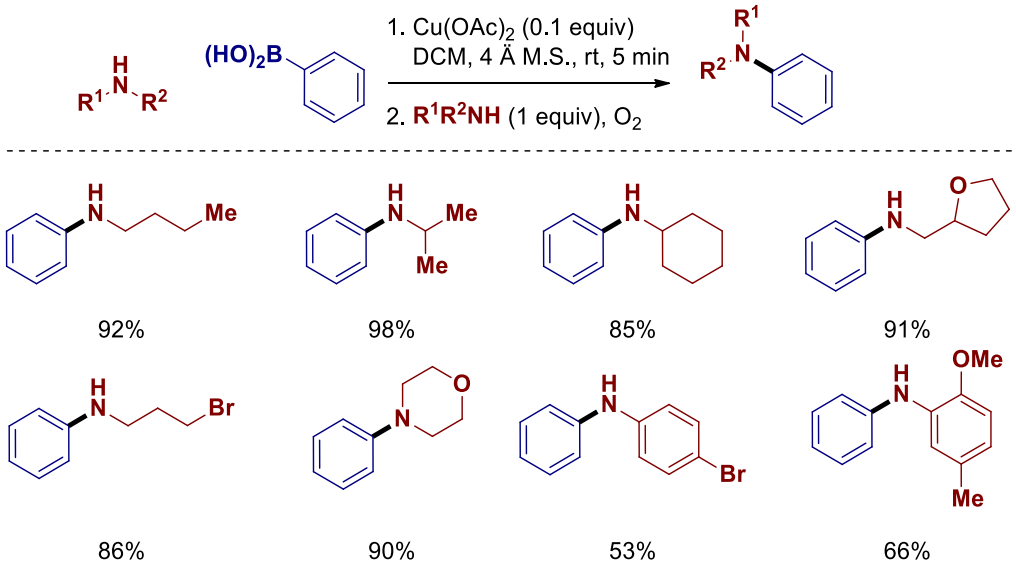
Scheme 24: Study of the effect of stoichiometric oxidants under catalytic Chan-Lam conditions by Lam *et al.*

Despite its efficiency, this new set of conditions suffered from two major limitations: the oxidation of the aryl boronic acid starting material and the variability of the oxidant depending on the nitrogen nucleophile used (**Scheme 25**).[44]



Scheme 25: Scope of the catalytic Chan-Lam reaction using stoichiometric amounts of oxidant or oxygen atmosphere.

In 2003, Batey and Quach reported a base-free Chan-Lam amination of aryl boronic acids (2 equiv) with both aryl and aliphatic amines (1 equiv), through a two-step procedure using catalytic amount of $Cu(OAc)_2$ (0.1 equiv) under oxygen atmosphere (**Scheme 26**).[47] The efficiency of these conditions lay in the premixing of the boronic acid starting material with the copper catalyst before adding the nucleophilic amine. For example, arylation of aliphatic amines, which was difficult to achieve under previous cross-coupling conditions, worked significantly better using this sequential procedure.

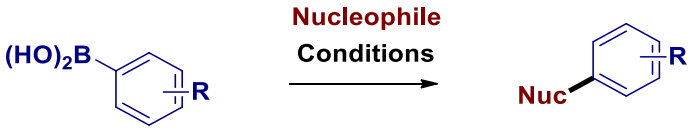


Scheme 26: Catalytic Chan-Lam reaction between aryl boronic acids and alkyl/aryl amines.

Through the years, several groups focused their efforts on the development of new conditions optimising the catalyst source to allow the efficient coupling of diverse nucleophiles under air or oxygen atmospheres (**Table 2**). In 2006, Kantam and co-workers reported a catalytic Chan-Lam amination using a recyclable CuFAP catalyst (**Table 2, entry 1**).[48] This new catalyst allowed the cross-coupling of diverse *N*-nucleophiles including imidazoles, anilines and aliphatic amines with arylboronic acids at room temperature under air. Later, Fu and co-workers published a Cu_2O procedure for the synthesis of primary aromatic amines using aqueous ammonia as the nucleophile (**Table 2, entry 2**).[49] Despite the broad scope, electron-rich and neutral-aryl boronic acids tended to form the diaryl amine as a side product. In 2010, the cross-coupling of alkyl- and aryl- carboxylic acids with arylboronic acids was achieved by Cheng and co-workers.[50] In their procedure, the use of catalytic amounts of $Cu(OTf)_2$ in the presence of one equivalent of urea in EtOAc at 60 ºC under air, allowed the formation of highly functionalised esters in good to very high yields (**Table 2, entry 3**). The group of Kianmehr and the group of Zhao, reported the useful Chan-Lam reaction of cyanate ions and *H*-phosphonate diesters respectively (**Table 2, entries 4** and

5).[51,52] In 2012, Singh and co-workers demonstrated for the first time that, $NiCl_2$ catalyst could promote efficient cross-coupling between arylboronic acids and amine nucleophiles in the presence of the 2,2-bipyridyl bidentate ligand (**Table 2, entry 6**).[53] The same year, Feng and co-workers successfully coupled thiols to aryl boronic acids at room temperature using a combination of $CuSO_4$ (0.05 equiv) and 1,10-phenanthroline (0.05 equiv).[54] An aqueous solution of tetra-*n*-butylammonium hydroxide was found to be the best base to afford the desired S-arylated product (**Table 2, entry 7**). In 2014, Kim and co-workers showed that, CuCl (0.1 equiv) allowed the base-free cross-coupling of sulfonyl azides and arylboronic acids at room temperature in methanol under air atmosphere within 2 hours (**Table 2, entry 8**).[55] Later, a similar protocol was applied for the synthesis of *N*-aryl carbamates from azidoformates and boronic acids (**Table 2, entry 9**).[56] Recently, the Phukan group synthesized a novel square pyramidal copper complex $[Cu(DMAP)_4I]I$ by a disproportionation reaction of CuI and DMAP in DMSO.[57] This catalyst allowed a quick (less than 5 minutes) and low catalyst loading (0.02 equiv) Chan–Lam reaction (**Table 2, entry 10**). In addition, a broad range of nucleophiles including amines, amides, azides, and thiols was tolerated and the reaction conditions gave the desired product in good to very high yields. In 2016, Das and co-workers developed a complementary set of Ni- and Cu-based catalyst systems for the selective *N*-arylation of 2-aminobenzimidazoles (**Table 2, entry 11**).[58] The successful selective *N*-arylation of the primary amine group was achieved by using $Ni(OAc)_2$ (0.2 equiv) in the presence of DBU (2 equiv) under air. An array of both the *N*-arylated isomers of 2-aminobenzimidazoles was obtained using this general and simple protocol. Finally, last year, the chemoselective copper-catalysed *N*-arylation of unprotected aminobenzamides was reported for the first time by the groups of Zhang and Xu (**Table 2, entry 12**).[59] The use of CuCl (0.15 equiv) catalyst enabled the selective arylation of

amino groups in *ortho/meta/para*-aminobenzamides under open-flask conditions. The reported procedure was scalable and compatible with a wide range of functional groups.



Entry	Year	Nucleophiles	Conditions	Isolated Yield	Group [Ref]
1	2006	Imidazole, aryl and aliphatic amines	**CuFAP (0.2 equiv)**, MeOH, air, rt	78-95%	Kantam [48]
2	2008	Aqueous ammonia	**Cu_2O (0.1 equiv)**, MeOH, air, rt	65-93%	Yufen [49]
3	2010	Carboxylic acid	**$Cu(OTf)_2$ (0.4 equiv)**, $CO(NH_2)_2$ (1 equiv), EtOAc, air, 60 ºC	51-98%	Cheng [50]
4	2011	Cyanate	**$CuBr_2$ (0.1 equiv)**, MeOH, air, 60 ºC	48-80%	Kianmehr [51]
5	2011	*H*-phosphonate diesters	**Cu_2O (0.05 equiv)**, Phenanthroline (0.1 equiv), $(i\text{-Pr})_2$Net, MeCN, air, rt	47-96%	Zhao [52]
6	2012	Aryl and aliphatic amines, amides, NH-heterocycles	**$NiCl_2$ (0.2 equiv)**, 2,2-bipyridyl (0.2 equiv), DBU (2 equiv), MeCN, air, rt	nr-85%	Singh [53]
7	2012	Thiols	**$CuSO_4$ (0.05 equiv)**, 1,10-phenanthroline (0.05 equiv), $n\text{Bu}_4\text{NOH}$ (0.4 equiv), EtOH, O_2, rt	nr-88%	Feng [54]
8	2014	Sulfonyl azide	**CuCl (0.1 equiv)**. MeOH, air, rt	13-99%	Kim [55]
9	2015	Azidoformates	**CuCl (0.1 equiv)**, MeOH, air, rt	nr-94%	Kim [56]
10	2015	Aryl and aliphatic amines, amides, azides and thiols	**$[Cu(DMAP)_4I]I$ (0.02 equiv)**, MeOH, air, rt	60-93%	Phukan [57]
11	2016	2-aminobenzimidazoles	**$Ni(OAc)_2$ (0.2 equiv)**, DBU (2 equiv), DMSO, air, 50 ºC	63-85%	Das [58]
12	2017	Aminobenzamides	**CuCl (0.15 equiv)**, Et_3N (0.5 equiv), MeOH, rt	31-90%	Zhang and Xu [59]

Table 2: Evolution of catalyst sources for the Chan-Lam reaction of various nucleophiles.

Thanks to the development of all these catalysts it is now easier to find a set of conditions to achieve specific Chan-Lam reaction, allowing synthetic chemists to access highly functionalised compounds in an efficient manner. In addition to the catalyst, the solvent system used in this reaction is crucial.

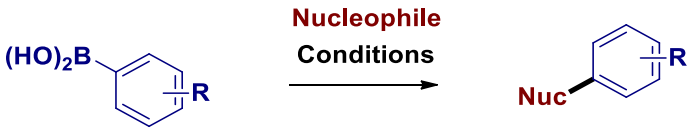
2.3.2. Solvent system

In their 1998 publication, Chan and Lam established the following order for the solvent in terms of reactivity:[41]

DCM > 1,4-dioxane = NMP = THF = DMF >> EtOAc = Toluene = DMSO.

It is important to notice that the use of methanol resulted in no product formation. This trend was confirmed by the first reports published by Chan, Evans, Lam, Collman and Batey where DCM reactions afforded good yields (**Table 3, entries 1** to **4**).[39-41,46-47] The only exception at that time was the work disclosed by Buchwald and Antilla (**Table 3, entries 5**).[60] In their publication, the authors reported the cross-coupling of aryl boronic acids (1.5 equiv) with amines (1 equiv), using $Cu(OAc)_2$ (0.1-0.2 equiv) as a catalyst, 2,6-lutidine (1 equiv) as a base, and myristic acid (0.1-0.2 equiv) as an additive, at room temperature in toluene under air or oxygen atmosphere. This new methodology using toluene as the solvent afforded a broad substrate scope regarding aniline-type nucleophiles, but only moderate yields when using aliphatic amines. Following this report, Yudin and co-workers used the same reaction conditions for the synthesis of N-aryl aziridines from the corresponding NH-aziridines (**Table 3, entries 6**).[61] The first example of a Chan-Lam amination using a protic solvent was reported in 2003 by Xie and co-workers.[62] They described the coupling of imidazole (1.1 equiv) with arylboronic acids (1 equiv) in the presence of a catalytic amount of $Cu(OAc)_2$ (0.05 equiv), in methanol at reflux yielding the corresponding *N*-arylimidazoles in quantitative yields

(**Table 3, entries 7**). During their optimisation, they selected DCM, DCE, Toluene, THF, Acetone, and MeCN as reaction solvents. Unfortunately, no reaction occurred using these solvents and catalytic amounts of $Cu(OAc)_2$. However, moving onto the unconventional MeOH, the desired *N*-arylimidazole product was obtained in high yields. Later, the same simple conditions were used for the base-free coupling of amines, amides, imides, and sulfonamides with stoichiometric amounts of boronic acid (**Table 3, entries 8**).[63] In addition, the groups of Bolm and Guo described a Chan–Lam coupling of a broad range of aryl boronic acids (2.3 equiv) with sulfoximines (1 equiv) and sodium azides (1 equiv) respectively (**Table 3, entries 9** and **10**).[64,65] These reactions proceeded using the set of conditions reported by Xie and co-workers but at room temperature. Since these reports, protic solvents were extensively used in the Chan-Lam reaction (**Table 3, entries 11** to **18**) allowing the coupling of anilines, aliphatic amines, amides, aqueous ammonia, cyanate ions, thiols, sulfonyl azides, and azidoformates with aryl boronic acids.[48,49,51,54-58] In addition, use of other solvents, for example, EtOAc and MeCN enabled the unprecedented Chan-Lam reaction of aryl boronic acids with carboxylic acids and H-phosphonate diesters respectively (**Table 3, entries 19** and **20**).[50,52] In all those cases, the right combination of catalyst and solvent afforded higher yields using lower catalyst loadings and shorter reaction times.



Entry	Year	Nucleophiles	Conditions	Isolated Yield	Group [Ref]
1	1997 - 1998	Aryl and aliphatic amines, amides, ureas, carbamates, sulfonamides	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (2-10 equiv), **DCM**, air, rt	4-96%	Chan, Evans, Lam [39-41]
2	2000	Imidazole	$[Cu(OH)\cdot TMEDA]_2Cl_2$ (0.1 equiv), **DCM**, air, rt	5-98%	Collman [46]

3	2001	Aryl and aliphatic amines, amides, sulfonamides, benzimidazole, indazole	$Cu(OAc)_2$ (0.1-0.2 equiv), pyridine N-oxide or TEMPO (1.1 equiv), Et_3N (2 equiv), **DCM**, air, rt	27-100%	Lam [43]
4	2003	Aryl and aliphatic amines, NH-heterocycles	$Cu(OAc)_2$ (0.1 equiv), **DCM**, O_2, rt or 40 ºC	nr-98%	Batey [47]
5	2001	Aryl and aliphatic amines	$Cu(OAc)_2$ (0.05-0.2 equiv), myristic acid (0.1-0.2 equiv), 2,6-lutidine (1 equiv), **Toluene**, air, rt	10-91%	Buchwald [60]
6	2003	Aziridines	$Cu(OAc)_2$ (0.1 equiv), myristic acid (0.2 equiv), 2,6-lutidine (1 equiv), **Toluene**, air, rt	nr-95%	Yudin [61]
7	2003	Imidazole	$Cu(OAc)_2$ (0.05 equiv), **MeOH**, air, reflux	92-98%	Xie [62]
8	2004	Amines, amides, imides, and sulfonamides	$Cu(OAc)_2$ (0.1 equiv), **MeOH**, air, reflux	nr-96%	Xie [63]
9	2005	Sulfoximines	$Cu(OAc)_2$ (0.1 equiv), **MeOH**, air, rt	62-93%	Bolm [64]
10	2007	Sodium azides	$Cu(OAc)_2$ (0.1 equiv), **MeOH**, air, rt	70-98%	Guo [65]
11	2006	Imidazole, aryl and aliphatic amines	CuFAP (0.2 equiv), **MeOH**, air, rt	78-95%	Kantam [48]
12	2008	Aqueous ammonia	Cu_2O (0.1 equiv), **MeOH**, air, rt	65-93%	Yufen [49]
13	2011	Cyanate	$CuBr_2$ (0.1 equiv), **MeOH**, air, 60 ºC	48-80%	Kianmehr [51]
14	2012	Thiols	$CuSO_4$ (0.05 equiv), 1,10-phenanthroline (0.05 equiv), $n$$Bu_4NOH$ (0.4 equiv), **EtOH**, O_2, rt	nr-88%	Feng [54]
15	2014	Sulfonyl azide	CuCl (0.1 equiv), **MeOH**, air, rt	13-99%	Kim [55]
16	2015	Azidoformates	CuCl (0.1 equiv), **MeOH**, air, rt	nr-94%	Kim [56]
17	2015	Aryl and aliphatic amines, amides, azides and thiols	$[Cu(DMAP)_4I]I$ (0.02 equiv), **MeOH**, air, rt	60-93%	Phukan [57]
18	2017	Aminobenzamides	CuCl (0.15 equiv), Et_3N (0.5 equiv), **MeOH**, rt	31-90%	Zhang and Xu [56]
19	2010	Carboxylic acid	$Cu(OTf)_2$ (0.4 equiv), $CO(NH_2)_2$ (1 equiv), **EtOAc**, air, 60 ºC	51-98%	Cheng [50]

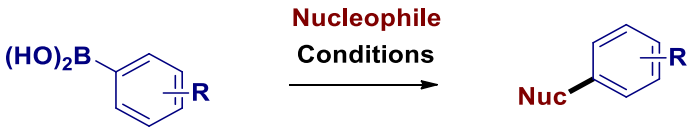
20	2011	*H*-phosphonate diesters	Cu_2O (0.05 equiv), Phenanthroline (0.1 equiv), $(i\text{-}Pr)_2NEt$, **MeCN**, air, rt	47-96%	Zhao [52]

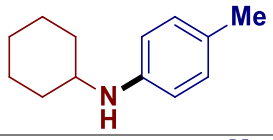
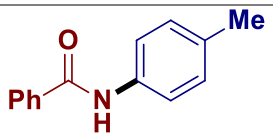
Table 3: Evolution of solvent system for the Chan-Lam reaction of various nucleophiles.

When considering the reaction conditions of the Chan-Lam amination, another important parameter is the use of bases.

2.3.3. Bases

The role of the base was first studied by the groups of Chan and Lam. The model substrate, the *p*-tolylboronic acid (2 equiv), was coupled to several nucleophiles in the presence of an excess of Et_3N or pyridine (2-3 equiv). Focusing on this substrate, the results obtained with various *N*-nucleophiles would draw the conclusion that Et_3N was the optimal base (**Table 4, entries 1 to 4**).[39,41] However, pyridine (2 equiv) was the only base suitable for the coupling of NH-heterocycles with aryl boronic acids (**Table 4, entries 5 to 7**).[39,41] In addition, Evans described that a mixture of Et_3N (5 equiv) and pyridine (5 equiv) was the best combination to afford the efficient synthesis of the *L*-throxine intermediate (**Table 4, entry 8**).[40]



Entry	Compound	Base	Isolated Yield	[Ref]
1		Et_3N (2 equiv) Pyridine (2 equiv)	56% 63%	[39]
2		Et_3N (2 equiv) Pyridine (2 equiv)	17% 4%	[39]

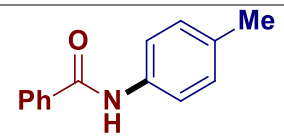
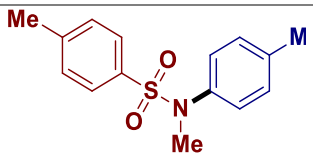
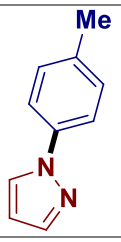
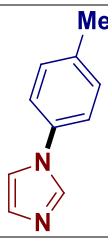
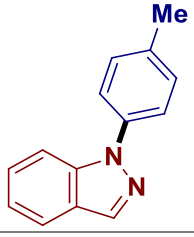
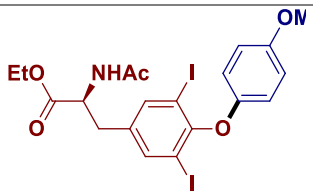
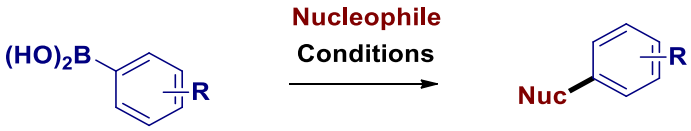
3		Et_3N (2 equiv) Pyridine (2 equiv)	45% 7%	[39]
4		Et_3N (2 equiv) Pyridine (2 equiv)	72% 23%	[39]
5		Et_3N (2 equiv) Pyridine (2 equiv)	nr 76%	[41]
6		Et_3N (2 equiv) Pyridine (2 equiv)	nr 72%	[41]
7		Et_3N (2 equiv) Pyridine (2 equiv)	nr 72%	[41]
8		Et_3N (5 equiv) and Pyridine (5 equiv)	81%	[40]

Table 4: Influence of the base for the Chan-Lam reaction.

Following these studies, several protocols were developed using different bases to enable unprecedented Chan-Lam couplings. For example, *N*-arylation of electron deficient indoles had always been a challenge in Chan-Lam cross-couplings when using Et_3N or pyridine, and required the use of an aldehyde directing group at the C2-position. In 2007, Bekolo overcame this limitation with the synthesis of *N*-arylated indole in good to excellent yields using diisopropylethylamine (**Table 5, entry 1**).[66] Last

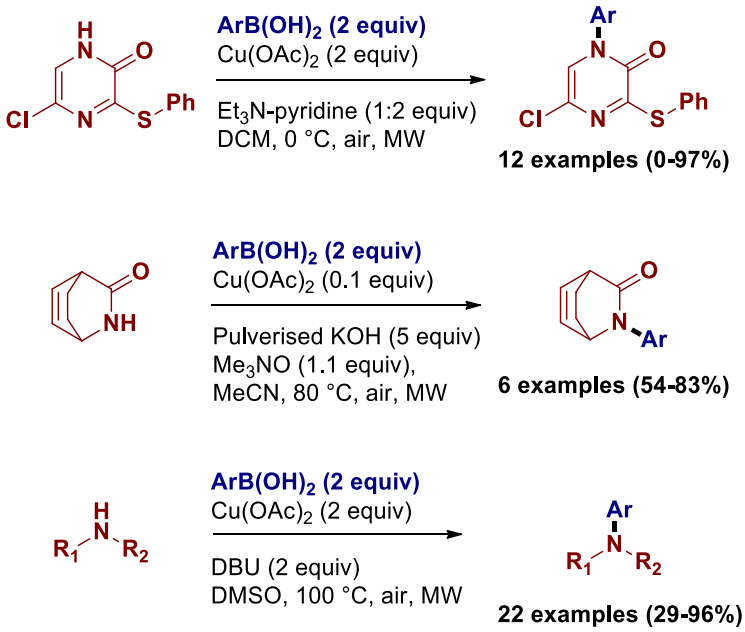
year, the group of Dong reported an unprecedented Chan-Lam set of conditions for the synthesis of *N*-aryl phosphinamides and phosphonamides (**Table 5, entry 2**).[67] This reaction was performed with high efficiency and good functional group tolerance in the absence of any ligands or co-catalysts.



Entry	Year	Nucleophiles	Conditions	Isolated Yield	Group [Ref]
1	2007	Indole	$Cu(OAc)_2$ (2.5 equiv), ***i*-Pr_2NEt** (2.5 equiv), DCM, air, rt	45-100%	Bekolo [66]
2	2017	Phosphonic and phosphinic amides	$Cu(OAc)_2$ (2 equiv), **Cs_2CO_3** (2 equiv), toluene, air, 80 ºC	46-83%	Dong [67]

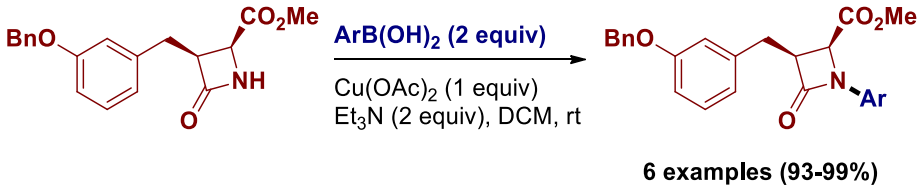
Table 5: Optimisation of difficult Chan-Lam reactions using unprecedented base systems.

Under microwave irradiation, a mixture of Et_3N and pyridine (1:2) allowed the arylation at the N1-position of the 2(*1H*)-pyrazinone scaffold, pulverised potassium hydroxide enabled the *N*-arylation of bridged lactams, and DBU afforded the cross-coupling of a broad range of amines (**Scheme 27**).[68-70]



Scheme 27: Examples of Chan-Lam amination using unprecedented base systems under microwave irradiations.

The use of weak bases allows the Chan-Lam reaction to operate under mild conditions and enables the use of chiral compounds without the risk of racemisation. A group from Bristol-Myers Squibb reported the *N*-arylation of labile azetidinone esters using the initial reaction conditions reported by Chan, Lam and co-workers (**Scheme 28**).[71] The desired products were obtained in high yields, and with no racemisation.

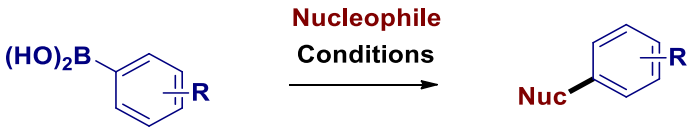


Scheme 28: *N*-arylation of labile azetidinone esters.

The set of reaction conditions described in this section afforded a good understanding of what bases can be used to perform an efficient Chan-Lam reaction. In addition to the base, several groups started using ligands to access new chemical space and to achieve faster reaction times.

2.3.4. Ligands

N1-arylation of nucleosides has always been a valuable but difficult transformation (<50% yield). In 2005, Yu and co-workers published an efficient avenue for the direct *N*-arylation of nucleobases with aryl boronic acids using $Cu(OAc)_2$ as catalyst (**Table 6, entry 1**).[72] TMEDA was found to be the only efficient ligand for the reaction to proceed in high yield. The *N*-arylnucleobases were obtained in excellent yields at room temperature within 45 min when methanol and water were used as a mixed solvent. Later, a combination of TMEDA ligand and copper(II) nitrate catalyst enabled the formation of carbon–nitrogen biaryls in high yields from both hindered imidazoles and aryl boronic acids (**Table 6, entry 2**).[73] In 2004, Evans and co-workers reported the arylation and methylation of sulfinic acid salts.[74] However, the use of stoichiometric amounts of copper catalyst limited its application. Three years later, catalytic reaction conditions were developed independently by two research groups. Tse and co-workers reported that the combination of $CuSO_4$ (0.2 equiv) and a substituted imidazole ligand efficiently catalysed the reaction between aryl boronic acids and sulfinic acid salts (**Table 6, entry 3**).[75] In the meantime, Batey and co-workers managed to achieve the same transformation using 1,10-phenanthroline (0.2 equiv) as the ligand and $Cu(OAc)_2$ (0.1 equiv) the catalyst (**Table 6, entry 4**).[76] In addition, 1,10-phenanthroline was used as a ligand for S-arylation of both aryl thiols and 1,2-bis(*o*-amino-1*H*-pyrazolyl) disulfides (**Table 6, entries 5** and **6**).[57,77] Recently, Sun and co-workers published a Chan-Lam thiocyanation of aryl boronic acids with trimethylsilylisothiocyanate using TMEDA as the ligand.[78] This reaction proceeded at room temperature, and was compatible with a wide range of functional groups (**Table 6, entries 7**).

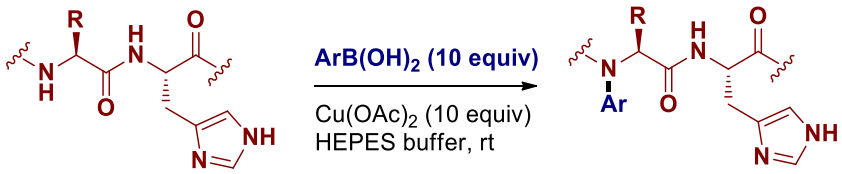


Entry	Year	Nucleophiles	Conditions	Isolated Yield	Group [Ref]
1	2005	Nucleosides	$Cu(OAc)_2$ (1 equiv), **TMEDA** (2 equiv), MeOH-H_2O (4:1), air, rt	50-90%	Yu [72]
2	2009	Hindered imidazole	$Cu(NO_3)_2$ (0.1-0.5 equiv), **TMEDA** (0.1-0.5 equiv), MeOH, O_2, rt	48-99%	Kozlowskia [73]
3	2007	Sulfinic acid salts	$Cu(OAc)_2$ (0.2 equiv), **1-benzylimidazole** (0.4 equiv), DMSO, Air, 60 ºC	22-83%	Tse [74]
4	2007	Sulfinic acid salts	$Cu(OAc)_2$ (0.1 equiv), **1,10-phenanthroline** (0.2 equiv), DCM-DMF, O_2, 40 ºC	22-83%	Batey [75]
5	2009	1,2-bis(*o*-amino-1*H*-pyrazolyl) disulfides	CuI (0.2 equiv), **1,10-phenanthroline** (0.2 equiv), H_2O-DMSO, O_2, 100 ºC	nr-100%	Zhong [76]
6	2012	Thiols	$CuSO_4$ (0.05 equiv), **1,10-phenanthroline** (0.05 equiv), nBu$_4$NOH (0.4 equiv), EtOH, O_2, rt	nr-88%	Feng [57]
7	2015	Trimethylsilylisothiocyanate	CuCl (0.2 equiv), **TMEDA** (0.2 equiv), NaF, K_2CO_3 MeCN, Air, rt	45-89%	Sun [77]

Table 6: Development of Chan-Lam reactions between aryl boronic acids and various nucleophiles using ligands.

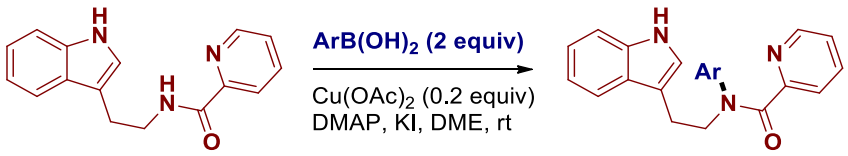
Finally, directing groups can serve as ligands through the catalysis process. In 2016, the group of Ball reported the first example of directed Chan-Lam amination.[79] They highlighted that histidine residues enabled oxidative coupling of boronic acids at the backbone NH of a neighbouring amino acid *via* chelation of the histidine moiety to the copper catalyst. In addition, they demonstrated that the mild reaction conditions used

(common physiological buffers and room temperature) are compatible with proteins and biological systems (**Scheme 29**).



Scheme 29: Chan-Lam reaction enabled by chelation of the histidine moiety.

Last year, Baidya and co-workers published a selective copper-catalysed amidation of aryl boronic acids with tryptamine-substituted picolinamide (**Scheme 30**).[80] The coupling occurred regioselectively at the amide moiety *via* a chelation-assisted event through the pyridine group in the picolinamide. This procedure enabled the synthesis of unsymmetrical amides in good to excellent yields.



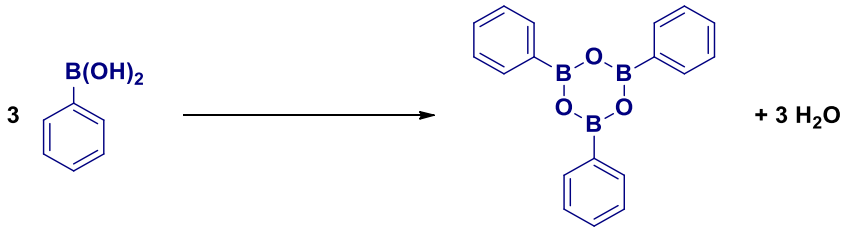
Scheme 30: Chan-Lam reaction enabled by chelation of the picolinamide moiety.

The design of all these ligand-based procedures allowed the development of diverse and robust Chan-Lam reactions. These new reactions highlighted the pivotal role of the ligand in copper catalysis. Monodentate or bidentate ligands enable difficult reactions to occur *via* chelation to the copper catalyst. Through the years, adding to the developments of the catalysts, the solvents, the bases and the ligands, several additives were shown to be efficient for the Chan-Lam reaction to occur in high yields.

2.3.5. Additives

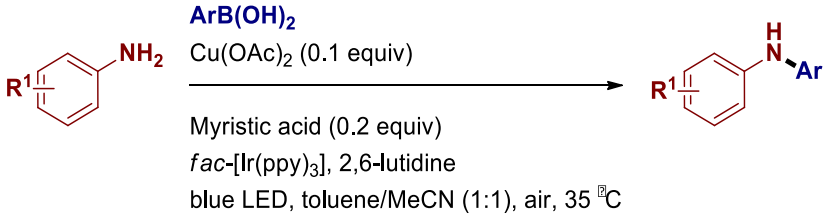
Molecular sieves were the first additive that was studied during the optimisation of the Chan-Lam reaction. Evans and co-workers reported that the use of 4 Å molecular sieves was beneficial for the reaction to occur in high yields.[40] It was found that water

could be generated *via* formation of the trimeric triaryl boroxine from the aryl boronic acid starting material (**Scheme 31**). Then, the water formed would oxidise the aryl boronic acid compound to the corresponding phenol, impeding the catalytic cycle of the reaction. Through the years, several methodologies reported the use of molecular sieves to lower the amounts of undesired by-products.



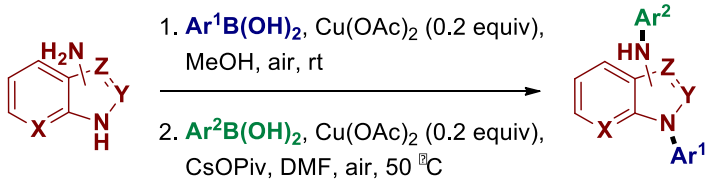
Scheme 31: Formation of triaryl boroxine from the aryl boronic acid.

As previously mentioned, Buchwald and Antilla reported the use of myristic acid for the coupling of aryl boronic acids with amines in the presence of a catalytic amount of $Cu(OAc)_2$.[58] They demonstrated that myristic acid facilitates the reaction by increasing the solubility of the copper catalyst. In their recent report, the group of Kobayashi highlighted that the same additive enabled the visible light-mediated photoredox cross-coupling of anilines with aryl boronic acids, in the presence of *fac*-[$Ir(ppy)_3$] as a co-catalyst (**Scheme 32**).[81] Interestingly, substrates that are challenging to synthesise under conventional Chan–Lam conditions were successfully converted under the present conditions.



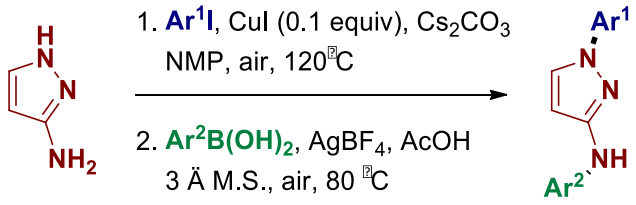
Scheme 32: Visible light-mediated photoredox cross-coupling of anilines with aryl boronic acids.

The use of unconventional additives can sometimes overcome long-standing limitations. For example, polynitrogenated heterocycles are challenging substrates for metal catalysed *N*-arylation, as they can lead to the formation of regioisomers and polyarylated products. In 2014, Das and co-workers developed a copper-catalysed sequential *N*-arylation of *C*-amino-NH-azoles (**Scheme 33**).[82] Under conventional Chan-Lam reaction conditions, this enabled the formation of the desired *N*-arylated products without any other isomers or polyarylated products observed. The use of CsOPiv as an additive allowed the sequential reaction to occur at the C-NH_2 position in good to excellent yields.



Scheme 33: Cu-catalysed sequential *N*-arylation of *C*-amino-NH-azoles.

Recently, Prestat and co-workers reported the first one-pot selective diarylation of 3-aminopyrazole by Cu(I)/Cu(II)-assisted tandem catalysis (**Scheme 34**).[83] This reaction was enabled *via* an oxidation from Cu(I) to Cu(II) using a mixture of $AgBF_4$ and AcOH in the second step of the procedure. This unprecedented methodology used a combination of an Ullmann reaction (at the N1 position) and a Chan-Lam reaction (at the N3 position of the *N1*-arylated product) to afford the desired diarylated product.



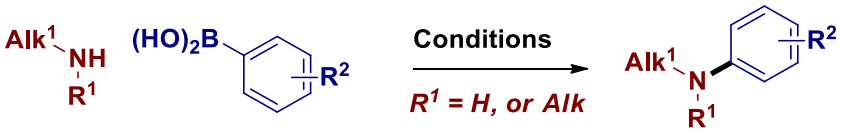
Scheme 34: One-pot selective diarylation of 3-aminopyrazole by Cu(I)/Cu(II)-assisted tandem catalysis.

The Chan-Lam cross-coupling between *N*-nucleophiles and aryl boronic acids has considerably evolved since its discovery more than twenty years ago. Fine-tuning of the reaction conditions, including screening of catalysts, solvents, bases, ligands, and additives, are continually being conducted. Therefore, significant progress has been made in expanding the scope of this useful transformation.

2.4. Scope of the Chan-Lam reaction

Since 1997, the scope of the Chan-Lam reaction has increased due to the development of new reaction conditions. Aryl boronic acids react efficiently with a broad range of coupling partners including amines, amides, anilines, azides, NH-heterocycles, carbamates, sulfonamides, phenols, thiols, carboxylic acids, and others nucleophiles. The reaction scope is show in Tables 7 to 17.

2.4.1. Alkyl amines



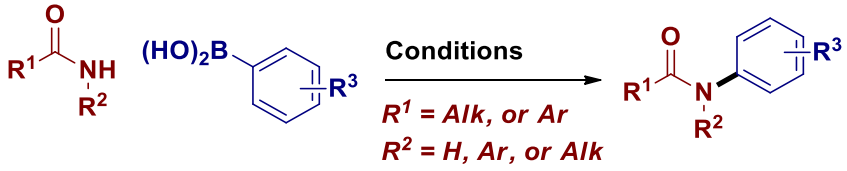
Entry	Year (Group) [Ref]	Conditions	Pros	Cons
1	1997-1998 (Chan and Lam) [39, 41]	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (2-10 equiv), DCM, air, rt	- Moderate to excellent yields	- Stoichiometric in copper - Stoichiometric in base - Only tolylboronic acid was coupled - No heterocycle
2	2001 (Lam) [44]	$Cu(OAc)_2$ (0.1-0.2 equiv), pyridine N-oxide or TEMPO (1.1 equiv), Et_3N (2 equiv), DCM, air, rt	- Catalytic in copper - Amount of base reduced - Good yields	- Need stoichiometric amounts of oxidant - Only aryl boronic acids were coupled - No heterocycle

3	2001 (Buchwald) [60]	$Cu(OAc)_2$ (0.05-0.2 equiv), myristic acid (0.1-0.2 equiv), 2,6-lutidine (1 equiv), Toluene, air, rt	- Catalytic in copper - Catalytic in myristic acid	- Low to moderate yields - No heterocycle - Only tolylboronic acid was coupled - Need a strong stirring and a large flask
4	2003 (Batey) [47]	$Cu(OAc)_2$ (0.1 equiv), DCM, O_2, rt or 40 ºC	- Catalytic in copper - Excellent yields - Aryl boronic acids and aryl BF_3K	- Sequential procedure - No heterocycle
5	2003 (Yudin) [61]	$Cu(OAc)_2$ (0.1 equiv), myristic acid (0.2 equiv), 2,6-lutidine (1 equiv), Toluene, air, rt	- Successful coupling of aziridines - Catalytic in copper - Catalytic in myristic acid	- Moderate yields - Only aryl boronic acids were coupled - No heterocycle
6	2004 (Xie) [63]	$Cu(OAc)_2$ (0.1 equiv), MeOH, air, reflux	- Moderate to good yields - Catalytic in copper - No additive	- Reflux - Only tolylboronic acid was coupled - No heterocycle
7	2006 (Fu) [49]	Cu_2O (0.1 equiv), MeOH, air, rt	- Successful coupling of Ammonia - Catalytic in copper - Good to excellent yields - Broad aryl boronic acids scope - Successful coupling of thiophene	- Only boronic acids were coupled - Thiophene as the only heterocyclic coupling partner
8	2006 (Kantam) [48]	CuFAP (0.25 equiv), MeOH, rt	- Excellent yields - Catalytic in copper - No additive - Reusable	- No heterocycle - Only tolylboronic acid was coupled - Need to

			catalyst	prepare the catalyst
9	2008 (Yufen) [49]	Cu_2O (0.1 equiv), MeOH, air, rt	- Catalytic in copper - Good to excellent yields - Broad aryl boronic acids scope	- Only aryl boronic acids were coupled - No heterocycle
10	2012 (Singh) [53]	$NiCl_2$ (0.2 equiv), 2,2-bipyridyl (0.2 equiv), DBU (2 equiv), MeCN, air, rt	- Good to excellent yields - Catalytic in nickel - Catalytic in ligand	- Need stoichiometric amounts of base - Only aryl boronic acids were coupled - No heterocycle
11	2015 (Phukan) [57]	$[Cu(DMAP)_4I]I$ (0.02 equiv), MeOH, air, rt	- Excellent yields - Fast reaction time - Catalytic in copper - Successful coupling of 3-pyridine boronic acid - No additive	- Need to prepare the catalyst - Only aryl boronic acids were coupled - 3-pyridine as the only heterocyclic coupling partner

Table 7: Scope of the Chan-Lam reaction between aryl boronic acids and alkyl amines.

2.4.2. Amides



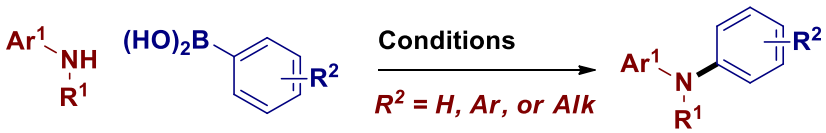
Entry	Year (Group) [Ref]	Conditions	Pros	Cons
1	1997-1998 (Chan and Lam) [39, 41]	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (2-10 equiv), DCM, air, rt	- Good yields for secondary and cyclic amides	- Stoichiometric in copper and base - Only tolylboronic acid was coupled

					-	No heterocycle - Low yields for primary amides
2	2001 (Lam) [44]	$Cu(OAc)_2$ (0.1-0.2 equiv), pyridine N-oxide or TEMPO (1.1 equiv), Et_3N (2 equiv), DCM, air, rt	-	Catalytic in copper - Amount of base reduced - Good yield	-	Need stoichiometric amount of oxidant - Only aryl boronic acid were coupled - No heterocycle
3	2004 (Xie) [62]	$Cu(OAc)_2$ (0.1 equiv), MeOH, air, reflux	-	Moderate to good yields - Catalytic in copper - No additive	-	Reflux - No heterocycle - Only tolylboronic acid was coupled
4	2008 (Yufen) [49]	Cu_2O (0.1 equiv), MeOH, air, rt	-	Catalytic in copper - Good to excellent yields - Broad aryl boronic acids scope	-	Only aryl boronic acids were coupled - No heterocycle
5	2008 (Ishikura) [69]	$Cu(OAc)_2$ (0.1 equiv) Pulverised KOH (5 equiv) Me_3NO (1.1 equiv), MeCN, 80°C, MW	-	Catalytic in copper - Successful coupling of bridge lactams - Good yields	-	Use of Microwave - Excess of KOH - High temperature - Only 6 examples - Only aryl boronic acids were coupled - No heterocycle
6	2008 (Liebeskind) [118]	CuTC (1 equiv) THF, 60°C	-	Successful coupling of *O*-acetyl hydroxamic acids - Good yields	-	Stoichiometric amounts of copper - High temperature - Only aryl boronic acids were coupled - No heterocycle - Expensive copper source
7	2015 (Phukan) [57]	$[Cu(DMAP)_4I]I$ (0.02 equiv), MeOH, air, rt	-	Excellent yields - Fast reaction time	-	Need to prepare the catalyst - Only aryl

			- Catalytic in copper - Successful coupling of 3-pyridine boronic acid - No additive	- boronic acids were coupled - 3-pyridine as the only heterocyclic coupling partner
8	2017 (Zhang and Xu) [59]	CuCl (0.15 equiv), Et_3N (0.5 equiv), MeOH, rt	- Chemoselective *N*-arylation of aminobenzamides - Catalytic in copper - Catalytic in base - Good to excellent yields	- Only boronic acids were coupled - No heterocycle
9	2017 (Baidya) [80]	$Cu(OAc)_2$ (0.2 equiv) DMAP (0.2 equiv), KI (0.2 equiv) DME, air, rt	- Successful coupling of amides *via* chelation assistance - Catalytic in copper - Catalytic in ligand - Catalytic in KI	- Only aryl boronic acids were coupled - No heterocycle

Table 8: Scope of the Chan-Lam reaction between aryl boronic acids and amides.

2.4.3. Anilines



Entry	Year (Group) [Ref]	Conditions	Pros	Cons
1	1997-1998 (Chan and Lam) [39,41]	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (2-10 equiv), DCM, air, rt	- Good to excellent yields	- Stoichiometric in copper - Stoichiometric in base - Only tolylboronic

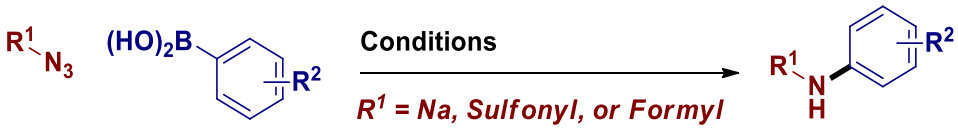
					- acid was coupled - No heterocycle
2	2001 (Lam) [44]	$Cu(OAc)_2$ (0.1-0.2 equiv), pyridine N-oxide or TEMPO (1.1 equiv), Et_3N (2 equiv), DCM, air, rt	- Catalytic in copper - Amount of base reduced - Good yields		- Need stoichiometric amounts of oxidant - Only aryl boronic acids were coupled - No heterocycle
3	2001 (Buchwald) [60]	$Cu(OAc)_2$ (0.05-0.2 equiv), myristic acid (0.1-0.2 equiv), 2,6-lutidine (1 equiv), Toluene, air, rt	- Catalytic in copper - Catalytic in myristic acid - Good yields		- 2,6-lutidine as base - No heterocycle - Only tolylboronic acid was coupled - Need a strong stirring and a large flask
4	2003 (Batey) [47]	$Cu(OAc)_2$ (0.1 equiv), DCM, O_2, rt or 40 ºC	- Catalytic in copper - Excellent yields - Aryl boronic acids and aryl BF_3K		- Sequential procedure - No heterocycle
5	2004 (Xie) [62]	$Cu(OAc)_2$ (0.1 equiv), MeOH, air, reflux	- Moderate to good yields - Catalytic in copper - No additive		- Reflux - No heterocycle - Only tolylboronic acid was coupled
6	2008 (Yufen) [49]	Cu_2O (0.1 equiv), MeOH, air, rt	- Catalytic in copper - Good to excellent yields - Broad aryl boronic acids scope		- Only aryl boronic acids were coupled - No heterocycle
7	2012 (Singh) [53]	$NiCl_2$ (0.2 equiv), 2,2-bipyridyl (0.2 equiv), DBU (2 equiv), MeCN, air, rt	- Good to excellent yields - Catalytic in nickel - Catalytic in ligand		- Need stoichiometric amounts of base - Only aryl boronic acids were coupled - No heterocycle

8	2014 (Vishwakarma) [82]	$Cu(OAc)_2$ (0.2 equiv), CsOPiv (0.4 equiv), DMF, air, 50 °C	- Good to excellent yields - Catalytic in copper - Catalytic in base - Successful coupling of 3-thiophene boronic acid	- High temperature - Only aryl boronic acids were coupled - 3-thiophene boronic acid as the only heterocycle
9	2015 (Prestat) [83]	From step 1: $AgBF_4$ (1.3 equiv), AcOH (1 equiv), 3 Å M.S., air, 80 °C	- Moderate to good yields - Catalytic in copper	- Sequential process - High temperature - Stoichiometric amounts of silver salt - Stoichiometric amount of AcOH - Only aryl boronic acids were coupled
10	2015 (Phukan) [57]	$[Cu(DMAP)_4I]I$ (0.02 equiv), MeOH, air, rt	- Excellent yields - Fast reaction time - Catalytic in copper - Successful coupling of 3-pyridine boronic acid - No additive	- Need to prepare the catalyst - Only aryl boronic acids were coupled - 3-pyridine as the only heterocyclic coupling partner
11	2015 (Kobayashi) [81]	$Cu(OAc)_2$ (0.1 equiv), Myristic acid (0.2 equiv), fac-[Ir(ppy)3], 2,6-lutidine, blue LED, toluene/MeCN (1:1), 35 °C, air	- Moderate to good yields - Catalytic in copper - Catalytic in myristic acid - Catalytic in iridium complex	- Need iridium catalyst - Need LED - Only aryl boronic acids were coupled - No heterocycle
12	2016 (Das) [58]	$Cu(OAc)_2$ (0.2 equiv), AgOAc (1.5 equiv), MeOH, air, rt	- Chemoselective *N*-arylation of 3-aminophenols - Catalytic in copper - Good to	- Stoichiometric in silver salt - No heterocycle

			- excellent yields - Successful for both aryl boronic acid and aryl BPin	
13	2016 (Das) [82]	$Cu(OAc)_2$ (0.2 equiv), benzoic acid (0.2 equiv), Cs_2CO_3 (1.5 equiv), 1,4-dioxane, air, 90 °C	- Chemoselective *N*-arylation of 4-aminophenols - Catalytic in copper - Catalytic in benzoic acid - Good to excellent yields - Successful for both aryl boronic acid and aryl BPin	- Stoichiometric in Cs_2CO_3 - No heterocycle

Table 9: Scope of the Chan-Lam reaction between aryl boronic acids and anilines.

2.4.4. Azides



Entry	Year (Group) [Ref]	Conditions	Pros	Cons
		Azides		
1	2007 (Gho) [130]	$Cu(OAc)_2$ (0.1 equiv), MeOH, air, rt	- Excellent yields - Catalytic in copper - No additive - Successful coupling of alkenyl boronic acids	- Only boronic acids were coupled - No heterocycle - Use of sodium azide
2	2015 (Phukan) [57]	$[Cu(DMAP)_4I]I$ (0.02 equiv), MeOH, air, rt	- Excellent yields - Fast reaction time - Catalytic in	- Need to prepare the catalyst - Only aryl boronic acids

			copper - No additive	were coupled - No heterocycle
Sulfonyl azides				
3	2014 (Kim) [55]	CuCl (0.1 equiv), MeOH, air, rt	- Excellent yields - Catalytic in copper - No additive - Successful coupling of heterocycles in low to good yields - Successful coupling of aryl BF_3K	- Low yields for aryl BPin
Azidoformates				
4	2015 (Kim) [56]	CuCl (0.1 equiv), MeOH, air, rt	- Excellent yields - Catalytic in copper - No additive - Successful coupling of alkenyl boronic acids - Successful coupling of heterocycles in low to good yields - Successful coupling of aryl BF_3K	- No reaction using aryl BPin

Table 10: Scope of the Chan-Lam reaction between aryl boronic acids and azides.

2.4.5. NH-heterocycles

Entry	Year (Group) [Ref]	Conditions	Pros	Cons
Imidazoles - Benzimidazoles				
1	1997-1998 (Chan and Lam) [39,41]	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (2-10 equiv), DCM, air, rt	- Good yields	- Stoichiometric in copper and base - Only

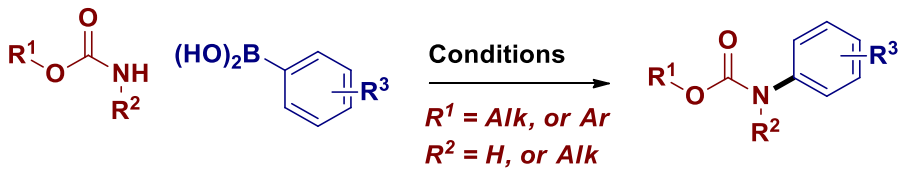
					-	tolylboronic acid was coupled No heterocycle
2	2000 (Collman) [45]	$[Cu(OH)\cdot TMEDA]_2Cl_2$ (0.1 equiv), DCM, air, rt	-	Moderate to excellent yields Catalytic in copper No additive	-	Need to prepare the catalyst Only aryl boronic acids No heterocycle
3	2003 (Xie) [62]	$Cu(OAc)_2$ (0.05 equiv), MeOH, air, reflux	-	Moderate to good yields Catalytic in copper No additive	-	Reflux No heterocycle Only tolylboronic acid was coupled
4	2006 (Kantam) [48]	CuFAP (0.2 equiv), MeOH, air, rt	-	Excellent yields Catalytic in copper No additive Reusable catalyst	-	Only aryl boronic acids No heterocycle Need to prepare the catalyst
5	2008 (Sreedhar) [140]	Cu_2O (0.55 equiv), MeOH, air, rt	-	Good to excellent yields Catalytic in copper No additive	-	Only aryl boronic acids No heterocycle
6	2009 (Kozlowski) [73]	$Cu(NO_3)_2$ (0.1-0.5 equiv), TMEDA (0.1-0.5 equiv), MeOH, O_2, rt	-	Good yields Catalytic in copper Catalytic in TMEDA Successful coupling of hindered aryl boronic acids	-	Expensive catalyst Only aryl boronic acids No heterocycle
7	2012 (Singh) [53]	$NiCl_2$ (0.2 equiv), 2,2-bipyridyl (0.2 equiv), DBU (2 equiv), MeCN, air, rt	-	Good yields Catalytic in nickel Catalytic inligand	-	Need stoichiometric amounts of base Only aryl boronic acids No heterocycle
8	2015 (Phukan) [57]	$[Cu(DMAP)_4I]I$ (0.02 equiv), MeOH, air, rt	-	Excellent yields Fast reaction time Catalytic in copper	-	Need to prepare the catalyst Only aryl boronic acids No heterocycle

			- No additive	
Indazoles				
9	1997-1998 (Chan and Lam) [39,41]	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (2-10 equiv), DCM, air, rt	- Good yields	- Stoichiometric in copper - Stoichiometric in base - Only tolylboronic acid was coupled - No heterocycles
10	2001 (Lam) [44]	$Cu(OAc)_2$ (0.1-0.2 equiv), pyridine N-oxide or TEMPO (1.1 equiv), Et_3N (2 equiv), DCM, air, rt	- Catalytic in copper - Amount of base reduced - Good yields	- Need stoichiometric amounts of oxidant - Only aryl boronic acids - No heterocycle
Pyrroles - Indoles				
11	2007 (Bekolo) [66]	$Cu(OAc)_2$ (2.5 equiv), *i*-Pr_2Net (2.5 equiv), DCM, air, rt	- Successful coupling of pyrroles and indoles - Good to excellent yields	- Stoichiometric amounts of copper - Stoichiometric amounts of base - Only aryl boronic acids - Need EWG on the pyrrole - No heterocycle
12	2008 (Liu) [70]	$Cu(OAc)_2$ (2 equiv), DBU (2 equiv), DMSO, air, 100 ºC	- Successful coupling of indoles - Good to excellent yields	- Stoichiometric amounts of copper - Stoichiometric amounts of base - Only aryl boronic acids - No heterocycle
Tetrazoles				
13	1997-1998 (Chan and Lam) [39,41]	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (2-10 equiv), DCM, air, rt	- Good yields	- Stoichiometric in copper - Stoichiometric in base - Only tolylboronic

				acid was coupled - No heterocycle

Table 11: Scope of the Chan-Lam reaction between aryl boronic acids and NH-heterocycles.

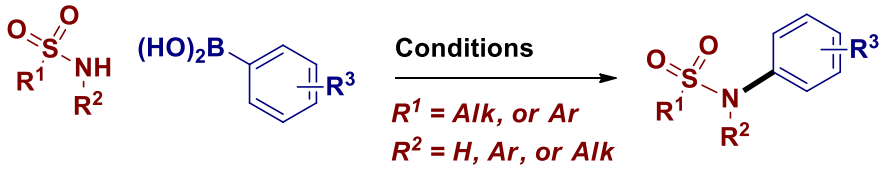
2.4.6. Carbamates



Entry	Year (Group) [Ref]	Conditions	Pros	Cons
1	1997-1998 (Chan and Lam) [39,41]	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (2-10 equiv), DCM, air, rt	- Good yields	- Stoichiometric in copper and base - Only tolylboronic acid was coupled - No heterocycle

Table 12: Scope of the Chan-Lam reaction between aryl boronic acids and carbamates.

2.4.7. Sulfonamides

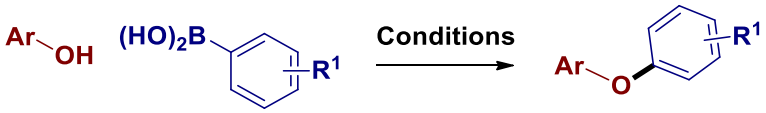


Entry	Year (Group) [Ref]	Conditions	Pros	Cons
1	1997-1998 (Chan and Lam) [39,41]	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (2-10 equiv), DCM, air, rt	- Successful coupling of secondary and cyclic sulfonamides - Good yields	- Stoichiometric in copper - Stoichiometric in base - Only tolylboronic acid was coupled - No heterocycle - No reaction

					with primary sulfonamides
2	2001 (Lam) [44]	$Cu(OAc)_2$ (0.1-0.2 equiv), pyridine N-oxide or TEMPO (1.1 equiv), Et_3N (2 equiv), DCM, air, rt	- Catalytic in copper - Amount of base reduced - Good yields - Successful coupling of primary sulfonamides	- Need stoichiometric amounts of oxidant - Only aryl boronic acids were coupled - No heterocycle - No example of secondary sulfonamides
3	2004 (Xie) [62]	$Cu(OAc)_2$ (0.1 equiv), MeOH, air, reflux	- Good yields - No additive	- Reflux - Only phenyl boronic acid was coupled - Stoichiometric in copper - No heterocycle

Table 13: Scope of the Chan-Lam reaction between aryl boronic acids and sulfonamides.

2.4.8. Phenol

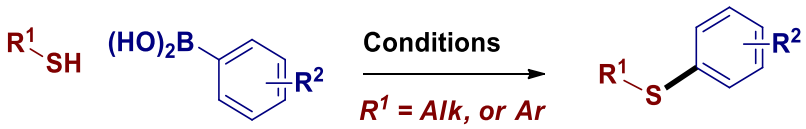


Entry	Year (Group) [Ref]	Conditions	Pros	Cons
1	1997 (Chan) [39]	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (2-10 equiv), DCM, air, rt	- Good yields	- Stoichiometric in copper - Stoichiometric in base - Only tolylboronic acid was coupled - No heterocycle
2	1998 (Evans) [40]	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (5-10 equiv), DCM, air, rt	- Good yields	- Stoichiometric in copper - Large excess of base - Only aryl

					boronic acids - No heterocycle
3	2001 (Lam) [44]	$Cu(OAc)_2$ (0.1-0.2 equiv), pyridine N-oxide or TEMPO (1.1 equiv), Et_3N (2 equiv), DCM, air, rt	- Catalytic in copper - Amount of base reduced - Good yields		- Need stoichiometric amounts of oxidant - Only aryl boronic acids - No heterocycle
4	2003 (Hoveyda) [92]	$Cu(OAc)_2$ (2 equiv), Et_3N (10 equiv), MeOH, air, rt	- Good yields		- Stoichiometric in copper - Large excess of base - Only aryl boronic acids - No heterocycle

Table 14: Scope of the Chan-Lam reaction between aryl boronic acids and phenols.

2.4.9. Thiols

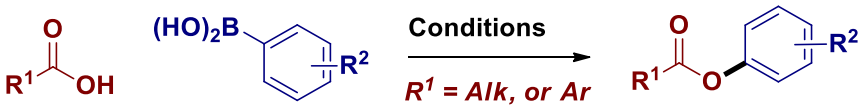


Entry	Year (Group) [Ref]	Conditions	Pros	Cons
1	2009 (Zhong) [77]	CuI (0.2 equiv), 1,10-phenanthroline (0.2 equiv), H_2O-DMSO, O_2, 100 ºC	- Selective *S*-Arylation of 1,2-Bis(o-amino-1*H*-pyrazolyl) disulfides - Low to good yields - Catalytic in coper - Catalytic in ligand - Successful coupling of 3-thiophene boronic acids - Successful coupling of 1,2-Diphenyldisulfane	- High temperature - Only aryl boronic acids - 3-thiophene boronic acids only heterocycle

2	2012 (Feng) [54]	$CuSO_4$ (0.05 equiv), 1,10-phenanthroline (0.05 equiv), nBu_4NOH (0.4 equiv), EtOH, O_2, rt	- Moderate to excellent yields - Catalytic in copper - Catalytic in ligand - Catalytic in additive - Successful coupling of several heterocycles	- Only aryl boronic acids
3	2015 (Phukan) [57]	$[Cu(DMAP)_4I]I$ (0.02 equiv), MeOH, air, rt	- Excellent yields - Fast reaction time - Catalytic in copper - No additive	- Need to prepare the catalyst - Only aryl boronic acids - No heterocycle

Table 15: Scope of the Chan-Lam reaction between aryl boronic acids and thiols.

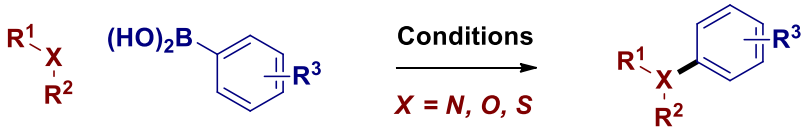
2.4.10. Carboxylic acids



Entry	Year (Group) [Ref]	Conditions	Pros	Cons
1	2010 (Cheng) [50]	$Cu(OTf)_2$ (0.4 equiv), $CO(NH_2)_2$ (1 equiv), EtOAc, air, 60 ºC	- Moderate to excellent yields - Catalytic in copper	- High temperature - Stoichiometric in urea - Only aryl boronic acids - No heterocycle

Table 16: Scope of the Chan-Lam reaction between aryl boronic acids and carboxylic acids.

2.4.11. Other nucleophiles



Entry	Year (Group)	Conditions	Pros	Cons

	[Ref]			
		Hydroxylamines		
1	2010 (Cheng) [50]	CuBr (0.2 equiv), K_2CO_3 (1.5 equiv), MeCN, 70 ºC	- Good to excellent yields - Catalytic in copper	- High temperature - Stoichiometric in base - Only aryl boronic acids
		Imides		
2	2004 (Xie) [62]	$Cu(OAc)_2$ (0.1 equiv), MeOH, air, reflux	- Good yields - No additive	- Reflux - Only phenyl boronic acid - No heterocycle
		Sulfoximines		
3	2001 (Lam) [44]	$Cu(OAc)_2$ (0.1-0.2 equiv), pyridine N-oxide or TEMPO (1.1 equiv), Et_3N (2 equiv), DCM, air, rt	- Catalytic in copper - Amount of base reduced - Good yields	- Need stoichiometric amounts of oxidant - Only aryl boronic acids - No heterocycle
4	2004 (Xie) [63]	$Cu(OAc)_2$ (0.1 equiv), MeOH, air, reflux	- Good yields - No additive	- Reflux - Only phenyl boronic acid - No heterocycle
5	2005 (Bolm) [64]	$Cu(OAc)_2$ (0.1 equiv), MeOH, air, rt	- Good yields - No additive	- Only aryl boronic acids - No heterocycle
		Ureas		
6	1997-1998 (Chan and Lam) [39,41]	$Cu(OAc)_2$ (1-2 equiv), Et_3N or pyridine (2-10 equiv), DCM, air, rt	- Good yields	- Stoichiometric in copper - Stoichiometric in base - Only tolylboronic acid - No heterocycle
		Aliphatic alcohols		
7	2003 (Batey) [47]	$Cu(OAc)_2$ (0.1 equiv), DMAP (0.2 equiv), DCM, O_2, rt	- Catalytic in copper - Excellent yields - Aryl boronic acids and aryl BF_3K	- Sequential procedure - No heterocycle

Table 17: Scope of the Chan-Lam reaction between aryl boronic acids and others nucleophiles.

3. Conclusion

The Chan-Lam reaction between aryl boronic acids and N-, O-, S-nucleophiles has been extensively studied. Through the years, synthetic chemists started to focus their efforts on the development of new sets of conditions to allow the copper-catalysed cross-coupling of a wide range of boronic acid derivatives. Therefore, methodologies to couple aryl-boroxines, -boronic esters, and -trifluoroborate salts have emerged. In addition, numerous publications reported the Chan-Lam reaction of alkynyl-, alkenyl, and alkyl boronic species. All these improvements expanded the scope of the Chan-Lam reaction.

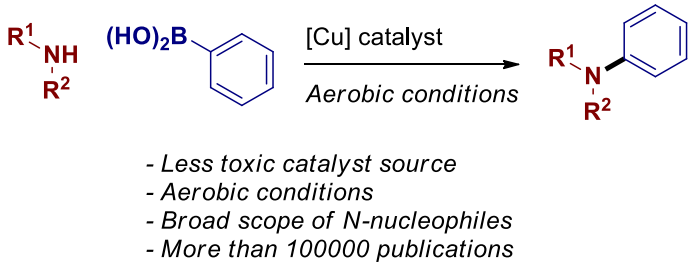
In that regard, aryl BPin esters emerged as a useful but challenging coupling partner for the Chan-Lam amination reaction.

Chapter 1:

Development of stoichiometric conditions for the Chan-Lam reaction of aryl boronic acid pinacol esters with aryl- and alkyl amines

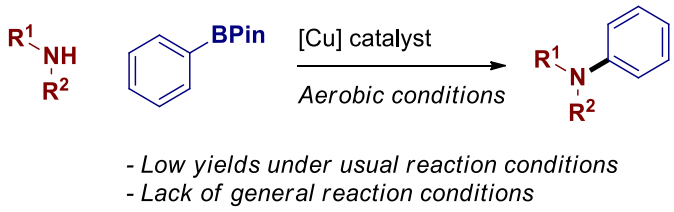
Chapter 1: Project Aims

As previously described, C-N bond formation reactions are fundamental transformations that enable the preparation of valuable amine products. Part of the numerous existing methodologies that enable this transformation, the Chan-Lam reaction has been widely practiced (**Scheme 35**).



Scheme 35: General scheme of the Chan-Lam amination of aryl boronic acids.

However, a major and routinely encountered problem with the Chan-Lam amination reaction is that aryl boronic acid pinacol esters are very poor substrates (**Scheme 36**).



Scheme 36: General scheme of the Chan-Lam amination of aryl boronic acid pinacol esters.

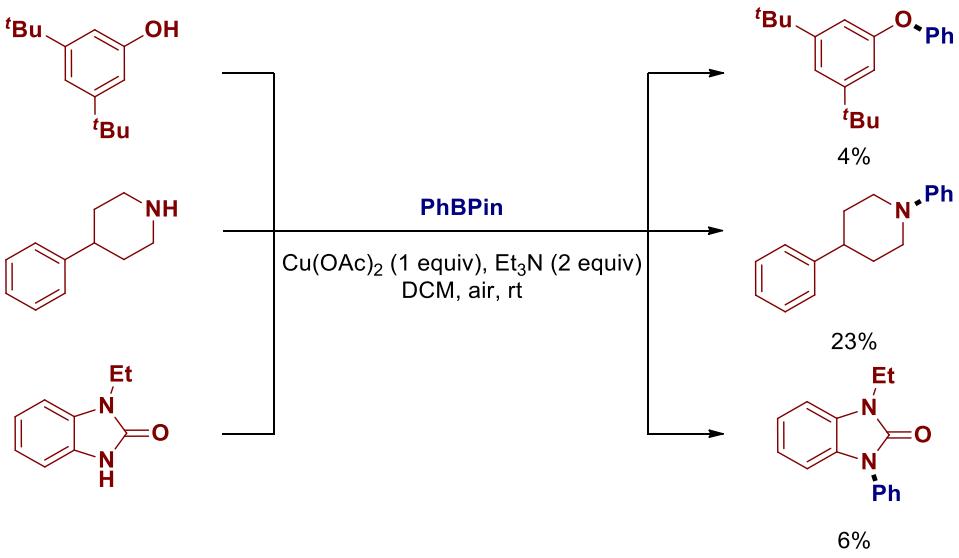
Developing conditions to enable the effective amination of aryl BPin esters is highly desirable due to the increased stability and accessibility of these species with respect to the parent boronic acids. Thus, we started to investigate the Chan-Lam reaction of aryl BPin ester compounds.

Chapter 1: Results and Discussion

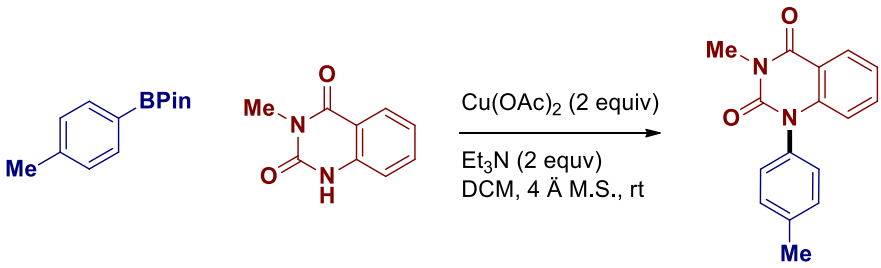
1. State of the art

In 2003, Chan, Lam and co-workers described for the first time the poor reactivity of aryl BPin esters in the Chan-Lam amination reaction (**Scheme 37**).[84] The coupling of these boronic acid derivatives with phenols, cyclic amines, or cyclic amides afforded the desired compounds in low yields.

In 2009, the Jones' group reported a mild, ligand-free methodology for the *N*-arylation of quinazolinediones using aryl boronic acid derivatives in the presence of stoichiometric amounts of $Cu(OAc)_2$. However, aryl BPin esters only performed in moderate yields (**Scheme 38**).[85]



Scheme 37: Poor reactivity of aryl BPin esters in the Chan-Lam amination reaction.



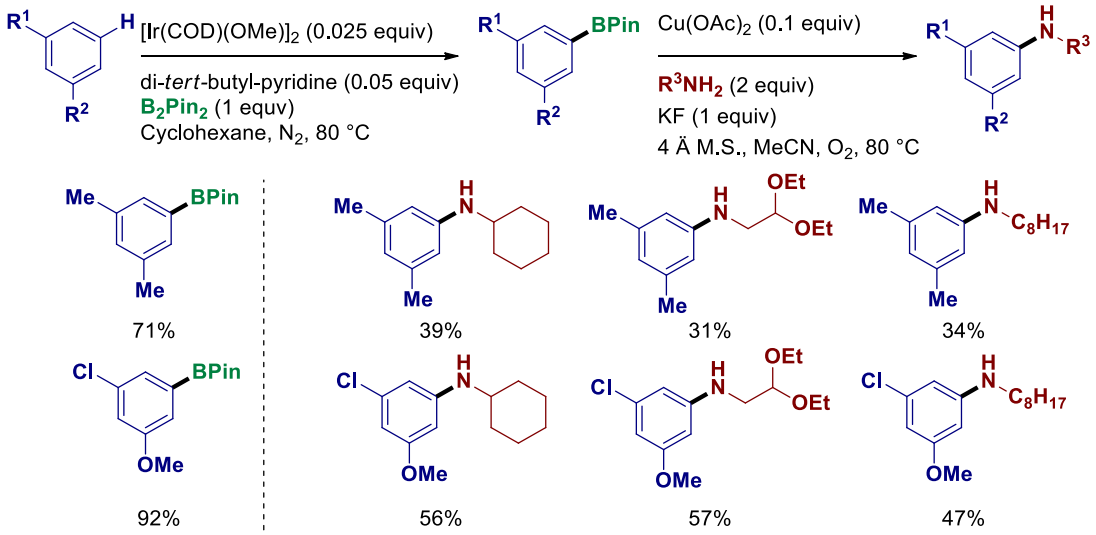
Scheme 38: *N*-arylation of quinazolinediones using aryl BPin.

This poor reactivity has been a recurrent problem through the years. Therefore, several groups tried to enable the effective amination of aryl BPin esters.

1.1. Coupling of aryl BPin with alkyl amines: Hartwig *et al.*

In 2007, Hartwig and co-workers reported the synthesis of aryl amines from arene compounds (**Scheme 39**).[86] The two-step sequence included an iridium-catalysed arene borylation, followed by a copper-mediated amination. This methodology is an excellent addition to the classical synthesis of aryl amines by nitration, reduction and alkylation, or by the coupling of amines with haloarenes generated by electrophilic aromatic halogenation.

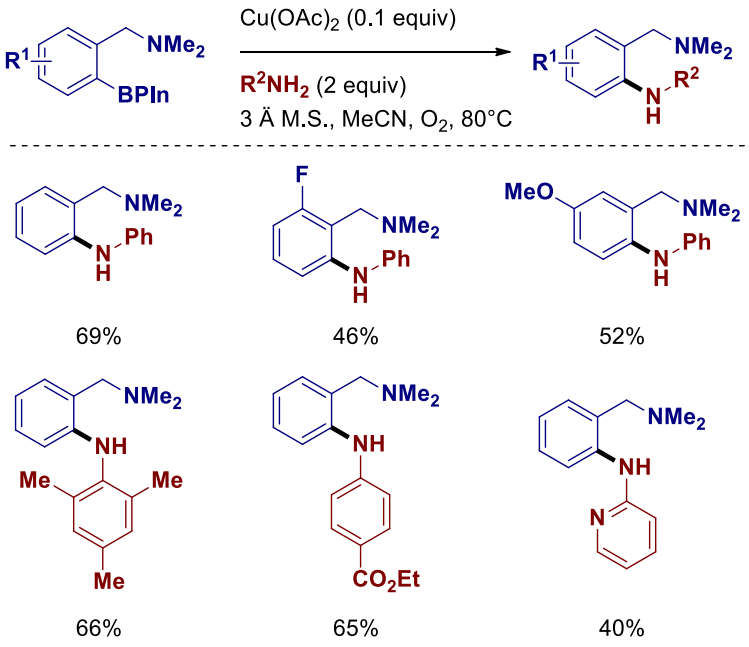
The Chan-Lam step of this sequential procedure occurred using potassium fluoride (1 equiv), catalytic amounts of $Cu(OAc)_2$ (0.1 equiv), and powdered molecular sieves in acetonitrile at 80 °C under an oxygen atmosphere. Despite the moderate to good yields obtained, this set of conditions displayed major limitations. For instance, secondary amines proceeded in low yields, and no *N*-arylated product was observed when using aniline as the *N*-nucleophile.



Scheme 39: Iridium-catalysed arene borylation followed by copper-mediated amination for the synthesis of aryl amines.

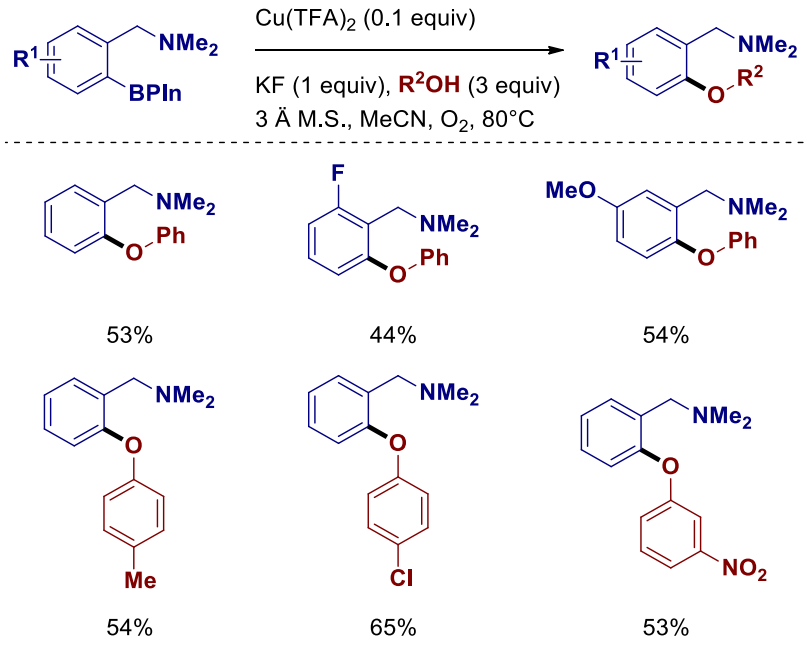
1.2. Coupling of aryl BPin with aryl amines and phenol using a tertiary amine directing group: Clark *et al.*

In 2015, Clark and co-workers published a methodology showing that substrates capable of chelation can be used to facilitate the copper catalysed *N*-arylation of aryl BPin esters (**Scheme 40**).[87] They investigated the coupling between benzylamino boronates esters and aryl amines. The desired *ortho*-aminobenzylamine products were obtained under oxidative conditions in the presence of catalytic amount of $Cu(OAc)_2$. During the study, the major side-product was obtained from the homocoupling reaction of the aryl boronate ester. However, in the absence of base, selectivity over this side-reaction was achieved.



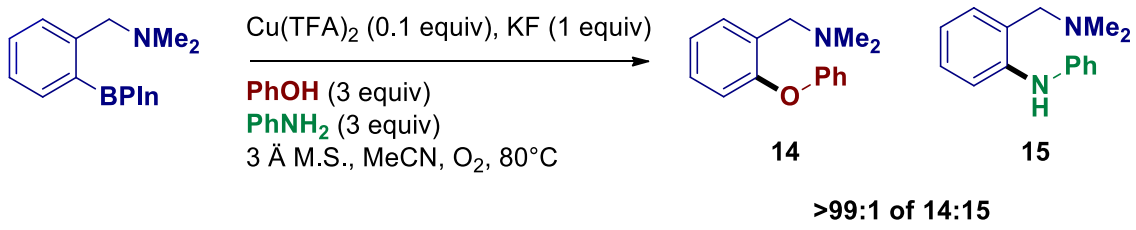
Scheme 40: Coupling of aryl BPin with aryl amines using a tertiary amine directing group.

More recently, the same group reported the etherification of aryl boronate ester model substrates derived from benzylic amines (**Scheme 41**).[88] The coupling with phenols 3proceeded smoothly using $Cu(CO_2CF_3)_2$ (0.1 equiv), and KF (1 equiv) as an additive in acetonitrile at 80 ºC under oxygen atmosphere. A wide range of aryl boronate esters and phenols were tolerated, affording the desired product in moderate to high yields.



Scheme 41: Coupling of aryl BPin with phenol using a tertiary amine directing group.

Finally, a competition experiment between phenol and aniline with a boronate ester revealed high selectivity for the phenol affording compound **14** and **15** in a 99:1 ratio (**Scheme 42**).



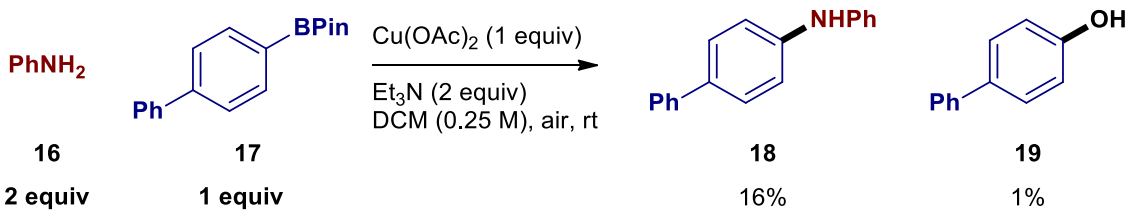
Scheme 42: Competition experiment between phenol and aniline for the coupling with aryl BPin.

Further research has been conducted around aryl BPin ester substrates. However, finding a general set of conditions has proven elusive due to the relatively poor reactivity of these boronic species. Most conditions only afforded moderate to good yields and appeared to be specific for a limited set of substrates. In addition, the Chan-Lam amination reaction between aryl BPin esters and aryl amines remained still an unsolved problem. Therefore, we decided to attempt to develop a simple set of general reaction conditions for this challenging cross-coupling reaction.

2. Optimisation

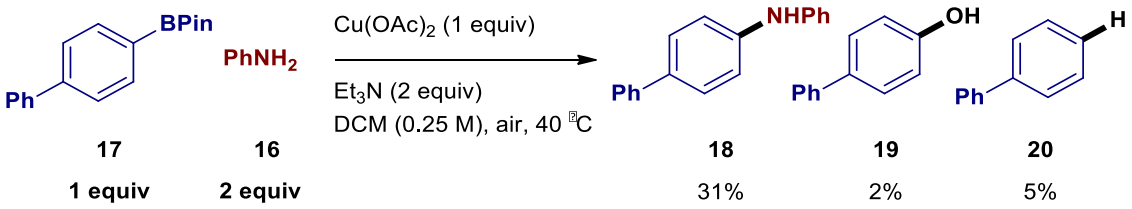
2.1. Evaluation of the general reactivity

We started the investigation of the Chan-Lam reaction between aryl BPin esters and aryl amines using a benchmark reaction between aniline **16** (2 equiv) and biphenyl BPin **17** (1 equiv) (**Scheme 43**). We performed the standard Chan-Lam reaction using $Cu(OAc)_2$ (1 equiv) as the catalyst, Et_3N (2 equiv) as the base, and DCM as the solvent. We established a general reactivity profile for this process. The desired amine product **18** was obtained in 16% yield, highlighting the problem with these substrates. In addition to **18**, the expected by-product of this reaction, phenol **19** was observed in 1%.



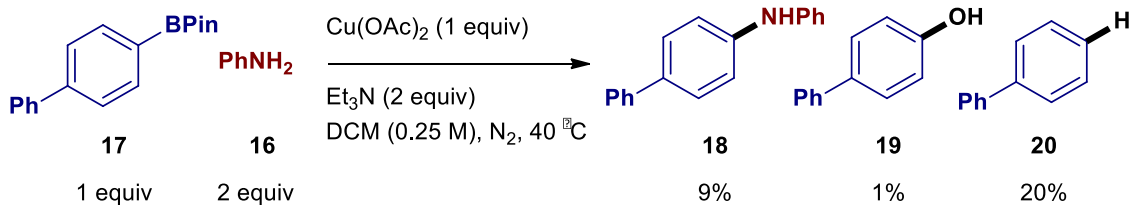
Scheme 43: Benchmark reaction between aniline 16 and biphenyl BPin 17.

When heating the reaction to 40 ºC, the conversion to the desired product **18** almost doubled, and the aryl BPin ester protodeboronated by-product **20** was detected in the crude mixture (**Scheme 44**).



Scheme 44: Benchmark reaction between aniline 16 and biphenyl BPin 17 at 40 ºC.

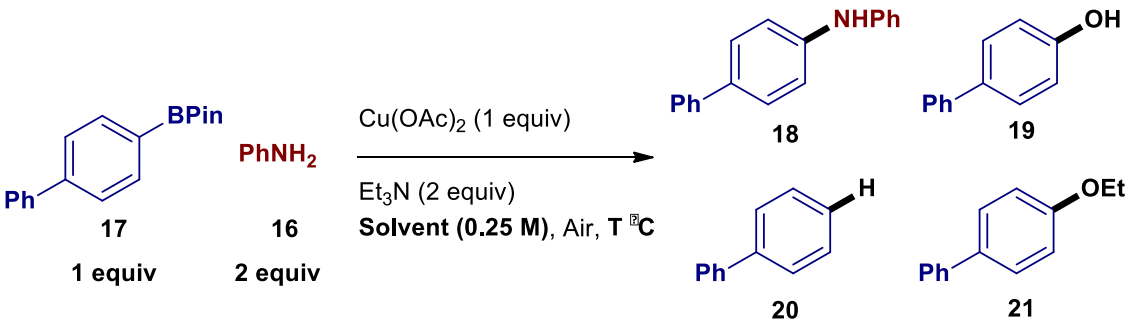
Performing the reaction under a nitrogen atmosphere considerably reduced the yield and favored the formation of the protodeboronated by-product **20** (**Scheme 45**).



Scheme 45: Benchmark reaction between aniline 16 and biphenyl BPin 17 under nitrogen atmosphere.

2.2. Effect of the solvent and temperature

Knowing the importance of the solvent system and the temperature, we conducted a survey of these two parameters (**Table 18**). Replacing DCM with MeCN provided a small increase in conversion to the desired amine product **18** with increases in formation of both by-products **19** and **20** (**Table 18, entry 2)**. The use of MeCN allowed an increase of the temperature affording a slightly better yield for the formation of product **18** (**Table 18, entry 3**). All the other non-protic solvents used, including EtOAc, Acetone, Toluene, DMSO, THF and DMF, did not afford the desired product **18** in good yields (**Table 18, entries 4** to **9**). Use of a polar protic solvent such as EtOH led to a significant quantity of the corresponding ether product **21** (**Table 18, entry 10**). However, a competitive quantity of **18** was produced and, more importantly, complete conversion of aryl BPin ester starting material **17** was observed for the first time (**Table 18, entry 10**). We hypothesised that EtOH drove the equilibrium from the aryl BPin to the corresponding aryl boronic acid. Thus, the aryl boronic acid was more efficient in the Chan-Lam reaction. To limit the production of **21** while attempting to retain this increase in reactivity, mixtures of MeCN:EtOH were evaluated (**Table 18, entries 11** to **16**). At 20:1 MeCN:EtOH, the formation of **21** was lowered significantly and the desired product **18** was obtained in 45% yield (**Table 18, entry 15**). Finally, increasing the temperature to 80 ºC afforded the amine product **18** in 60% yield (**Table 18, entry 17**).

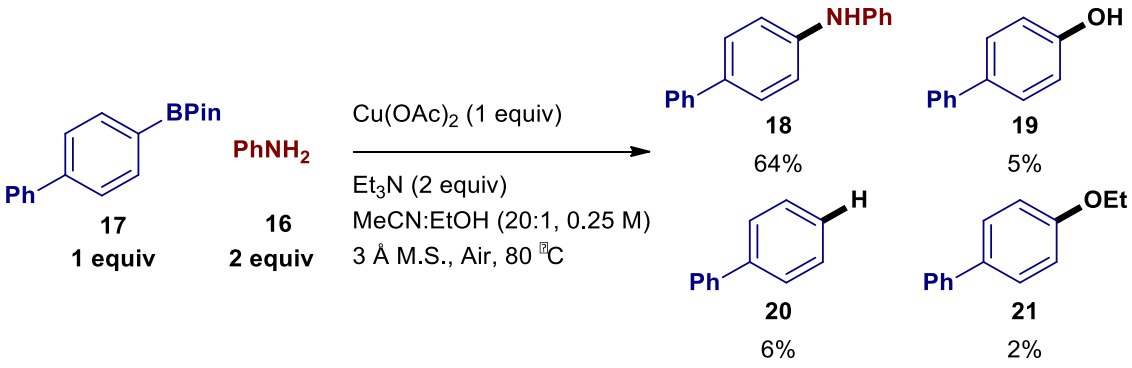


entry	Solvent, Temperature	18:19:20:21 (HPLC %)
1	CH_2Cl_2, 40 ºC	31:2:5:--
2	MeCN, 40 ºC	35:5:7:--
3	MeCN, 60 ºC	36:7:6:--
4	EtOAc, 60 ºC	3:1:0:--
5	Toluene, 60 ºC	2:7:12:--
6	DMSO, 60 ºC	7:4:5:--
7	Acetone, 60 ºC	5:6:3:--
8	DMF, 60 ºC	16:6:7:--
9	THF, 60 ºC	5:1:0:--
10	EtOH, 60 ºC	43:12:15:38
11	MeCN:EtOH (1:1), 60 °C	47:14:12:20
12	MeCN:EtOH (2:1), 60 °C	46:15:11:14
13	MeCN:EtOH (5:1), 60 °C	46:14:13:12
14	MeCN:EtOH (10:1), 60 °C	47:14:13:9
15	MeCN:EtOH (20:1), 60 °C	45:13:10:1
16	MeCN:EtOH (30:1), 60 °C	38:11:7:0
17	MeCN:EtOH (20:1), 80 °C	60:15:10:1

Table 18: Optimisation of the solvent system for the Chan-Lam amination reaction between aniline 16 and biphenyl BPin 17.

2.3. Effect of molecular sieves

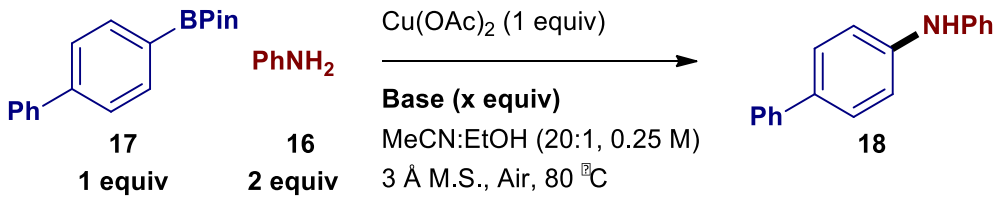
Based on the study conducted by Evans *et al.*, we investigated the impact of molecular sieves on the reaction. Addition of 3 Å molecular sieves reduced the levels of phenolic by-product **19** to 5% and increased the yield of the desired product **18** to 64% (**Scheme 43**).



Scheme 46: Impact of molecular sieves on the Chan-Lam amination between aniline 16 and biphenyl BPin 17.

2.4. Effect of the base

We first evaluated the impact of the amount of base (**Table 19, entries 1** to **5**). Decreasing or increasing the amount of base lowered the yield of the reaction (**Table 19, entries 2,3** and **5**). Running the reaction without any base impeded considerably the conversion to the desired product **18** (**Table 19, entry 4**). Then, we selected a representative panel of bases, known in the literature for being efficient in the Chan-Lam coupling (**Table 19**). TMEDA, K_2CO_3 and Cs_2CO_3 afforded the desired product **18** in low yields (**Table 19, entries 6** to **8**). Moderate yields were obtained when using Pyridine, K_3PO_4 and KOAc (**Table 19, entries 9** to **11**). However, none of the tested bases was as efficient as Et_3N (**Table 19, entry 1**).

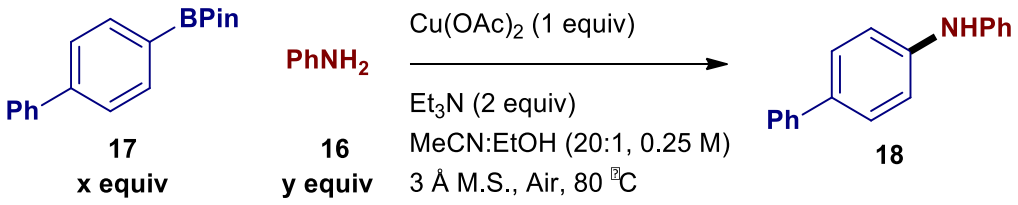


entry	Base, Equivalents	18 (HPLC %)
1	Et_3N, 2 equiv	64
2	Et_3N, 1.5 equiv	59
3	Et_3N, 1 equiv	54
4	Et_3N, 0 equiv	10
5	Et_3N, 3 equiv	58
6	TMEDA, 2 equiv	9
7	K_2CO_3, 2 equiv	11
8	Cs_2CO_3, 2 equiv	17
9	Pyridine, 2 equiv	37
10	K_3PO_4, 2 equiv	45
11	KOAc, 2 equiv	30

Table 19: Optimisation of the base for the Chan-Lam amination reaction between aniline 16 and biphenyl BPin 17.

2.5. Ratio aryl BPin *vs.* aniline

Following the base study, we undertook the optimisation of the ratio aryl BPin *vs.* aryl amine (**Table 20**). Reducing the amount of amine from 2 to 1.5 or 1 equivalents was detrimental for the reaction (**Table 20, entries 2** and **3**). Increasing the amount of amine from 2 to 3 equivalents did not lead to higher conversion to the desired product **18** (**Table 20, entry 4**). Finally, using an excess of aryl BPin ester favored the formation of the protodeboronated by-product **20** and lowered the formation of the desired product **18** (**Table 20, entries 5** and **6**).

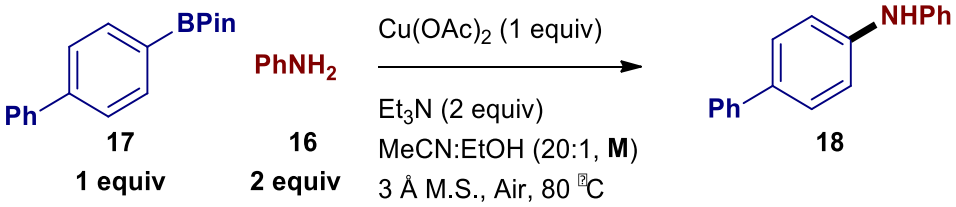


entry	Ratio aryl BPin *vs.* aniline	18 (HPLC %)
1	1 : 2	64
2	1 : 1.5	40
3	1 : 1	31
4	1 : 3	62
5	1.5 : 1	42
6	2 : 1	34

Table 20: Optimisation of the ration aryl BPin *vs.* aniline for the Chan-Lam amination reaction between aniline 16 and biphenyl BPin 17.

2.6. Effect of the reaction concentration

The impact of the concentration on the formation of the desired amine product was significant (**Table 21, Figure 2**). During our optimisation we found that increasing the molarity from 0.25 M to 1M boosted the yield of **18** to 82%, providing relatively good efficiency (**Table 21, entry 6**).



entry	Concentration (M)	18 (HPLC %)
1	0.05	38
2	0.1	54
3	0.25	64

4	0.5	75
5	0.75	78
6	1	82

Table 21: Optimisation of the concentration for the Chan-Lam amination reaction between aniline 16 and biphenyl BPin 17.

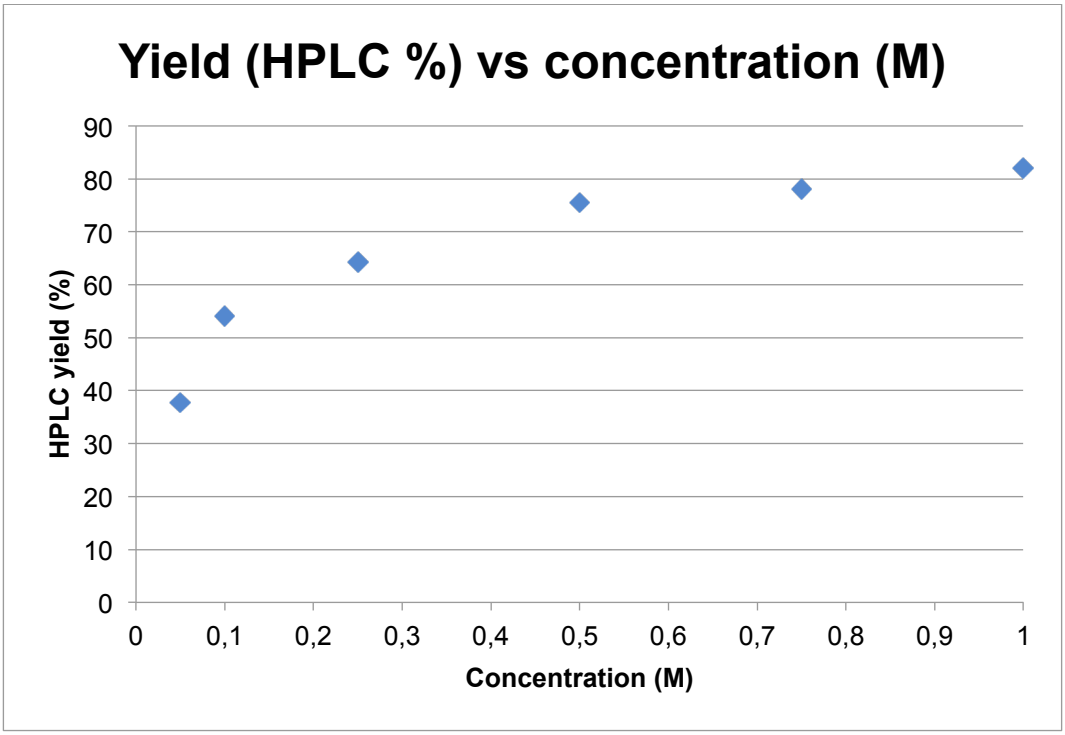
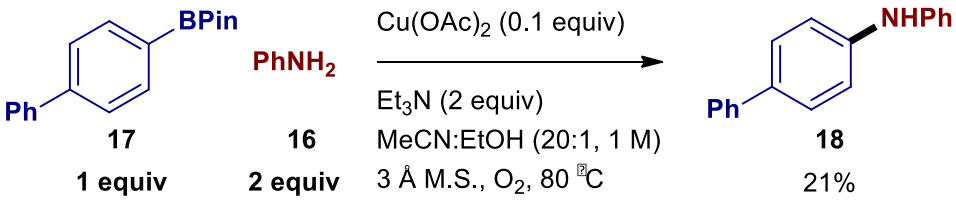


Figure 2: Impact of the concentration on the formation of the desired amine product 18.

2.7. Catalytic reaction

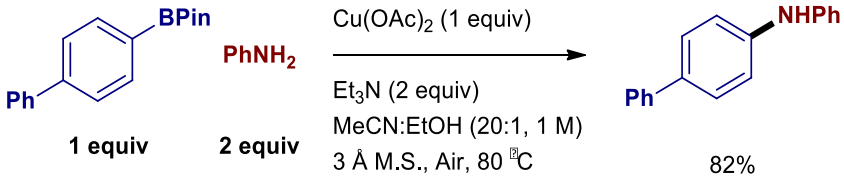
We finally attempted to render the process catalytic. Unfortunately using catalytic amounts of $Cu(OAc)_2$ (0.1 equiv) under an O_2 atmosphere led to only 21% conversion to **11** (**Scheme 47**).



Scheme 47: Attempt to render the Chan-Lam amination reaction between aniline 16 and biphenyl BPin 17 catalytic.

2.8. Optimised conditions

Based on the parameter optimisation described above, the following optimum stoichiometric set of reaction conditions was developed for the Chan-Lam reaction between aryl BPin esters and aryl amines (**Scheme 48**).

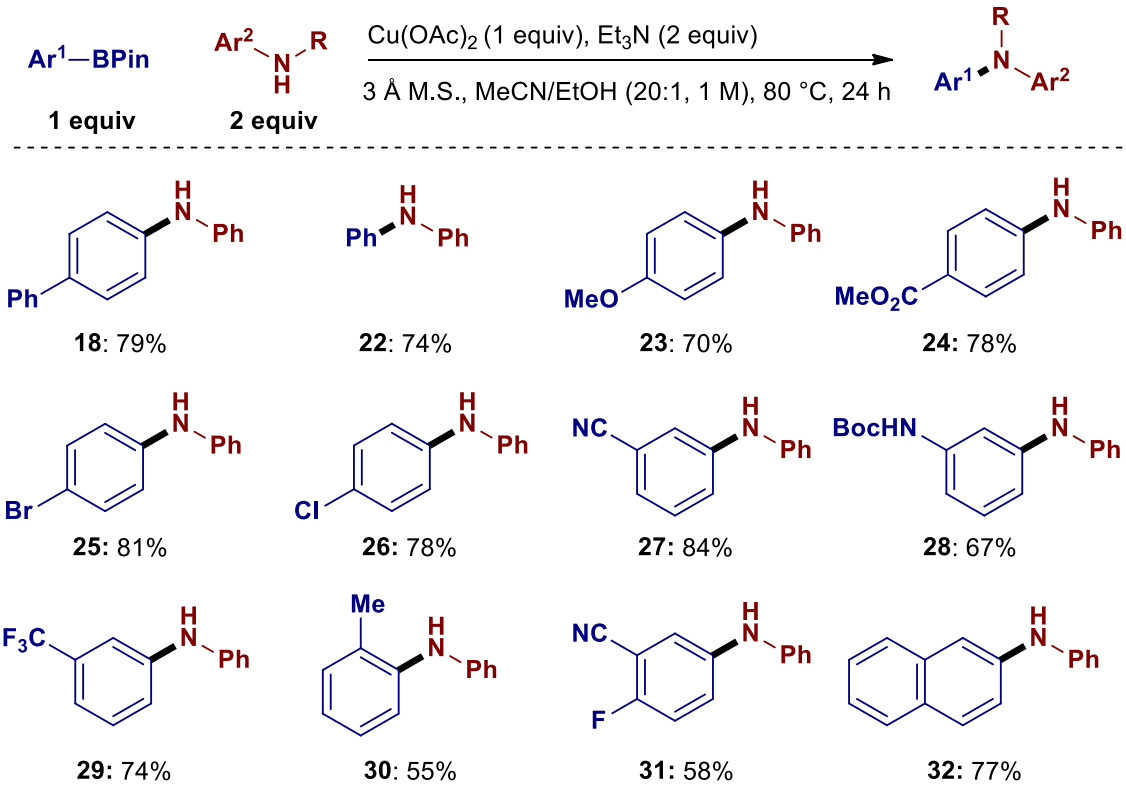


Scheme 48: Optimised reaction conditions for the Chan-Lam amination reaction between aniline 16 and biphenyl BPin 17.

3. Scope of the reaction

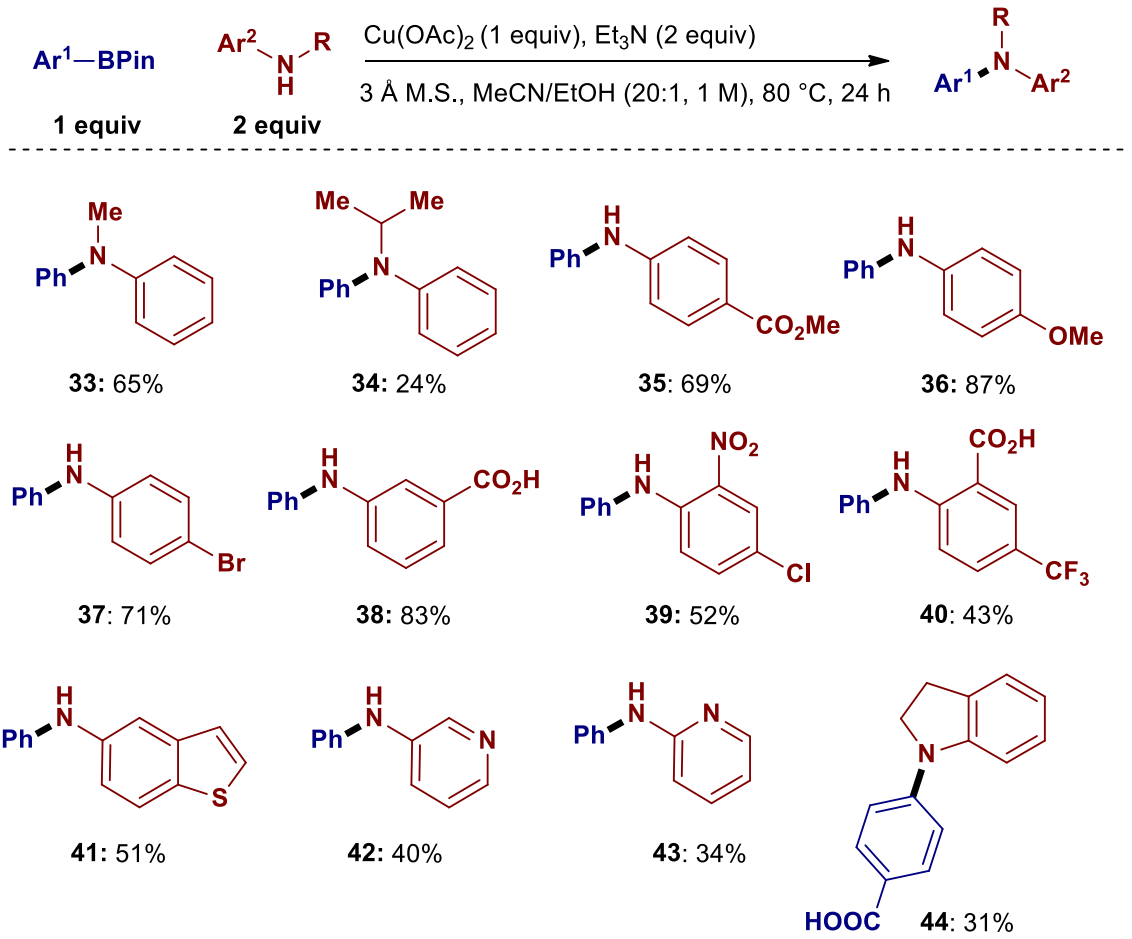
3.1. Aryl amines

We applied the developed protocol to a range of Aryl BPin ester and aniline substrates (**Scheme 49** and **50**). Pleasingly, the stoichiometric reaction conditions tolerated a wide range of functionalities on both the aryl BPin and aryl amine components. Electron-rich (**Scheme 49, 18** and **23**), -neutral (**Scheme 49, 22** and **32**), and –withdrawing groups (**Scheme 49, 24-29** and **31**) were tolerated on the aryl BPin ester.



Scheme 49: Scope of the aryl BPin for the Chan-Lam amination using aniline as the coupling partner.

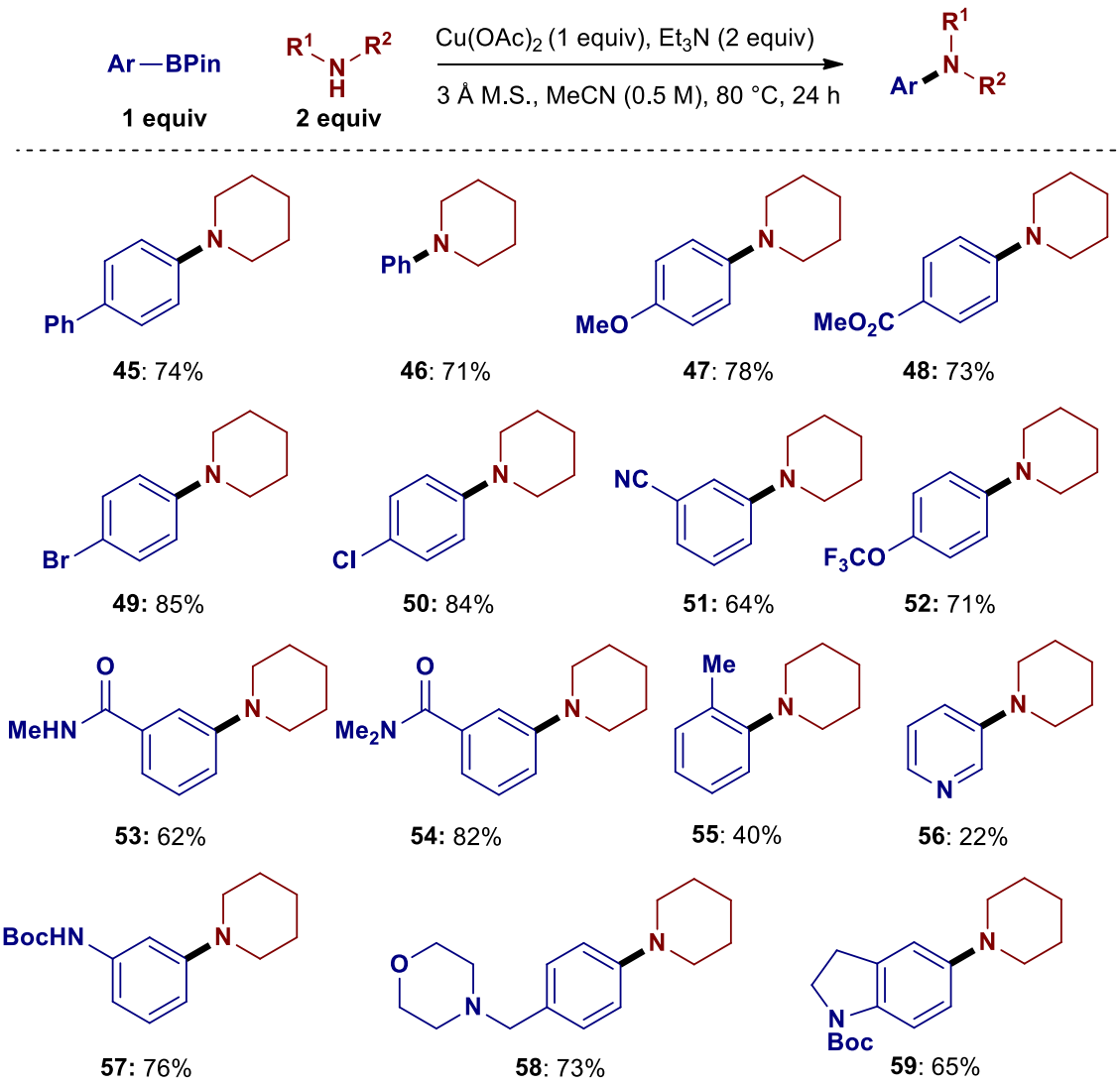
The aryl amine was also broadly tolerant of functionality and substitution (**Scheme 50, 35-40**). Yields were generally >70% with some diminished yields observed with specific components, including heterocycles (**Scheme 50, 41** to **44**) and secondary aryl amines (**Scheme 50, 33** and **34**).



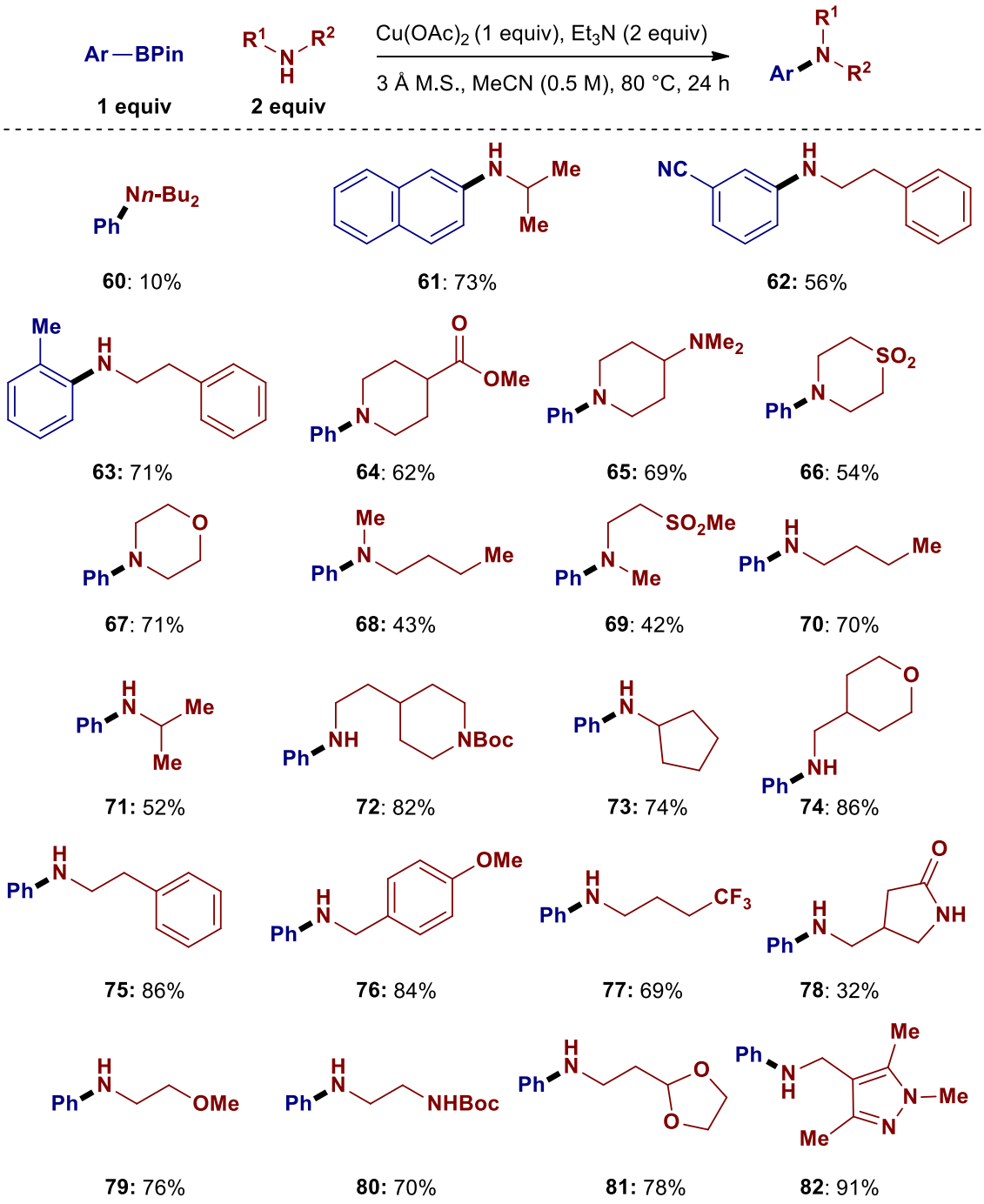
Scheme 50: Scope of the aryl amine for the Chan-Lam amination using phenyl Bpin as the coupling partner.

3.2. Alkyl amines

The developed reaction conditions were also found to allow the successful coupling of alkyl amines (**Scheme 51** and **52**). Interestingly, in this case, the addition of EtOH was not necessary to achieve good levels of reaction efficiency. Once more, a good diversity of BPin (**Scheme 51**) and amine (**Scheme 52**) components was tolerated. Similar trends were observed with some heterocyclic (**56** and **59**) and secondary amines (**60, 68,** and **69**) delivering lower yields. While product **78** was isolated in relatively low yield due to competing arylation of the lactam, the reactions of other amides and carbamates were more chemoselective (**53** and **80**).



Scheme 51: Scope of the aryl BPin for the Chan-Lam amination using piperidine as the coupling partner.

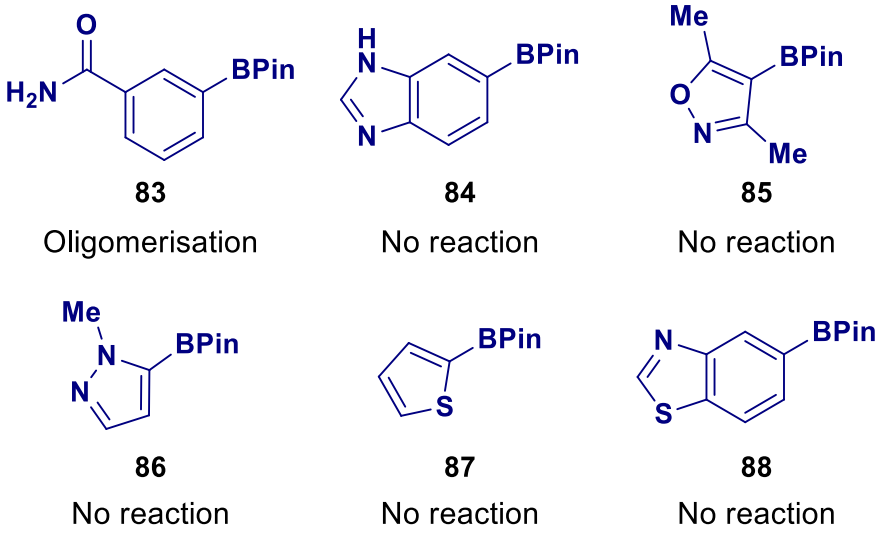


Scheme 52: Scope of the alkyl amine for the Chan-Lam amination using phenyl BPin as the coupling partner.

3.3. Unsuccessful substrates

3.3.1. Aryl BPin esters

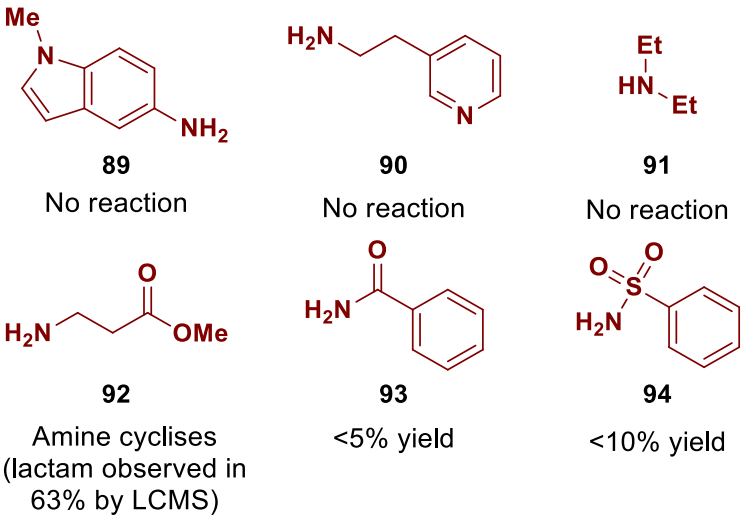
The aryl BPin esters scope highlighted some limitations of the developed procedure (**Scheme 53**). Aryl BPin compound **83** bearing a primary amide did not afford any desired product due to oligomerisation. Free N-H heterocyclic BPin substrates like **84** suffered from the same oligomerisation issue. Finally, no conversion to the amine desired product was observed when using heterocyclic coupling partners such as isoxazole **85**, pyrazole **86**, thiophene **87** and benzo[*d*]thiazole **88**.



Scheme 53: Unsuccessful aryl BPin coupling partners.

3.3.2. Amines

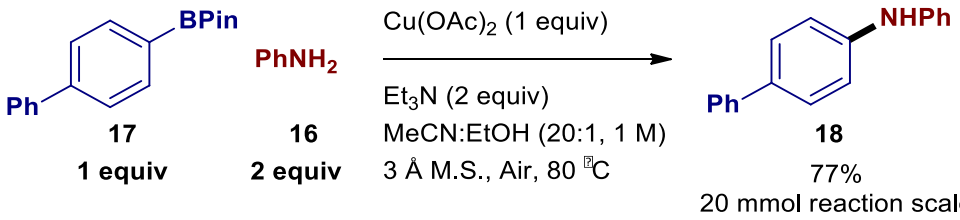
Unsuccessful reactions were also observed when focusing on the aryl- and alkyl amines scope (**Scheme 54**). Indolamine **89,** 2-(pyridin-3-yl)ethanamine **90** and diethylamine **91** did not afford the desired amine product. In addition, methyl 3-aminopropanoate **92** was not a successful coupling partner for the developed Chan-Lam reaction due to competitive cyclisation side reaction. Finally, primary amide **93** and primary sulfonamide **94** were not suitable *N*-nucleophiles.



Scheme 54: Unsuccessful aryl/alkyl amines, amide, and sulfonamide coupling partners.

4. Scale-up experiment

We finally evaluated the scalability of our developed reaction conditions. The Chan-Lam coupling between biphenyl BPin ester **17** (1 equiv) and aniline **16** (2 equiv) on a 20 mmol scale afforded the desired amine product **18** in 77% yield after purification, highlighting the good scalability of the protocol (**Scheme 55**).



Scheme 55: Scale-up of the Chan-Lam amination between aniline 16 and biphenyl BPin 17.

5. Conclusions

In summary, the efficient Chan-Lam coupling of aryl BPin and aryl amines was achieved using a straightforward set of reaction conditions. These developed conditions were also suitable for the coupling of alkyl amines. This provided the first general set of reaction conditions for the Chan-Lam reaction of aryl BPin reagents with both aryl- and alkyl amines.

However, this optimised protocol has still some limitations such as the necessity to use stoichiometric amounts of copper catalyst, the low yields obtained using heterocyclic aryl BPin esters, and the poor reactivity of several substrates.

Chapter 2:

Mechanistic investigation of the Chan-Lam reaction amination reaction and Development of general catalytic conditions for the coupling of aryl boronic acid pinacol esters with aryl- and alkyl amines

Chapter 2: Project Aims

Despite the extensive literature on the Chan-Lam reaction, its mechanism is not fully understood. Stahl and co-workers were the first to report a full mechanistic study of copper-catalysed aerobic oxidative cross-couplings.[89,90] After this initial report, other mechanistic investigations were conducted offering a better picture of what the mechanism could be. However, in most reports, the efforts were focused on the synthetic outcome; therefore only experimental observations were reported, leading to succinct mechanism proposals.

Following our first report we thought that studying the mechanism of the Chan-Lam reaction would allow us to understand the fundamentals of the transformation, and assist us in the development of general catalytic reaction conditions.

Chapter 2: Results and Discussion

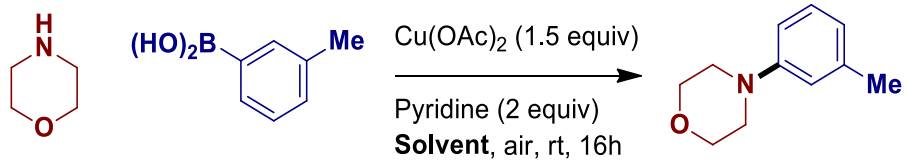
1. State of the art

1.1. Reported experimental observations

Effects of the solvent, the electronic properties of both coupling partners, the base, and the ligand, the additives to the Chan-Lam have been studied.

1.1.1. Effect of the solvent

Lam and co-workers investigated the effect of the solvent during the *N*-arylation of morpholine with *m*-tolylboronic acid (**Table 22**).[44] It was found that the use of DCM and 1,4-dioxane afforded the highest yield. Lower yields were observed with more and less polar solvents, including DMF, DMSO and toluene. However, the choice of an optimal solvent system appeared to be substrate-dependent. For example, DMF was the best solvent to use for the *N*-arylation of benzimidazole. Whereas later, Snapper, Hoveyda and Xie demonstrated that methanol could improve the yields of other coupling reactions.[62,63,91]



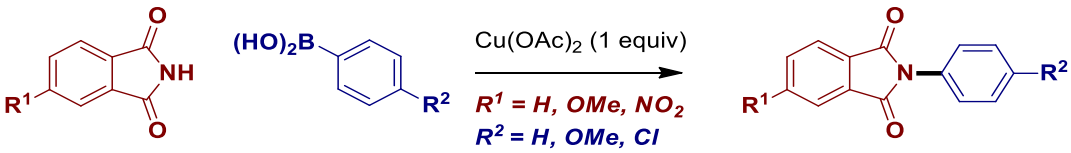
Solvent	DCM	1,4-dioxane	DMF	EtOAc	THF	toluene	DMSO
Yield	62%	73%	43%	26%	23%	18%	16%

Table 22: Investigation of the effect of the solvent during the *N*-arylation of morpholine with *m*-tolylboronic acid.

1.1.2. Electronic effects

Lam and co-workers investigated the influence of electronic effects on the Chan-Lam reaction using various substituted phthalimides and arylboronic acids.[44] In their study, they concluded that electron-rich phthalimides afforded higher yield than the nitro-

substituted phthalimide (**Scheme 56, Figure 3**). However, only little electronic effect was observed for arylboronic acid substrates (**Scheme 56, Figure 3)**.



Scheme 56: Chan-Lam reaction using different substituted phthalimides and arylboronic acids.

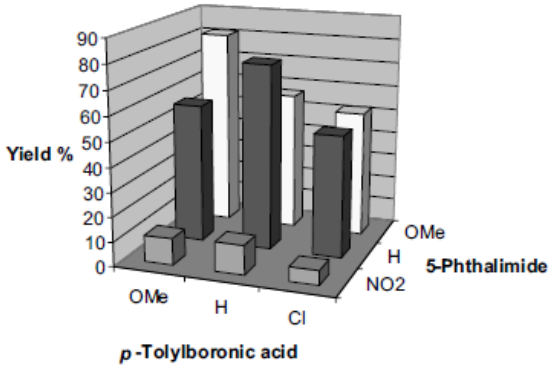


Figure 3: Study of electronic effects on the Chan-Lam reaction using different substituted phthalimides and arylboronic acids (*copyright obtained from Synthesis*).

1.1.3. Effects of bases and ligands

Another important element of the Chan-Lam reaction is the external base or ligand.[39-41] Et_3N and pyridine were used in the original *N*-arylation conditions of aryl boronic acids. In 2003, Takeya and co-workers demonstrated that in the absence of Et_3N, the amine starting material reacted with arylboronic acid to form an arylboronic acid mono-amide adduct, which appeared to be inactive.[92] In addition, they highlighted that a large excess of Et_3N inhibited the reaction by chelating the copper centre. However, in many cases, it was observed that *N*-arylation did not require the use of any additives as the amine coupling partner was acting as a base or ligand. The role of the base or ligand seems to be substrate-dependent and it is difficult to define a general effect. As an example, in *O*-arylation, it has been shown that DMAP prevented protodeboronation of the boronic acid starting material, but it had no effect when using an aryl trifluoroborate salt.

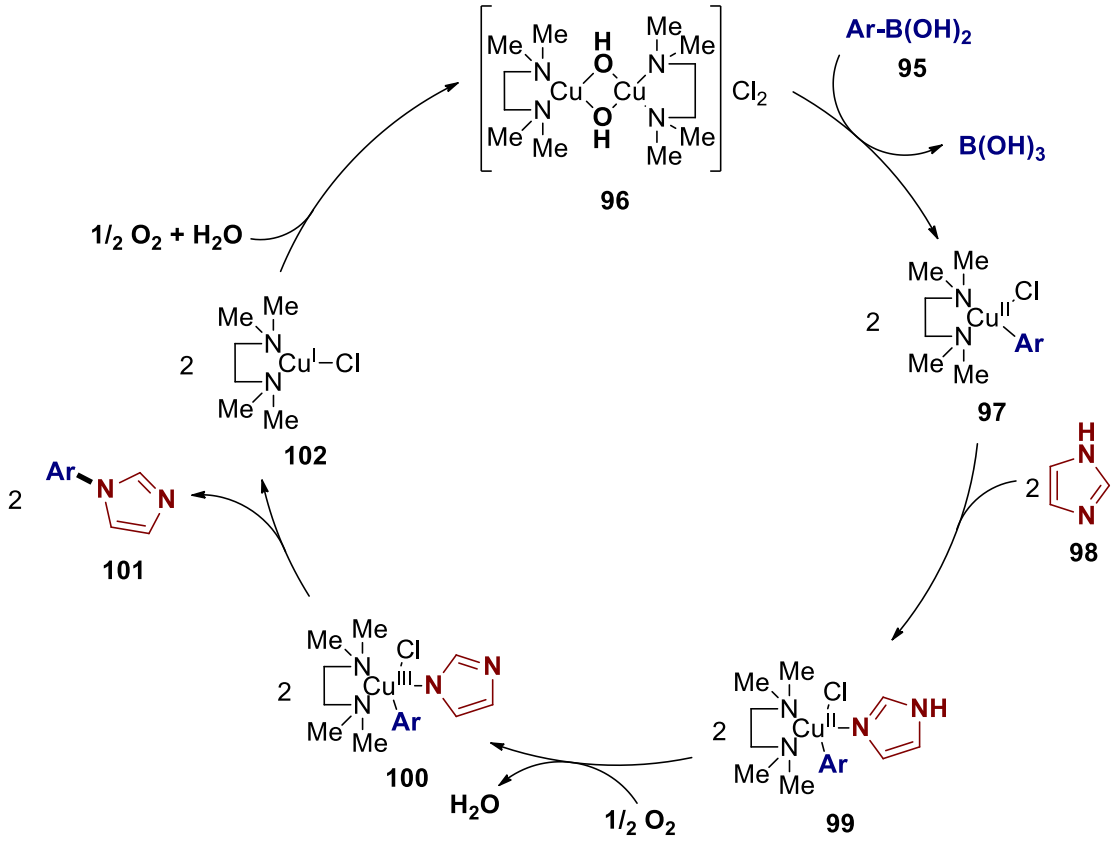
1.1.4. Summary

All these experimental observations offered useful insights, but also demonstrated the complexity of the Chan-Lam reaction. The role of several parameters remained unclear and therefore it was difficult to propose a full catalytic cycle.

1.2. Mechanistic investigations

1.2.1. First speculations

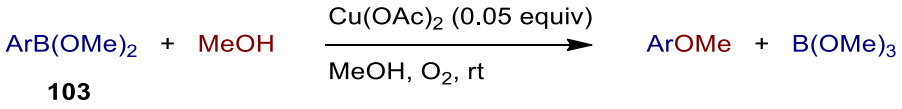
Based on Evans and Lam studies,[40,44] Collman and Zhong were the first to describe the mechanism of the catalytic Chan-Lam reaction between arylboronic acid and imidazoles (**Scheme 57**).[46] Transmetalation of the arylboronic acid **95** with the catalyst **96** afforded the Cu(II) species **97**. Coordination of the imidazole coupling partner **98** gave the copper complex **99**. Then, oxidation of **99** in the presence of oxygen generated the Cu(III) species **100**. Reductive elimination afforded the desired product **101**. Finally, oxidation of the Cu(I) species **102** allowed the regeneration of the active catalyst **96**. However, this mechanism was still very speculative.



Scheme 57: Speculative mechanism of the Chan-Lam reaction by Collman and Zhong.

1.2.2. First systematic study: Stahl *et al.* mechanistic report

In 2009, Stahl and co-workers elucidated the key mechanistic events of the Chan-Lam reaction.[89] Based on the conditions reported by Xie *et al*. (**Scheme 58**), they described the identity of the catalyst resting state, the turnover limiting step, and the role of the oxygen for the methoxylation of boronic ester **103**.



Scheme 58: Investigation of the Chan-Lam reaction between aryl boronate and methanol.

First, they observed that the amounts of product formed compared to the amount of O_2 consumed, reflected a 2:1 stoichiometry, suggesting that O_2 acted as a 4-electron oxidant (**Figure 4**). Then, they monitored the quantities of product formed compared to the initial Cu(II) concentration under anaerobic conditions. They observed that the

[Cu(II) *vs.* product] stoichiometry is 2:1, demonstrating that Cu(II) served as a one-electron oxidant (**Figure 5**). Finally, they exposed the Cu(I) containing solutions to oxygen, and the gas-uptake experiments indicated that Cu(I) reacted with O_2 in a 4:1 stoichiometry (**Figure 6**).

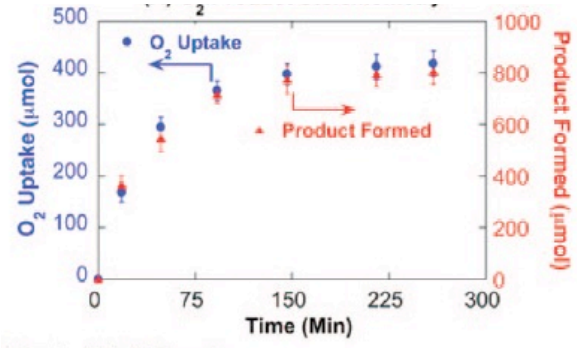


Figure 4: Role of the oxygen (*copyright obtained from ACS).*

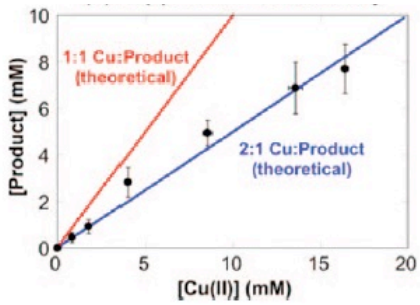


Figure 5: Role of Cu(II) (*copyright obtained from ACS).*

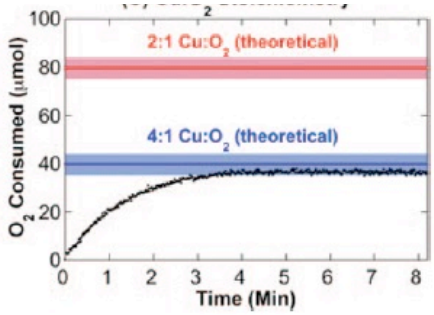
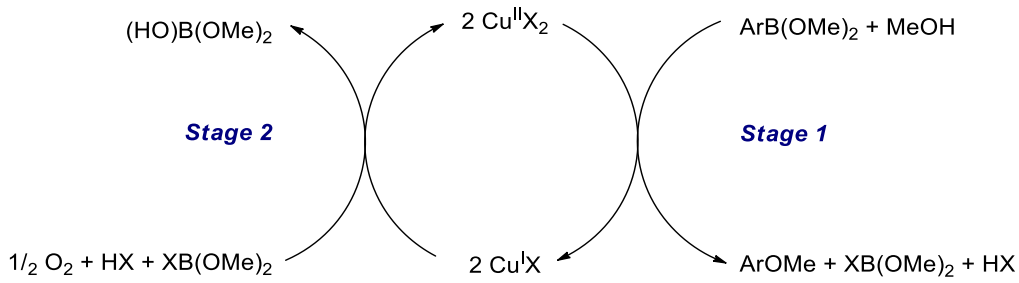


Figure 6: Reactivity of Cu(I) with oxygen(*copyright obtained from ACS).*

These three experiments were consistent with the following 2-step mechanism (**Scheme 59**):

- Oxidative coupling of the boronic ester and methanol by two equivalents of Cu(II)

- Reoxidation of Cu(I) to Cu(II) by oxygen



Scheme 59: Proposed 2-step mechanism based on the O_2 uptake and Cu(II) catalyst control experiments.

In the same study, kinetic data highlighted a first order dependence on $Cu(OAc)_2$, a saturation dependence on $ArB(OMe)_2$, and a zero dependence in oxygen (**Figures 7 and 8**). These observations suggested that the transmetalation is the turnover-limiting step. In addition, EPR studies revealed that the copper in the reactions existed as Cu(II), and confirmed that the formation of an arylcopper(II) species was the turnover-limiting step.

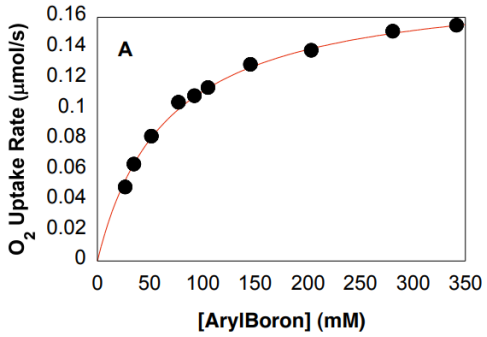


Figure 7: Kinetic data based on O_2 uptake vs. aryl boronate concentration(*copyright obtained from ACS).*

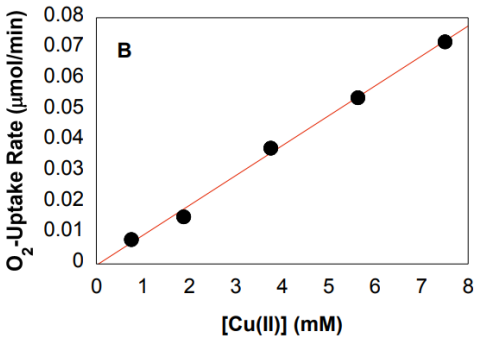
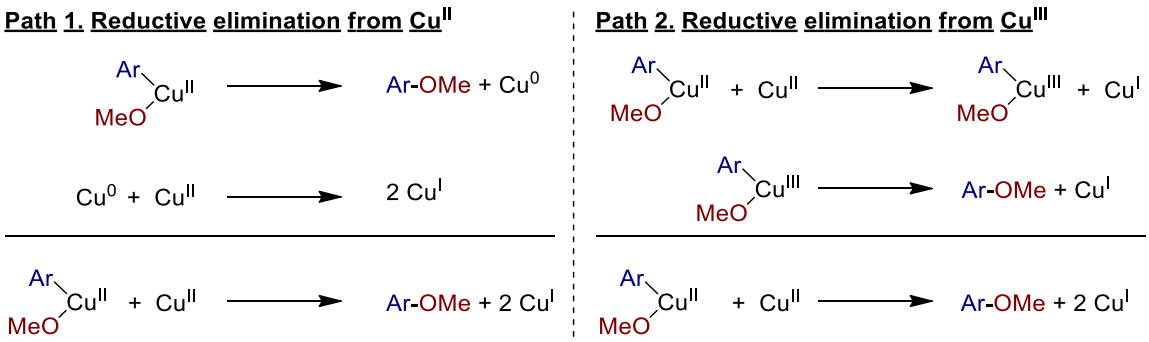


Figure 8: Kinetic data based on O_2 uptake vs. Cu(II) concentration(*copyright obtained from ACS*).

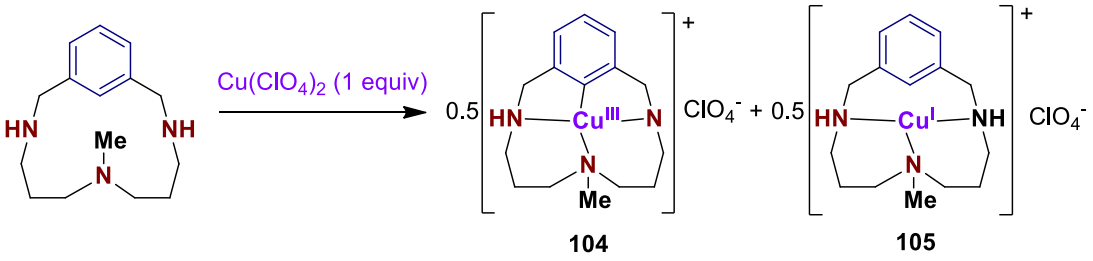
The C-O bond formation step could not be investigated under catalytic conditions as it happened after the turnover-limiting step. Therefore, two possible pathways were mentioned (**Scheme 60**):

- Reductive elimination from Cu(II) involving a comproportionation event
- Reductive elimination from Cu(III) involving a disproportionation event



Scheme 60: Two possible pathways for the reductive elimination step.

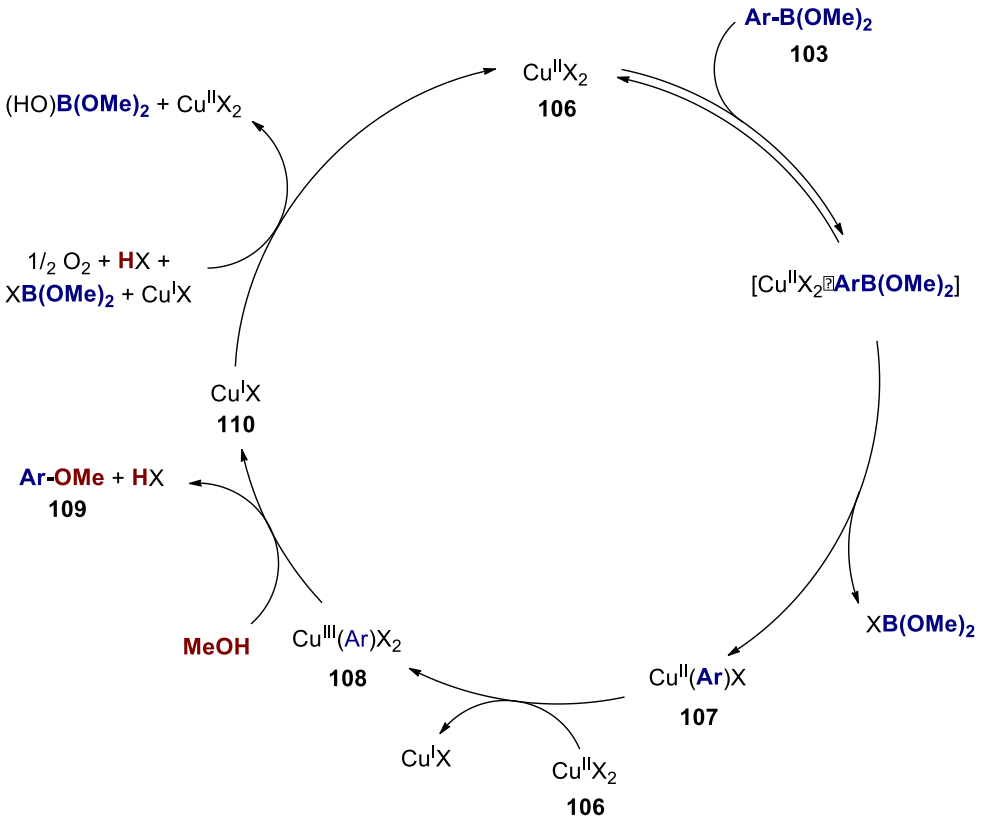
The second path was identified to be the more plausible, as it matched the observations reported by Ribas *et al*. in their Cu(II)-mediated C-H activation (**Scheme 61**). The authors highlighted the formation of a Cu(III) species **104** alongside a Cu(I) complex **105**, after a Cu(II) disproportionation event. In addition, the reductive elimination from the Cu(III) species was found to be fast in the presence of *N*- and *O*-nucleophiles.



104 105

Scheme 61: Study of the disproportionation by Ribas *et al.*

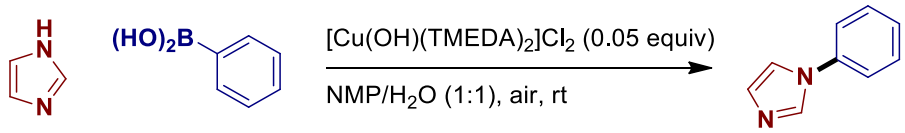
All this data allowed a proposed mechanism for the Chan-Lam reaction to be described (**Scheme 62**). The catalytic cycle started with the transmetalation of the aryl group from **103** to Cu(II) **106**. The resulting aryl-Cu(II) species **107** was oxidised by another equivalent of Cu(II) **106** to yield an aryl-Cu(III) intermediate **108** that could undergo reductive elimination to give the desired product **109**. Finally, oxidation of Cu(I) **110** by O_2 regenerated the initial Cu(II) **106**.



Scheme 62: Proposed mechanism for the Chan-Lam reaction of aryl boronate with methanol by Stahl *et al.*

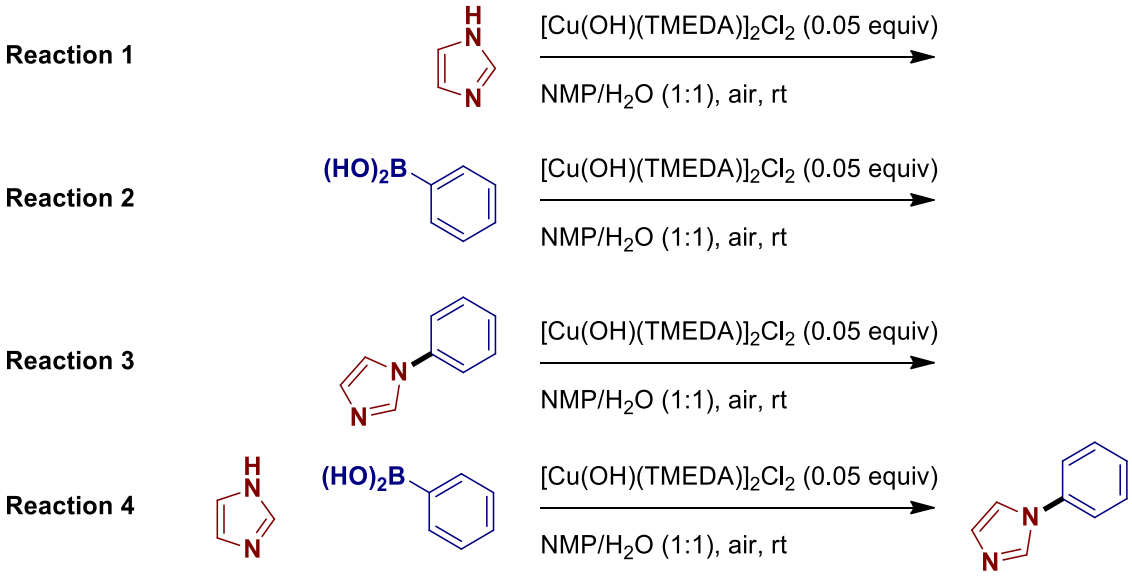
1.2.3. Multi-technique approach: Tromp *et al.* mechanistic report

Directly following the Stahl *et al.* publication, Tromp and co-workers studied the mechanism of the coupling of imidazole with phenylboronic acid, using $[Cu(OH)(TMEDA)]_2Cl_2$ **111** as the catalyst in a mixture of NMP/H_2O at room temperature under ambient atmosphere (**Scheme 63**).[93] In a previous report, they had shown that water was required for the reaction to proceed in high yield. In addition, they highlighted that the use of a base and/or an oxidant was not necessary for the desired product to be formed.



Scheme 63: Coupling of imidazole with phenylboronic acid using $[Cu(OH)(TMEDA)]_2Cl_2$ as the catalyst.

They first demonstrated that premixing stoichiometric amounts of the Cu(II) dimer with phenylboronic acid, followed by the addition of imidazole, did not allow the C-N bond formation to occur. However, reversing the order of addition afforded the desired C-N coupled product. Therefore, they concluded that the reaction between the copper complex and the imidazole was the selectivity-determining step. In addition, they highlighted that increasing the amount of imidazole, inhibited the reaction. Then, they decided to use a combination of spectroscopic techniques, including UV-vis, XAFS (X-ray absorption fine structure spectroscopy), NMR and EPR to determine the intermediates of the reaction. Four reactions were studied before proposing a mechanism (**Scheme 64**).



Scheme 64: Selected reactions to study the mechanism of the Chan-Lam reaction between imidazole and phenylboronic acid.

From reaction **1**, they observed disappearance of the dimeric copper complex **111** and formation of a mononuclear Cu(II) structure corresponding to the formation of a [(TMEDA) (imidazolate)$_2$Cu(II)] square planar complex **112** or [(TMEDA)(imidazolate)$_2$Cu(II)(L)] square pyramidal complex **113** where L is either H_2O or imidazole. They also managed to isolate a [(TMEDA)(imidazolate)Cu(II)(Cl)] complex **114** from the reaction mixture.

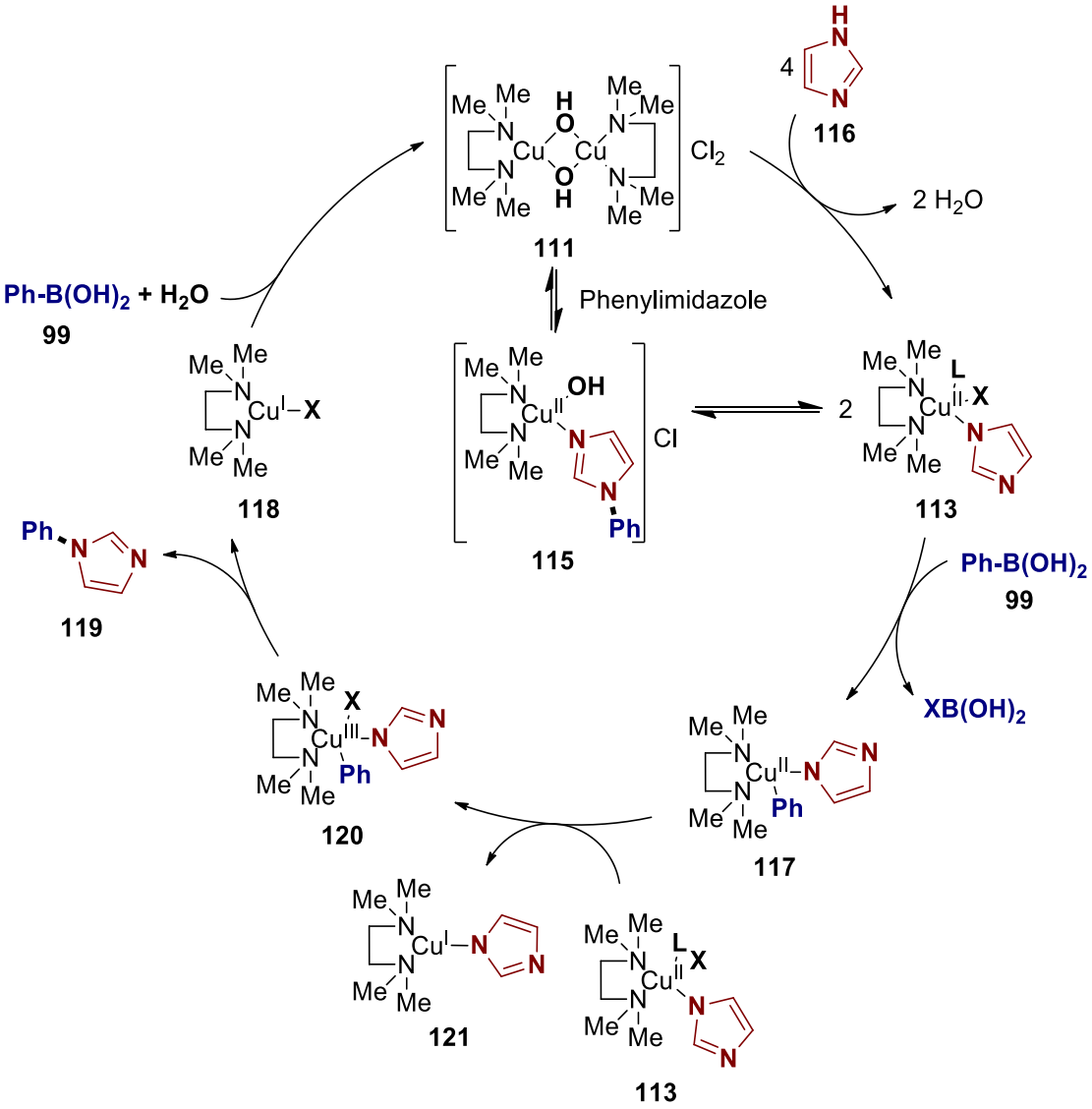
From reaction **2**, they showed that the addition of phenylboronic acid to the copper complex afforded the homocoupled product and the residual copper species in solution was a Cu^{I} complex.

From reaction **3**, they observed that the product inhibited the reaction by chelating the copper catalyst to form the copper complex **115**.

From reaction **4**, they first demonstrated that the isolated complex **114** was catalytically active. Then, they highlighted that the addition of phenylboronic acid **99** to a mixture of the copper complex **111** and imidazole **116** resulted in the formation of a new [(TMEDA)(imidazole)$_2$Cu(II)(Ph)] copper complex **117**. They allowed the mixture to

react for 10 minutes at 60 ºC, and observed a disappearance of the Cu(II) signal by EPR, suggesting the formation of a Cu(I) species **118**. Finally, they demonstrated that addition of excess phenylboronic acid to this reaction mixture resulted in the reoxidation of Cu(I) **118** to Cu(II) **111**.

From these experiments, they proposed the following mechanistic pathways (**Scheme 65**). First, formation of the [Cu(imidazolate)(imidazole)(TMEDA)(L)] complex **113** from the reaction of imidazole **116** with the starting $[Cu(OH)(TMEDA)]_2Cl_2$ complex **111**. The imidazole ligand could potentially dissociate and be replaced by another ligand (*e.g.* product or H_2O). This ligand exchange matched with the observed inhibition of the reaction by addition of the desired product to the mixture. Then, the reaction of **113** with phenylboronic acid **99** formed the copper complex **117**, and the desired phenylimidazole product **119** and a Cu(I) intermediate **118** were observed. This Cu(I) oxidised to complex **111** in the presence of water and phenylboronic acid **99**. In the absence of relevant intermediates, the authors could not conclude which pathway was preferred for the formation of the desired product. They mentioned two possibilities: *via* electrophilic attack of a phenylboronic acid species on the nucleophilic imidazole, or *via* reductive elimination from a Cu(III)(aryl)(imidazolate) species **120**. This formation of a Cu(III) species suggested either the addition of a phenyl radical to the Cu(II)(imidazolate) complex **112**, or the disproportionation of **113** with **117** into Cu(I) **121** and Cu(III) **120** species.



Scheme 65: Proposed mechanism for the Chan-Lam reaction of aryl boronic acid with imidazole by Tromp *et al.*

With their study Tromp *et al.* characterised five important intermediates of the Chan-Lam reaction and offered important insights into the mechanism (**Scheme 65**). Unfortunately, they did not manage to establish which oxidative pathway afforded the desired product.

1.2.4. Boron to Cu(II) transmetalation: Stahl *et al.* second report

In 2012, Stahl and co-workers published a more detailed study of the aerobic copper-catalysed methoxylation of arylboronic esters focusing on the transmetalation step.[90]

They first demonstrated that more electron-rich arylboronic acids increased the catalyst turnover (**Figure 9**). Therefore, they confirmed that transmetalation was the turnover-limiting step of the catalytic process.

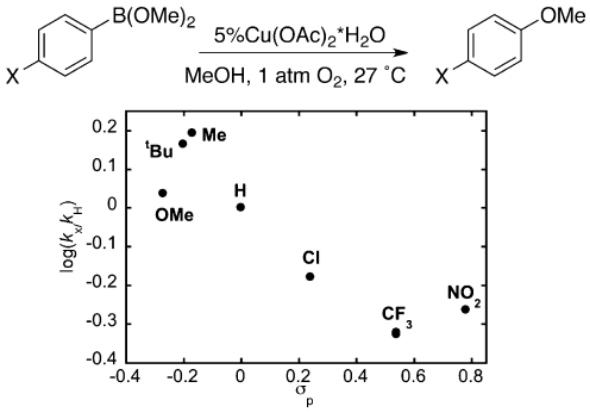
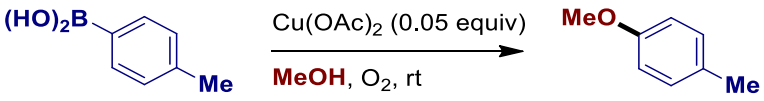


Figure 9: Catalyst turnover measurement based on the nature of the aryl boronic acid coupling partners (*copyright obtained from ACS*).

Then, they studied how small modifications impacted the outcome of the reaction (**Table 23, entry 1**). They first observed that addition of acetate or acetic acid inhibited the reaction (**Table 23, entries 2** and **3**). Then, replacing $Cu(OAc)_2$ by $Cu(ClO_4)_2$ had a very negative impact on the catalyst activity (**Table 23, entry 4**). However, the combination of $Cu(ClO_4)_2$ with NaOAc (1 equiv) or NaOMe (1 equiv) led to a better turnover than the original conditions (**Table 23, entries 5** and **6**).



Entry	Deviation from original conditions	Effect on reactivity
1	-	88% yield
2	Added acetate	Inhibition
3	Added acetic acid	Inhibition
4	$Cu(ClO_4)_2$ instead of $Cu(OAc)_2$	Negligible reactivity
5	$Cu(ClO_4)_2$ + 1 equiv NaOAc	Acceleration
6	$Cu(ClO_4)_2$ + 1 equiv NaOMe	Acceleration

Table 23: Results obtained from the modification of the original reaction conditions.

Based on these preliminary observations, they conducted several kinetic and spectroscopic studies including EPR, and ^{11}B NMR experiments. The main observations are summarized below:

- Using $Cu(ClO_4)_2$, kinetic studies highlighted the slow rate of the reaction (**Figure 10**). Addition of NaOAc to the reaction mixture accelerated the rate, and a maximum was observed for a 1:1 ratio Cu(II):AcO^- (**Figure 10**).

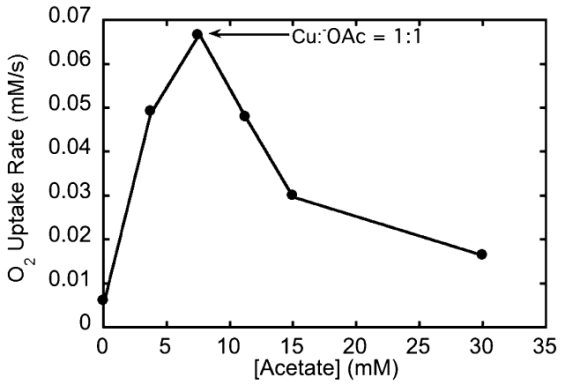


Figure 10: Influence of acetate on the rate of the Chan-Lam reaction (*copyright obtained from ACS*).

- Using $[Cu(OMe)_2]_n$ led to an increase of the catalytic reactivity compared to the original set of conditions.
- Addition of NaOMe (1 equiv) to the reaction mixture resulted in the formation of a tetracoordinate boronate species, $[TolB(OMe)_3]^-$ (**Figure 11**).

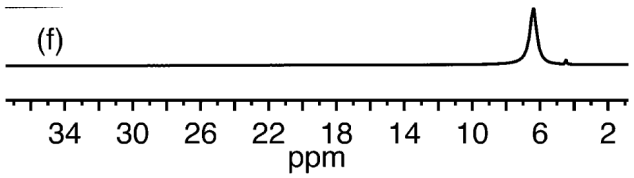
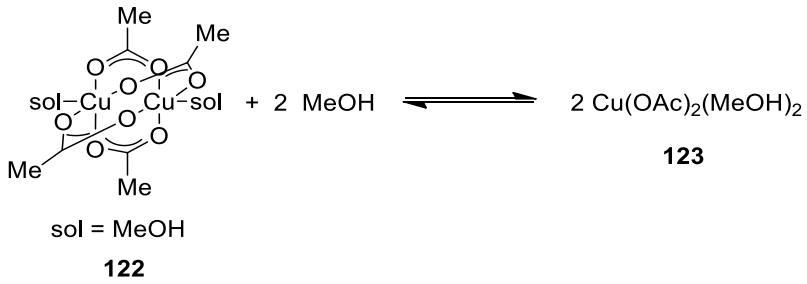


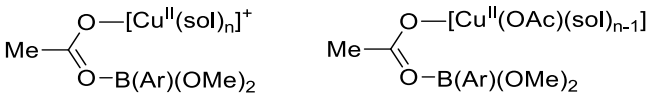
Figure 11: Boronate formation by addition of NaOMe (*copyright obtained from ACS*).

- In solution, $Cu(OAc)_2$ displayed an EPR-silent paddlewheel dimer **122** (**Scheme 66**). In MeOH, $Cu(OAc)_2$ exhibited small dissociation to the mononuclear species **123** (**Scheme 66**).



Scheme 66: Dissociation equilibrium of the paddlewheel $Cu(OAc)_2$ dimer.

- Addition of *p*-tolylboronic ester to $Cu(OAc)_2$ occasioned a strong Cu(II) EPR signal.
- Addition of NaOAc or AcOH resulted in a stabilisation of the EPR-silent paddlewheel dimer **122**.
- The kinetic saturation dependence on the concentration of tolylboronic ester adding to the strong EPR signal observed upon addition of tolylboronic ester to $Cu(OAc)_2$ indicated that the resting state was related to a Cu(II)-tolylboronic ester adduct. Species **124** and **125** were then observed by EPR (**Scheme 67**).

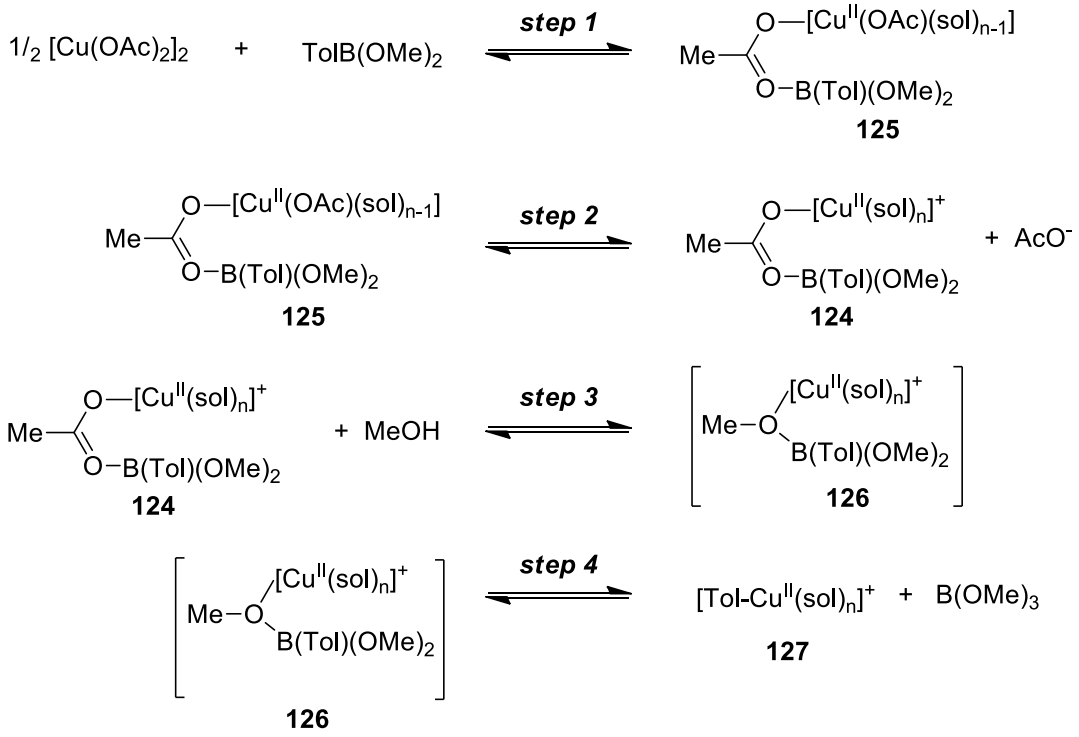


124 **125**

Scheme 67: Species 125 and 126 observed by EPR.

From these observations, Stahl *et al.* concluded on the boron to Cu(II) transmetalation step (**Scheme 68**). *Step 1* was the dissociation of the paddlewheel dimer in the presence of tolylboronic ester leading to the formation of species **125**. *Step 2* is the equilibrium between species **125** and **124** involving the addition/loss of acetate. *Step 3* afforded the formation of **126** from species **124**, highlighting the inhibitory effect of AcOH and the need to lose an acetate from the kinetic data. In addition, the formation of the methoxide bridge species **126** was suggested by ^{11}B NMR spectroscopic and

kinetic data. Finally, *Step 4* highlighted the rate-limiting transmetalation which afforded the aryl-Cu(II) species **127** and $B(OMe)_3$.

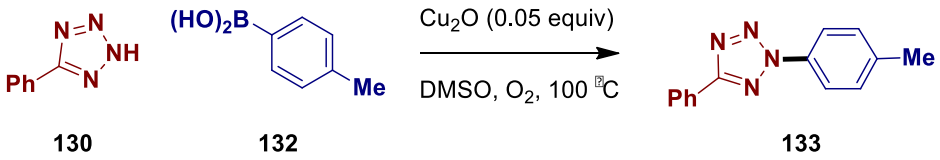


Scheme 68: Proposed boron to Cu(II) transmetalation step by Stahl *et al.*

This work gave an excellent insight into the transmetalation step of the Chan-Lam reaction. However, it is important to consider that the study was completed on a C-O bond formation rather than on a C-N bond formation.

1.2.5. Crucial roles of solvent and oxygen: Han *et al.* study

Following their report on the development and optimisation of catalytic conditions for the coupling of H-tetrazoles with arylboronic acid, Han and co-workers decided to investigate the mechanism of the reaction (**Scheme 69**).[94]



130 132 133

Scheme 69: Coupling of H-tetrazoles with arylboronic acid under Cu-catalysed reaction conditions.

They first highlighted that mixing 5-phenyltetrazole with Cu_2O in DMSO under an oxygen atmosphere resulted in the formation of sky-blue colour crystals. XPS and NMR analyses of the isolated copper complex **128** crystals and comparison with a Cu(II) complex **129** obtained from a $Cu(OAc)_2$/tetrazole mixture, confirmed that Cu^I was oxidised to Cu(II) (**Figures 12 and 13**). In addition, the powder X-ray diffraction demonstrated that both complexes had the same XRD patterns (**Figure 14**). Elemental analysis showed that the structure of both complexes **128** and **129** consisted of Cu, tetrazole (T) **130**, and DMSO (D) in a 1:2:1 ratio, defined as CuT_2D **131**.

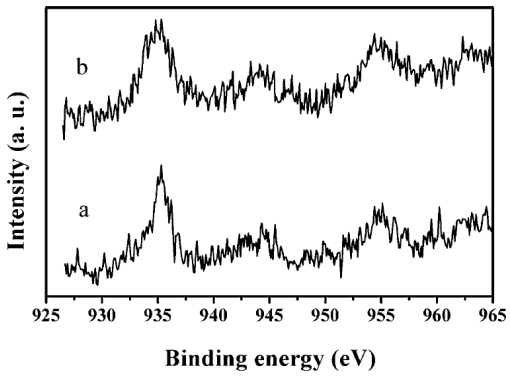


Figure 12: XPS analysis of copper complexes 128 and 129 (*copyright obtained from Wiley*).

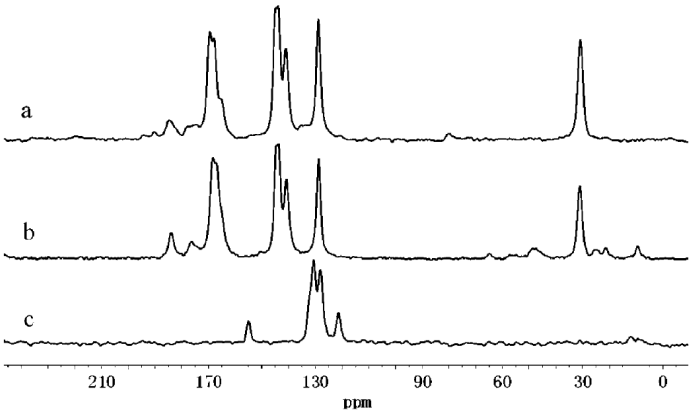


Figure 13: NMR analysis of copper complex 128. Comparison with complex 129 (*copyright obtained from Wiley*).

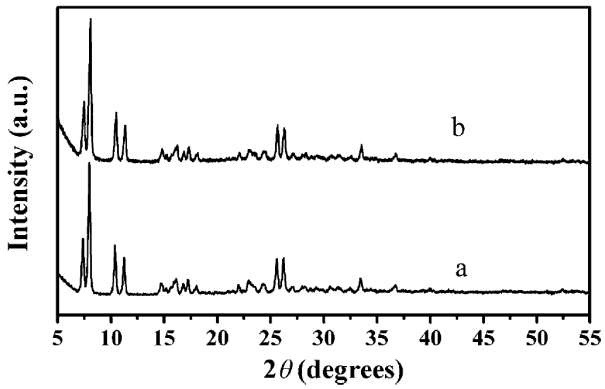
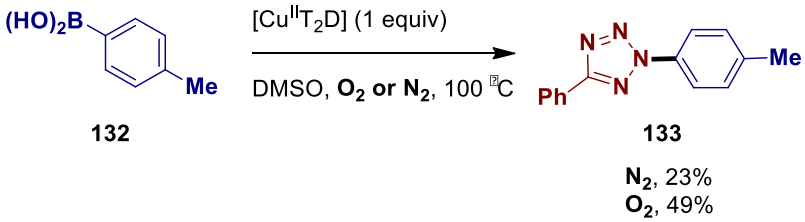


Figure 14: XRD patterns of both complexes 128 and 129 (*copyright obtained from Wiley*).

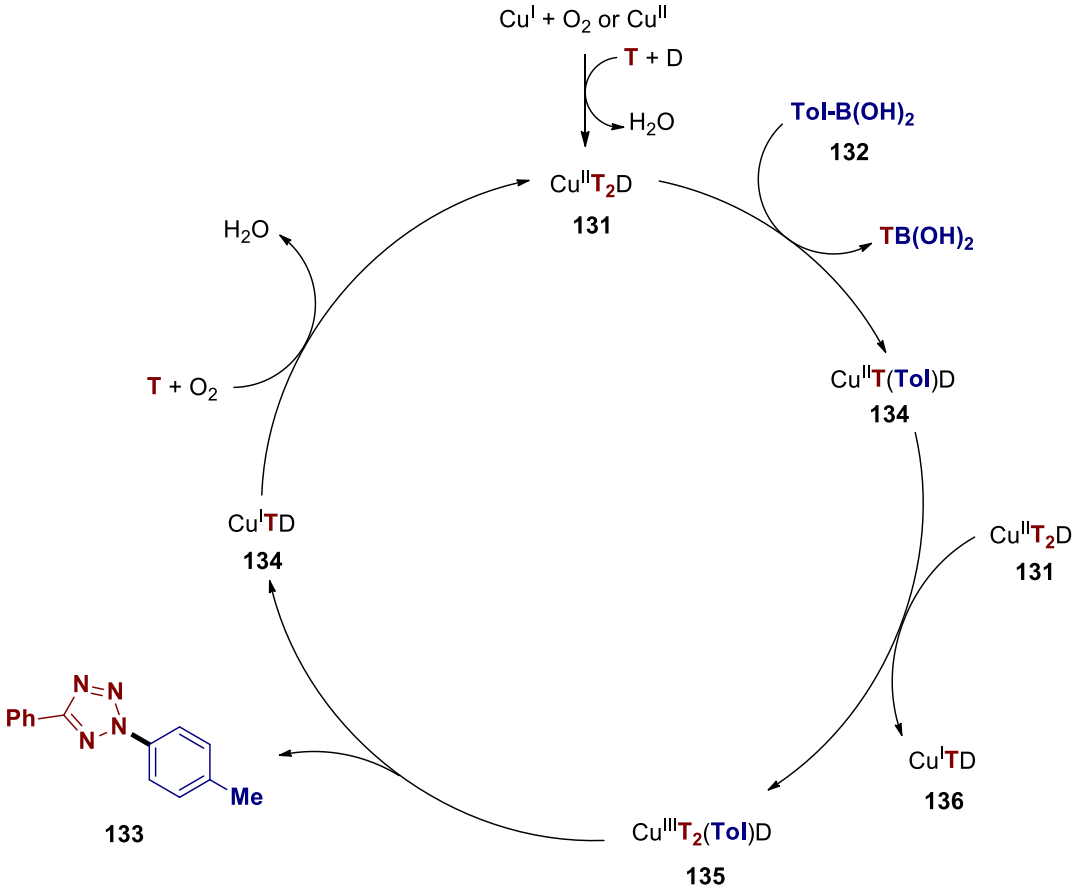
Once the structure of complex **131** was identified, they treated it with tolylboronic acid **132** in a 1:4 molar ratio (**Scheme 70**). The desired product **133** was obtained in 23% and 49% under nitrogen or oxygen atmosphere, respectively. No side-product was detected, and XPS analyses indicated the conversion of Cu(II) to Cu(I) with no detection of Cu(0). Therefore, the desired product was formed *via* reductive elimination of a Cu(III) species. Based on the yield obtained and the reports from the groups of Stahl, Tromp, and Ribas; the authors validated the disproportionation mechanism from Cu(II) to generate Cu(III) and Cu(I) without the assistance of oxygen. They also established that the disproportionation event was the rate-limiting step in the reaction cycle as lower temperature afforded the desired product **133** in lower yield. Finally, they mentioned that in their case, water was not required for disproportionation to occur and that the phenyl radical did not participate in the reaction.



Scheme 70: Influence of O_2 and N_2 atmosphere on the outcome of the Chan-Lam reaction.

Based on these experiments they reported the following plausible mechanism for the Chan-Lam reaction of tetrazole **130** with tolylboronic acid **132** (**Scheme 71**). *Step 1*

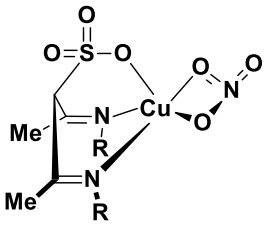
involved the formation of a Cu(II) complex **131** from Cu(I) or Cu(II) catalyst salts. *Step 2* was the transmetalation of the tolyl-group from boronic acid to **131**, delivering [Cu(II)T(Tol)D] **134**. In *Step 3*, disproportionation of [Cu(II)T(Tol)D] **134** generated complex [Cu(III)T_2(Tol)D] **135** and [Cu(I)TD] **136**. Then, *Step 4* corresponded to the facile reductive elimination of [Cu(III)T_2(Tol)D] **135** to give the desired product **133** and [Cu(I)TD] **136**. Finally, step 5 was the re-oxidative copper amination of [Cu(I)TD] **136** by oxygen to regenerate complex [Cu(II)T_2D] **131**.



Scheme 71: Proposed mechanism of the Chan-Lam reaction between tetrazole and aryl boronic acid by Han *et al.*

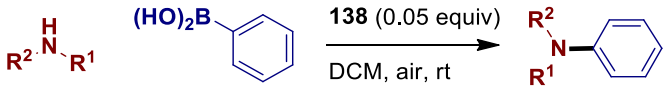
1.2.6. Development of ligand/copper complexes: Shaper and Duparc report

Last year, Shaper and Duparc reported the synthesis of sulfonato-diketimine copper complexes **137** and **138** (**Figure 15**).[95] They demonstrated their high activity for the Chan−Lam coupling of various amines and anilines (**Scheme 72**). These couplings do not require the use of base, ligand, or molecular sieves. Therefore, Shaper and Duparc started to investigate the mechanism of the Chan-Lam reaction between anilines and phenylboronic acid using complex **137**.



R = 2-6-$Me_2C_6H_3$, **137**
R = 2-6-$^{i}Pr_2C_6H_3$, **138**

Figure 15: Structure of sulfonato-diketimine copper complexes 137 and 138.



0-100%
21 examples

Scheme 72: Chan−Lam coupling of various amines and anilines with phenylboronic acid using copper complex 138.

They first studied the role of the solvent, and showed that coordinating solvents reduced the activity (**Table 24, entries 1** to **5**). This reactivity order changed considerably from the original order established for Chan−Lam couplings with $Cu(OAc)_2$. The authors explained this dissimilarity by the difference in solubility of the copper catalyst sources, and the subsequent coordination competition.

Entry	Solvent	Yield (%)
1	MeCN	2
2	THF	12

3	MeOH	40
4	Toluene	66
5	DCM	71

Table 24: Influence of the solvent on the Chan-Lam reaction between aryl boronic acids and various amines using of sulfonato-diketimine copper complex 138.

Then, they investigated the role of the base, and demonstrated that addition of stoichiometric amounts of triethylamine was detrimental for the reaction to proceed in high yield (**Table 25, entry 1**). Lower amounts of base did not alter the yield observed with no base (**Table 25, entries 2** to **4**). However, the use of base was required for the coupling of phenol substrates demonstrating that a base-assisted proton transfer occurred during the reaction. For aryl amine, the substrate or the desired product could act in the proton transfer, removing the need for an external base.

Entry	Solvent	Modification	Yield (%)
1	DCM	-	71
2	DCM	Et_3N (1 equiv)	14
3	DCM	Et_3N (0.05 equiv)	67
4	DCM	Et_3N (0.025 equiv)	70

Table 25: Influence of the base on the Chan-Lam reaction between aryl boronic acids and various amines using of sulfonato-diketimine copper complex 138.

They highlighted that the presence of water led to slightly higher conversions (**Table 26, entries 2** to **4**). Intriguingly, the presence of molecular sieves decreased the conversion to 35% (**Table 26, entries 5**). In addition, it was found that NH_4Cl was equally suitable for the reaction to proceed in higher yields (**Table 26, entries 6**). Therefore, the authors concluded that the presence of acidic protons facilitated proton transfer steps in the mechanism.

Entry	Solvent	Modification	Yield (%)
1	DCM	-	71
2	DCM	H_2O (0.025 equiv)	61
3	DCM	H_2O (1 equiv)	81
4	DCM	H_2O (20 equiv)	76
5	DCM	Sieves	35
6	DCM	NH_4Cl (0.025 equiv)	83

Table 26: Influence of the water, sieves and NH_4Cl on the Chan-Lam reaction between aryl boronic acids and various amines using of sulfonato-diketimine copper complex 138.

Regarding the oxidation step, Shaper *et al.* showed that use of nitrogen atmosphere considerably decreased conversion to 5% (**Table 27, entry 2**). Thus, they mentioned that the Chan-Lam reaction with complex **138** followed an oxidative coupling mechanism with oxygen as the oxidant.

Entry	Solvent	Modification	Yield (%)
1	DCM	-	71
2	DCM	N_2 atmosphere	5

Table 27: Influence of a nitrogen atmosphere on the Chan-Lam reaction between aryl boronic acids and various amines using of sulfonato-diketimine copper complex 138.

Finally, they reported that the reaction was pseudo-first-order, and did not depend on the concentration of phenylboronic acid (**Figure 16)**. Therefore, the transmetalation step was not the rate determining step of the mechanism, validating the involvement of the sulfonate group in this key event. In addition, they mentioned that electron-rich-anilines deactivated the catalyst by blocking one of its coordination sites needed for transmetalation. Unfortunately, the authors did not manage to conclude on the nature of the rate-determining step as kinetics indicated independence from boronic acid concentration and dependence on nucleophile concentration.

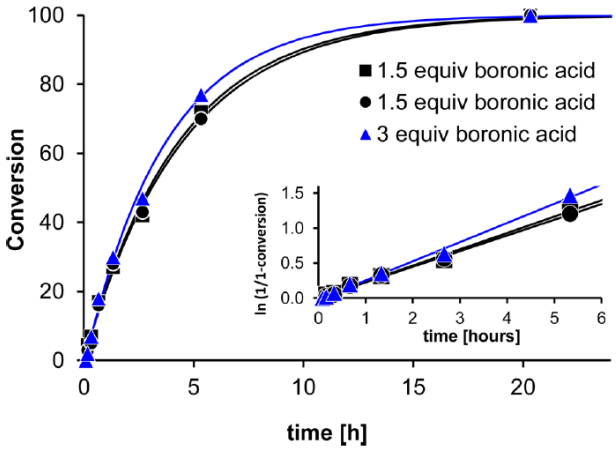
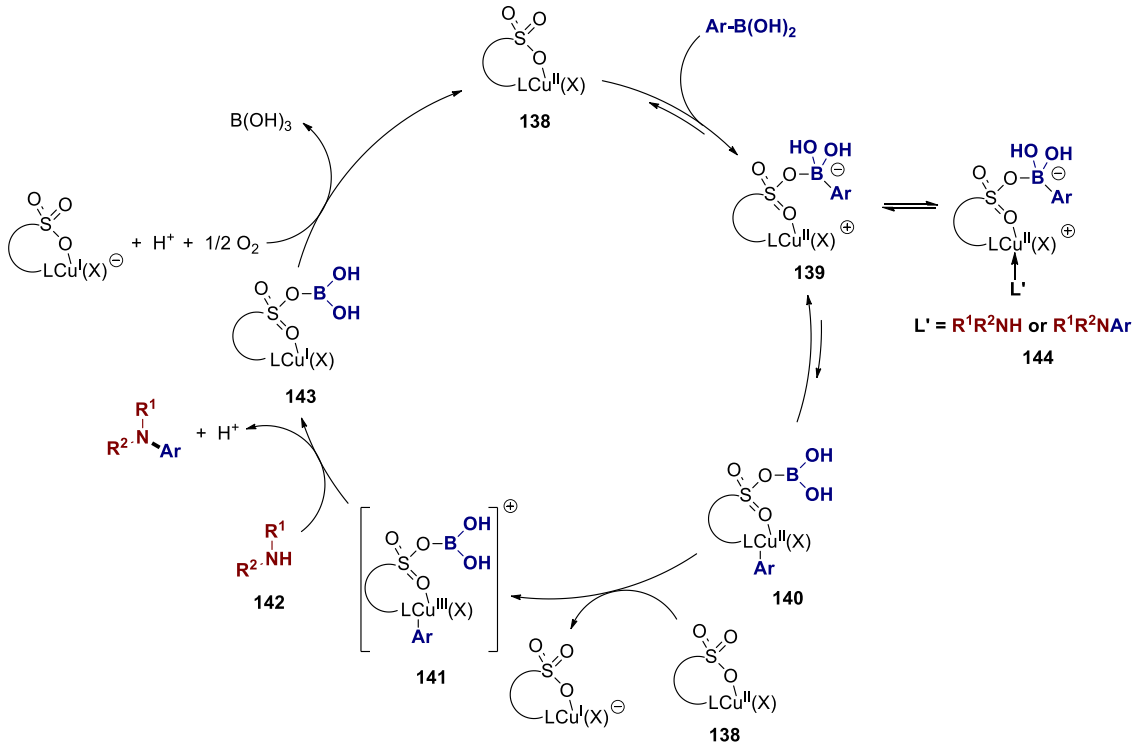


Figure 16: Demonstration of the pseudo first order of the reaction: no dependence on phenylboronic acid concentration (*copyright obtained from ACS*).

These observations allowed the authors to propose the following mechanism (**Scheme 73**). The first step involved the coordination of complex **138** to the boronic acid via its sulfonato-diketimine ligand to afford complex **139**. This complex underwent transmetalation to give intermediate **140**. The structure of Cu(III) species **141** was only putative as no data confirmed its formation. The amine coordination could occur prior to or after oxidation. Reductive elimination from intermediate **141** in presence of the amine **142** gave the Cu(I) complex **143**, which oxidised to the original complex **138** under oxygen atmosphere. Finally, the reduced conversions with more nucleophilic anilines highlighted the formation of off-cycle complexes **144**, and that transmetalation had to occur before nucleophilic displacement.



Scheme 73: Proposed mechanism of the Chan-Lam reaction between aryl boronic acid and amines using copper complex 138 by Shaper and Duparc.

1.3. Conclusions

Despite offering key insights on the Chan-Lam mechanism, in most occasions, the published investigations focused on particular substrates rather than on a general

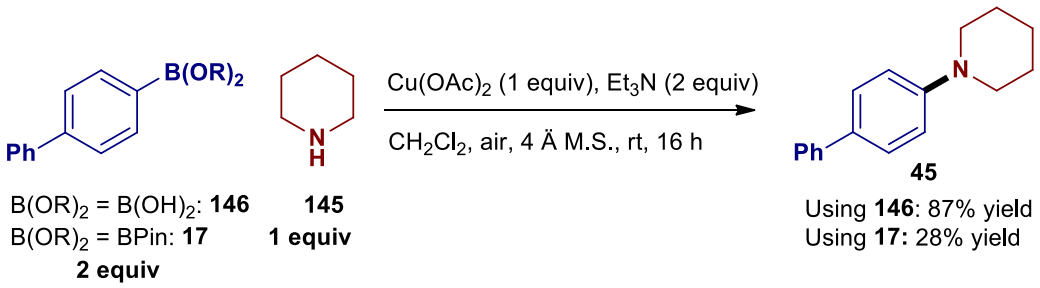
solution. In addition, the Chan-Lam amination of BPin esters is hampered by significant unsolved problems with unexplained by-product formations, and reactivity issues. Therefore, a deeper understanding of the Chan-Lam reaction mechanism and the development of more general reaction conditions are required.

2. Results

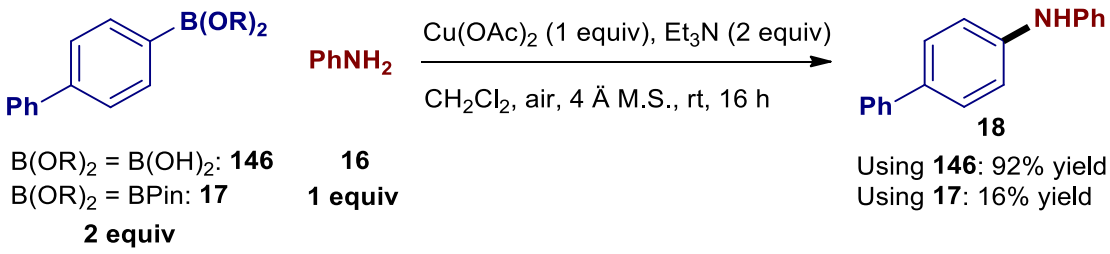
2.1. Reaction profiles and identification of by-products

We started our mechanistic investigations with a series of control experiments to evaluate the performance of the Chan-Lam amination using representative members of two amine classes (1 equiv), piperidine **145** and aniline **16** and two organoboron compounds (2 equiv), boronic acid **146** and BPin ester **17**. The reactions were conducted under standard conditions using $Cu(OAc)_2$ (1 equiv) as the catalyst, Et_3N (2 equiv) as the base, 4Å M.S. molecular sieves in DCM at room temperature under air (**Scheme 74** and **75**).

When using piperidine **145** as the amine component, boronic acid **146** was converted to product **45** in 87% yield while the corresponding BPin **17** provided only 28% yield (**Scheme 74**). Using aniline **16** as the amine coupling partner with aryl boronic acid **146** afforded product **18** in 92% yield and only 16% yield using aryl BPin **17** (**Scheme 75**).

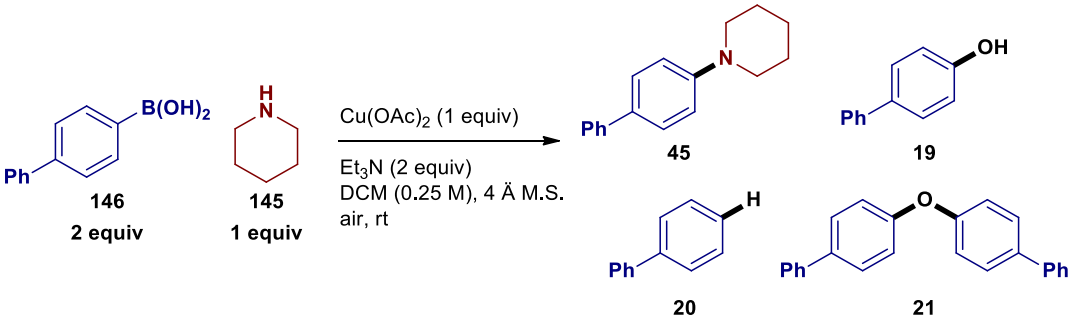


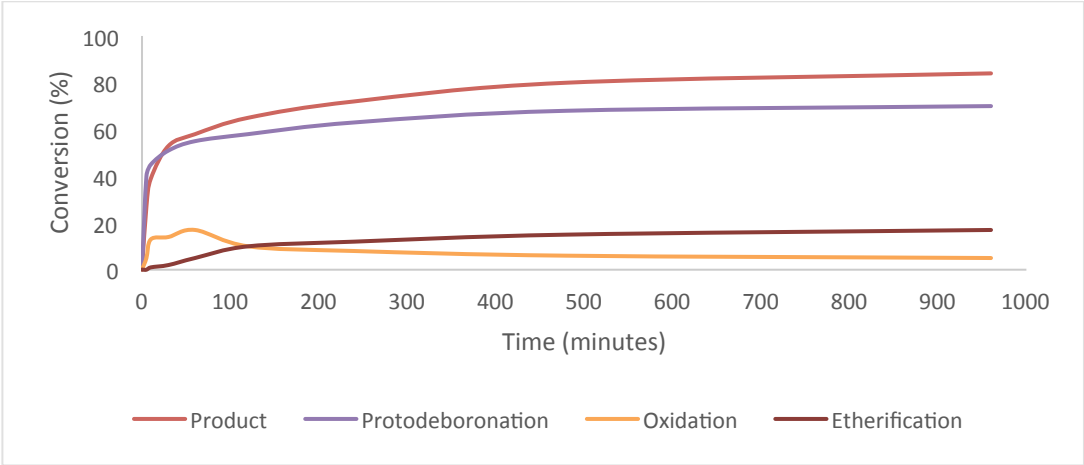
Scheme 74: Control experiments to evaluate the performance of the Chan-Lam amination of piperidine 145 with aryl boronic acid 146 or aryl BPin ester 17.



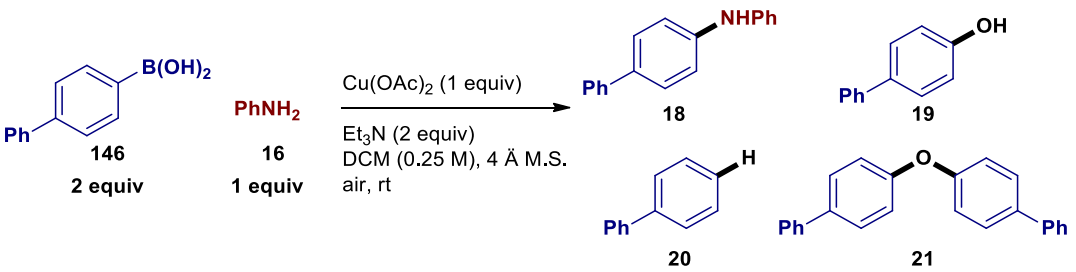
Scheme 75: Control experiments to evaluate the performance of the Chan-Lam amination of aniline 16 with aryl boronic acid 146 or aryl BPin ester 17.

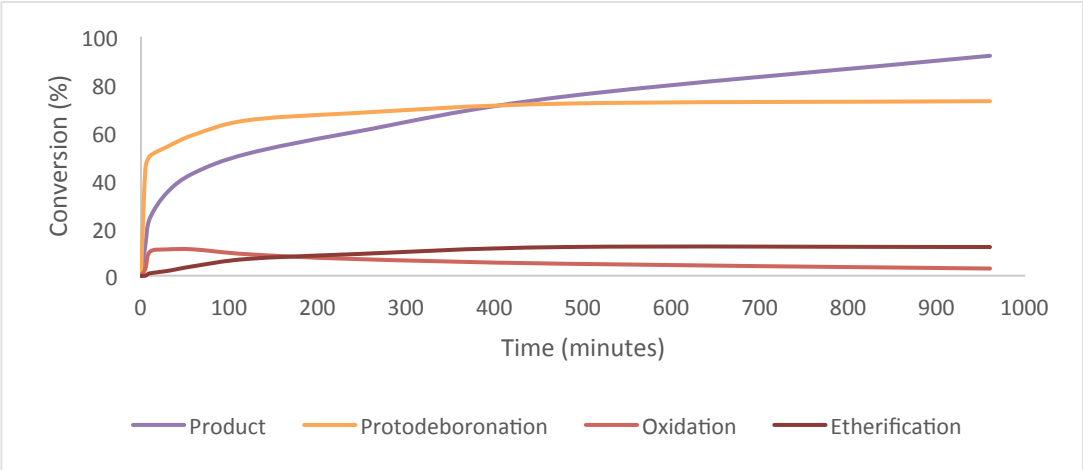
Then, we studied the reaction profiles for both reactions (**Scheme 76** and **77**). Several by-products were identified including phenol **19**, protodeboronation product **20**, and oxidative homocoupling product **21**. Protodeboronation was comparable to amination, while competing oxidation delivered **19** and, as the concentration of **19** increased, competing Cu-catalysed etherification delivered **21**. In addition, the reaction profiles highlighted the difference in reactivity between alkyl- and aryl amines.





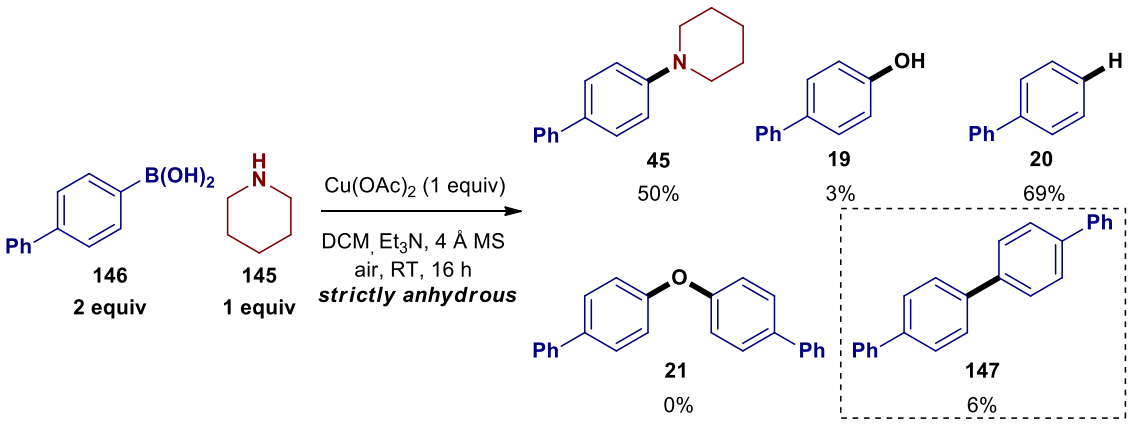
Scheme 76: Reaction profile of the Chan-Lam amination of piperidine 145 with aryl boronic acid 146.





Scheme 77: Reaction profile of the Chan-Lam amination of aniline 16 with aryl boronic acid 146.

Under strictly anhydrous reaction conditions, the quantity of **19** and **21** can be lowered significantly (**Scheme 78**). In addition, it is only under these rigorously dried conditions that we managed to observe the homocoupled by-product **147** previously reported in the literature. However, this by-product was significantly less problematic than those of oxidation and protodeboronation (**Scheme 78**).



Scheme 78: Evaluation of by-products formation for the Chan-Lam amination of piperidine 145 with aryl boronic acid 146 under strictly anhydrous reaction conditions.

The previously described experiments highlighted the difference in reactivity between aryl boronic acids and aryl BPin esters, but also between alkyl- and aryl amines. In addition, all the products and by-products issued from the reaction were quantified, isolated and characterised.

2.2. Assessment of inhibitors

Stahl *et al.* reported that the addition of AcOH and AcOK inhibited the Chan-Lam etherification process. These two components were also involved in our designed Chan-Lam amination reaction, as well as pinacol which could come from the aryl BPin ester starting material. Therefore, we assessed the outcome of the reactions of amines **16** and **145** with aryl boronic acid **146** in the presence of added AcOH, AcOK, as well as pinacol to probe any inhibitory effects (**Figures 17, 18** and **19**).

AcOH was found to inhibit the amination of both aniline **16** and piperidine **145** (**Figure 17**). AcOK inhibited only the reaction of aniline **16** (**Figure 18, red line**) and was found to be beneficial to efficiency for the reaction using piperidine **145** (**Figure 18, blue line**). Pinacol was found to inhibit both amination reactions, with a stronger effect on the reaction of aniline **16** than that of piperidine **145** (**Figure 19, red line**).

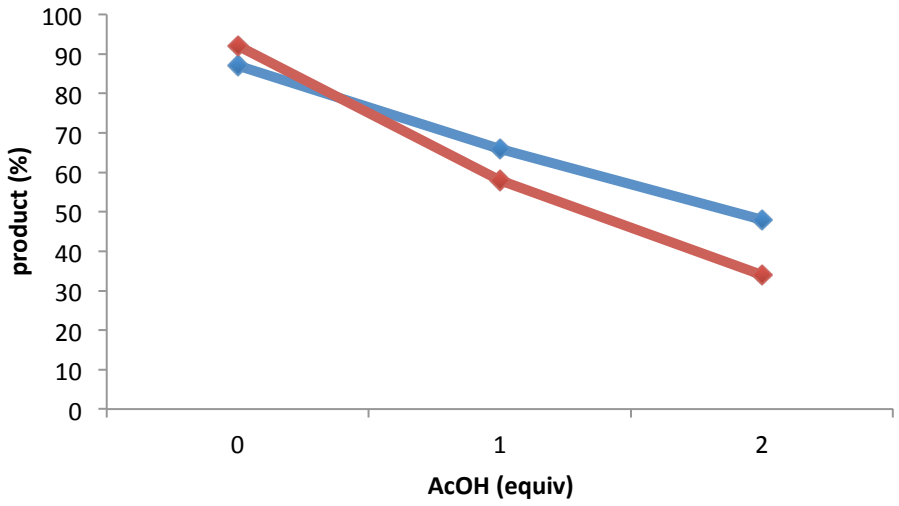


Figure 17: Effect of AcOH on the Chan-Lam reaction between aryl boronic acid 146 and aniline 16 (red line) or piperidine 145 (blue line).

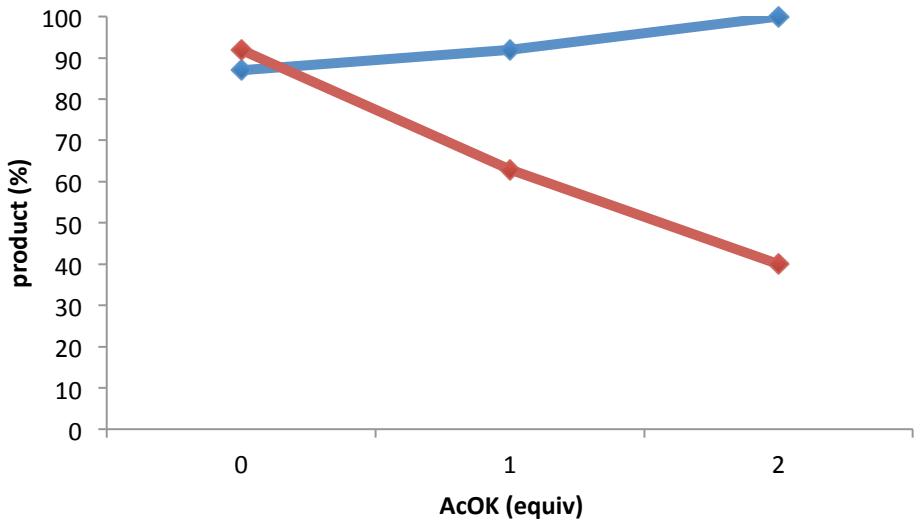


Figure 18: Effect of AcOK on the Chan-Lam reaction between aryl boronic acid 146 and aniline 16 (red line) or piperidine 145 (blue line).

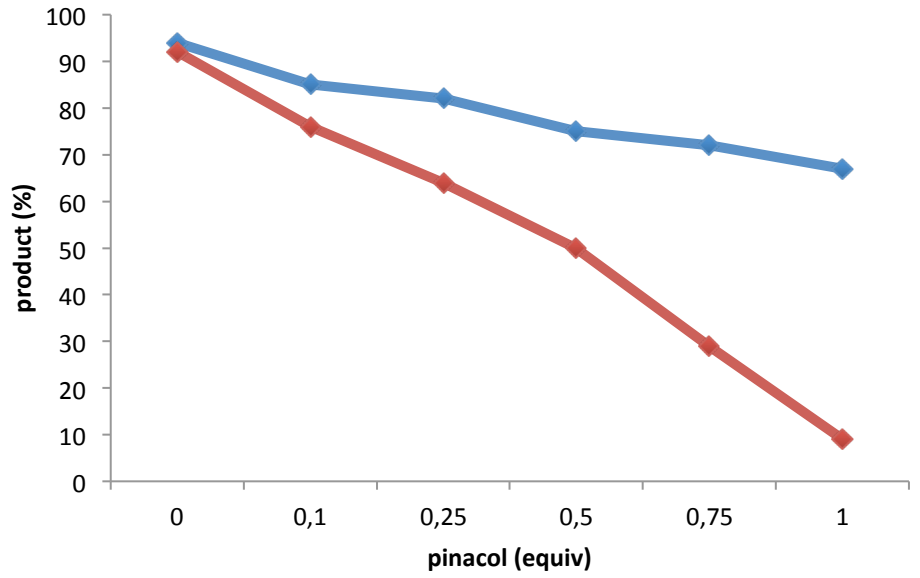


Figure 19: Effect of pinacol on the Chan-Lam reaction between aryl boronic acid 146 and aniline 16 (red line) or piperidine 145 (blue line).

2.3. Identification and analysis of Cu(II) complexes

We also tried to identify copper complexes present in the Chan-Lam amination reaction mixture.

2.3.1. EPR Analysis of Paddlewheel Dissociation

EPR analysis were conducted to determine the nature of the copper complex issued from the amination process. We first studied the $[Cu(OAc)_2]_2.2H_2O$ complex which is used as standard in most of the Chan-Lam amination reactions, and examined the effect of the amine and organoboron components on this complex.

The fluid solution EPR spectrum of $[Cu(OAc)_2]_2.2H_2O$ in MeCN only showed minor trace of a monocopper(II) species, with the dimeric paddlewheel structure (**Figure 20**) intact in solution as shown by a frozen solution spectrum (150 K) that is characteristic of the S = 1 complex (**Figure 21**, **a**). Treatment of the paddlewheel dimer with only organoboron compounds gave no observable change to the EPR spectrum (**Figure 21, b**).

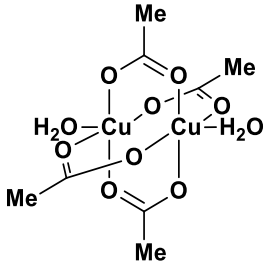


Figure 20: Dimeric paddlewheel structure of $[Cu(OAc)_2]_2.2H_2O$.

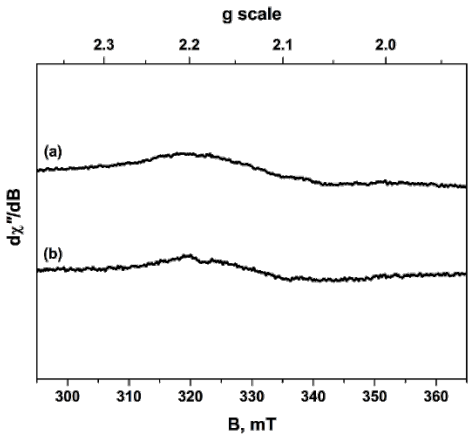
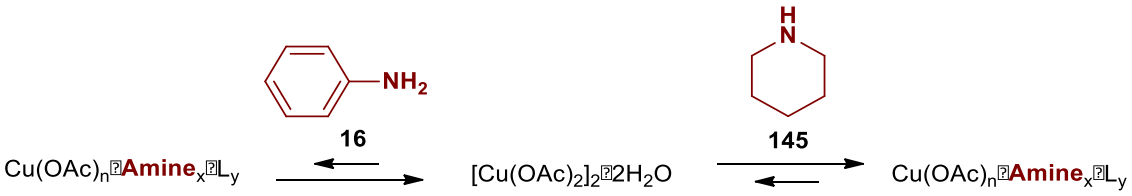


Figure 21: EPR analysis of paddlewheel dissociation in presence of organoboron.

In contrast, treatment of $[Cu(OAc)_2]_2.2H_2O$ with piperidine **145** immediately results in a deep blue solution. EPR confirmed the dissociation of the paddlewheel dimer to a mononuclear species (**Scheme 79** and **Figure 22**). The characteristic four-line signal resulting from the hyperfine coupling of the S = 1/2 Cu(II) d9 centre with its nuclear spin I = 3/2 of the $^{63,65}Cu$ isotopes (100% abundany). A similar effect is exhibited upon treatment of $[Cu(OAc)_2]_2.2H_2O$ with aniline **16** (**Scheme 79** and **Figure 23**). However, the effect is notably weaker, only becoming significant at increased concentration of aniline **16** (**Figure 24**). Finally, EPR confirmed that pinacol could dissociate the paddlewheel dimer to a mononuclear species in the presence of Et_3N (**Scheme 80 and Figure 25)**.



Scheme 79: Dimeric paddlewheel dissociation in presence of aniline 16 and piperidine 145.

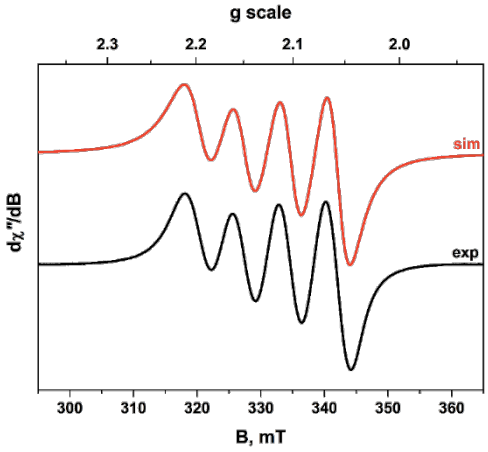


Figure 22: EPR spectrum of the paddlewheel dissociation in presence of piperidine 145.

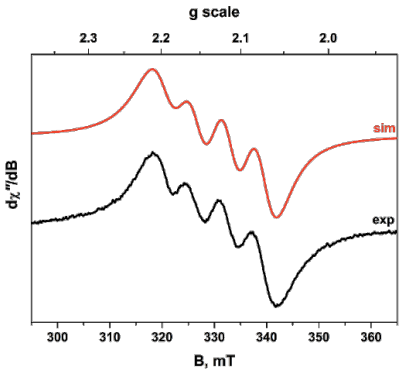


Figure 23: EPR spectrum of the paddlewheel dissociation in presence of aniline 16.

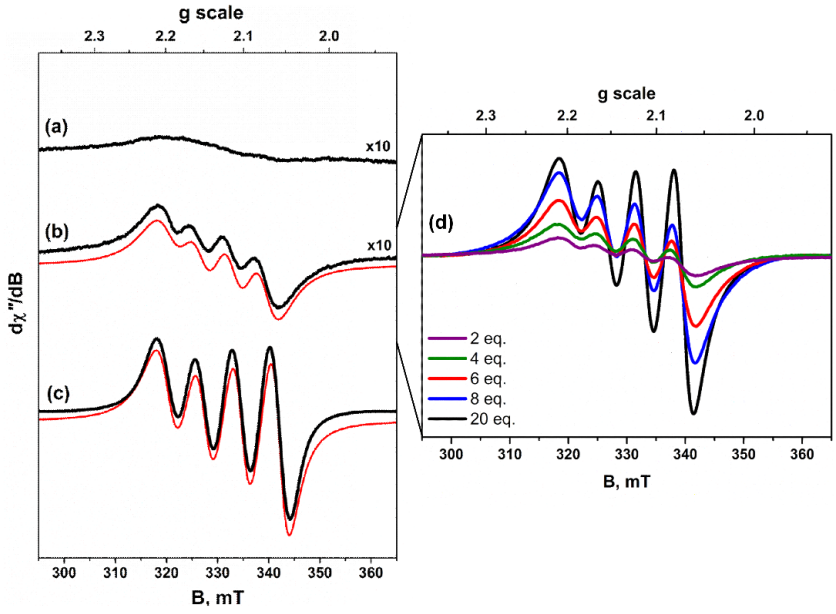


Figure 24: EPR spectrum of the paddlewheel dissociation in presence of aniline 16 at different concentration.

$$[Cu(OAc)_2]_2 \cdot 2H_2O \xrightarrow[Et_3N]{\textbf{Pinacol}} Cu(OAc)_n \cdot (\textbf{Pinacol})_x \cdot L_y$$

Scheme 80: Paddlewheel dissociation in presence of pinacol.

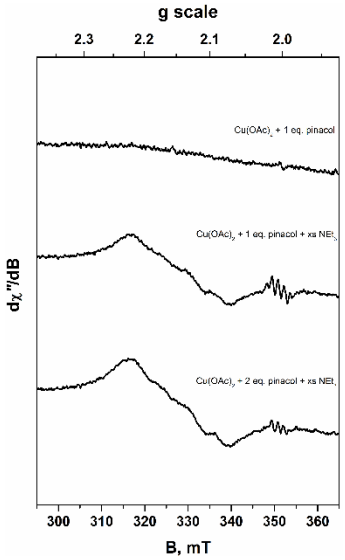
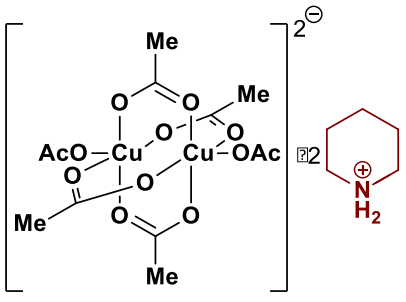


Figure 25: EPR spectrum of the paddlewheel dissociation in presence of pinacol.

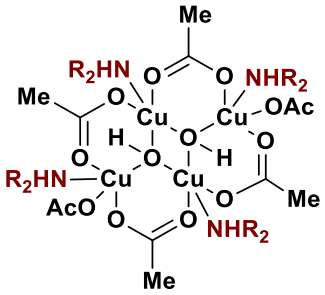
2.3.2. Structural Characterization of Cu(II) Complexes

During the optimisation of our stoichiometric reaction conditions, we observed that the Chan-Lam reaction of piperidine **145** with aryl BPin ester **17** delivered two different diffraction quality crystals. The hexa-acetate paddlewheel **148** had an analogous structure to $[Cu(OAc)_2]_2.2H_2O$ with AcO^- replacing H_2O at the axial sites and with the resulting anionic charge balanced by piperidinium ions (**Figure 26**). The tetracopper complex **149**, contained two bridging oxo units, four bridging acetates, two terminal acetates, and four neutral piperidine ligands (**Figure 27**).



148

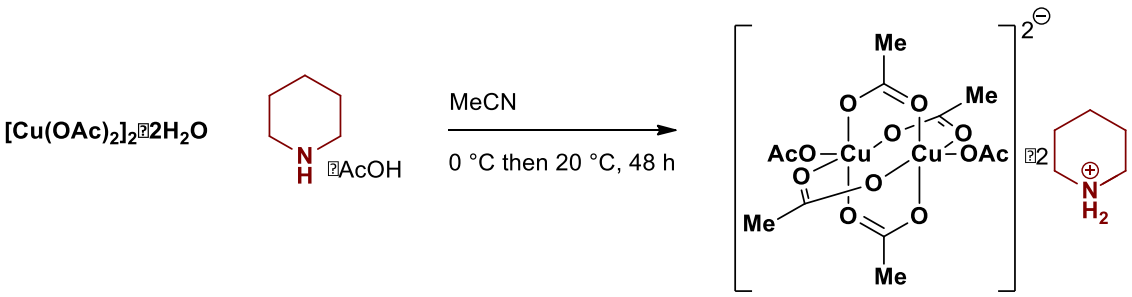
Figure 26: Structure of the hexa-acetate paddlewheel 148 charge balanced by piperidinium ions



149

Figure 27: Stucture of the tetracopper complex 149.

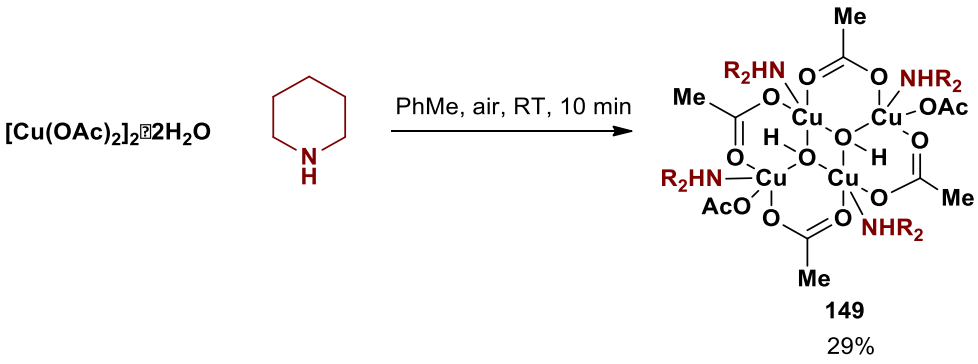
Independent preparation of both **148** and **149** was possible on gram scale (**Scheme 81 and 82**). Treatment of $[Cu(OAc)_2]_2.2H_2O$ with piperidinium acetate in MeCN at -20 °C delivered **148** as green crystals in 11% yield, while treatment of $[Cu(OAc)_2]_2.2H_2O$ with piperidine in PhMe at room temperature provided the large blue crystals of **149** in 29% yield. Both complexes were found to be stable at room temperature over a period of weeks.



148

11%

Scheme 81: Synthesis of copper complex 148.



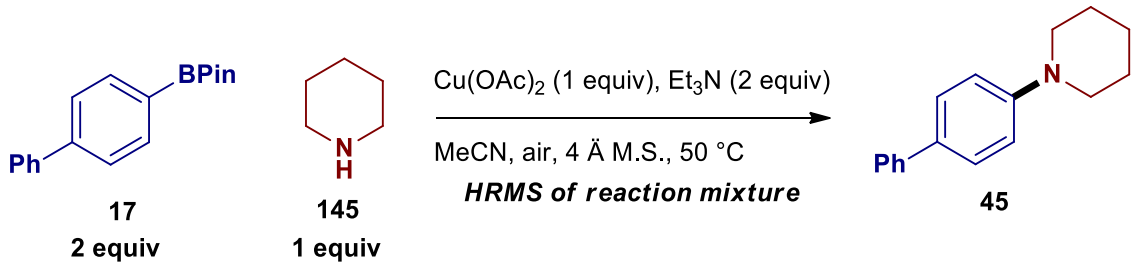
149

29%

Scheme 82: Synthesis of copper complex 149.

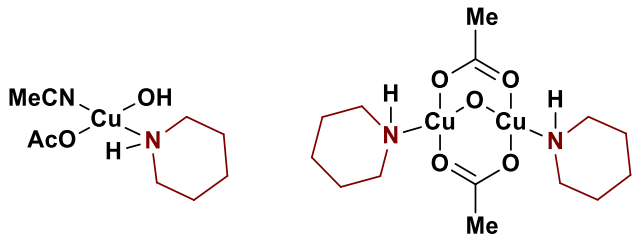
2.3.3. HRMS identification of Cu(II) complexes in solution

After the isolation of complexes **148** and **149**, we analysed by high-resolution mass spectrometry the Chan-Lam reaction between aryl BPin ester **17** and piperidine **145** under our developed stoichiometric set of conditions (**Scheme 83**). Aliquots from the reaction of **17** and **145** were analysed to identify organometallic complexes in solution. Mass ions consistent with several reaction-relevant structures were detected (**Figures 28** to **31**).



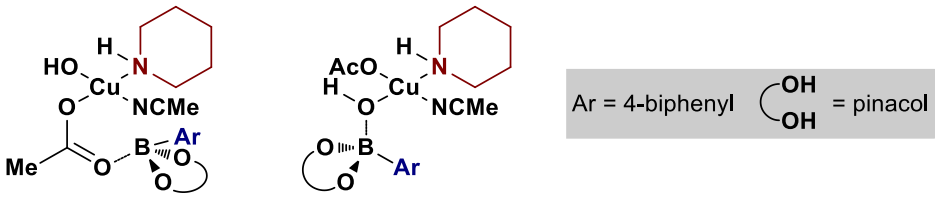
Scheme 83: HRMS analysis of the Chan-Lam reaction of aryl BPin ester 17 and piperidine 146.

Two amine-ligated Cu(II) complexes, **150** and **151** (**Figure 28**), were identified in relatively high abundance. These two complexes are clearly related to each other and to the tetracopper complex **149** (**Figure 26**). Mass ions consistent with the pre-transmetallation intermediate structural isomers **152** and **153** were detected (**Figure 29**). In addition, the corresponding post-transmetallation complex **154** was also identified (**Figure 30**). Finally, a Cu(II)(Pin)$_2$ complex **155** was also observed (**Figure 31**).



m/z (M+H$^+$)	**150**	**151**
Theoretical	266.0686	431.0663
Observed	266.0683	431.0668

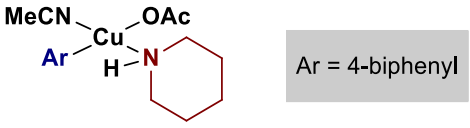
Figure 28: Detection of amine-ligated Cu(II) complexes 150 and 151.



152 153

m/z (M+H$^+$)	
Theoretical	545.2321
Observed	545.2332

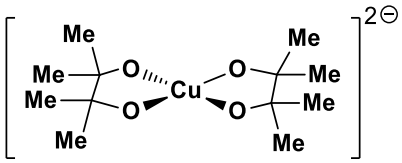
Figure 29: Detection of pre-transmetallation intermediates 152 and 153.



154

m/z (M+H$^+$)	
Theoretical	402.1363
Observed	402.1351

Figure 30: Detection of post-transmetallation complex 154.



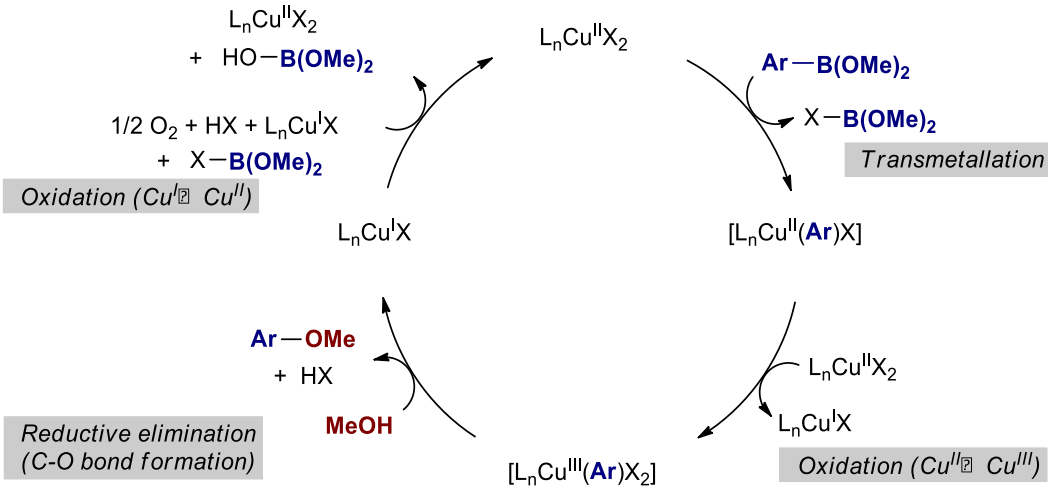
155

m/z (M^{2-})	
Theoretical	295.1054
Observed	295.1051

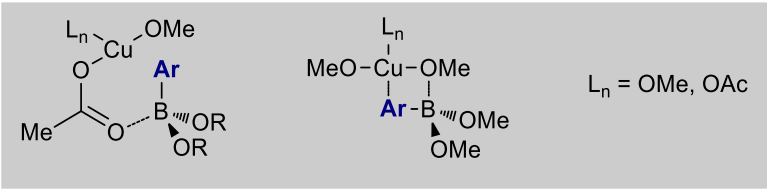
Figure 31: Detection of Cu(II)(Pin)$_2$ complex 155.

2.4. Reoxidation of Cu(I) to Cu(II)

Then, we studied the reoxidation from Cu(I) to Cu(II). Understanding this step is of great interest as it ends the catalytic cycle giving access to the active Cu(II) species. In the etherification process, Stahl and co-workers demonstrated that oxidation of Cu(I) to Cu(II) took place using molecular oxygen and additional Cu(I), with the requirement of acid (HX) and BX_3 (**Scheme 84**).



Proposed resting states/pre-transmetallation intermediates



Scheme 84: Stahl and co-workers catalytic cycle for the Chan-Lam etherification.

To analyse the reoxidation step under the Chan-Lam amination conditions, the oxidation of Cu(I)OAc to Cu(II)X_2 was monitored under air by UV-Vis spectroscopy allowing assessment of additives (**Figure 32** and **33**).

In the absence of any additive, no oxidation was seen by simply stirring Cu(I)OAc in MeCN under air (**Figure 32**). Similarly, no oxidation was observed in the presence of Et_3N alone. However, oxidation was relatively fast in the presence of AcOH. Finally, oxidation was slower in the buffered system using both AcOH and Et_3N.

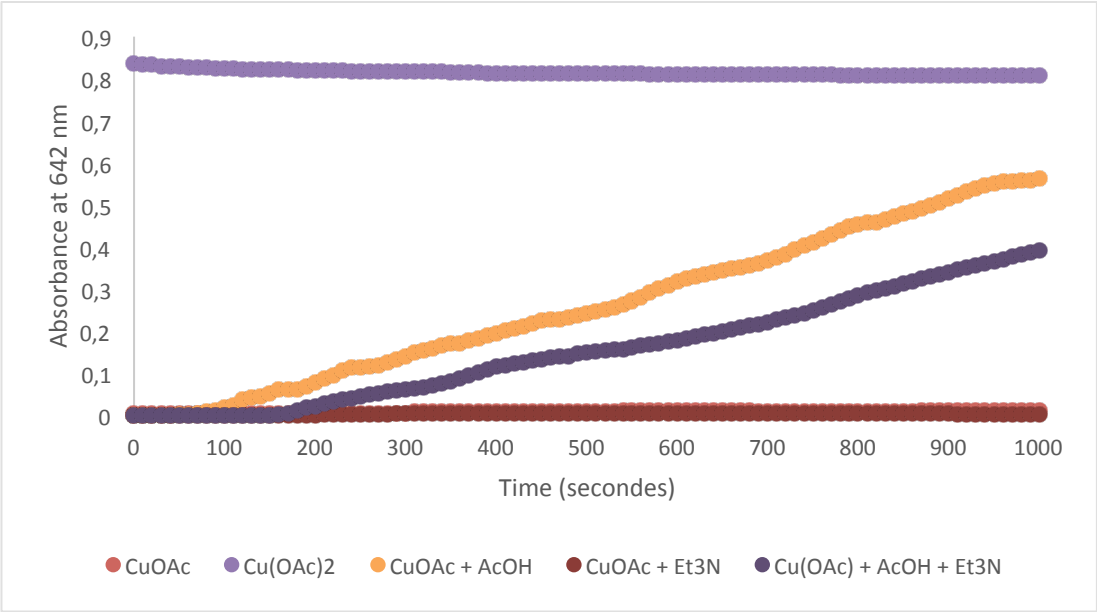


Figure 32: Study of the reoxidation from Cu(I) to Cu(II) in presence of additives.

Similar trends were observed when the same analysis was repeated in the presence of piperidine **145** and aniline **16** (**Figure 33**). Interestingly, the Cu(I) oxidation was generally more rapid in the presence of **145** than **16**, including in the presence of Et_3N, although this was marginal.

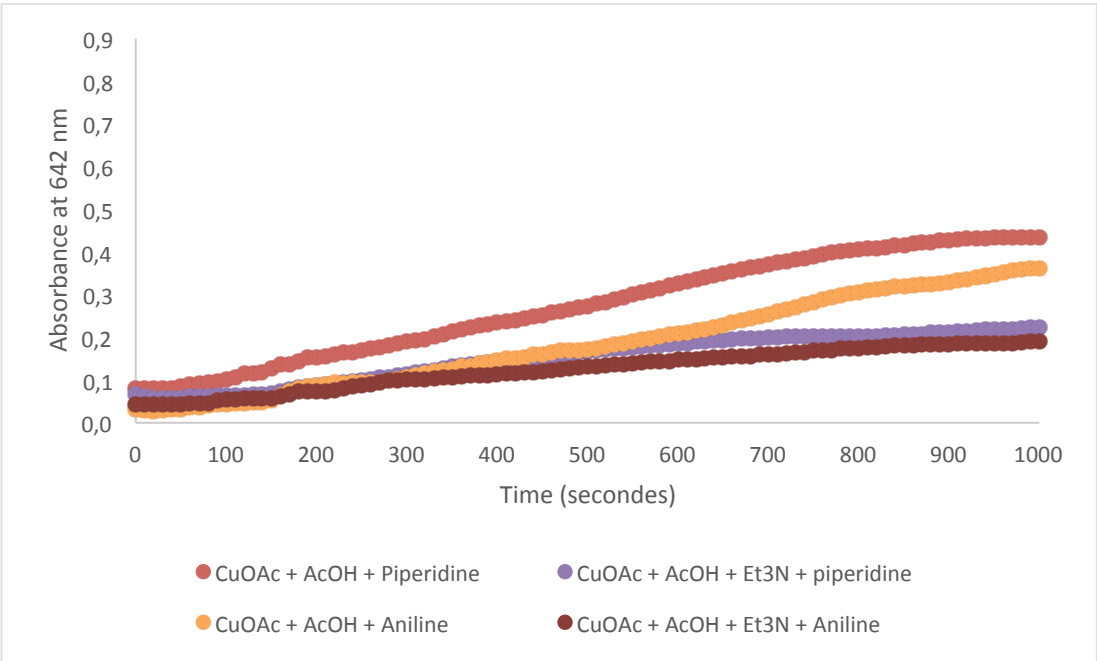


Figure 33: Study of the reoxidation from Cu(I) to Cu(II) in presence of piperidine 145 and aniline 16.

3. Discussion

The reaction profiles, the EPR analysis, and the HRMS study allowed the characterisation of products, by-products, and intermediates involved in the Chan-Lam amination reaction. In addition, the inhibition studies and analysis of the oxidation step highlighted the role of the amine coupling partners, and additives. Combination and careful analysis of these results allowed us to propose a plausible mechanistic pathway of the Chan-Lam amination.

3.1. Amines/organoboron reactivity and by-product formation

Clear differences in reactivity between piperidine **145** and aniline **16**, and boronic acid **146** and BPin ester **17** were observed when using the previously described benchmark reactions (**Schemes 74** and **75**). Reactions of piperidine **145** are generally successful while simply moving to aniline **16** leads to a loss in efficiency (**Tables 28** and **29**).

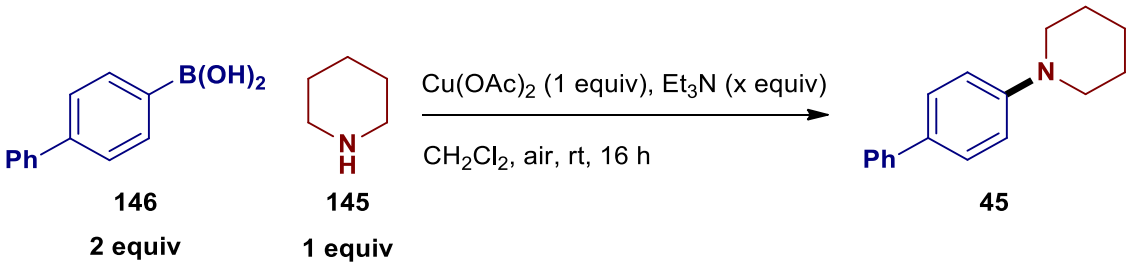
With regards to by-product formation (**Tables 28** and **29**), while formation of the desired products **45** and **18,** respectively, can be excellent (**Tables 28** and **29, entries 3 and 5**), formation of by-products was still significant. The improvement in yield is not due to inhibition of side-reactions but rather improvement in general reactivity. Starting material **146** persisted in the absence of Et_3N when product distribution remained approximately constant (**Tables 28** and **29, entries 1** *vs.* **2**). Hence, it was concluded that amination is marginally competitive with side reactions under these conditions.

Other observations were:

- The addition of Et_3N was beneficial. Efficiency markedly improved with 1 equivalent but was optimum with 3 equivalents (**Tables 28** and **29, entries 1** to **3,** and **5**). This is consistent with previous publications.
- Molecular sieves are beneficial to lower production of the oxidation product **12** (**Tables 28** and **29, entries 3** *vs.* **4**). This is consistent with the ^{18}O labelling

experiments of Lam demonstrating that oxidation arises from H_2O, and observations by Evans on the effect of molecular sieves.

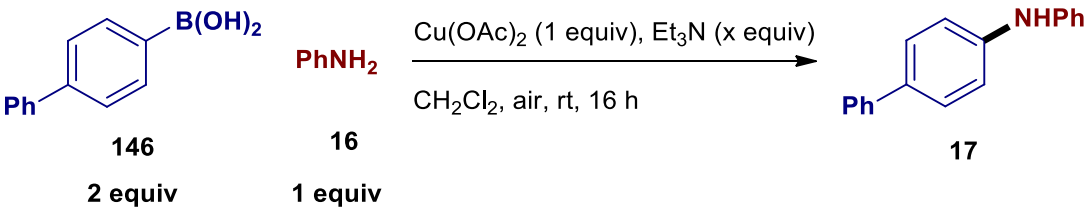
- The most significant observation was the extent of the production of side products **19** and **21**. Oxidation can be tempered with molecular sieves but production of **19** persisted at ca. 5-10% while **21** varied from 12-25%. Protodeboronation was also a significant issue (50-68%) of **20** generated throughout. Accordingly, even for high yielding reactions (**Tables 28** and **29, entry 5**) approximately half of the total input of **146** was consumed in side reactions, explaining the necessity for superstoichiometric quantities of **146**.
- Organoboron homocoupling was found to be minimal and was not further considered (**Scheme 79**).



146 **2 equiv** | **145** **1 equiv** | **45**

Entry	Et_3N (equiv)	SM **146** (%)[a]	Product **45** (%)[a]	Byproducts **19** (%)[a]	**20** (%)[a]	**21** (%)[a]
1	0	32	66	1	51	21
2	1	2	76	7	67	25
3	2	2	87	6	68	16
4[b]	2	2	65	45	65	12
5	3	3	97	13	62	13

Table 28: Benchmark reaction between piperidine 145 and aryl boronic acid 146. [a] HPLC yields, [b] No molecular sieves.



146 **16** **17**

2 equiv **1 equiv**

Entry	Et_3N (equiv)	SM **146** (%)[a]	Product[b] **18** (%)[a]	Byproducts[c] **19** (%)[a]	**20** (%)[a]	**21** (%)[a]
1	0	46	46	1	61	22
2	1	12	69	7	67	20
3	2	8	92	4	65	15
4[b]	2	3	60	51	50	15
5	3	1	93	10	67	13

Table 29: Benchmark reaction between aniline 16 and aryl boronic acid 146. [a] HPLC yields, [b] No molecular sieves.

3.2. Mechanistic investigation

3.2.1. Entry to catalysis

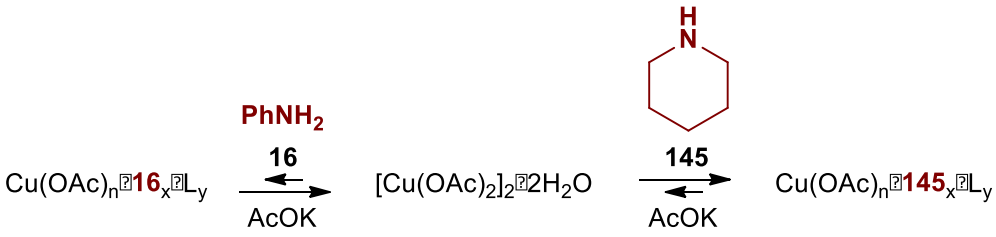
3.2.1.1. Paddlewheel dissociation, reformation, and reaction inhibition

Paddlewheel complexes are unreactive in Cu-catalysed oxidative coupling reactions, and must undergo dissociation as the first mechanistic event. In etherification reactions, paddlewheel dissociation is promoted in the alcoholic media. However, alcoholic media are not feasible in the amination reaction due to chemoselectivity issues (amination *vs.* etherification).

EPR studies demonstrated that $[Cu(OAc)_2]_2 \bullet 2H_2O$ can be readily dissociated using piperidine **145** but less readily by aniline **16** (**Figures 22** and **23)**. Aniline **16** was only able to induce a comparable level of dissociation of the paddlewheel complex when the concentration was >10 fold greater than that of piperidine **145**. This highlighted an immediate reactivity difference between the amine types (**Scheme 85**): dissociation of the paddlewheel dimer is dependent on Lewis basicity.

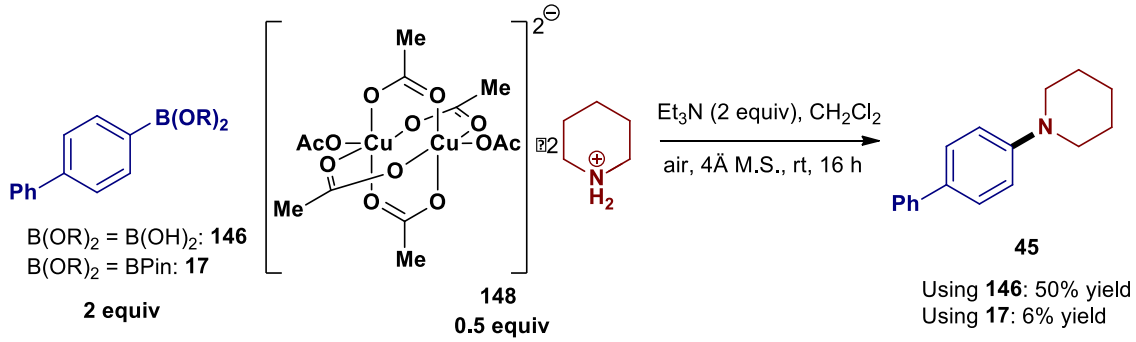
The competitive nature of this key event was reinforced by additive experiments (**Figure 18** and **19**). AcOK promoted reformation of dinuclear Cu(II) species from mononuclear complexes. Piperidine **145** could induce denucleation even in the presence of additional AcOK (**Figure 19, blue line**), while aniline **16**, as a poorer ligand, does not compete with AcOK (**Figure 19, red line**), thus generating significantly less monomeric species (**Scheme 85**).

AcOH displays a similar inhibitory effect to that of AcOK, promoting reformation of dinuclear Cu(II) species but with an additional inhibitory function. Piperidine could induce denucleation in the presence of AcOK (**Figure 19**) but not in the presence of AcOH (**Figure 18**) due to N-protonation, thereby requiring the addition of a base like Et_3N.



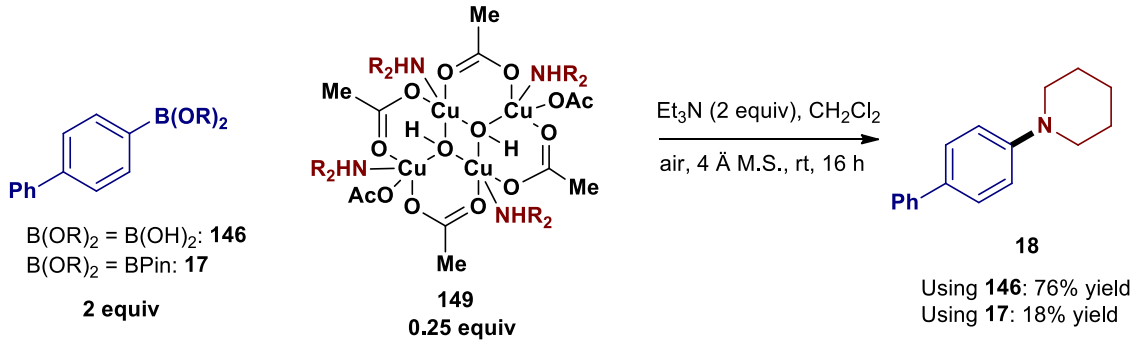
Scheme 85: Denucleation of $[Cu(OAc)_2]_2 \cdot 2H_2O$ by piperidine 145 and aniline 16.

Indeed, treatment of **146** or **17** with complex **148** under reaction-like conditions led to 50% and 6% yield of **45**, respectively (**Scheme 86**) – less effective than standard conditions (**Scheme 74**).



Scheme 86: Reaction of 146 or 17 with complex 148 under Chan-Lam-like conditions.

In contrast, exposing **146** or **17** to **149** under reaction-like conditions gave **18** in 76% and 18% yield, respectively (**Scheme 87**) – very similar to the typical yield for these substrates under standard conditions 87% and 28%, respectively (**Scheme 74**). Unfortunately, complexes derived from aniline **16** were not isolated preventing a similar evaluation.



Scheme 87: Reaction of 146 or 17 with complex 149 under Chan-Lam-like conditions.

These experiments indicated that one of the roles of Et_3N in Chan-Lam aminations was to sequester HX, generating sufficient amine freebase to drive denucleation of paddlewheel species and allowed the formation of reactive amine-ligated Cu(II) complexes, such as **149**.

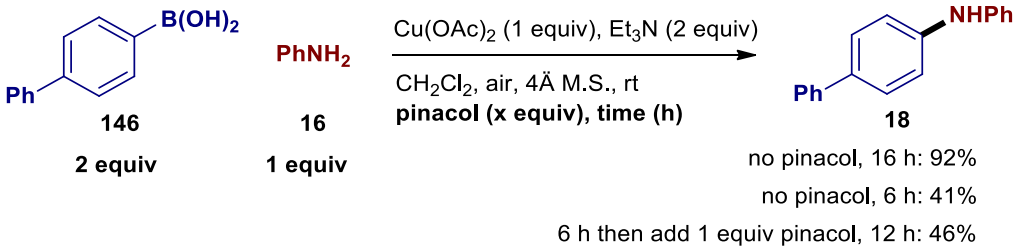
All together, these data highlighted:

- The requirement for paddlewheel dissociation as a first key mechanistic event
- The reactivity differences between amine classes begin at this initial event
- The increase in reactivity in the presence of Et_3N.

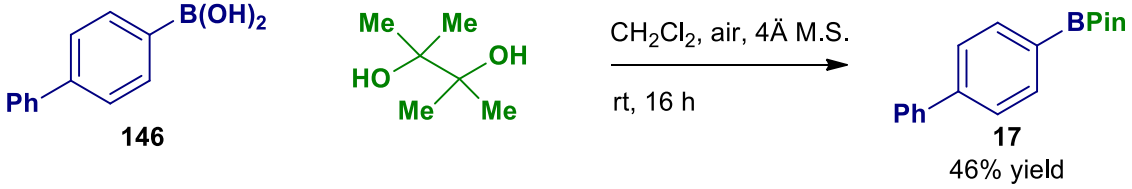
3.2.1.2. Organoboron reactivity differences: reaction inhibition by pinacol

The disparity in reactivity between aryl boronic acid **146** and aryl BPin ester **17** could be attributed to the presence of pinacol, which had a notable inhibitory effect on the amination reaction of **146** using both piperidine **145** and aniline **16**, with a greater effect on the latter (**Figure 20**).

Pinacol had an immediate inhibitory function (**Scheme 88**). The reaction of **146** with aniline **16** proceeded to deliver 92% of **17** over 16 h, with 41% conversion to **18** over 6 h. When pinacol (1 equiv) was added after 6 h of reaction, conversion to **18** after 12h is commensurate with the 6 h time point. In addition, under reaction-like conditions in the absence of amine or $Cu(OAc)_2$ catalyst, treatment of **146** with pinacol gave 46% of **17** over 16 h (**Scheme 89**). This slow esterification cannot account for the levels of inhibition observed in reactions of **146**. Hence, the inhibitory function of pinacol did not appear to be driven by differences in rates of transmetallation.



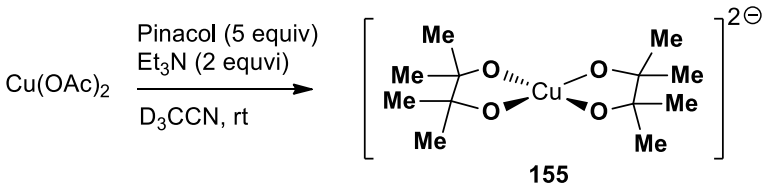
Scheme 88: Immediate inhibitory effect of pinacol



Scheme 89: Slow esterification of aryl boronic acid 146 to aryl BPin ester 17 in presence of pinacol.

This suggests that the observed inhibitory effect (**Figure 20**) was not necessarily due to formation of **17**, but rather due to some other interaction of pinacol. Various diols are known to form complexes with Cu(II), including derivatives of pinacol. While a crystalline structure of a Cu(II)-pinacol complex was not obtained, NMR and HRMS analysis confirmed the presence of $Cu(II)(pinacol)_2$ **155** in solution in both isolated experiments and in samples from amination reaction mixtures using **17** (**Scheme 90** and **Figure 34**). Accordingly, the observed BPin reactivity issues in the Chan-Lam amination could arise from catalyst inhibition by pinacol, generated either by hydrolysis

of the organoboron starting material **17** or of the organoboron by-product following the transmetallation event.



155

Scheme 90: Formation of Cu(II)(pinacol)$_2$ complex 155.

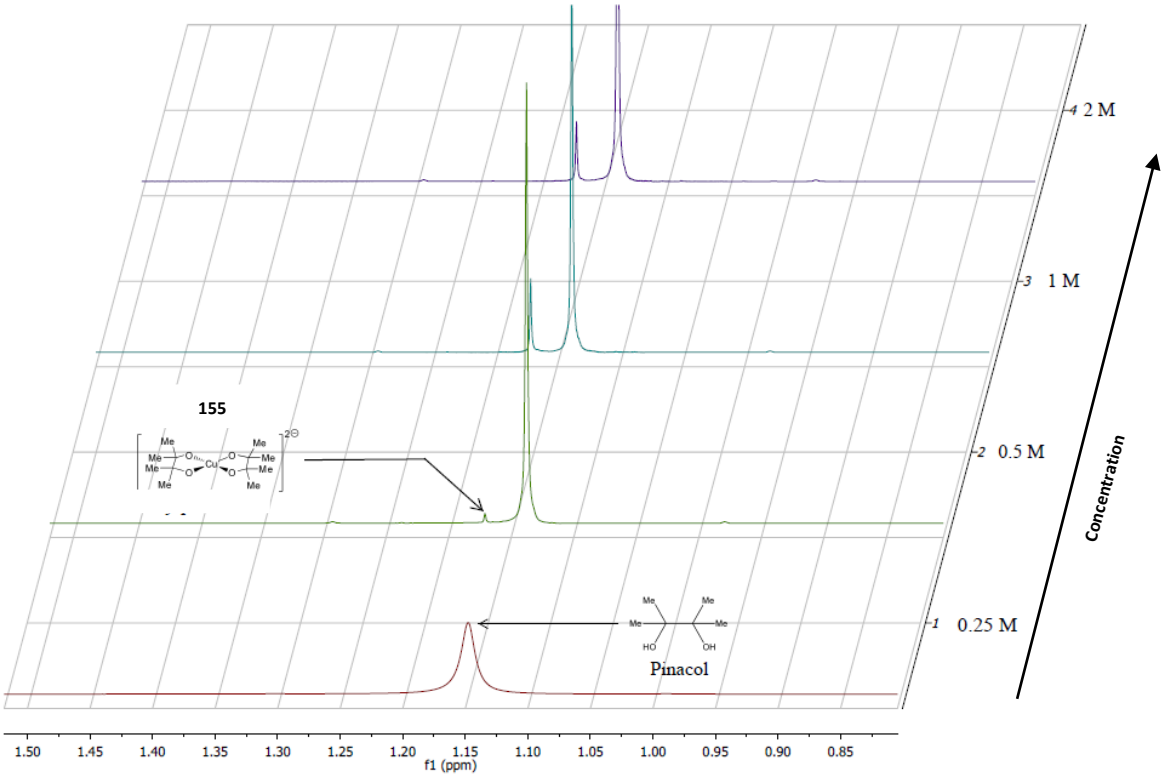


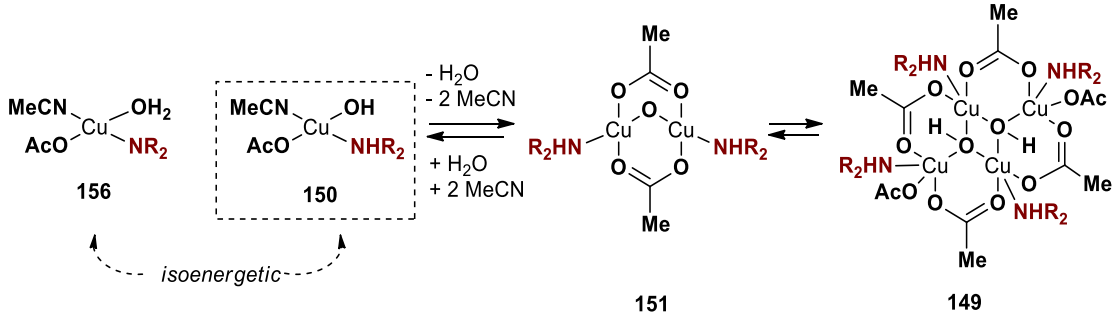
Figure 34: ^{1}H NMR identification of Cu(II)(pinacol)$_2$ complex 155.

3.2.1.3. Solution structure of the mononuclear Cu(II) species

The ligands on a transition metal species can profoundly affect its reactivity. Accordingly, we attempted to provide an understanding of the ligands on any Cu-based species. To achieve this, we used a combination of HRMS analysis coupled with computational modeling. Mass ions were identified from the benchmark reactions using aryl BPin ester **17** and piperidine **145**. The potential structures, and their interconversion, were rationalized by computational modeling

A high abundance of mass ions consistent with the Cu(II) complex **149** was observed (**Figure 28**). In addition, a mass ion consistent with dinuclear complex **151** was also detected (**Figure 28**). Significantly, the isolated tetracopper complex **149** appeared to be a dimer of **151**, which itself is a dimer of **150** (**Scheme 91**). That **149** was competent in the amination reaction of aryl boronic acid **146** and piperidine **145** (**Scheme 87**) suggested that **149**, **151**, and **150** were in equilibrium in the reaction mixture and that **150** was the mono-nuclear complex produced following dissociation of $[Cu(OAc)_2]_2 \bullet 2H_2O$ with piperidine **145** a resting state.

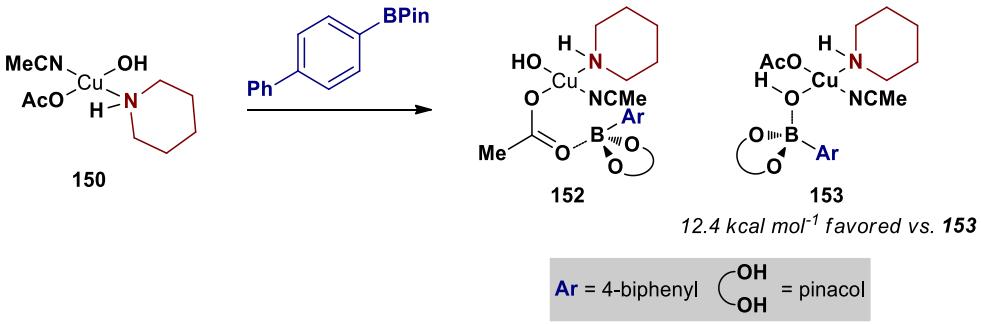
In relation to the proposed structure of **150**, calculations revealed this complex and its amide isomer **156** are isoenergetic. However, we postulated **150** as the likely structure based on the structure of **149** and previous observations.



Scheme 91: Equilibrium between copper complexes 149, 151, and 150.

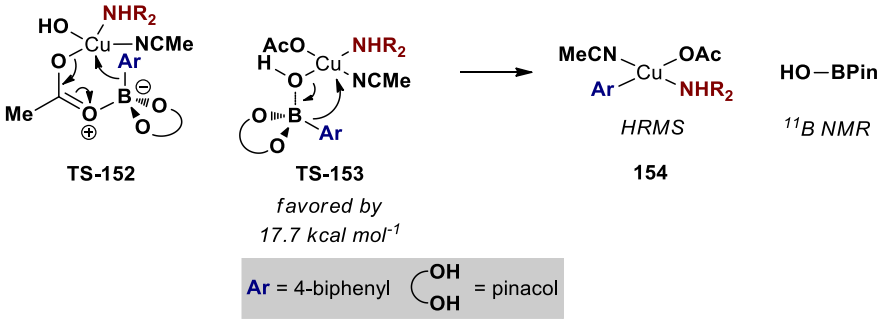
3.2.2. Transmetallation

HRMS analysis of the reaction mixture using aryl BPin ester **17** also allowed detection of mass ions consistent with isostructural Cu(II) complexes **152** and **153** (**Figure 29**), which was consistent with a pre-transmetallation intermediate arising from ligation of **10** to **150** (**Scheme 92**). Copper complex **152** was consistent with the resting state **124** proposed by Stahl (**Scheme 68**). However, molecular modeling of these structural isomers showed that the hydroxide-bound complex species **153** was 12.4 kcal mol^{-1} more stable than the acetate-bound complex **152**. Accordingly, whether **153** had a role was unclear.



Scheme 92: Molecular modeling of the pre-transmetallation intermediates 152 and 153.

However, HRMS also allowed detection of a post-transmetallation intermediate **154** (**Figure 30** and **Scheme 93)**. In agreement with Stahl, a molecular modeling comparison of transmetallation via a 4-membered transition state beginning from **153** and the 6-membered transition state beginning from **152** favoured the 4-membered transition state by 17.7 kcal mol^{-1}. The production of the expected boron by-product, HO–BPin, could be observed by ^{1}H NMR and ^{11}B NMR (**Figures 35 and 36**).



Scheme 93: Comparison of transmetallation via a 4- or 6-membered transition state.

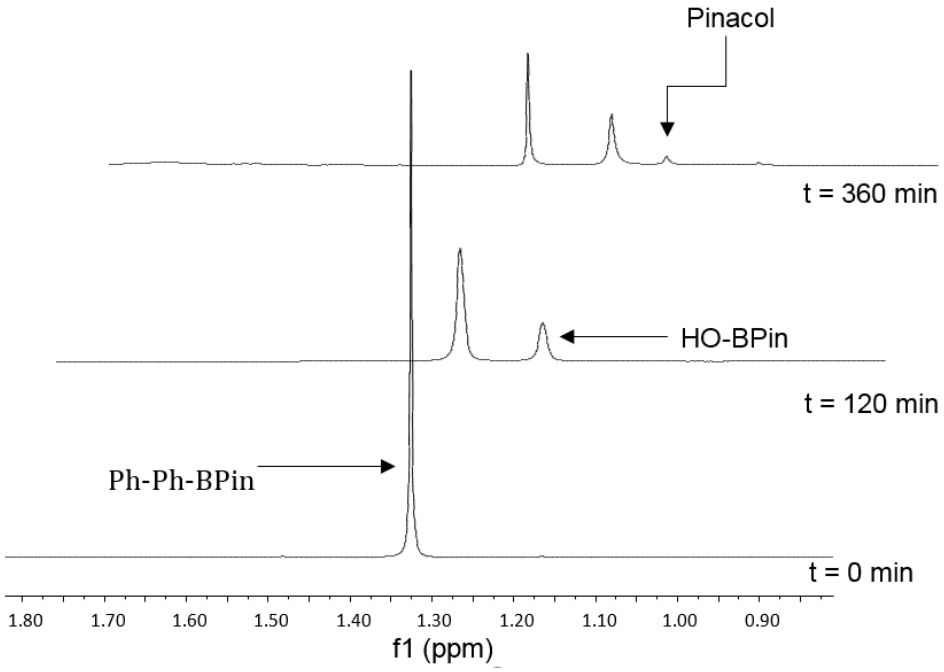


Figure 35: ^{1}H NMR of BPinOH.

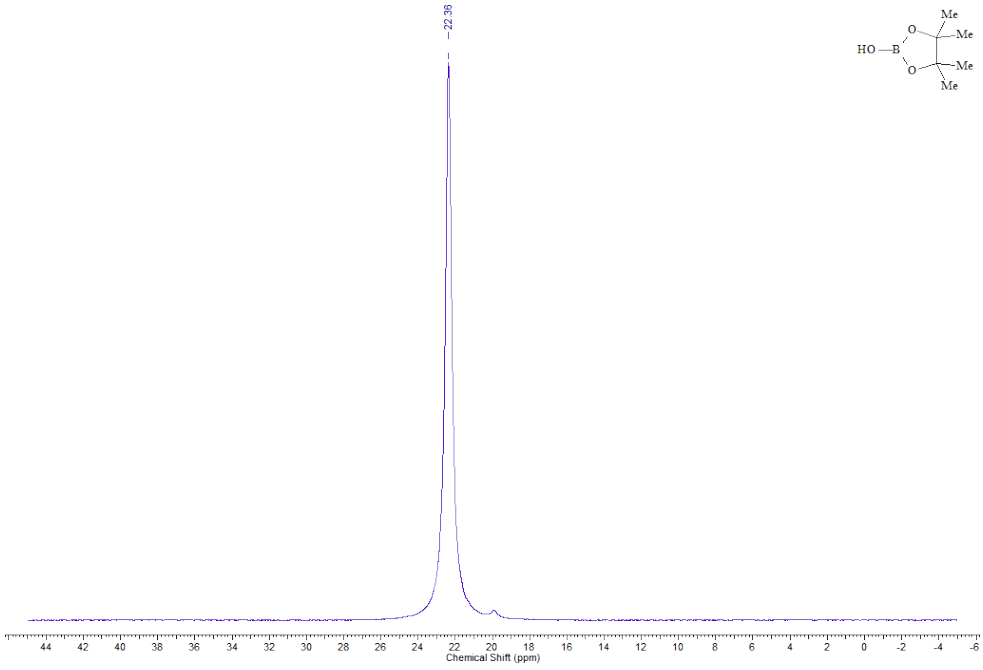


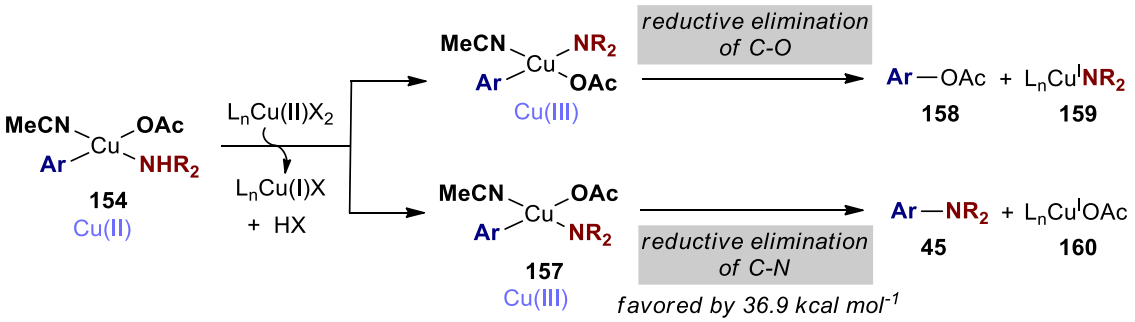
Figure 36: ^{11}B NMR of BPInOH.

More holistically, a 4-membered oxo-metal transmetallation pathway was consistent with organoboron transmetallation in other transition metal-catalysed coupling

reactions. For example, within Suzuki-Miyaura cross-coupling using Pd and Ni, and Rh-catalysed conjugate addition. Accordingly, there was potentially an elegant symmetry and generality in the transmetallation of organoboron compounds to these metal species.

3.2.3. Reductive elimination: C-N vs. C-O

Based on Stahl's mechanism, following transmetallation, oxidation *via* disproportionation generates a Cu(III) intermediate that undergoes reductive elimination to give the product and a Cu(I) species. While not detected, a structure of this Cu(III) intermediate **157** was proposed based on the structure of **154**, allowing investigation of the reductive elimination event (**Scheme 94**).



Scheme 94: Comparison of reductive elimination pathways.

As discussed above, phenol formation and subsequent etherification are problematic in Chan-Lam processes. It could be rationalised that reductive elimination from **157** could proceed via C-N bond formation to deliver the desired amine product **45** or C-O bond formation to the undesired phenolic ester **158**. Fensterbank has shown that reductive elimination of formally Cu(III) complexes with N- and O-ligands takes place with selective C-N bond formation.[96] Computational modeling of reductive elimination from **157** also favours the C-N bond-forming event over the C-O bond forming event by 36.9 kcal mol^{-1}. Accordingly, we did not believe that formation of phenol side products happened from competitive reductive elimination of **157** but from other processes described in the following section.

3.2.4. Reoxidation of Cu(I)

3.2.4.1. Completion of the catalytic cycle

Completion of the catalytic cycle requires reoxidation of Cu(I) to Cu(II). Stahl has shown that this takes place using molecular oxygen and additional Cu(I), with the requirement of acid (HX) and BX_3 (**Scheme 84**). As proposed above, Cu(I)OAc is the product of the reductive elimination event (**Scheme 94**). Evaluation of the oxidation of Cu(I)OAc to Cu(II)X_2 in the presence of various reaction-relevant additives was informative, highlighting the fundamental effects of the amine components (**Figures 32 and 33**).

The requirement for HX is consistent with our observations of the oxidation process (**Figure 32**). In the presence of only Et_3N, no oxidation takes place and in the presence of AcOH, oxidation is relatively rapid. With both AcOH and Et_3N, oxidation proceeds more slowly. When the same analysis is repeated in the presence of piperidine **145** and aniline **16 (Figure 33**), the same trends are observed but, notably, the Cu(I) oxidation is more rapid in the presence of **145** than **16**, highlighting a second difference between the amine classes. Oxidation was comparably slow for both amines in the presence of Et_3N.

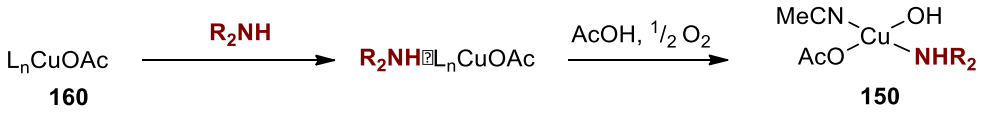
These observations point to two fundamental roles for Et_3N:

- To sequester AcOH to avoid (re)formation of inactive paddlewheel complexes.
- The resulting salt (Et_3N•AcOH) provides the necessary H^+ to promote Cu(I) oxidation.

Similarly, the amine substrates have two essential roles beyond acting as the coupling partner:

- To induce dissociation of paddlewheel complexes
- To promote Cu(I) oxidation. The fact that oxidation is more rapid in the presence of piperidine **145** *vs.* aniline **16** indicates that oxidation takes place

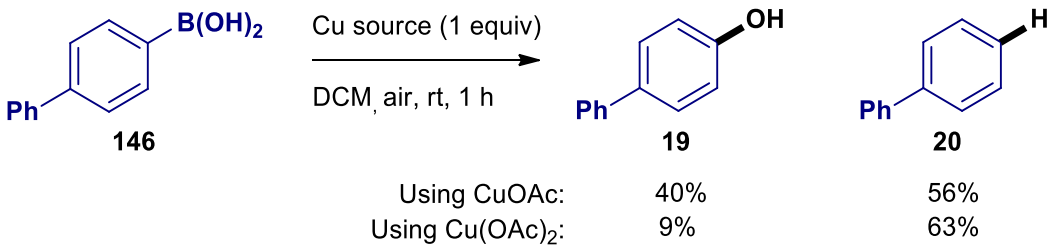
from an amine-ligated Cu(I) complex. This, then, allows direct access to Cu(II) complex **150** (**Scheme 95**).



Scheme 95: Role of the amine and AcOH in the reoxidation step.

3.2.4.2. Cu(I) and by-product generation

The reoxidation event of Cu(I) to Cu(II) has important ramifications on amination reaction performance, specifically with respect to by-product generation. Oxidation to deliver **19** and protodeboronation to deliver **20** are problematic and both processes are known to be facilitated by Cu(I) species more than Cu(II). Indeed, treatment of aryl boronic acid **146** with CuOAc delivers 40% oxidation and 56% protodeboronation while the corresponding reaction with $Cu(OAc)_2$ gives 9% and 63%, respectively (**Scheme 96**). Accordingly, we believe that oxidation issues arise primarily through the side reactions of the Cu(I)X species generated after reductive elimination prior to reoxidation to Cu(II). Protodeboronation was equally problematic for both Cu(I) and Cu(II) in these control experiments. However, additional data that will be discussed in the next section suggests that protodeboronation takes place when the reaction is unable to take any alternative course (e.g., amination), such as in this control reaction. Consequently, we believe that a slow Cu(I) to Cu(II) oxidation will lead to increased levels of side-reactions.



Scheme 96: Facilitation of by-products formation by Cu(I).

3.2.5. Proposed mechanism for the Chan-Lam amination

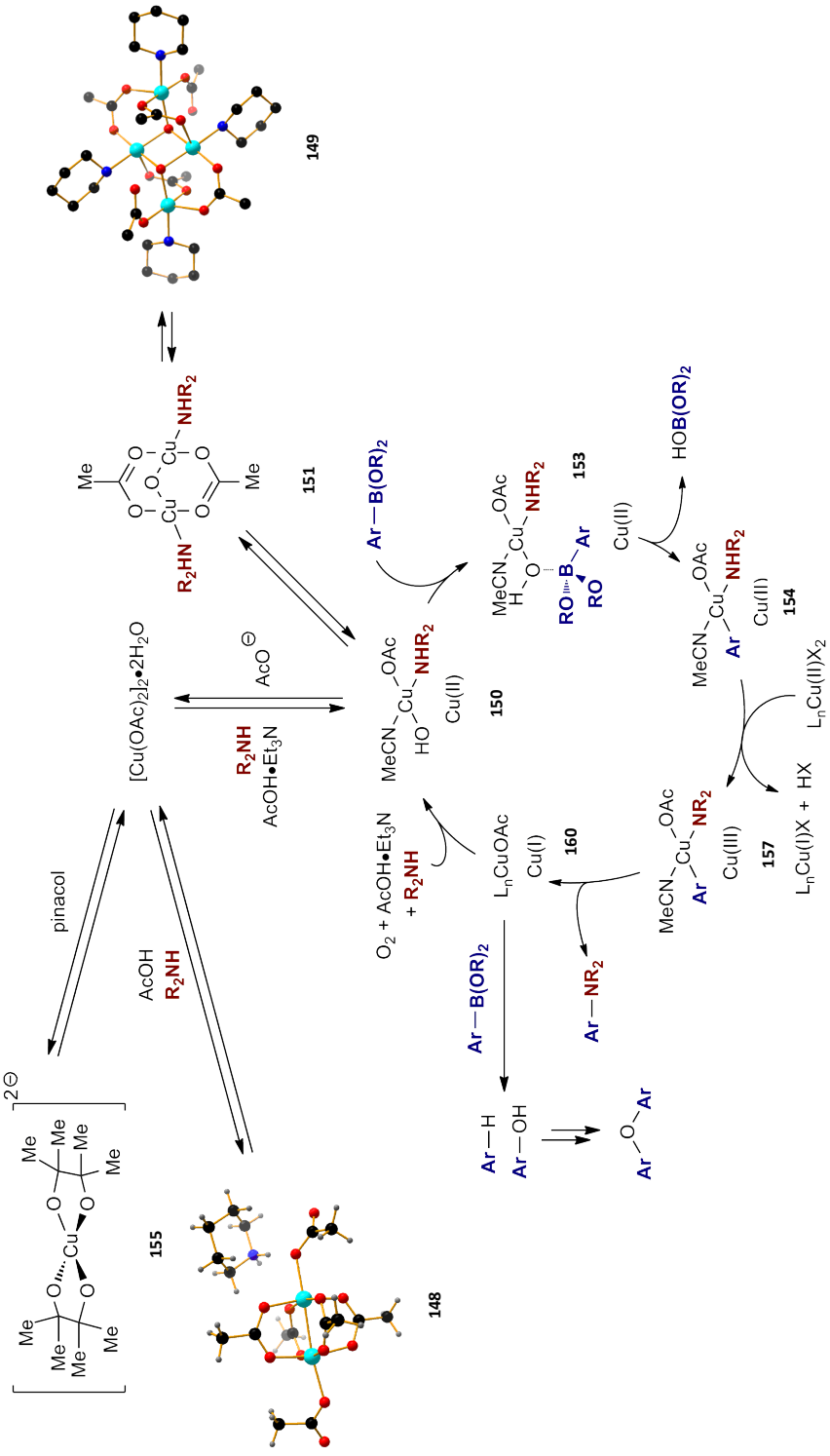
Based on previous work by Stahl on the etherification process, and the isolated stoichiometric experiments detailed above, a complete mechanistic picture of the Chan-Lam amination can be proposed (**Scheme 97**).

$[Cu(OAc)_2]_2 \bullet 2H_2O$ undergoes denucleation by action of the amine to a mononuclear Cu(II) complex **150**, which exists in equilibrium with its dimer, **151**, and tetramer, **149**, derivatives. This initial amine-driven denucleation event is essential to catalysis and can be inhibited by action of AcO^- and AcOH, both of which promote reformation of paddlewheel species. AcOH simultaneously inhibits denucleation by protonation of the amine, giving the hexa-acetate paddlewheel **148**. Engagement of the organoboron component leads to transmetallation via 4-membered transition state **153** to deliver Cu(II) species **154**. Oxidation to Cu(III) *via* disproportionation gives complex **157**. A selective C-N reductive elimination liberates the desired amine product and a Cu(I)OAc species **160**. Completion of the catalytic cycle is achieved *via* oxidation to Cu(II) in the presence of O_2 and HX and is promoted in the presence of the amine substrate. Side product generation is a function of this reoxidation event: a slow oxidation provides sufficient opportunity for Cu(I)-promoted oxidation and protodeboronation.

The origin of chemotype reactivity issues reactivity issues has also been identified:

- The reactivity issue of aryl amines compared to their alkyl counterparts is a function of the Lewis basicity – decomplexation of the paddlewheel dimer is more readily achieved with piperidine **145** *vs.* aniline **16.**
- The reoxidation event from Cu(I) to Cu(II) is slower with aniline **16** *vs.* piperidine **145**.

Finally, BPin substrates are problematic due to catalyst inhibition by pinacol generating **155** shown on page 110 as a by-product during the reaction.



Scheme 97: Proposed mechanism for the Chan-Lam amination

4. Development of a general Chan-Lam Amination

4.1. Observations

Based on the above discussion, there are three key events that must be controlled to resolve the substrate reactivity and side product issues associated with the Chan-Lam amination:

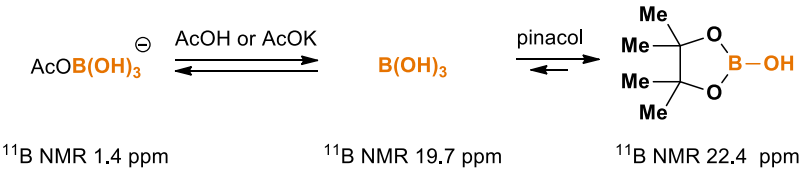
- Sequestration of AcO^- and AcOH
- Removal of free pinacol
- Promotion of Cu(I) oxidation.

These are not intuitively/simply solved since AcOH has previously shown is both beneficial and inhibitory.

4.2. Straightforward solutions

4.2.1. Boric acid as a scavenger and oxidation promoter

$B(OH)_3$ reversibly forms borates with AcO^-/AcOH and forms stable boric acid esters with diols, including pinacol (**Scheme 98, Figures 37** to 3**9**).



Scheme 98: Boric acid as a scavenger of AcOH, AcOK and pinacol.

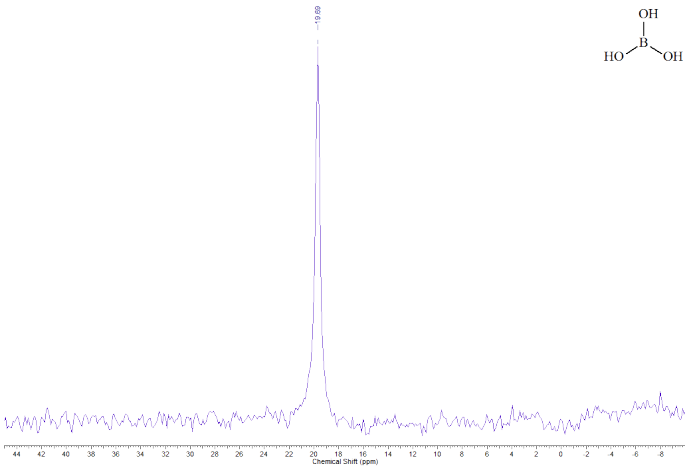


Figure 37: ^{11}B NMR of $B(OH)_3$.

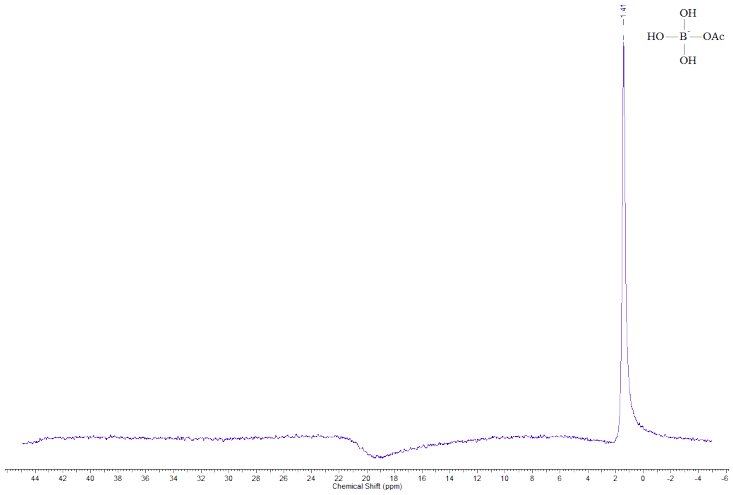


Figure 38: ^{11}B NMR of $B(OH)_3(OAc)^-$.

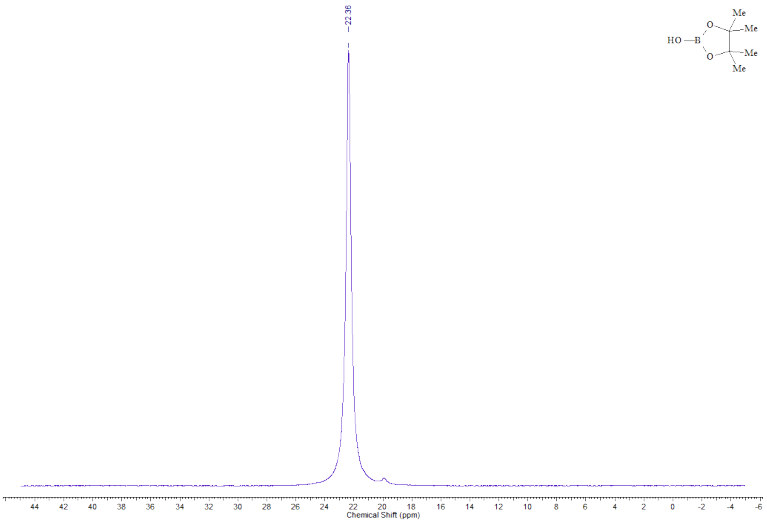


Figure 39: ^{11}B NMR of BPInOH.

Lastly, control experiments demonstrated that $B(OH)_3$ promotes reoxidation of Cu(I) to Cu(II) more effectively than piperidine **145** or aniline **16** in the presence of AcOH and Et_3N (**Figure 40** *vs.* **Figure 33**).

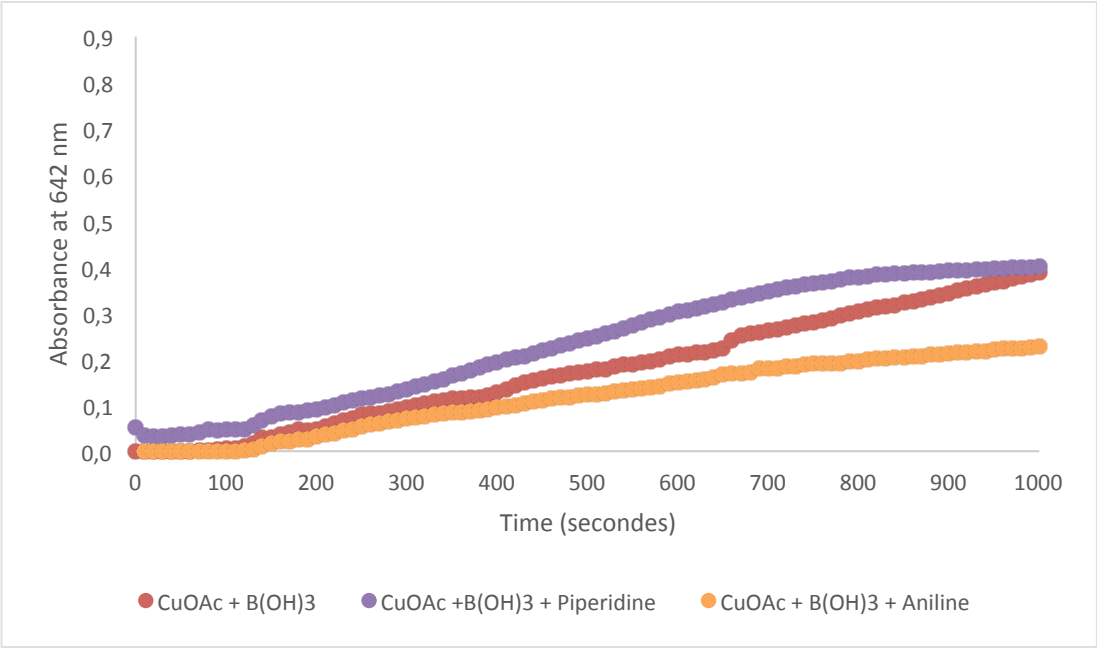
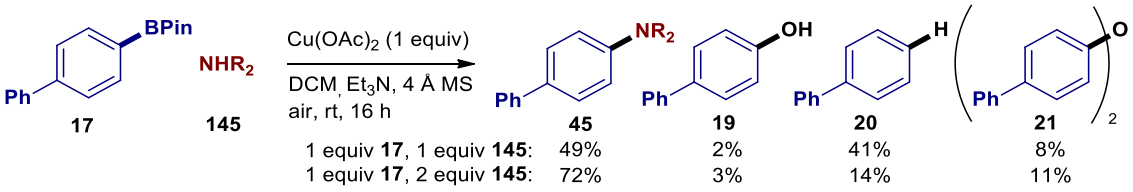


Figure 40: $B(OH)_3$ promotes reoxidation of Cu(I) to Cu(II).

4.2.2. Reverse stoichiometry to help oxidation and denucleation

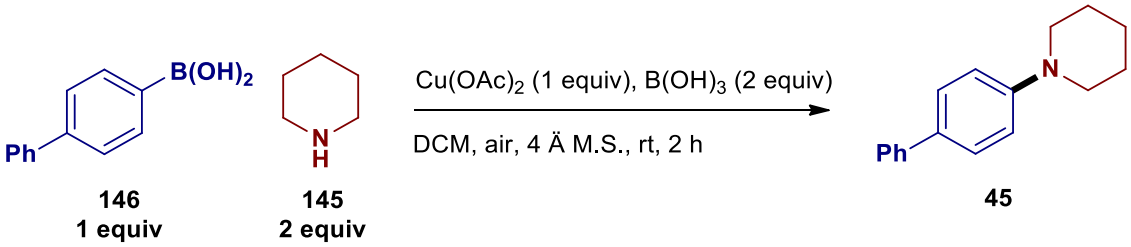
In addition, based on the findings above, Cu(I) oxidation is dependent on the amine concentration. Increasing amine concentration would be expected to facilitate Cu(I) oxidation and lower by-product generation. Increased amine concentration would also have a second beneficial effect by driving denucleation of paddlewheel complexes. This simple change in stoichiometry was found to be effective, leading to a significant improvement in reaction profile. Yield of desired product increased while overall by-product generation was decreased (**Scheme 99**).



Scheme 99: Increasing amine 145 concentration to facilitate Cu(I) reoxidation and lower by-product generation.

4.3. Improved reaction profile

Based on all of this, in the context of the Chan-Lam reaction using stoichiometric $Cu(OAc)_2$, upon replacing the conventional organic base Et_3N directly with $B(OH)_3$ and inverting the organoboron:amine stoichiometry, the amination process can be improved considerably (**Figure 41**). In comparison with the previously described reaction profile (**Scheme 76**), a dramatic improvement in product distribution is observed and in a significantly improved timeframe (2 h *vs.* 16 h).



146
1 equiv

145
2 equiv

45

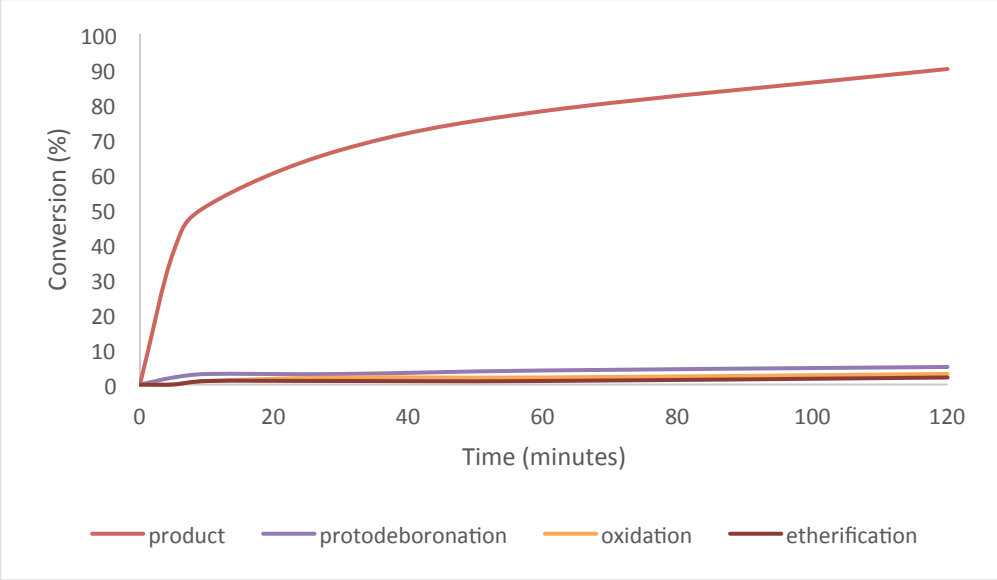


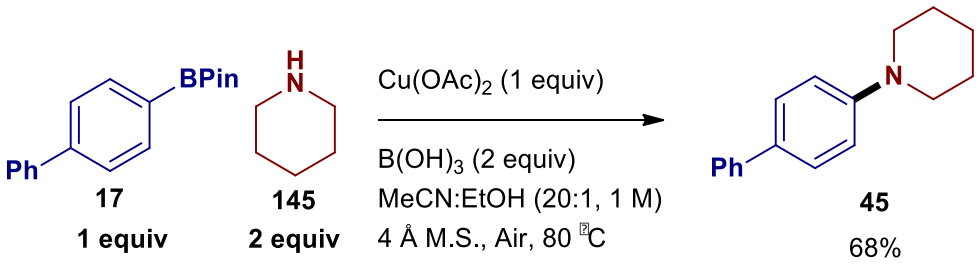
Figure 41: Reaction profile of the Chan-Lam amination between aryl boronic acid 146 and piperidine 145 using $B(OH)_3$ and reversing stoichiometry.

4.4. Application to the Chan-Lam amination of aryl BPin esters

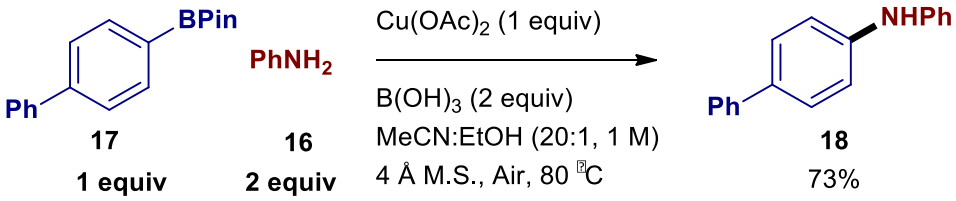
4.4.1. Optimisation

Based on the previous reaction profile, we replaced Et_3N with $B(OH)_3$ in our developed stoichiometric reaction conditions for the coupling of aryl BPin esters with both alkyl

and aryl amines (**Scheme 100 and 101**). The desired products **45** and **18** were obtained in 68% and 73% yield, respectively.

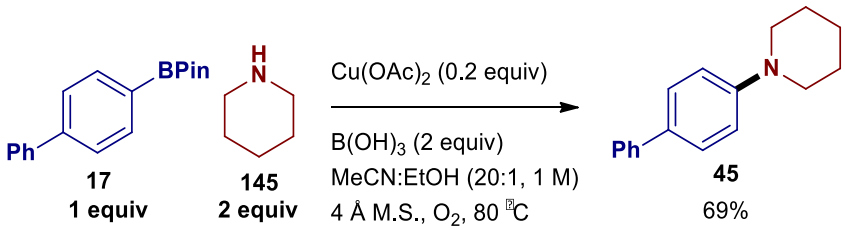


Scheme 100: Replacement of Et_3N with $B(OH)_3$ in our developed stoichiometric reaction conditions for the coupling of aryl BPin ester 17 with piperidine 145.

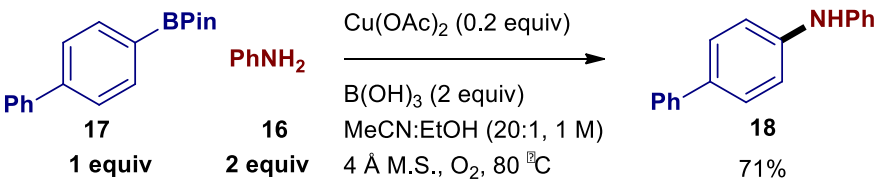


Scheme 101: Replacement of Et_3N with $B(OH)_3$ in our developed stoichiometric reaction conditions for the coupling of aryl BPin ester 17 with aniline 16.

Pleasingly, effective Chan-Lam amination could also be obtained using catalytic amounts of copper (0.2 equiv) under oxygen atmosphere without impacting the yield of the reaction (**Scheme 102**). The amine products **45** and **18** were isolated in 69% and 71% yield, respectively.

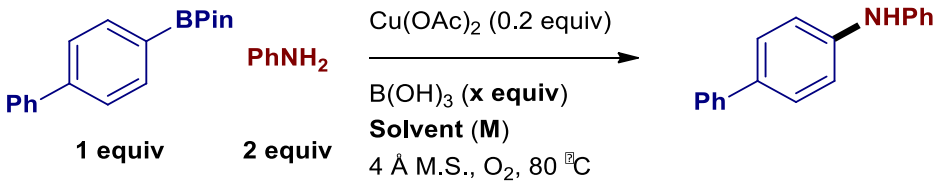


Scheme 102: Effective catalytic Chan-Lam amination between aryl BPin 17 and piperidine 145.



Scheme 103: Effective catalytic Chan-Lam amination between aryl BPin 17 and aniline 16.

Then, the optimisation of the reaction conditions for the coupling of aryl BPin ester **17** with aniline **16** was conducted using catalytic amounts of $Cu(OAc)_2$ (0.2 equiv) under oxygen atmosphere (**Table 30**). A quick solvent study highlighted that the desired product was obtained in good yield using MeCN (**Table 30, entry 2**). Other solvents including DMF, THF and toluene were detrimental to reaction efficiency (**Table 30, entries 3** to **5**). Concentration of the reaction mixture was again a key parameter to investigate (**Table 30, entries 2, 6** and **7**). The best conversion to the desired product **11** was obtained by lowering the concentration to 0.66 molar (**Table 30, entry 6**). Decreasing the temperature did not afford the amine product in good yields (**Table 30, entries 8** and **9**). A maximum of 79% yield was obtained for the desired product when using 2 equivalents of boric acid (**Table 30, entries 6** and **10** to **12**). Finally, a significant drop in the yield was observed when running the reaction under air and when decreasing the amount of copper to 10 mol% (**Table 30, entries 13** and **14**).

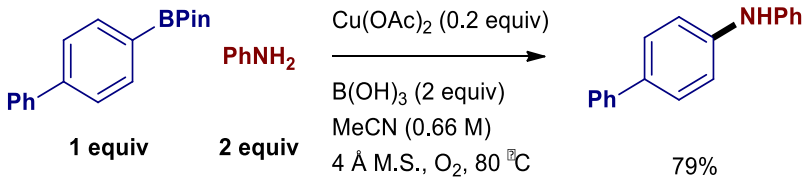


#	reaction conditions	18:19:20:21 (HPLC %)	Isolated Yield (%)
1	MeCN:EtOH (20:1, 1 M), 80 °C, Boric acid (2 equiv)	71:3:3:2	
2	MeCN, 1 M, 80 °C, Boric acid (2 equiv)	61:2:6:1	
3	DMF, 1 M, 80 °C, Boric acid (2 equiv)	26:18:6:5	
4	THF, 1 M, 80 °C, Boric acid (2 equiv)	19:2:12:3	
5	Toluene, 1 M, 80 °C, Boric acid (2 equiv)	2:0:1:0	
6	MeCN, 0.66 M, 80 °C, Boric acid (2 equiv)	82:4:6:4	79
7	MeCN, 0.5 M, 80 °C, Boric acid (2 equiv)	73:2:10:2	70
8	MeCN, 0.66 M, 60 °C, Boric acid (2 equiv)	46:2:3:3	
9	MeCN, 0.66 M, 40 °C, Boric acid (2 equiv)	19:1:1:2	

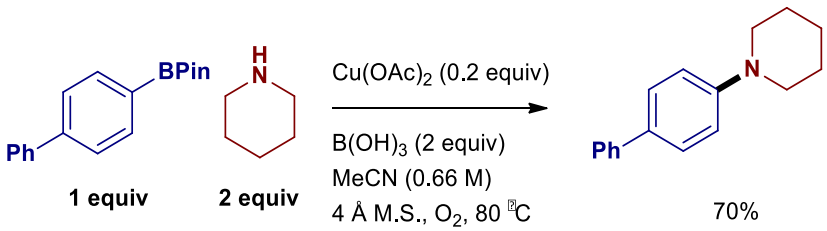
10	MeCN, 0.66 M, 80 °C, Boric acid (1 equiv)	61:5:6:1
11	MeCN, 0.66 M, 80 °C, Boric acid (1.5 equiv)	70:4:6:1
12	MeCN, 0.66 M, 80 °C, Boric acid (3 equiv)	75:4:4:4
13[a]	MeCN, 0.66 M, 80 °C, Boric acid (2 equiv)	56:2:5:2
14[b]	MeCN, 0.66 M, 80 °C, Boric acid (2 equiv)	40:2:23:3

Table 30: Optimisation of the $B(OH)_3$-based reaction conditions ([a] Under air, [b] No molecular sieves).

Based on the optimization parameters described above, the optimum catalytic reaction conditions for the reaction between aryl BPin ester **17** and aniline **16** afforded the desired amine product **18** in 79% isolated yield (**Scheme 104**). The exact same set of conditions afforded product **38**, issued form the coupling of aryl BPin **17** with piperidine **145**, in 70% yield (**Scheme 105**).



Scheme 104: Optimised catalytic reaction conditions for the coupling of aryl BPin ester 17 with aniline 16 using $B(OH)_3$.

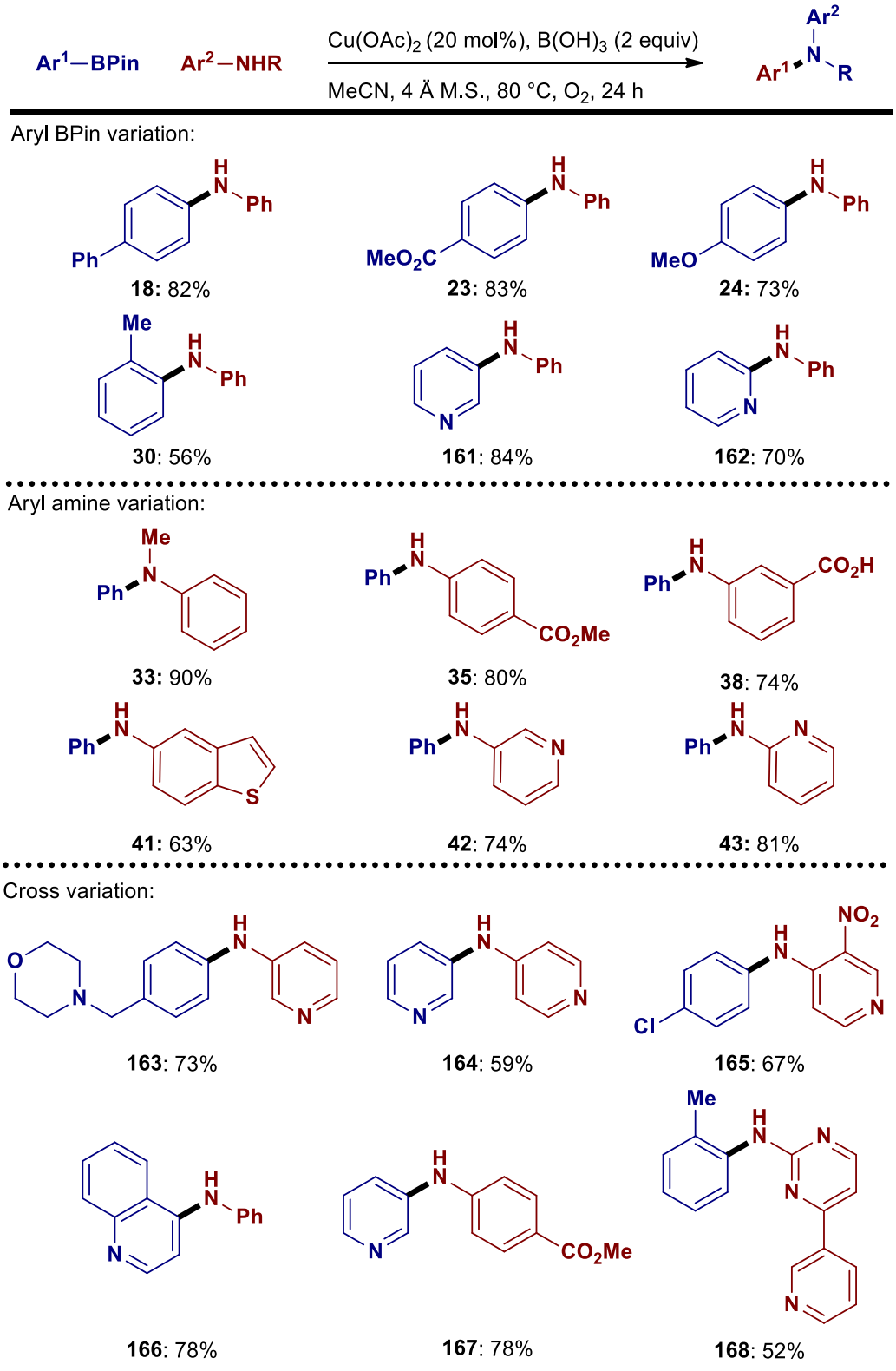


Scheme 105: Optimised catalytic reaction conditions for the coupling of aryl BPin ester 17 with piperidine 145 using $B(OH)_3$.

4.4.2. Aryl amine scope

We applied the developed reaction conditions to a wide range of Aryl BPin ester and aniline substrates (**Scheme 106**). The catalytic procedure tolerated a broad range of functionalities on both the aryl BPin and aryl amine components. Similarly to the stoichiometric process, electron-rich (**Scheme 106, 18** and **23**), -neutral (**Scheme 106, 33, 35, 38** and **41** to **43**), and –withdrawing groups (**Scheme 106, 24**) were tolerated

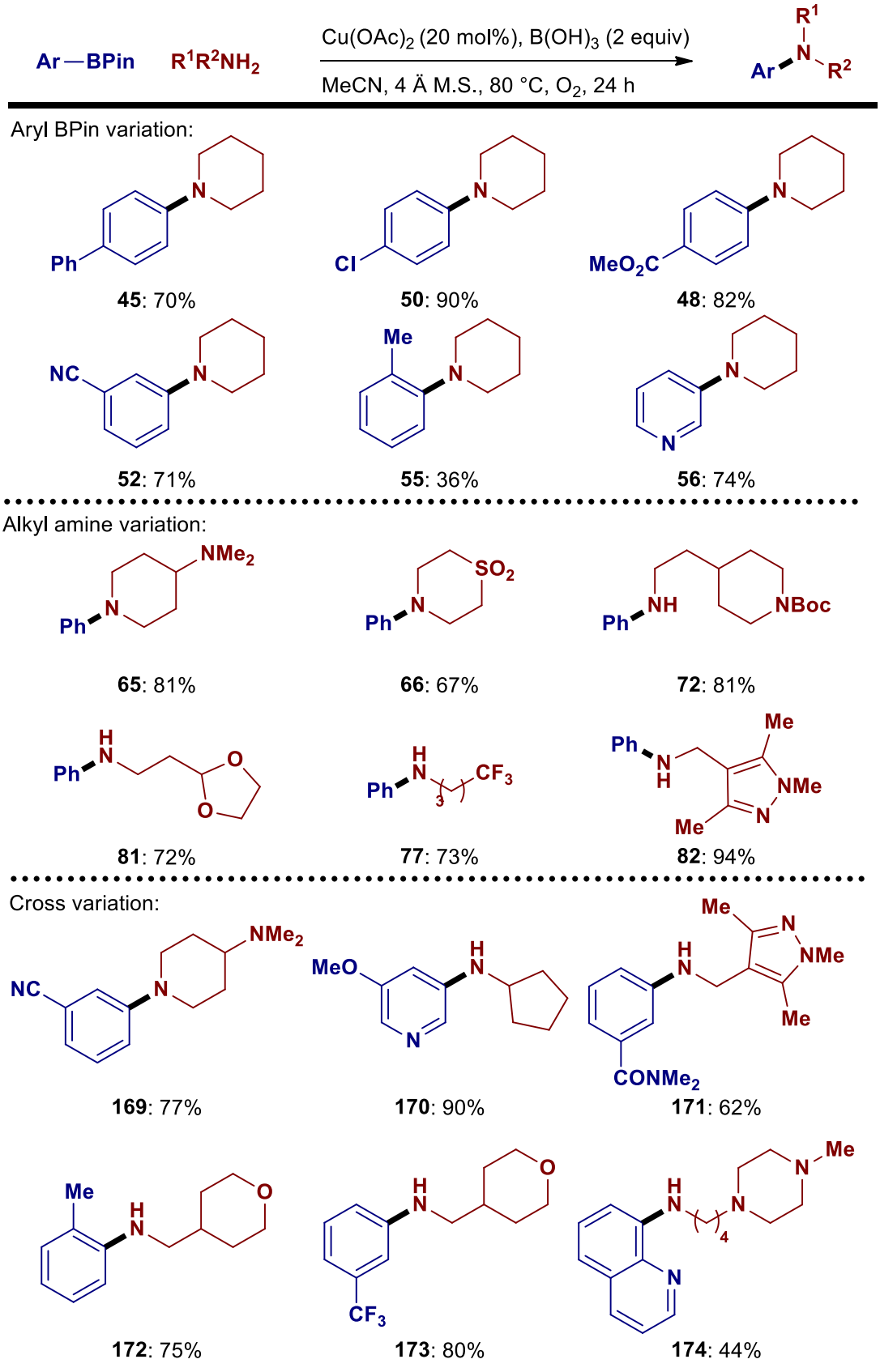
on the aryl BPin ester coupling partner. Pleasingly, heterocyclic BPin ester coupling partners afforded good yields, highlighting the overall better performance of the boric acid-based conditions. In addition, the aryl amine was also generally tolerant of functionality and substitution (**Scheme 106, 33, 35, 38** and **41** to **43**). Finally, cross variations between challenging coupling partners were evaluated and confirmed the applicability of the new reaction conditions to access highly functionalised compounds (**Scheme 106, 163** to **168**).



Scheme 106: Scope of the catalytic Chan-Lam reaction between aryl BPin esters and aryl amines.

4.2.3. Alkyl amine scope

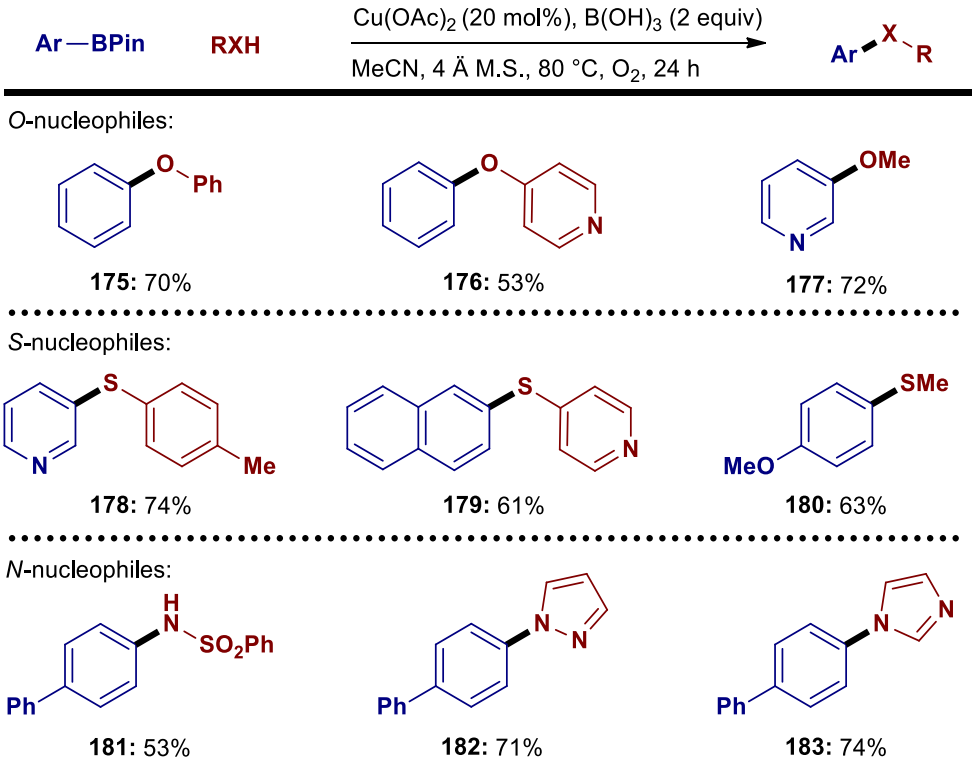
The developed reaction conditions were also found to allow the effective coupling of alkyl amines (**Scheme 107**). Once more, a good range of BPin esters and amine compounds was tolerated. However, it should be noted that *ortho*-substitution on the aryl component generally results in poorer yields when using secondary or bulky primary amines (**Scheme 107, 55**).



Scheme 107: Scope of the catalytic Chan-Lam reaction between aryl BPin esters and alkyl amines.

4.2.4. Coupling of other nucleophiles

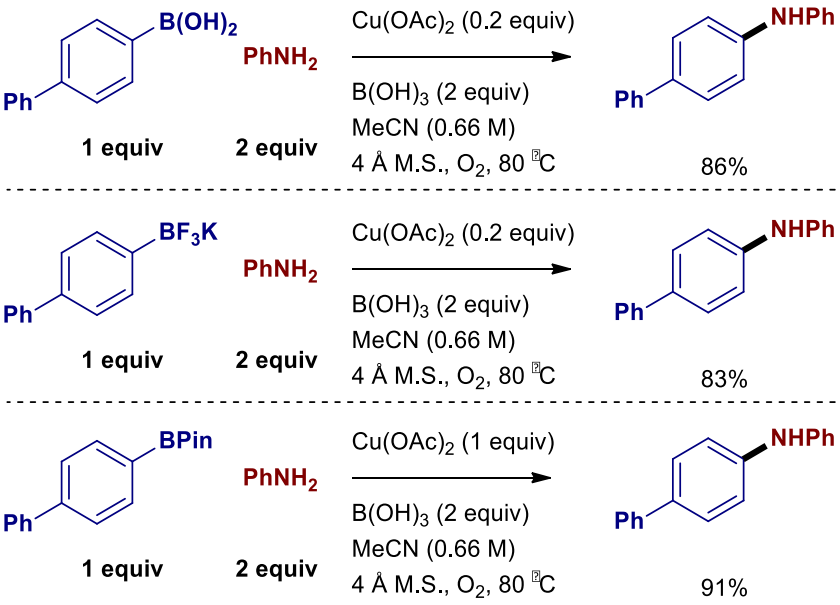
The same reaction conditions were also effective for etherification and thiolation reactions (**Scheme 108, 175** to **180**). In addition, other *N*-nucleophiles including sulfonamides, imidazoles, and pyrazoles were coupled in moderate to good yields (**Scheme 108, 181** to **183**).



Scheme 108: Scope of the catalytic Chan-Lam reaction between aryl BPin esters and various nucleophiles.

4.2.5. Coupling of other boronic acid derivatives.

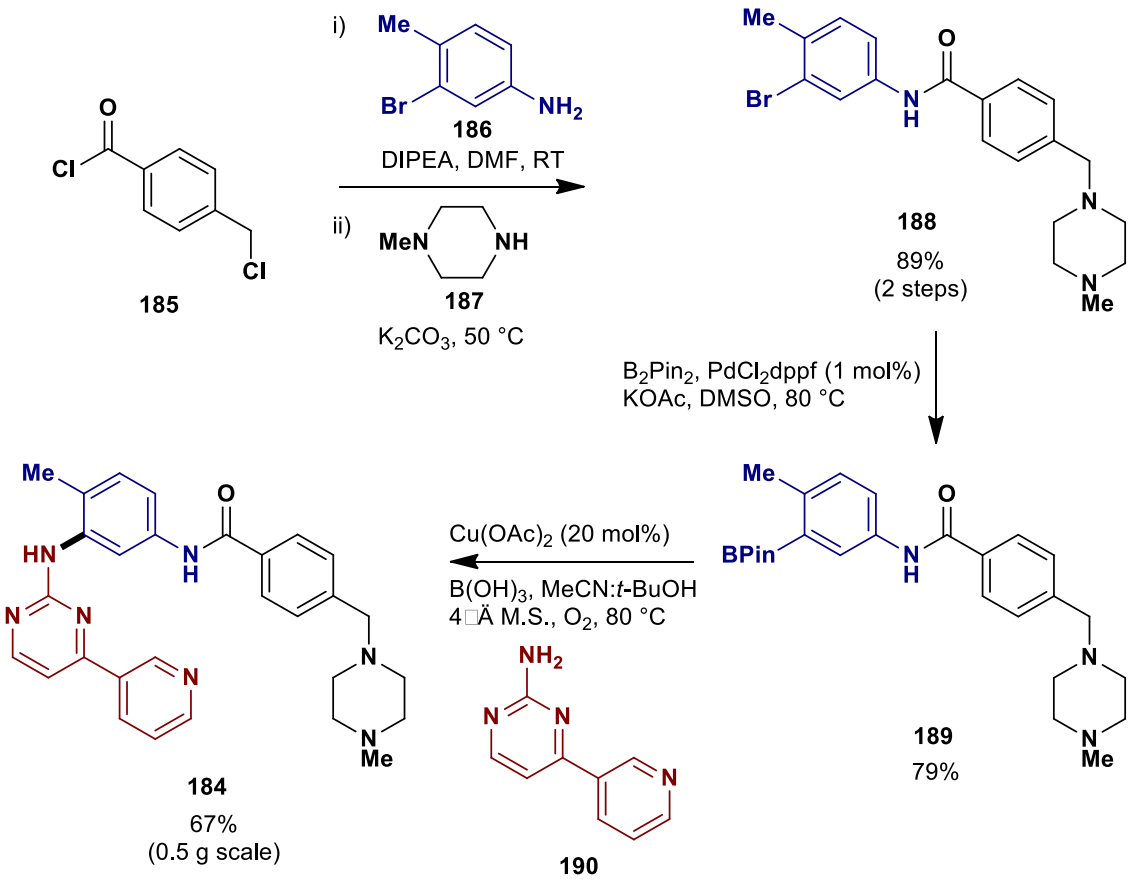
Comparable levels of efficiency were noted for BPin *vs.* boronic acid, and *vs.* BF_3K as well as catalytic *vs.* stoichiometric $Cu(OAc)_2$, which denoted the generality of the developed conditions (**Scheme 109**).



Scheme 109: Catalytic Chan-Lam reaction between aryl boronic acid derivatives and aniline 9, and stoichiometric Chan-Lam reaction between aryl BPin ester 10 and aniline 9.

4.2.6. Application to the synthesis of Imatinib

To further support the applicability of our developed method on a biologically relevant molecule with increased functionality and higher molecular weight, we evaluated the developed reaction conditions within the synthesis of the tyrosine-kinase inhibitor Imatinib **184** (Gleevec®, **Scheme 110**). Formation of the required BPin compound was achieved over three steps via an acylation/alkylation sequence using dichloride **185** and amines **186** and **187**. Subsequent Miyaura borylation of **188** gave aryl BPin ester **189**. Application of the developed reaction conditions towards Chan-Lam amination of **190** gave access to **184** in 67% isolated yield on 0.5 g scale.



Scheme 110: Application of the catalytic Chan-Lam reaction conditions for the synthesis of the tyrosine-kinase inhibitor Imatinib.

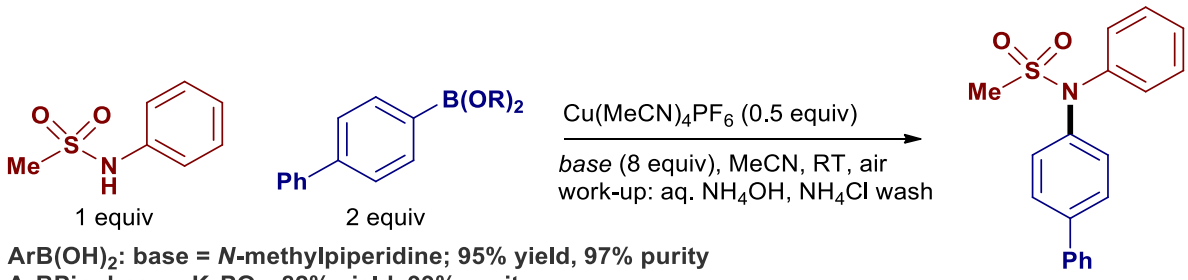
5. Conclusions and future directions

In summary, we firstly developed a straightforward stoichiometric set of reaction conditions that allows the efficient Chan-Lam coupling of aryl BPin and aryl amines. These conditions are also suitable for the coupling of alkyl amines. This provided the first general set of reaction conditions for the Chan-Lam reaction of aryl BPin reagents. Then, an investigation of the Chan-Lam amination has allowed a complete mechanistic description to be assembled. Spectroscopic analyses have provided insight into the course of the reaction with a formative identification of key reactive intermediates. This has allowed the origin of three specific issues: the BPin reactivity problem, the aryl amine problem, and side reactions (oxidation, protodeboronation) to be determined.

Finally, synergistic promotive effects of boric acid including sequestration of AcO^- and AcOH, removal of free pinacol and promotion of Cu(I) oxidation. were identified. Then, they have have been leveraged to overcome these issues, providing the first generally efficient BPin Chan-Lam amination conditions proceeding under non-basic reaction conditions.

However, through the course of our optimisation and mechanistic investigation we observed limitations for a few NH-based substrates including: sulfonamides, amides, and dialkylamines. Allowing the cross-coupling of these useful substrates with aryl BPin would be of high interest, and would yield the Chan-Lam amination to be one of the most powerful C-N bond formation reactions.

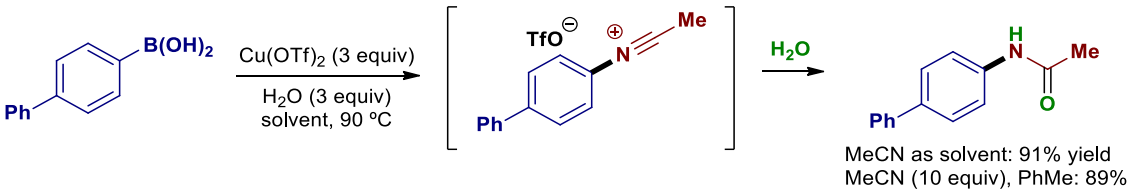
Our ongoing work is therefore focusing on the coupling of sulfonamides with aryl boronic acid and aryl boronic acid pinacol esters. Our mechanistic understanding of the Chan-Lam amination allowed us to find suitable conditions to achieve this coupling at room temperature in high efficiency (**Scheme 111**).



Scheme 111: Development of a practical, scalable, room temperature Chan-Lam *N*-arylation of *N*-aryl sulfonamides

Finally, we recently found that reductive elimination from a Cu(III) intermediate can be controlled to promote C-N bond formation to a bound neutral nitrile ligand, generating reactive nitrilium ions. We investigated the mechanism and demonstrated synthetic utility in the development of an aryl Ritter reaction. In the broader context, reductive

elimination is a fundamental step in catalysis, often viewed as the terminal event. This work will introduce a concept for extending the utility of this key event beyond the product-forming step (**Scheme 112**).



Scheme 112: Control of the reductive elimination from a Cu(III) intermediate to promote C-N bond formation to a bound neutral nitrile ligand.

Experimental

1. General information

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. All solvents used for dry reactions were obtained from capped bottles from commercial suppliers or from a PureSolv SPS-400-5 solvent purification system. These solvents were transferred to and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves and purged with and stored under nitrogen. Cyclohexane, dichloromethane, diethyl ether, ethyl acetate, methanol, and petroleum ether 40-60^{o} for purification purposes were used as obtained from suppliers without further purification. Optimisation and scope reactions were carried out using capped 5 mL microwave. Glassware was oven-dried (150 °C) and purged with N_2 before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature was generally *ca*. 20 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer. 3 Å and 4 Å molecular sieves were purchased from Aldrich Chemical Company in powdered form, and activated and stored in an oven at 150 °C until their use.

2. High Performance Liquid Chromatography (HPLC)

Reverse phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column. Analysis was performed using a gradient method, eluting with 5–80% MeCN/H_2O over 16 minutes at a flow rate of 2 mL/min. Samples for HPLC analysis were prepared through the addition of 2 mL of caffeine standard to the reaction mixture. The resulting solution was then stirred before the removal of a 200 µL aliquot. The aliquot was diluted to 1 mL with MeCN. A 200 µL aliquot of the diluted solution was then filtered and further diluted with 800 µL MeCN and 500 µL H_2O for HPLC analysis against established conversion factors.

3. Thin layer chromatography

Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light or developed using potassium permanganate solution.

4. Liquid Chromatography Mass Spectrometry (LCMS)

LC conditions: The UPLC analysis was conducted on an Acquity UPLC BEH C18 column (50 mm x 2.1 mm, i.d. 1.7 µm packing diameter) with a flow rate of 1 mL/min at 40 °C. The UV detection was a summed signal from wavelength of 210 nm to 350 nm.

MS conditions: Mass spectra were conducted on a Waters ZQ mass spectrometer, with an ionisation mode of alternate–scan positive and negative electrospray. The scan range was 100 to 1000 AMU, the scan time was 0.27 sec and the inter–scan delay was 0.10 sec.

- **Method A (formic acid modifier)**

LC and MS conditions as reported above. The solvents employed were: A = 0.1% v/v solution of formic acid in water; B = 0.1% v/v solution of formic acid in acetonitrile. The gradient (A:B) employed was from 97:3 to 3:97 over 2 min.

- **Method B (TFA modifier)**

LC and MS conditions as reported above. The solvents employed were: A = 0.1% v/v solution of trifluoroacetic acid in water; B = 0.1% v/v solution of trifluoroacetic acid in acetonitrile. The gradient (A:B) employed was from 97:3 to 3:97 over 2 min.

- **Method C (ammonium bicarbonate modifier)**

LC and MS conditions as reported above. The solvents employed were: A = ammonium hydrogen carbonate in water adjusted to pH 10 with ammonia solution; B = acetonitrile. The gradient (A:B) employed was from 99:1 to 0:100 over 2 min.

5. Purification by flash chromatography

At the University of Strathclyde, flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel.

At GSK, column chromatography was conducted on a Combiflash® Rf automated flash chromatography system, from Teledyne Isco using disposable, normal or reverse phase, SPE Redisep cartridges (4 g to 330 g). The CombiFlash® Rf uses RFID (Radio Frequency Identification) technology to automate setting the parameters for purification runs and fraction collection. The system is equipped with a UV variable dual-wavelength and a Foxy® fraction collector enabling automated peak cutting, collection, and tracking. Reverse phase chromatography employing modified water (high pH) used a pH 10 aqueous ammonium bicarbonate solution.

6. Nuclear Magnetic Resonance (NMR) spectrometry

NMR spectra were recorded using a Bruker DPX250, DPX400 or AV400 (with cyroprobe) referenced to tetramethylsilane. ^{1}H and ^{13}C NMR spectra were obtained at 400 MHz and 101 MHz, respectively. ^{19}F NMR spectra were obtained at 387 MHz. ^{11}B NMR spectra were obtained at 128 MHz. Chemical shifts are reported in parts per million (ppm) to the nearest 0.01 ppm (^{1}H NMR) or 0.1 ppm (^{13}C). Coupling constants (J) are reported in Hz to the nearest 0.1 Hz. Spectra were recorded at room temperature unless otherwise stated with $CDCl_3$ referenced at 7.27 ppm (^{1}H) and 77.36 ppm (^{13}C), DMSO-d_6 referenced at 2.50 ppm (^{1}H) and 39.52 ppm (^{13}C), and MeCN-d_3 referenced at 1.94 ppm (^{1}H) and 1.32 (^{13}C). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad.

7. High Resolution Mass Spectrometry (HRMS)

ESI (+) high resolution mass spectra (HRMS) were obtained on a Micromass Q-Tof 2 hybrid quadrupole time-of-flight mass spectrometer, equipped with a Z-spray interface,

over a mass range of 100 – 1100 Da, with a scan time of 0.9 s and an interscan delay of 0.1 s. Reserpine was used as the external mass calibrant ($[M+H]^+$ = 609.2812 Da). The Q-Tof 2 mass spectrometer was operated in W reflectron mode to give a resolution (FWHM) of 16000-20000. Ionisation was achieved with a spray voltage of 3.2 kV, a cone voltage of 50 V, with cone and desolvation gas flows of 10-20 and 600 L/h, respectively. The source block and desolvation temperatures were maintained at 120 °C and 250 °C, respectively. The elemental composition was calculated using MassLynx v4.1 for the $[M+H]^+$ and the mass error quoted as ppm.

An Agilent 1100 Liquid Chromatography equipped with a model G1367A autosampler, a model G1312A binary pump and a HP1100 model G1315B diode array detector was used. The method used was generic for all experiments. All separations were achieved using a Phenomenex Luna C18 (2) reversed phase column (100 x 2.1 mm, 3 µm particle size). Gradient elution was carried out with the mobile phases as (A) water containing 0.1 % (v/v) formic acid and (B) acetonitrile containing 0.1 % (v/v) formic acid. The conditions for the gradient elution were initially 5 % B, increasing linearly to 100 % B over 6 minutes, remaining at 100 % B for 2.5 min then decreasing linearly to 5 % B over 1 min, followed by an equilibration period of 2.5 min prior to the next injection. The flow rate was 0.5 mL/min, temperature controlled at 35 °C with an injection volume of between 2 to 5 µL. All samples were diluted with DMSO (99.9 %) prior to LCMS analysis.

8. Infra-Red (IR) measurements

IR spectra were obtained on a PerkinElmer spectrum one FT-IR with peaks reported in cm^{-1}.

9. Ultra-violet measurements

UV spectra were recorded using the Spectroquant Pharo 100 spectrometer at 672 nM (maximum wavelength absorbance of $Cu(OAc)_2$ and tetrameric copper complex **149**). A blank analysis was performed before any measurements using MeCN.

Model	Pharo 300
Light source	Xenon
Optical design	Single beam
Wavelength range (nm)	190-1100
Spectral bandwidth (nm)	4
Wavelength accuracy (nm)	±1
Photometric range	±3.3 A
Photometric accuracy	0.003 A at <0.600 A; 0.5% of reading for 0.600 ≤ A ≥ 2.000
Scan	1 nm increments with selectable wavelength range
Measuring modes	Concentration, absorbance, transmission, multi-wavelengths, scans + kinetics in A or T mode
Results storage	1000 single measured values, 4 MB for scans and kinetics
Interfaces	RS232, USB-A, USB-B

10. Electron Plasma Resonance (EPR)

X-band EPR spectra were recorded on a Bruker ELEXSYS E500 spectrometer, and simulations performed with Bruker's Xsophe software package.[97] Samples were prepared with 50 mM concentration of copper acetate in MeCN and loaded to a height of 2 cm in a 2.8 mm o.d. quartz tube. Data were collected at ambient temperature and 150 K, wherein a glassing solvent (MeOH or THF) was added to the sample.

11. Melting points

Melting points were measured on a Stuart automatic melting point apparatus, SMP40. For compounds that decomposed over a wide temperature range, it was possible to watch a recorded video of the experiment to manually determine the melting point range.

12. Calculations

The program package ORCA was used for all calculations.[98] The input geometry for all molecules were generated using ArgusLab. The geometries of all molecules were fully optimized by a spin-unrestricted DFT method employing the BP functional with acetonitrile as solvent.[99,100] Triple-ξ-quality basis sets with one set of polarization functions (def2-TZVP) were used all atoms with enhanced in enhanced integration accuracy was used for copper (SPECIALGRIDINTACC 10).[101,102] A scalar relativistic correction was applied using the zeroth-order regular approximation (ZORA) method.[103-105] The RIJCOSX approximation combined with the appropriate Ahlrichs auxiliary basis set was used to speed up the calculations.[106-108] The conductor like screening model (COSMO) was used for all calculations.[109] The self-consistent field calculations were tightly converged (1×10^{-8} E_h in energy, 1×10^{-7} E_h in the density charge, and 1×10^{-7} in the maximum element of the DIIS9 error vector). The geometry was converged with the following convergence criteria: change in energy $<10^{-5}$ E_h, average force $<5 \times 10^{-4}$ E_h $Bohr^{-1}$, and the maximum force 10^{-4} E_h $Bohr^{-1}$. The geometry search for all complexes was carried out in redundant internal coordinates without imposing geometry constraints. The stability of all solutions was checked by performing frequency calculations: No negative frequencies were observed. Thermodynamic quantities were generated using the numerical frequency module to correct for zero-point and thermal energy, and entropy contributions at 298.15 K.

13. X-ray crystallographic data collection and structure refinement

Diffraction quality crystals of $[C_5H_{12}N]_2[Cu_2(OAc)_6]$ as green blocks and $[Cu_4(\mu^3\text{-}OH)_2(OAc)_6(C_5H_{11}N)_4]\cdot 2CH_3CN$ as deep blue prisms were obtained by slow diffusion of pentane vapour into a dichloromethane solution of stoichiometric mixture of copper acetate dihydrate and piperidine. The crystals were coated with paratone oil and mounted on the end of a nylon loop attached to the end of the goniometer. Data were

collected with a Bruker SMART APEX CCD diffractometer equipped with a Kryoflex attachment supplying a nitrogen stream at 150 K. X-ray diffraction data were collected using an Oxford Diffraction Gemini Ultra with an ATLAS CCD detector and graphite monochromated Mo-Kα radiation (λ = 0.71074 Å) at 150 K. Data reduction was performed using the CrysAlis software package and structure solution and refinement were performed using SHELXS-97 and SHELXL-97 via WinGX.[110-112] Corrections for incident and diffracted beam absorption effects were applied using analytical numeric absorption correction using a multifaceted crystal model.[113]

14. Chapter 1

14.1. General experimental procedures

14.1.1. General procedure A for the Chan-Evans-Lam amination of boronic acid pinacol (BPin) esters with aryl amines.

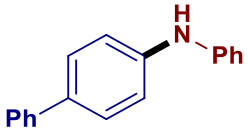
A solution of aryl BPin (1 equiv, 0.30 mmol, 1 M), aryl amine (2 equiv, 0.60 mmol), $Cu(OAc)_2$ (1 equiv, 0.30 mmol, 54 mg), Et_3N (2 equiv, 0.60 mmol, 61 mg, 84 µL), and powdered activated 3 Å molecular sieves in MeCN-EtOH (20:1 ratio, 300 µL) was sealed into an oven dried round-bottomed 5 mL microwave vial under air and stirred at 80 °C (preheated sand bath, sand temperature) for 24 h. The reaction mixture was allowed to cool to room temperature, filtered through Celite, and the filtrate was evaporated to give a residue that was purified by silica chromatography (EtOAc/petroleum ether with 1% Et_3N modifier). Appropriate fractions were evaporated to afford the desired product.

14.1.2. General procedure B for the Chan-Evans-Lam amination of boronic acid pinacol (BPin) esters with alkyl amines.

A solution of aryl BPin (1 equiv, 0.20 mmol, 0.5 M), alkyl amine (2 equiv, 0.40 mmol), $Cu(OAc)_2$ (1 equiv, 0.20 mmol, 36 mg), Et_3N (2 equiv, 0.40 mmol, 41 mg, 56 µL), and powdered activated 3 Å molecular sieves in MeCN (400 µL) was sealed in an oven dried round-bottomed 5 mL microwave vial under air and stirred at 80 °C (preheated sand bath, sand temperature) for 24 h. The reaction mixture was allowed to cool to room temperature, filtered through Celite, and the filtrate was evaporated to give a residue that was purified by silica chromatography (EtOAc/petroleum ether with 1% Et_3N modifier). Appropriate fractions were evaporated to afford the desired product.

14.2. Compound characterisation

***N*-Phenyl-[1,1'-biphenyl]-4-amine, Compound 18.**[114]



Prepared according to the general procedure A using 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (84 mg, 0.30 mmol), aniline (54 µL, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether), fractions were evaporated to afford the desired product as an orange solid (57 mg, 0.24 mmol, 79%).

Appearance: Orange solid.

M.pt.: 110-111 °C.

^{1}H NMR (400 MHz; DMSO-d_6): δ 7.00 (t, *J* = 7.3 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 4H), 7.20-7.27 (m, 3H), 7.30-7.47 (m, 2H), 7.48-7.66 (m, 4H), 8.30 (br. s., 1H).

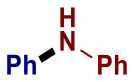
^{13}C NMR (101 MHz, DMSO-d_6): δ 117.2, 117.6, 119.6, 120.4, 126.2, 126.8, 127.8, 129.3, 129.7, 131.6, 140.5, 143.5.

LCMS (ESI): t_R = 1.43 min, $[M+H]^+$ 246.2.

HRMS (ESI): ($C_{18}H_{16}N$) $[M+H]^+$ requires 246.1277, found $[M+H]^+$ 246.1279.

υ_{max} (neat): 3372, 1596, 1523, 1505, 1485, 1323, 846, 759, 745, 693 cm^{-1}.

Diphenylamine, Compound 22.[115]



Prepared according to the general procedure A using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), aniline (54 µL, 0.60 mmol), $Cu(OAc)_2$ (54 mg,

0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether), fractions were evaporated to afford the desired product as a white solid (38 mg, 0.22 mmol, 74%).

Appearance: White solid.

M.pt.: 51-52 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.81 (t, *J* = 7.3 Hz, 2H), 7.05-7.07 (m, 4H), 7.20-7.24 (m, 4H), 8.10 (s, 1H).

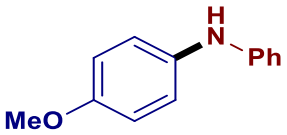
^{13}C NMR (101 MHz, DMSO-d_6): δ 116.7, 119.6, 129.1, 143.4.

LCMS (ESI): t_R = 1.21 min, $[M+H]^+$ 170.2.

HRMS (ESI): ($C_{12}H_{12}N$) $[M+H]^+$ requires 170.0964, found $[M+H]^+$ 170.0965.

υ_{max} (neat): 3407, 3383, 3042, 1595, 1519, 1494, 1458, 1418, 1316, 1242, 1172, 876, 743, 689 cm^{-1}.

4-Methoxy-*N*-phenylaniline, Compound 23.[116]



Prepared according to the general procedure A using 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70 mg, 0.30 mmol), aniline (54 µL, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a yellow solid (42 mg, 0.21 mmol, 70%).

Appearance: Yellow solid.

M.pt.: 104-105 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.85-6.92 (m, 4H), 7.03-7.05 (m, 2H), 7.13-7.15 (m, 2H), 7.79 (s, 1H).

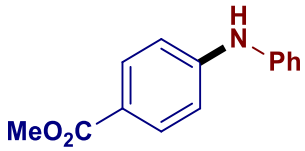
^{13}C NMR (101 MHz, DMSO-d_6): δ 55.2, 114.5, 114.8, 118.2, 120.3, 129.0, 136.1, 145.1, 153.8.

LCMS (ESI): t_R=1.17 min, $[M+H]^+$ 200.3.

HRMS (ESI): ($C_{13}H_{14}NO$) $[M+H]^+$ requires 200.1070, found $[M+H]^+$ 200.1073.

υ_{max} (neat): 3388, 1596, 1501, 1443, 1316, 1298, 1249, 1181, 1033, 812, 750, 695 cm^{-1}.

Methyl-4-(phenylamino)benzoate, Compound 24.[117]



Prepared according to the general procedure A using methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (79 mg, 0.30 mmol), aniline (54 µL, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-5% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a white solid (54 mg, 0.23 mmol, 78%).

Appearance: White solid.

M.pt.: 108-109 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.78 (s, 3H), 6.99 (t, *J* = 7.3 Hz, 1H), 7.05-7.07 (m, 2H), 7.17-7.20 (m, 2H), 7.30-7.32 (m, 2H), 7.79-7.81 (m, 2H), 8.74 (s, 1H).

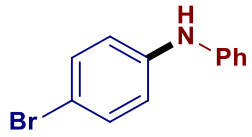
^{13}C NMR (101 MHz, DMSO-d_6): δ 51.4, 113.9, 119.0, 119.4, 121.9, 129.2, 131.0, 141.2, 148.5, 165.9.

LCMS (ESI): t_R = 1.17 min, $[M+H]^+$ 228.2.

HRMS (ESI): ($C_{14}H_{14}NO_2$) $[M+H]^+$ requires 228.1019, found $[M+H]^+$ 228.1023.

υ_{max} (neat): 3334, 1687,1589, 1532, 1496, 1433, 1344, 1281, 1251, 1172, 1109, 851, 767, 747, 692 cm^{-1}.

4-Bromo-*N*-phenylaniline, Compound 25.[118]



Prepared according to the general procedure A using methyl 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (85 mg, 0.30 mmol), aniline (54 µL, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a white solid (60 mg, 0.24 mmol, 81%).

Appearance: White solid.

M.pt.: 88-89 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.87 (t, *J* = 7.5 Hz, 1H), 6.99-7.01 (m, 2H), 7.06-7.08 (m, 2H), 7.23-7.27 (m, 2H), 7.34-7.37 (m, 2H), 8.27 (s, 1H).

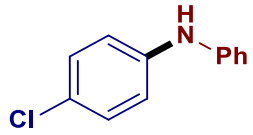
^{13}C NMR (101 MHz, DMSO-d_6): δ 110.0, 117.4, 118.0, 120.3, 129.2, 131.7, 142.6, 143.0.

LCMS (ESI): t_R = 1.34 min, $[M+H]^+$ 250.1.

HRMS (ESI): ($C_{12}H_{11}BrN$) $[M+H]^+$ requires 248.0069, found $[M+H]^+$ 248.0076.

υ_{max} (neat): 3401, 1579, 1500, 1481, 1312, 1070, 803, 748, 704, 690 cm^{-1}.

4-Chloro-*N*-phenylaniline, Compound 26.[118]



Prepared according to the general procedure A using 2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (72 mg, 0.30 mmol), aniline (54 µL, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a colourless solid (48 mg, 0.23 mmol, 78%).

Appearance: Colourless solid.

M.pt.: 65-66 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.86 (t, *J* = 7.2 Hz, 1H), 7.04-7.08 (m, 4H), 7.23-7.27 (m, 4 H), 8.25 (s, 1H).

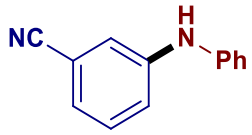
^{13}C NMR (101 MHz, DMSO-d_6): δ 117.2, 117.7, 120.2, 122.5, 128.9, 129.2, 142.5, 142.7.

LCMS (ESI): t_R = 1.32 min, $[M+H]^+$ 204.2.

HRMS (ESI): ($C_{12}H_{11}ClN$) $[M+H]^+$ requires 204.0575, found $[M+H]^+$ 204.0579.

υ_{max} (neat): 3402, 1585, 1500, 1482, 1443, 1394, 1307, 1298, 1171, 1069, 874, 804, 749, 710, 690 cm^{-1}.

3-(Phenylamino)benzonitrile, Compound 27.[119]



Prepared according to the general procedure A using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (69 mg, 0.30 mmol), aniline (54 µL, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (81 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a colourless solid (49 mg, 0.25 mmol, 84%).

Appearance: Colourless solid.

M.pt.: 95-96 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.95 (t, *J* = 7.4 Hz, 1H), 7.12-7.14 (m, 3H), 7.30-7.32 (m, 4H), 7.33-7.39 (m, 1H), 8.52 (s, 1H).

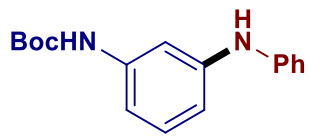
^{13}C NMR (101 MHz, DMSO-d_6): δ 111.9, 117.6, 118.3, 119.1, 120.2, 121.4, 122.2, 129.3, 130.4, 141.7, 144.7.

LCMS (ESI): t_R = 1.15 min, $[M+H]^+$ 195.2.

HRMS (ESI): ($C_{13}H_{11}N_2$) $[M+H]^+$ requires 195.0917, found $[M+H]^+$ 195.0921.

υ_{max} (neat): 3338, 2233, 1592, 1533, 1495, 1482, 1416, 1338, 1303, 1153, 993, 962, 863, 778, 763, 711, 695, 677 cm^{-1}.

***tert*-Butyl-(3-(phenylamino)phenyl)carbamate, Compound 28.**



Prepared according to the general procedure A using *tert*-butyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (96 mg, 0.30 mmol), aniline (54 µL, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-5% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a colourless solid (57 mg, 0.20 mmol, 67%).

Appearance: Colourless solid.

M.pt.: 87–88 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.47 (s, 9H), 6.67 (t, *J* = 7.1 Hz, 1H), 6.80 (m, 1H), 6.90 (m, 1H), 7.05-7.09 (m, 3H), 7.19-7.23 (m, 2H), 7.31 (s, 1H), 8.08 (s, 1H), 9.18 (s, 1H).

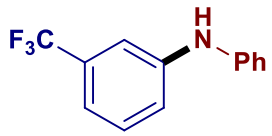
^{13}C NMR (101 MHz, DMSO-d_6): δ 28.1, 78.7, 106.6, 109.9, 110.7, 116.7, 119.4, 129.0, 140.3, 143.4, 143.6, 152.7 (1 signal not observed).

LCMS (ESI): t_R = 1.29 min, $[M+H]^+$ 285.2.

HRMS (ESI): ($C_{17}H_{21}N_2O_2$) $[M+H]^+$ requires 285.1598, found $[M+H]^+$ 285.1604.

υ_{max} (neat): 3331, 1692, 1595, 1526, 1497, 1450, 1398, 1368, 1275, 1247, 1153, 1053, 859, 761, 696 cm^{-1}.

***N*-Phenyl-3-(trifluoromethyl)aniline, Compound 29.[119]**



Prepared according to the general procedure A using 4,4,5,5-tetramethyl-2-(3-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (82 mg, 0.30 mmol), aniline (54 µL, 0.60

mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-5% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a colourless oil (53 mg, 0.22 mmol, 74%).

Appearance: Colourless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.93 (t, *J* = 7.3 Hz, 1H), 7.12-7.14 (m, 3H), 7.19-7.23 (m, 4H), 7.40-7.42 (m, 1H), 8.51 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 111.5 (q, J_{C-F} = 4.2 Hz), 115.0 (q, J_{C-F} = 4.2 Hz), 118.2, 118.9 (q, J_{C-F} = 1 Hz), 121.2, 125.6 (q, J_{C-F} = 273 Hz), 129.5, 129.8, 130.4 (q, J_{C-F} = 35 Hz), 142.0, 144.7.

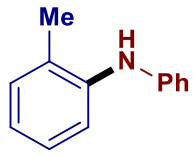
^{19}F-NMR (282 MHz, DMSO-d_6): δ -61.5 (s).

LCMS (ESI): t_R = 1.34 min, $[M+H]^+$ 238.2.

HRMS (ESI): ($C_{13}H_{11}F_3N$) $[M+H]^+$ requires 238.0838, found $[M+H]^+$ 238.0841.

υ_{max} (neat): 3404, 1658, 1049, 1023, 999, 824, 761 cm^{-1}.

3-Methyl-*N*-phenylaniline, Compound 30.[119]



Prepared according to the general procedure A using 4,4,5,5-tetramethyl-2-(m-tolyl)-1,3,2-dioxaborolane (65 mg, 0.30 mmol), aniline (54 µL, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography,

0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a yellow oil (30 mg, 0.17 mmol, 55%).

Appearance: Yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H), 6.51 (t, *J* = 7.5 Hz, 1H), 6.74-6.91 (m, 3H), 7.10-7.19 (m, 5H), 7.33 (s, 1H).

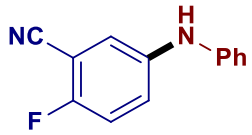
^{13}C NMR (101 MHz, DMSO-d_6): δ 17.9, 116.0, 118.7, 119.7 121.8, 126.4, 128.9, 129.4, 130.8, 141.3, 145.0.

LCMS (ESI): t_R = 1.29 min, $[M+H]^+$ 184.2.

HRMS (ESI): ($C_{13}H_{14}N$) $[M+H]^+$ requires 184.1121 , found $[M+H]^+$ 184.1123.

υ_{max} (neat): 3407, 3383, 3042, 1595, 1519, 1494, 1458, 1418, 1318, 1242, 1172, 1083, 1023, 993, 876, 846 cm^{-1}.

2-Fluoro-5-(phenylamino)benzonitrile, Compound 31.



Prepared according to the general procedure A using 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (74 mg, 0.30 mmol), aniline (54 µL, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a colourless solid (37 mg, 0.17 mmol, 58%).

Appearance: Colourless oil.

M.pt.: 90– 91 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.92 (t, *J* = 7.3 Hz, 1H), 7.08-7.10 (m, 2H), 7.26-7.30 (m, 2H), 7.35-7.37 (m, 3H), 8.43 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 100.1 (d, J_{C-F} = 2.8 Hz), 114.2, 117.3 (d, J_{C-F} = 24 Hz), 117.6, 119.5 (d, J_{C-F} = 253 Hz), 123.3 (d, J_{C-F} = 8 Hz), 129.3, 141.1, 142.1, 154.7, 157.2.

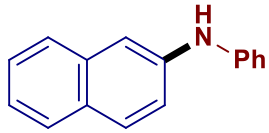
^{19}F-NMR (282 MHz, DMSO-d_6): δ -121.2 (s).

LCMS (ESI): t_R = 1.18 min, $[M+H]^+$ 213.2.

HRMS (ESI): ($C_{13}H_{10}FN_2$) $[M+H]^+$ requires 213.0828, found $[M+H]^+$ 213.0823.

υ_{max} (neat): 3345, 3039, 2243, 1595, 1533, 1493, 1402, 1348, 1241, 1226, 1171, 818, 755, 718, 693 cm^{-1}.

***N*-Phenylnaphthalen-2-amine, Compound 32.[119]**



Prepared according to the general procedure A using 4,4,5,5-tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane (76 mg, 0.30 mmol), aniline (54 µL, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a colourless solid (51 mg, 0.17 mmol, 77%).

Appearance: Colourless solid.

M.pt.: 107–108 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ (6.90 (t, *J* = 7.2 Hz, 1H), 7.18-7.27 (m, 6H), 7.31-7.46 (m, 2H), 7.66-7.78 (m, 3H), 8.38 (s, 1H).

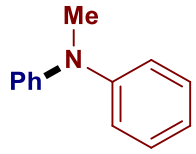
^{13}C NMR (101 MHz, DMSO-d_6): δ 108.9, 117.3, 119.9, 120.1, 122.7, 126.1, 126.2, 127.3, 128.1, 128.7, 129.2, 134.3, 141.3, 143.0.

LCMS (ESI): t_R = 1.35 min, $[M+H]^+$ 220.2.

HRMS (ESI): ($C_{16}H_{14}N$) $[M+H]^+$ requires 220.1121, found $[M+H]^+$ 220.1127.

υ_{max} (neat): 3401, 1596, 1496, 1304, 854, 737, 690 cm^{-1}.

***N*-Methyl-*N*-phenylaniline, Compound 33.**[120]



Prepared according to the general procedure A using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), N-methylaniline (64 mg, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a colourless solid (36 mg, 0.20 mmol, 65%).

Appearance: Colourless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.25 (s, 3H), 6.93 (t, *J* = 7.2 Hz, 2H), 6.98-7.00 (m, 4H), 7.25-7.29 (m, 4H).

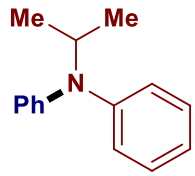
^{13}C NMR (101 MHz, DMSO-d_6): δ 120.0, 121.1, 129.1, 148.6 (one signal obscured by DMSO signals).

LCMS (ESI): t_R = 1.36 min, $[M+H]^+$ 184.2.

HRMS (ESI): ($C_{13}H_{14}N$) $[M+H]^+$ requires 184.1121, found $[M+H]^+$ 184.1123.

υ_{max} (neat): 3036, 1584, 1493, 1340, 1271, 1251, 1185, 1156, 1130, 1091, 1074, 1023, 991, 864, 747, 722, 690 cm^{-1}.

***N*-Isopropyl-*N*-phenylaniline, Compound 34.**[121]



Prepared according to the general procedure A using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), N-isopropylaniline (81 mg, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a colourless solid (15 mg, 0.7 mmol, 24%).

Appearance: Colourless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, *J* = 4.1 Hz, 6H), 4.32 (sept, *J* = 2.3 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 2H), 6.97-7.01 (m, 4H), 7.23-7.27 (m, 4H).

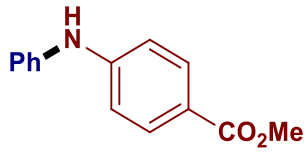
^{13}C NMR (101 MHz, DMSO-d_6): δ 21.4, 48.3, 122.0, 123.1, 129.8, 146.8.

LCMS (ESI): t_R = 1.52 min, $[M+H]^+$ 212.2.

HRMS (ESI): ($C_{15}H_{18}N$) $[M+H]^+$ requires 212.1434, found $[M+H]^+$ 212.1425.

υ_{max} (neat): 3042, 1586, 1498, 1340, 1242, 1183, 1132, 1092, 1088, 993, 880, 777, 710, 690 cm^{-1}.

Methyl-4-(phenylamino)benzoate, Compound 35.[116]



Prepared according to the general procedure A using methyl 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), methyl 4-aminobenzoate (91 mg, 0.60

mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-5% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a white solid (54 mg, 0.21 mmol, 69%).

Appearance: White solid.

M.pt.: 108-109 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.78 (s, 3H), 6.99 (t, *J* = 7.3 Hz, 1H), 7.05-7.07 (m, 2H), 7.17-7.20 (m, 2H), 7.30-7.32 (m, 2H), 7.79-7.81 (m, 2H), 8.74 (s, 1H).

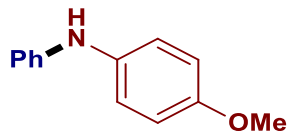
^{13}C NMR (101 MHz, DMSO-d_6): δ 51.4, 113.9, 119.0, 119.4, 121.9, 129.2, 131.0, 141.2, 148.5, 165.9.

LCMS (ESI): t_R = 1.17 min, $[M+H]^+$ 228.2.

HRMS (ESI): ($C_{14}H_{14}NO_2$) $[M+H]^+$ requires 228.1019, found $[M+H]^+$ 228.1023.

υ_{max} (neat): 3334, 1687,1589, 1532, 1496, 1433, 1344, 1281, 1251, 1172, 1109, 851, 767, 747, 692 cm^{-1}.

4-Methoxy-*N*-phenylaniline, Compound 36.[117]



Prepared according to the general procedure A using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), 4-methoxyaniline (74 mg, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica

chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a yellow solid (52 mg, 0.26 mmol, 87%).

Appearance: Yellow solid.

M.pt.: 104-105 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.85-6.92 (m, 4H), 7.03-7.05 (m, 2H), 7.13-7.15 (m, 2H), 7.79 (s, 1H).

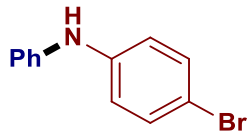
^{13}C NMR (101 MHz, DMSO-d_6): δ 55.2, 114.5, 114.8, 118.2, 120.3, 129.0, 136.1, 145.1, 153.8.

LCMS (ESI): t_R = 1.17 min, $[M+H]^+$ 200.3.

HRMS (ESI): ($C_{13}H_{14}NO$) $[M+H]^+$ requires 200.1070, found $[M+H]^+$ 200.1073.

υ_{max} (neat): 3388, 1596, 1501, 1443, 1316, 1298, 1249, 1181, 1033, 812, 750, 695 cm^{-1}.

4-Bromo-*N*-phenylaniline, Compound 37.[118]



Prepared according to the general procedure A using methyl 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), 4-bromoaniline (103.2 mg, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a white solid (53 mg, 0.21 mmol, 71%).

Appearance: White solid.

M.pt.: 88-89 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.87 (t, *J* = 7.5 Hz, 1H), 6.99-7.01 (m, 2H), 7.06-7.08 (m, 2H), 7.23-7.27 (m, 2H), 7.34-7.37 (m, 2H), 8.27 (s, 1H).

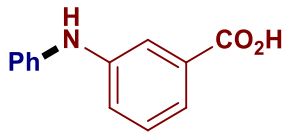
^{13}C NMR (101 MHz, DMSO-d_6): δ 110.0, 117.4, 118.0, 120.3, 129.2, 131.7, 142.6, 143.0.

LCMS (ESI): t_R = 1.34 min, $[M+H]^+$ 250.1.

HRMS (ESI): ($C_{12}H_{11}BrN$) $[M+H]^+$ requires 248.0069, found $[M+H]^+$ 248.0076.

υ_{max} (neat): 3401, 1579, 1500, 1481, 1312, 1070, 803, 748, 704, 690 cm^{-1}.

3-(Phenylamino)benzoic acid, Compound 38.[122]



Prepared according to the general procedure A using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), 3-aminobenzoic acid (82 mg, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a white solid (53 mg, 0.25 mmol, 83%).

Appearance: White solid.

M.pt.: 140-141 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.88 (t, *J* = 7.1 Hz, 1H), 7.09-7.11 (m, 2H), 7.25-7.37 (m, 5H), 7.65 (s, 1H), 8.33 (s, 1H), 12.81 (s, 1H).

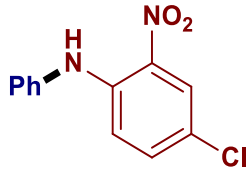
^{13}C NMR (101 MHz, DMSO-d_6): δ 116.5, 117.5, 120.1, 120.2, 120.4, 129.2, 129.3, 131.7, 142.7, 143.9, 167.4.

LCMS (ESI): t_R = 1.01 min, $[M+H]^+$ 214.2.

HRMS (ESI): ($C_{13}H_{12}NO_2$) $[M+H]^+$ requires 214.0863, found $[M+H]^+$ 214.0865.

υ_{max} (neat): 3407, 2989, 1686, 1593, 1512, 1463, 1427, 1296, 1279, 996, 934, 882, 786, 749, 698, 681, 664 cm^{-1}.

4-Chloro-2-nitro-*N*-phenylaniline, Compound 39.



Prepared according to the general procedure A using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), 4-chloro-2-nitroaniline (103 mg, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-15% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a red solid (39 mg, 0.15 mmol, 52%).

Appearance: Red solid.

M.pt.: 59-61 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.16 (t, *J* = 7.3 Hz, 1H), 7.19-7.23 (m, 1H), 7.31-7.33 (m, 2H), 7.41-7.43 (m, 2H), 7.45-7.52 (m, 1H), 8.12 (s, 1H), 9.40 (s, 1H).

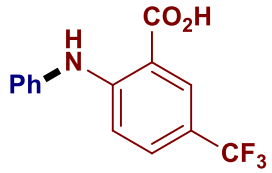
^{13}C NMR (101 MHz, DMSO-d_6): δ 118.7, 120.8, 124.0, 125.0, 125.2, 129.5, 133.4, 135.6, 138.9, 141.0.

LCMS (ESI): t_R = 1.38 min, $[M+H]^+$ 249.1.

HRMS (ESI): ($C_{12}H_{10}ClN_2O_2$) $[M+H]^+$ requires 249.0425, found $[M+H]^+$ 249.0432.

υ_{max} (neat): 3338, 1618, 1593, 1566, 1526, 1498, 1456, 1407, 1345, 1246, 1213, 1148, 1074, 902, 885, 849, 819, 766, 759, 725, 694, 667 cm^{-1}.

2-(Phenylamino)-5-(trifluoromethyl)benzoic acid, Compound 40.



Prepared according to the general procedure A using methyl 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), 2-amino-5-(trifluoromethyl)benzoic acid (123 mg, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-10% (EtOAc + 1% Et3N)/petroleum ether) fractions were evaporated to afford the desired product as a white solid (36 mg, 0.13 mmol, 43%).

Appearance: White solid.

M.pt.: 77-78 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.23-7.25 (m, 2H), 7.31-7.33 (m, 2H), 7.41-7.45 (m, 2H), 7.63-7.65 (m, 1H), 8.14 (s, 1H), 9.97 (s, 1H), 13.57 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 111.5, 113.7, 116.7 (q, J_{C-F} = 24 Hz), 123.1, 124.7, 125.7, 129.6, 130.3 (dt, J_{C-F} = 168 Hz, 7.3 Hz), 139.0, 150.1, 168.9.

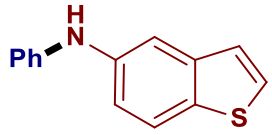
^{19}F-NMR (282 MHz, DMSO-d_6): δ -60.1 (s).

LCMS (ESI): t_R = 1.41 min, $[M+H]^+$ 282.

HRMS (ESI): ($C_{14}H_{11}F_3NO_2$) $[M+H]^+$ requires 282.0736, found $[M+H]^+$ 282.0739.

υ_{max} (neat): 3330, 2901, 1666, 1592, 1577, 1524, 1499, 1435, 1417, 1321, 1243, 1139, 1068, 904, 823, 792, 758, 745, 682, 662 cm^{-1}.

***N*-Phenylbenzo[b]thiophen-5-amine, Compound 41.**



Prepared according to the general procedure A using methyl 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), benzo[b]thiophen-5-amine (90 mg, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a grey solid (33 mg, 0.15 mmol, 51%).

Appearance: Grey solid.

M.pt.: 120-121 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.81 (t, *J* = 7.3 Hz, 1H), 7.09-7.11 (m, 3H), 7.21-7.23 (m, 2H), 7.32 (d, *J* = 6.3 Hz, 1H), 7.57 (d, *J* = 6.2 Hz, 1H), 6.67 (d, *J* = 6.7 Hz, 1H), 7.81 (d, *J* = 6.7 Hz, 1H), 8.16 (s, 1H).

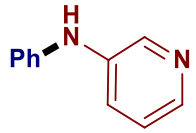
^{13}C NMR (101 MHz, DMSO-d_6): δ 110.1, 116.3, 117.1, 119.4, 122.9, 123.6, 127.7, 129.1, 130.9, 140.5, 143.9.

LCMS (ESI): t_R = 1.33 min, $[M+H]^+$ 226.1.

HRMS (ESI): ($C_{14}H_{12}NS$) $[M+H]^+$ requires 226.0685, found $[M+H]^+$ 226.0686.

υ_{max} (neat): 3376, 3053, 1667, 1596, 1512, 1497, 1433, 1344, 1298, 1267, 1246, 1201, 1153, 1086, 1049, 1028, 892, 861, 825, 802, 745, 712, 670 cm^{-1}.

***N*-Phenylpyridin-3-amine, Compound 42.**[123]



Prepared according to the general procedure A using methyl 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), pyridin-3-amine (56 mg, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a white solid (20 mg, 0.12 mmol, 40%).

Appearance: White solid.

M.pt.: 140-141 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.71 (t, *J* = 7.2 Hz, 1H), 6.72-6.87 (m, 2H), 7.23-7.27 (m, 2H), 7.54 (m, 1H), 7.67 (m, 2H), 8.15 (s, 1H), 8.96 (s, 1H).

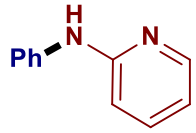
^{13}C NMR (101 MHz, DMSO-d_6): δ 110.6, 114.1, 117.9, 120.2, 128.5, 137.1, 141.7, 147.1, 155.8.

LCMS (ESI): t_R = 0.36 min, $[M+H]^+$ 171.2.

HRMS (ESI): ($C_{11}H_{11}N_2$) $[M+H]^+$ requires 171.0917, found $[M+H]^+$ 171.0915.

υ_{max} (neat): 3008, 1667, 1588, 1574, 1530, 1493, 1464, 1442, 1430, 1327, 1253, 1159, 1148, 1159, 992, 768, 747, 695 cm^{-1}.

***N*-Phenylpyridin-2-amine, Compound 43.**[124]



Prepared according to the general procedure A using methyl 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol), pyridin-2-amine (56 mg, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a white solid (17 mg, 0.10 mmol, 34%).

Appearance: White solid.

M.pt.: 140-141 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.73 (t, *J* = 7.2 Hz, 1H), 6.81-6.87 (m, 2H), 7.23-7.27 (m, 2H), 7.54 (m, 1H), 7.67 (m, 2H), 8.14 (s, 1H), 8.95 (s, 1H).

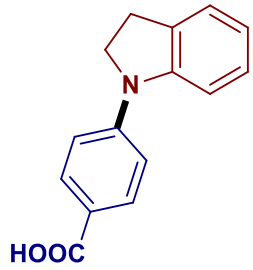
^{13}C NMR (101 MHz, DMSO-d_6): δ 110.6, 114.1, 117.9, 120.2, 128.5, 137.1, 141.7, 147.1, 155.8.

LCMS (ESI): t_R = 0.36 min, $[M+H]^+$ 171.2.

HRMS (ESI): ($C_{11}H_{11}N_2$) $[M+H]^+$ requires 171.0917, found $[M+H]^+$ 171.0915.

υ_{max} (neat): 3088, 1589, 1537, 1494, 1464, 1444, 1327, 992, 770, 748, 696 cm^{-1}.

4-(Indolin-1-yl)benzoic acid, Compound 44.



Prepared according to the general procedure A using methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (69 mg, 0.30 mmol), indoline (72 mg, 0.60 mmol), $Cu(OAc)_2$ (54 mg, 0.30 mmol), Et_3N (83 µL, 0.60 mmol) and powdered activated 3 Å molecular sieves (225 mg) in MeCN-EtOH (20:1 ratio, 300 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/petroleum ether) fractions were evaporated to afford the desired product as a grey solid (20 mg, 0.09 mmol, 31%).

Appearance: Grey solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.09 (t, *J* = 7.2 Hz, 2H), 3.94 (t, *J* = 7.7 Hz, 2H), 6.71-6.75 (m, 1H), 7.13-7.15 (m, 1H), 7.16-7.19 (m, 4H), 7.85-7.88 (m, 2H).

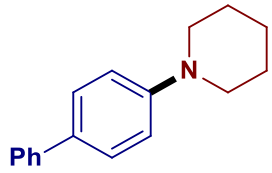
^{13}C NMR (101 MHz, DMSO-d_6): δ 27.4, 51.4, 108.1, 115.3, 118.8, 125.0, 126.9, 130.2, 131.4, 144.4, 146.0, 169.1, 178.8.

LCMS (ESI): t_R = 1.15 min, $[M+H]^+$ 240.1.

HRMS (ESI): ($C_{15}H_{14}NO_2$) $[M+H]^+$ requires 240.1019, found $[M]^+$ 240.1007.

υ_{max} (neat): 3341, 2861, 1684, 1594, 1568, 1529, 1511, 1482, 1457, 1402, 1320, 1295, 1187, 1170, 928, 790, 740, 708 cm^{-1}.

1-([1,1'-Biphenyl]-4-yl)piperidine, Compound 45.[125]



Prepared according to the general procedure B using 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (56 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as a colourless oil (35 mg, 0.15 mmol, 74%).

Appearance: White solid.

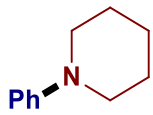
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55-1.64 (m, 2H), 1.67-1.76 (m, 4H), 3.20 (t, *J* = 5.1 Hz, 4H), 6.98 (d, *J* = 8.8 Hz, 1H), 7.23-7.28 (m, 1 H), 7.35-7.41 (m, 2H), 7.49 (d, *J* = 8.8 Hz, 1H) 7.53-7.57 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 24.4, 25.8, 50.4, 116.4, 126.3, 126.5, 127.6, 128.7, 131.6, 141.1, 151.4.

LCMS (ESI): t_R = 0.89 min, $[M+H]^+$ 238.3.

υ_{max} (neat): 2934, 2814, 1604, 1525, 1488, 1448, 1384, 1337, 1236, 1125, 917, 820, 760, 718, 691 cm^{-1}.

1-Phenylpiperidine, Compound 46.[126]



Prepared according to the general procedure B using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (41 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36

mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as a colourless oil (23 mg, 0.14 mmol, 71%).

Appearance: Colourless oil.

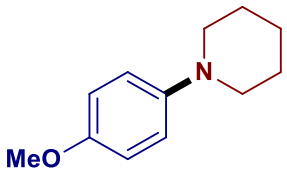
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53-1.61 (m, 2H), 1.66-1.75 (m, 4H), 3.15 (t, *J* = 5.4 Hz, 4H), 6.78-6.84 (m, 1H), 6.93 (dd, *J* = 8.7, 0.9 Hz, 2H), 7.20-7.27 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 24.4, 25.9, 50.7, 116.5, 119.1, 129.0, 152.3.

LCMS (ESI): t_R = 1.29 min, $[M+H]^+$ 162.3.

υ_{max} (neat): 2932, 2853, 2805, 1597, 1493, 1450, 1384, 1334, 1235, 1220, 1131, 1025, 993, 916, 859, 753, 690 cm^{-1}.

1-(4-Methoxyphenyl)piperidine, Compound 47.[127]



Prepared according to the general procedure B using 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (47 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1.5% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as an off-white gum (30 mg, 0.157 mmol, 78%).

Appearance: Off-white gum.

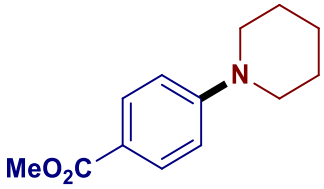
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50-1.58 (m, 2H), 1.67-1.75 (m, 4H), 3.02 (t, *J* = 5.4 Hz, 4H), 3.76 (s, 3H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 24.2, 26.2, 52.3, 55.6, 114.4, 118.7, 147.0, 153.6.

LCMS (ESI): t_R = 1.21 min, $[M+H]^+$ 121.3.

υ_{max} (neat): 2934, 2802, 1510, 1453, 1243, 1182, 1121, 1041, 920, 823 cm^{-1}.

Methyl 4-(piperidin-1-yl)benzoate 48.[128]



Prepared according to the general procedure B using methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (52 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1.5% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as a white solid (32 mg, 0.146 mmol, 73%).

Appearance: White solid.

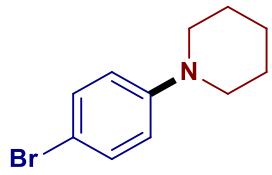
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59-1.72 (m, 6H), 3.32 (t, *J* = 4.6 Hz, 4H), 3.85 (s, 3H), 6.84 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 24.4, 25.4, 48.8, 51.5, 113.6, 118.7, 131.2, 154.5, 167.2.

LCMS (ESI): t_R = 1.28 min, $[M+H]^+$ 220.3.

υ_{max} (neat): 2847, 2843, 1704, 1606, 1516, 1436, 1287, 1247, 1191, 1110, 964, 916, 827, 771, 694 cm^{-1}.

1-(4-Bromophenyl)piperidine, Compound 49.[129]



Prepared according to the general procedure B using 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (57 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as a white solid (41 mg, 0.171 mmol, 85%).

Appearance: White solid.

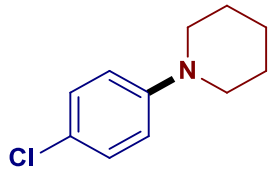
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54-1.61 (m, 2H), 1.64-1.73 (m, 4H), 3.12 (t, *J* = 5.4 Hz, 4H), 6.79 (d, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 9.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 24.2, 25.7, 50.4, 111.1, 118.0, 131.7, 151.2.

LCMS (ESI): t_R = 1.46 min, $[M+H]^+$ 240.2.

υ_{max} (neat): 2941, 2858, 2817, 1588, 1494, 1450, 1387, 1340, 1280, 1243, 1223, 1127, 992, 917, 860, 808 cm^{-1}.

1-(4-Chlorophenyl)piperidine, Compound 50.[130]



Prepared according to the general procedure B using 2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (47 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å

molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1.5% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as a white solid (33 mg, 0.169 mmol, 84%).

Appearance: White solid.

M.pt.: 67-69 °C.

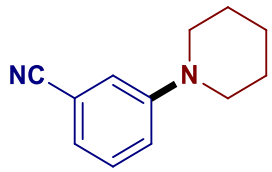
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51-1.61 (m, 2H), 1.65-1.74 (m, 4H), 3.11 (t, *J* = 5.4 Hz, 4H), 6.81-6.87 (m, 2H), 7.15-7.20 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 24.2, 25.7, 50.6, 117.6, 123.9, 128.8, 150.8.

LCMS (ESI): t_R = 1.43 min, $[M+H]^+$ 196.3.

υ_{max} (neat): 2940, 2810, 1596, 1492, 1441, 1383, 1338, 1242, 1223, 1127, 993, 916, 858, 808, 747 cm^{-1}.

1-(3-Cyanophenyl)piperidine, Compound 51.[26]



Prepared according to the general procedure B using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (46 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-2.5% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as an off-white gum (24 mg, 0.129 mmol, 64%).

Appearance: Off-white gum.

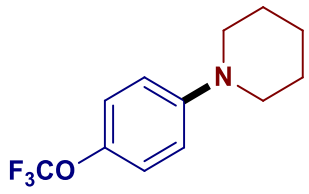
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58-1.74 (m, 6H), 3.19 (t, *J* = 5.4 Hz, 4H), 7.03 (d, *J* = 7.3 Hz, 1H), 7.07-7.12 (m, 2H), 7.25-7.31 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 24.1, 25.4, 49.7, 112.9, 118.6, 119.5, 120.1, 121.7, 129.7, 151.9.

LCMS (ESI): t_R = 1.25 min, $[M+H]^+$ 187.3.

υ_{max} (neat): 2937, 2861, 2216, 1595, 1572, 1493, 1438, 1383, 1247, 1123, 996, 955, 784, 688 cm^{-1}.

1-(4-(Trifluoromethoxy)phenyl)piperidine, Compound 52.



Prepared according to the general procedure B using 4,4,5,5-tetramethyl-2-(4-(trifluoromethoxy)phenyl)-1,3,2-dioxaborolane (58 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 2% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as a colourless oil (35 mg, 0.143 mmol, 71%).

Appearance: Colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52-1.62 (m, 2H), 1.65-1.74 (m, 4H), 3.13 (t, *J* = 5.4 Hz, 4H), 6.88 (d, *J* = 9.0 Hz, 2H), 7.08 (dd, *J* = 9.2, 0.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 24.2, 25.8, 50.7, 116.9, 120.7 (q, J_{C-F} = 255.3 Hz), 121.8, 141.6 (q, J_{C-F} = 2.0 Hz), 151.0.

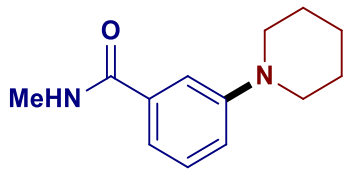
^{19}F NMR (376 MHz, $CDCl_3$): δ -58.32 (s).

LCMS (ESI): t_R = 1.48 min, $[M+H]^+$ 246.3.

HRMS (ESI): ($C_{12}H_{14}F_3NO$) $[M+H]^+$ requires 246.1100, found $[M+H]^+$ 246.1101.

υ_{max} (neat): 2938, 1509, 1260, 1232, 1206, 1155, 1131, 1026, 920, 835, 807 cm^{-1}.

***N*-Methyl-3-(piperidin-1-yl)benzamide, Compound 53.**



Prepared according to the general procedure B using *N*-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (52 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-35% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated *in vacuo*. The product was further purified by ion exchange chromatography (1 g Biotage sulphonic acid (SCX) cartridge, using sequential solvents methanol, 2 M ammonia/methanol). Fractions were evaporated to afford the desired product as an off-white solid (27 mg, 0.124 mmol, 62%).

Appearance: Off-white solid.

M.pt.: 96-98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53-1.62 (m, 2H), 1.64-1.73 (m, 4H), 2.98 (d, *J* = 4.9 Hz, 3H), 3.19 (t, *J* = 5.1 Hz, 4H), 6.27 (br. s., 1H), 7.02 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 7.05-7.10 (m, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.35-7.39 (m, 1H).

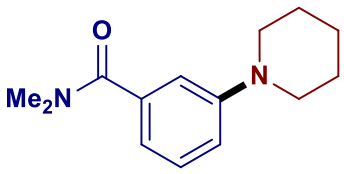
^{13}C NMR (101 MHz, $CDCl_3$): δ 24.2, 25.7, 26.8, 50.3, 114.9, 116.5, 119.0, 129.0, 135.6, 152.3, 168.8.

LCMS (ESI): t_R = 0.91 min, $[M+H]^+$ 219.3.

HRMS (ESI): ($C_{13}H_{18}N_2O$) $[M+H]^+$ requires 219.1492, found $[M+H]^+$ 219.1492.

υ_{max} (neat): 3315, 2934, 2854, 2806, 1636, 1598, 1576, 1543, 1489, 1443, 1365, 1343, 1239, 1127, 940, 755, 693 cm^{-1}.

***N,N*-Dimethyl-3-(piperidin-1-yl)benzamide, Compound 54.**



Prepared according to the general procedure B using *N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (55 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-30% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated *in vacuo*. The product was further purified by ion exchange chromatography (1 g Biotage sulphonic acid (SCX) cartridge, using sequential solvents methanol, 2 M ammonia/methanol). Fractions were evaporated to afford the desired product as an off-white gum (38 mg, 0.164 mmol, 82%).

Appearance: Off-white gum.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51-1.63 (m, 2H), 1.65-1.74 (m, 4H), 2.97 (br. s., 3H), 3.09 (br. s., 3H), 3.17 (t, *J* = 5.6 Hz, 4H), 6.79 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.91-6.97 (m, 2H), 7.20-7.25 (m, 1H).

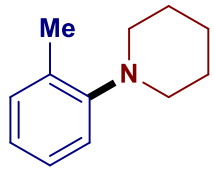
^{13}C NMR (101 MHz, $CDCl_3$): δ 24.3, 25.7, 35.2, 39.5, 50.3, 114.7, 117.2, 117.2, 128.9, 137.2, 152.1, 172.2.

LCMS (ESI): t_R = 1.00 min, $[M+H]^+$ 233.4.

HRMS (ESI): ($C_{14}H_{20}N_2O$) $[M+H]^+$ requires 233.1648, found $[M+H]^+$ 233.1648.

υ_{max} (neat): 2932, 2854, 1635, 1599, 1575, 1485, 1444, 1389, 1267, 1244, 1096, 994, 911, 749 cm^{-1}.

1-(o-Tolyl)piperidine, Compound 55.[131]



Prepared according to the general procedure B using 4,4,5,5-tetramethyl-2-(o-tolyl)-1,3,2-dioxaborolane (44 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-0.5% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as an off-white gum (14 mg, 0.080 mmol, 40%).

Appearance: Off-white gum.

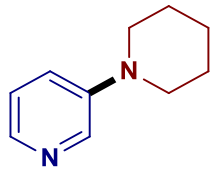
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54-1.60 (m, 2H), 1.66-1.74 (m, 4H), 2.30 (s, 3H), 2.83 (t, *J* = 4.9 Hz, 4H), 6.94 (ddd, *J* = 7.3, 1.0 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 7.11-7.18 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 17.8, 24.5, 26.6, 53.4, 119.0, 122.6, 126.4, 130.9, 132.7, 153.0.

LCMS (ESI): t_R = 1.52 min, $[M+H]^+$ 176.3.

υ_{max} (neat): 2933, 2852, 2801, 1599, 1491, 1451, 1442, 1379, 1326, 1227, 1124, 1106, 1028, 923, 759, 723 cm^{-1}.

3-(Piperidin-1-yl)pyridine, Compound 56.[132]



Prepared according to the general procedure B using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (41 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-20% 3:1 EtOAc:EtOH/cyclohexane), fractions were evaporated *in vacuo*. The product was further purified by ion exchange chromatography (500 mg Biotage sulphonic acid (SCX) cartridge, using sequential solvents methanol, 2 M ammonia/methanol). Fractions were evaporated to afford the desired product as a brown gum (7 mg, 0.043 mmol, 22%).

Appearance: Brown gum.

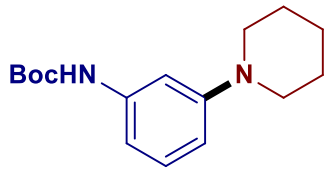
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55-1.65 (m, 2H), 1.67-1.76 (m, 4H), 3.19 (t, *J* = 5.4 Hz, 4H), 7.13 (ddd, *J* = 8.6, 4.6, 0.7 Hz, 1H), 7.18 (ddd, *J* = 8.3, 2.7, 1.5 Hz, 1H), 8.05 (dd, *J* = 4.5, 1.3 Hz, 1H), 8.31 (d, *J* =2.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 24.1, 25.6, 49.9, 122.6, 123.3, 139.0, 140.0, 147.7.

LCMS (ESI): t_R = 0.94 min, $[M+H]^+$ 163.3.

υ_{max} (neat): 2935, 2854, 2810, 1582, 1488, 1451, 1424, 1384, 1346, 1245, 1131, 919, 859, 797, 707 cm^{-1}.

***tert*-Butyl (3-(piperidin-1-yl)phenyl)carbamate, Compound 57.**



Prepared according to the general procedure B using *tert*-butyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (64 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-5% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as a white solid (42 mg, 0.152 mmol, 76%).

Appearance: White solid.

M.pt.: 94-95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (s, 9 H), 1.53-1.60 (m, 2H), 1.68 (dt, *J* = 11.2, 5.6 Hz, 4H), 3.14 (t, *J* = 5.6 Hz, 4H), 6.44 (br. s., 1H), 6.60 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.68 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.08 (br. s., 1H), 7.09-7.14 (m, 1H).

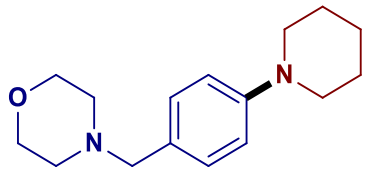
^{13}C NMR (101 MHz, $CDCl_3$): δ 24.4, 25.8, 28.4, 50.5, 80.2, 106.6, 109.3, 111.3, 129.3, 139.2, 152.7, 153.0.

LCMS (ESI): t_R = 1.36 min, $[M+H]^+$ 277.3.

HRMS (ESI): ($C_{16}H_{24}N_2O_2$) $[M+H]^+$ requires 277.1911, found $[M+H]^+$ 277.1914.

υ_{max} (neat): 3328, 2933, 1698, 1607, 1532, 1497, 1443, 1366, 1236, 1155, 1053, 1026, 979, 954, 901, 861, 768, 692 cm^{-1}.

4-(4-(Piperidin-1-yl)benzyl)morpholine, Compound 58.



Prepared according to the general procedure B using 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine (61 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-45% (EtOAc + 2% Et_3N)/cyclohexane), fractions were evaporated *in vacuo*. The product was further purified by ion exchange chromatography (500 mg Biotage sulphonic acid (SCX) cartridge, using sequential solvents methanol, 2 M ammonia/methanol). Fractions were evaporated to afford the desired product as a colourless oil (38 mg, 0.146 mmol, 73%).

Appearance: Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53-1.61 (m, 2H), 1.66-1.75 (m, 4H), 2.42 (t, *J* = 4.6 Hz, 4H), 3.14 (t, *J* = 5.1 Hz, 4H), 3.41 (s, 2H), 3.69 (t, *J* = 4.9 Hz, 4H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H).

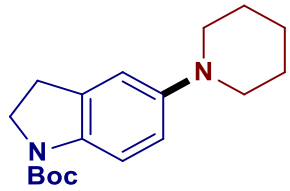
^{13}C NMR (101 MHz, $CDCl_3$): δ 24.3, 25.9, 50.7, 53.6, 63.0, 67.1, 116.2, 128.0, 130.0, 151.4.

LCMS (ESI): t_R = 1.17 min, $[M+H]^+$ 261.4.

HRMS (ESI): ($C_{16}H_{24}N_2O$) $[M+H]^+$ requires 261.1961, found $[M+H]^+$ 261.1961.

υ_{max} (neat): 2932, 2853, 2804, 1613, 1515, 1453, 1237, 1118, 1006, 915, 866 cm^{-1}.

***tert*-Butyl 5-(piperidin-1-yl)indoline-1-carboxylate, Compound 59.**



Prepared according to the general procedure B using *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1-carboxylate (69 mg, 0.20 mmol), piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-7% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as an off-white solid (39 mg, 0.129 mmol, 65%).

Appearance: Off-white solid.

M.pt.: 88-91 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51-1.56 (m, 2H), 1.55 (s, 9H), 1.66-1.76 (m, 4H), 2.98-3.08 (m, 6H), 3.94 (br. s., 2H), 6.75 (d, *J* = 8.6 Hz, 1H), 6.80 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 0.5H), 7.74 (d, *J* = 8.2 Hz, 0.5H).

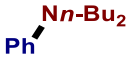
^{13}C NMR (126 MHz, $CDCl_3$): δ 24.2, 26.0, 27.3, 27.8, 28.5, 47.5, 47.7, 52.2, 52.3, 80.0, 81.1, 114.7, 114.8, 114.9, 116.0, 116.4, 131.7, 132.7, 135.3, 136.4, 148.3, 152.5, 152.8.

LCMS (ESI): t_R = 1.50 min, $[M+H]^+$ 303.3.

HRMS (ESI): ($C_{18}H_{26}N_2O_2$) $[M+H]^+$ requires 303.2037, found $[M+H]^+$ 303.2069.

υ_{max} (neat): 2932, 2855, 2793, 1692, 1494, 1453, 1380, 1366, 1331, 1244, 1174, 1140, 1127, 1018, 950, 862, 813, 762 cm^{-1}.

***N*,*N*-Dibutylaniline, Compound 60.**[133]



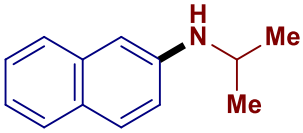
Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), dibutylamine (52 mg, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as a colourless oil (4 mg, 0.02 mmol, 10%).

Appearance: Brown oil (4 mg, 10% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.3 Hz, 6H), 1.35-1.39 (m, 4H), 1.54-1.62 (m, 4H), 3.25-3.29 (m, 4H), 6.61-6.67 (m, 3H), 7.18-7.22 (m, 2H).

LCMS (ESI): t_R = 1.64 min, $[M+H]^+$ 206.4.

***N*-Isopropylnaphthalen-2-amine, Compound 61.**[134]



Prepared according to the general procedure B using 4,4,5,5-tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane (51 mg, 0.20 mmol), isopropylamine (34 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated *in vacuo*. The product was further purified by ion exchange chromatography (1 g Biotage sulphonic acid (SCX) cartridge, using sequential solvents methanol, 2M

ammonia/methanol). Fractions were evaporated to afford the desired product as an off-white oil (27 mg, 0.146 mmol, 73%).

Appearance: Brown oil.

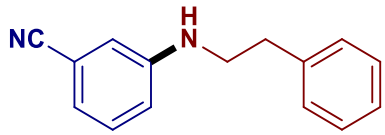
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (d, *J* = 6.3 Hz, 6H), 3.58 (br. s., 1H), 3.75 (sept, *J* = 6.3 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.16 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.33 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 22.9, 44.3, 105.0, 118.3, 121.8, 125.8, 126.2, 127.3, 127.6, 128.9, 135.3, 145.1.

LCMS (ESI): t_R = 1.31 min, $[M+H]^+$ 186.3.

υ_{max} (neat): 3403, 2966, 1627, 1603, 1522, 1485, 1398, 1361, 1225, 1191, 828, 807, 744 cm^1.

3-(Phenethylamino)benzonitrile, Compound 62.



Prepared according to the general procedure B using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (46 mg, 0.20 mmol), 2-phenylethanamine (50 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as an off-white solid (25 mg, 0.112 mmol, 56%).

Appearance: Off-white solid.

M.pt.: 61-63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 (t, *J* = 7.0 Hz, 2H), 3.35-3.45 (m, 2H), 3.88 (br. s., 1H), 6.73-6.81 (m, 2H), 6.95 (dt, *J* = 7.5, 1.1 Hz, 1H), 7.17-7.28 (m, 4H), 7.30-7.36 (m, 2H).

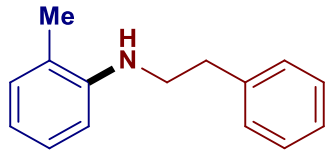
^{13}C NMR (101 MHz, $CDCl_3$): δ 35.2, 44.6, 113.0, 115.0, 117.3, 119.4, 120.8, 126.7, 128.7, 128.8, 129.9, 138.6, 148.2.

LCMS (ESI): t_R = 1.26 min, $[M+H]^+$ 223.3.

HRMS (ESI): ($C_{15}H_{14}N_2$) $[M+H]^+$ requires 223.1230, found $[M+H]^+$ 223.1231.

υ_{max} (neat): 3392, 3028, 2930, 2857, 2227, 1602, 1583, 1514, 1493, 1428, 1335, 1303, 780, 751, 700, 682 cm^{-1}.

2-Methyl-*N*-phenethylaniline, Compound 63.



Prepared according to the general procedure B using 4,4,5,5-tetramethyl-2-(o-tolyl)-1,3,2-dioxaborolane (44 mg, 0.20 mmol), 2-phenylethanamine (50 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1.5% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as a yellow gum (30 mg, 0.142 mmol, 71%).

Appearance: Yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H), 2.96 (t, *J* = 6.8 Hz, 2H), 3.44 (t, *J* = 6.8 Hz, 2H), 3.51 (br. s., 1H), 6.62-6.70 (m, 2H), 7.03 (d, *J* = 7.1 Hz, 1H), 7.09-7.16 (m, 1H), 7.20-7.27 (m, 3H), 7.28-7.35 (m, 2H).

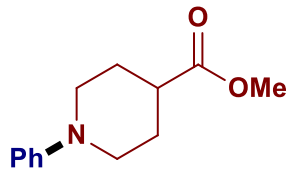
^{13}C NMR (101 MHz, $CDCl_3$): δ 17.3, 35.5, 45.0, 109.9, 117.0, 122.1, 126.4, 127.1, 128.6, 128.8, 130.1, 139.4, 145.9.

LCMS (ESI): t_R = 1.39 min, $[M+H]^+$ 212.3.

HRMS (ESI): ($C_{15}H_{17}N$) $[M+H]^+$ requires 212.1434, found $[M+H]^+$ 212.1435.

υ_{max} (neat): 3419, 3023, 2920, 2853, 1606, 1587, 1514, 1473, 1453, 1317, 1263, 1130, 1052, 746, 700 cm^{-1}.

Methyl 1-phenylpiperidine-4-carboxylate, Compound 64.



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), methyl piperidine-4-carboxylate (57 mg, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as an off-white oil (27 mg, 0.123 mmol, 62%).

Appearance: Light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81-1.93 (m, 2H), 1.97-2.07 (m, 2H), 2.45 (tt, *J* = 11.1, 4.0 Hz, 1H), 2.78 (td, *J* = 11.9, 2.9 Hz, 2H), 3.64 (dt, *J* = 12.7, 3.3 Hz, 2H), 3.70 (s, 3H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 2H), 7.21-7.28 (m, 2H).

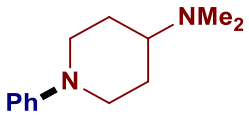
^{13}C NMR (101 MHz, $CDCl_3$): δ 28.1, 41.0, 49.3, 51.7, 116.7, 119.7, 129.1, 151.6, 175.3.

LCMS (ESI): t_R = 1.15 min, $[M+H]^+$ 220.3.

HRMS (ESI): ($C_{13}H_{17}NO_2$) $[M+H]^+$ requires 220.1332, found $[M+H]^+$ 220.1338.

υ_{max} (neat): 2951, 2811, 1733, 1598, 1496, 1448, 1388, 1314, 1251, 1194, 1168, 1043, 922, 757, 694 cm^{-1}.

***N,N*-Dimethyl-1-phenylpiperidin-4-amine, Compound 65.**



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), *N,N*-dimethylpiperidin-4-amine (56 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-7% (2 M NH_3 in MeOH)/DCM), fractions were evaporated to afford the desired product as a yellow solid (28 mg, 0.137 mmol, 69%).

Appearance: Yellow solid.

M.pt.: 45-48 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (qd, *J* = 12.1, 3.9 Hz, 2H), 1.89-1.97 (m, 2H), 2.24-2.31 (m, 1H), 2.32 (s, 6H), 2.71 (td, *J* = 12.3, 2.6 Hz, 2H), 3.68-3.77 (m, 2H), 6.82 (t, *J* = 7.2 Hz, 1H), 6.94 (dd, *J* = 8.7, 0.9 Hz, 2H), 7.20-7.28 (m, 2H).

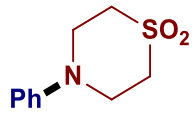
^{13}C NMR (101 MHz, $CDCl_3$): δ 28.3, 41.7, 49.2, 62.2, 116.5, 119.4, 129.0, 151.5.

LCMS (ESI): t_R = 0.97 min, $[M+H]^+$ 205.3.

HRMS (ESI): ($C_{13}H_{20}N_2$) $[M+H]^+$ requires 205.1699, found $[M+H]^+$ 205.1701.

υ_{max} (neat): 2945, 2770, 1600, 1499, 1378, 1220, 1190, 1153, 1065, 1040, 994, 918, 757, 692 cm^{-1}.

4-Phenylthiomorpholine 1,1-dioxide, Compound 66.



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), thiomorpholine 1,1-dioxide (54 mg, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-35% (EtOAc + 1% Et_3N)/cyclohexane). Fractions were evaporated *in vacuo* and the solid was triturated with cyclohexane and dried under vacuum to afford the desired product as a white solid (23 mg, 0.109 mmol, 54%).

Appearance: White solid.

M.pt.: 123-124 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05-3.14 (m, 4H), 3.79-3.88 (m, 4H), 6.86-6.97 (m, 3H), 7.26-7.34 (m, 2H).

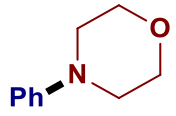
^{13}C NMR (101 MHz, $CDCl_3$): δ 47.7, 50.6, 116.4, 120.9, 129.8, 147.7.

LCMS (ESI): t_R = 0.78 min, $[M+H]^+$ 212.3.

HRMS (ESI): ($C_{10}H_{13}NO_2S$) $[M+H]^+$ requires 212.0740, found $[M+H]^+$ 212.0737.

υ_{max} (neat): 2930, 1598, 1498, 1309, 1384, 1276, 1227, 1176, 1121, 975, 858, 756, 694 cm^{-1}.

4-Phenylmorpholine, Compound 67.[135]



Prepared according to the general procedure B using phenyl boronic acid pinacol ester (41 mg, 0.20 mmol), morpholine (35 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol),

Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1.2% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as a white solid (23 mg, 0.141 mmol, 71%).

Appearance: White solid.

M.pt.: 54-55 °C.

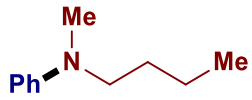
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.16 (t, *J* = 4.9 Hz, 4H), 3.86 (t, *J* = 4.9 Hz, 4H), 6.85-6.94 (m, 3H), 7.26-7.31 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 49.4, 67.0, 115.7, 120.0, 129.2, 151.3.

LCMS (ESI): t_R = 0.92 min, $[M+H]^+$ 164.3.

υ_{max} (neat): 2953, 2844, 1603, 1501, 1453, 1331, 1263, 1239, 1123, 1067, 925, 758, 695 cm^{-1}.

***N*-Butyl-*N*-methylaniline, Compound 68.**[133]



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), *N*-methylbutan-1-amine (47 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/heptane), fractions were evaporated to afford the desired product as an off-white gum (14 mg, 0.086 mmol, 43%).

Appearance: Off-white gum.

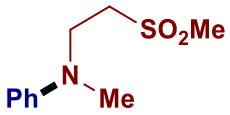
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.3 Hz, 3H), 1.29-1.40 (m, 2H), 1.49-1.60 (m, 2H), 2.91 (s, 3H), 3.30 (t, *J* = 7.3 Hz, 2H), 6.63-6.72 (m, 3H), 7.18-7.26 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 14.0, 20.4, 28.9, 38.3, 52.5, 112.1, 115.8, 129.2, 149.4.

LCMS (ESI): t_R = 1.42 min, $[M+H]^+$ 164.3.

υ_{max} (neat): 2958, 2869, 1600, 1507, 1366, 1207, 746, 691 cm^{-1}.

***N*-Methyl-*N*-(2-(methylsulfonyl)ethyl)aniline, Compound 69.**



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), *N*-methyl-2-(methylsulfonyl)ethanamine (50 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-36% (EtOAc + 1% Et_3N)/heptane), fractions were evaporated *in vacuo*. The product was further purified by ion exchange chromatography (1 g Biotage sulphonic acid (SCX) cartridge, using sequential solvents methanol, 2 M ammonia/methanol). Fractions were evaporated to afford the desired product as a colourless oil (18 mg, 0.084 mmol, 42%).

Appearance: Colourless oil (18 mg, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (s, 3H), 2.98 (s, 3H), 3.25 (t, *J* = 6.8 Hz, 2H), 3.89 (t, *J*=7.0 Hz, 2H), 6.76-6.84 (m, 3H), 7.25-7.31 (m, 2H).

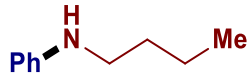
^{13}C NMR (101 MHz, $CDCl_3$): δ 38.8, 42.1, 46.7, 51.4, 113.2, 118.2, 129.6, 148.1.

LCMS (ESI): t_R = 0.82 min, $[M+H]^+$ 214.2.

HRMS (ESI): ($C_{10}H_{15}NO_2S$) $[M+H]^+$ requires 214.0896, found $[M+H]^+$ 214.0899.

υ_{max} (neat): 2927, 1600, 1505, 1362, 1362, 1301, 1134, 955, 752, 695 cm^{-1}.

***N*-Butylaniline, Compound 70.**[136]



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), 1-butylamine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as a colourless oil (21 mg, 0.141 mmol, 70%).

Appearance: Colourless oil.

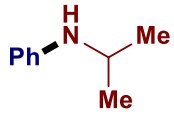
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, *J*=7.3 Hz, 3H), 1.37-1.48 (m, 2H), 1.55-1.64 (m, 2H), 3.10 (t, *J* = 7.1 Hz, 2H), 3.53 (br. s., 1H), 6.59 (d, *J* = 7.8 Hz, 2H), 6.67 (t, *J* = 7.3 Hz, 1H), 7.13-7.20 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 13.9, 20.3, 31.7, 43.7, 112.7, 117.1, 129.2, 148.6.

LCMS (ESI): t_R = 1.26 min, $[M+H]^+$ 150.3.

υ_{max} (neat): 3414, 2958, 2869, 1603, 1506, 1320, 1262, 1179, 747, 692 cm^{-1}.

***N*-Isopropylaniline, Compound 71.**[137]



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), isopropylamine (34 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification

outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as an off-white oil (14 mg, 0.104 mmol, 52%).

Appearance: Yellow oil.

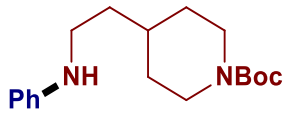
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (d, *J* = 6.4 Hz, 6H), 3.37 (br. s., 1H), 3.62 (sept, *J* = 6.3 Hz, 1H), 6.58 (d, *J* = 7.6 Hz, 2H), 6.66 (t, *J* = 7.3 Hz, 1H), 7.11-7.18 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 23.0, 44.2, 113.3, 117.0, 129.3, 147.5.

LCMS (ESI): t_R = 1.12 min, $[M+H]^+$ 136.2.

υ_{max} (neat): 3397, 2696, 1603, 1506, 1317, 1256, 1179, 748, 693 cm^{-1}.

***tert*-Butyl (2-(phenylamino)ethyl)carbamate, Compound 72.**



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), *tert*-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (91 mg, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-12% (EtOAc + 1% Et_3N)/heptane), fractions were evaporated to afford the desired product as an off-white solid (50 mg, 0.164 mmol, 82%).

Appearance: Off-white solid.

M.pt.: 92-94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06-1.23 (m, 2H), 1.46 (s, 9H), 1.52-1.60 (m, 3H), 1.69 (d, *J* = 13.0 Hz, 2H), 2.69 (t, *J* = 12.2 Hz, 2H), 3.14 (t, *J* = 7.0 Hz, 2H), 3.53 (br. s., 1H), 4.01-4.16 (m, 2H), 6.59 (dd, *J* = 8.6, 1.0 Hz, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 7.17 (dd, *J* = 8.4, 7.5 Hz, 2H).

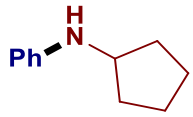
^{13}C NMR (101 MHz, $CDCl_3$): δ 28.5, 32.2, 33.9, 36.3, 41.3, 44.0, 79.3, 112.7, 117.3, 129.3, 148.4, 154.9.

LCMS (ESI): t_R = 1.39 min, $[M+H]^+$ 305.3.

HRMS (ESI): ($C_{18}H_{28}N_2O_2$) $[M+H]^+$ requires 305.2224, found $[M+H]^+$ 305.2231.

υ_{max} (neat): 3375, 2922, 2850, 1675, 1602, 1507, 1423, 1365, 1278, 1244, 1166, 1143, 1090, 968, 866, 747, 693 cm^{-1}.

***N*-Cyclopentylaniline, Compound 73.**[138]



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), cyclopentylamine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as an off-white gum (24 mg, 0.149 mmol, 74%).

Appearance: Off-white gum.

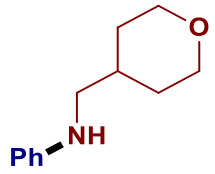
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40-1.53 (m, 2H), 1.55-1.78 (m, 4H), 1.95-2.08 (m, 2H), 3.61 (br. s., 1H), 3.73-3.82 (m, 1H), 6.59 (dd, *J* = 8.6, 1.0 Hz, 2H), 6.66 (t, *J* = 7.3 Hz, 1H), 7.10-7.20 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 24.1, 33.6, 54.7, 113.2, 116.9, 129.2, 148.1.

LCMS (ESI): t_R = 1.27 min, $[M+H]^+$ 162.3.

υ_{max} (neat): 3397, 2955, 2868, 1602,1504, 1429, 1313, 1180, 747, 692 cm^{-1}.

***N*-((Tetrahydro-2*H*-pyran-4-yl)methyl)aniline, Compound 74.**[139]



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), (tetrahydro-2*H*-pyran-4-yl)methanamine (46 mg, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-9% (EtOAc + 1% Et_3N)/heptane), fractions were evaporated to afford the desired product as an off-white oil (33 mg, 0.173 mmol, 86%).

Appearance: Yellow oil.

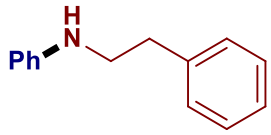
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30-1.43 (m, 2H), 1.66-1.75 (m, 2H), 1.78-1.91 (m, 1H), 3.03 (d, *J* = 6.6 Hz, 2H), 3.39 (td, *J* = 11.8, 2.1 Hz, 2H), 3.71 (br. s., 1H), 3.94-4.03 (m, 2H), 6.60 (dd, *J* = 8.6, 1.0 Hz, 2H), 6.66 - 6.72 (m, 1H), 7.13 - 7.20 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 31.1, 34.9, 50.0, 67.8, 112.7, 117.3, 129.3, 148.3.

LCMS (ESI): t_R = 1.02 min, $[M+H]^+$ 192.3.

υ_{max} (neat): 3372, 2929, 2843, 1603, 1508, 1327, 1264, 1141, 1091, 1014, 984, 853, 749, 693 cm^{-1}.

***N*-Phenethylaniline, Compound 75.**[140]



Prepared according to the general procedure B using phenyl boronic acid pinacol ester (41 mg, 0.20 mmol), 2-phenylethanamine (50 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150

mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1.2% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as an off-white gum (34 mg, 0.172 mmol, 86%).

Appearance: Off-white gum.

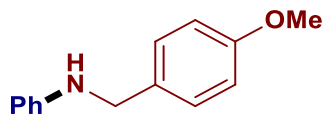
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (t, *J* = 7.0 Hz, 2H), 3.40 (t, *J* = 7.0 Hz, 2H), 3.66 (br. s., 1H), 6.61 (dd, *J* = 8.6, 1.0 Hz, 2H), 6.70 (tt, *J* = 7.3, 1.0 Hz, 1H), 7.14-7.26 (m, 5H), 7.28-7.34 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 35.6, 45.1, 113.0, 117.5, 126.4, 128.6, 128.8, 129.3, 139.3, 148.0.

LCMS (ESI): t_R = 1.31 min, $[M+H]^+$ 198.3.

υ_{max} (neat): 3409, 3025, 2928, 2861, 1602, 1506, 1454, 1319, 1262, 1180, 748, 693 cm^{-1}.

***N*-(4-Methoxybenzyl)aniline, Compound 76.**[140]



Prepared according to the general procedure B using phenyl boronic acid pinacol ester (41 mg, 0.20 mmol), 4-methoxybenzylamine (52 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-2% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as an off-white oil (36 mg, 0.169 mmol, 84%).

Appearance: Yellow oil.

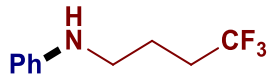
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.92 (br. s., 1H), 4.25 (s, 2H), 6.63 (d, *J* = 7.8 Hz, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 7.14-7.20 (m, 2H), 7.28 (d, *J* = 8.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 47.8, 55.3, 112.9, 114.1, 117.5, 128.8, 129.2, 131.4, 148.2, 158.9.

LCMS (ESI): t_R = 1.22 min, $[M-H]^-$ 212.2.

υ_{max} (neat): 3416, 3011, 2927, 2835, 1603, 1509, 1465, 1431, 1302, 1246, 1177, 1033, 824, 750, 693 cm^{-1}.

***N*-(4,4,4-Trifluorobutyl)aniline, Compound 77.**[139]



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), 4,4,4-trifluorobutan-1-amine (51 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/heptane), fractions were evaporated to afford the desired product as an off-white oil (28 mg, 0.138 mmol, 69%).

Appearance: Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81-1.93 (m, 2H), 2.12-2.28 (m, 2H), 3.21 (t, *J* = 7.0 Hz, 2H), 3.59 (br. s., 1H), 6.60 (dd, *J* = 8.7, 0.9 Hz, 2H), 6.68-6.76 (m, 1H), 7.13-7.22 (m, 2H).

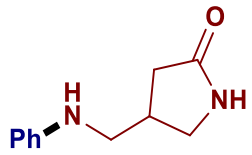
^{13}C NMR (101 MHz, $CDCl_3$): δ 22.2 (q, J_{C-F} = 2.7 Hz), 31.5 (q, J_{C-F} = 28.6 Hz), 42.7, 112.8, 117.8, 127.1 (q, J_{C-F} = 275.8 Hz), 129.4, 147.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.14 (t, *J*=10.4 Hz, 3F).

LCMS (ESI): t_R = 1.21 min, $[M+H]^+$ 204.3.

υ_{max} (neat): 3414, 2948, 1604, 1508, 1391, 1316, 1295, 1250, 1225, 1144, 1028, 750, 693 cm^{-1}.

4-((Phenylamino)methyl)pyrrolidin-2-one, Compound 78.



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), 4-(aminomethyl)pyrrolidin-2-one (45 mg, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 10-100% (EtOAc + 10% EtOH + 1% Et_3N)/cyclohexane). Fractions were evaporated *in vacuo* and the solid was triturated with cyclohexane and dried under vacuum to afford the desired product as an off-white solid (12 mg, 0.063 mmol, 32%).

Appearance: Off-white solid.

M.pt.: 95-98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (dd, *J* = 17.1, 6.1 Hz, 1H), 2.51 (dd, *J* = 16.9, 8.8 Hz, 1H), 2.72-2.85 (m, 1H), 3.15-3.26 (m, 3H), 3.55 (dd, *J* = 9.5, 8.1 Hz, 1H), 3.77 (br. s., 1H), 6.28 (br. s., 1H), 6.61 (d, *J* = 7.8 Hz, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 2H).

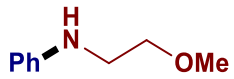
^{13}C NMR (101 MHz, $CDCl_3$): δ 34.3, 34.6, 45.9, 47.7, 112.8, 117.9, 129.4, 147.7, 177.6.

LCMS (ESI): t_R = 0.71 min, $[M+H]^+$ 191.3.

HRMS (ESI): ($C_{11}H_{14}N_2O$) $[M+H]^+$ requires 191.1179, found $[M+H]^+$ 191.1176.

υ_{max} (neat): 3335, 2924, 1682, 1602, 1499, 1321, 1262, 750, 694 cm^{-1}.

***N*-(2-Methoxyethyl)aniline, Compound 79.**[137]



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), 2-methoxyethanamine (35 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-6% (EtOAc + 1% Et_3N)/heptane), fractions were evaporated to afford the desired product as an off-white oil (23 mg, 0.152 mmol, 76%).

Appearance: Yellow oil.

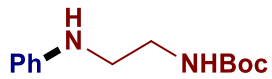
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (t, *J* = 5.3 Hz, 2H), 3.38 (s, 3H), 3.60 (t, *J* = 5.3 Hz, 2H), 4.00 (br. s., 1H), 6.60-6.66 (m, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 7.13-7.20 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 43.5, 58.7, 71.1, 113.1, 117.6, 129.2, 148.2.

LCMS (ESI): t_R = 0.90 min, $[M+H]^+$ 152.3.

υ_{max} (neat): 3401, 2891, 1603, 1507, 1459, 1320, 1277, 1193, 1117, 749, 693 cm^{-1}.

***tert*-Butyl 4-(2-(phenylamino)ethyl)piperidine-1-carboxylate, Compound 80.**



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), *tert*-butyl (2-aminoethyl)carbamate (64 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/heptane), fractions were evaporated to afford the desired product as an off-white solid (33 mg, 0.140 mmol, 70%).

Appearance: Off-white solid (33 mg, 70% yield).

M.pt.: 83-85 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.22-3.29 (m, 2H), 3.32-3.41 (m, 2H), 3.94 (br. s., 1H), 4.77 (br. s., 1H), 6.61 (d, *J* = 8.3 Hz, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 7.13-7.21 (m, 2H).

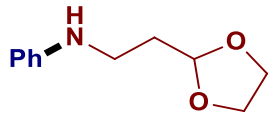
^{13}C NMR (101 MHz, $CDCl_3$): δ 28.4, 40.2, 44.4, 79.6, 112.8, 117.6, 129.3, 148.0, 156.4.

LCMS (ESI): t_R = 1.11 min, $[M+H]^+$ 237.4.

HRMS (ESI): ($C_{13}H_{20}N_2O_2$) $[M+H]^+$ requires 237.1598, found $[M+H]^+$ 237.1602.

υ_{max} (neat): 3380, 2977, 1691, 1604, 1509, 1366, 1253, 1169, 989, 749, 693 cm^{-1}.

***N*-(2-(1,3-Dioxolan-2-yl)ethyl)aniline, Compound 81.**



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), 2-(1,3-dioxolan-2-yl)ethanamine (45 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-6% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated to afford the desired product as an off-white oil (30 mg, 0.155 mmol, 78%).

Appearance: Light brown oil.

M.pt.: 95-98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (dd, *J* = 17.1, 6.1 Hz, 1H), 2.51 (dd, *J* = 16.9, 8.8 Hz, 1H), 2.72-2.85 (m, 1H), 3.15-3.26 (m, 3H), 3.55 (dd, *J* = 9.5, 8.1 Hz, 1H), 3.77 (br. s., 1H), 6.28 (br. s., 1H), 6.61 (d, *J* = 7.8 Hz, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 2H).

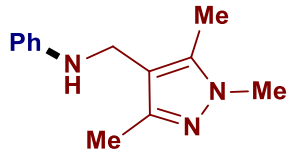
^{13}C NMR (101 MHz, $CDCl_3$): δ 34.3, 34.6, 45.9, 47.7, 112.8, 117.9, 129.4, 147.7, 177.6.

LCMS (ESI): t_R = 0.71 min, $[M+H]^+$ 191.3.

HRMS (ESI): ($C_{11}H_{14}N_2O$) $[M+H]^+$ requires 191.1179, found $[M+H]^+$ 191.1176.

υ_{max} (neat): 3335, 2924, 1682, 1602, 1499, 1321, 1262, 750, 694 cm^{-1}.

***N*-((1,3,5-Trimethyl-1H-pyrazol-4-yl)methyl)aniline, Compound 82.**[137]



Prepared according to the general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), (1,3,5-trimethyl-1*H*-pyrazol-4-yl)methanamine (56 mg, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to the purification outlined in the general procedure (silica chromatography, 0-100% (EtOAc + 1% Et_3N)/cyclohexane), fractions were evaporated *in vacuo*. The product was further purified by ion exchange chromatography (1 g Biotage sulphonic acid (SCX) cartridge, using sequential solvents methanol, 2 M ammonia/methanol). Fractions were evaporated to afford the desired product as a white solid (39 mg, 0.181 mmol, 91%).

Appearance: White solid.

M.pt.: 106-107°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.21 (s, 3H), 3.41 (br. s., 1H), 3.72 (s, 3H), 3.99 (s, 2H), 6.65 (dd, *J* = 8.4, 0.9 Hz, 2H), 6.69-6.75 (m, 1H), 7.16-7.23 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 9.6, 11.7, 35.8, 38.1, 112.7, 113.5, 117.4, 129.3, 137.6, 146.3, 148.4.

LCMS (ESI): t_R = 0.98 min, $[M+H]^+$ 216.3.

υ_{max} **(neat):** 3300, 2925, 2823, 1601, 1511, 1470, 1436, 1384, 1317, 1256, 1177, 1150, 1098, 1069, 990, 870, 750, 697 cm^{-1}.

Unsuccessful compounds.

Aryl boronic pinacol esters **76**, **77**, **78**, **79**, **80** and **81** were tested following general procedure B using piperidine (40 µL, 0.40 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to LCMS analysis. No corresponding desired product was observed.

Amines **82**, **83**, **84**, **85**, **86** and **87** were tested following general procedure B using phenylboronic acid pinacol ester (41 mg, 0.20 mmol), $Cu(OAc)_2$ (36 mg, 0.20 mmol), Et_3N (56 µL, 0.40 mmol) and powdered activated 3 Å molecular sieves (150 mg) in MeCN (400 µL). After 24 hr, the reaction mixture was subjected to LCMS analysis. No desired product was observed for amines **82**, **83** and **84**. Cyclisation of amine **85** to the corresponding lactam was observed (Method A, t = 0.43 min, $[M+H]^+$ = 72.1, 63%) and only trace amount of desired product was observed (Method A, t = 1.08 min, $[M+H]^+$ = 180.2,.< 5%). Amide **86** afforded the desired product in really low yield (Method A, t = 1.16 min, $[M+H]^+$ = 198.3,.< 10%). Similarly, sulfonamide **87** afforded low conversion to the desired product (Method A, t = 1.18 min, $[M+H]^+$ = 234.1,.< 20%).

15. Chapter 2

15.1. General experimental procedures.

15.1.1. General Procedure A for the Chan–Lam amination of boronic acid using Et_3N.

Aryl boronic acid (2 equiv, 0.40 mmol, 0.25 M), amine (1 equiv, 0.20 mmol), $Cu(OAc)_2$ (1 equiv, 0.20 mmol, 36 mg), Et_3N (2 equiv, 0.40 mmol, 41 mg, 56 µL), and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt for 16 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give a residue that was purified by silica chromatography (EtOAc/cyclohexane with 1% Et_3N modifier). Appropriate fractions were concentrated under vacuum to afford the desired product.

15.1.2. General Procedure B for the Chan–Lam amination of boronic acid pinacol (BPin) esters using Et_3N.

Aryl BPin (2 equiv, 0.40 mmol, 0.25 M), amine (1 equiv, 0.20 mmol), $Cu(OAc)_2$ (1 equiv, 0.20 mmol, 36 mg), Et_3N (2 equiv, 0.40 mmol, 41 mg, 56 µL), and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt for 16 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give a residue that was purified by silica chromatography (EtOAc/cyclohexane with 1% Et_3N modifier). Appropriate fractions were concentrated under vacuum to afford the desired product.

15.1.3. General Procedure C for the Chan–Lam amination of boronic acid using $B(OH)_3$.

Aryl boronic acid (1 equiv, 0.20 mmol), amine (2 equiv, 0.40 mmol, 0.25 M), $Cu(OAc)_2$ (1 equiv, 0.20 mmol, 36 mg), $B(OH)_3$ (2 equiv, 0.40 mmol, 24 mg), and powdered

activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt for 16 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give a residue that was purified by silica chromatography (EtOAc/cyclohexane with 1% Et_3N modifier). Appropriate fractions were concentrated under vacuum to afford the desired product.

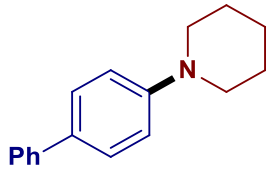
15.1.4. General Procedure D for the Chan–Lam amination of boronic acid pinacol (BPin) esters using $B(OH)_3$.

Aryl BPin (1 equiv, 0.30 mmol, 0.66 M), alkyl amine (2 equiv, 0.60 mmol), $Cu(OAc)_2$ (0.2 equiv, 0.06 mmol, 11 mg), $B(OH)_3$ (2 equiv, 0.60 mmol, 36 mg), and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL) were sealed in an oven dried 5 mL microwave vial under O_2 atmosphere and stirred at 80 °C (preheated sand bath, sand temperature) for 24 h. The reaction mixture was allowed to cool down to room temperature, filtered through Celite, and the filtrate was concentrated under vacuum to give a residue that was purified by silica chromatography (EtOAc/cyclohexane with 1% Et_3N modifier). Appropriate fractions were concentrated under vacuum to afford the desired product.

15.2. Results

15.2.1. Identification of products and by-products

1-([1,1'-Biphenyl]-4-yl)piperidine, Compound 45.



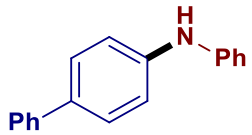
Prepared according to General Procedure A using [1,1'-biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), piperidine (20 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv) and powdered activated 4 Å

molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M). After 24 hr, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (41 mg, 87%).

Prepared according to General Procedure B using 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (112 mg, 0.40 mmol, 2 equiv), piperidine (20 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M). After 24 hr, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (13 mg, 28%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

_N_-Phenyl-[1,1'-biphenyl]-4-amine, Compound 18.

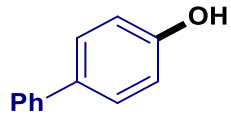


Prepared according to General Procedure A using [1,1'-biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), aniline (18 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M). After 24 hr, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (45 mg, 92%).

Prepared according to General Procedure B using 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (112 mg, 0.40 mmol, 2 equiv), aniline (18 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M). After 24 hr, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (8 mg, 16%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

[1,1'-Biphenyl]-4-ol, Compound 19.[141]



Prepared according to General Procedure A using [1,1'-biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), piperidine (20 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M). After 24 hr, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (2 mg, 6%).

Appearance: White solid.

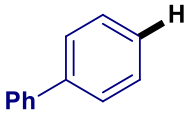
M.pt.: 164-165°C.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 6.84-6.87 (m, 2H), 7.25-7.29 (m, 1H), 7.38-7.42 (m, 2H), 7.46-7.50 (m, 2H), 7.55-7.58 (m, 2H), 9.51 (s, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 115.7, 125.9, 126.3, 127.7, 128.7, 130.9, 140.2.

LCMS (ESI): t_R = 0.89 min.

1,1'-Biphenyl, Compound 20.[142]



Prepared according to General Procedure A using [1,1'-biphenyl]-4-ylboronic acid (40 mg, 0.40 mmol, 2 equiv), piperidine (20 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol,2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M). After 24 hr, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (21 mg, 68%).

Appearance: White solid.

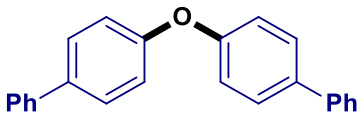
M.pt.: 69-71°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.39 (m, 2H), 7.45-7.49 (m, 4H), 7.62-7.64 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 127.1, 127.2, 128.7, 141.2.

LCMS (ESI): t_R = 1.31 min.

4,4''-Oxydi-1,1'-biphenyl, Compound 21.[143]



Prepared according to General Procedure A using [1,1'-biphenyl]-4-ylboronic acid (40 mg, 0.40 mmol, 2 equiv), piperidine (20 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M). After 24 hr, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (10 mg, 16%).

Appearance: White solid.

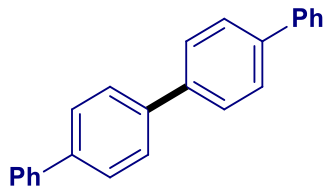
M.pt.: 191-194°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.16 (m, 4H), 7.33-7.37 (m, 2H), 7.43-7.47 (m, 4H), 7.58-7.81 (m, 8H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 119.2, 126.9, 127.1, 128.5, 128.8, 136.5, 140.5, 156.8.

LCMS (ESI): t_R = 1.67 min.

1,1':4',1'':4'',1'''-Quaterphenyl, Compound 147.[144]



To a flame dried 5 mL microwave vial were added [1,1'-biphenyl]-4-ylboronic acid (40 mg, 0.40 mmol, 2 equiv), distilled piperidine (20 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), distilled Et_3N (56 µL, 0.40 mmol,2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M). After 24 hr at rt, the reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give a residue that was purified by silica chromatography (0-10% (EtOAc + 1% Et_3N)/cyclohexane). Appropriate fractions were concentrated under vacuum to afford the desired product as a white solid (2 mg, 0.01 mmol, 6%).

Appearance: White solid.

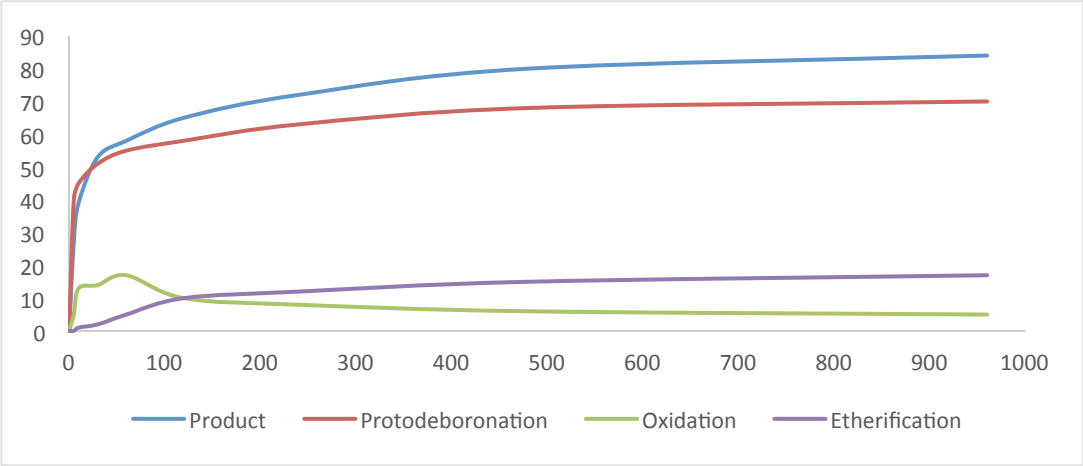
M.pt.: 318-320°C.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.36-7.40 (m, 2H), 7.43-7.49 (m, 8H), 7.55-7.59 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 121.5, 126.9, 127.6, 128.7, 128.9, 131.9, 140.0, 140.1.

LCMS (ESI): t_R = 1.67 min.

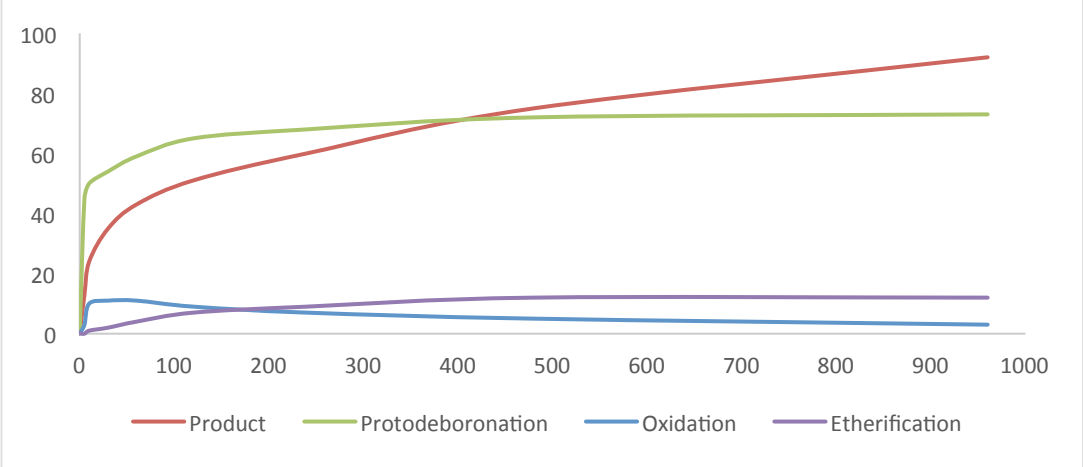
15.2.2. Reaction profile of the Chan-Lam amination of 146 with piperidine 145.



[1,1'-Biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), piperidine (20 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt. The reaction profile was monitored by aliquoting the reaction mixture over time intervals of 5, 10, 15, 30, 60, 120, 180, 240, 360, 480, and 960 minutes. The aliquots were analysed by HPLC against an internal standard.

Time (min)	45 (%)	19 (%)	20 (%)	21 (%)
0	0	0	0	0
5	5	40	27	0
10	13	45	39	1
30	14	51	53	2
60	17	55	58	5
120	10	58	65	10
240	8	63	72	12
480	6	68	80	15
960	5	70	84	17

15.2.3. Reaction profile of the Chan-Lam amination of 146 with aniline 16.



[1,1'-Biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), aniline (14 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt. The reaction profile was monitored by aliquoting the reaction mixture over time intervals of 5, 10, 15, 30, 60, 120, 180, 240, 360, 480, and 960 minutes. The aliquots were analysed by HPLC against an internal standard.

Time (min)	18 (%)	19 (%)	20 (%)	21 (%)
0	0	0	0	0
5	3	45	13	0
10	10	50	24	1
30	11	54	35	2
60	11	59	43	4
120	9	65	51	7
240	7	68	60	9
480	5	72	75	12
960	3	73	92	12

15.2.4. Assessment of Inhibitors

15.2.4.1. Effect of AcOH using piperidine 145.

[1,1'-Biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), piperidine (20 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv), AcOH (x equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt. After 16 h, an aliquot of the reaction mixture was analysed by HPLC against an internal standard.

Experiment number	Equivalents of AcOH	HPLC yield
1	0	87%
2	1	66%
3	2	48%

15.2.4.1. Effect of AcOH using aniline 16.

[1,1'-Biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), aniline (18 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv), AcOH (x equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt. After 16 h, an aliquot of the reaction mixture was analysed by HPLC against an internal standard.

Experiment number	Equivalents of AcOH	HPLC yield
1	0	92%
2	1	58%
3	2	34%

15.2.4.3. Effect of AcOK using piperidine 145.

[1,1'-Biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), piperidine (20 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv), AcOK (x equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM

(0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt. After 16 h, an aliquot of the reaction mixture was analysed by HPLC against an internal standard.

Experiment number	Equivalents of AcOK	HPLC yield
1	0	87%
2	1	92%
3	2	100%

15.4.2.4. Effect of AcOK using aniline 16.

[1,1'-Biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), aniline (18 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv), AcOK (x equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt. After 16 h, an aliquot of the reaction mixture was analysed by HPLC against an internal standard.

Experiment number	Equivalents of AcOK	HPLC yield
1	0	92%
2	1	63%
3	2	40%

15.4.2.5. Effect of pinacol using piperidine 145.

[1,1'-Biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), piperidine (20 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv), pinacol (x equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt. After 16 h, an aliquot of the reaction mixture was analysed by HPLC against an internal standard.

Experiment number	Equivalents of pinacol	HPLC yield
1	0	87%
2	0.1	85%
3	0.25	82%

4	0.5	75%
5	0.75	72%
6	1	67%

15.2.4.6. Effect of pinacol using aniline 16.

[1,1'-Biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), aniline (18 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv), pinacol (x equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt. After 16 h, an aliquot of the reaction mixture was analysed by HPLC against an internal standard.

Experiment number	Equivalents of pinacol	HPLC yield
1	0	92%
2	0.1	76%
3	0.25	64%
4	0.5	50%
5	0.75	29%
6	1	9%

15.2.5. Identification and analysis of Cu(II) complexes.

15.2.5.1. EPR spectrum of $[Cu(OAc)_2]$.

X-band EPR spectrum of $[Cu(OAc)_2]$ recorded in MeCN/MeOH solution at 150 K (experimental conditions: frequency, 9.4278 GHz; power, 2.0 mW; modulation, 0.8 mT). Experimental data are represented by the black line; simulation is depicted by the red trace which is composed of two subspectra. Asterisk denotes mathematical artifact from the simulation.

Subspectrum 1 (93%): g = (2.46, 2.12, 2.12)

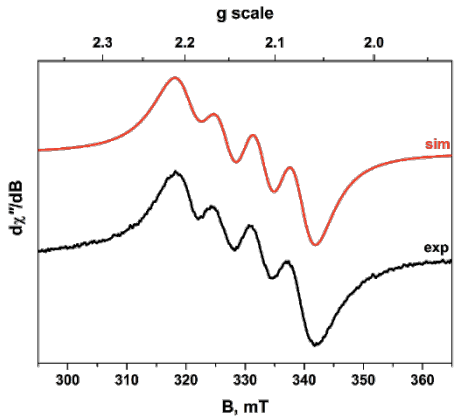
D = 0.357 cm^{-1}

E/D = 0

Subspectrum 2 (7%): g = (2.359, 2.089, 2.053)

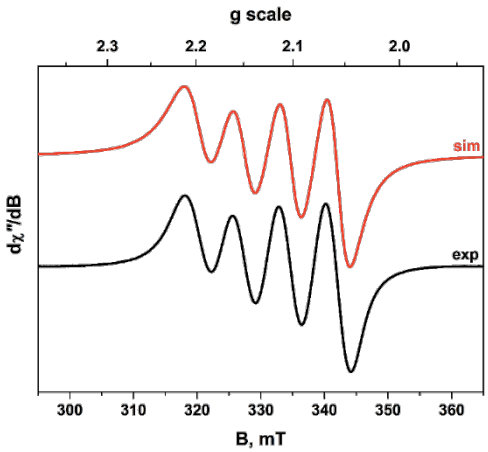
$A\{^{63,65}Cu\} = (143, 8, 0) \times 10^{-4}$ cm^{-1}

15.2.5.2. EPR spectrum of [Cu(OAc)$_2$] with aniline 16.



X-band EPR spectrum of [Cu(OAc)$_2$] with 2 equiv. **4** in MeCN solution at 293 K (experimental conditions: frequency, 9.8475 GHz; power, 6.3 mW; modulation, 0.8 mT). Experimental data are represented by the black line; simulation is depicted by the red trace: g_{iso} = 2.131, $A_{iso}\{^{63,65}Cu\}$ = 61 × 10^{-4} cm^{-1}.

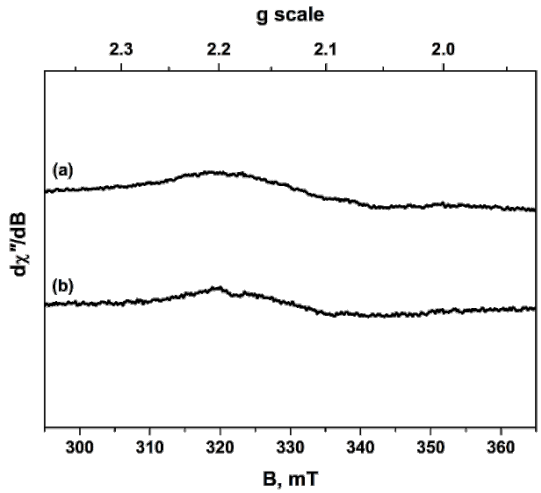
15.2.5.3. EPR spectrum of [Cu(OAc)$_2$] with piperidine 145.



X-band EPR spectrum of [Cu(OAc)$_2$] with 2 equiv. **2** in MeCN solution at 293 K (experimental conditions: frequency, 9.8483 GHz; power, 6.3 mW; modulation, 0.8 mT).

Experimental data are represented by the black line; simulation is depicted by the red trace: g_{iso} = 2.124, $A_{iso}\{^{63,65}Cu\}$ = 70.5 × 10^{-4} cm^{-1}.

15.2.5.4. EPR spectrum of [Cu(OAc)$_2$] with aryl BPin 17.



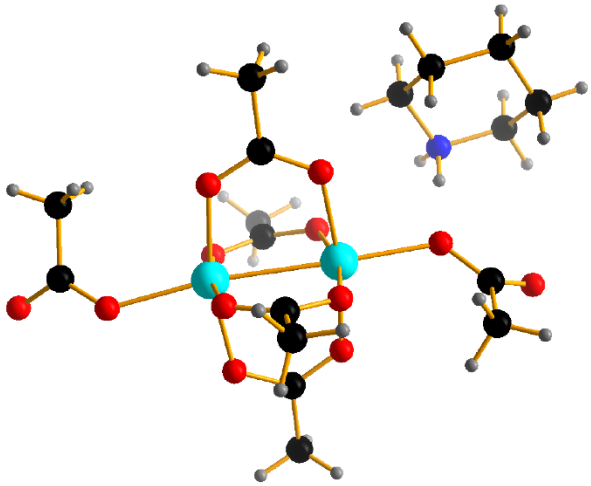
Comparison of the X-band EPR spectra of (a) $Cu(OAc)_2$ (experimental conditions: frequency, 9.8483 GHz; power, 6.3 mW; modulation, 0.8 mT), and (b) $Cu(OAc)_2$ with 1 equiv. **10** (experimental conditions: frequency, 9.8492 GHz; power, 6.3 mW; modulation, 0.8 mT) in MeCN solution at 293 K.

15.2.5.5. Structural characterisation of Cu(II) complexes.

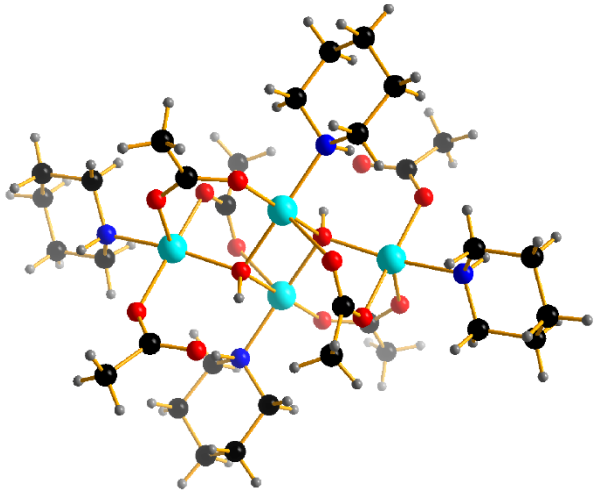
compound	$[C_5H_{12}N]_2[Cu_2(OAc)_6]$	$[Cu_4(\mu^3$-
solvent	none	CH_3CN
formula	$C_{22}H_{42}N_2O_{12}Cu_2$	$C_{32}H_{58}N_6O_{14}Cu_4$
fw	653.66	1065.14
***T*, K**	150	150
***λ*, Å**	0.71073	0.71073
2θ range, deg	4.62 – 46.11	7.67 – 58.27
crystal system	monoclinic	monoclinic
space group	*I*2/*a*	$P2_1/n$
***a*, Å**	16.850(10)	10.5862(4)
***b*, Å**	9.878(8)	15.0155(6)
***c*, Å**	18.290(11)	15.7337(6)

α, deg	90	90
β, deg	105.79(6)	109.653(5)
γ, deg	90	90
V, Å^3	2929(3)	2355.3(2)
Z	4	2
ρ, g cm^{-3}	1.482	1.502
μ, mm^{-1}	1.511	1.847
crystal size	0.05 × 0.05 × 0.05	0.22 × 0.28 × 0.32
color, habit	green block	blue prism
limiting indices, h	-21 < h < 21	-13 < h < 14
limiting indices, k	-12 < k < 12	-14 < k < 20
limiting indices, l	-22 < l < 22	-19 < l < 20
reflections collected	13606	11497
independent data	3008	5377
restraints	0	0
parameters refined	175	275
GoF[a]	1.036	1.043
R1,[b,c] wR2[d,c]	0.0483, 0.1045	0.0342, 0.0724
R1,[b,e] wR2[d,e]	0.0831, 0.1226	0.0474, 0.0790
largest diff. peak, e	0.567	0.430
largest diff. hole, e	-0.650	-0.507

[a] GoF = $\{\Sigma[w(F_o^2 - F_c^2)^2]/(n - p)\}^{1/2}$, where n = number of reflections and p is the total number of parameters refined. [b] R1 = $\Sigma||F_o| - |F_c||/\Sigma|F_o|$. [c] R indices for data cut off at $I > 2\sigma(I)$. [d] wR2 = $\{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, $P = (F_o^2 + 2F_c^2)/3$. [e] R indices for all data.



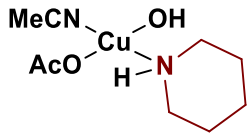
Molecular structure of $[C_5H_{12}N]_2[Cu_2(OAc)_6]$ (only one piperidinium cation is shown) (Atom colours: Cu = cyan, O = red, N = blue, C = black, H = grey).



Structure of the neutral complex in crystals of $[Cu_4(\mu^3\text{-}OH)_2(OAc)_6(NC_5H_{11})_4]\cdot 2CH_3CN$ (Atom colours: Cu = cyan, O = red, N = blue, C = black, H = grey).

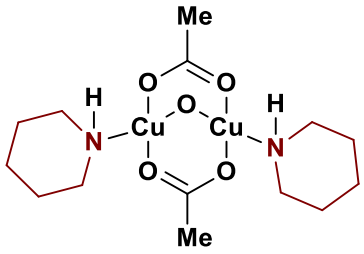
15.2.5.6. HRMS identification of Cu(II) complexes in solution.

Complex 150.



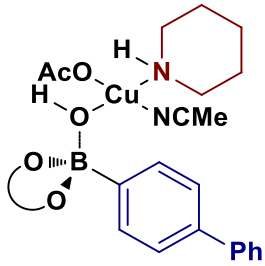
HRMS (ESI): ($C_9H_{19}CuN_3O_2$) $[M+H]^+$ requires 266.0686, found $[M+H]^+$ 266.0683.

Complex 151.



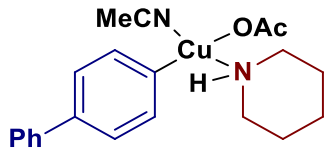
HRMS (ESI): ($C_{14}H_{29}Cu_2N_2O_5$) $[M+H]^+$ requires 431.0663, found $[M+H]^+$ 431.0668.

Complex 153.



HRMS (ESI): ($C_{27}H_{40}BCuN_2O_5$) $[M+H]^+$ requires 546.2321, found $[M+H]^+$ 546.2332.

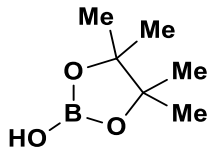
Complex 154.



HRMS (ESI): ($C_{21}H_{27}CuN_2O_2$) $[M+H]^+$ requires 402.1363, found $[M+H]^+$ 402.1351.

15.2.6. Transmetallation step.

15.2.6.1. Detection of BPinOH.



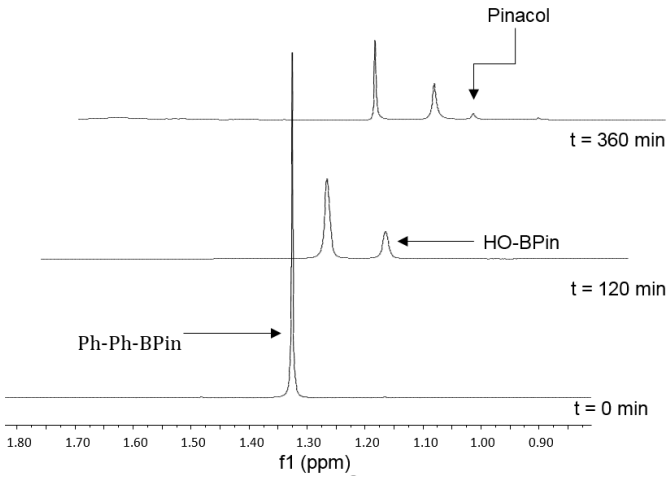
To a solution of 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (28 mg, 0.10 mmol) in MeCN (450 µL) was added aniline (18 µL, 0.20 mmol), $Cu(OAc)_2$ (11 mg, 0.1 mmol), Et_3N (28 µL, 0.2 mmol) and powdered activated 4 Å molecular sieves (100 mg). The reaction mixture was stirred at RT and ^1H NMR were recorded at t = 0, 120, and 360 minutes. A ^{11}B NMR was recorded at 360 min.

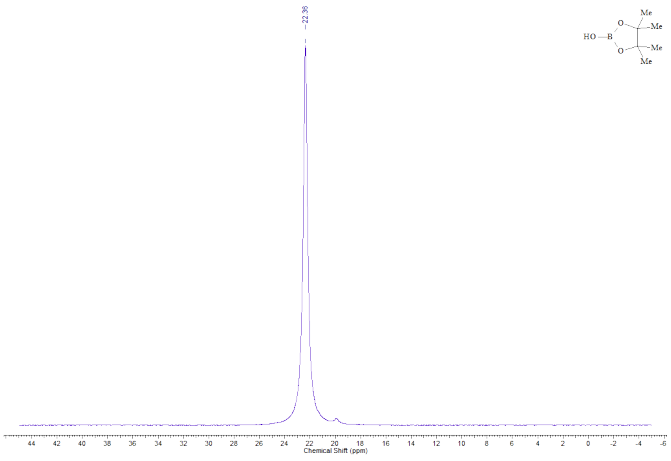
^1H NMR 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (400 MHz, CD_3CN): δ 1.33.

^1H NMR BPinOH (400 MHz, CD_3CN): δ 1.23.

^1H NMR pinacol (400 MHz, CD_3CN): δ 1.13.

^{11}B NMR BPin-OH (128 MHz, CD_3CN): δ 22.4.

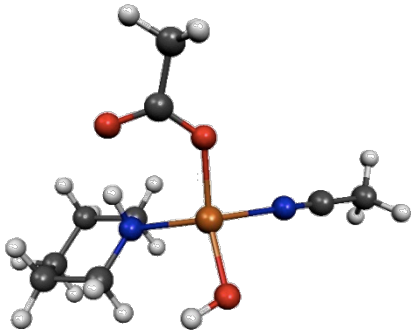




15.2.6.2. Molecular modeling of the transmetallation and reductive eliminations steps

Note: *cis/trans* isomerism was also evaluated in molecular modeling; however, these were isoenergic within the experimental error limits of the program (<1.5 kcal mol^{-1} difference).

Geometry Optimized Coordinates for a model of 150.



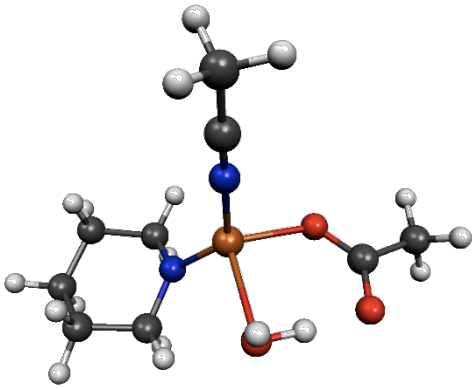
Cu	-0.27621755818233	12.04823613751653	0.66262214737683
O	1.12545840135707	11.25908850270950	3.53097114514547
O	-0.01286559725544	11.55514001343177	-1.13728913507343
N	-0.52674477388380	10.20312703654218	1.52166965223370
C	-2.07512660324267	14.58576624880768	-0.15703810425941
C	-2.94925647699254	15.67971926302897	-0.51866926821912
C	-1.74443843687534	7.57677658725053	2.05055222484074
C	-0.12123443443627	9.00817540376488	0.74278153742478
C	-1.92136519247086	10.09960965824866	2.02992459668367

C	-0.30556771170103	7.70827939937808	1.53694627304076
C	-2.14271297578006	8.82196516646095	2.85143888793059
C	0.91932030906679	12.48058117275149	3.33195026372546
C	1.43578302106170	13.51482193993500	4.32050431057310
O	0.28189041367982	12.97762999243163	2.31800302704505
N	-1.37456156947763	13.70733993073715	0.12938208461863
H	0.12123115863216	10.35113097598024	2.32935252634749
H	-2.53492256958690	16.21298175659842	-1.38511912664748
H	-3.04227652987531	16.37644758489299	0.32574517753460
H	-3.94272218104393	15.28926003388192	-0.77698719915634
H	-1.84912292801910	6.67283419728154	2.67000324813434
H	-2.42874963990851	7.45864908057334	1.19262308251406
H	0.92846460750436	9.13656517224971	0.44373398827532
H	-0.73521326585010	8.97854399184394	-0.17079787859455
H	-2.59978089242845	10.11551401497675	1.16202187263021
H	-2.12747702530829	10.99407465869764	2.63452083668288
H	-0.03892955526657	6.86018341063762	0.88707271248504
H	0.39877463407139	7.69560663559206	2.38594664851457
H	-1.54481716131739	8.87983860200631	3.77627381341812
H	-3.19997099432117	8.77785672741837	3.15487925640031
H	0.61582632135700	14.17228601768069	4.64105281688206
H	2.18776563208377	14.14793373403758	3.82639931287736
H	1.88676260083415	13.03019343666229	5.19364944276648
H	0.33543238057547	10.64758788199355	-1.18240674215127

Total energy = -2330.13172513 E_h

Total Gibbs enthalpy = -2329.91503204 E_h

Geometry Optimized Coordinates for a model of 156.



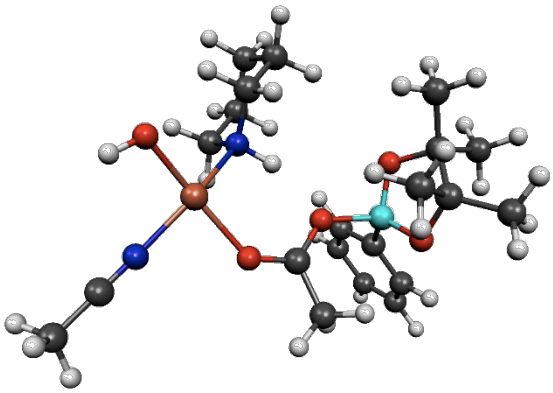
Cu	-0.88401223951011	12.58743029700788	0.15805763543864
O	-0.67758111163715	11.42441557094577	3.23130614847945
O	-2.52871278738815	11.40078056524072	1.37958418705716
C	-2.08706239837562	15.41086485278061	0.55591038620001
C	-2.64947091478890	16.72920419338261	0.74790002489256
C	0.35863105909495	12.03091769372193	2.82406772499909
C	1.54652110468076	12.11659117944145	3.77228377589007
O	0.49565434679650	12.56962516349498	1.67139030846210
N	-1.63359102566259	14.35287473571477	0.40058842569675
H	-3.20739435341764	12.05059746894449	1.63393484718229
H	-2.12614891114416	17.45267579579261	0.10813585337402
H	-2.54094096380315	17.03190868595468	1.79862780375556
H	-3.71577174475231	16.72033942680211	0.48276694598469
H	1.21396095599769	12.48208949266027	4.75341130863743
H	2.33492802328135	12.76885064581552	3.37973072408741
H	1.95694908515359	11.10711831944873	3.92322781608164
C	0.46068181472803	11.68745965992708	-2.30741962459826
C	-0.10461841375814	11.86181640071726	-3.73483186063034
C	-1.00191383717177	10.67747628691198	-4.11002972647597
C	-2.06562272864489	10.44427087446859	-3.03209669953755
C	-1.40921542787999	10.32438274145503	-1.63846374487421
N	-0.60041278903605	11.49315564763929	-1.33173401815639

H	1.06596705144804	12.55919650665590	-2.02326232277135
H	1.12628362132826	10.79814234820556	-2.30531719052784
H	0.73557099118686	11.96639346738698	-4.43861938343885
H	-0.68266721354638	12.80020922754244	-3.77368913613238
H	-1.47685331080514	10.85178986003144	-5.08839166120180
H	-0.38248614205057	9.76908016952347	-4.21206356748068
H	-2.64429180661623	9.52909026711253	-3.23354215144178
H	-2.77868421936607	11.28591747973677	-3.01728638385473
H	-2.16772680389926	10.19831812350010	-0.85524658391641
H	-0.76104027432060	9.42178808616407	-1.63960652635855
H	-1.85891949612116	11.39901901987241	2.15104240417823

Total energy = -2330.13294743 E_h

Total Gibbs enthalpy = -2329.91798942 E_h

Geometry Optimized Coordinates for a model of 152.



Cu	-0.05531969944551	11.99415017439532	1.27136727766436
O	0.41272631275963	10.61059403298983	4.32674332232371
O	0.07827222010807	11.57344386020974	-0.57275290258747
N	-0.68781884503190	10.09113527974435	1.69248581183611
C	-0.26749258816899	15.10195043791924	0.65780851574351
C	-0.37518654795757	16.51149461635258	0.36018735978283

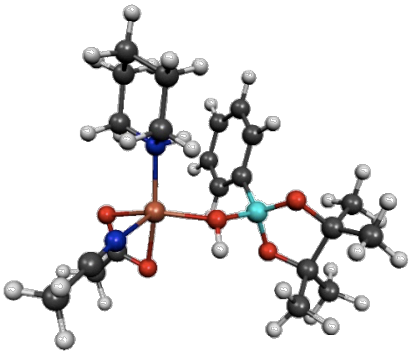
C	-2.09971546182587	7.58677955554857	1.04982220959884
C	-0.02000866924940	9.02250514378936	0.90633015387953
C	-2.16869589688974	10.06295655462571	1.54300495274551
C	-0.57840114414489	7.63203655460856	1.23273929424346
C	-2.76727943508997	8.69131760363080	1.87618254012942
C	0.55936052493760	11.88499862929404	4.24997293466773
C	0.95007181905034	12.68875177083166	5.46124861053218
O	0.37461243032431	12.51682283939871	3.16269861436643
N	-0.17949722611158	13.97114745852158	0.89689912252191
B	0.66220440340535	9.59829311671039	5.68930725574281
O	0.69154285010897	8.29562065436308	5.05776959782362
O	1.96276790343246	9.84812613183718	6.25200574071410
C	2.89043550065557	8.88237018197623	5.69986100385525
C	1.94628794155432	7.65747466722448	5.38899097506156
C	1.71467827980334	6.76594346570193	6.62108405754313
C	2.39273425824121	6.79082109122185	4.21108430895843
C	3.97195132143695	8.60635875502209	6.74350469418583
C	3.53570943420956	9.47594481169082	4.43747998911045
C	-2.77612948569413	10.37918367268590	8.41759025622025
C	-1.46311644289434	10.58115451054101	8.85619943684961
C	-0.38983290711756	10.34790426329802	7.98702340625395
C	-3.00028452867850	9.94121593952828	7.10621469003355
C	-1.91763219570712	9.71608829763225	6.24915617135584
C	-0.58493878921599	9.91318098544270	6.66230864774456
H	-0.42446321188990	9.99321269570667	2.68877696852448
H	0.54333515493544	16.85429303056909	-0.13599647845637
H	-0.51642855943345	17.07670868228324	1.29109910375975
H	-1.23241722037163	16.68420807939341	-0.30497270970385
H	-2.49188393149373	6.60112505273988	1.34383809974581
H	-2.34987314848950	7.72498070388380	-0.01652862149752
H	1.05674658279178	9.07557568212266	1.11946607279446
H	-0.16225172115781	9.26723420589103	-0.15579514586039

H	-2.39125966602481	10.32987170058887	0.49865180635201
H	-2.59167088406699	10.84594227400532	2.18835396385249
H	-0.08068552618784	6.89363395104381	0.58576442510041
H	-0.32208066776224	7.37496998437937	2.27414022506900
H	-2.63185712106595	8.48334208484505	2.95156418480491
H	-3.85232956056732	8.72721684749692	1.69190914683592
H	1.81146423730337	12.21755950667510	5.95174694900639
H	0.11993717994441	12.66707811543625	6.18387186390228
H	1.16771083452443	13.72422821098232	5.18243786916566
H	1.41306394001565	7.36637107351313	7.49077069388822
H	2.61231198124204	6.18761431906076	6.88669795889850
H	0.90537567599243	6.05729462127941	6.39485916683833
H	3.38240391310773	6.34802477337512	4.40028014784658
H	2.44042984422987	7.36870489662320	3.27948054308223
H	1.67808893372439	5.96764766006769	4.06604761701250
H	3.53223055352952	8.31562062601938	7.70516176306040
H	4.57643763971034	9.51245022261478	6.89968648146380
H	4.64644992299794	7.80368388331514	6.40895008750445
H	4.00066579015836	10.43814428772829	4.69770360969971
H	2.78602999715248	9.65616658189331	3.65584321538645
H	4.31886626851364	8.81753906344311	4.03322229913248
H	-3.61751090390152	10.55954198980252	9.08998872738996
H	-1.27545901095184	10.92164408027552	9.87735884518576
H	0.63158917800732	10.50193187407506	8.34353403982795
H	-4.02129919121242	9.77452592599470	6.75417063675678
H	-2.11592960835108	9.37092060685615	5.23058105334667
H	0.10149408624233	12.42332914428348	-1.04975222961721

Total energy = -2973.28049414 E_h

Total Gibbs enthalpy = -2972.81298692 E_h

Geometry Optimized Coordinates for a model of 153.



Cu	-0.26163872828714	11.63847221303279	3.57402824947036
O	0.67341253167243	13.05960163828041	4.79409749828802
O	1.09153794502957	10.16814120807488	3.64967260436188
N	-1.69095506239919	10.38504478007787	2.82697923888791
C	0.95426211791962	13.29985554715827	0.87243529235477
C	1.52179871413928	14.14032852694100	-0.16126248798588
C	-3.75822563154850	9.34287475991717	1.00266127477182
C	-1.32497557211798	9.82068109538222	1.49799913711401
C	-3.06453200459278	10.95900460777776	2.82443526373641
C	-2.33490197254942	8.77106836240420	1.02073368245581
C	-4.11392061897389	9.93661903927573	2.37127265631871
C	-0.43612770868019	13.68814411118811	4.85951978304123
C	-0.57370252477178	14.96022041480758	5.64423749103496
O	-1.44574183867659	13.19529758248406	4.23905930927421
N	0.49784372998548	12.62542100905583	1.70012779411464
B	1.27499168234411	9.13723546595534	4.81863530055188
O	1.87433166735976	7.92937906171847	4.21968672144846
O	2.26630726294942	9.62832542957593	5.78922489386649
C	3.50055699904029	8.90763354570620	5.60462405968930
C	3.00150526608701	7.53076898959094	5.02278930302588
C	2.50606418586695	6.58027050791741	6.12721707105725
C	4.01147405139940	6.80292584313144	4.13538460396223
C	4.22044464780896	8.81079114241970	6.95106346611723
C	4.39333974688690	9.67483948641450	4.61081144089148

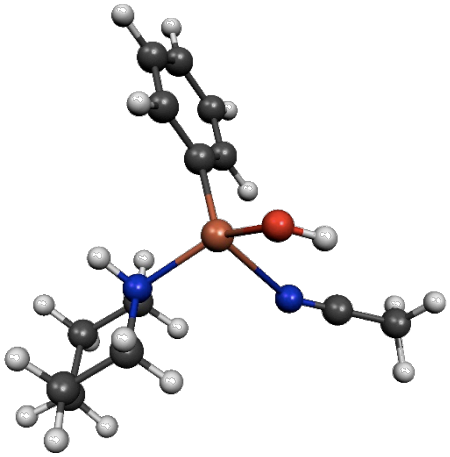
C	-2.79633265031873	8.57793162118429	6.59177253400291
C	-2.00225138555190	9.66791425005362	6.96924084017226
C	-0.73148655640702	9.83802943748045	6.40763066142557
C	-2.30239933844576	7.66319513061598	5.65574515602112
C	-1.02470633552068	7.84287488331468	5.10633508204256
C	-0.20559741432222	8.93330744034845	5.46239479633641
H	-1.65384657456711	9.62000405582768	3.51965880426024
H	1.73862092130260	13.53813938004228	-1.05384150665150
H	2.45301792796140	14.59642658162332	0.20053822635442
H	0.81041693125847	14.93435399404319	-0.42573693920839
H	-4.48292850078912	8.56310165452649	0.72331484300003
H	-3.82370438232425	10.13197319325882	0.23287761902480
H	-0.31408066589919	9.40205334664768	1.58349123735823
H	-1.28455695833194	10.66257229513658	0.79039118857154
H	-3.05469558578850	11.82554149436559	2.14556465670974
H	-3.27818033589096	11.33284898016630	3.83304917846120
H	-2.03504505702959	8.42409652547616	0.02010868729286
H	-2.29048863928675	7.89395014161449	1.68923343063760
H	-4.18013803387819	9.12901706887429	3.12049119459316
H	-5.09794554611299	10.42974893120078	2.34560866458130
H	0.40301339131110	15.31867351774862	5.98656356255000
H	-1.21780599620491	14.77813052074004	6.51732121074402
H	-1.06222062687296	15.72886275427651	5.02971946782959
H	1.80033168730411	7.09424086091165	6.79423093146639
H	3.33507152109981	6.17977936597722	6.72853280613645
H	1.98225388696526	5.73426715936109	5.65881015191042
H	4.92139457312014	6.54448980625426	4.69772189253634
H	4.29848237860640	7.41125222320285	3.26782295960584
H	3.57082184576696	5.86545823313250	3.76482024663095
H	3.56469436408724	8.38936322147831	7.72358644240424
H	4.53544179965197	9.81328513601787	7.27716556589638
H	5.12256723964972	8.18475697004479	6.87356720325767

H	4.50240886811290	10.71204940411118	4.95943588667305
H	3.95474969476486	9.68991091682024	3.60235423943846
H	5.39767784829032	9.23241077582339	4.53507488705567
H	-3.78879242483987	8.44224627924465	7.02582625254366
H	-2.37663839792843	10.38591892718249	7.70333083591537
H	-0.12401175108005	10.69175093412392	6.72114556737826
H	-2.91100953130246	6.80588375450325	5.35767001120709
H	-0.64196233573084	7.10920535639073	4.39141031649309
H	1.96594838227949	10.56014068356554	3.46781802149194

Total energy = -2973.29900247 E_h

Total Gibbs enthalpy = -2972.83271203 E_h

Geometry Optimized Coordinates for [Cu(II)(OH)(Ph)(NHC$_5$H$_{10}$)(NCCH$_3$)].



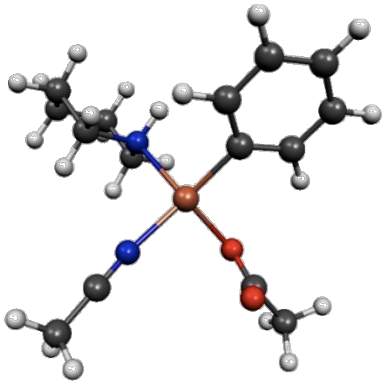
Cu	-1.00115039785686	9.54554833986654	1.77942863582781
O	0.32010580274737	8.92049370367751	0.59245230877241
N	-3.05989194735637	9.65562304502604	1.79580631425849
C	0.06318064267275	12.74753098081167	0.97001885733354
C	0.95740112844695	13.83655203925613	0.62915823042489
C	-5.73981454770516	10.70315800073101	1.12552787876093
C	-3.60344029395812	9.55612045260959	0.40943715757266
C	-3.63367895018336	10.82231844499610	2.52233162829111

C	-5.13461452246837	9.50553165699608	0.38265420654131
C	-5.16471722249749	10.80377687139865	2.54434106955637
N	-0.64995149740591	11.86964531674782	1.24383182212659
C	-0.16306205677954	8.81629497659410	6.45652372243401
C	-0.16517683355849	10.11442419134778	5.93347245517644
C	-0.41795195703527	10.32419368931215	4.56891403572705
C	-0.41439026429802	7.73386845421247	5.60611207590835
C	-0.66239755964641	7.95058558987680	4.24147869531279
C	-0.66962409705397	9.24831872612141	3.69882851535694
H	-3.33740928898074	8.80681227575847	2.30325679484550
H	1.94259795876964	13.43889573632915	0.35051144953518
H	1.07278891454305	14.50884049885964	1.49047117922903
H	0.54826708690657	14.40448363215407	-0.21754894609857
H	-6.83672809174274	10.61944079179674	1.16077240577486
H	-5.50886419181679	11.63015465580626	0.57054692416948
H	-3.16841116396740	8.66294402707556	-0.06029000834493
H	-3.23961699618620	10.43723680205037	-0.14249611710716
H	-3.26584243431708	11.72561885969355	2.01315349445391
H	-3.21705507967867	10.81902962691931	3.53807657838268
H	-5.47313889873717	9.47728044929810	-0.66455644358828
H	-5.46980196828815	8.56540360730332	0.85420037041515
H	-5.50939297635697	9.94585482075903	3.14815484994697
H	-5.52548434517486	11.71325071430444	3.05019239390790
H	0.03533452055281	8.64901091158864	7.51734950465873
H	0.03231310462402	10.96848421565205	6.58669906776593
H	-0.41290037196197	11.34979957284555	4.18799089146014
H	-0.41428604885066	6.71494015146466	6.00262044960449
H	-0.84857288451837	7.08269331920989	3.60189588920735
H	0.89798310811799	9.67322155254934	0.37426287839995

Total energy = -2333.21660047 E_h

Total Gibbs enthalpy = -2332.96534770 E_h

Geometry Optimized Coordinates for a model of 154.



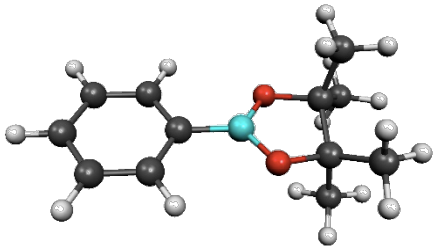
Cu	-0.87022558858361	10.86965389222706	3.07883199976379
O	2.08256323445738	11.59768963023686	3.60344887470228
N	-2.89897073866025	10.52491927037773	2.53020898966148
C	0.03198744736197	12.39215765440860	0.44806785664253
C	0.55743401675130	13.07385972757723	-0.71368476374936
C	-5.46866249788601	11.04719085037868	1.17365746988456
C	-3.14742709980156	10.04405950731545	1.14524704686492
C	-3.69933217709943	11.74154384074526	2.84271191942542
C	-4.63399228513650	9.79671105390013	0.86738213136699
C	-5.19948528137281	11.53766024681907	2.60223097348593
C	1.31289492102852	12.32755193428105	4.26242306518595
C	1.88655314561371	13.41612606686374	5.17070612827188
O	0.02206018770148	12.23441822021012	4.27789066648447
N	-0.38667552756530	11.84484464319477	1.38145077556881
C	-0.58119134627131	6.98478182297100	5.88891531555833
C	-0.32163176433367	8.25359970775677	6.42046918813571
C	-0.41403845281007	9.39203395824107	5.60670040865808
C	-0.93921224922838	6.86415854241635	4.54241958651406
C	-1.03992223692823	8.00959163937833	3.73622191297298
C	-0.76970351821202	9.29087200026848	4.25115787227707

H	-3.17323325013393	9.78362341696661	3.18443646924229
H	1.65598049135420	13.04970515223402	-0.69237043359545
H	0.21982158501414	14.11911445618087	-0.71392551639483
H	0.20237342206980	12.58006586077801	-1.62819633897976
H	-6.54037966271689	10.83625464861609	1.03664155042714
H	-5.20603697355023	11.84489502225684	0.45710047237192
H	-2.55699033911242	9.13009545798065	0.99062519464909
H	-2.75552299600332	10.81148854420981	0.46108226763357
H	-3.31739539627062	12.55306170010632	2.20328927701705
H	-3.50080778087039	12.01827442893407	3.88737120434769
H	-4.75429071236451	9.49126119677131	-0.18359032388260
H	-4.98434955391796	8.95283809789166	1.48678471995607
H	-5.58353827408745	10.80108678050053	3.32878402904995
H	-5.72399608921386	12.48553257167781	2.79964857154715
H	2.86640296186238	13.74547673792392	4.80475162037668
H	2.02230499368482	12.99662798983038	6.17959801879332
H	1.20655045894667	14.27352082854186	5.25371287873392
H	-0.50655268572261	6.09660002406795	6.51977249460645
H	-0.04104889344053	8.35874345379689	7.47168374014973
H	-0.19779983979956	10.37246084300533	6.03686774189522
H	-1.14424155952525	5.87946144283347	4.11467154251882
H	-1.32711014622768	7.87809168432790	2.68829709786068

Total energy = -2485.96385986 E_h

Total Gibbs enthalpy = -2485.67663842 E_h

Geometry Optimized Coordinates for a model of phenyl BPin.



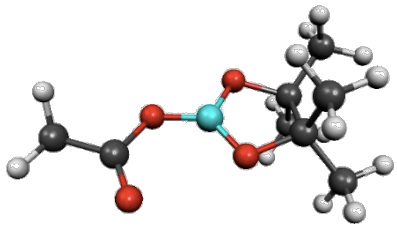
B	6.60363416270880	8.64755306932872	3.00372100870356
C	5.43312412418123	6.68844984848478	4.22035341388033
C	5.87633360806448	7.26723351209484	3.01315871078709
C	5.64248516856343	6.55964753867987	1.81583685876664
C	4.99225347577267	5.32260797139710	1.82272713962315
C	4.56009592989898	4.76667934263743	3.03265628471808
C	4.78119104017694	5.45231259730466	4.23303327502435
O	6.77944345551480	9.42182144242192	4.13523006887961
O	7.13882715689758	9.21852768246630	1.86433225459997
C	7.70356282358175	10.51515714582607	3.77569516159533
C	7.52836175472866	10.60010305581201	2.20988523769154
C	7.29405003836464	11.76851979284768	4.53911118571871
C	9.10240655608231	10.06099359838908	4.20459874865132
C	8.79581135487675	10.95245131891827	1.44199397041627
C	6.36953634184510	11.50079800250706	1.77520966384632
H	5.97386901782136	6.98687251234354	0.86714781894015
H	4.82118944313518	4.79006908564000	0.88532598767241
H	4.05299192719565	3.80025452623510	3.04015555480680
H	4.44612715325389	5.02113162761088	5.17802270950032
H	7.42880345754222	11.60492423253680	5.61799602552682
H	7.92653676438003	12.61907083651320	4.24605566750096
H	6.24548458473349	12.03409029319086	4.35812412177736
H	9.84865962628612	10.84656137836545	4.02223128287459
H	9.41297908368093	9.15331180921073	3.66838911730568

H	9.09141748698104	9.83965753226699	5.28072156926966
H	9.15842680935647	11.94753156329752	1.73826339580988
H	8.58131142518516	10.97814852212751	0.36414236649059
H	9.59552355846597	10.22288506456994	1.61996627534981
H	6.18939818882991	11.35768175152708	0.70048147543507
H	6.60420006695402	12.56098685942821	1.94442490231648
H	5.44444342091726	11.25705967031392	2.31607056689026
H	5.60443762302318	7.21446382570648	5.16206847663090

Total energy = -643.16928925 E_h

Total Gibbs enthalpy = -642.94611554 E_h

Geometry Optimized Coordinates for AcO-BPin.



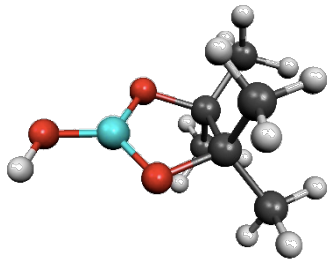
O	1.91486506250150	11.55977647046731	5.66384385206149
C	1.20552607430925	11.80504113906536	4.51086952725996
C	0.45389905018757	13.10044897794529	4.61292155243375
O	1.20965749606312	11.06035847160843	3.55215029574908
B	2.69795319651063	10.42996192224542	5.92630639708521
O	2.91353620025358	9.35184572540067	5.10801708959638
O	3.32809282624060	10.37373657729620	7.14839072147742
C	4.24402541312496	9.21253369810230	7.08712096180946
C	3.59203126572405	8.33365909935151	5.94760532478457
C	2.49531467021943	7.39850065877513	6.45865059566048
C	4.58145841240536	7.57848072731459	5.07095151946212
C	4.27875484123683	8.55582048313857	8.46118620748591

C	5.62131012668460	9.76601760793045	6.71722474186713
H	-0.19068059733766	13.09105286159143	5.50318137725046
H	-0.14674037810085	13.25959414833078	3.71203731988812
H	1.16684047487901	13.92835574455859	4.73745723384157
H	1.76849470035815	7.93471148155491	7.08508009318837
H	2.91972475607758	6.57366245969057	7.04729762099965
H	1.96215422777209	6.96887435793283	5.59995051184434
H	5.15042737163668	6.85369742413777	5.67071764861699
H	5.28953732867776	8.25497107503202	4.57685533184545
H	4.03685724150664	7.02112426502258	4.29627348120313
H	3.27440851912288	8.28717442137606	8.81018488290657
H	4.72596338774412	9.24734523189190	9.18905340419202
H	4.89462769583862	7.64598199476533	8.43513562215951
H	5.92055971829170	10.51182336209365	7.46629778990578
H	5.61035608314927	10.25134318576454	5.73123758813708
H	6.37767657292249	8.96882730361574	6.70565055128797

Total energy = -640.06245000 E_h

Total Gibbs enthalpy = -639.87606552 E_h

Geometry Optimized Coordinates for HO-BPin.



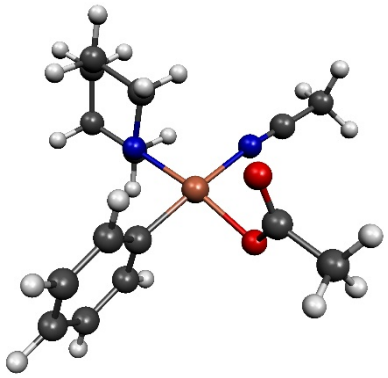
O	0.84234676885992	9.01208440198255	3.28349243392667
B	1.82722172483078	8.87271815737435	4.22781886995772
O	2.52267996286671	7.70383189359714	4.48644601096889
O	2.20781446125727	9.94457160116727	5.01437048374095
C	3.43171699722908	9.52479083053347	5.72248718837129

C	3.29895402206378	7.94894875111616	5.71927378381248
C	2.45721963973751	7.41318089366796	6.87971776631262
C	4.61814610911491	7.19436077371493	5.61820704161470
C	3.43240123513801	10.16550232433358	7.10436197708523
C	4.61427564614867	10.03087188427633	4.89237444611456
H	1.50381585481947	7.95251587745604	6.96376032158131
H	2.99366932666987	7.49864482475336	7.83467006924039
H	2.23880069223386	6.35079440634308	6.70365942111120
H	5.25430588688704	7.42014139757921	6.48655004250555
H	5.16971687236757	7.45429903333536	4.70543968744534
H	4.42619042824478	6.11192597718191	5.61122274151399
H	2.52112463165084	9.92647281051126	7.66775772178290
H	3.49941136961684	11.25803966168333	7.00201692706760
H	4.30281864177845	9.82798528547966	7.68626117026096
H	4.53114079454622	11.12064136738350	4.77809299915556
H	4.62220249197757	9.57871513723404	3.89113540554350
H	5.57169467266499	9.80983275915029	5.38423789958116
H	0.62327552229583	8.17283570414517	2.84204769530540

Total energy = -487.34829355 E_h

Total Gibbs enthalpy = -487.19287930 E_h

Geometry Optimized Coordinates for a model of 157.



Cu	-0.80909131534126	10.89895425775365	2.91727917495828

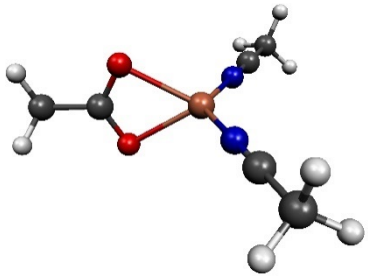
O	1.06436030917033	11.19484194610681	3.45890985999577
N	-2.66081190988641	10.42413866732304	2.59873147112355
C	-0.31221236591054	12.87732217678100	0.52627835821240
C	0.00685521830031	13.77783501875164	-0.55687692152559
C	-5.15498423060230	10.61461427278972	1.15603557659875
C	-2.77523746351567	9.77603778034769	1.29630640847575
C	-3.41308219595945	11.67711509027717	2.64604819693574
C	-4.24987751645283	9.38209670572558	1.06343774763217
C	-4.91515492240448	11.36218663449766	2.47238583668218
C	1.05354692110896	12.22753669073362	4.25030037344876
C	2.40381772481661	12.63263642478508	4.81630317218373
O	0.00936419321441	12.84256314015899	4.55658542810767
N	-0.57119602364375	12.15706198535103	1.39560737740481
C	-1.00221329456231	7.44697558331987	6.09591642029558
C	-1.42925948131085	8.73391862393138	6.44377989212912
C	-1.41990942960393	9.76581821210068	5.49425996966302
C	-0.55730809263221	7.19251364741600	4.79532966626237
C	-0.53960119970450	8.21996168400596	3.83790045118001
C	-0.96915425962874	9.49545918872128	4.20327403301288
H	1.08029132688846	13.71873611338821	-0.78265502631555
H	-0.24624542139050	14.80695062911863	-0.26634959099097
H	-0.56904118669020	13.50202829912352	-1.45039482566766
H	-6.21427027172824	10.32563173116525	1.06289821131587
H	-4.93343505138338	11.28963495951307	0.31038578936464
H	-2.14634318318403	8.87204015189593	1.28473026182690
H	-2.44851041493884	10.42261909565972	0.44907140864405
H	-3.11637194602996	12.40012650798080	1.85356562468628
H	-3.24865280439027	12.16504943363228	3.62047003493924
H	-4.33878606498873	8.89587727643517	0.07804469939925
H	-4.54162621257328	8.64435900546635	1.82818056834518
H	-5.25046773215883	10.74695674854567	3.32316771085650
H	-5.47980863894612	12.30774361735480	2.50063861432174

H	3.22182569517734	12.37443284228451	4.13252117816104
H	2.56592844288806	12.08956890306683	5.75973085566770
H	2.41607201908815	13.70714123286469	5.03527079257778
H	-1.01617842570470	6.64550052305462	6.83693586124081
H	-1.77821917029137	8.94263639612089	7.45752263963039
H	-1.76037804225870	10.76348077951746	5.77441537955274
H	-0.21621697710898	6.19379405447291	4.51416031396581
H	-0.18202141172728	8.00418515346073	2.82895424770140

Total energy = -2485.32860819 E_h

Total Gibbs enthalpy = -2485.05529994 E_h

Geometry Optimized Coordinates for [Cu^{I}(OAc)($NCCH_3$)$_2$].



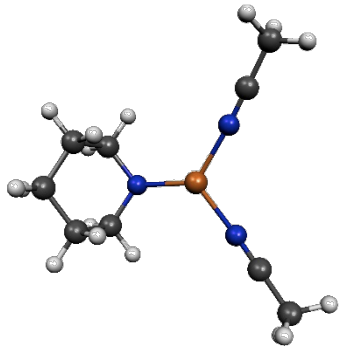
Cu	0.47167197087089	12.37781235954337	0.40087382560030
N	1.17984627993405	13.33379850764532	1.86643533104148
O	0.88868993930062	10.18941358710205	0.58006424589750
C	1.62265337599396	13.90984218853368	2.77498813999713
C	2.17303698919925	14.62976961848236	3.90190215262314
N	0.25507525881468	12.88521425156286	-1.40438230608636
C	0.10545122486664	13.18549549275498	-2.51830135671851
C	-0.07921897092908	13.56150013822801	-3.90249003443921
C	-0.31973215927040	10.00810000587913	0.94575760179650
O	-1.14132905111599	10.97753981337067	1.04808023340504
C	-0.78486669714940	8.59470507169707	1.25079175547934
H	1.37563947779492	15.19085051480969	4.40908452044394
H	2.94278553408301	15.33436940067912	3.55695629444587

H	2.62343299173486	13.92457958213256	4.61438404365334
H	0.83984331515792	14.02355770505412	-4.28945121640773
H	-0.90460439557270	14.28276378135349	-3.98467099555201
H	-0.31628127081478	12.67393464541562	-4.50524028715751
H	-0.79355336210211	8.00826364540951	0.31970969343939
H	-0.07955420078678	8.10551830318740	1.93734505798145
H	-1.79096183700958	8.58704544715900	1.68573394455694

Total energy = -2135.1033690 E_h

Total Gibbs enthalpy = -2135.00455040 E_h

Geometry Optimized Coordinates for [$Cu^{I}(NC_5H_{10})(NCCH_3)_2$].



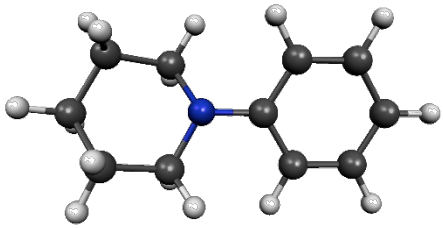
Cu	0.24437372725844	11.76556920889498	0.94711541336888
N	1.04254673159885	12.87092819485625	2.31385754256438
N	-1.43209141534297	10.90844878812642	1.13355424902201
C	-1.94740053913706	8.21495690182907	2.23432127044727
C	-1.80851465946076	9.79803963658696	0.26935966454219
C	-2.03850981867191	10.73258901403002	2.44579227637505
C	-1.38203633862517	8.42183380533894	0.82078743406446
C	-1.63073588775801	9.41606965490574	3.13925692765375
C	1.50938757655313	13.46781193054959	3.19915409460266
C	2.08449556952170	14.20543194049161	4.30456633726234
H	-1.56759050786069	7.27864126128333	2.67599746205924
H	-3.04544913747515	8.10397188493343	2.16386800877978

H	-1.37684609227518	9.94848811338641	-0.73382633431398
H	-2.92087703490562	9.76464081407255	0.13694721362977
H	-3.15596072894831	10.72539575949107	2.36111801632861
H	-1.77589587216737	11.58775808475239	3.09034124923312
H	-1.71837180754744	7.61105983310515	0.14902282462602
H	-0.27816290003078	8.39048673458219	0.85174900325877
H	-0.54574528971290	9.45553859627285	3.34076048703483
H	-2.14538520638444	9.31217177346232	4.11112383167725
H	1.52182309163852	15.13539413522316	4.46491212179268
H	3.13220300944136	14.45581335790139	4.08806442367367
H	2.04229253696269	13.60117797633716	5.22197546087247
N	1.36912930909316	11.71826667002506	-0.61170994729664
C	2.04778791497891	11.62282334600583	-1.55424398475599
C	2.88656508863020	11.50050218771808	-2.72791779873081
H	3.43338841620291	10.54746835267781	-2.69885364670373
H	3.61090226300960	12.32659450978998	-2.76402747988505
H	2.26754283641428	11.52742676537021	-3.63539680818298

Total energy = -2157.85152169 E_h

Total Gibbs enthalpy = -2330.13172599 E_h

Geometry Optimized Coordinates for a model of 38.



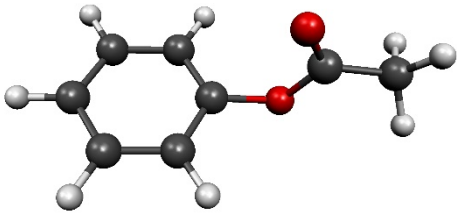
N	-1.89751547957774	10.73386177120918	0.96483875806540
C	-1.90298828973498	8.14950778315242	2.34214408790306
C	-1.86607188305117	9.48989696602491	0.18823085005351
C	-2.56385974363566	10.57978242676131	2.27199578868050

C	-1.22279277631937	8.35038532523279	0.98526084204520
C	-1.92428384211333	9.47392595741198	3.11118228231922
C	-2.32192520153316	14.42825021706146	-1.10258545015223
C	-2.13588098560711	14.39326150687749	0.28613260779655
C	-2.01587783274823	13.18220228541010	0.96470026044354
C	-2.38929841551982	13.21679422591485	-1.79450034470706
C	-2.27834978406756	11.99403324751075	-1.12429643097953
C	-2.07724892268149	11.94400614868145	0.27631517859852
H	-1.38615320739656	7.36923976453897	2.92145921270148
H	-2.93925584618250	7.79996519703599	2.18716263808430
H	-1.28057154196495	9.66330413230138	-0.72422104124671
H	-2.89014120498058	9.19510086866680	-0.12707166609767
H	-3.63783372475880	10.34318489477654	2.11061577926964
H	-2.52122215111778	11.53100948472661	2.81178763815860
H	-1.27049317276864	7.43103072113451	0.38094762708496
H	-0.15541660563202	8.58340850839755	1.13867477905992
H	-0.89505416098069	9.76939681631187	3.37450843294929
H	-2.48700461283783	9.37549503792488	4.05223896245717
H	-2.41393910066044	15.37905618558685	-1.62936556563009
H	-2.07245958818136	15.32486066396520	0.85281099871293
H	-1.84033048255171	13.19974419158398	2.04050819222295
H	-2.54723333867999	13.21223618161349	-2.87552968349450
H	-2.36657769471649	11.07476588018667	-1.70075540629897

Total energy = -483.12599033 E_h

Total Gibbs enthalpy = -482.92935627 E_h

Geometry Optimized Coordinates for a model of 160.

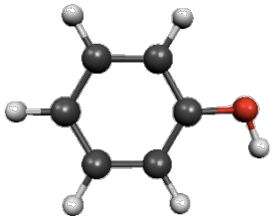


O	-2.05086660456893	11.36085245151214	1.42663588526088
C	-2.79005404336886	14.30237407360614	-1.45924234832784
C	-2.07722399455484	14.62325278835815	-0.29846612013562
C	-1.80282612153066	13.63782836959433	0.65589038980283
C	-3.23129724214377	12.99087846836979	-1.66764586528142
C	-2.96248314195989	11.99676206748558	-0.72092312524372
C	-2.24994158083768	12.33734698962846	0.42783221535006
C	-0.90643775380398	10.59904034851882	1.36033136479263
H	-3.00531847192005	15.07467481854226	-2.19927285466915
H	-1.73283126106615	15.64467863151483	-0.13017387701974
H	-1.25543642805970	13.87334633624968	1.56920160090384
H	-3.78977336045146	12.73662995113785	-2.56978328435183
H	-3.30512652070560	10.97160054317327	-0.86496006386980
O	-0.06521307515227	10.74277147029932	0.49446235897570
C	-0.87685839000756	9.59014826603822	2.47112588501753
H	-1.19500502649896	10.04098978753600	3.41936476340121
H	0.13019330532931	9.17209623649767	2.56276684860571
H	-1.58283972169895	8.77960176293748	2.23544163178875

Total energy = -460.31904239 E_h

Total Gibbs enthalpy = -460.21468106 E_h

Geometry Optimized Coordinates for a model of 11.



O	-1.70193624236275	10.92634495960853	1.16450989189038
C	-2.45366040365055	14.33720787109316	-1.12627535082356
C	-1.44416051989734	14.36554898433021	-0.15818998436821
C	-1.17289547641822	13.23643201522168	0.62109096276527
C	-3.19374342024273	13.16235063350352	-1.30964147362490
C	-2.93390207379739	12.02697855232019	-0.53851017664491
C	-1.92030345836816	12.06521364194060	0.42968785696225
H	-0.97398873373533	11.08649080880665	1.79448204636967
H	-2.66265759404312	15.22074339227980	-1.73082643681208
H	-0.85905064508746	15.27394850207841	-0.00267810005760
H	-0.38499482574526	13.26134776772783	1.37860980889789
H	-3.98524633345833	13.12623264553832	-2.06100638881492
H	-3.50853584519336	11.10943671355109	-0.67641507473930

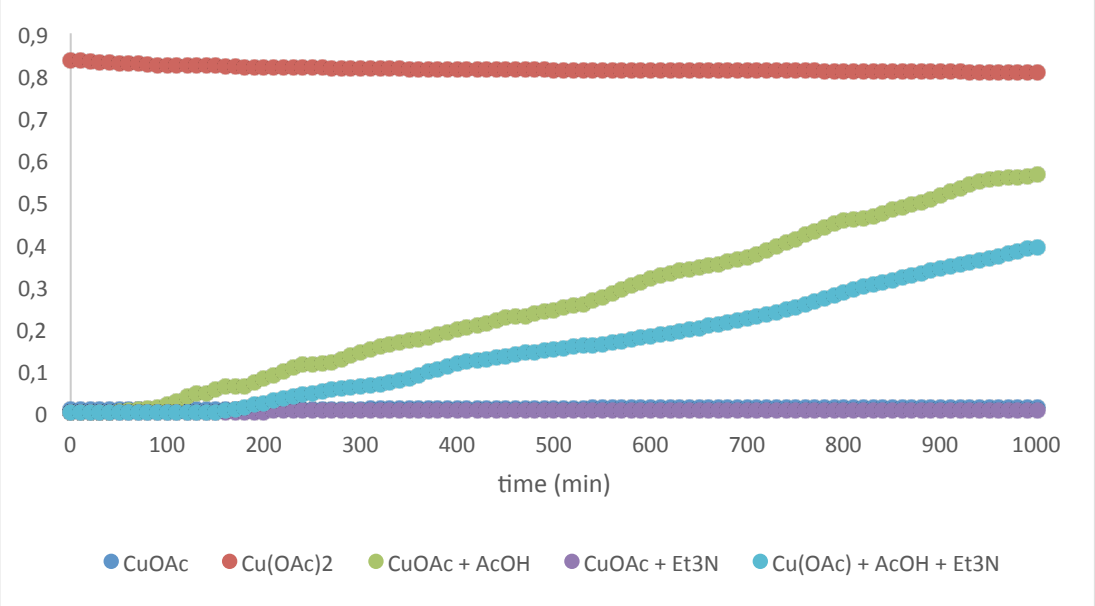
Total energy = -307.60024997 E_h

Total Gibbs enthalpy = -307.52698935 E_h

15.2.7. Oxidation of Cu(I) to Cu(II) in the presence of relevant additives.

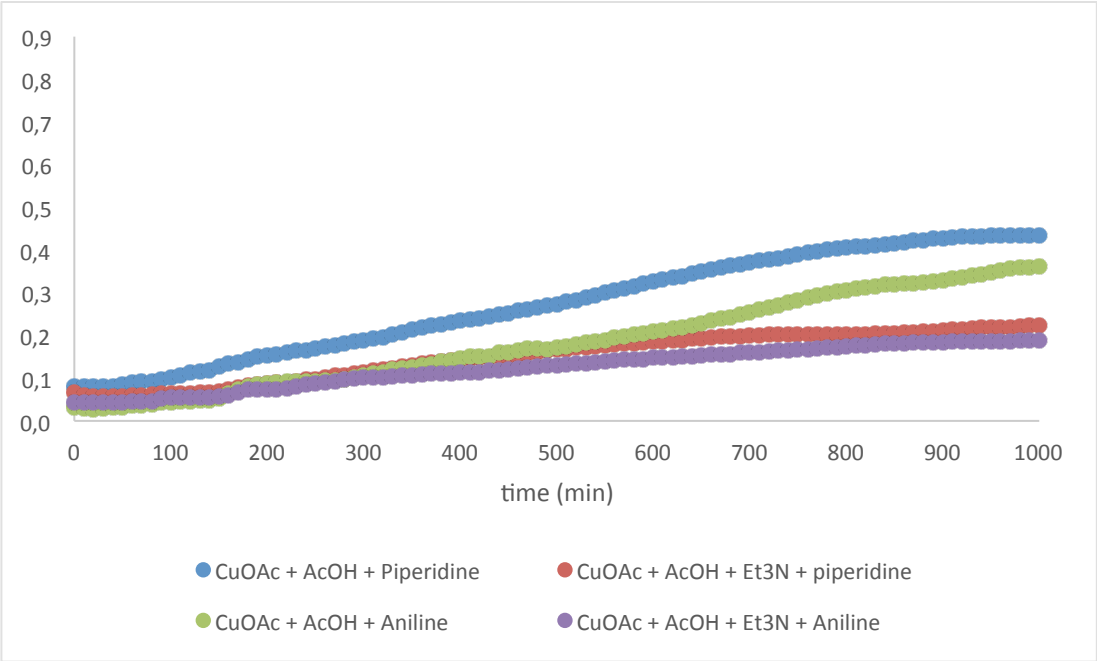
15.2.7.1. Cu(OAc) oxidation in presence of AcOH and Et_3N.

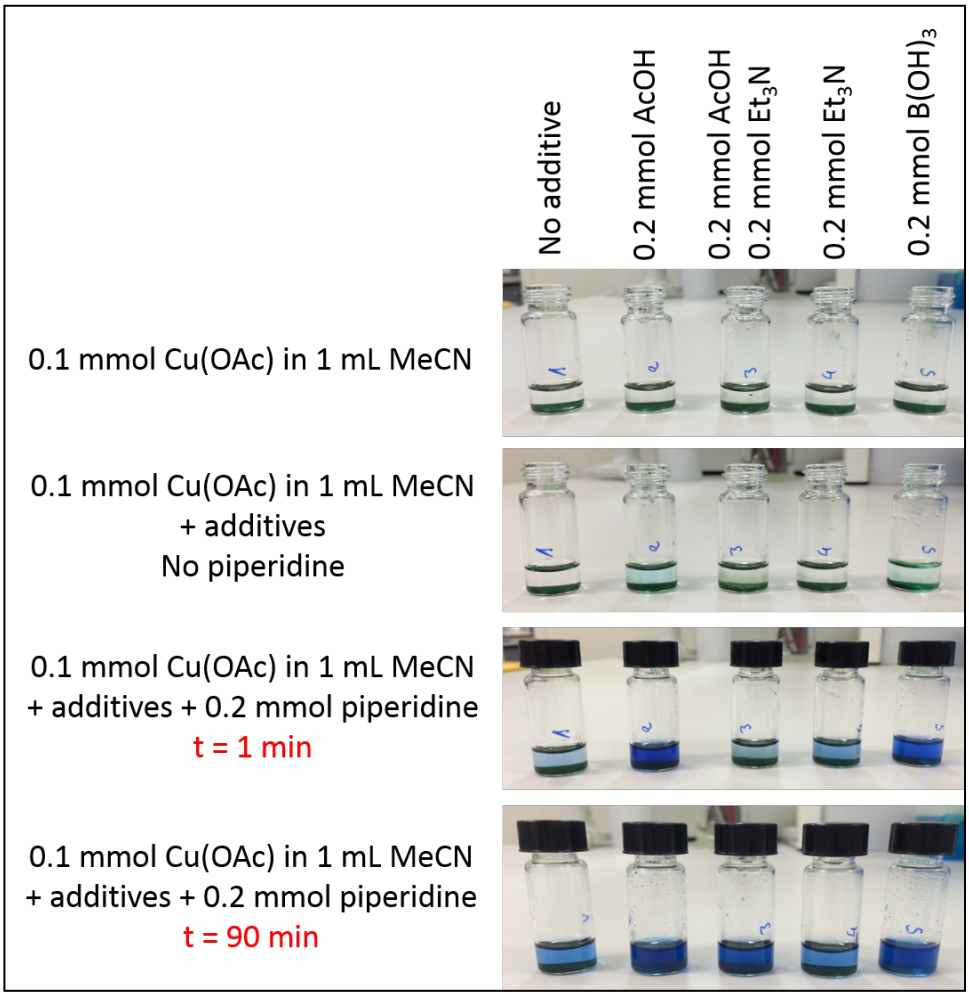
To a 5 mL cuvette was added 4 mL of a CuOAc solution in MeCN (2.5 mM). Depending on the experiment, were added different additives AcOH, Et_3N, or the buffer AcOH-Et_3N (2 equiv). The oxidation was monitored at 672 nm for 1000s, with an interval of 10 seconds between all acquisition time points.



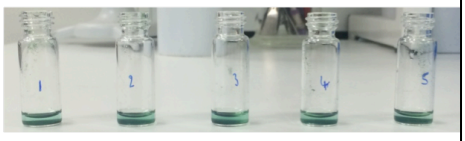
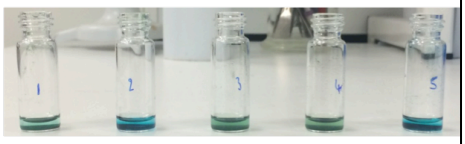
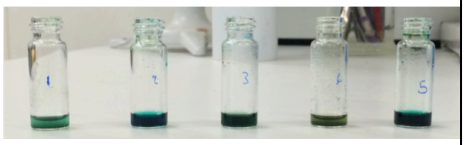
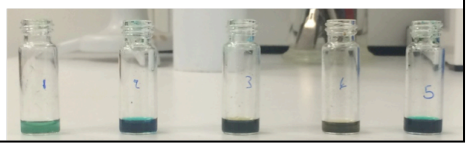
15.2.7.2. Cu(OAc) oxidation in presence of aniline 9, piperidine 145, AcOH, and Et_3N.

To a 5 mL cuvette was added 4 mL of a Cu(OAc) solution in MeCN (2.5 mM) followed by the addition of piperidine or aniline (2 equiv). Depending on the experiment, were added different additives AcOH, Et_3N, or the buffer AcOH•Et_3N (2 equiv). The oxidation was monitored at 672 nm for 1000s, with an interval of 10 seconds between all acquisition time points.





Oxidation of CuOAc in the presence of piperidine 145 using relevant additives

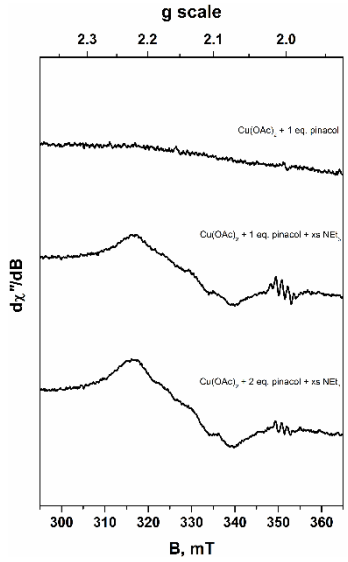
	No additive	0.2 mmol AcOH	0.2 mmol AcOH 0.2 mmol Et_3N	0.2 mmol Et_3N	0.2 mmol $B(OH)_3$
0.1 mmol Cu(OAc) in 0.2 mL MeCN					
0.1 mmol Cu(OAc) in 1 mL MeCN + additives No aniline					
0.1 mmol Cu(OAc) in 0.2 mL MeCN + additives + 0.2 mmol aniline t = 10 min					
0.1 mmol Cu(OAc) in 0.2 mL MeCN + additives + 0.2 mmol aniline t = 120 min					

15.2.8. Entry to catalysis.

15.2.8.1. Reaction inhibition by pinacol.

*Formation of complex **155** by EPR analysis*.

To a solution of $Cu(OAc)_2$ (18 mg, 0.1 mmol) in MeCN (0.5 M) was added pinacol ((**a**) 12 mg, 0.1 mmol or (**b**, and **c**) 24 mg, 0.2 mmol) and Et_3N ((**b**, and **c**) 56 µL, 0.4 mmol). The reaction mixture was stirred an hour for at rt. An EPR spectra was then recorded.

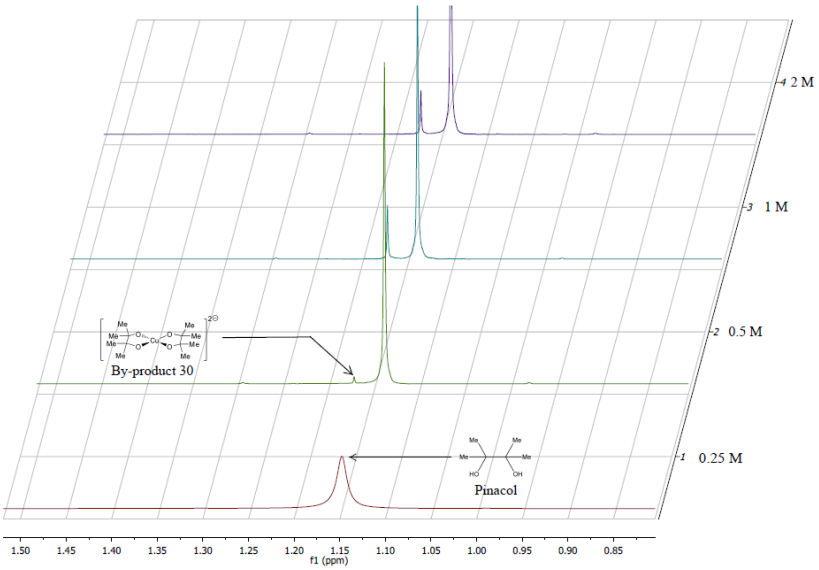


*Formation of complex **155** by NMR analysis.*

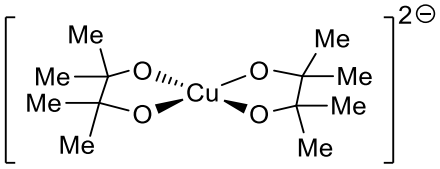
To a solution of $Cu(OAc)_2$ (18 mg, 0.1 mmol) in CD_3CN (0.25 to 2 M) was added pinacol (60 mg, 0.5 mmol). The reaction mixture was stirred for an hour at rt. A ^1H NMR was then recorded.

^1H NMR pinacol (400 MHz, CD_3CN): δ 1.12.

^1H NMR by-product 27 (400 MHz, CD_3CN): δ 1.17.



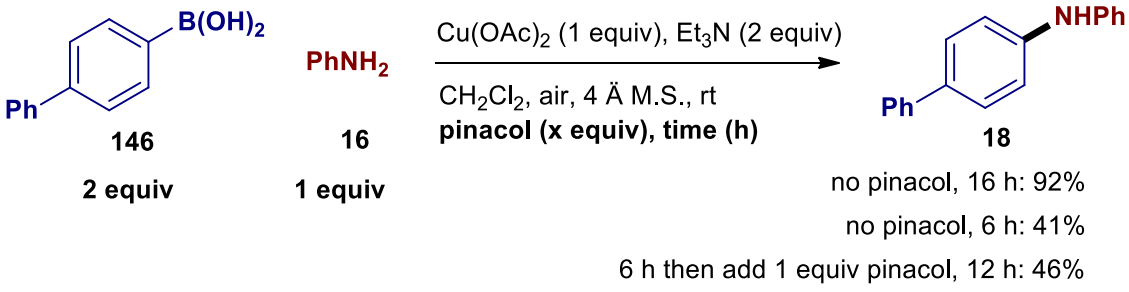
*Formation of complex **155** by HRMS analysis.*



To a solution of $Cu(OAc)_2$ (18 mg, 0.1 mmol) in MeCN (1 M) was added pinacol (60 mg, 0.5 mmol). The reaction mixture was stirred for an hour at rt. An HRMS was then recorded.

HRMS (ESI): ($C_{12}H_{24}CuO_4$) $[M]^{2-}$ requires 295.1054, found $[M]^{2-}$ 295.1051.

Inhibition of the Chan-Lam reaction by pinacol.



146 **16** **18**

2 equiv **1 equiv**

no pinacol, 16 h: 92%

no pinacol, 6 h: 41%

6 h then add 1 equiv pinacol, 12 h: 46%

[1,1'-Biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), aniline (18 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv), and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt. The reaction

was monitored by aliquoting the reaction mixture at 6 h, and 16 h. The aliquots were analysed by HPLC against an internal standard.

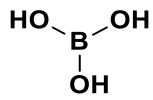
[1,1'-Biphenyl]-4-ylboronic acid (80 mg, 0.40 mmol, 2 equiv), aniline (18 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt for 6 h. Then, pinacol (12 mg, 0.20 mmol, 1 equiv) was added and the reaction was stirred for another 12 h. The reaction was monitored by aliquoting the reaction mixture at 16h. The aliquots were analysed by HPLC against an internal standard.

15.3. Development of a general Chan-Lam amination.

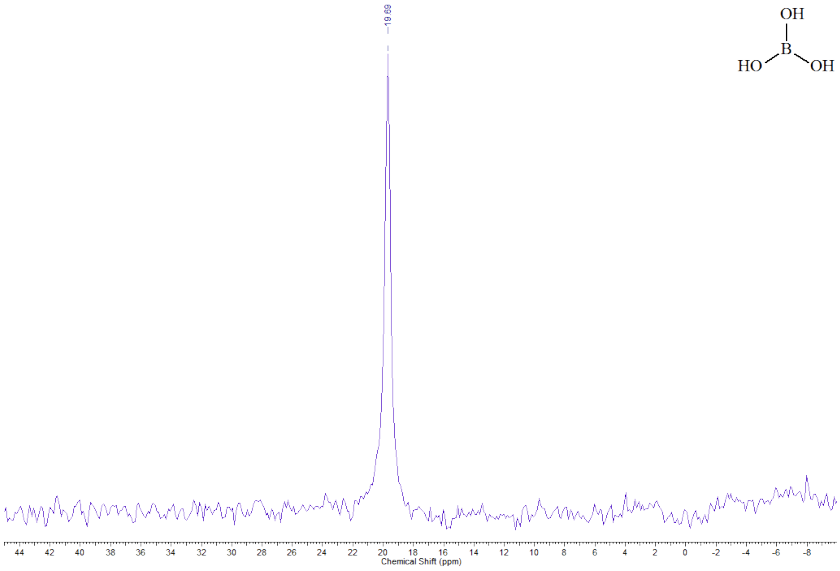
15.3.1. Synergistic roles of $B(OH)_3$.

15.3.1.1. Reversible borate formation using $B(OH)_3$ and AcOH/KOAc.

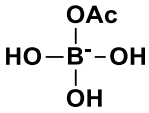
Boric acid.



^{11}B NMR (128 MHz, CD_3CN): δ 19.9.

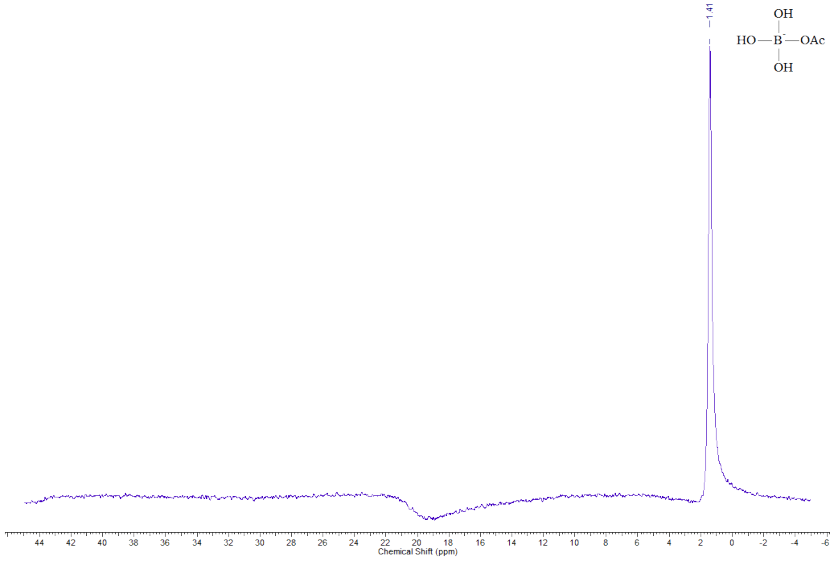


$AcOB(OH)_3^-$.

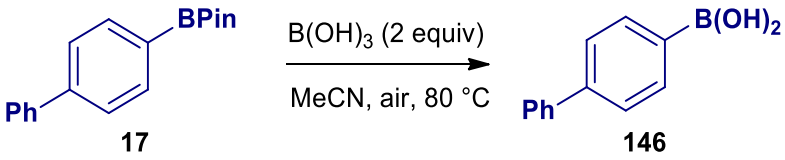


To a solution of $B(OH)_3$ (6 mg, 0.1 mmol) in MeCN (1 mL, 0.1 M) was added AcOH (6 mg, 0.1 mmol) or AcOK (10 mg, 0.1 mmol). The reaction mixture was stirred for 30 min at rt. An ^{11}B NMR spectra was then recorded.

^{11}B NMR (128 MHz, CD_3CN): δ 1.8.



*<u>$B(OH)_3$ promotes speciation equilibria with **17**.</u>*



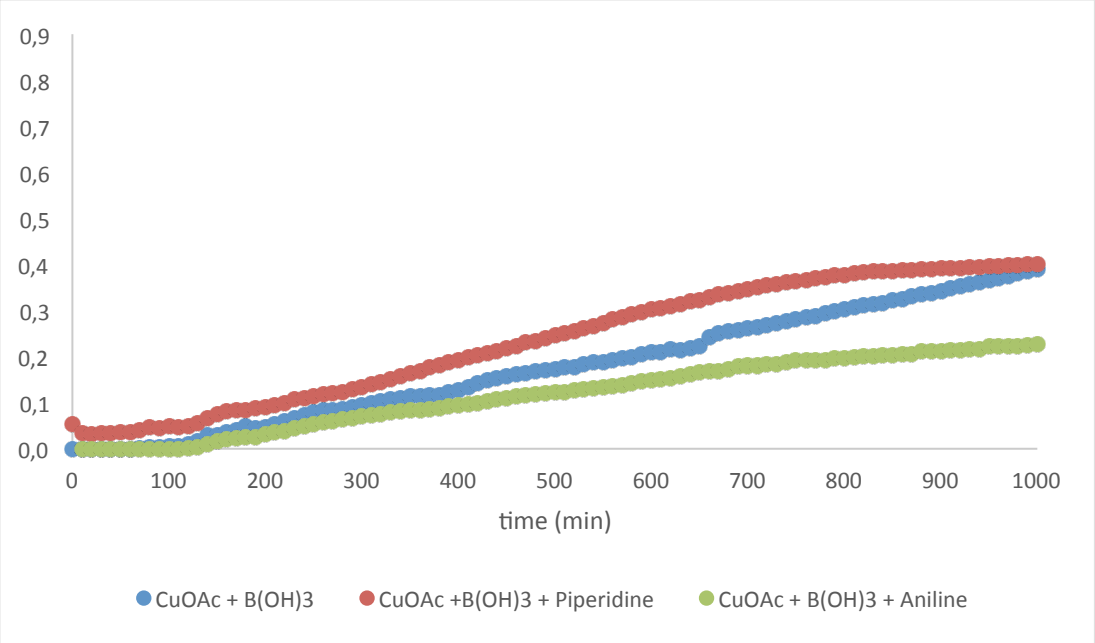
17 **146**

32%

2-([1,1'-Biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (84 mg, 0.30 mmol, 1 equiv), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) in MeCN (450 µL) were sealed in an oven dried 5 mL microwave vial under air and stirred at 80 °C for 16 h. The reaction mixture was allowed to cool to rt, filtered through Celite, and the filtrate was concentrated under vacuum to give a residue that was analysed by HPLC using an internal standard. 32% of the starting material BPin was hydrolyzed to the corresponding boronic acid.

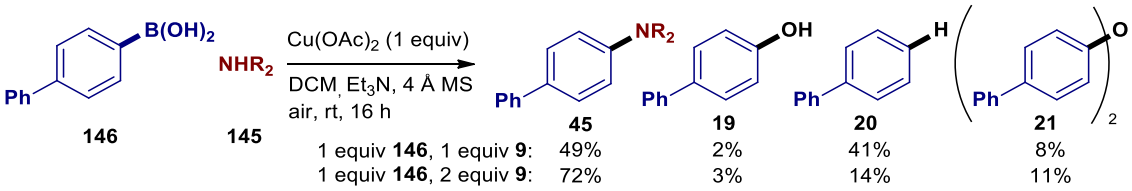
15.3.1.2. $B(OH)_3$ promotes Cu(I) oxidation.

To a 5 mL cuvette was added 4 mL of a Cu(OAc) solution in MeCN (2.5 mM) followed by the addition of $B(OH)_3$ (2 equiv). Depending on the experiment, were added piperidine or aniline (2 equiv). The oxidation was monitored at 672 nm for 1000s, with an interval of 10 seconds between all acquisition time points.



15.3.2. Impact of amine stoichiometry on side product formation.

15.3.2.1. Chan-Lam amination using a 1:1 ratio and 1:2 of 10 and piperidine 145.



146 **145** **45** **19** **20** **21**

1 equiv **146**, 1 equiv **9**: 49% 2% 41% 8%
1 equiv **146**, 2 equiv **9**: 72% 3% 14% 11%

*Chan-Lam amination using a 1:1 ratio of **146** and piperidine **145**.*

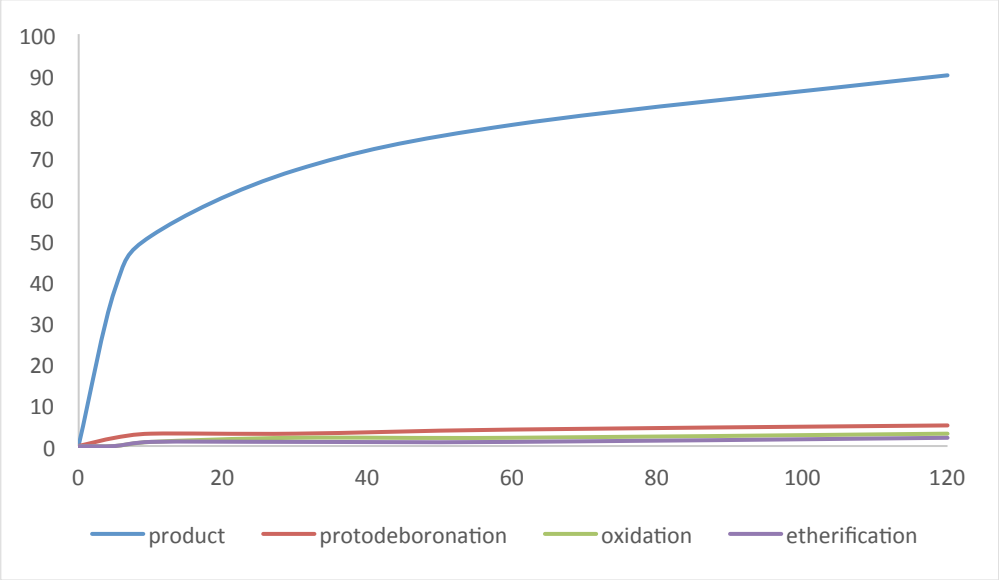
[1,1'-Biphenyl]-4-ylboronic acid (40 mg, 0.20 mmol, 1 equiv), piperidine (20 µL, 0.20 mmol, 1 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M)

were sealed in an oven dried 5 mL microwave vial under air and stirred at rt for 16 h. The reaction was analysed by HPLC against an internal standard.

*Chan-Lam amination using a 1:2 ratio of **146** and piperidine **145**.*

[1,1'-Biphenyl]-4-ylboronic acid (40 mg, 0.20 mmol, 1 equiv), piperidine (40 µL, 0.40 mmol, 2 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), Et_3N (56 µL, 0.40 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt for 16 h. The reaction was analysed by HPLC against an internal standard.

14.3.3. Reaction profile for the $B(OH)_3$ promoted Chan-Lam amination.

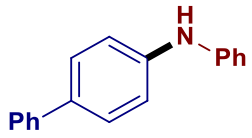


[1,1'-Biphenyl]-4-ylboronic acid (40 mg, 0.20 mmol, 1 equiv), piperidine (40 µL, 0.40 mmol, 2 equiv), $Cu(OAc)_2$ (36 mg, 0.20 mmol, 1 equiv), $B(OH)_3$ (24 mg, 0.40 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (200 mg) in DCM (0.8 mL, 0.25 M) were sealed in an oven dried 5 mL microwave vial under air and stirred at rt. The reaction profile was monitored by aliquoting the reaction mixture over time intervals of 5, 10, 15, 30, 60, 120 minutes. The aliquots were analysed by HPLC against an internal standard.

Time (minutes)	38 (%)	12 (%)	13 (%)	14 (%)
0	0	0	0	0
5	2	0	38	0
10	3	1	51	1
30	3	2	67	1
60	4	2	78	1
120	5	3	90	2

15.4. Compound Characterisation.

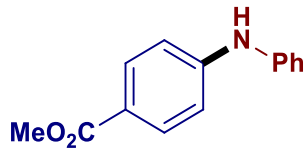
_N_-Phenyl-[1,1'-biphenyl]-4-amine, Compound 18.



Prepared according to General Procedure D using 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (84 mg, 0.30 mmol, 1 equiv), aniline (54 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as an orange solid (61 mg, 82%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

Methyl 4-(phenylamino)benzoate, Compound 24.

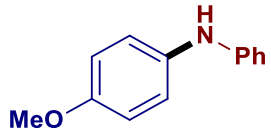


Prepared according to General Procedure D using methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (79 mg, 0.30 mmol, 1 equiv), aniline (54 µL, 0.60 mmol, 2

equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-5% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (57 mg, 83%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

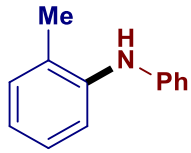
4-Methoxy-*N*-phenylaniline, Compound 23.



Prepared according to General Procedure D using 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70 mg, 0.30 mmol, 1 equiv), aniline (54 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a yellow solid (44 mg, 73%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

2-Methyl-*N*-phenylaniline, Compound 30.

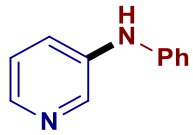


Prepared according to General Procedure D using 4,4,5,5-tetramethyl-2-(*m*-tolyl)-1,3,2-dioxaborolane (65 mg, 0.30 mmol, 1 equiv), aniline (54 µL, 0.60 mmol, 2 equiv),

$Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-5% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a yellow oil (31 mg, 56%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

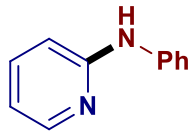
_N_-Phenylpyridin-3-amine, Compound 161.



Prepared according to General Procedure D using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (62 mg, 0.30 mmol, 1 equiv), aniline (54 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-25% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (43 mg, 84%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

_N_-Phenylpyridin-2-amine, Compound 162.

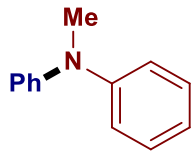


Prepared according to General Procedure D using 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (62 mg, 0.30 mmol, 1 equiv), aniline (54 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv)

and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-30% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (36 mg, 70%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

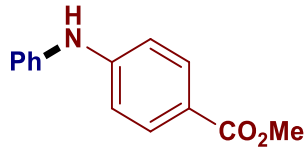
_N_-Methyl-_N_-phenylaniline, Compound 33.



Prepared according to General Procedure D using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol, 1 equiv), *N*-methylaniline (64 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a colourless oil (51 mg, 90%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

Methyl 4-(phenylamino)benzoate, Compound 35.

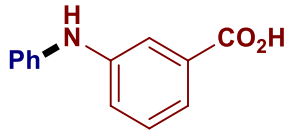


Prepared according to General Procedure D using methyl 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol, 1 equiv), methyl 4-aminobenzoate (91 mg,

0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-5% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (59 mg, 80%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

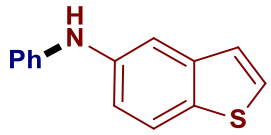
3-(Phenylamino)benzoic acid, Compound 38.



Prepared according to General Procedure D using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol, 1 equiv), 3-aminobenzoic acid (82 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmo, 2 equivl) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-3% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (48 mg, 74%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

***N*-Phenylbenzo[b]thiophen-5-amine, Compound 41.**

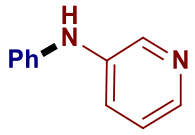


Prepared according to General Procedure D using methyl 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol, 1 equiv), benzo[b]thiophen-5-amine (90 mg,

0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as an off-white solid (43 mg, 63%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

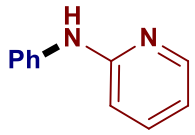
_N_-Phenylpyridin-3-amine, Compound 42.



Prepared according to General Procedure D using methyl 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol, 1 equiv), pyridin-3-amine (56 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-25% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (38 mg, 74%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

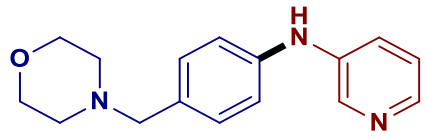
_N_-Phenylpyridin-2-amine, Compound 43.



Prepared according to General Procedure D using methyl 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol, 1 equiv), pyridin-2-amine (56 mg, 0.60 mmol,

2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-30% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (41 mg, 81%). *Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.*

***N*-(4-(Morpholinomethyl)phenyl)pyridin-3-amine, Compound 163.**



Prepared according to General Procedure D using 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine (91 mg, 0.30 mmol, 1 equiv), pyridin-3-amine (56 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-45% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (59 mg, 73%).

Appearance: White solid.

M. pt.: 119-122 ºC.

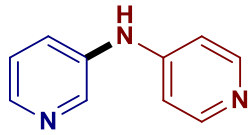
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 2.33-2.35 (m, 4H), 3.38 (s, 2H), 3.56-3.58 (m, 4H), 7.05 (d, *J* = 7.3 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 2H), 7,45 (d, *J* = 7.3 Hz, 2H), 8.31 (s, 1H). 2 aromatic signals were not detected/coincident.

LCMS (ESI): t_R = 0.79 min, $[M+H]^+$ 270.3.

HRMS (ESI): ($C_{16}H_{20}N_3O$) $[M+H]^+$ requires 270.1601, found $[M+H]^+$ 270.1600.

NB. ^{13}C NMR not reported for this compound. Seven different methods of acquisition were attempted but no peaks could be viewed due to apparent relaxation problems.

_N_-(Pyridin-4-yl)pyridin-3-amine, Compound 164.



Prepared according to General Procedure D using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (62 mg, 0.30 mmol, 1 equiv), pyridin-4-amine (56 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-35% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (30 mg, 59%).

Appearance: White solid.

M. pt.: 154-155 ºC.

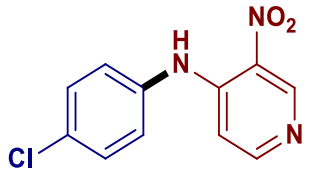
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 1H), 6.85 (d, *J* = 7.2 Hz, 2H), 7.29-7.33 (m, 1H), 7,57-7.60 (m, 1H), 8.33-8.39 (m, 3H), 8.52 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 109.7, 119.6, 123.9, 128.1, 136.5, 143.5, 145.1, 150.0, 150.6.

LCMS (ESI): t_R = 0.15 min, $[M+H]^+$ 172.3.

HRMS (ESI): ($C_{10}H_{10}N_3$) $[M+H]^+$ requires 172.0869, found $[M+H]^+$ 172.0864.

***N*-(4-Chlorophenyl)-3-nitropyridin-4-amine, Compound 165.**



Prepared according to General Procedure D using 2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (71 mg, 0.30 mmol, 1 equiv), 3-nitropyridin-4-amine (84mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-25% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (50 mg, 67%).

Appearance: White solid.

M. pt.: 162-164 ºC.

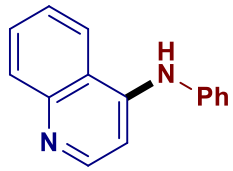
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 6.90 (d, *J* = 7.2 Hz, 1H), 7.39-7.42 (m, 2H), 7.51-7.54 (m, 2H), 8.26 (d, *J* = 7.3 Hz, 1H), 9.10 (s, 1H), 9.80 (s, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 109.7, 119.1, 127.3, 129.5, 130.5, 130.6, 146.5, 148.1, 153.1.

LCMS (ESI): t_R = 0.80 min, $[M+H]^+$ 250.2.

HRMS (ESI): ($C_{11}H_9ClN_3O_2$) $[M+H]^+$ requires 250.0378, found $[M+H]^+$ 250.0374.

***N*-Phenylquinolin-4-amine, Compound 166.**



Prepared according to General Procedure D using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (77 mg, 0.30 mmol, 1 equiv), aniline (54 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-50% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (50 mg, 70%).

Appearance: White solid.

M. pt.: 230-232 ºC.

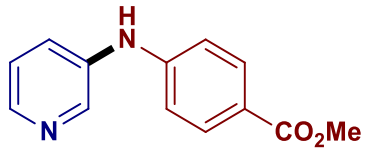
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 6.77 (d, *J* = 7.5 Hz, 1H), 7.42-7.44 (m, 1H), 7.51-7.52 (m, 2H), 7.55-7.59 (m, 2H), 7.78 (t, *J* = 7.1 Hz, 1H), 8.01 (t, *J* = 6.9 Hz, 1H), 8.14 (d, *J* = 7.4 Hz, 1H), 8.49 (d, *J* = 7.1 Hz, 1H), 8.94 (d, *J* = 7.4 Hz, 1H), 11.19 (s, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 99.8, 117.1, 120.1, 123.9, 125.5, 126.9, 127.4, 129.9, 133.8, 137.2, 138.2, 142.5, 155.0

LCMS (ESI): t_R = 0.50 min, $[M+H]^+$ 221.3.

HRMS (ESI): ($C_{15}H_{13}N_2$) $[M+H]^+$ requires 221.1073, found $[M+H]^+$ 221.1066.

Methyl 4-(pyridin-3-ylamino)benzoate, Compound 167.



Prepared according to General Procedure D using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (62 mg, 0.30 mmol, 1 equiv), methyl 4-aminobenzoate (91 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the

General Procedure (silica chromatography, 0-55% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (53 mg, 78%).

Appearance: White solid.

M. pt.: 141-143 ºC.

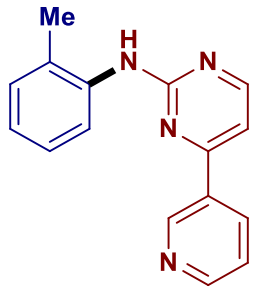
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 1H), 6.11 (s, 1H). 7.02 (d, *J* = 7.3 Hz, 2H), 7.27-7.29 (m, 7.55 (d, *J* = 7.3 Hz, 1H), 7.96 (d, *J* = 7.5 Hz, 1H), 8.32-8.48 (br. m, 2H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 51.8, 115.1, 119.6, 122.4, 126.5, 131.6, 142.3, 143.9, 147.0, 166.7. One aromatic signal missing.

LCMS (ESI): t_R = 0.49 min, $[M+H]^+$ 229.3.

HRMS (ESI): ($C_{13}H_{13}N_2O_2$) $[M+H]^+$ requires 229.0972, found $[M+H]^+$ 229.0966.

4-(Pyridin-3-yl)-*N*-(*o*-tolyl)pyrimidin-2-amine, Compound 168.



Prepared according to General Procedure D using 4,4,5,5-tetramethyl-2-(*m*-tolyl)-1,3,2-dioxaborolane (65 mg, 0.30 mmol, 1 equiv), 4-(pyridin-3-yl)pyrimidin-2-amine (103 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-20% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a yellow solid (39 mg, 52%).

Appearance: Yellow solid.

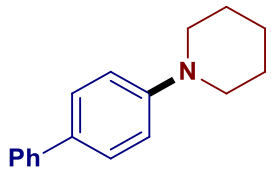
M. pt.: 222-224 ºC.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 2.25 (s, 3H), 7.08 (t, *J* = 7.9 Hz, 1H), 7.19-7.25 (m, 2H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.53-7.55 (m, 2H), 8.38-8.41 (m, 1H), 8.49 (d, *J* = 7.4 Hz, 1H), 8.69 (d, *J* = 7.4 Hz, 1H), 8.91 (s, 1H), 9.24 (s, 1H)

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 29.0, 106.0, 123.7, 125.3, 128.1, 128.8, 132.5, 134.1, 137.3, 147.9, 151.1, 159.3, 161.5, 163.8.

LCMS (ESI): t_R = 1.02 min, $[M+H]^+$ 263.3.

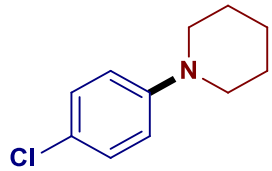
1-([1,1'-Biphenyl]-4-yl)piperidine, Compound 45.



Prepared according to General Procedure D using 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (84 mg, 0.30 mmol, 1 equiv), piperidine (60 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (50 mg, 70%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

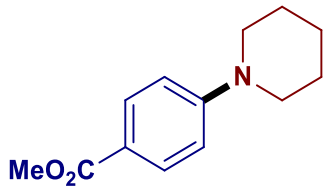
1-(4-Chlorophenyl)piperidine, Compound 50.



Prepared according to General Procedure C using 2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (71 mg, 0.30 mmol, 1 equiv), piperidine (60 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-1.5% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (53 mg, 90%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

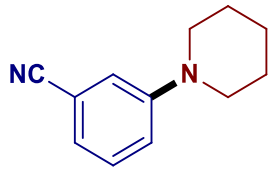
Methyl 4-(piperidin-1-yl)benzoate, Compound 48.



Prepared according to General Procedure C using methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (78 mg, 0.30 mmol, 1 equiv), piperidine (60 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-1.5% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (54 mg, 82%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

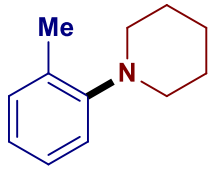
1-(3-Cyanophenyl)piperidine, Compound 51.



Prepared according to General Procedure D using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (69 mg, 0.30 mmol, 1 equiv), piperidine (60 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-2.5% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (40 mg, 71%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

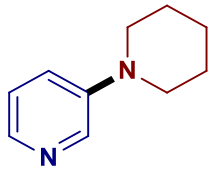
1-(*o*-Tolyl)piperidine, Compound 55.



Prepared according to General Procedure D using 4,4,5,5-tetramethyl-2-(o-tolyl)-1,3,2-dioxaborolane (66 mg, 0.30 mmol, 1 equiv), piperidine (60 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (19 mg, 36%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

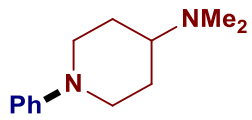
3-(Piperidin-1-yl)pyridine, Compound 56.



Prepared according to General Procedure D using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (62 mg, 0.30 mmol, 1 equiv), piperidine (60 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was purified by ion exchange chromatography (500 mg Biotage sulphonic acid (SCX) cartridge, using sequential solvents methanol, 2 M ammonia/methanol). Fractions were concentrated under vacuum to afford the desired product as a brown solid (38 mg, 74%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

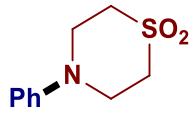
***N,N*-Dimethyl-1-phenylpiperidin-4-amine, Compound 65.**



Prepared according to General Procedure D using phenylboronic acid pinacol ester (62 mg, 0.30 mmol, 1 equiv), *N,N*-dimethylpiperidin-4-amine (84 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (2 M NH_3 in MeOH)/DCM), fractions were concentrated under vacuum to afford the desired product as a yellow solid (50 mg, 81%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

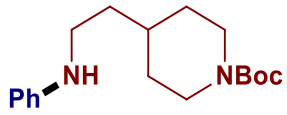
4-Phenylthiomorpholine 1,1-dioxide, Compound 66.



Prepared according to General Procedure D using phenylboronic acid pinacol ester (62 mg, 0.30 mmol, 1 equiv), thiomorpholine 1,1-dioxide (81 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-35% (EtOAc + 1% Et_3N)/cyclohexane). Fractions were concentrated under vacuum to afford the desired product as a white solid (42 mg, 67%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

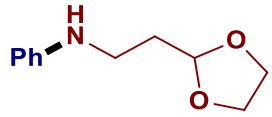
***tert*-Butyl 4-(2-(phenylamino)ethyl)piperidine-1-carboxylate, Compound 72.**



Prepared according to General Procedure D using phenylboronic acid pinacol ester (62 mg, 0.30 mmol, 1 equiv), *tert*-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (135 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-15% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (74 mg, 81%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

***N*-(2-(1,3-Dioxolan-2-yl)ethyl)aniline, Compound 81.**



Prepared according to General Procedure D using phenylboronic acid pinacol ester (62 mg, 0.30 mmol, 1 equiv), 2-(1,3-dioxolan-2-yl)ethanamine (68 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a brown oil (42 mg, 72%).

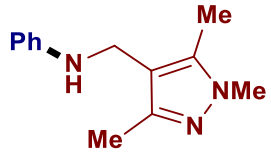
Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

***N*-(4,4,4-Trifluorobutyl)aniline, Compound 77.**

Prepared according to General Procedure D using phenylboronic acid pinacol ester (62 mg, 0.30 mmol, 1 equiv), 4,4,4-trifluorobutan-1-amine (76 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.30 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-1% (EtOAc + 1% Et_3N)/heptane), fractions were concentrated under vacuum to afford the desired product as a yellow oil (44 mg, 73%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

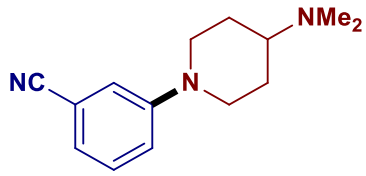
_N_-((1,3,5-Trimethyl-1_H_-pyrazol-4-yl)methyl)aniline, Compound 82.



Prepared according to General Procedure D using phenylboronic acid pinacol ester (62 mg, 0.30 mmol, 1 equiv), (1,3,5-trimethyl-1*H*-pyrazol-4-yl)methanamine (84 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was purified by ion exchange chromatography (1 g Biotage sulphonic acid (SCX) cartridge, using sequential solvents methanol, 2 M ammonia/methanol). Fractions were concentrated under vacuum to afford the desired product as a white solid (61 mg, 94%).

Spectral data were previously described in Section 13. Chapter 1 of Experimental Part.

3-(4-(Dimethylamino)piperidin-1-yl)benzonitrile, Compound 169.



Prepared according to General Procedure D using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (69 mg, 0.30 mmol, 1 equiv), *N,N*-dimethylpiperidin-4-amine (84 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (2 M NH_3 in MeOH)/DCM), fractions were concentrated under vacuum to afford the desired product as a white solid (53 mg, 77%).

Appearance: White solid.

M. pt.: 101-103 ºC.

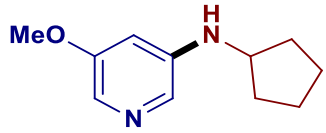
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 1.42 (qd, *J* = 12.4, 3.9 Hz, 2H), 1.79-1.82 (m, 2H), 2.34 (s, 6H), 2.19 (td, *J* = 12.4, 3.9 Hz, 2H), 2.20-2.22 (m, 1H), 3.70-3.77 (m, 2H), 7.10 (dt, *J* = 7.2 Hz, 0.9 Hz, 1H), 7.24-7.27 (m, 1H), 7.29-7.30 (m, 1H), 7.35 (t, *J* = 8.7, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 27.4, 41.4, 46.9, 61.1, 111.9, 117.6, 119.3, 119.7, 121.0, 130.1, 150.9.

LCMS (ESI): t_R = 0.42 min, $[M+H]^+$ 230.4.

HRMS (ESI): ($C_{14}H_{20}N_3$) $[M+H]^+$ requires 230.1652, found $[M+H]^+$ 230.1647.

***N*-Cyclopentyl-5-methoxypyridin-3-amine, Compound 170.**



Prepared according to General Procedure D using 3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (71 mg, 0.30 mmol, 1 equiv), cyclopentylamine (60 µL, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 25-75% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (52 mg, 90%).

Appearance: White solid.

M. pt.: 97-99 ºC.

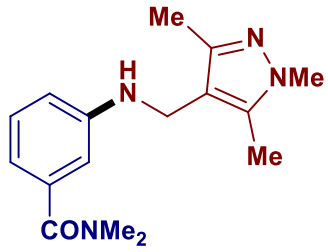
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 1.41-1.45 (m, 2H), 1.53-1.59 (m, 2H), 1.65-1.69 (m 2H), 1.88-1.96 (m, 2H), 3.34 (s, 1H), 3.69-3.71 (m, 1H), 3.72 (s, 3H), 5.85 (s, 1H), 6.44 (s, 1H), 7.25-7.75 (br. m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 23.1, 33.4, 54.4, 55.5, 101.6. 119.6, 124.7, 129.3. One aromatic signal not observed/coincident.

LCMS (ESI): t_R = 0.52 min, $[M+H]^+$ 193.3.

HRMS (ESI): ($C_{11}H_{17}N_2O$) $[M+H]^+$ requires 193.1335, found $[M+H]^+$ 193.1352.

***N,N*-Dimethyl-3-(((1,3,5-trimethyl-1*H*-pyrazol-4-yl)methyl)amino)benzamide, Compound 171.**



Prepared according to General Procedure D using *N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (83 mg, 0.30 mmol, 1 equiv), (1,3,5-trimethyl-1*H*-pyrazol-4-yl)methanamine (84 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was purified by ion exchange chromatography (1 g Biotage sulphonic acid (SCX) cartridge, using sequential solvents methanol, 2 M ammonia/methanol). Fractions were concentrated under vacuum to afford the desired product as a white solid (53 mg, 62%).

Appearance: White solid.

M. pt.: 105-107 ºC.

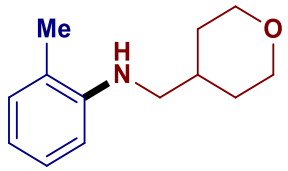
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 2.08 (s, 3H), 2.18 (s, 3H), 2.91 (br. s., 6H), 3.62 (s, 3H), 3.90 (d, *J* = 6.3 Hz, 2H), 5.64 (t, *J* = 6.4 Hz, 1H), 6.49-6.51 (m, 1H), 6.57-6.58 (m, 1H), 6.64-6.67 (m, 1H), 7.10 (t, *J* = 8.3 Hz, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 9.2, 11.6, 35.5, 36.8, 110.2, 112.7, 112.8, 113.7, 114.3, 128.5, 137.0, 137.1, 144.7, 148.7, 170.8.

LCMS (ESI): t_R = 0.60 min, $[M+H]^+$ 287.3.

HRMS (ESI): ($C_{16}H_{23}N_4O$) $[M+H]^+$ requires 287.1866, found $[M+H]^+$ 287.1865.

2-Methyl-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)aniline, Compound 172.



Prepared according to General Procedure D using 4,4,5,5-tetramethyl-2-(*o*-tolyl)-1,3,2-dioxaborolane (66 mg, 0.30 mmol, 1 equiv), (tetrahydro-2*H*-pyran-4-yl)methanamine (69 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (0.06 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a colourless oil (46 mg, 75%).

Appearance: Colourless oil.

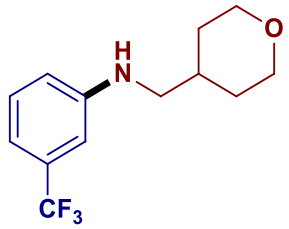
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29-1.43 (m, 2H), 1.72-1.76 (m, 2H), 1.91-2.01 (m, 1H), 2.15 (s, 3H), 3.10 (d, *J* = 6.6 Hz, 2H), 3.42 (td, *J* = 11.6, 2.2 Hz, 2H), 4.00-4.04 (m, 2H), 6.62-6.69 (m, 2H), 7.07 (d, *J* = 8.5 Hz, 1H), 7.14 (dt, *J* = 8.5, 2.0 Hz, 1H). N-H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 17.4, 31.1, 34.7, 50.0, 67.8, 109.6, 116.8, 121.8, 127.1, 130.1, 146.0.

LCMS (ESI): t_R = 0.96 min, $[M+H]^+$ 206.3.

HRMS (ESI): ($C_{13}H_{20}NO$) $[M+H]^+$ requires 206.1539, found $[M+H]^+$ 206.1560.

***N*-((Tetrahydro-2*H*-pyran-4-yl)methyl)-3-(trifluoromethyl)aniline, Compound 173.**



Prepared according to General Procedure D using 4,4,5,5-tetramethyl-2-(3-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (81 mg, 0.30 mmol, 1 equiv), (tetrahydro-2*H*-pyran-4-yl)methanamine (69 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (0.06 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-25% (EtOAc + 1% Et_3N)/cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (62 mg, 80%).

Appearance: White solid.

M. pt.: 100-103 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38-1.43 (m, 2H), 1.71-1.75 (m, 2H), 1.87-1.88 (m, 1H), 3.08 (d, *J* = 6.7 Hz, 2H), 3.44 (td, *J* = 11.3, 2.2 Hz, 2H), 4.00 (br. s., 1H), 4.01-4.05 (m, 2H), 6.74-6.81 (m, 2H), 6.94 (d, *J* = 8.3 Hz, 1H), 7.26 (dt, *J* = 8.3, 1.8 Hz, 1H).

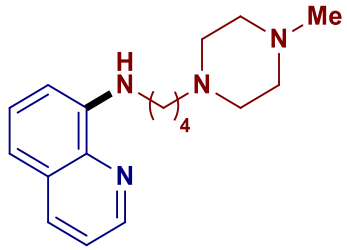
^{13}C NMR (101 MHz, $CDCl_3$): δ 31.0, 34.9, 49.8, 67.7, 108.7 (d, *J* = 2.3 Hz), 113.6 (q, *J* = 2.3 Hz), 115.6, 124.4 (q, *J* = 271.8 Hz), 129.6, 131.6 (q, *J* = 28.1 Hz), 148.4

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.5.

LCMS (ESI): t_R = 1.20 min, $[M+H]^+$ 260.3.

HRMS (ESI): ($C_{13}H_{17}F_3NO$) $[M+H]^+$ requires 260.1257, found $[M+H]^+$ 260.1279.

***N*-(4-(4-Methylpiperazin-1-yl)butyl)quinolin-8-amine, Compound 174.**



Prepared according to General Procedure D using 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (78 mg, 0.30 mmol, 1 equiv), 4-(4-methylpiperazin-1-yl)butan-1-amine (103 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was purified by ion exchange chromatography (1 g Biotage sulphonic acid (SCX) cartridge, using sequential solvents methanol, 2 M ammonia/methanol). Fractions were concentrated under vacuum to afford the desired product as a red solid (39 mg, 44%).

Appearance: Red solid.

M. pt.: 135-137 ºC.

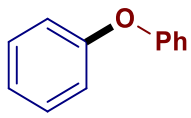
^{1}H NMR (400 MHz, CD_3OD): δ 1.94-1.98 (m, 2H), 2.07-2.12 (m, 2H), 3.38 (s, 3H), 3.40-3.42 (m, 2H), 3.51-3.54 (m. 2H), 4.82 (br. s, 8H), 7.44 (d, *J* = 4.3 Hz, 1H), 7.68 (d, *J* = 4.3 Hz, 1H), 7.77-7.80 (m, 1H), 7.92-7.95 (m, 1H), 8.91 (d, *J* = 4.2 Hz, 1H), 9.02 (d, *J* = 4.3 Hz, 1H),

LCMS (ESI): t_R = 0.41 min, $[M+H]^+$ 299.4.

HRMS (ESI): ($C_{18}H_{27}N_4$) $[M+H]^+$ requires 299.2230, found $[M+H]^+$ 299.2225.

NB. ^{13}C NMR not reported for this compound. Seven different methods of acquisition were attempted but no peaks could be viewed due to apparent relaxation problems.

Oxydibenzene, Compound 175.[145]



Prepared according to General Procedure D using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol, 1 equiv), phenol (55 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-10% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (53 mg, 70%).

Appearance: White solid.

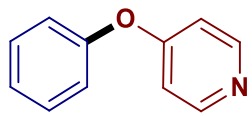
M. pt.: 31-33 ºC.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 7.02 (d, *J* = 8.1 Hz, 4H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.32-7.38 (m, 4H)

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 118.9, 123.2, 129.7, 157.3.

LCMS (ESI): t_R = 1.29 min.

4-Phenoxypyridine, Compound 176.



Prepared according to General Procedure D using 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (61 mg, 0.30 mmol, 1 equiv), pyridin-4-ol (86 mg, 0.90 mmol, 3 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure

(silica chromatography, 0-40% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (27 mg, 53%).

Appearance: White solid.

M. pt.: 45-47 ºC.

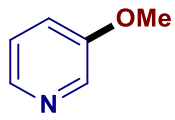
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 6.90 (d, *J* = 7.3 Hz, 2H), 7.18 (d, *J* = 7.3 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.47-7.51 (m, 2H), 8.46 (d, *J* = 7.3 Hz, 2H)

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 112.0, 120.6, 125.5, 130.4, 151.5, 153.6, 164.0.

LCMS (ESI): t_R = 0.40 min, $[M+H]^+$ 172.3.

HRMS (ESI): ($C_{11}H_{10}NO$) $[M+H]^+$ requires 172.0757, found $[M+H]^+$ 172.0753.

3-Methoxypyridine, Compound 177.



Prepared according to General Procedure D using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (62 mg, 0.30 mmol, 1 equiv), methanol (29 mg, 0.90 mmol, 3 equiv), $Cu(OAc)_2$ (54 mg, 0.30 mmol, 1 equiv), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 50-100% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (24 mg, 72%).

Appearance: White solid.

M. pt.: 203-205 ºC.

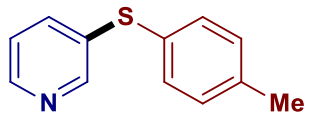
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 3.98 (s, 1H), 7.95-7.98 (m, 1H), 8.15-8.18 (m, 1H), 8.51 (d, *J* = 7.7 Hz, 1H), 8.67 (d, *J* = 7.6 Hz, 1H)

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 57.0, 127.6, 129.1, 130.6, 134.4, 157.5.

LCMS (ESI): t_R = 0.56 min, $[M+H]^+$ 110.1.

HRMS (ESI): (C_6H_8NO) $[M+H]^+$ requires 110.0600, found $[M+H]^+$ 110.0604.

3-(*p*-Tolylthio)pyridine, Compound 178.



Prepared according to General Procedure D using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (62 mg, 0.30 mmol, 1 equiv), 4-methylbenzenethiol (74 mg, 0.60 mmol, 2 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-30% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (44 mg, 74%).

Appearance: White solid.

M. pt.: 159-161 ºC.

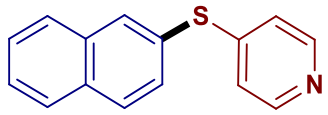
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 2.31 (s, 1H), 7.23-7.25 (m, 2H), 7.32-7.37 (m, 3H), 7.61-7.6 (m, 1H), 8.43-8.45 (m, 2H)

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 20.4, 124.4, 129.2, 130.5, 132.2, 133.5, 137.1, 138.1, 147.7, 149.6.

LCMS (ESI): t_R = 1.04 min, $[M+H]^+$ 202.3.

HRMS (ESI): ($C_{12}H_{12}NS$) $[M+H]^+$ requires 202.0685, found $[M+H]^+$ 202.0678.

4-(Naphthalen-2-ylthio)pyridine, Compound 179.



Prepared according to General Procedure D using 4,4,5,5-tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane (110 mg, 0.30 mmol, 1 equiv), pyridine-4-thiol (99 mg, 0.90 mmol, 3 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-40% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (43 mg, 61%).

Appearance: White solid.

M. pt.: 117-119 ºC.

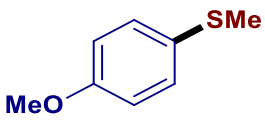
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 7.06 (d, *J* = 7.3 Hz, 2H), 7.58-7.64 (m, 3H), 7.99-8.07 (m, 3H), 8.27 (s, 1H), 8.36 (d, *J* = 7.7 Hz, 2H)

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 120.7, 126.0, 127.1, 127.6, 127.8, 127.9, 129.9, 130.8, 132.9, 133.5, 134.6, 148.9, 149.6.

LCMS (ESI): t_R = 0.76 min, $[M+H]^+$ 238.3.

HRMS (ESI): ($C_{15}H_{12}NS$) $[M+H]^+$ requires 238.0685, found $[M+H]^+$ 238.0679.

(4-Methoxyphenyl)(methyl)sulfane, Compound 180.



Prepared according to General Procedure D using 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70 mg, 0.30 mmol, 1 equiv), methanethiol (29 mg, 0.90 mmol, 3 equiv), $Cu(OAc)_2$ (54 mg, 0.30 mmol, 1 equiv), $B(OH)_3$ (36 mg, 0.60

mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-25% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a brown solid (29 mg, 63%).

Appearance: Brown solid.

M. pt.: 29-31 ºC.

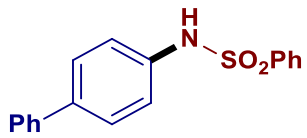
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 2.41 (s, 3H), 3.73 (s, 3H), 6.90 (d, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 7.3 Hz, 2H)

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 16.6, 55.1, 114.7, 128.2, 129.1, 157.5.

LCMS (ESI): t_R = 1.09 min, $[M+H]^+$ not detected.

HRMS (ESI): ($C_8H_{11}OS$) $[M+H]^+$ requires 155.0525, found $[M+H]^+$ 155.0524.

***N*-([1,1'-Biphenyl]-4-yl)benzenesulfonamide, Compound 181.**



Prepared according to General Procedure D using 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (84 mg, 0.30 mmol, 1 equiv), benzenesulfonamide (61 mg, 0.39 mmol, 1.3 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-25% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (47 mg, 53%).

Appearance: White solid.

M. pt.: 147-148 ºC.

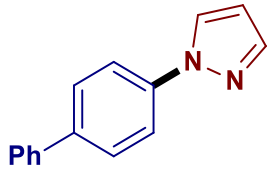
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 6.94 (s, 1H), 7.15-7.19 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.40-7.58 (m, 9H), 7.85 (d, *J* = 7.3 Hz, 2H)

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 121.9, 126.8, 127.2, 127.3, 127.9, 128.7, 129.0, 133.0, 135.5, 138.5, 139.1, 140.0.

LCMS (ESI): t_R = 1.21 min, $[M+H]^+$ 309.8.

HRMS (ESI): ($C_{18}H_{16}NO_2S$) $[M+H]^+$ requires 310.0896, found $[M+H]^+$ 310.0887.

1-([1,1'-Biphenyl]-4-yl)-1*H*-pyrazole, Compound 182.



Prepared according to General Procedure D using 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (84 mg, 0.30 mmol, 1 equiv), 1*H*-pyrazole (27 mg, 0.39 mmol, 1.3 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-20% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (46 mg, 71%).

Appearance: White solid.

M. pt.: 135-137 ºC.

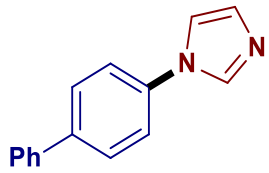
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 6.57 (s, 1H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.72 (d, *J* = 7.3 Hz, 2H), 7.78-7.81 (m, 3H), 7.93-7.95 (m, 2H), 8.55 (s, 1H)

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 107.9, 118.7, 126.5, 127.5, 127.6, 128.9, 137.8, 139.0, 139.1, 141.0.

LCMS (ESI): t_R = 1.24 min, $[M+H]^+$ 221.1.

HRMS (ESI): ($C_{15}H_{13}N_2$) $[M+H]^+$ requires 221.1073, found $[M+H]^+$ 221.1066.

1-([1,1'-Biphenyl]-4-yl)-1*H*-imidazole, Compound 183.



Prepared according to General Procedure D using 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (84 mg, 0.30 mmol, 1 equiv), 1*H*-imidazole (27 mg, 0.39 mmol, 1.3 equiv), $Cu(OAc)_2$ (11 mg, 0.06 mmol, 20 mol%), $B(OH)_3$ (36 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (100 mg) in MeCN (450 µL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-30% (EtOAc + 1% Et_3N)/cyclohexane) fractions were concentrated under vacuum to afford the desired product as a white solid (46 mg, 74%).

Appearance: White solid.

M. pt.: 150-152 ºC.

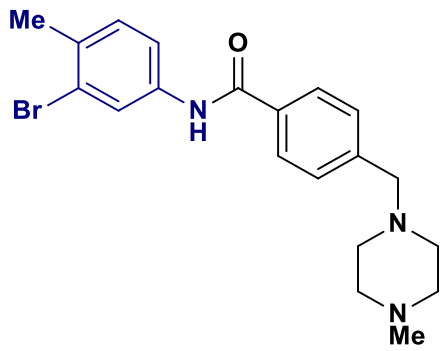
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 7.25 (s, 1H), 7.33 (s, 1H), 7.38-7.42 (m, 1H), 7.46-7.50 (m, 4H), 7.60-7.63 (m, 2H), 7.69-7.72 (m, 2H), 7.91 (s, 1H)

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 118.4, 122.1, 127.3, 128.1, 128.8, 129.2, 130.8, 135.8, 136.8, 140.0, 140.8.

LCMS (ESI): t_R = 1.10 min, $[M+H]^+$ 221.1.

HRMS (ESI): ($C_{15}H_{13}N_2$) $[M+H]^+$ requires 221.1073, found $[M+H]^+$ 221.1066.

***N*-(3-Bromo-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide, Compound 185.**



To a round-bottom flask was added 4-(chloromethyl)benzoyl chloride **35** (1.0 g, 5.3 mmol, 1.0 equiv) in dry DMF (50 mL) under argon. DIPEA (2.8 mL, 15.9 mmol, 3 equiv) and 3-bromo-4-methylaniline **36** (1.1 g, 5.8 mmol, 1.1 equiv) were subsequently added and the reaction was stirred at RT for 3 h. The reaction mixture was diluted with water and extracted with EtOAc (4×50 mL). The collected organic layers were combined and washed with LiCl (50 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was added in dry DMF (25 mL) to a round-bottom flask. K_2CO_3 (2.2 g, 15.9 mmol, 3 equiv) and 1-methylpiperazine **37** (0.7 mL, 6.4 mmol, 1.2 equiv) were subsequently added and the reaction was stirred at 50 °C for 16 h. The reaction mixture was diluted with water and extracted with EtOAc (4×25 mL). The collected organic layers were combined and washed with LiCl (25 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified using flash chromatography (0-30% (EtOAc/Cyclohexane), fractions were concentrated under vacuum to afford the desired product as a yellow solid (1.9 g, 89%).

Appearance: White solid.

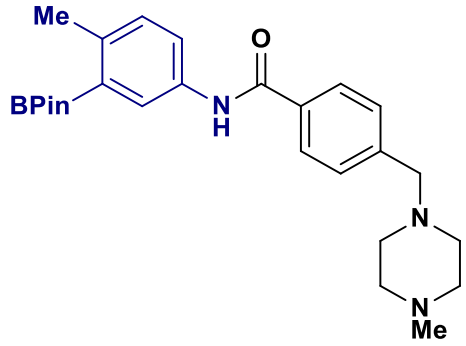
M. pt.: 148-149 ºC.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 2.18 (s, 3H), 2.31 (s, 3H), 2.38-2.51 (m, 8H), 3.59 (s, 2H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.67 (dd, *J* = 8.1 Hz and *J* = 1.9, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 8.13 (d, *J* = 8.3 Hz, 1H).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 21.7, 45.5, 52.4, 54.5, 61.5, 119.4, 123.3, 123.5, 127.6, 128.6, 130.8, 131.9, 133.2, 138.4, 142.3, 165.3.

LCMS (ESI): t_R = 0.68 min, $[M+H]^+$ 404.2.

***N*-(4-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide, Compound 188.**



N-(3-Bromo-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (1.9 g, 4.7 mmol, 1 equiv) was dissolved in DMSO (20 mL) and treated with bis(pinacolato)diboron (1.8 g, 7.1 mmol, 1.5 equiv) and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (0.4 g, 0.5 mmol, 0.1 equiv) followed by KOAc (2.3 g, 23.5 mmol, 5 equiv) at RT. The reaction was then heated to 80 ºC and stirred for 2 h. The solvent was removed by rotary evaporation to provide a dark brown solid residue that was purified using flash chromatography (0-30% (EtOAc/Cyclohexane), fractions were concentrated under vacuum to afford the desired product as a white solid (1.9 g, 89%).

Appearance: White solid.

M. pt.: 140-142 ºC.

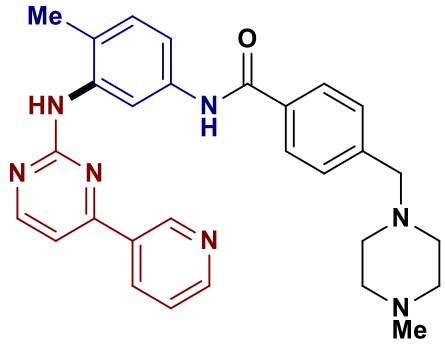
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 1.31 (s, 12H), 2.33 (s, 3H), 2.43 (s, 3H), 2.40-2.47 (m, 4H), 2.50-2.58 (m, 4H), 3.59 (s, 2H), 7.15 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.85 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.91-7.97 (m, 3H).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 21.2, 24.4, 24.7, 44.6, 51.5, 54.0, 61.2, 83.3, 119.1, 123.1, 127.5, 128.6, 129.8, 133.5, 136.1, 139.2, 164.9.

LCMS (ESI): t_R = 0.80 min, $[M+H]^+$ 450.4.

HRMS (ESI): ($C_{26}H_{37}BN_3O_3$) $[M+H]^+$ requires 450.2923, found $[M+H]^+$ 450.2911.

***N*-(4-Methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide, Compound 184.**



Prepared according to General Procedure D using *N*-(4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (500 mg, 1.11 mmol, 1 equiv), 4-(pyridin-3-yl)pyrimidin-2-amine (379 mg, 2.22 mmol, 2 equiv), $Cu(OAc)_2$ (40 mg, 0.22 mmol, 20 mol%), $B(OH)_3$ (132 mg, 0.60 mmol, 2 equiv) and powdered activated 4 Å molecular sieves (450 mg) in MeCN-*t*BuOH (3:1 ratio, 1.7 mL). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica chromatography, 0-50% (EtOAc + 1% Et_3N)/Cyclohexane) fractions were concentrated under vacuum to afford the desired product as an orange solid (367 mg, 67%).

Appearance: Orange solid.

M. pt.: 207-209 ºC.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 7.25 (s, 1H), 7.33 (s, 1H), 7.38-7.42 (m, 1H), 7.46-7.50 (m, 4H), 7.60-7.63 (m, 2H), 7.69-7.72 (m, 2H), 7.91 (s, 1H)

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 17.6, 42.1, 48.9, 52.0, 59.9, 107.6, 116.8, 117.3, 124.1, 127.7, 129.2, 130.0, 132.5, 134.4, 135.3, 137.1, 137.7, 147.4, 150.5, 158.2, 158.5, 159.5, 161.1, 161.3, 164.9.

LCMS (ESI): t_R = 0.96 min, $[M+H]^+$ 494.4.

HRMS (ESI): ($C_{29}H_{32}N_7O$) $[M+H]^+$ requires 494.2663, found $[M+H]^+$ 494.2661.

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