Copper Mediated Transformations of Alkyl Boronic Esters

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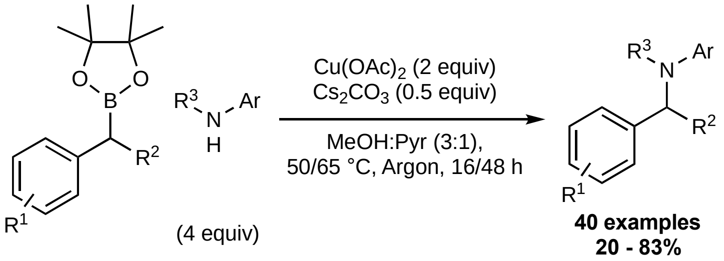
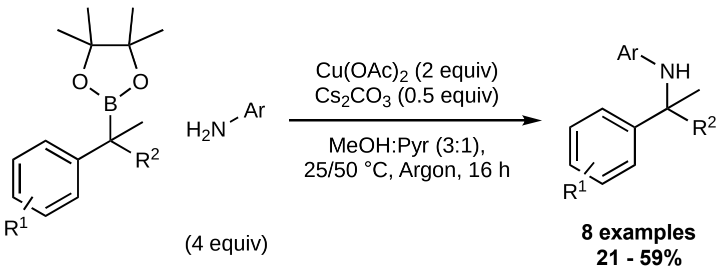
1 Abstract

Alkyl boron reagents have a lot of potential as synthetic building blocks. However, in comparison to their aryl boron counterparts, catalytic transformations of alkyl boronic esters are highly underdeveloped. For example, the Chan-Evans-Lam coupling of aryl boronic acids to form aryl amines is a well explored method, but examples of similar couplings with alkyl boronic esters are scarce. The successful development of such a transformations would give a powerful synthetic method to prepare valuable alkyl amines.

Conditions have been developed for the copper-mediated coupling of a range of 2° alkyl pinacol boronic esters and anilines. This functional group tolerant method uses stoichiometric $Cu(OAc)_2$ and inert argon atmosphere to overcome the formation of oxidation side-products. Complementary to current reports, coupling is shown to be selective for amine over amide functionalities. Low conversion of 2° amines and non-benzylic boronic esters show a limitation of these conditions. Preliminary mechanistic data suggests the formation of a radical intermediate. The conditions have been applied to analogous *O*- and *S*- coupling partners showing varied success.

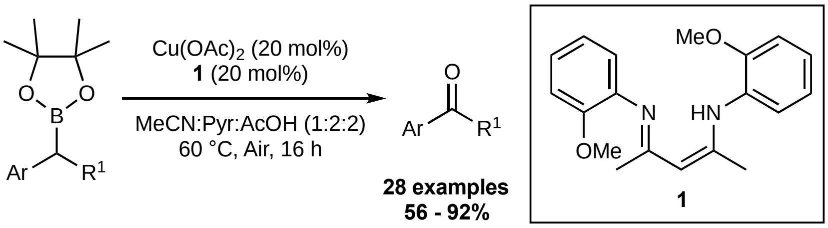


This method has been extended to the coupling of 3° boronic ester and anilines. To our knowledge, this is the first example of the use of 3° boronic esters in a Chan-Evans-Lam reaction. This is an attractive method for the formation of synthetically challenging 3° amines, which cannot be prepared through reductive amination.



Cu-catalysed conditions for the direct conversion of benzylic boronic esters to the corresponding carbonyl have been developed. This mild and functional group tolerant method uses an ambient atmosphere of air as the terminal oxidant. The oxidation occurs selectively even in the presence of an unprotected alcohol. Preliminary investigations suggest the

reaction proceeds through an alkyl boron to Cu transmetallation, peroxide formation, and rearrangement to give the carbonyl. To our knowledge this is the first example of a copper-catalysed C-B bond oxidation to the carbonyl oxidation state.



2 Acknowledgments

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Table of Contents

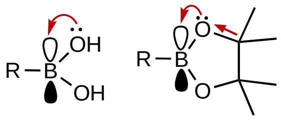
3 Abbreviations

1°	Primary
2°	Secondary
3°	Tertiary
9-BBN	9-Borabicyclo[3.3.1]nonane
ABNO	9-Azabicyclo[3.3.1]nonane-*N*-oxyl
AIBN	α,α′-Azoisobutyronitrile
Ar	Aryl
BINAP	(2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl)
BIPY	2,2'-Bipyridine
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
br	Broad
br. d	Broad Doublet
br. s	Broad Singlet
Bu	Butyl
Cb	N,N-Diisoproyplcarbamoyl
d	Doublet
dbu	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
dd	Doublet Doublet
ddd	Doublet Doublet doublet
DG	Directing Group
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppBz	1,2-Bis(diphenylphosphino)benzene
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric Ratio
dt	Doublet Triplet
DTBM	3,5-Di-tert-butyl-4-methoxyphenyl
DTBP	Di-tert-butyl peroxide
dtd	Doublet Triplet Doublet
EI	Electronic Ionisation
equiv	Equivalent(s)
er	Enantiomeric Ratio
ESI	Electrospray Ionisation
GC	Gas Chromatography
GC-MS	Gas Chromatography - Mass Spectrometry
HMBC	Heteronuclear Multiple Bond Coherence
HMDS	Hexamethyldisilazane
HPLC	High-Performance Liquid Correlation spectroscopy
HRMS	High Resolution Mass Chromatography spectrometry
HSQC	Heteronuclear Single Quantum Coherence
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolinium chloride
J	Coupling Constant (NMR)
LHS	Left Hand Side
m	Meta
m	Multiplet
m/z	Mass/charge ratio
mp	Melting Point
MS	Molecular Sieves
MTBE	Methyl tert-butyl ether
M	Concentration
nbd	Norbornadiene
ND	Not Determined
NHC	*N*-Heterocyclic Carbene
NMI	*N*-Methylimidazole
NMO	*N*-Methylmopholine-*N*-oxide
NMR	Nuclear magnetic resonance
Np	1-Naphthyl
o	Ortho
p	Para
p	Pentet
PCC	Pyridinium chlorochromate

PFC	Pyridinium fluorochromate
Ph	Phenyl
pin	Pinacol
***p*TSA**	Para-tolylsulfonic acid
Pyr	Pyridine
q	Quartet
Q-TOF	Quadrupole Time Of Flight
quin	Quintet
RHS	Right Hand Side
rr	Regiomeric Ratio
RT	Room temperature
s	Singlet
sept	Septet
t	Tert
T	Temperature
t	Triplet
td	Triplet Doublet
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TM	Transition Metal
TMEDA	N,N,N‟,N‟-Tetramethylethyldiamine
Tol	Tolyl
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl
TS	Transition State
δ	Chemical Shift

1 Introduction

Over the past half a century, research into the production and transformation of organoboron reagents (boranes, boronic acids and esters) has grown rapidly, culminating in one of the most versatile and diverse class of building blocks in organic chemistry.[1,2] Due to their excellent functional group tolerance and orthogonal reactivity, they have been widely applied to pharmaceutical and agrochemical science in a range of stoichiometric, catalytic and enantioselective transformations.



2 **3**

Figure 1: π-Back donation of electron density from oxygen to empty p-orbital on boron.

The stability, and consequent ease of manipulation and purification of trigonal planar, tri-coordinate organoboron reagents is linked to the Lewis acidity and availability of the empty p-orbital on boron (Figure 1). Due to the increased bond strength of B-O compared with B-C bonds arising from the π-back donation of electron density from oxygen to the empty p-orbital on boron (**2**), triorganoboranes are often susceptible to oxidation under air to the borinic acid and then the boronic acid (Figure 2). Oxygen coordination lowers the Lewis acidity of the empty p-orbital on boron due to the aforementioned π-back donation (**2**). The corresponding borinic or boronic esters typically exhibit reduced Lewis acidity when compared with their acid analogues. This occurs due to the σ-donating ability of carbon to oxygen. This effect reduces the polarisation of the B-O bond and increases the electron density on the oxygen available for π-back donation (**3**).[3,4] Although reduced in Lewis acidity, the empty p-orbital on boronic acids and esters is still available to reaction, including degradation pathways such as protodeboronation or oxidation.[5] Additionally, boronic esters display a decreased reactivity and subsequent increased stability when compared to boronic acids due to the increased steric bulk from the ligand around the boron centre. For relatively bulky pinacol boronic esters, this reduces the propensity for erroneous decomposition during purification and further transformation.[6]

BR_3		BR_2OH		BR_2OR		$BR(OH)_2$		$BR(OR)_2$		$B(OH)_3$		$B(OR)_3$
	>		>		>		>		>		>	
Borane		Borinic acid		Borinic ester		Boronic acid		Boronic ester		Boric acid		Borate

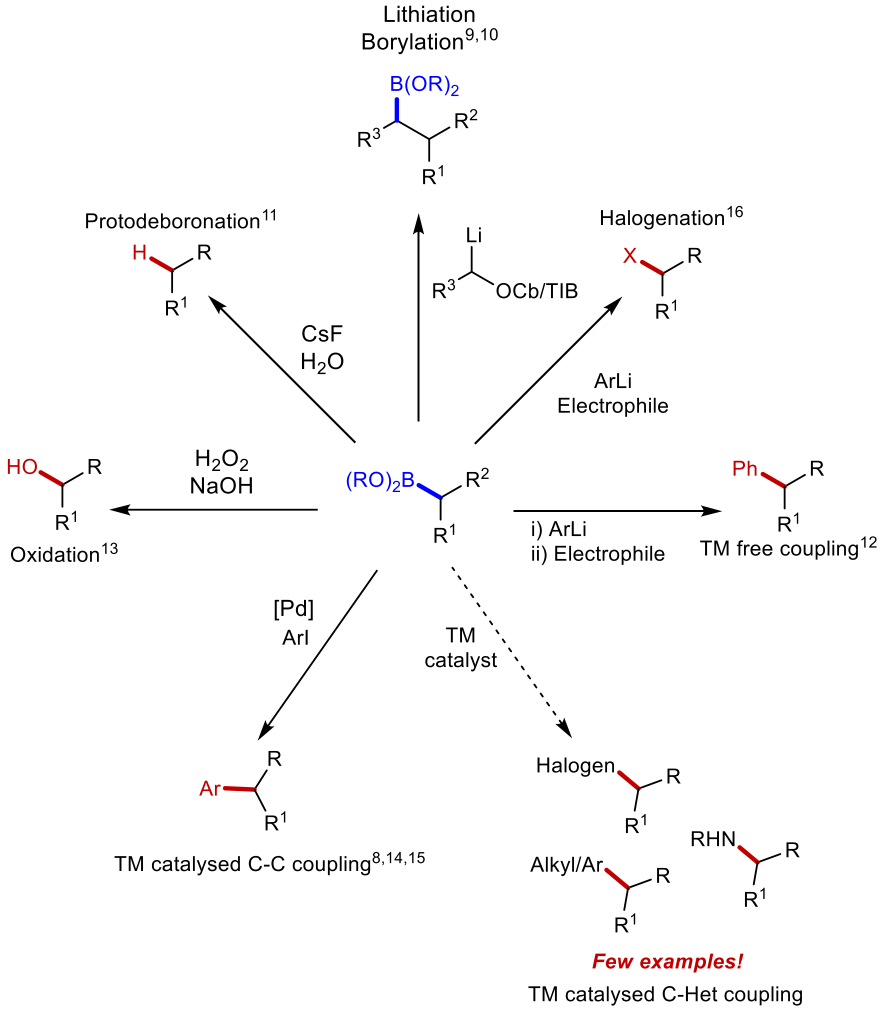
$\xrightarrow{\hspace{10cm}}$

Decreasing Lewis Acidity

Figure 2: Decreasing Lewis acidity of organoboron reagents as the electron density on boron increases.

The transformations of arylboronic acids and esters have become a well-developed area of research, particularly when compared to alkylboronic acids and esters. Arylboronic esters benefit from an increased reactivity towards transmetallation, and after transmetallation arylmetal intermediates do not suffer from β-hydride elimination unlike many alkylmetal intermediates. Noteworthy is arylboronic esters use in the Suzuki-Miyaura reaction, the most common C-C bond forming reaction in medicinal chemistry.[4] The transformations of arylboronic acids and esters expanded with the growth of metal catalysed borylation reactions of aryl halides, and wide commercial availability of arylboronic acids and esters.[2] Consequently, research into the transformation of arylboronic acids and esters has given access to a vast number of C-C and C-heteroatom bond forming reactions.[4]

Although alkylboronic esters can now be readily prepared (Section 1.1), their further transformations are underdeveloped when compared to arylboronic esters. The challenges with the relatively reduced rate of transmetallation and the subsequent alkylmetal's propensity for β-hydride elimination, has driven reactions of alkylboron reagents to remain underdeveloped. Currently, there are a number of stoichiometric transformations to form C-C and C-heteroatom bonds that often suffer from harsh conditions (e.g. use of organolithiums), and so lack functional group tolerance (Scheme 1).[3] Therefore, complementary catalytic transformations under milder conditions may overcome these issues. However, there are relatively few metal-mediated methods for the formation of C-C bonds and fewer still for the formation of C-heteroatom bonds (Scheme 1).[7]



Scheme 1: Examples of stoichiometric and catalytic transformations of alkylboronic esters.[8–16]

The aim of this research is to develop new transformations of alkylboronic pinacol esters for C-X bond formations. Through this work we hope to expand on the synthetic toolbox of alkylboronic esters with novel and beneficial transformations.

1.1 *Methods of Alkyl Boronic Ester Synthesis*

The transformation of C-sp^3 boron reagents presents an appealing route to access functionalised C-sp^3 centres found often in medicinal and agrochemicals. The potential of alkylboronic esters has prompted their synthesis to become a popular area of research. Recent advances mean that 2° and 3° alkylboronic esters can be readily prepared through a range of methods, some of which are stereoselective.[17–20] Throughout this section, focus is given to the preparation 2° and 3° alkylboronic pinacol esters.

1.1.1 Borylation of Organohalides and Pseudo Halides

Organohalides are used both as electrophiles and to create nucleophilic organometallic reagents in processes to form boronic esters. For example, organomagnesium or lithium reagents formed from alkyl halides are reacted with an electrophilic source of boron (e.g. $B(OMe)_3$) to provide the boronic ester (Figure 3). Due to the basic carbon nucleophiles produced, these conditions often lack functional group compatibility and, air and moisture stability.[21,22]

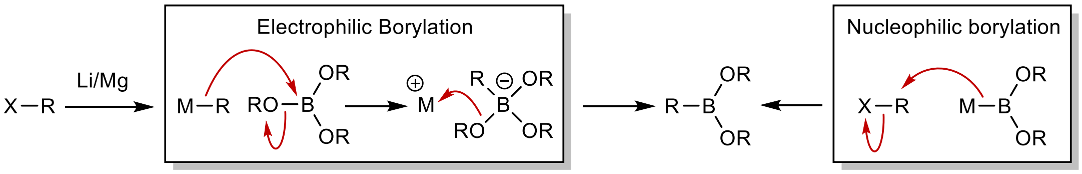
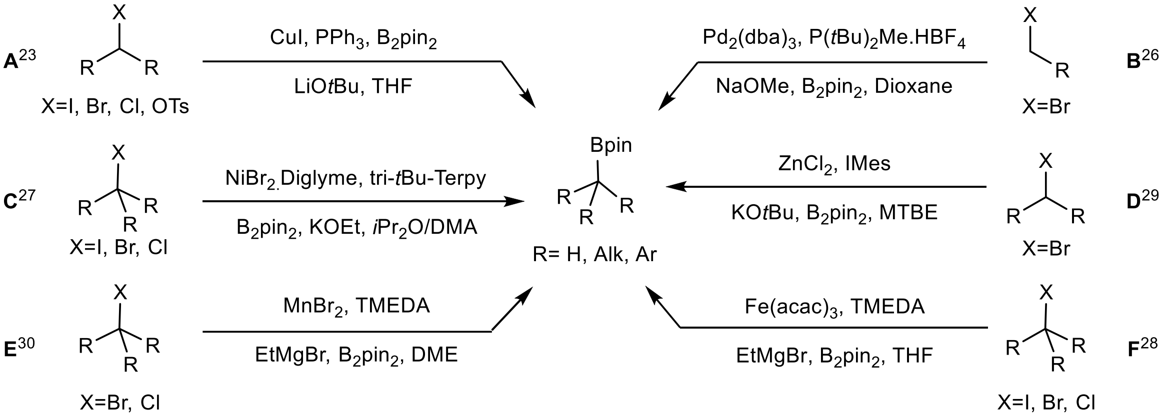


Figure 3: Electrophilic and nucleophilic borylation of organohalides.

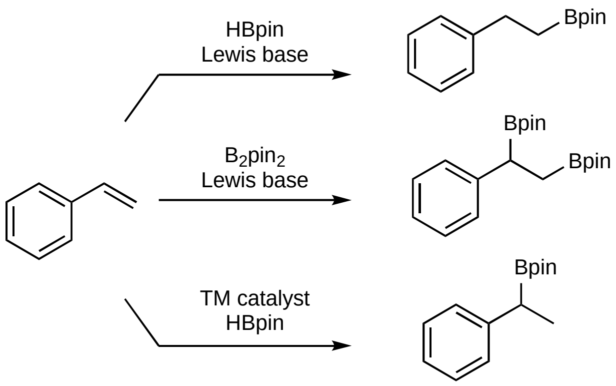
To overcome these limitations, transition metal-catalysed nucleophilic boryl substitution reactions of organohalides have been developed (Figure 3). A number of transition metals have been shown to mediate the synthesis of alkylboronic esters from alkyl halides including Cu, Pd, Fe, Zn and Mn. Metal and ligand combinations have allowed divergent transformations of 1°, 2° and 3° alkyl electrophiles (I, Br, Cl, OTs etc.) (Scheme 2).



Scheme 2: Selected examples of transformations of alkyl electrophiles to alkylboronic esters.

Phosphine ligated copper(I) species have been shown to borylate 1° and 2° alkyl electrophiles (I, Br, Cl and OTs) (Scheme 2A).[23,24] In comparison, palladium catalysed boryl substitution conditions have been reported for 1° bromides, but were unsuccessful with 2° bromides (Scheme 2B).[23–26] 3° alkyl halides were first successfully borylated with nickel catalysts (Scheme 2C).[27] Similar reactivity from Zn, Mn, and Fe catalysts have also been reported (Scheme 2D, E, F).[26–30] The relatively mild conditions of the transition metal catalysts allow borylation in the presence of a range of functional groups.[23,24,26,27,29,30]

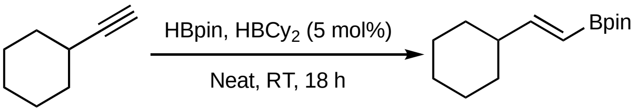
1.1.2 Hydroboration



Scheme 3: Common products formed from non-catalytic anti-Markovnikov hydroboration, diboration and metal catalysed hydroboration.

Alkene hydroboration has been a staple method for the synthesis of organoboron compounds since Brown's seminal report.[31,32] This paved the way for research spanning over half a century providing a wide range of non-metal and metal catalysed hydroboration conditions (Scheme 3).[17–20] Metal-free conditions for the hydroboration of alkenes has become an effective and green method to produce 1° pinacol boronic esters.[33] Concurrent with the observations of Brown, the borylation of unsymmetrical alkenes with pinacolborane affords the anti-Markovnikov regioisomer as the major product. Being less reactive than borane, the B-H bond of pinacolborane generally requires activation from e.g. a Lewis base for the hydroboration of alkenes.[34]

Synonymous with alkene hydroboration, catalytic activation of pinacol borane, and similar R_2B-H reagents, from a metal or Lewis base, are generally required for alkyne hydroboration. However, conditions reported by Arase-Hoshi formed alkenyl boronic ester **5** in the presence of dicyclohexylborane in excellent yield without contamination from an activating catalyst (Scheme 4).[35]

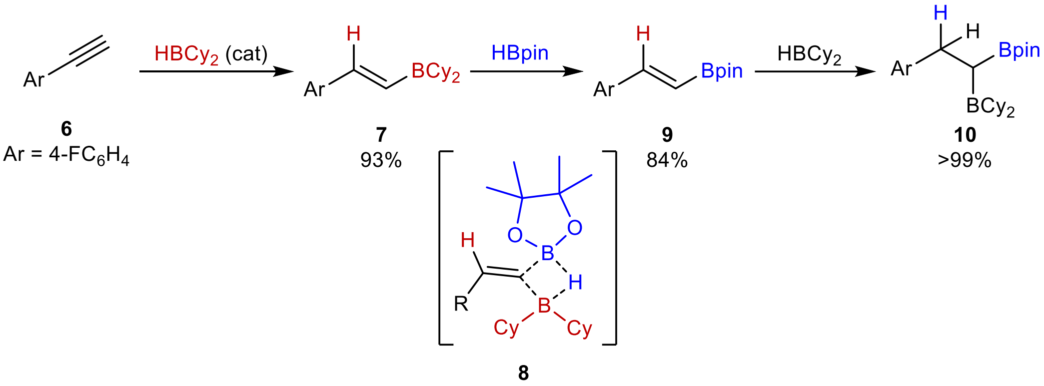


4

5
93%

Scheme 4: $HBCy_2$ catalysed hydroboration of alkynes.[35]

Subsequently, disproportionation of pinacol borane under Lewis base mediation has been shown to generate borates and BH_3 capable of reactions with alkynes. A recent report by Thomas and co-workers explores the ability of common hydroboration catalysts to form BH_3 from pinacol borane.[36] Guy Lloyd-Jones and co-workers recently published a mechanistic investigation into the Arase-Hoshi alkyne hydroboration highlighting the catalytic activity of borates in alkyne hydroboration (Scheme 5).[37] Concurrent with Arase-Hoshi's observations, initial investigations identified no hydroboration of para-fluorophenylacetylene (**6**) occurred in the absence of a catalyst. The addition of dicyclohexylborane and formation of the corresponding hydroborated product **7** in 93% yield suggests **7** is an intermediate. Subsequent conversion of **7** with the addition of pinacol borane to hydroborated product **9** supports the formation of **7**. DFT and isotope labelling studies suggest the formation of product **9** and, turnover of HBCy$_2$ catalyst occurs via metathesis mechanism **8**. Finally, doubly hydroborated product **10** is observed to form from the addition of HBCy$_2$ across alkene **9** in quantitative yield.



Scheme 5: Simplified mechanism, proposed by Guy Lloyd-Jones and co-workers, for the Arase-Hoshi alkyne hydroboration.[37]

Fernandez and co-workers have also suggested a mechanism for the formation of 1,2-diborated products from the diboration of alkenes (Figure 4).[38] Diboron compounds are activated the by coordination of a Lewis base to perturb the polarisation of the B-B bond (**11**). The sp^2 hybridised boron gains a strong nucleophilic character reacting with the unsubstituted carbon of the alkene (**12**). After the interaction, the sp^3 hybridised boron becomes electrophilic in nature and can interact with the overall negatively charged alkene-Bpin fragment. The external carbon becomes bonded to the originally sp^3 hybridised boron (**14**) and internal carbon bonded to the sp^2 hybridised boron via structure **13**.[38]

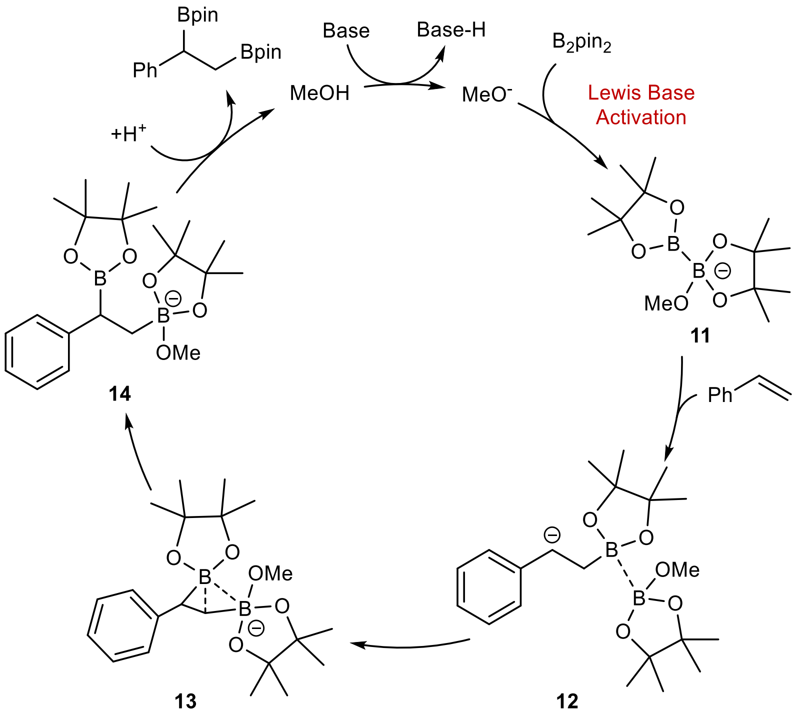


Figure 4: Mechanism, proposed by Fernandez and co-workers, for alkene diboration.[38]

A large number of early and late transition metals (e.g. Pd, Zr, Ru, Ti, Cu, Fe, Ir, Ni, etc) have been utilised for the hydroboration of alkenes to control regioselectivity. Early reports often used expensive rare earth metals such as rhodium to catalyse the reaction.[19] Manning and Noth's discovery of rhodium's ability to chemoselectively catalyse the borylation of olefins over the reduction of carbonyls sparked interest in the metal's use in hydroborations.[39] Utilising Wilkinsons catalyst, they displayed rhodium's ability to hydroborate alkenes in the least hindered position via a different mechanism than Brown's hydroboration. Research into the mechanism provided a number of important observations when altering the electronic nature of the rhodium catalyst.[18] It was found that neutral rhodium complexes, such as Wilkinsons catalyst, produced the 1° (anti-Markovnikov) boronic ester as the major product. However, when using cationic rhodium complexes, the 2° (Markovnikov) boronic ester product is formed as the major product (Figure 5). Both mechanisms are believed to follow an oxidative addition/reductive elimination pathway. However, the regioselectivity was proposed to be determined by the cationic rhodium species forming a stabilised η^3-benzyl complex (**15**). Instead, the neutral rhodium catalyst is thought to form the 1° product due to steric factors (**16**).

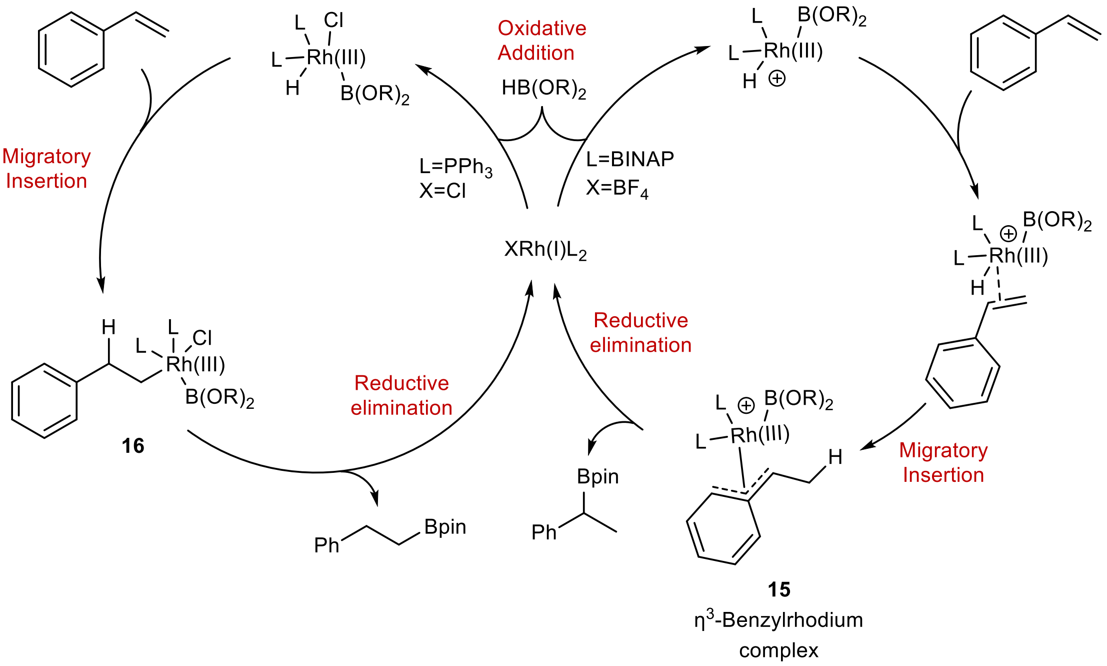
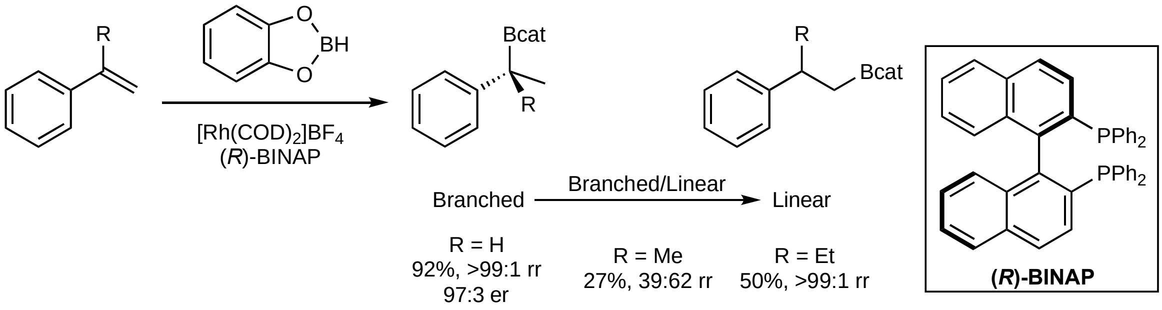


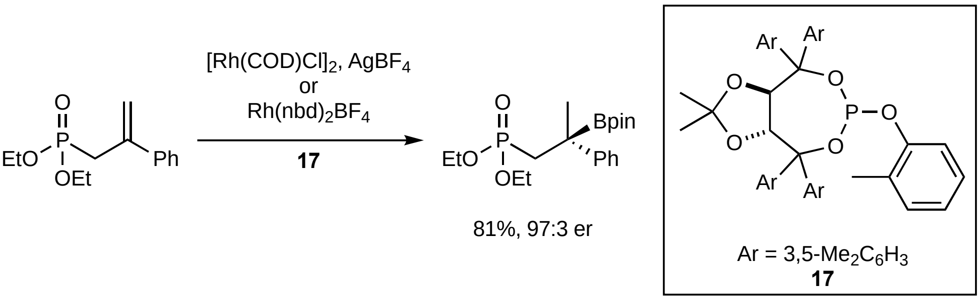
Figure 5: Simplified catalytic cycles for the hydroboration of styrene with neutral (LHS) and cationic (RHS) rhodium species producing the anti-Markovnikov and Markovnikov products respectively.[18]

Steric factors were also shown to affect the regioselectivity of 1,1-disubstituted alkenes providing a greater quantity of the anti-Markovnikov product even with cationic rhodium complexes (Scheme 6).[40]



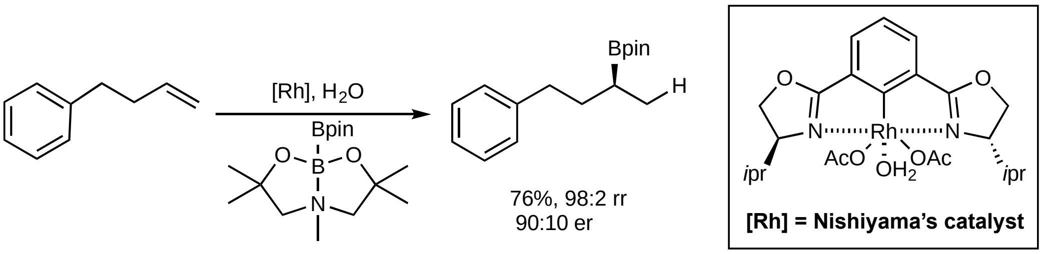
Scheme 6: Steric effects dictating regioselectivity of the cationic rhodium catalysed hydroboration of substituted styrenes.[40]

Further developments have led to new rhodium catalyst complexes, boron sources and functionalised olefins to overcome some issues with hydroboration, and to perform asymmetric synthesis. For instance, using directing group strategies can help control the site selectivity of borylation. An example of this was reported by Takacs *et al.* demonstrating that phosphonate ligated rhodium complexes can overcome the steric implications of 1,1-disubstituted alkenes and form chiral 3° pinacol boronic esters (Scheme 7).[41] The use of a phosphonate substrate leads to the delivery of boron mainly to the more substituted β-position with high enantio-induction.



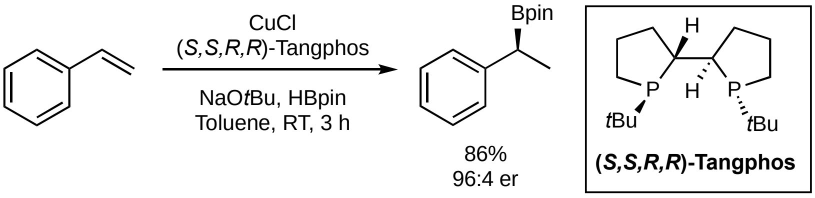
Scheme 7: Phosphonate-ligated rhodium catalysed enantioselective synthesis of 3° boronic esters.[41]

Aggarwal and co-workers have developed conditions for the regioselective and asymmetric hydroboration of unactivated alkenes forming the Markovnikov product preferentially (Scheme 8).[42] They used Santos's "pre-activated" diboron reagent, and Nishiyama's catalyst to give selective addition across the alkene forming an intermediate alkylrhodium species. Proto-demetallation then provided the desired region-selective product in high er.[43,44]



Scheme 8: Alkene hydroboration using Santos "preactivated" diboron and Nishiyama's catalyst.[42]

Recently, efforts have been directed towards the use of more abundant metals such as copper for the hydroboration of alkenes. Yun and co-workers reported the asymmetric hydroboration of styrene's with a copper(I) catalyst, bisphosphine ligands and pinacolborane (Scheme 9).[45]



Scheme 9: Cu-catalysed asymmetric hydroboration of alkenes.[45]

The mechanism was later evaluated by Hartwig and co-workers, which led to an improved method for hydroboration extending to internal un-activated alkenes.[46,47] Currently it is thought the mechanism proceeds via a transmetallation of the Cu(I) source with pinacolborane providing a Cu-H species (Figure 6, **18**). This then inserts into the alkene giving an alkyl-copper species (**19**) that undergoes σ-bond metathesis with pinacolborane (**20**) producing the desired product and regenerating the Cu-H species. The regioselectivity of the Cu-H addition is presumably due to the increased stability of the resulting organocuprate intermediate. Benzylic organocuprates are stabilised by the electron withdrawing nature of the aromatic ring system.

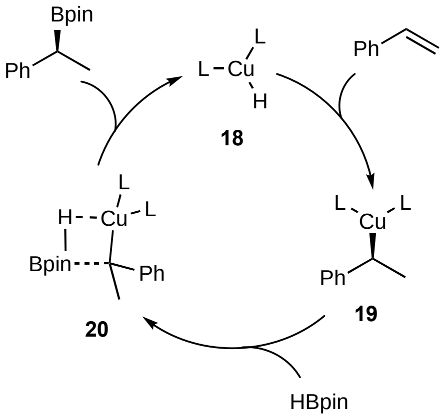
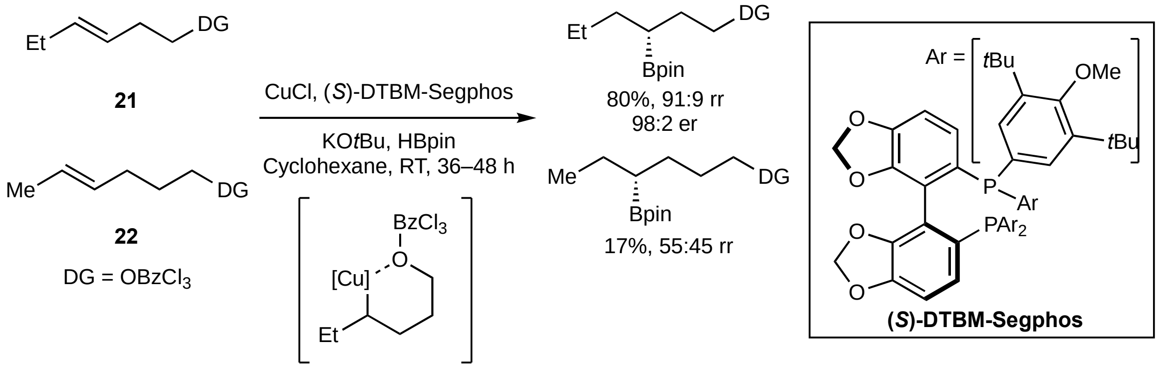


Figure 6: Mechanism for the copper catalysed hydroboration of alkenes.[46,47]

For the reaction of alkene **21**, the alkyl organocuprate formed is stabilised by coordination of the directing group (DG)(Scheme 10).[46,47] A loss of regioselectivity is observed when the alkene (**22**) is further away from the DG. This is due to an increased ring size of the Cu-DG chelate.



Scheme 10: Directed copper catalysed hydroboration of alkenes.[46,47]

1.1.3 1,4-Borylation

Borylation of the alkene moiety of α,β-unsaturated carbonyls differs from that of non-electron deficient alkenes. Although the alkene moiety possesses the potential to undergo Brown's hydroboration, the carbonyl moiety is also a potential target for borohydride reagent reduction (Figure 7). This can lead to a mixture of 1,4- and 1,2- reduced products (**23** and **24**).[48] Additionally, when following a similar metal-catalysed borylation method such as hydroboration (Section 1.1.2), stabilisation of the organometal intermediate favours the α-position (**25**). The α-organometal intermediate (**25**) or subsequent α-borylated product (**24**) are prone to enolization to form a more favourable O-B bond (after transmetallation) (**26**).[49] The O-B bond is readily hydrolysed to the corresponding ketone **27** and ketone reduced to an alcohol **28**.

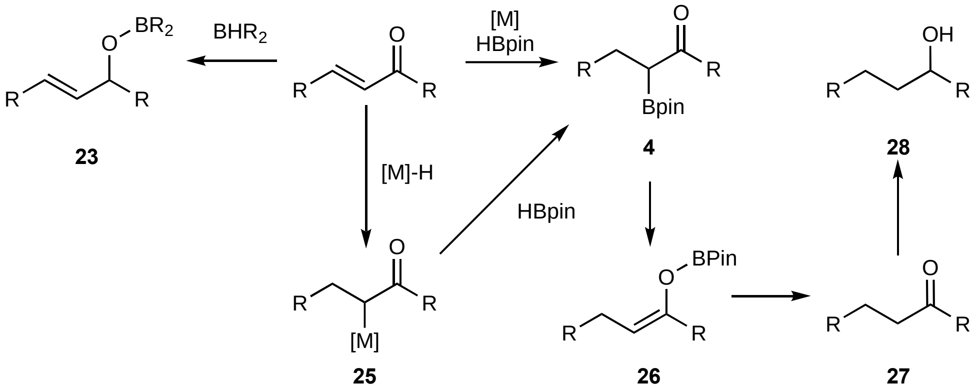


Figure 7: Reduction of α,β-unsaturated carbonyl compounds using boranes.

1,4-Borylation takes advantage of this enolization to provide β-borylated products from diboration of the alkene moiety. The metal-free borylation of α,β-unsaturated ketones undergoes addition across the alkene moiety and rearrangement when in the presence of a Lewis base catalyst such as *N*-heterocyclic carbene (NHC), amine bases and phosphine ligands.[50] As proposed by Hoveyda and co-workers, the activation and mechanism of B_2pin_2 is thought to occur in a similar manner to that of the diborylation of alkenes (Section 1.1.2).[51] Coordination of the Lewis base to B_2pin_2 gives polarisation of the B-B bond (**29**) enabling attack of the electrophilic α,β-unsaturated carbonyl (Figure 8, **30**). It has been proposed that diboration across the alkene gives **31** which subsequently isomerises the α-boron bond to give a boron enolate intermediate (**32**). This is then quenched under aqueous conditions and tautomerized to form the corresponding ketone product (**33**).

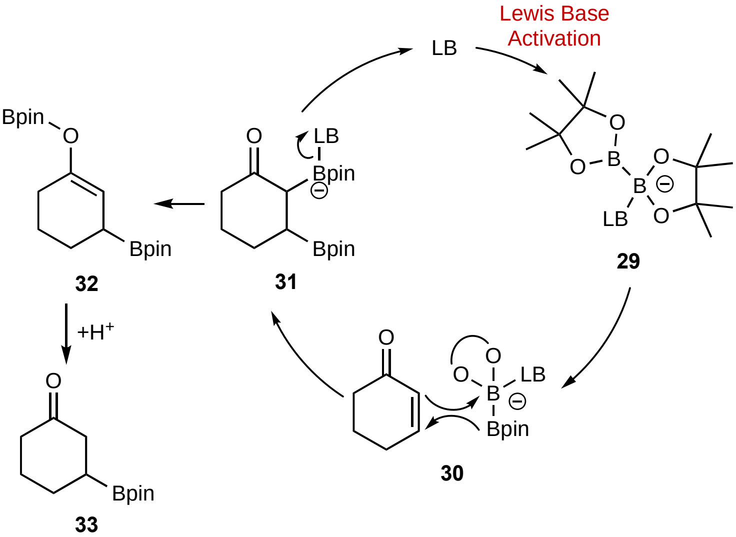
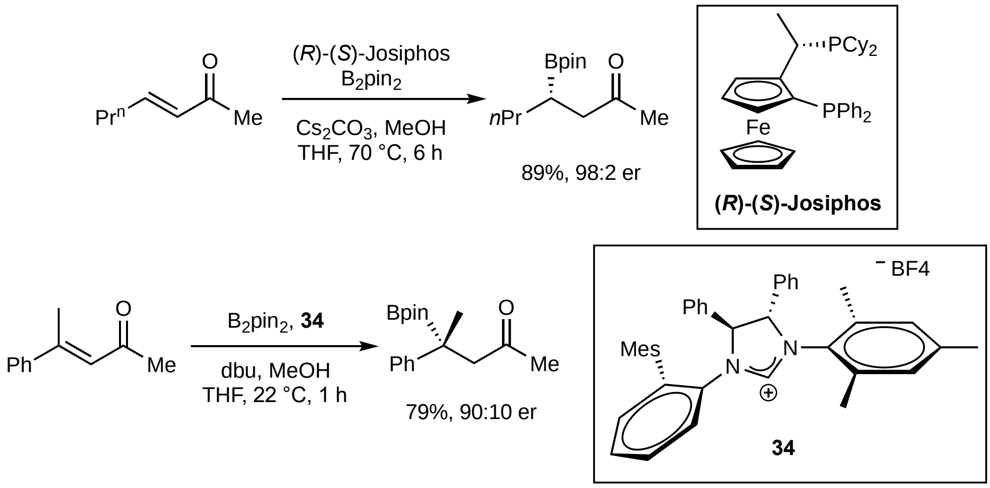


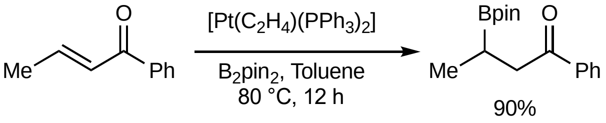
Figure 8: Mechansim for the Lewis base promoted 1,4-borylation of α,β-unsaturated ketones.[51]

Additional reports expand the research to include different Lewis base activating catalysts, such as bases or phosphines, and chiral variants of the catalysts allowing enantioselective syntheses.[52] This method also tolerates the formation of 3° alkyl boronic esters from β,β-disubstituted substrates (Scheme 11).[50,53]



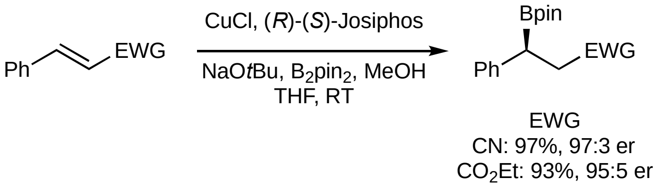
Scheme 11: Enantioselective 1,4-borylation of α,β-unsaturated ketones using chiral catalysts.

Marder and co-workers first reported transition metal-catalysed 1,4-borylation in 1997 (Scheme 12), building on reports from Miyaura and co-workers on platinum catalysed 1,4-additon of B_2pin_2 to 1,3-dienes.[54,55] Several years later, Miyaura and Hosomi released their copper catalysed conditions reporting milder conditions and wider substrate scopes.[56,57] Copper salts have appeared as one of the most prolific catalysts for this transformation. Enhancements of the conditions highlighted methanol as a beneficial additive to promote reactivity lowering catalyst loading and temperatures.



Scheme 12: Platinum catalysed 1,4-Borylation of α,β-unsaturated ketones.[54]

In 2008, Yun and co-workers reported the first example of a transition metal catalysed asymmetric β-borylation using a Cu-catalysed system with a chiral bisphosphine ligand (Scheme 13).[58]



Scheme 13: Copper catalysed asymmetric 1,4-Borylation of α,β-unsaturated ketones.

The mechanism has been investigated and was hypothesised to follow that of the non-metal catalysed method described above.[59] Differences arise from the organocuprate intermediate (**35**) possessing the ability to undergo protonolysis directly (**33**) or isomerise to the O bound intermediate (Figure 9, **36**). This can then undergo transmetallation with B_2pin_2 to provide the boron enolate intermediate (**37**) which can collapse.

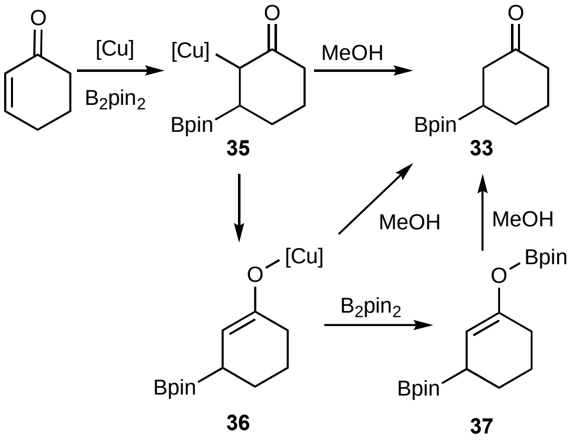
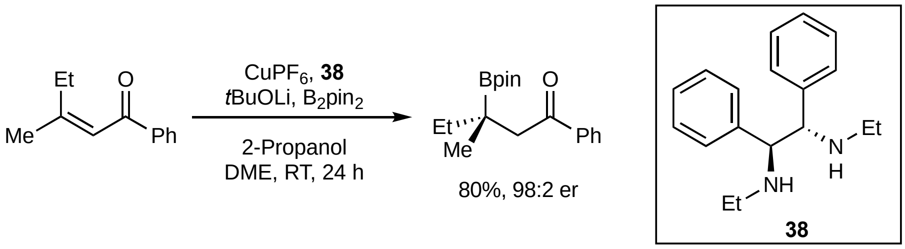


Figure 9: Proposed mechanism for the copper catalysed 1,4-Borylation of α,β-unsaturated ketones.[59]

β-Borylations are now possible with copper(I) salts in combination with a range of ligands including, NHCs, diamines, bipyridines and *P,N*-ligands.[60–64] Conditions are also tolerant of a range of α,β-unsaturated systems such as α,β-unsaturated imines and β,β-di-substituted substrates for borylation in an asymmetric manner (Scheme 14).[61–63,65,66]



Scheme 14: Copper catalysed asymmetric 1,4-Borylation of β,β-di-substituted alkenylketones.

1.1.4 Methods Involving 1,2-Metallate Rearrangement

Homologation reactions involving the organoboron directed nucleophilic displacement of leaving groups has become a powerful method for preparing alkylboronic esters. Matteson and Mah were the first to report a method for the one carbon homologation of boronic esters in 1963.[67] Their seminal work described the addition of organomagnesium nucleophiles to α-bromo organoboron reagents and displacement of α-bromides (Figure 10). They suggested that the formation of a boron 'ate' complex (**39**), upon warming, underwent a 1,2-metallate rearrangement to provide the homologated product (**40**). The displacement of bromide from

S_N1 or S_N2 pathways was discounted as alkylboron product **41** was observed when quenching the reaction at -70 °C.

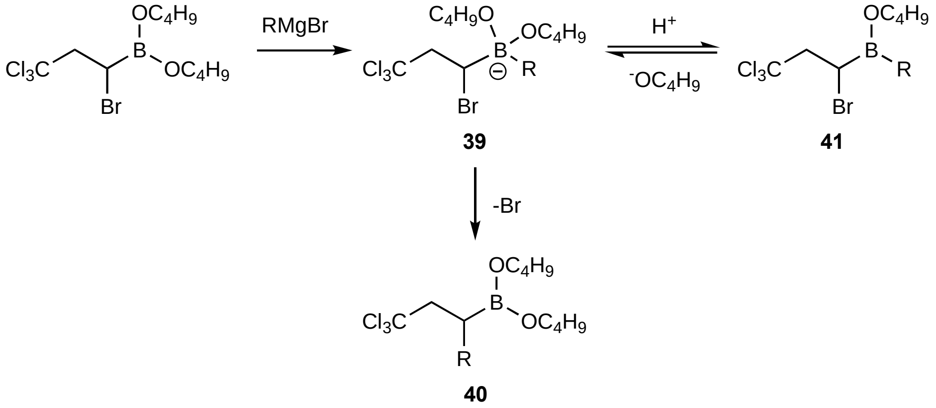
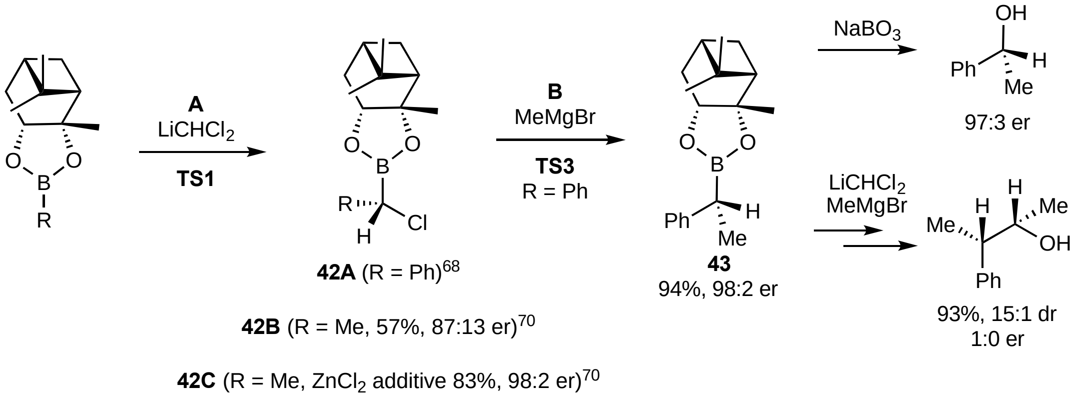


Figure 10: One carbon homologation to give **40** and observed by-product **41**.[67]

Although possessing great potential, the method was hindered by a lack of general conditions for making α-halo-boronic esters.[68] Matteson addressed this by reporting the formation of α-chloro boronic esters from the homologation of (dichloromethyl)lithium reagents (Scheme 15, **42**).[69,70] Using a chiral auxiliary as the diol of the boronic ester allowed the reaction to be carried out in high enantioselectivity (**43**). Later papers by Matterson showed the addition of zinc chloride to be beneficial in promoting both reactivity and stereoselectivity (**42C**).[71]



Scheme 15: Matteson homologation to give α-chloro boronic ester (**42**) and subsequent reaction.

Corey and Midland proposed that 1,2-metallate rearrangement proceeded through the favoured transition state **TS1** (Figure 11) to account for the high diastereoselectivity observed.[72,73] This transition state stabilises the configuration of the boron ‘ate’ complex and activates the α-halo for 1,2-metallate rearrangement. Other potential transitions states were disregarded due to increased steric interactions (**TS2**). The Matteson homologation of α-chloro boronic esters also proceed in high diastereoselectivity without the addition of zinc chloride.[71,74] Midland proposed **TS3** (Figure 11) as a key intermediate in the homologation process replacing zinc with the available magnesium metal. The migration proceeds through an anti-periplanar alignment of the migrating and leaving groups.[72,73]

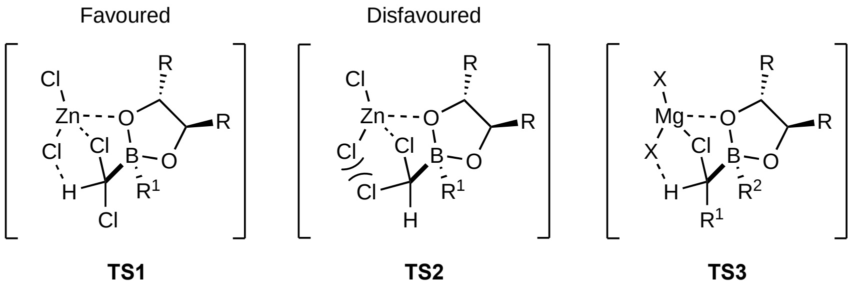
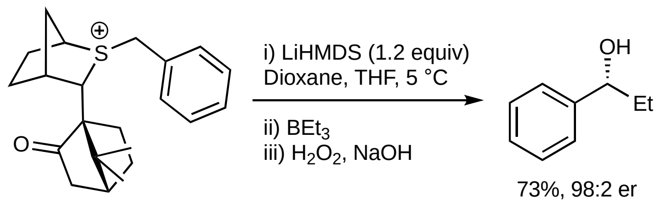


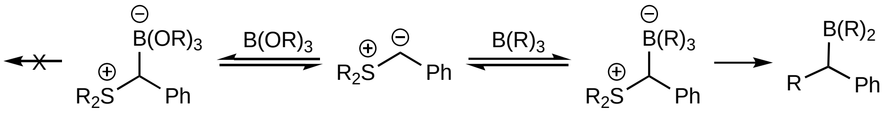
Figure 11: Transition states to explain the stereoselectivity of the Matterson homologation.[72,73]

Matterson homologation is an example of substrate control as the chiral boronic ester used determines the stereochemical outcome of the reaction. Due to substrate control, when the pinanediol boronic ester does not initially possess the migrating substituent and is reacted with an organolithium reagent, low stereoselectivity is observed.[75,76] Also, low stereoselectivity is observed when producing 3° boronic esters. Further limitations include the lack of ability to quickly access the opposite stereoisomer. Additionally, α-halo-boronic esters can suffer from a lack of stability to air and moisture. Despite this, the Matteson homologation has been used in the synthesis of a number of complex natural products.[77]



Scheme 16: Homologation of sulphur ylides with boranes.

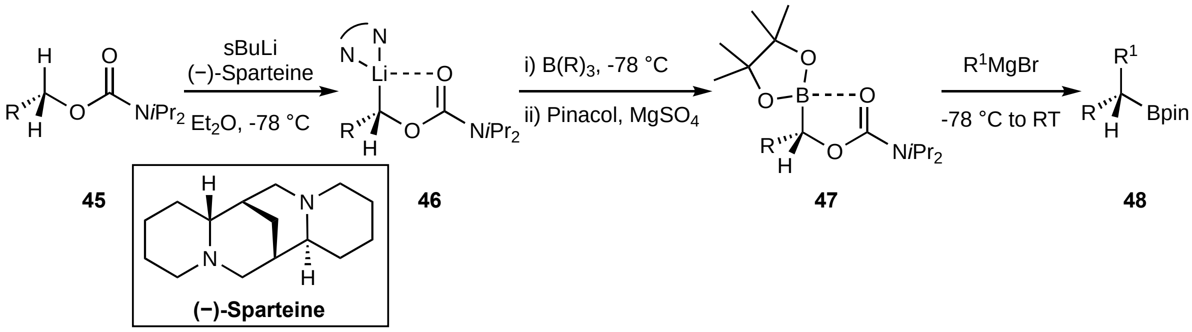
Chiral carbenoids possess the potential to control the stereochemical outcome of homologations with achiral boronic esters. This is an example of reagent control. This method has been developed to include several leaving groups such as sulphur ylides (Scheme 16), and carbamates.[78] Issues have been identified with the lithiated intermediates of sulphur ylides as they do not successfully react with boronic esters (Figure 12). This is caused by the reduced electrophilicity of the boronic esters (when compared to boranes) and increased stability of the carbanion due to the sulphur cation. Although the boron ‘ate’ complex may form (**44**), the barrier of migration is high enough to result in reversibility of the boron ‘ate’ complex. Subsequently the lithiated sulphur ylides can undergo decomposition.[18,77]



44

Figure 12: Reversibility of boron 'ate' species produced from lithiated sulphur ylides. Alkyl boranes undergo 1,2-metallate rearrangement whereas boronic esters do not.

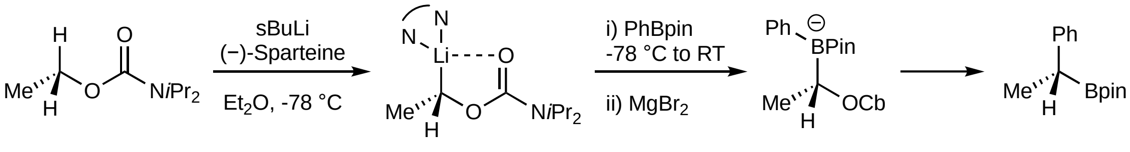
To overcome these issues, Hoppe *et al*. reported the use of lithiated carbamates in a Matteson-type homologation (Scheme 17).[79,80] Like other leaving groups, chiral carbamates provide an electron deficient carbon for deprotonation. However, they also provide a sufficiently activated leaving group for 1,2-metallate rearrangement. The carbamate functionality overcomes previous issues with decomposition of the carbenoid intermediate by stabilising the lithiated carbanion formed (**46**). The carbamate directs lithiation alpha to the carbamate, with coordination of the carbonyl oxygen thought to stabilise intermediate **46**. Additionally, it is proposed that the alkyl boronic ester is stabilised by donation of electron density from the carbonyl oxygen into the empty p-orbital on boron (**47**). This interaction prevents erroneous decomposition of the boronic ester but does not prevent the 1,2-metallate rearrangement with organomagnesium reagents.



Scheme 17: Lithiated carbamates in a Matteson-type homologation reaction.[79,80]

The seminal report shows the asymmetric lithiation of carbamate **45** with (–)-sparteine ligated *s*BuLi. The (–)-sparteine imparts stereochemical information onto the carbenoid displaying reagent control. Borylation of the organolithium with a borane and ligation of pinacol gives the asymmetric boronic ester (**47**) This can then undergo a Matterson type homologation with a Grignard reagent to provide the chiral boronic ester with stereoretention (**48**). Hoppe's method does constitute a valuable reagent-controlled homologation method. However, it does require two steps to provide the desired product.

Building on this work, Aggarwal and co-workers developed their conditions for a one-step lithiation-borylation method.[81] Following the same core steps as Hoppe, lithiation of the carbamate (**49**) occurs enantioselectively under reagent control (**50**). Attack of the empty p-orbital of a boronic ester provides a pre-prepared intermediate for 1,2-metallate rearrangement (**51**). By employing a boronic ester, Aggarwal and co-workers combined the boronic ester formation and Matteson-type homologation of Hoppe's method. Succeeding reports have highlighted some boron 'ate' complexes undergo slower 1,2-metallate rearrangements.[10] Concurrent with Matteson's observations Lewis acids such as magnesium bromide were shown to promote the 1,2-metallate rearrangement with sluggish boron reagents (e.g. boronic esters).

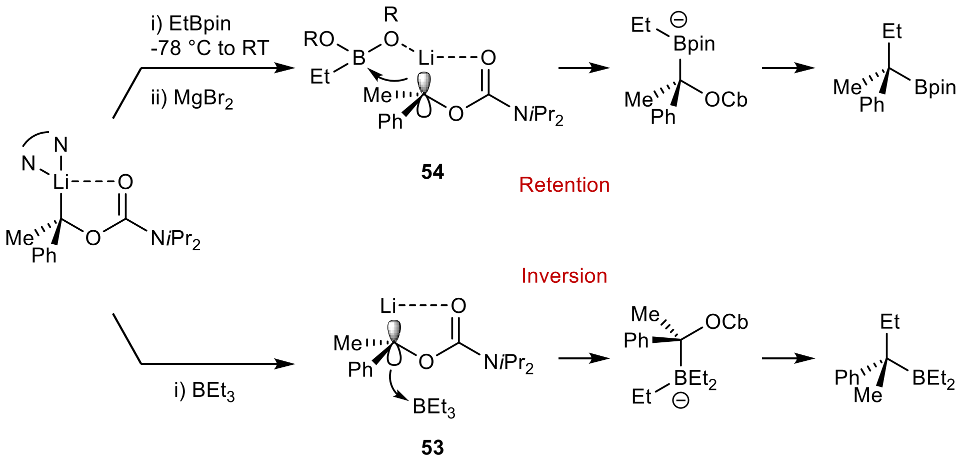


49 **50** **51** **(*R*)-52**

Scheme 18: Homologation of boronic esters through lithiation borylation.[81]

Additionally, it was suggested that the remaining magnesium bromide present within the homologation step of Hoppe's conditions, aided in the same manner.[77] Despite the improvement to the rate of 1,2-metallate rearrangement with Lewis acid addition, certain boronic esters (Me and $(CH_2)_2COOtBu$) were slow to migrate resulting in lower yields. Aggarwal and co-workers addressed the issue suggesting hindered benzoates as improved leaving groups. 2,4,6-Triisopropylbenzoates was shown to successfully improve the rate of rearrangement and access the products of reluctant migrating groups in higher yields.[10]

Unlike the Matterson homologation, Aggarwal's method allows access to the corresponding 3° borane or boronic esters in excellent er.[82–86] Interestingly, when producing 3° benzylic boron reagents through 1,2-metallate rearrangement, the stereochemical outcome is determined by the boron source.[87] The formation of the boron 'ate' intermediate proceeds with inversion of stereochemistry for boranes (**53**), but conversely its formation proceeds with retention of stereochemistry for boranes esters (**54**). The retention of stereochemistry is suggested to be due to an O-Li interaction between the diol ligand of the boronic ester and organolithium. This interaction directs the addition of the boronic ester to the same face as the lithium carbenoid (**54**). As boranes do not possess ligated diol moieties, the face of addition is controlled by a build-up of electron density on the opposite face of the lithium. The benzylic group adds increased stabilisation to the organolithium intermediate leading to a relatively flattened structure. This allows a build-up of electron density on the opposite face giving the inversion of stereochemistry (**53**). Due to the phenyl ring's impact on the intermediate structure, the change of stereochemistry is only observed with benzylic carbamates. Non-benzylic carbamates maintain a 'classical' tetrahedral sp^3 centre during lithiation and provide homologation with retention of stereochemistry.



Scheme 19: Divergent mechanisms for the homologation of boronic esters and boranes with 3° carbamates.[87]

Functional group tolerance throughout 1,2-metallate rearrangement methodology is heavily dependent on the ability of functionalities to withstand highly nucleophilic species. However, this limitation has not stopped the method's synthetic application in the total synthesis of natural products.[18]

1.2 *Traditional Methods to Prepare C-N Bonds*

Nitrogen-based functional groups bound to sp^3 carbon centres are prevalent within a multitude of pharmaceutical, agrochemical, and biologically significant molecules.[25–27,88] Alkyl C-N bonds are therefore one of the most commonly formed bonds within synthetic chemistry, and the development of methods for their enantioselective installation is an active and competitive field.

The *N*-alkylation of alkyl halides and reductive amination of aldehydes and ketones constitutes a large proportion of heteroatom manipulations performed by medicinal chemists.[89,90] These traditional methods are regularly handicapped by an absence of control (e.g. over alkylation), and poor stereocontrol.

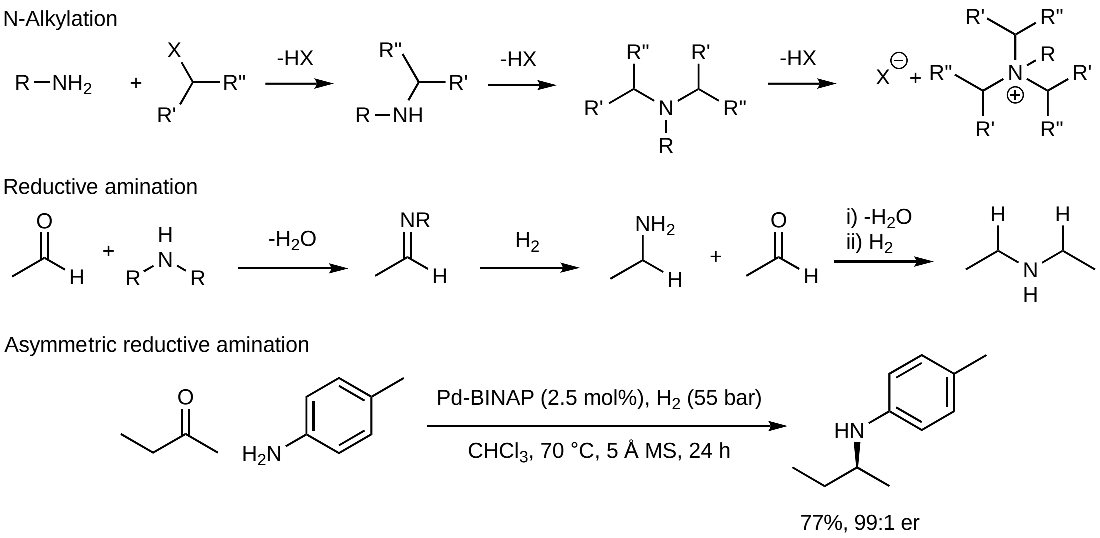
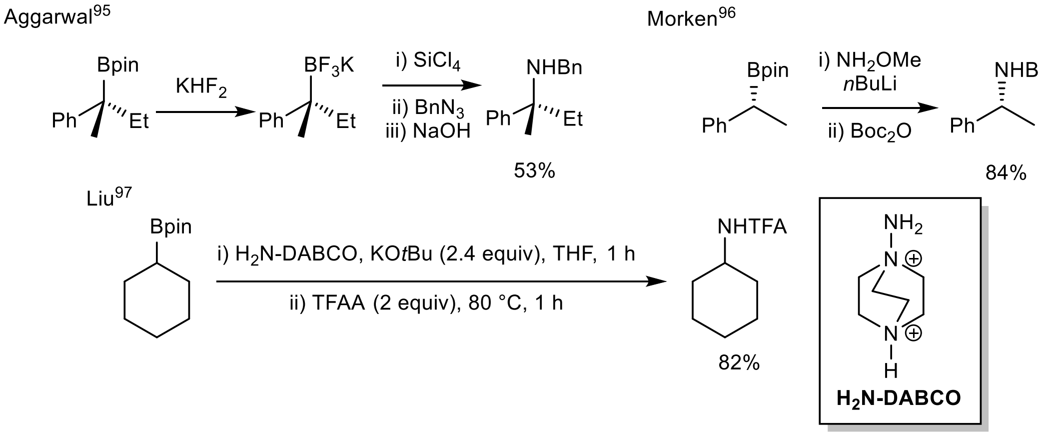


Figure 13: *N*-alkylation of alkyhalides, racemic reductive amination and palladium catalysed asymmetric reductive amination.

Nucleophilic substitution of alkyl halides regularly leads to products with various degrees of alkylation due to increased nucleophilicity of the resulting amine. To overcome this, protecting group strategies are often employed, which reduces atom economy.[91]

Although reductive amination offers a greater level of control over product reactivity, it is only equally as popular as *N*-alkylation.[92] Reaction optimisation and reducing agent selection is often needed to prevent side reactions, such as carbonyl reduction and aldol condensation reactions. The reducing agent, e.g. $NaBH(OAc)_3$, is commonly used in super-stoichiometric quantities, lowering atom economy.[93] Alternatively, catalysts can be used to perform the reduction step. However, these often require the use of molecular hydrogen as the reductant, which can be less practical. In addition, conditions for stereoselective imine and enamine reduction lack generality (Figure 13).[94] Finally, reductive amination is limited to 1° and 2° C-sp^3 amine formation. Despite these limitations, traditional amination methods continue to have a relatively large impact in molecule construction.

The orthogonal reactivity of boronic esters means that amine formation from these functionalities may overcome the issues with the aforementioned traditional methods. Furthermore, alkylboronic esters are configurationally stable and so possess the potential to transfer their stereochemical information to the corresponding amine product. Current methods, however, require the use of harsh conditions and stoichiometric reagents (e.g. lithiated methoxyamine, $SiCl_4$ or H_2N-DABCO). (Scheme 20)[3,95–97]



Scheme 20: Methods for the amination of alkylboronic esters.

Metal mediated aminations of C-X bonds often require milder conditions, display greater functional group tolerance and have an increased atom economy. Palladium and copper catalysts have been extensively used for the coupling of amines with aryl halides or organoboron reagents.[98] These processes, known as the Buchwald-Hartwig, Ullmann and Chan-Evans-Lam coupling reactions, have become ubiquitous within academia and industry.

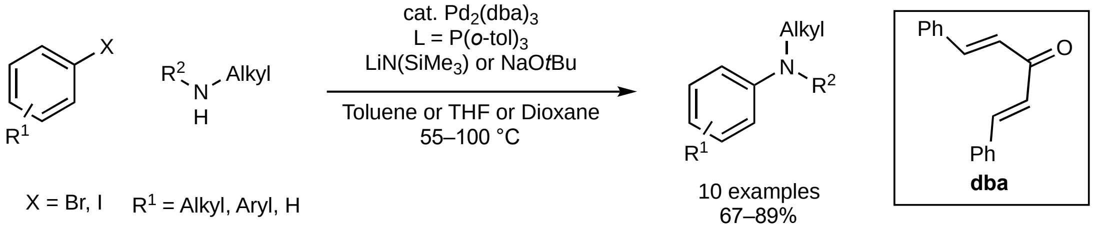
1.3 *Transition Metal Mediated C-N Bond Formation*

1.3.1 The Buchwald-Hartwig Reaction

The Pd-catalysed cross-coupling of aryl (pseudo)halides and amines has become common practice for the formation of C(sp^2)-N bonds. Initial reports by Migita and co-workers in 1983 described the Pd-catalysed formation of aryl amines from aryl bromides and aminostannanes.[99] This pioneering work was further developed by the groups of Stephen Buchwald and John Hartwig to overcome the use of toxic aminostannanes and the limited substrate scope. In 1995 both Buchwald and Hartwig independently reported the Pd-catalysed tin-free coupling of aryl halides and amines.[100,101] Due to further development of the methodology and mechanism of this process by each group, the reaction is now known as the Buchwald-Hartwig amination reaction. Subsequent research developed the palladium catalysts to tolerate the electronic and steric features of different coupling substrates. This has led to the production of four generations of catalysts each with advantages and limitations.[102,103]

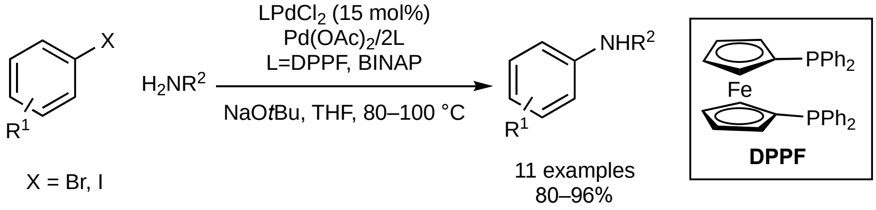
The first generation originated from the catalytically active Pd[P(o-tol)$_3$] complex identified by Migita and co-workers in the presence of a base and performed in THF (Scheme 21).[99] Although this catalyst allowed access to a number of aryl amines from a range of aryl bromides and 2° amines, this catalyst gave low yields for the coupling of 1° alkyl amines due to competitive β-hydride elimination.[100–103] Aryl iodides gave lower yields than bromides in THF.

However, when 1,4-dioxane was used as the reaction solvent aryl iodides were superior substrates. Pd source, $Pd_2(dba)_3$ in conjunction with $P(o\text{-tol})_3$ became the optimal conditions for the first generation of catalyst.



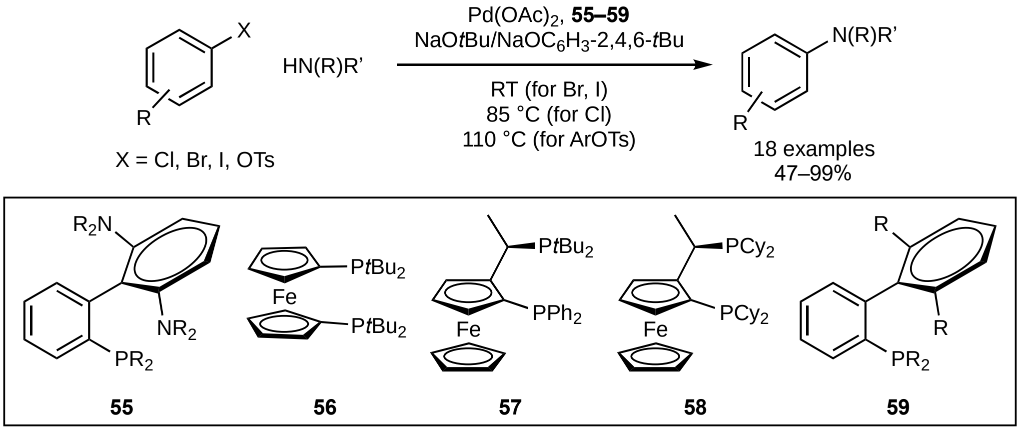
Scheme 21: First generation palladium catalyst for Buchwald-Hartwig amination.

The second generation of catalyst utilised chelating aromatic bisphosphine ligands (e.g. DPPF, BINAP) (Scheme 22).[104] The catalyst improves on the generality of the reaction with increased yields for 2° amines and access to coupling with 1° amines. The chelating effects of the ligands to the metal centre promotes reductive elimination to give the product, reducing amounts of β-hydride elimination. Under similar conditions this system allowed the coupling of aryl bromides, iodides and triflates but was unsuccessful for aryl chlorides and tosylates.



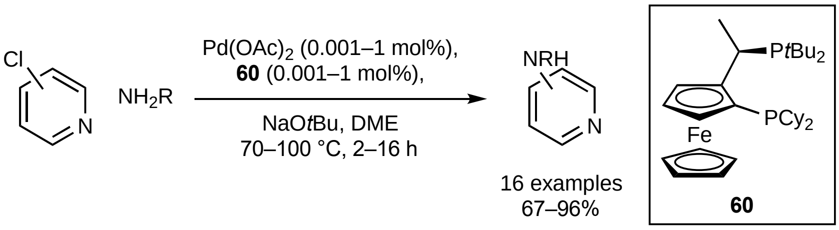
Scheme 22: Second generation palladium catalyst for Buchwald-Hartwig amination.[104]

To promote the reaction of aryl chlorides and tosylates under mild conditions, sterically hindered aminophosphine, ferrocene-based dialkylphosphine and biarylphosphine ligands were employed (Scheme 23).[105] The use of bulky and electron rich ligands increases electron density on the metal centre, enabling a faster oxidative addition, whilst also promoting reductive elimination. This resulted in a broader substrate scope, including the amination of aryl bromides, iodides, chlorides and tosylates. The coupling of aryl bromides, iodides and chlorides were shown to be possible at room temperature.



Scheme 23: Third generation palladium catalyst for Buchwald-Hartwig amination.[105]

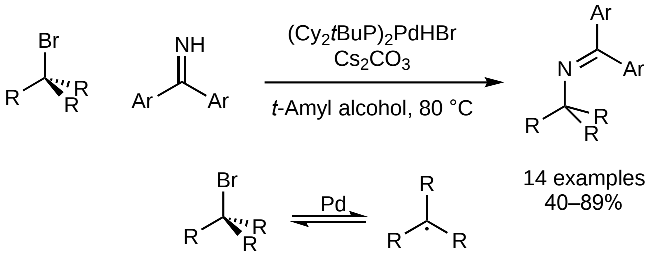
The fourth generation of catalyst was developed to overcome the requirement for high catalyst loading when coupling heteroaromatic halides, and the lack of selectivity for monoarylation of 1° amines (Scheme 24).[106] Bidentate Josiphos-type ligands were selected to increase the propensity of the ligand to remain bound to the palladium when in the presence of heterocycles and exploit their steric properties around the coordination site to prevent over arylation occurring. These electron rich ligands also allow reaction of less active C-X bonds.



Scheme 24: Fourth generation palladium catalyst for Buchwald-Hartwig amination.[106]

Although four generations of catalyst exist, the classical Buchwald-Hartwig reaction is limited to the amination of aryl halides.[107,108] Aryl metal-alkyl amine and alkyl metal intermediates formed from transmetallation have the potential to undergo β-hydride elimination. Ligand effects suppress the β-hydride elimination of aryl metal-alkyl amine intermediates allowing reductive elimination to occur. However, reductive elimination of alkyl-amine metal intermediates is unfavourable allowing β-hydride elimination to occur. This makes alkyl amine formation unfavourable.

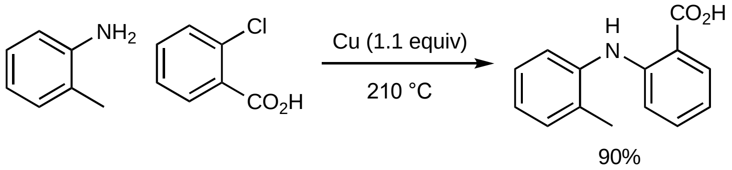
In 2016 Hartwig and co-workers developed conditions for the Pd-catalysed coupling of 2° and 3° alkyl bromides and benzophenone imine to overcome limitations with traditional methods (Scheme 25).[109] While this is the first example of a thermal transition metal catalysed coupling of 2° and 3° alkyl bromides and a nitrogen nucleophile, the reaction displayed a limited substrate scope and proceeded via a single electron transfer (SET). This is common for Pd-catalysed transformations of alkyl halides and resulted in the loss of stereochemical information.



Scheme 25: Pd-catalysed coupling of alkylbromides and benzophenone imines.[109]

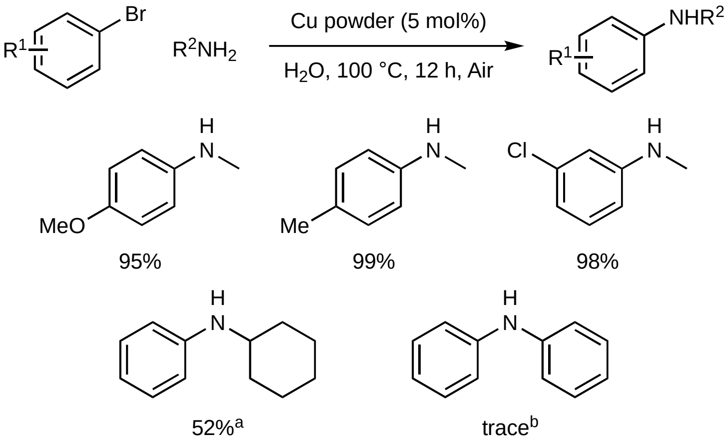
1.3.2 Ullmann Coupling

From as early as 1903, copper has been known for its ability to mediate the formation of C-N bonds (Scheme 26).[110] However, when compared to Pd-catalysed chemistry, Cu-mediated chemistry often requires harsh reaction conditions, stoichiometric quantities of copper and has a limited reaction scope.[111] Conversely, copper is cheaper than other metals, often requires simple ligand designs and shows complementary reactivity to that of palladium. Fritz Ullmann initially witnessed this use of copper when coupling an electron-poor aryl halide and amine in a process that is now known as the Ullmann coupling reaction.[110]



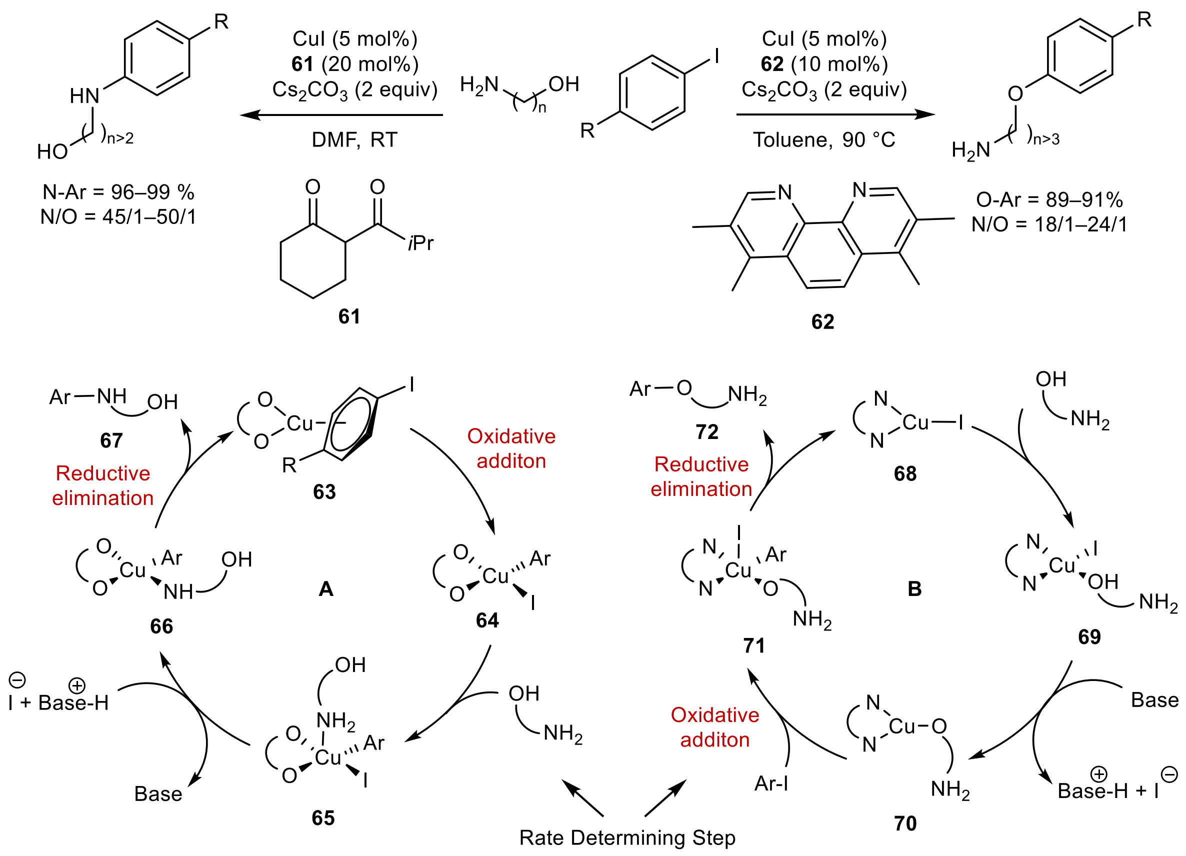
Scheme 26: The first reported Ullmann coupling reaction.[110]

Subsequently, development of the reaction has led to milder reaction conditions (weaker bases, lower temperatures and shorter reactions times), an increased reaction scope and the use of various copper sources (Scheme 27).[112] Ongoing investigations into the active copper species has provided some insight into the reaction mechanism. (For an example see ref[113])



Scheme 27: Ullmann coupling reaction, with the active catalyst formed from Cu(0) *in situ*. a) Reaction time of 24 h, b) Reaction time of 36 h.[112]

Ullmann coupling conditions have been applied to *N*- and *O*- arylation. Two possible reaction pathways were proposed by Fu and co-workers where the initial step was either oxidative addition or nucleophile coordination (Scheme 28).[114] The order in which the mechanism proceeds may be dependent on the substrates, conditions and ligands on copper. Ligand effects have been shown to mediate divergent mechanistic pathways when coupling amino-alcohols and aryl iodides.[115] Fu and co-workers conducted computational studies and proposed a non-radical, oxidative addition, reductive elimination catalytic cycle. It was suggested the order of nucleophile coordination and oxidative addition determined the selectivity of the catalytic cycle. The order of these steps were, in turn, controlled by the ligand. In the presence of Cs_2CO_3, **61** forms an anionic ligand that, on coordination to the copper salt, forms a neutral Cu(I) species (**63**). Neutral copper species **63** is prone to increased rates of oxidative addition with the aryl halide when compared to non-neutral Cu(I) complex **68**. As the oxidative addition to **63** is fast, the turnover-limiting step of cycle **A** (Scheme 28) is thought to be nucleophile coordination. Due to electronic properties determined by ligand **61**, complex **64** selectively coordinates to the more nucleophilic amine, resulting in *N*-arylation (**67**) as the major product.

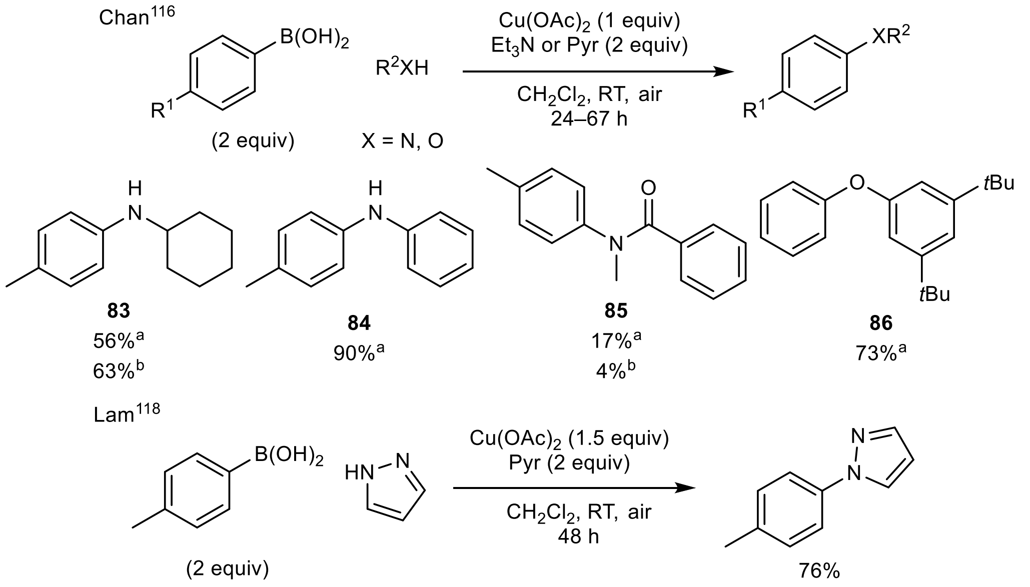


Scheme 28: Proposed catalytic cycles for the ligand dependant *N*- and *O*- arylation.[115]

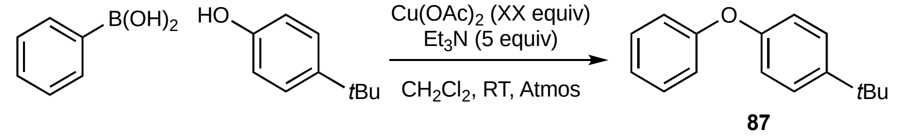
Instead, due to the neutral nature of **62** and effect on complex **68**, nucleophile coordination is preferential over oxidative addition. Having a higher acidity than the amine moiety, the hydroxyl group deprotonates preferentially when coordinated to Cu(I) species **69**.[115] The turnover-limiting step is suggested to be oxidative addition giving complex **71** (Scheme 28, cycle **B**).

1.3.3 Chan-Evans-Lam Coupling Using Aryl Boron Reagents

A more recent approach to C-heteroatom bond formation was pioneered by Chan,[116] Evans[117] and Lam[118] in 1998. Unlike the Buchwald-Hartwig and Ullmann coupling reactions, that utilise an electrophile-nucleophile cross-coupling, this complementary approach employs an oxidative nucleophile-nucleophile cross-coupling. More specifically, this method exploits the reactivity of arylboron reagents to provide a coupling partner for a nucleophile. Published in back to back papers, Chan, Evans and Lam independently addressed this approach reporting similar reaction conditions for the coupling of N and O nucleophiles and arylboronic acids. The reaction conditions use stoichiometric or super-stoichiometric loadings of $Cu(OAc)_2$ and an excess of base (pyridine or trimethylamine) to give full conversion. Chan, Evans and Lam showed the synthetic utility of the reaction by displaying collectively, a wide range of coupling partners (Scheme 29). Chan reported various functionalities including amines (**83**), anilines (**84**), amides (**85**), imides, sulphonamides, carbamates and phenols (**86**).[116] Lam focussed on the coupling of heteroarene substrates,[118] and Evans the coupling of phenols.[117] Typically, the reactions were performed under mild conditions (ambient atmosphere of air and room temperature).[117] Evans noted that the inclusion of an oxygen-containing atmosphere was advantageous, and when under an oxygen-rich atmosphere turnover of the catalyst was achieved (Table 1, Entry 2). Evans showed the utility of these conditions by applying the method to the synthesis of Thyroxine.



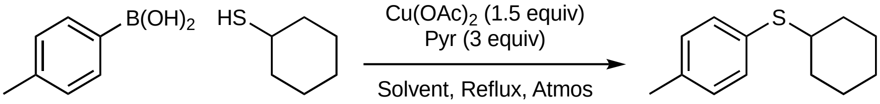
Scheme 29: Boronic acid coupling with a range of nitrogen-based nucleophiles.[116,118] a) Et_3N b) Pyr.



Entry	Cu (equiv)	Atmos	**87**
1	0.1	Argon	9%
2	0.1	Oxygen	30%
3	1	Argon	34%
4	1	Oxygen	71%
5	1	Argon	71%

Table 1: Boronic acid coupling with phenols under inert and oxygen atmospheres.[117]

Building on this series of publications, a number of reports detailing conditions for the formation of various C-X bonds has emerged (C-N, C-O, C-S, C-Se, C-Te, C-Cl, C-Br, C-I).[1] This report focusses on common nucleophilic coupling partners such as HN-, HO- and HS-. Guy and co-workers first expanded the scope of nucleophiles to alkyl thiols forming C-S bonds.[119] Similar conditions to those pioneered by Chan, Evans and Lam were chosen and showed tolerance with a range of arylboronic acids and alkyl thiols. These conditions required super-stoichiometric quantities of copper and the reaction to be performed under an inert atmosphere (Table 2). The reduced yield, when under an atmosphere of air, was proposed to be due to the oxidation of the thiol to form dithianes.

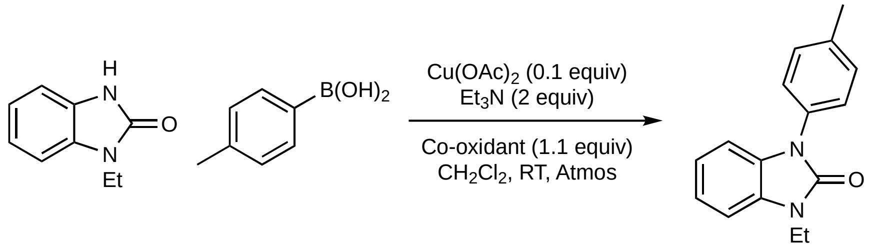


88

Entry	Solvent	Atmos	**88**
1	THF	Air	55%
2	THF	Argon	68%
3	DMF	Argon	88%

Table 2: Boronic acid coupling with alkyl thiols.[119]

Currently, oxidant-free methods for the Chan-Evans-Lam coupling are believed to require a minimum of two equivalents of Cu(II) per new C-X bond formed.[1] The proposed catalytic cycle (Section 1.3.4) requires an initial Cu(II) source as the beginning species and a second equivalent is required for a disproportionation of Cu(II) to Cu(III). Where less than two equivalents of copper are used an external oxidant is required for catalyst turnover. Based on reactions with sub-stoichiometric quantities of copper demonstrated by Evans, a positive pressure of O_2 is used as a common oxidant in the Chan-Evans-Lam reaction. Lam demonstrated the ability of several common copper oxidants to turnover and promote intermediate copper complexes within the catalytic cycle (Table 3).[120–122] The addition of co-oxidants such as TEMPO and pyridine *N*-oxide in the presence of ambient air showed synthetic utility allowing increased yields with certain substrates when compared to O_2 alone.

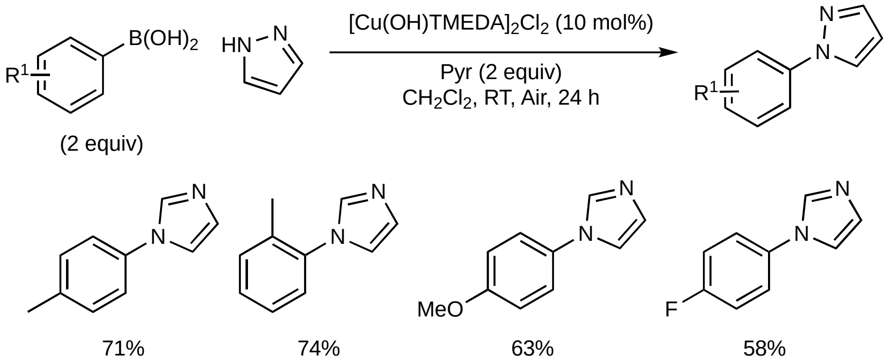


89

Entry	Co-oxidant	Atmos	**89**
1	None	O_2	57%
2	TEMPO	Air	64%
3	Pyridine *N*-oxide	Air	69%

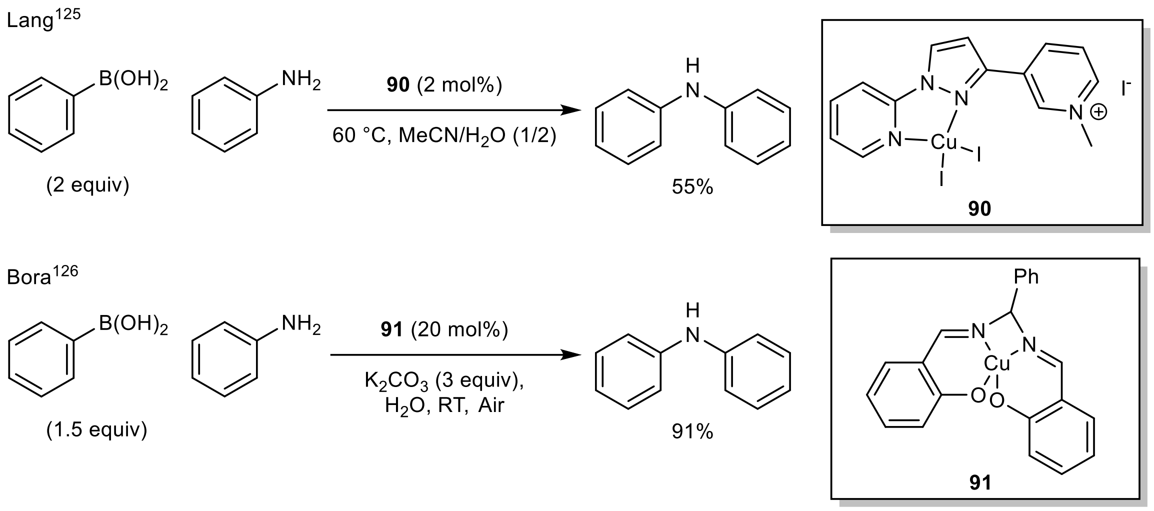
Table 3: Investigation of co-oxidants for the formation of **89**.[120–122]

Despite the other oxidants possessing some advantages, O_2 (ambient pressure from air or positive pressure) has been the most popular oxidant as it is cheap, mild and reduces the complexity of the reaction set up. O_2 has been used in a range of catalytic coupling reactions of arylboronic acids and *N*- and *O*- functionalities (e.g. amine, amide, imide, oxime, sulfoximines, carbamates, phenols and enol ethers).[123] Although many Chan-Evans-Lam conditions do not use a dedicated ligand or preformed catalyst, 3° nitrogen bases are often used in excess and have the ability to ligate to copper. In 2000, Collman and co-workers reported the first copper catalysed conditions for the formation of C-N bonds from the Chan-Evans-Lam coupling (Scheme 30).[124] The conditions required a preformed catalyst ($[Cu(OH.TMEDA]_2Cl_2$) and an oxygen atmosphere for catalyst turnover. The product yields were comparable to that of Lam with considerably lower catalyst loadings.



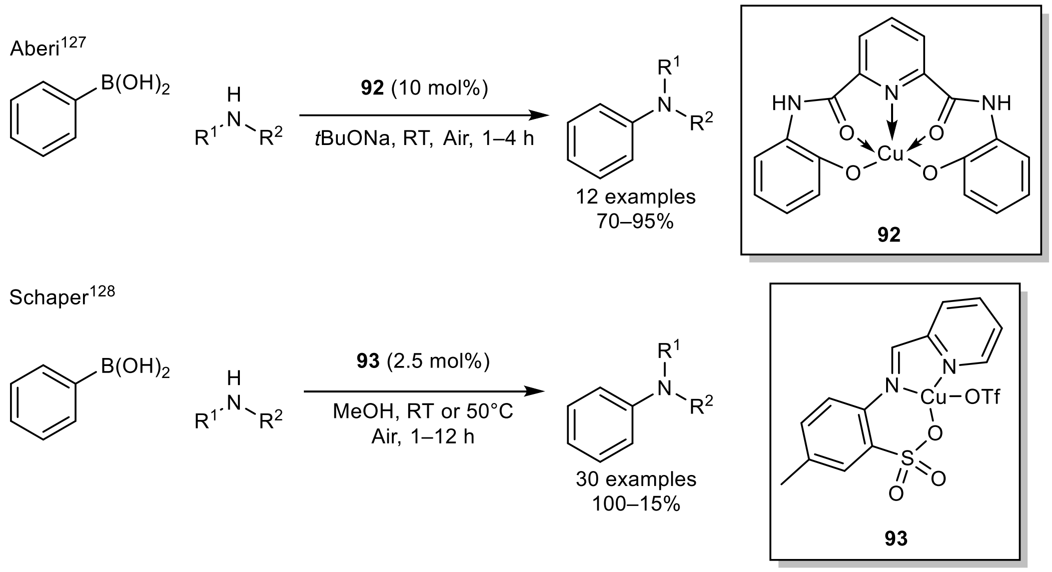
Scheme 30: $[Cu(OH)TMEDA]_2Cl_2$ catalysed Chan-Evans-Lam reaction.[124]

Subsequently, Cu-ligand complexes have been developed to successfully decrease copper loading and allow reaction of less reactive coupling partners under milder conditions. Bidentate, tetradentate and polydentate ligands have been shown to benefit the Chan-Evans-Lam reaction. Lang and co-workers report a cationic pyridine based bi-dentate ligand (**90**) allowing a water/acetonitrile solvent system to be used (Scheme 31).[125] The reaction allows copper loadings as low as 2 mol% with a range of boronic acids and nitrogen nucleophiles. Bora and co-workers developed Cu-salen type complexes (**91**) for the coupling of arylboronic acids with, anilines and imidazoles in water and iso-propanol respectively (Scheme 31).[126] Although a higher copper loading is required (20 mol%) when compared with Lang's conditions, the yields for the coupling of aniline are much higher.



Scheme 31: *N,N*- and *N,O*-based ligands for Chan-Evans-Lam reactions**.**

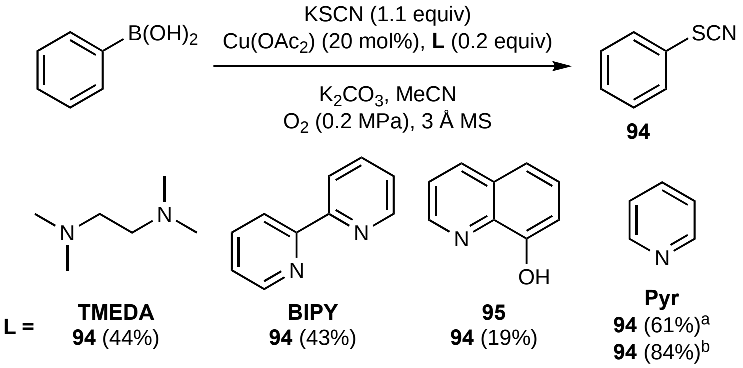
Aberi and co-workers reported a reusable polydentate pyridine-based ligand **92** under solvent free or nearly solvent free conditions (Scheme 32).[127] The copper complex allowed access to a range of products in very short reaction times. Schaper has reported several copper complexes for the successful coupling of a range of arylboronic acids and amine functionalities (Scheme 32, **93**).[128,129] The sulfonate complexes allow significant reductions in copper and boronic acid loading, side product formation, and increased catalyst stability.



Scheme 32: Polydentate ligands for Chan-Evans-Lam reactions.

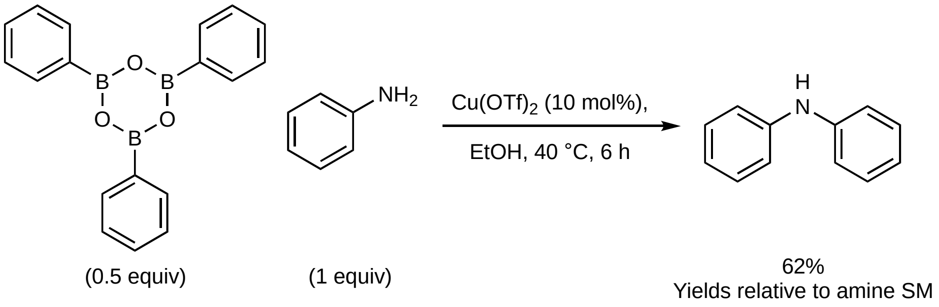
Although many have been tested, ligands give a range of success within Chan-Evans-Lam coupling reactions. Hu and co-workers reported their catalytic conditions for the coupling of aryl boronic acids and potassium thiocyanate (Scheme 33).[130] Nitrogen based ligands were screened in the presence of a dedicated base (K_2CO_3). *N*-Monodentate ligands out performed

N,N- and *N,O*-bidentate ligands with pyridine based monodentate ligands providing the highest yields. Removal of the base provided a higher yield over a range of arylboronic acids.



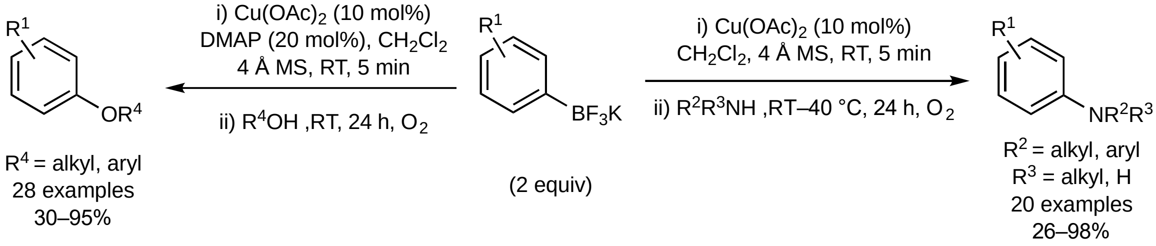
Scheme 33: Use of mono- and bi-dentate ligands in Chan-Evans-Lam coupling. a) Pyr (0.4 equiv), b) No K_2CO_3 added.[130]

A variety of organoboron reagents have been explored for their utility in Chan-Evans-Lam coupling reactions. Due to the comparative difficulty with other organoboron sources, boronic acids are most commonly employed. Arylboroxines, which form the boronic acid *in situ*, have been shown to undergo coupling reactions. Yu and co-workers reported a $Cu(OTf)_2$ catalysed *N*-arylation of amines, amides, imines and sulfonamides with arylboroxines, in the absence of both ligand and base (Scheme 34).[131] Reduced quantities of arylboroxines were required for the full conversion of the coupling partner due to the *in situ* formation of arylboronic acid.



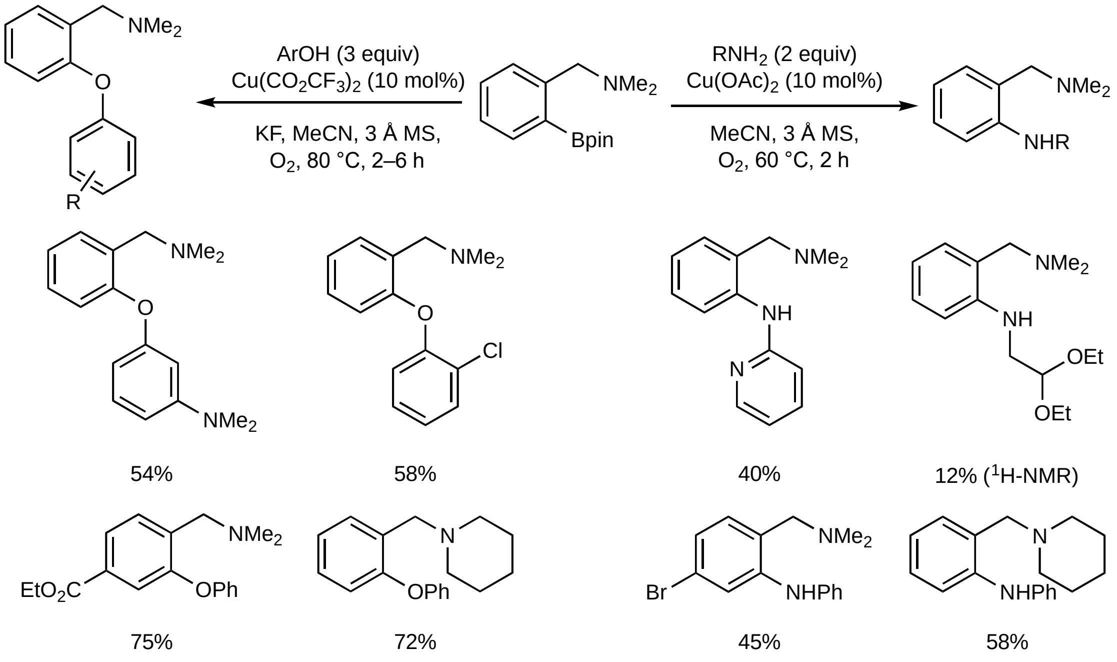
Scheme 34: Chan-Evans-Lam amination using arylboroxines.[131]

Aryl potassium trifluoroborates were also shown to be a viable coupling partner by Batey and co-workers for both *O*- and *N*-based nucleophiles (Scheme 35). Although yields with boronic acids were higher when coupling *N*-nucleophiles, trifluoroborates removed unwanted by-products such as oxidation to phenol, and are more stable. Conversely, coupling of *O*-nucleophiles gave lower yields with arylboronic acids when compared with the corresponding trifluoroborate.[132,133]



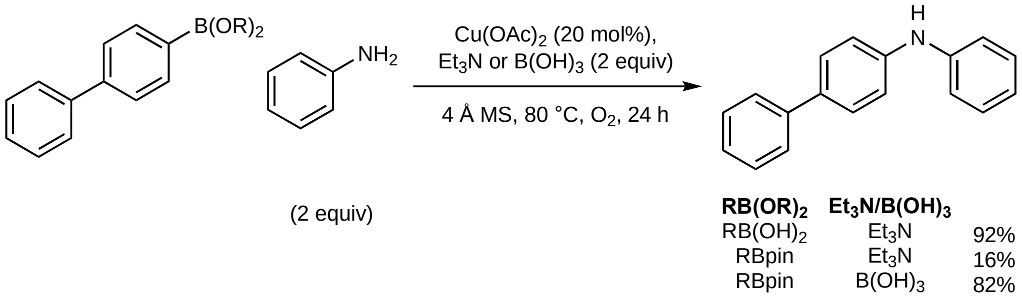
Scheme 35: *O*- and *N*-coupling of aryl potassium trifluoroborates.[132,133]

Boronic esters are of interest due to their increased stability in comparison to boronic acids. However, boronic esters are less reactive under most common conditions. Several approaches have been taken to improve the reactivity of arylboronic esters including the formation of boronic acids from the corresponding esters,[134] activation of copper via intermolecular and intramolecular ligation,[135,136] and the optimisation of conditions containing additives to promote reactivity.[137] Clarke and co-workers reported the activation of arylboronic esters aided by coordination to a pendant benzylamine groups (Scheme 36). This coordination is thought to promote transmetallation, overcoming the low inherent reactivity of the boronic ester. This system has been used for both *O*- and *N*- coupling.[135,136]



Scheme 36: Aryl boronic ester *O*- and *N*- coupling promoted by an amine directing group.[135,136]

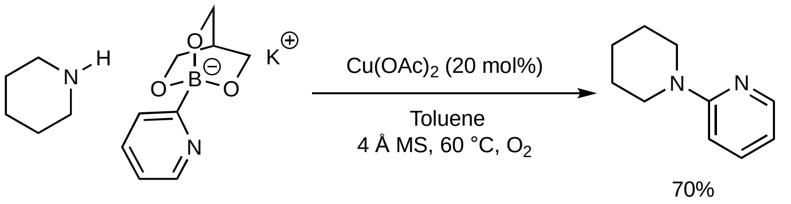
Watson and co-workers used additive effects to successfully couple aryl pinacol boronic esters with a range of substrates. The addition of ethanol was shown to greatly improve the efficiency of the reaction in the presence of stoichiometric quantities of copper.[137] Shortly after this, Watson and co-workers reported catalytic conditions employing $B(OH)_3$ as an additive instead of a base such as Et_3N (Scheme 37).[138] It was proposed that $B(OH)_3$ acted by sequestering pinacol, generated as a side product after reaction of the pinacol boronic esters. $B(OH)_3$ has been known to coordinate to copper, leading to catalyst deactivation. This allows re-oxidation of Cu(I) to Cu(II) to occur more effectively than in the presence of Et_3N, improving catalyst turnover.



$RB(OR)_2$	**$Et_3N/B(OH)_3$**	
$RB(OH)_2$	Et_3N	92%
RBpin	Et_3N	16%
RBpin	$B(OH)_3$	82%

Scheme 37: The effect of additives on the *N*-arylation of aniline with arylboron reagents.[138]

Air and moisture stable cyclic triolborates have been shown by Miyaura and co-workers to be robust coupling partners for amine functionalities (Scheme 38).[139] Noteworthy is the successful coupling of 2-pyridyl triolboronate, as the corresponding boronic acid and ester are known to undergo facile protodeboronation.



Scheme 38: The coupling of 2-pyridyl triolborate with piperidine.[139]

1.3.4 Mechanism of the Chan-Evans-Lam Reaction

Over recent years a number of studies have provided evidence and hypotheses for the mechanism by which the Chan-Evans-Lam coupling occurs.[138] Due to issues that complicate reaction mechanism elucidation, such as copper speciation, the several roles copper plays, and a variety of conditions, the mechanism is not fully understood. Watson and co-workers have recently published their proposed mechanism for the aryl Chan-Evans-Lam amination based on prior work conducted by Stahl and co-workers investigating a related esterification process.

It was proposed that ligation of the nucleophilic amine leads to de-nucleation of dimeric copper species **73** to mononuclear species **74**.[138] Co-ordination of the hydroxyl group to the empty p-orbital on boron gives intermediate **75**. The intermediate is proposed to facilitate transmetallation through a 4-membered transition state to give Cu(II) species **76**. Oxidation to Cu(III) through disproportionation of a second Cu(II) species gives complex **77**. This is necessary for reductive elimination of the C-N bond to occur, which provides the amine product **78** and a Cu(I)OAc species (**79**). Finally, Cu(I) is oxidised to Cu(II) in the presence of O_2 to regenerate the active catalyst (**74**). If the oxidation process is slow, side products such as the arene **80** formed though protodeboronation, alcohol (**81**) and oxidative homo-coupled (**82**) products may form.

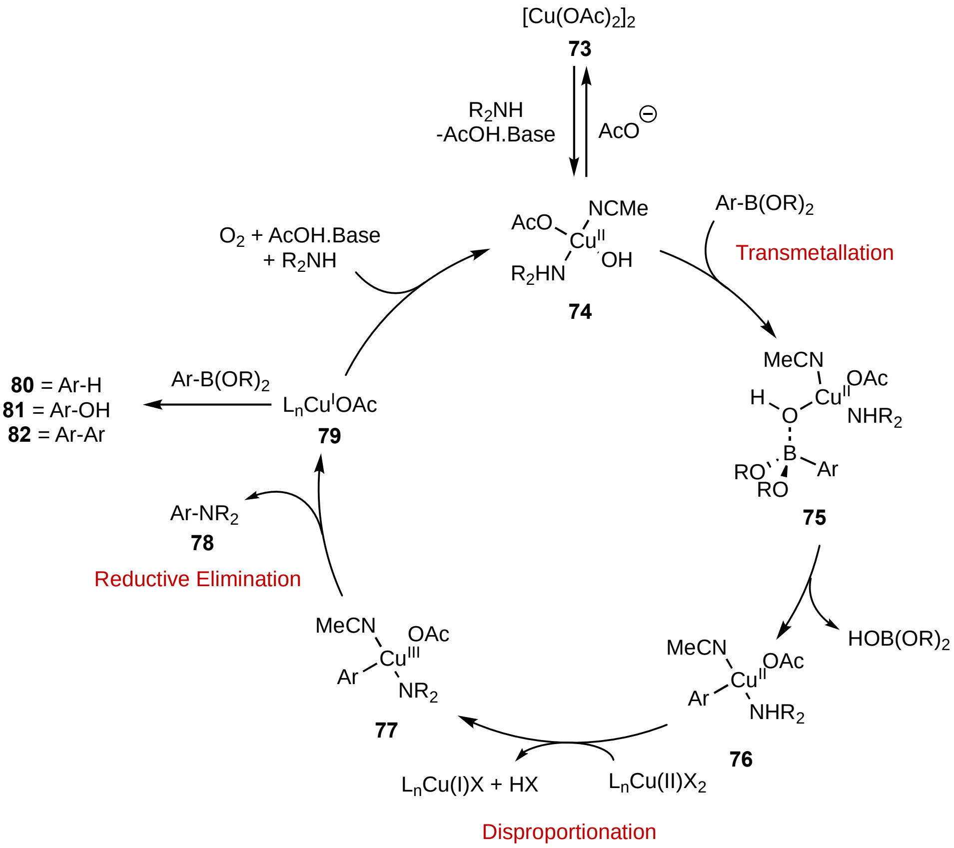


Figure 14: Simplified mechanism, proposed by Watson and co-workers, for Chan-Evans-Lam amination.[138]

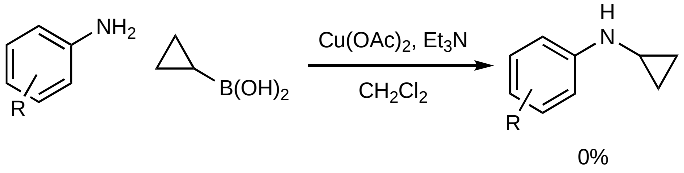
2 Development of an Alkyl Chan-Evans-Lam Coupling

Cross-coupling reactions of alkyl halides have been developed displaying considerable advantages over classical substitution reactions. These reactions have been largely limited to C-B and C-C bond formation and most significantly encompass 2° and 3° alkyl halides and the ability to form enantioenriched products.[90,140] The analogous reaction, coupling alkyl halides and nitrogen nucleophiles, is far less developed despite the presence of alkyl amines in natural products.[109] The lack of examples is thought to be due to the propensity for alkyl metal intermediates to undergo β-hydride elimination and that reductive elimination of alkyl-amine metal intermediates is slow. This is common in many early and late-stage transition metal catalysed processes such as palladium, rhodium, ruthenium and copper chemistries.[141–143]

The Chan-Evans-Lam amination may be a suitable strategy to overcome these challenges. Generally, alkyl copper species do not undergo β-hydride elimination. In addition, the literature provides examples to suggest, that under the correct conditions, reductive elimination to give alkyl C-N bonds is feasible.

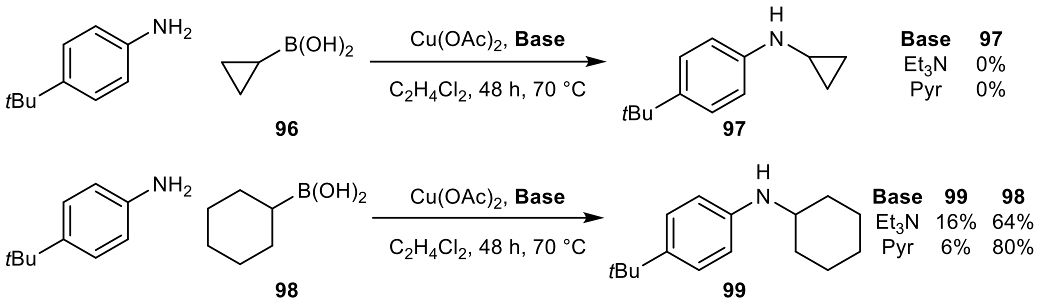
2.1 *Background*

The first unsuccessful attempt at a copper mediated coupling of cyclopropylboronic acid and aniline was reported by Wallace and co-workers in 2002 whilst exploring the parallel Suzuki cross-coupling reaction of cyclopropylboronic acids and hetero arylbromides (Scheme 39).[144]



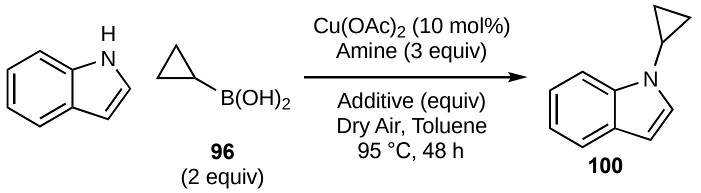
Scheme 39: Unsuccessful coupling of cyclopropylboronic acid and aniline.[144]

Shortly after, Hall *et al*. described unpublished results by Lam *et al*. of, to our knowledge, the first successful example of a Chan-Evans-Lam coupling reaction between cyclohexylboronic acid (**98**) and 4-tertbutyl aniline, albeit in a low yield (Scheme 40).[145] They also reported the lack of reaction between aniline and cyclopropylboronic acid under these conditions. The difference in reactivity is of interest due to the significant sp^2 character of the carbons on the cyclopropyl ring (**96**). This distortion in hybridisation has previously resulted in the subsequent organometallic species possessing a greater 's' character and promoting transmetallation as described by Tsuritani a number of years later.[146]

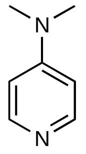


Scheme 40: Successful coupling of cyclohexylboronic acid and aniline.[145]

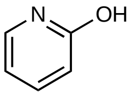
Tsuritani noted the extensive studies on arylboronic acids and turned his attention to cyclopropylboronic acids, due to their similar reactivities.[146] They reported the copper catalysed *N*-cyclopropylation of indoles and cyclic amides. During optimisation they rationalised that an amine base/ligand such as pyridine or Et_3N was required for the reaction to occur (Table 4, entry 1, 2 and 3). Increasing the basicity of the amine ligand and addition of NaHMDS as a strong base was beneficial (Table 4, entry 5). Conversely the addition of an acid had detrimental effects (Table 4, entry 6). Several ligands were tested but were found to have minimal or negative effects (Table 4, entry 7 and 8).



Entry	Amine	Additive (equiv)	**100**
1	-	-	0%
2	Et_3N	-	20%
3	Pyr	-	40%
4	DMAP	-	45%
5	DMAP	NaHMDS (1.0)	65%
6	Pyr	$n C_9H_{19}C(O)_2H$ (0.2)	20%
7	Pyr	BIPY (0.1)	9%
8	Pyr	**101** (0.1)	36%



DMAP

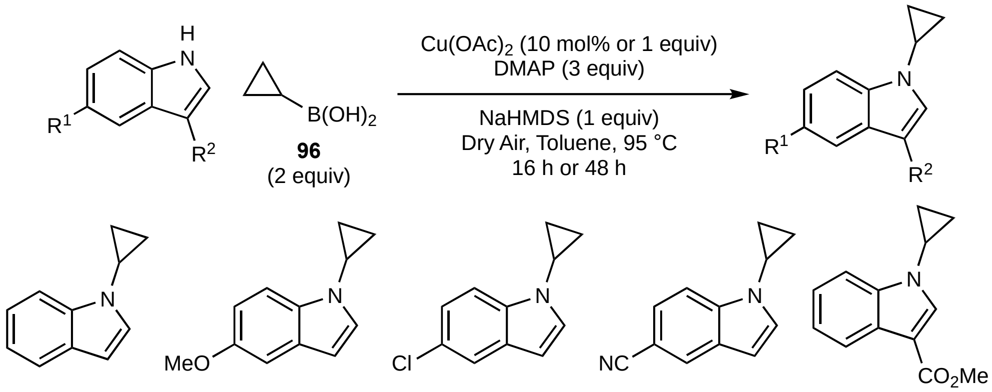


101

Table 4: The effect of additives on the coupling of cycloproylboronic acid with indole.[146]

The reaction was found to tolerate a number of functional groups including ether (**103**), chloro (**104**), nitro, ketone, nitrile (**105**) and ester (Scheme 41, **106**).[146] Electron deficient indoles gave significantly lower yields when sub-stoichiometric quantities of copper were used.

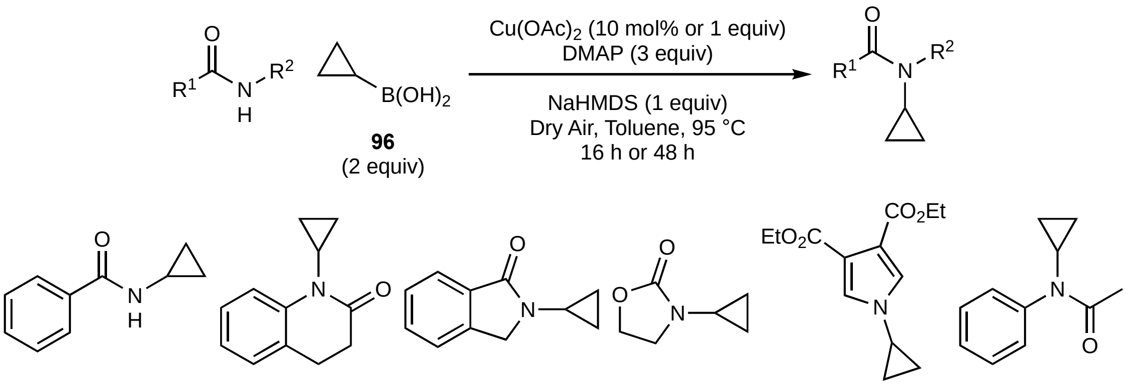
The yields could be improved with stoichiometric loadings of copper (**106**). In contrast, electron rich indoles gave considerably lower yields at higher catalyst loading, though no rational was given (**103**).



102	**103**	**104**	**105**	**106**
62%[a]	65%[a]	68%[a]	28%[a]	34%[a]
35 %[b]	15%[b]	78%[b]	86%[b]	93%[b]

Scheme 41: Scope of reaction for the cyclopropylation of *N*-heterocycles. a) Reaction time of 48 h and $Cu(OAc)_2$ (10 mol%) b) Reaction time of 16 h and $Cu(OAc)_2$ (1 equiv).[146]

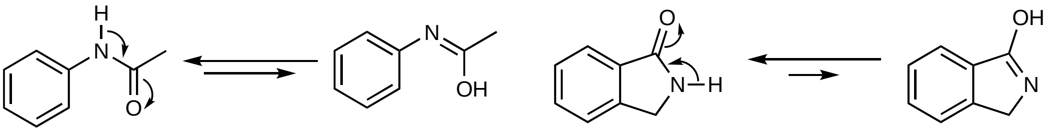
The conditions were next applied to the coupling of cyclopropylboronic acid with amides (Scheme 42). Benzamides (**107**), lactams (**108** and **109**), imides and carbamates worked well.[146] However, acyclic amide (N-phenylacetamide) (**111**) did not form the corresponding product and the starting material was recovered.



107	**108**	**109**	**110**	**111**	**112**
70%[a]	67%[a]	71%[a]	48%[a]	<5%[a]	0%[a]
76%[b]	72%[b]	89%[b]	49%[b]	78%[b]	0%[b]

Scheme 42: Scope of reaction for the cyclopropylation of acyclic and cyclic amides. a) Reaction time of 48 h and $Cu(OAc)_2$ (10 mol%) b) Reaction time of 16 h and $Cu(OAc)_2$ (1 equiv).[146]

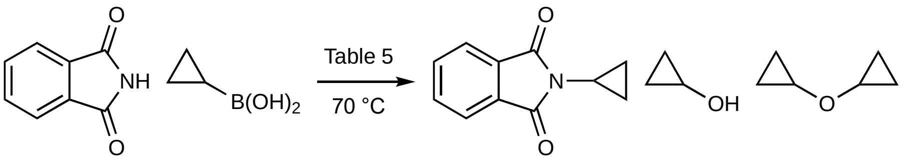
It was hypothesised that this poor reactivity was due to the acyclic amides tendency to prefer the *Z*-conformation over the *E*-conformation that cyclic amines are forced to adopt (Figure 15).[146] The *Z*-conformation places the N-H bond antiperiplanar to the carbonyl increasing the iminol character (**113B**).



113A **113B** **114A** **114B**

Figure 15: An explanation for the difference in reactivity of acyclic and cyclic 2° amides.[146]

Shortly after this, Zhu and co-workers reported conditions for the Cu-catalysed coupling of cyclopropylboronic acid with amides, azoles and sulphonamides.[147] Zhu chose to explore coupling partners with more acidic N-H bonds expecting to see an increased reactivity. More basic amines like anilines were avoided. The addition of an amine base/ligand again proved beneficial and addition of an inorganic base drove the reaction to completion (Table 4, entry 2). Substoichiometric loadings of copper could be used albeit with a slight reduction in yield (Table 5, entry 5). Ligands were examined, and BIPY was found to be beneficial. Excess cyclopropylboronic acid was employed to counter the formation of oxidation side products (alcohol (**116**) and ether (**117**)).



96
(2 equiv)

115 **116** **117**

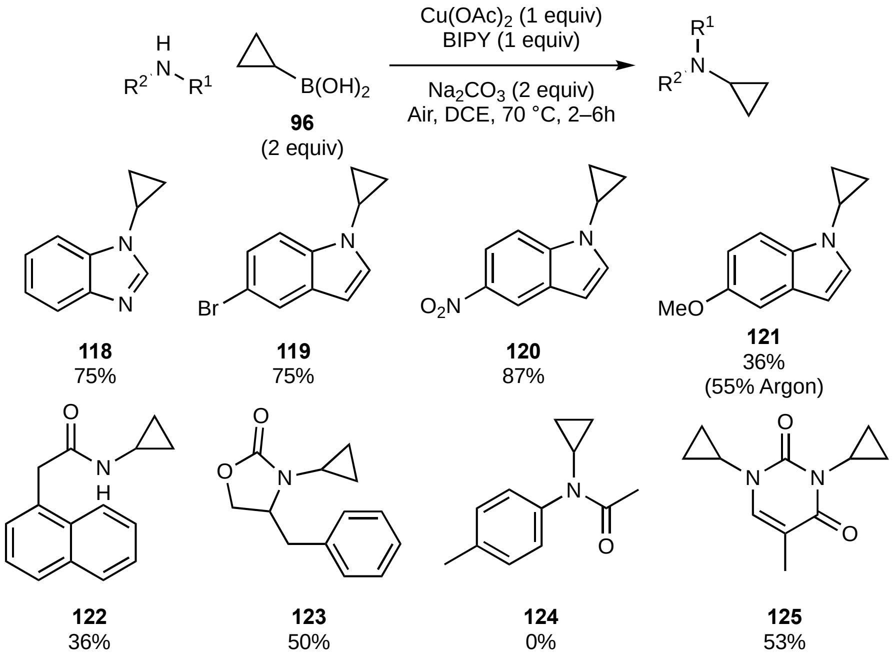
Entry	$Cu(OAc)_2$ (equiv)	Solvent	Base (equiv)	Ligand (equiv)	**115**
1	1.0	Toluene	Pyr (2.0)	-	70%
2	1.0	Toluene	Na_2CO_3 (2.0)	Pyr (2.0)	>95%
3	0.2	Toluene	Na_2CO_3 (2.0)	Pyr (0.4)	75%
4	0.2	Toluene	Na_2CO_3 (2.0)	BIPY (0.2)	80%
5	0.2	DCE	Na_2CO_3 (2.0)	BIPY (0.2)	80%
6	1.0	DCE	Na_2CO_3 (2.0)	BIPY (1.0)	100%

Table 5: Optimisation for the coupling of phthalimide with cyclopropylboronic acid.[147]

Similar to the results of Tsuritani, Zhu noted electron deficient indoles (**120**) gave excellent results when stoichiometric quantities of copper were used (Scheme 43).[147] However, electron rich indoles gave much poorer results (**121**). The reaction conditions tolerate halogen (**119**), nitro (**120**), ester, and ether (**121**) functionalities. Interestingly and contradictory to Tsuritani's results, when performed under an inert atmosphere, electron donating indole (**121**) gave an increased yield with a stoichiometric loading of copper.

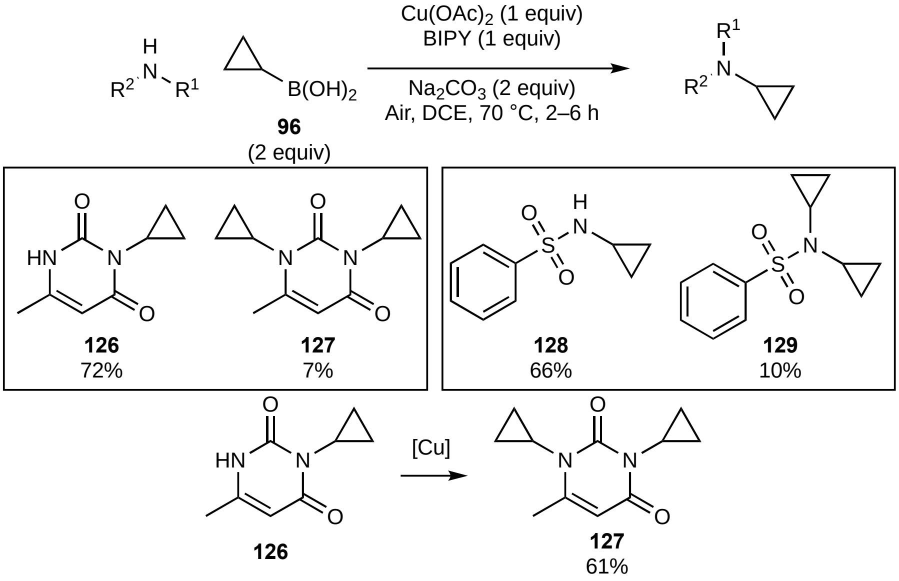
Benzylic amides, aliphatic amides (**122**) and carbamates (**123**) were shown to couple under the standard conditions, albeit with a reduced yield for aliphatic amines and carbamates.[147] Again, acyclic amide 4-methoxy-acetanilide (**124**) was found to be unreactive.

Imidazole, benzimidazole, benzotriazole, carbazole, 2-acetylpyrrole and oxazolidinone were coupled with cyclopropylboronic acid in good to excellent yield.



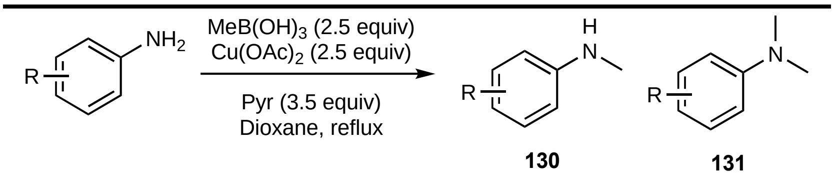
Scheme 43: Scope of reaction for the cyclopropylation *N*-heterocycles.[147]

Cyclopropylation of nucleobases thymine and methyluracil possess the potential to give the mono- and di-alkylated products.[147] Thymine afforded only the dialkylated product **125** (Scheme 44) and methyluracil the mono- (**126**) and di-alkylated (**127**) products as the major and minor products respectively (Scheme 44). The steric hindrance of the methyl group of methyluracil was proposed to be the cause of the regioselectivity. When **126** was re-subjected to the reaction, the dialkylated product **127** was formed in a 61% yield. A sulfonamide was alkylated to give the mono (**128**) and di-alkylated (**129**) products as the major and minor products respectively.



Scheme 44: Mono- and di-cyclopropylation of methyluracil and sulfonamide.[147]

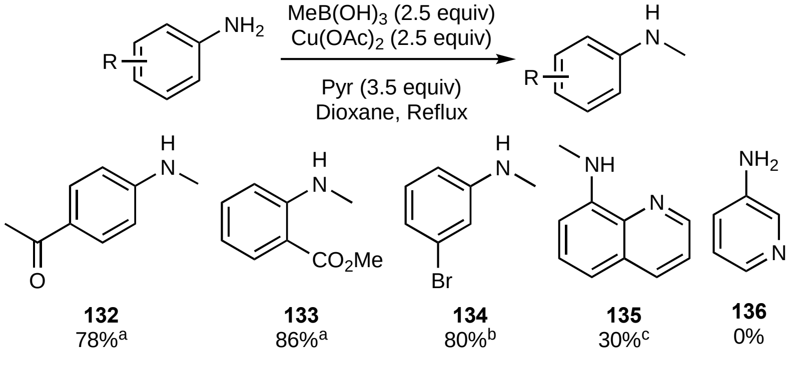
The *N*-methylation of anilines was reported by Cruces and co-workers in 2009 as the first non-cyclopropyl-based alkyl Chan-Evans-Lam reaction.[148] Initially three different methylboron sources were examined, methylboronic acid, potassium methyl-trifluoroborate and trimethylboroxine. Only methylboronic acid showed any conversion to the monoalkylated product with super-stoichiometric quantities of copper acetate. The corresponding reaction provided no conversion with palladium sources. Corroborating previous observations, the methylation required a nitrogen-based additive that gave little effect to conversion when changing its quantity above excess.[148] Significant effects were observed when altering the ratio of copper source and boronic acid. Copper and boronic acid in excess have the potential to form di-methylated products over longer reaction times. The optimum ratio was 2.5 equivalents of $Cu(OAc)_2$ and 2.5 equivalents of $MeB(OH)_2$. This ratio gives a compromise between reaction efficiency and the formation of the di-methylation product. Cruces also alludes to the order of addition being crucial for conversion with the copper catalyst requiring an incubation period (10-15 min) before the addition of the boronic acid.



Entry	R	Time (h)	Yield of **130**	**130:131**
1	2-Me	2.5	69%	9.4:1
2	3-Me	2.5	70%	6.1:1
3	4-Me	1.5	69%	3.4:1
4	2-OMe	3	66%	1:0
5	3-OMe	1.5	72%	6:1
6	4-OMe	1.5	63%	3.5:1
7	2-CN	3.5	59%	1:0
8	3-CN	3	70%	18:1
9	4-CN	2.5	74%	38:1

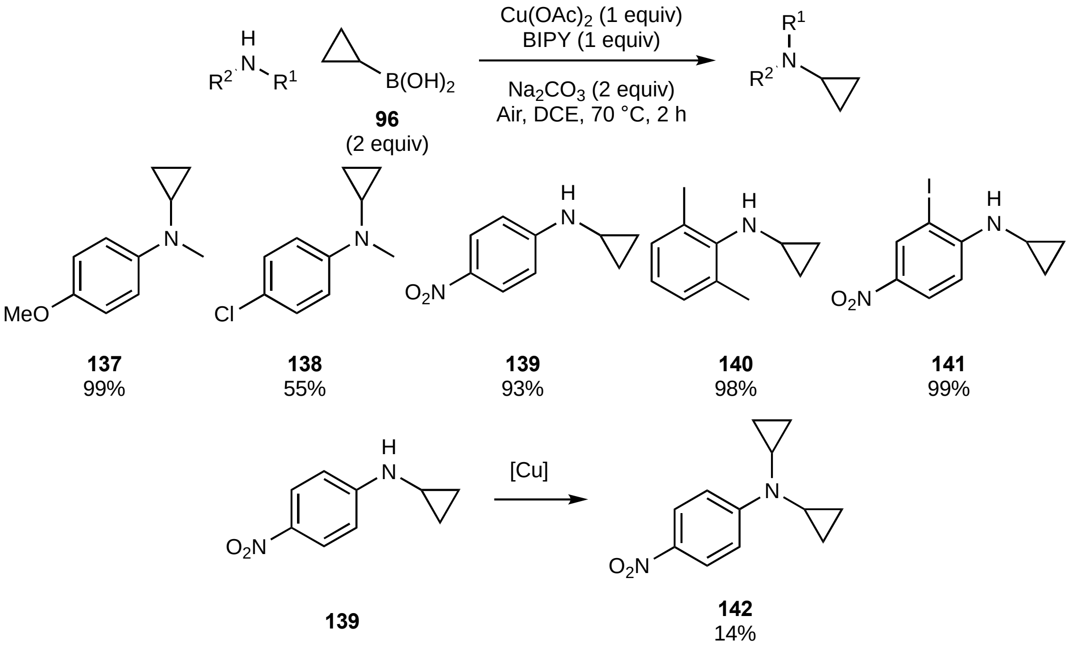
Table 6: *N*-Methylation of anilines. Isolated yields represent the average of two runs, and the ratio **130**:**131** was determined by HPLC-MS .[148]

Both electron rich (Table 6, entry 6), electron deficient (Table 6, entry 9) and sterically demanding (Table 6, entry 1) anilines reacted with good conversion.[148] Electron poor substrates and sterically demanding substrates provided less di-methylated products. Functional groups found to be problematic in reductive amination such as ketone (**132**) and ester (**133**) due to their reduction, were successfully methylated (Scheme 45). Aryl halides (**134**) were also tolerated allowing further functionalisation. Noteworthy is the lower yield of aminoquinoline (**135**) and lack of coupling with 3-aminopyridine (**136**).



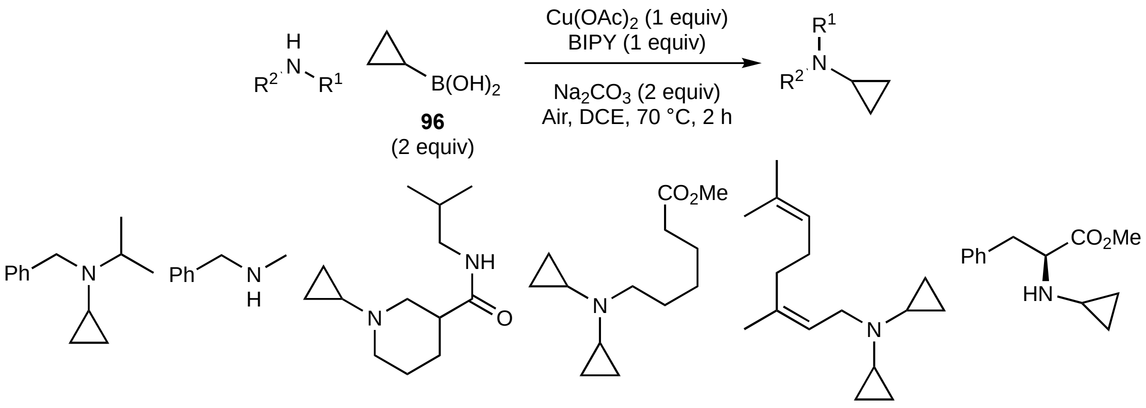
Scheme 45: Scope of reaction for *N*-methylation of anilines. a) Reaction time of 4.5 h, b) Reaction time of 2.5 h, c) Reaction time of 2 h.[148]

In the same year, Zhu and co-workers reported the *N*-cyclopropylation of anilines and aliphatic amines based on their previous conditions.[149] As before, when using substoichiometric quantities of copper and ligand (0.1 equiv) the product was isolated in a reduced yield (19%). As seen with Cruces methylation, when alkyl trifluoroborate sources were employed, the reaction was far less effective. A range of functionalised anilines, including substrates with electron donating (**137**) and withdrawing groups (**139**), were coupled in good to excellent yield (Scheme 46). Sterically hindered ortho-substituted anilines were tolerated (**140**) and *N*-methylanilines coupled in excellent and fair yields (**137** and **138**). Interestingly, no dialkylation was observed, and re-subjecting the monoalkylated product (**139**) to the conditions gave the dialkylated product (**142**) in only 14% yield. As with previous reports *N*-phenylacetamide derivatives were found to be unreactive.



Scheme 46: Scope of reaction for the cyclopropylation of anilines.[149]

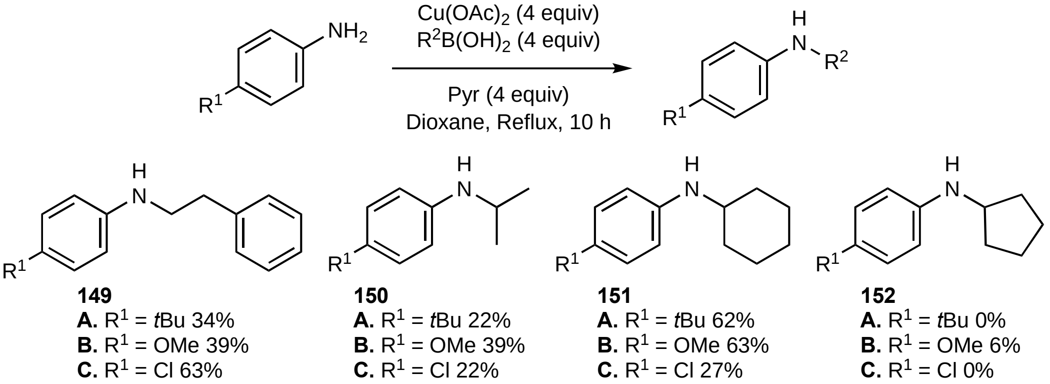
Several 2° cyclic amines and *N*-isopropylbenzylamine (**143**) were successfully cyclopropylated (Scheme 47).[149] The reaction of *N*-methylbenzylamine (**144**) was unsuccessful, presumably due to the sensitivity of benzylamines to *N*-dealkylation under oxidative conditions.[150–152] Aliphatic amines were shown to be selectively cyclopropylated in the presence of 2° amides (**145**).[149] The reaction of 1° amines gave the corresponding dialkylated products in modest yield under standard conditions. However, increasing the amount of boronic acid significantly improved the yield (**146** and **147**). Contrary to this, L-methylphenylalanate was isolated as the mono-cyclopropylated product (**148**). Zhu and co-workers speculated that steric factors as well as the chelating ability of the α-aminoester could have disfavoured dialkylation. In addition, the use of Na_2CO_3 gave an increased degree of racemisation (83:17 er) when compared with $NaHCO_3$ (93:7 er).



143 40%
144 0%
145 45%
146 60%[a]
147 55%[a]
148 47%[b], 93:7 er

Scheme 47: Scope of reaction for the cyclopropylation of aliphatic amines. a) $RB(OH)_2$ (4 equiv), b) $NaHCO_3$ (2 equiv).[149]

Based on their previously optimised conditions for methylation, Cruces and co-workers expanded on unpublished work by Lam *et al.*[153] reporting the coupling of aromatic amines with a variety of alkylboronic acids. Similarly, Cruces observed limited coupling of cyclohexylboronic acid and no coupling of cyclopropylboronic acid with aniline in the presence of 2.5 equivalents of boronic acid and copper. Increasing the loading of all reagents to 4 equivalents allowed for full conversion of the aniline to the mono-alkylated product for cyclohexylboronic acid, but no conversion was observed for cyclopropylboronic acid. A range of alkylboronic acids varying in chain length, steric hindrance and ring size were coupled to 4-tertbutyl- (**149A-152A**), 4-methoxy- (**149B-152B**) and 4-chloroaniline (Scheme 48, **149C-152C**). The rate of conversion was observed to be slower for anilines with electron withdrawing substituents and faster for electron donating substituents. For the reaction of electron rich 4-methoxyaniline, moderate yields were attributed to the formation of the dialkylated product. To minimise dialkylation, Cruces decreased the boronic acid excess for electron neutral and electron rich anilines and suggested that the reaction conditions should be tailored for each substrate. 2° boronic acids appeared reagent dependant. Low yields were reported for the reaction of 2-propylboronic acid (**150**), and low conversion was observed for the reaction of cyclopentylboronic acid with 4-methoxyaniline (**152B**).



149
A. R^1 = *t*Bu 34%
B. R^1 = OMe 39%
C. R^1 = Cl 63%

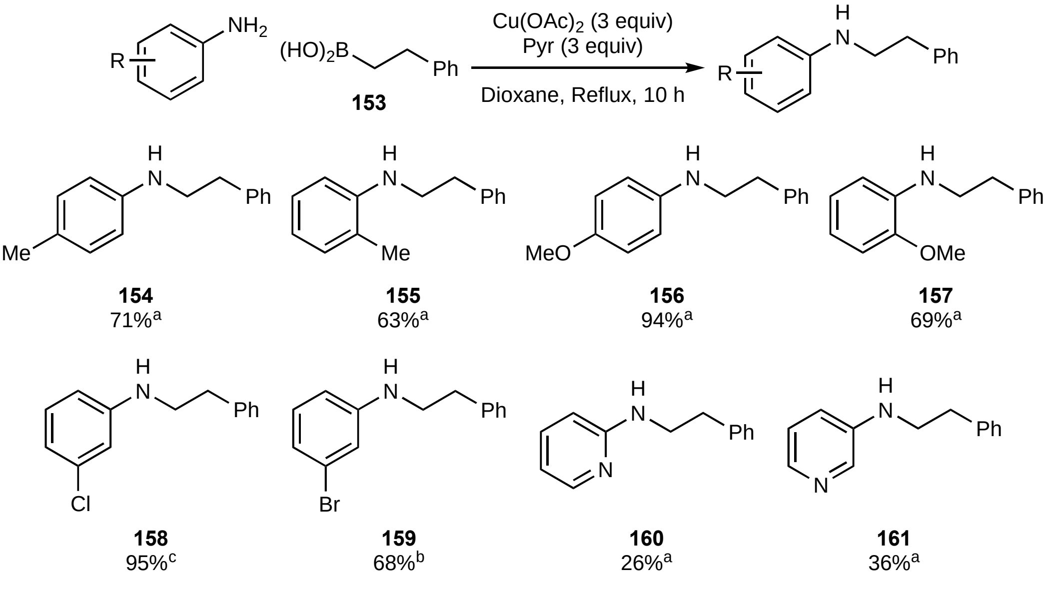
150
A. R^1 = *t*Bu 22%
B. R^1 = OMe 39%
C. R^1 = Cl 22%

151
A. R^1 = *t*Bu 62%
B. R^1 = OMe 63%
C. R^1 = Cl 27%

152
A. R^1 = *t*Bu 0%
B. R^1 = OMe 6%
C. R^1 = Cl 0%

Scheme 48: The effects of electron-withdrawing and donating substituents on the amination of alkylboronic acids.[153]

The reaction of phenylethylboronic acid (**153**) was explored in detail due to the prevalence of this moiety in bioactive molecules.[153] Various anilines displaying electron withdrawing and donating substituents and sterically hindered anilines were reacted to give the monoalkylated amines in good to excellent yields (Scheme 49). Electronic effects of the aniline partner mirrored previous observations, and sterically hindered 2-methylaniline required increased reaction times (**155**). Reactions with various aminopyridines were found to be low yielding (**160** and **161**).



154 71%[a]

155 63%[a]

156 94%[a]

157 69%[a]

158 95%[c]

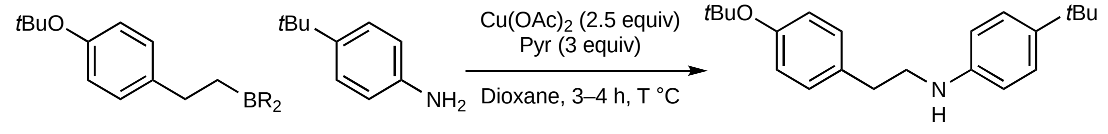
159 68%[b]

160 26%[a]

161 36%[a]

Scheme 49: Scope of reaction for the alkylation of anilines. a) $RB(OH)_2$ (1.3 equiv), b) $RB(OH)_2$ (2.0 equiv), c) $RB(OH)_2$ (2.5 equiv).[153]

In 2012 Cruces and co-workers extended their scope to more reactive alkylboranes.[154] Due to the inherent instability of alkylboranes to air, the boranes formed by the hydroboration of styrene's, were used without further purification. Phenylethylanilines (**163**) remained the targets of choice with 9-borabicyclo(3.3.1)nonane (9-BBN) and trialkylboranes tested as precursors. Trialkylboranes were found to be more reactive providing full conversion within 3 hours at reflux and moderate yield at room temperature (Table 7, entry 2 and 3). Alkyl 9-BBN provided low yields of the desired product even, at reflux and increased borane equivalence (Table 7, entry 4 and 5). This was presumably due to the formation of by-products from BBN.



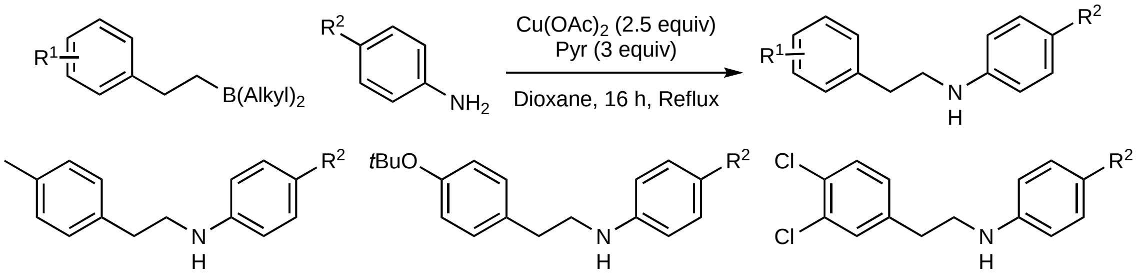
162

163

Entry	**162** (equiv)	T (°C)	**163**
1	Alkyl$_3$B (0.4)	Reflux	47%
2	Alkyl$_3$B (1.1)	Reflux	86%
3	Alkyl$_3$B (1.1)	RT	26%
4	9-BBN (4.0)	RT	0%
5	9-BBN (4.0)	Reflux	35%

Table 7: Amination of trialkyl boranes and 9-BBN derivatives.[154]

A range of neutral, electron rich and electron poor anilines, and several trialkylborane reagents were reacted (Scheme 50).[154] Electronic effects were concurrent with previous rate observations. Electron donating substituents on the aniline gave a faster rate of conversion to the corresponding product, but often gave lower yields due to the formation of the dialkylated products (**164B-166B**). Anilines with electron withdrawing substituents reacted at a slower rate, but were less prone to dialkylation (**164C-166C**). 4-Chloroaniline and 3,4-dichlorostyrene did not proceed to full conversion even after 16 hours (**166C**).



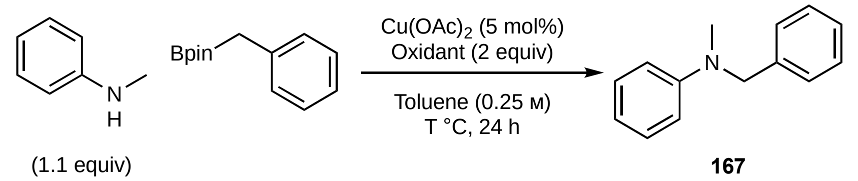
164
A. R^2 = *t*Bu 89%
B. R^2 = OMe 90%
C. R^2 = Cl 75%

165
A. R^2 = *t*Bu 86%
B. R^2 = OMe 68%
C. R^2 = Cl 62%

166
A. R^2 = *t*Bu 90%
B. R^2 = OMe 71%
C. R^2 = Cl 47%

Scheme 50: Scope of reaction for the coupling of boranes and aniline.[154]

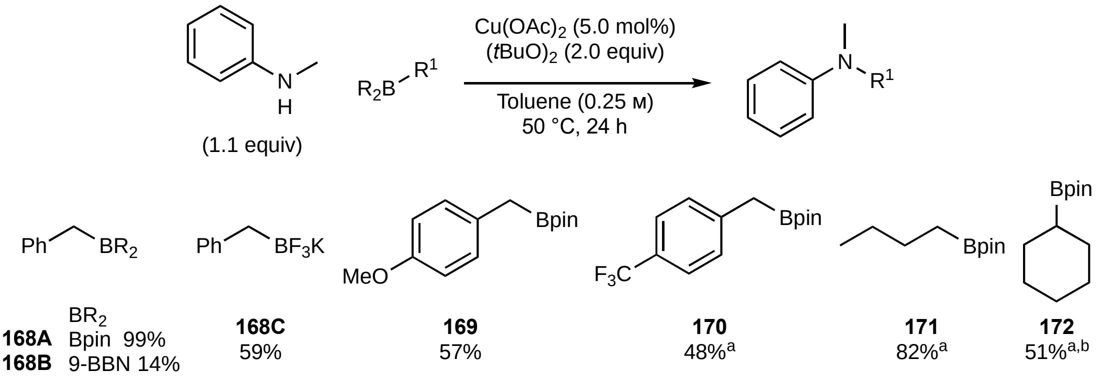
One year later Kuninobu and co-workers reported the first successful catalytic coupling of alkyl boronic pinacol esters and aryl amines.[155] Copper(II) salts and various oxidation sources were screened. Initial results with $Cu(OAc)_2$ (5 mol%) in the presence of air gave a low yield. The turnover of copper catalyst was explored using a range of oxidation sources. Full conversion was observed only using di-tert-butyl peroxide (DTBP) and Ag_2CO_3 as terminal oxidants (Table 8, 7 and 8). DTBP was chosen due to the reduced cost. Consistent with previous reports, $Cu(OAc)_2$ appeared to be the most effective pre-catalyst, with other Cu sources giving little to no conversion in the presence of DTBP. Unlike previous examples, an excess of amine was used.



Entry	Oxidant	T (℃)	**167**
1	$(tBuO)_2$	100	47%
2	$PhI(OAc)_2$	100	<1%
3	$K_2S_2O_8$	100	5%
4	AgOAc	100	31%
5	Ag_2CO_3	100	55%
6	O_2	100	13%
7	$(tBuO)_2$	50	99%
8	Ag_2CO_3	50	96%

Table 8: Effect of oxidant and temperature on the formation of **167**.[155]

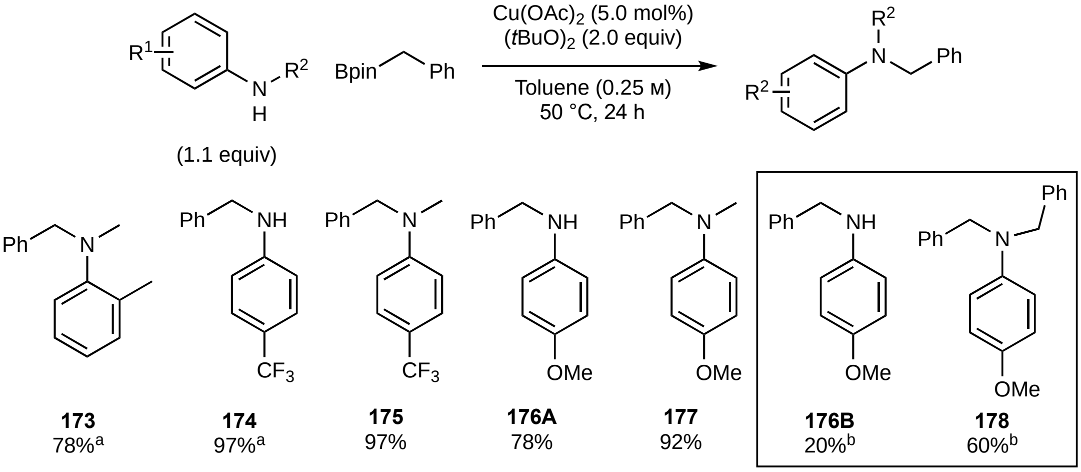
The use of borane (9-BBN) (**168B**) and potassium trifluoroborate (**168C**) reagents showed a decreased reactivity when compared to the corresponding boronic ester (Scheme 51, **168A**).[155] Both electron rich (**169**) and electron poor (**170**) substituents on the benzylic boronic esters gave marginally reduced yields. In addition, 1° (**171**) and 2° (**172**) aliphatic boronic esters were well tolerated, though the reaction of 2° benzylic boronic esters were not reported.



Scheme 51: Scope of reaction for the amination of alkyl boron reagents. a) *N*- methyl aniline (1.5 equiv, 0.5 м), b) Reaction performed in hexane.[155]

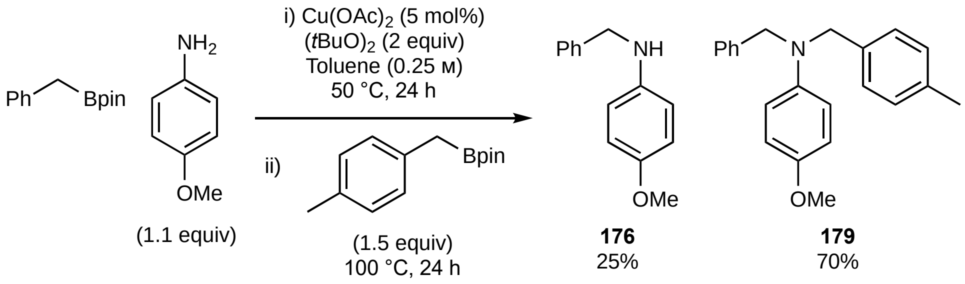
Benzyl boronic ester was successfully coupled to a range of anilines, but coupling of aliphatic amines such as morpholine and butyl amine were unsuccessful.[155] The cross-coupled product of sterically hindered 2-methylaniline (**173**) and electron deficient 4-

trifluoromethyl aniline (**174**) were obtained in high yield at increased temperatures (Scheme 52). Lower temperatures were required for the corresponding *N*-methylated 2° anilines that possess electron withdrawing substituents, e.g. 4-(trifluoromethyl)-*N*-methylaniline (**175**). 4-Methoxyaniline was coupled successfully (**176A**), with a slight reduction in yield due to the formation of the dialkylated product. Coupling the corresponding *N*-methyl aniline (4-(methoxy)-*N*-methylaniline) provided a higher yield (**177**). The dialkylated product of 4-methoxy aniline (mono-alkylated **176B** and dialkylated **178**) was isolated in good yield when the boronic ester loading was increased to 2 equivalents.



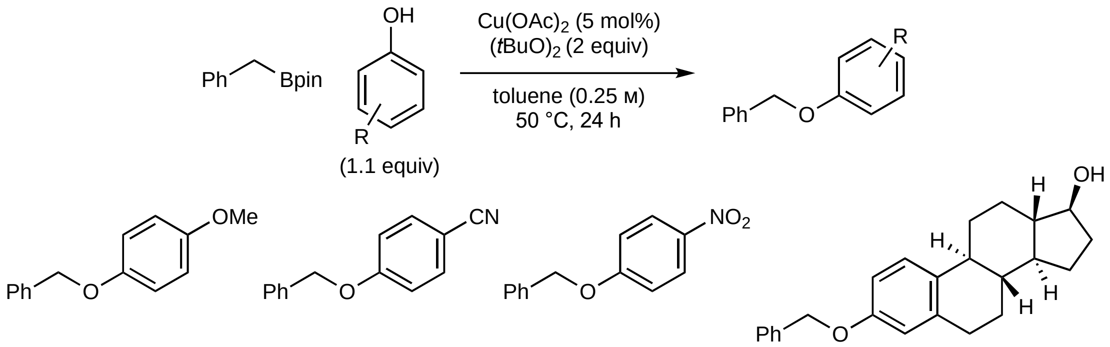
Scheme 52: Scope of reaction for the amination of an alkyl boronic ester. a) Reaction temperature of 100 °C, b) Bpin (2.0 equiv).[155]

This prompted an investigation into the formation of an unsymmetrical dialkylated product (Scheme 53).[155] The sequential one pot addition of two different benzylic boronic esters to 4-methoxy aniline yielded 25% of the monoalkylated product **176** and 70% of the unsymmetrical dialkylated product **179**.



Scheme 53: Sequential alkylation of *p*-anisidine.[155]

The coupling of phenols could also be achieved under the same conditions (Scheme 54).[155] Electron rich and electron poor phenols, 4-methoxyphenol (**180**) and 4-cyanophenol (**181**) were successfully coupled in good yield. 4-Nitrophenol was successfully coupled and showed the ability to scale up the reaction (**182)**. A tyrosine and steroid scaffold were also successfully coupled displaying the utility of the reaction (**183**). However, the coupling of thiophenols was unsuccessful under these conditions.



180 42%[a]

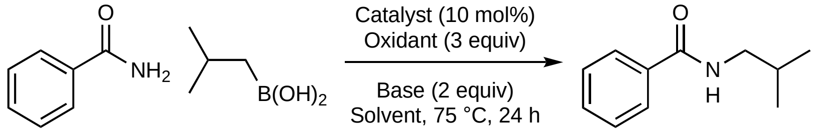
181 44%[a]

182 70%[a] 65%[b]

183 44%[a]

Scheme 54: Scope of reaction for the alkylation of phenols. a) Reaction conducted on a 0.125 mmol scale b) Reaction conducted on a 1.0 mmol scale.[155]

Watson and co-workers provided a general catalytic procedure for the cross-coupling of alkylboronic acids and 1° amides.[156] When stoichiometric copper loading was tested, the alkylated product **184** was formed in only 5% yield. External oxidants were tested, under a nitrogen atmosphere, to enable catalyst turnover. However, of the oxidants tested, only DTBP was successful in promoting alkylation. $NaOSiMe_3$ was used as a weak base to reduce amide deprotonation and subsequent ligation to copper. Ligands (e.g. BIPY) tested also hindered the reaction. Various copper sources were tested and CuBr was found to significantly improve conversion (Table 9, entry 3).

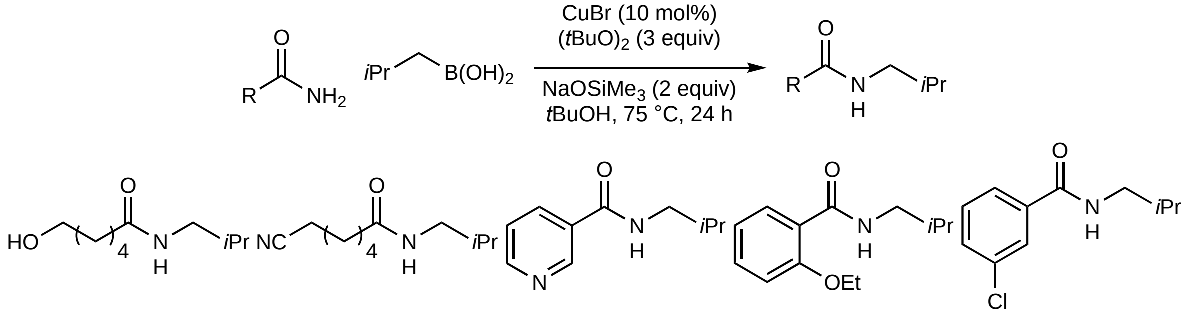


184

Entry	Catalyst	Base	Solvent	Oxidant	**184**
1	$Cu(OAc)_2$	Na_2CO_3	DCE	Air	Trace
2	$Cu(OAc)_2$	Na*t*OBu	DCE	DTBP	31%
3	CuBr	$NaOSiMe_3$	*t*BuOH	DTBP	92%

Table 9: Optimisation of conditions for the formation of **184**.[156]

The reaction conditions appeared tolerant to a range of functional groups on both the alkylboronic acid and amide (Scheme 55).[156] The reaction provided solely the mono-alkylated product, which was found to be inert to further alkylation. Both benzamides and alkylamides reacted successfully, with functional groups tolerated including alcohols **185**, nitrile **186,** pyridine **187**, silylether, and ortho-substituted benzamide **188**. However, substituted benzamides with stronger electron withdrawing groups than *p*-alkylamides failed to react. Aryl chloro- (**189**) and fluoro-benzamide reacted well but the corresponding aryl bromide reacted in low yield. Esters (both aromatic and alkyl) were unsuitable, presumably due to competitive hydrolysis.



185
52%[a]

186
44%

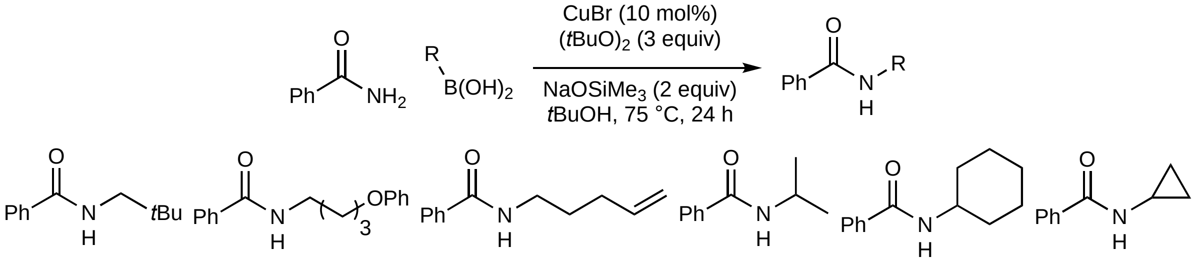
187
63%

188
85%

189
81%[b]

Scheme 55: Scope of reaction for the alkylation of amides. a) CuBr (20 mol%) $RB(OH)_2$ (2 equiv), b) Reaction conducted on a 3 g scale.[156]

1° and 2° alkyl boronic acids could be reacted (Scheme 56).[156] Functional groups tolerated include ethers **191** and alkenes **192**. However, 3° boronic acids (such as tert-butylboronic acid) were not suitable. In general, the reaction of 2° boronic acids (**193-195**) appeared sluggish with isopropylboronic acid requiring increased loading of both boronic acid and catalyst (**195**).



190
76%[a]

191
69%

192
60%[a]

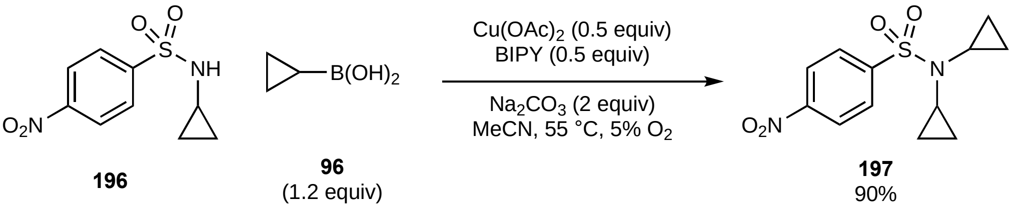
193
42%[a]

194
52%

195
40%

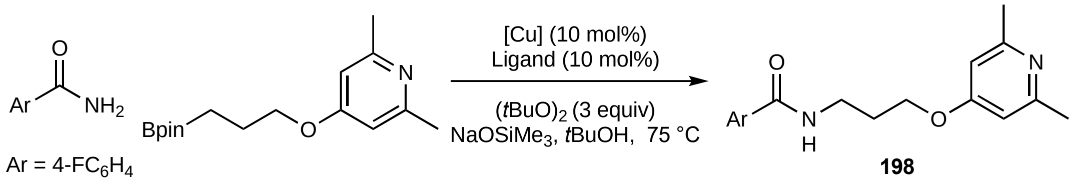
Scheme 56: Scope of reaction for the alkylation of benzylamide. a) CuBr (20 mol%), $RB(OH)_2$ (2 equiv).[156]

Aiming to use Chan-Evans-Lam coupling to produce synthetically useful dicyclopropylamine hydrochloride salt (**197**), Mudryk and co-workers developed conditions for the coupling of sulphonamide **196** with cyclopropyl boronic acid (Scheme 57).[157] Building on work by Zhu in 2008 on coupling sulphonamides, optimisation of reaction conditions allowed access to the desired product, *N,N*-dicyclopropylated sulphonamide (**197**), efficiently and in high yield. Later removal of the nosylate protecting group with a highly nucleophilic thiolate anion and formation of the HCl salt provided the end product. Notably, this reaction could be scaled up to between 60 and 80 kg.

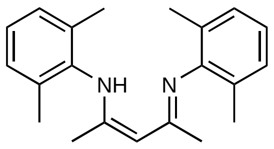


Scheme 57: *N*-Cyclopropylation of sulphonamide **196** on 60-80 kg scale.[157]

Progressing their previous conditions coupling alkyl boronic acids and amides, Watson and co-workers extended their conditions to the successful coupling of boronic esters.[158] They reported the use of two copper diketimine (NacNac) ligated catalysts for the coupling alkyl boronic esters and amides. Under their previous conditions, the coupling of boronic esters occurred in modest yield (Table 10, entry 1). Reduction in the amount of base excess increased the yield, contrary to the corresponding reaction with alkylboronic acids (Table 10, entry 2). Molecular sieves were employed to reduce water content, and in turn supress protodeboronation and copper inhibition. Copper sources were tested and Cu(acac)$_2$ appeared the most efficient in the absence of a ligand (Table 10, entry 4). Diamine NacNac ligands, analogues of acetylacetone (acac), were screened varying the steric and electronic properties around the aryl ring such as 2,6-dimethyl (**199**), *o*-methoxy (**202**) and *p*-methoxy (**1**). The NacNac ligands tested combined with Cu(OAc)$_2$ displayed similar performances. Electron rich NacNac ligand (**200**) was chosen as it gave consistently higher yields over a range of amides and 1° boronic ester substrates. Interestingly, the use of other diamine ligands (BIPY, 1,10-phenanthroline and 2,2',2''-tripyridine) led to much lower yields. Their new conditions allow the coupling of 1° and 2° functionalised alkylboronic esters to a range of amides giving the selectively monoalkylated products in good to excellent yields.



Entry	[Cu]	$NaOSiMe_3$ (equiv)	Ligand	Additive	**198**
1	CuBr	2.2	-	-	33%
2	CuBr	1.1	-	-	48%
3	$Cu(acac)_2$	1.1	-	-	61%
4	$Cu(acac)_2$	1.1	-	4 Å MS	75%
5	$Cu(OAc)_2$	1.1	**199**	4 Å MS	90%
6	$Cu(OAc)_2$	1.1	**1**	4 Å MS	95%
7	$Cu(OAc)_2$	1.1	**200**	4 Å MS	94%



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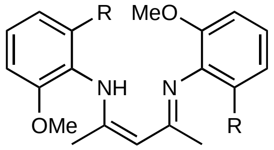
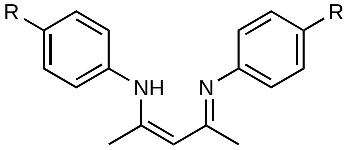


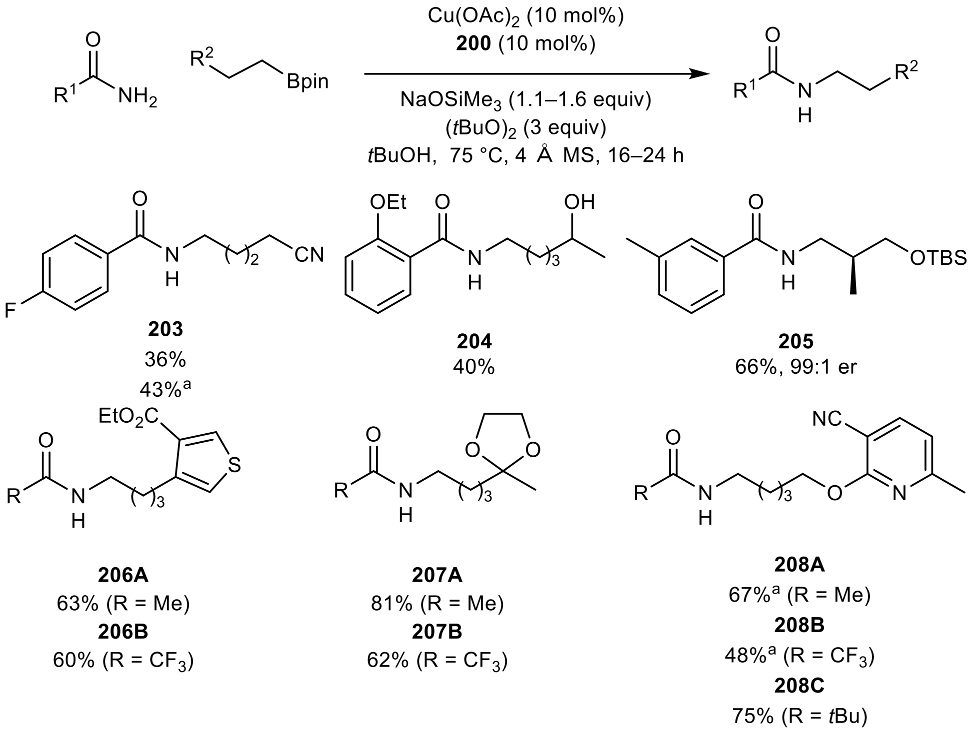
1 (R = H)
200 (R = Me)



201 (R = H)
202 (R = OMe)

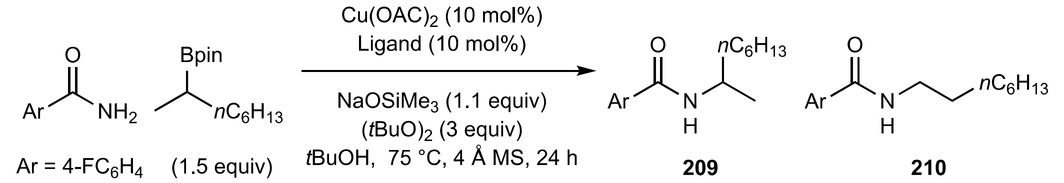
Table 10: Optimisation for the formation of amide **198**.[158]

1° boronic esters possessing a range of functional groups including heterocycles, 2° amines, halides, alkenes and carbamates, were successfully coupled to alkyl, heteroalkyl, aryl and heteroaryl amides.[158] Notably, esters are tolerated, whereas they have not been tolerated under previous alkyl boronic ester coupling conditions. The conditions are also tolerant of free alcohols, although with reduced yields (**204**). Nitrile functionalised boronic ester **203** experienced a relative drop in yield with when NacNac ligand **200** was used. Changing to ligand **1** increased the yield. Boronic ester with a β-stereogenic centre (**205**) was coupled retaining 99:1 er suggesting that β-hydride elimination and re-insertion does not occur. Notably, the reaction was extended to the use of acetamides **206A**-**208A**, which have previously not been effective coupling partners. It is proposed the increased catalytic efficiency of this system allows for their alkylation.

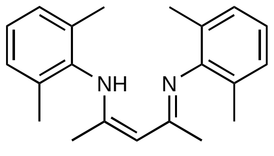


Scheme 58: Scope of reaction for the alkylation of amides. a) Reaction conducted with ligand **1**.[158]

2° boronic esters provided little product when subjected to the reaction conditions with ligand **200**.[158] The product recovered consisted of a 3:1 mixture of the corresponding coupling product **209** and rearranged linear product **210**. To further understand this trend, a series of sterically and electronically varied NacNac ligands were tested. Similar results were observed when using $Cu(OAc)_2$ without a ligand (Table 11, entry 2) and with dimethylaniline-derived ligand (**199**). Reduction of the steric hindrance around copper, using **201**, provided the product with high regioselectivity. This indicated that the formation of rearrangement product was sensitive to the steric bulk of the ligand, with the amount of rearrangement product observed lower for less bulky ligands. Ligand (**202**) bearing a para-substituted methoxy group gave the product in comparable yield to aniline-derived ligand (**201**). This suggests electronic factors of the ligand have little effect on the yield, and success with ligand **1** is presumably due to the chelating ability of the ether substituent. Subsequently, ligand **1** formed the corresponding product with excellent yield and regioselectivity. The scope of 2° boronic esters was then evaluated. Pleasingly, the reaction conditions are tolerant of a range of heterocycles, alkenes, acetals, ethers and carbamates, and alkyl and aryl amides.



Entry	Ligand	Yield of **209** + **210**	**209**:**210**
1	**200**	8%	74:26
2	-	10%	80:20
3	**199**	3%	74:26
4	**1**	82%	97:3
5	**201**	36%	95:5
6	**202**	36%	> 95:5



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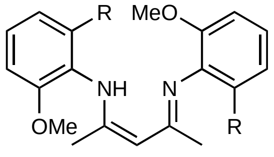
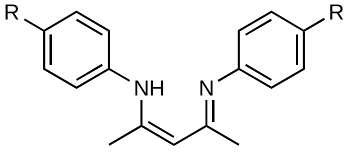


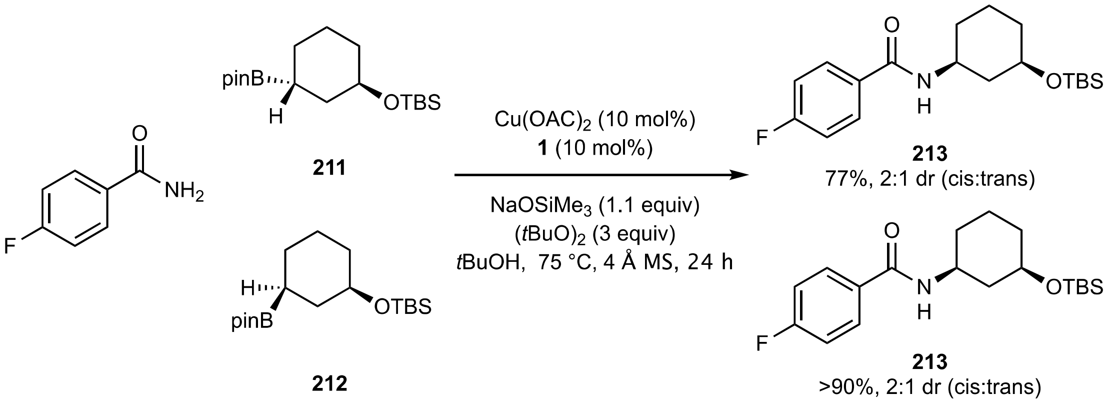
1 (R = H)
200 (R = Me)



201 (R = H)
202 (R = OMe)

Table 11: Effect of ligand structure on the formation of linear and branched products **209** and **210**. Yields and regiospecificity determined using ^{1}H-NMR analysis.[158]

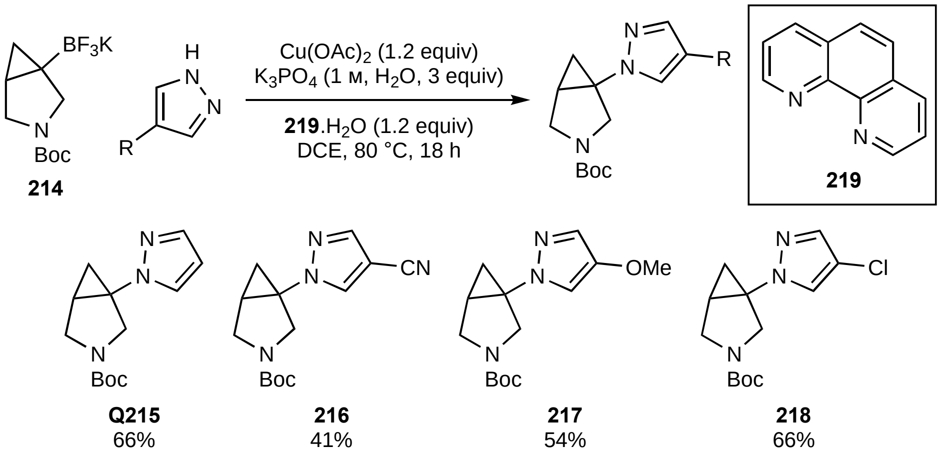
The stereochemical outcome of the reaction was probed using boronic esters **211** and **212**.[158] It was found that both boronic esters gave amide **213A** and **213B** in an identical 2:1 diastereomeric ratios (dr), as determined by ^{19}F-NMR. No mechanistic explanation was given for the loss of stereochemical information other than exclusive invertive or retentive transmetallation does not occur. A radical pathway was not ruled out. However, since this paper was reported, Knochel and co-workers have reported that alkyl Cu(I) species only show configurational stability below −50 °C.[159,160]



Scheme 59: The reaction of 4-fluorobenzamide with diastereomeric boronic esters **211** and **212**.[158]

Most recently, Harris and co-workers published the first example of the Chan-Evans-Lam coupling of 3° potassium trifluoroborates (**214**) with pyrazoles.[161] The 1-aryl-3-

azabicyclo[3.1.0]hexane core was of interest within medicinal chemistry, and the formation of a carbon nitrogen bond at the ring juncture has not been previously reported. Pyrazoles, with both electron donating and withdrawing substituents, were coupled in good yield.



Scheme 60: Scope of reaction for the amination of 3° potassium trifluoroborate salts.[161]

2.2 *Aims*

Currently, examples of alkyl Chan-Evans-Lam reactions are largely limited to the amination of cyclopropylboronic acids. The inherent activated nature of cyclopropylboron reagents made them an attractive coupling partner. Recent advances in this area include the coupling of 1° alkylboronic esters with 2° amines and, 1° and 2° alkylboronic esters with amides. Although catalytic, both methods require stoichiometric quantities of di-tert-butylperoxide as a terminal oxidant. Limitations of current conditions include a narrow substrate scope with respect to both the alkylboron reagents and nitrogen-based coupling partner, and the absence of a stereoselective methods.

The initial focus of this project was on the development of mild and functional group tolerant conditions for the amination of 2° alkylboronic esters. Overcoming the barrier of transmetallation of “non-activated” alkylboronic esters is a common issue with Chan-Evans-Lam coupling reactions. To aid transmetallation, we proposed the use of a 2° benzylic boronic ester. Charge stabilisation of the organocuprate intermediate from the aryl ring is rational for the assisted transmetallation.

The second aim of the project is to investigate the possibility of a stereoselective amination from enantioenriched alkylboronic esters. Several possible pathways have been hypothesized for the preservation of stereochemical information such as, the retention or inversion of stereochemistry from transmetallation. This relies on a configurationally stable organocuprate intermediate. However, few reports document the stereoselectivity of B to Cu transmetallation. If stereochemical information is lost, there are several possible explanations. Either the alkyl copper intermediate is configurationally unstable. Alternatively, transmetallation could occur through a 2-electron pathway, but with a mixture of inversion or retention of stereochemistry. Finally, transmetallation via heterolytic cleavage of a C-B bond would provide a radical intermediate which could epimerise before subsequent reaction. As part of the investigation, we aim to gather information which supports the mechanism of transmetallation. The use of a chiral ligated copper species would potentially impart stereochemical information on racemic alkylboronic esters.

Finally, we hope to expand our conditions to the coupling of 3° boronic esters. To our knowledge, there is only one previous report of 3° boron compounds undergoing Chan-Evans-Lam coupling. Formation of 3° amines poses great applicability, as methods such as reductive amination are unable to form them.

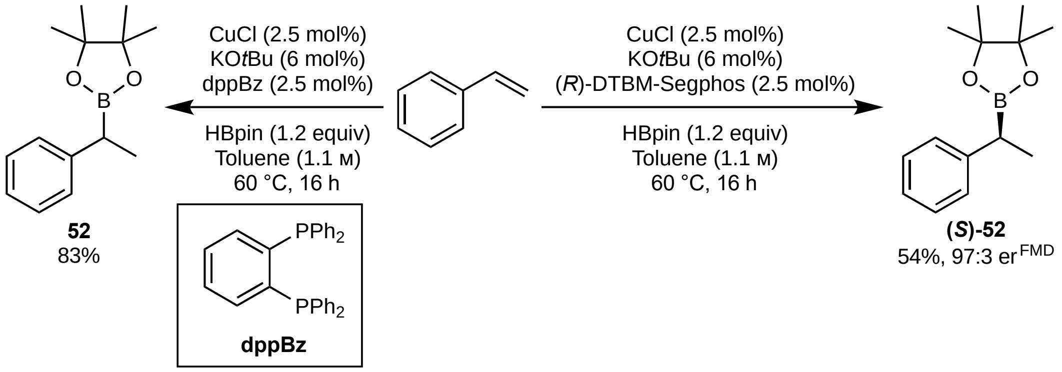
2.3 *Results and Discussion: Amination of Alkylboronic Esters*

2.3.1 Boronic ester synthesis

This section of work was done in collaboration with Francesca Dennis. Organoboron compounds produced by Francesca are denoted by 'FMD'.

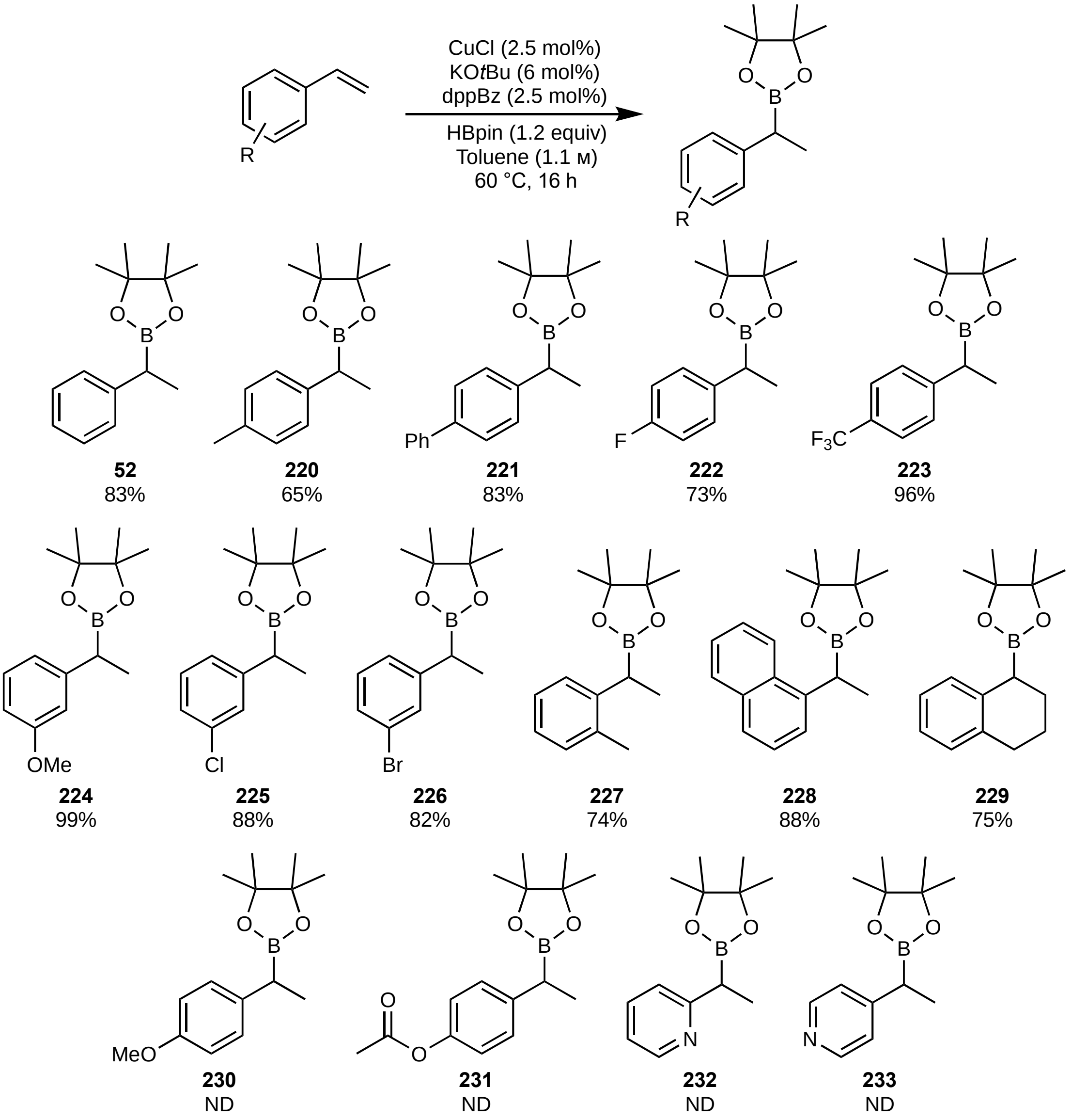
To investigate the functional group compatibility of conditions developed within this report a range of boronic esters were required. Using documented procedures discussed within section 1.1, the synthesis of targeted alkylboronic esters was developed. Alkylboronic esters were produced through a range of methods, including borylation of organohalides, hydroboration, 1,2-metalate rearrangement processes and 1,4-borylation. A combination of several methods was sometimes required to produce the desired product. Methods developed within this report are screened against this range of electronically and sterically varied alkyl boronic esters.

Throughout the development of our amination reaction, 2° benzylic boronic ester **52** was used as the standard optimisation substrate. This was prepared through the copper-catalysed hydroboration of styrene using HBpin, reported by Yun and co-workers.[162] Racemic boronic ester **52** was produced using a catalyst generated from CuCl and bisphosphine dppBz (Scheme 61). This was found to be a reliable and robust method to form boronic ester **52**. The loading of copper, ligand and base could be reduced from the literature protocol without decrease in yield. The procedure could be scaled up to the hydroboration of 10 g of styrene. Using (*R*)-DTBM-segphos as a chiral ligand, hydroboration could be performed to give boronic ester **(S)-52** in high er.



Scheme 61: Copper-catalysed hydroboration of styrene.

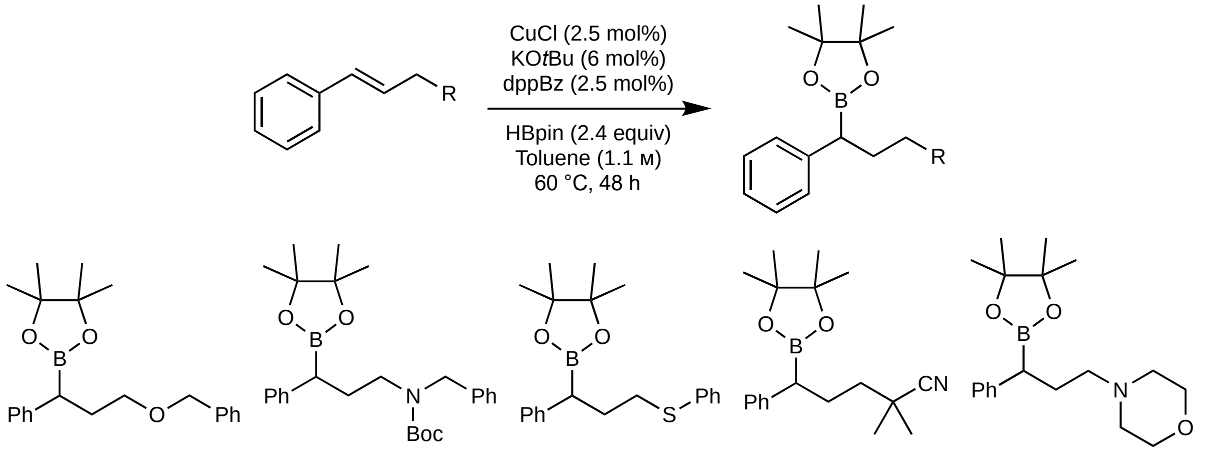
Due to a wide array of styrenes being commercially available, a collection of benzylic boronic esters could be produced relatively quickly using this hydroboration method (Scheme 62). This included styrenes with electron withdrawing and mildly electron donating arene substituents. Substitution at the ortho position is also tolerated. Cyclic alkene, 1,2-dihydronapthylene, was successfully hydroborated under the standard conditions to give boronic ester **229**. Compatible functional groups include aryl halides, trifluoromethyl and *m*-methyl ether groups.



Scheme 62: Scope of reaction for the hydroboration of styrenes.

However, electron rich 4-methoxystyrene failed to provide the hydroborated product (**230**) in reasonable yield (Scheme 62). This could be because under the standard conditions, protodecupration or protodeboronation is favoured. 4-Acetoxystyrene was also subjected to the conditions producing a complex mixture of 4-phenolstyrene and 4-ethylphenol. Heteroaromatic substrates failed to provide any of the desired products **232** and **233**. This is not uncommon for unsubstituted pyridine-based benzylic boronic esters due to their high propensity for protodeboronation.[86]

To expand the scope, we explored the hydroboration of 1,2-disubstituted arylalkenes (Scheme 63). Cinnamyl alcohol and chloride were utilised as simple building blocks to form 1,2-disubstituted arylalkenes for borylation. Transformations of these substrates formed the desired styrene starting materials. However, subjecting these alkenes to the hydroboration generally led to a sluggish reaction. To access enough material, longer reaction times or increased loading of catalyst, ligand and pinacol borane were required. The borylation was successful in the presence of an ether (**234**), Boc-protected amine (**235**) and thioether (**236**). A nitrile-substituted alkene provided a very low yield of boronic ester product **237** and the reaction was irreproducible. Additionally, a morpholine substituted substrate was not tolerated, resulting in a complex mixture of products (**238**). Presumably the presence of a basic amine hinders the borylation.



234[a,b] 26%

235 57%

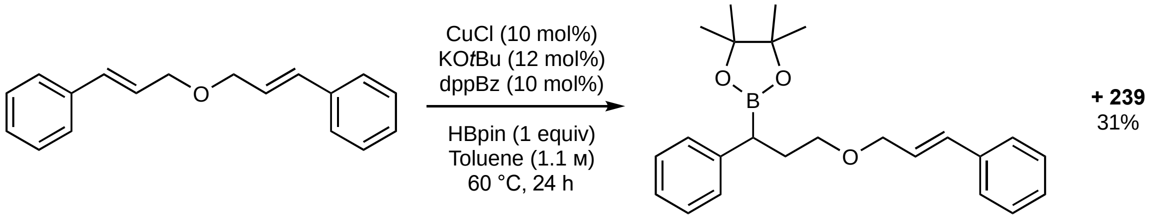
236[c] 13%

237[d] >5%

238 ND

Scheme 63: Hydroboration of 1,2-disubstituted alkenes. a) Reaction time of 16 h, b) HBpin (1.2 equiv), c) Reaction time of 26 h, d) CuCl (5 mol%) dppBz (5 mol%).

To access a mono-borylated alkene containing boronic ester (**240**), diene **239** was subjected to the copper-catalysed hydroboration conditions with increased copper and ligand loading but with a single equivalent of HBpin (Scheme 64). This was in the hope of minimising the formation of the dihydroborated product, but also allowing a reasonable reaction time. The dihydroborated product was not observed. However, the low yield isolated of boronic ester **240** and return of starting material **239** suggests that a statistical mixture of mono- and diboration products were formed.

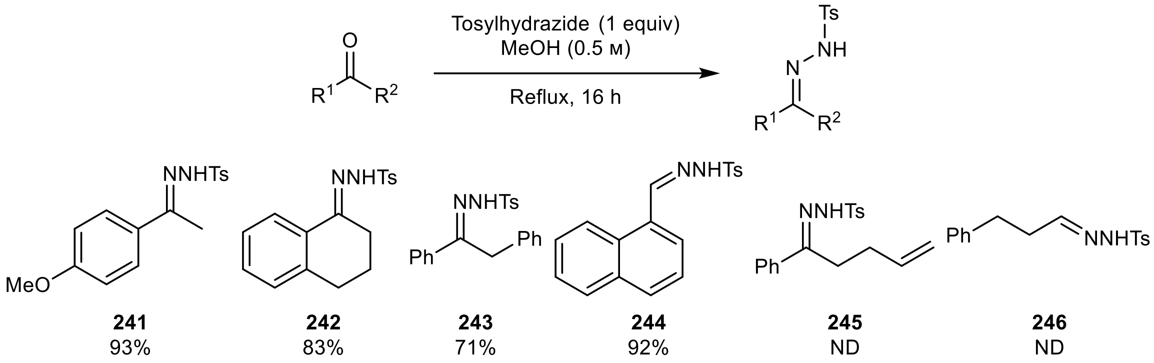


239

240 22%

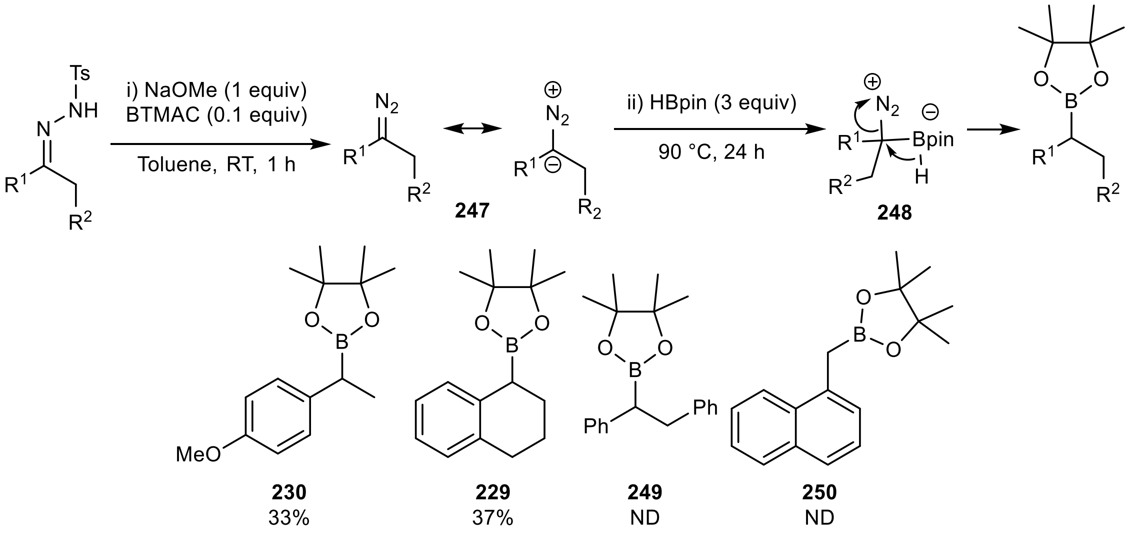
Scheme 64: Copper-catalysed hydroboration of dialkene **239**.

To access 1° and 2° boronic esters that are not possible by hydroboration, the metal-free borylation of tosylhydrazones was explored (Scheme 65).[163] Tosylhydrazones were formed successfully from 1° and 2° benzylic carbonyls (**241**, **242**, **243**, **244**). However, hydrazone formation of an alkene-containing ketone and an aliphatic aldehyde resulted in a complex mixture of products (**245** and **246**).



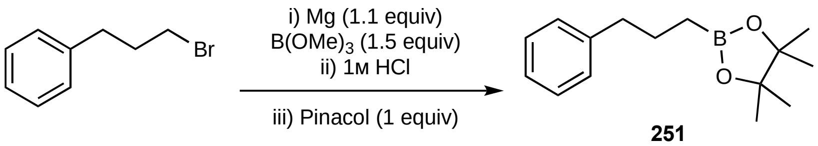
Scheme 65: Tosylhydrazone formation from 1° and 2° carbonyls.

The NaOMe deprotonation of benzylic tosylhydrazones forms a nucleophilic diazo compound that is identified by a characteristic red colour (Scheme 66, **247**). The nucleophilic species attacks pinacolborane, and subsequent 1,2-metalate rearrangement eliminates N_2 to give the boronic ester (**248**). Pleasingly, *p*-methoxy tosylhydrazone **241** was successfully borylated to give **230** albeit in a low yield. Tetralone-derived hydrazone **242** was borylated (**229**), but in lower yield than copper catalysed hydroboration (Scheme 61). Additionally, the reaction of 1° and 2° tosylhydrazones, **249** and **250**, resulted in a complex mixture of products.



Scheme 66: Mechanism and scope of borylation of tosylhydrazones.

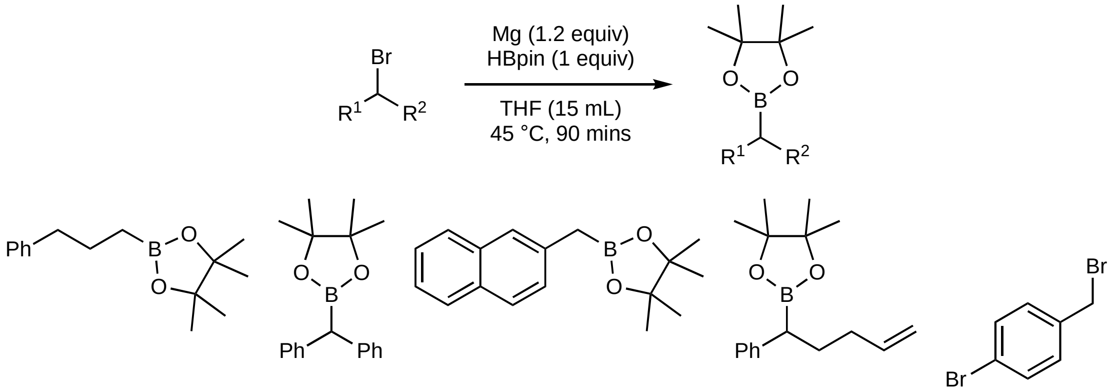
To expand the scope, the borylation of 1° and 2° alkyl halides was explored. Grignard formation, followed by addition of trimethylborate, hydrolysis to give the boronic acid, and esterification with pinacol gave boronic ester **251** in good yield (Scheme 67).



251
65%

Scheme 67: Boronic ester formation using trimethylborate.

Complementary to this, reaction of the Grignard with pinacolborane under Barbier conditions (Scheme 68) provided the boronic ester in a single step and higher yield (**251**).[164,165] Using this method, several 1° and 2° alkylhalides were successfully borylated. The method was compatible with an alkene (**254**). However, subjecting dibromide **255** gave a complex mixture of products, presumably due to competitive Grignard formation of both halide groups.



251
82%

252
79%

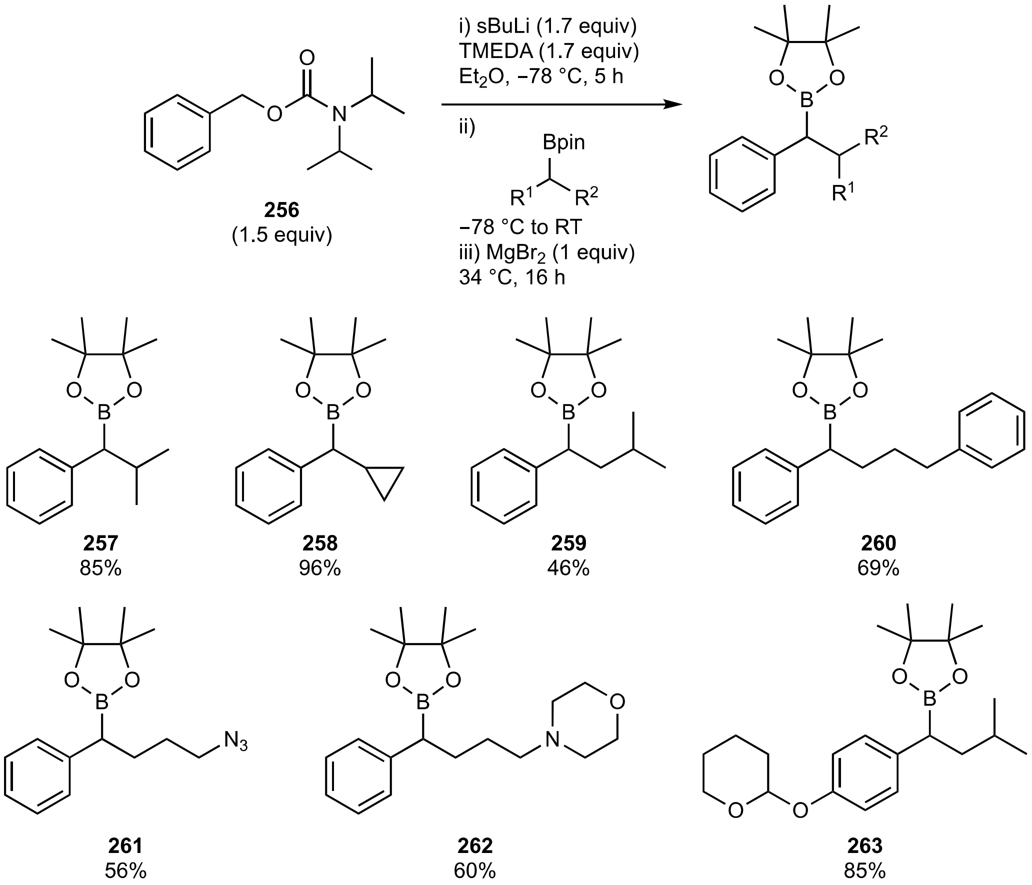
253
44%

254
47%

255
ND

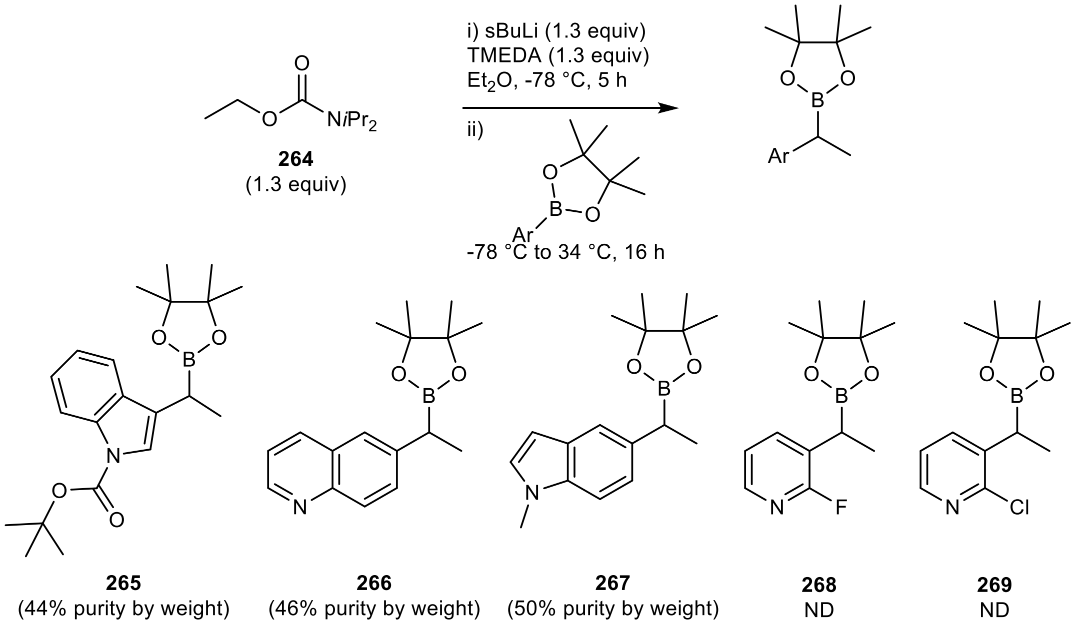
Scheme 68: Boronic ester formation using pinacolborane.

In order to produce more complex boronic esters, we explored the use of homologation chemistry to access compounds not possible by other methods (Scheme 69). An array of boronic esters could be produced though lithiation-borylation,[8] by changing the boronic ester or carbamate starting materials. The homologation of 1° and 2° alkyl boronic esters with 1° benzylic lithiated carbamate **256** gave 2° benzylic boronic esters **257-263**. Compatible functional groups include THP ether (**263**), cyclopropyl (**258**), azide (**261**) and morpholine (**262**). Sterically hindered isopropyl boronic ester **257** was also successfully formed in good yield.



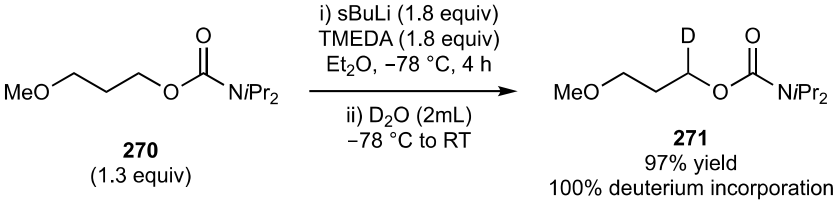
Scheme 69: Homologation of 1° and 2° alkyl boronic esters with carbamate **256**.

Heterocycles are often found in biologically active compounds, such as natural products and medicinal drugs. The tolerance of these motifs in any new methods developed will help broaden their applicability. To access heterocycle containing boronic esters, the corresponding heteroaromatic boronic esters were homologated with lithiated carbamates.[166] However, unsubstituted and unprotected heteroaryl boronic esters, such as pyridine or pyrrole, are prone to protodeboronation.[167] The boronic esters used were chosen due to their relative stability towards protodeboronation, commercial availability, and successful reports of homologation within the literature.[166] Pleasingly, when using ethyl carbamate **264**, homologation was successful (Scheme 70). However, upon purification by column chromatography, the boronic ester products co-eluted with unreacted arylboronic ester starting material. Using an internal standard, the purity of boronic esters **265, 266** and **267** were determined by ^{1}H NMR analysis. In our hands, pyridyl boronic esters **268** and **269** could be homologated, but underwent protodeboronation during isolation.[167]



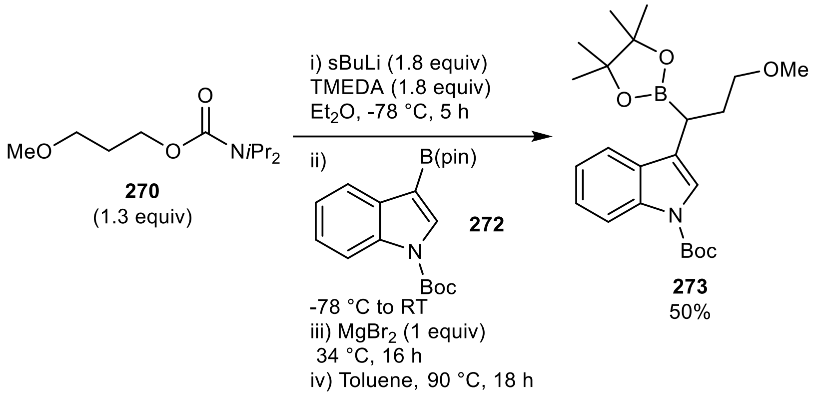
Scheme 70: Homologation of heteroaryl boronic esters with carbamate **264**.

To aid purification, an alternative carbamate **270** was reacted with boronic ester **272**, containing an ether group to add polarity. Under the standard conditions, small amounts of homologated boronic ester **273**, with starting material boronic ester **272** and carbamate **270** were returned. The deprotonation of the carbamate was investigated, quenching with D_2O. It was found that 100% deuterium incorporation was achieved when lithiation was carried out for 4 h at −78 °C using 1.5 equivalents of *s*BuLi (Scheme 71).



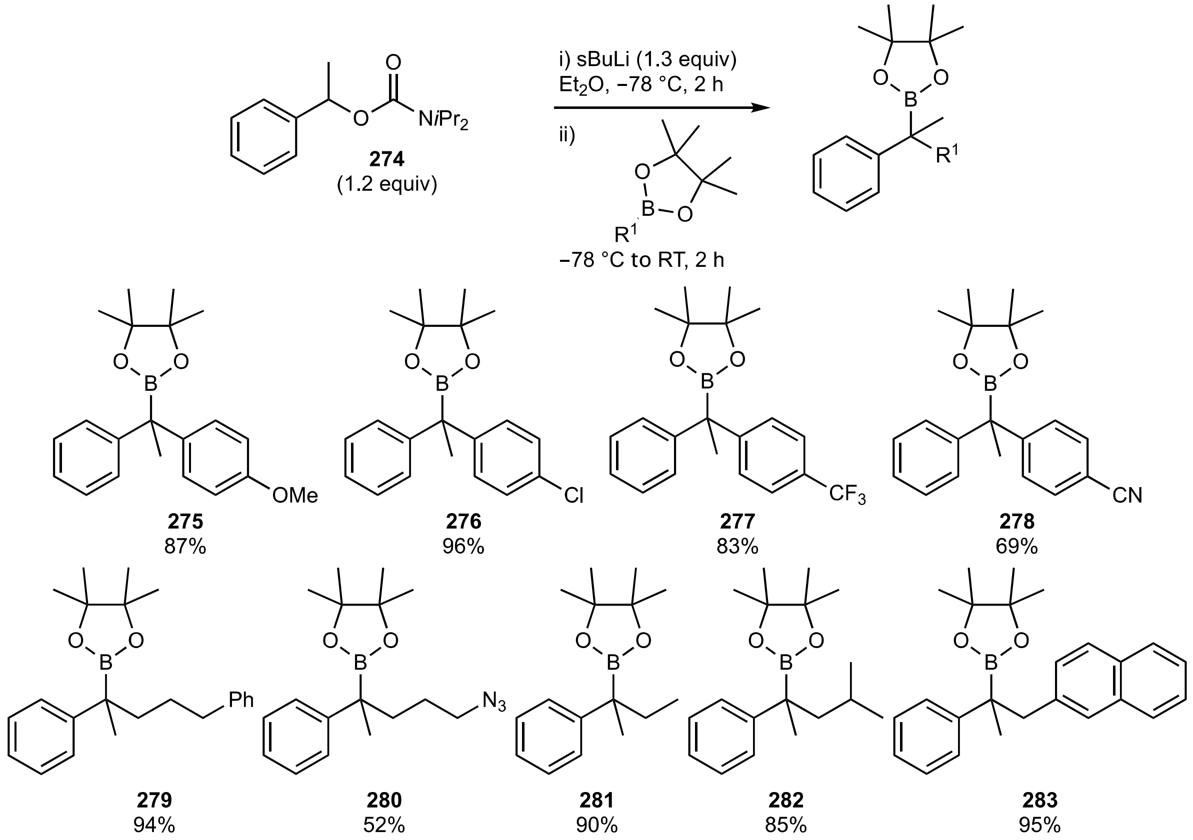
Scheme 71: Lithiation-deuteration of carbamate **270**.

The lithiation-borylation reaction was repeated, using an increased excess of *s*BuLi (Scheme 72). ^{11}B-NMR analysis of the crude reaction mixture after 16 h at 34 °C showed the presence of the boron ‘ate’ species, suggesting 1,2-metallate rearrangement had not occurred. The mixture was stirred at to 90 °C to promote 1,2-metalate rearrangement, and boronic ester **273** was successfully isolated.



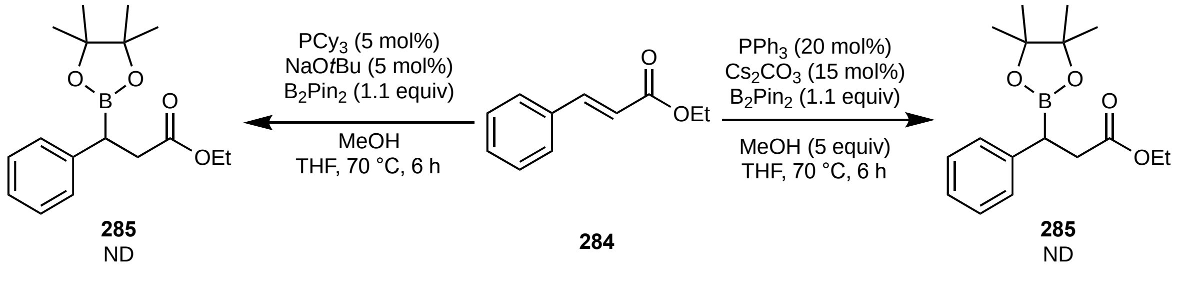
Scheme 72: Homologation of carbamate **270** with boronic ester **272**.

To the best of our knowledge, 3° boronic esters have not been used in the Chan-Evans-Lam amination reaction. In order to test their suitability as substrates, formation of 3° boronic esters was carried out using lithiation-borylation reactions (Scheme 73).[168] Homologation of 2° carbamate **274** with aryl and alkyl boronic esters was performed. Aryl boronic esters, with electron withdrawing and electron donating arene substituents, reacted to form 3° di-benzylic boronic esters in excellent yields. Also, 1° alkyl boronic esters could be used successfully to form 3° mono-benzylic boronic esters in good yield. 3° boronic esters, containing functional groups including methyl ether (**275**), halide (**276**), trifluoromethyl (**277**), nitrile (**278**) and azide (**280**), were successfully prepared.



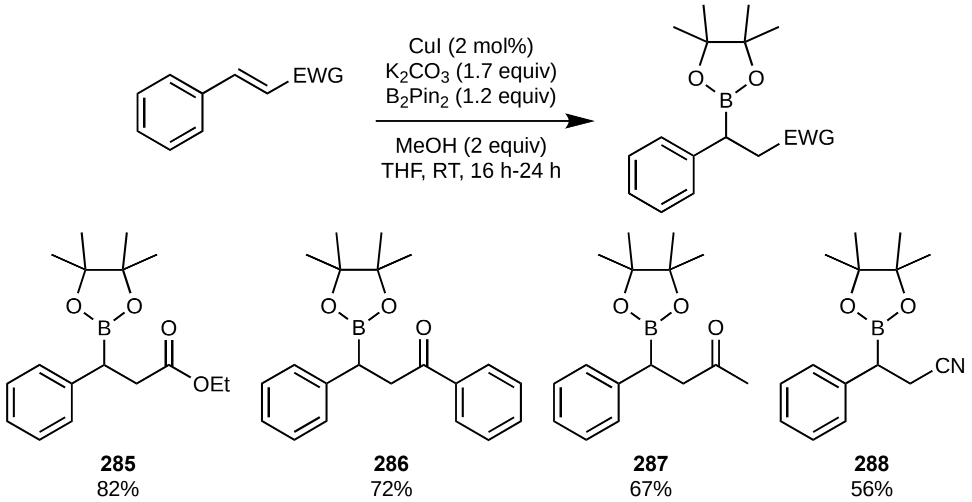
Scheme 73: Homologation of aryl and alkyl boronic esters with carbamate **274**.

To access boronic ester substrates containing functional groups susceptible to nucleophilic attack, we explored conjugated borylation methods. Metal and non-metal-mediated conditions for 1,4-borylation were tested on substrate **284**. The use of triphenylphosphine[169] and tricyclohexylphosphine[170] as organocatalysts did not lead to the formation of the conjugate borylation product **285** in isolatable quantities (Scheme 74). Instead, we found that a complex mixture of products was produced.



Scheme 74: Attempted phosphine-catalysed 1,4-borylation of ethyl cinnamate **284**.

Pleasingly, copper-catalysed conditions allowed for the formation of the desired product in excellent yield.[171] The method was applied to enone and alkenylnitrile substrates to give the corresponding boronic esters in good to excellent yield (Scheme 75).



285 82%

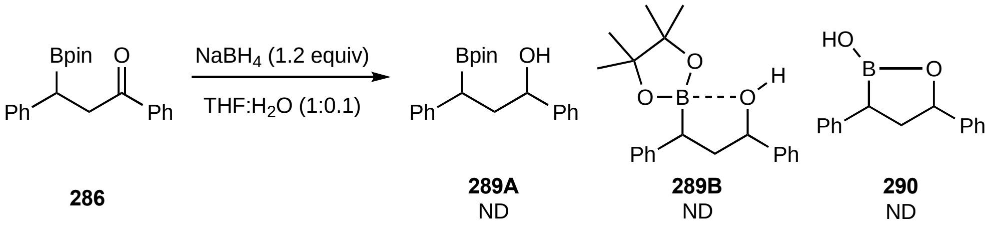
286 72%

287 67%

288 56%

Scheme 75: Scope of copper-catalysed 1,4-borylation.

To generate an alcohol-containing boronic ester, ketone **286** was reduced to the corresponding alcohol. Purification of boronic ester **289A** by silica chromatography was complicated, with degradation of boronic ester **289A** observed. Presumably, coordination of the alcohol into the empty *p*-orbital of the boronic ester helps to promote protodeboronation (**289B**).[167] This interaction could potentially lead to oxaborole formation (**290**).



286

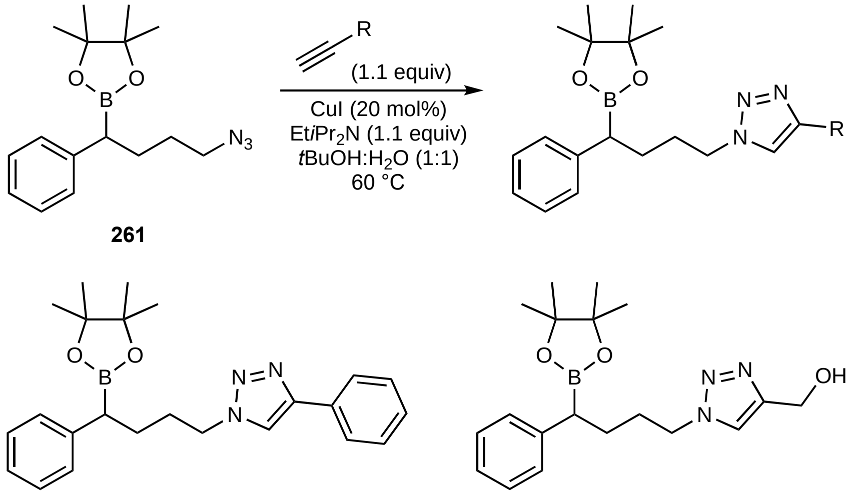
289A ND

289B ND

290 ND

Scheme 76: Reduction of **286**, and β-boron interaction with the resultant alcohol.

To expand the range of boronic ester substrates, click coupling of azide **261** with alkynes was carried out (Scheme 77). Triazoles with pendant phenyl **291** and alcohol **292** functional groups were produced in excellent and good yields respectively.



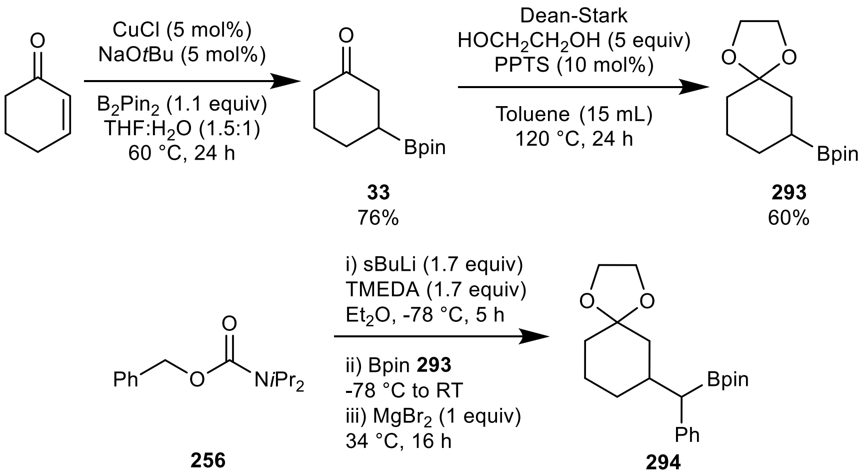
261

291
71%

292
49%

Scheme 77: Triazole formation using azide **261**.

The multistep manipulation of a boronic ester scaffold **33** was explored to access multiple boronic ester substrates (Scheme 78). 2-Cyclohexene-1-one underwent successful copper-catalysed 1,4-borylation in excellent yield. The ketone functionality of **33** is susceptible to nucleophilic attack, preventing homologation reactions to be performed directly on this molecule. Successful acetal protection of the ketone provided compound **293**. This compound underwent lithiation borylation with carbamate **256** successfully, to give boronic ester **294**, in excellent yield.



33
76%

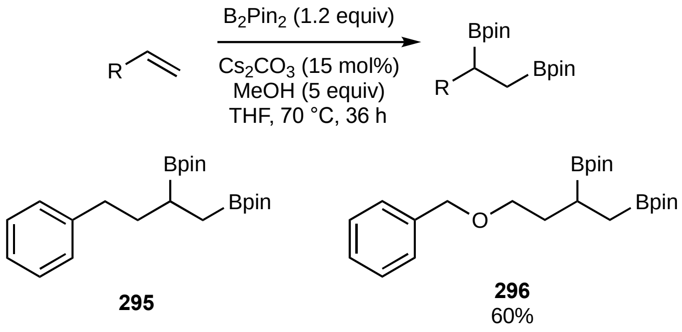
293
60%

256
(1.5 equiv)

294
87%
1:1 dr

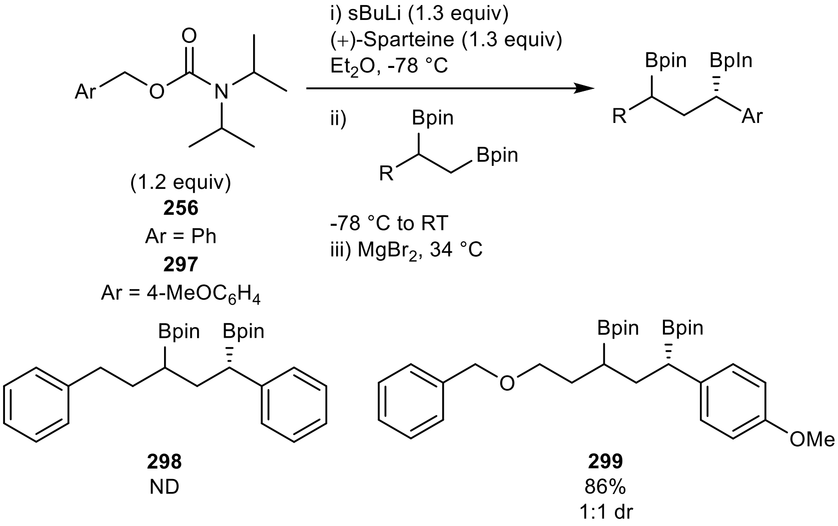
Scheme 78: Synthesis of boronic ester **294** through 1,4-borylation, protection and homologation.

To produce a compound suitable for testing the chemoselectivity of our developed reactions, 1,3-diboron structures were prepared (Scheme 79). Initially, 1,2-diboron substrates **295** and **296** were produced by alkene diboration (section 1.1.2).



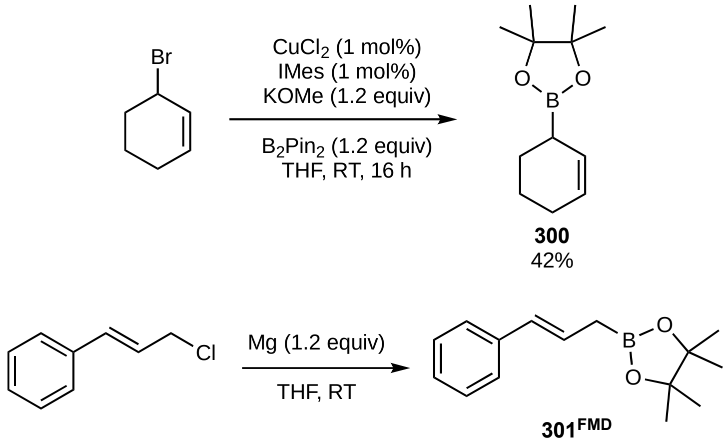
Scheme 79: Diboration of alkenes.

Selective homologation of the 1° boronic ester with benzylic carbamates was achieved with (+)-sparteine as the diamine ligand, instead of TMEDA (Scheme 80). It was suggested the increased steric hindrance of (+)-sparteine-ligated organolithium, compared with corresponding TMEDA complex, prevents attack of the 2° boronic ester.[172] 1,2-Diboronic ester **295** and benzylcarbamate **256** successfully formed 1,3-diboron **298**. However, adequate purification was not possible, as the product **298** coeluted with unreacted 1,2-diboronic ester **295**. To overcome this, more polar 1,2-diboronic ester **296** and carbamate **297** were homologated to give 1,3-diboronic ester **299**, which was isolated in good yield.



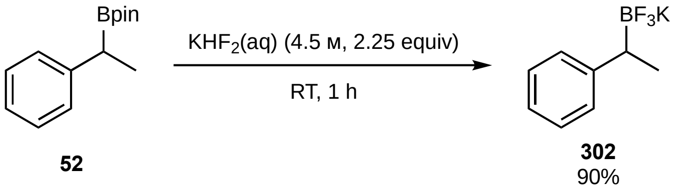
Scheme 80: Homologation of diboronic ester **295** and **296** with carbamates **256** and **297**.

To explore boronic esters that have analogous reactivity to that of benzylic boronic esters, symmetrical and unsymmetrical allyl boronic esters **300** and **301** were prepared (Scheme 81). Using Cu-catalysed borylation, allyl boronic ester **300** was successfully formed in reasonable yield.[173] Unsymmetrical boronic ester **301** was produced from cinnamyl chloride in poor yield.[164]



Scheme 81: Formation of allyl boronic esters.

Finally, in order to explore the reactivity of other organoboron reagents, boronic ester **302** was converted into the corresponding trifluoroborate salt (Scheme 82).[174]

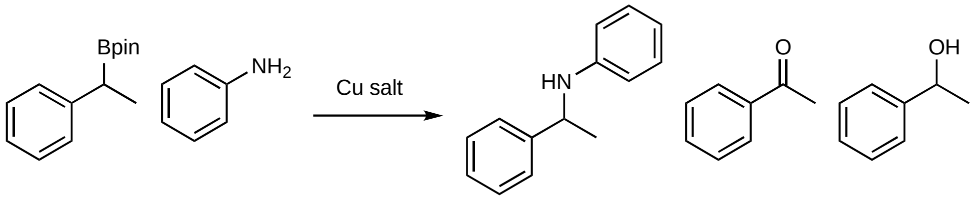


Scheme 82: Trifluoroborate salt formation from boronic ester **52**.

2.3.2 Method Development for the Amination of Boronic Ester 52

2.3.2.1 Initial Investigation of Conditions

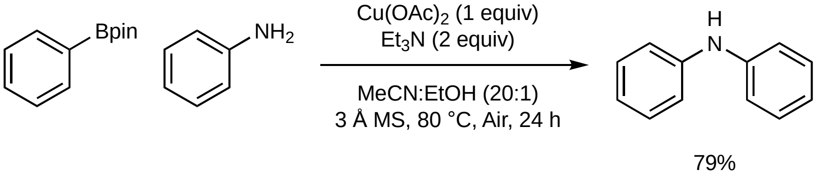
Initial investigations were focussed on the reaction of 2° benzylic boronic ester **52** and aniline in the presence of Cu salts (Scheme 83). 2° benzylic boronic esters were chosen as we presumed transmetalation would be promoted due to charge stabilisation from the phenyl group of the resulting benzyl copper species. Also, this class of boronic ester had not been used previously in reports of Chan-Evans-Lam aminations. Optimisation reactions were performed on a 0.05 mmol scale, with yields determined through ^{1}H-NMR analysis of the crude material using 1,3,5-trimethoxybezene internal standard. The observed formation of amine **303** (and other by-products) was confirmed by the formation of an authentic sample, and subsequent doping of NMR samples. It has been assumed that throughout optimisation any incomplete mass balance is due to protodeboronation, to give ethyl benzene. This is presumably lost during work up due to its low boiling point.



52 **303** **304** **305**

Scheme 83: General scheme for the amination of boronic ester **52.**

The first conditions tested were directly taken from Watson's paper coupling anilines and arylboronic esters (Scheme 84).[137] The conditions used stoichiometric $Cu(OAc)_2$ to overcome pinacol, formed as a by-product, poisoning the catalyst. A mixture of a polar aprotic solvent and alcohol aid in the solvation of the copper salt. Alcohols are potential *O*-coupling partners, giving ether side products, though C-N coupling is presumably more favourable. The benefits of alcohol additives typically outweigh the ether product formation. Molecular sieves are employed to remove water, which has been shown to promote protodeboronation and the formation of alcohol by-products.[137] The formation of the alcohol **305** could occur through copper-mediated coupling of water, similar to the report of Hu and co-workers for the copper-catalysed hydroxylation of arylboronic acids (Scheme 83).[175] Alternatively, alcohol **305** could be formed through oxidation if hydrogen peroxide is generated during the reaction.

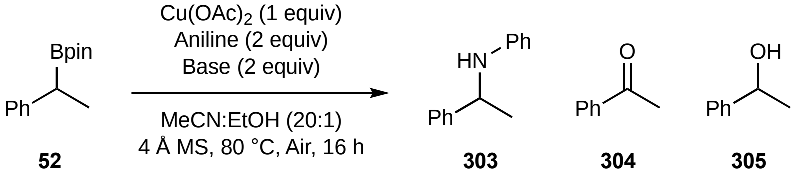


Scheme 84: Coupling of aryl boronic esters with aniline by Watson and co-workers.[137]

Typically, Chan-Evans-Lam reactions use an organic base such as Et_3N or pyridine. These presumably ligate and de-nucleate the copper species, as well as neutralise acid generated in the reaction. Also, in Ullmann coupling reactions, inorganic carbonate bases, such as Cs_2CO_3, have been shown to be beneficial for catalyst activation, stabilisation of organocuprate intermediates by counter-cation interactions and, deprotonation.[176]

Due to formation of multiple by-products, Chan-Evans-Lam reactions often employ an excess of organoboron reagent to give reasonable yields. However, unlike arylboronic acids, alkylboron reagents are often the most valuable coupling partner. For our methodology, we are therefore aiming to develop conditions which minimise by-product formation and allow the boron reagent to be the limiting reagent.

The first set of conditions tested looked at the reaction of boronic ester **52**, aniline and $Cu(OAc)_2$ in the presence of organic and inorganic bases (Table 12, entry 1 and 2). Pleasingly, conditions using triethylamine or Cs_2CO_3 gave the desire product, amine **303**, albeit in fairly low yields. Two side products were identified, ketone **304** and alcohol **305**. Due to the low mass balance, we presume both reactions gave a considerable quantity of protodeboronated product. However, the reaction using Cs_2CO_3 gave a far better mass balance, and gave a larger quantity of amine product. Pyridine as a base, significantly increased the formation of ketone **304** and appeared to disfavour the formation of the amine **303** (Table 12, entry 3). Pyridine could have an adverse effect on amine formation or increase the rate of ketone formation. Additionally, in the presence of pyridine the ratio of alcohol **305** to ketone **304** is reduced in comparison to the reaction of Cs_2CO_3.

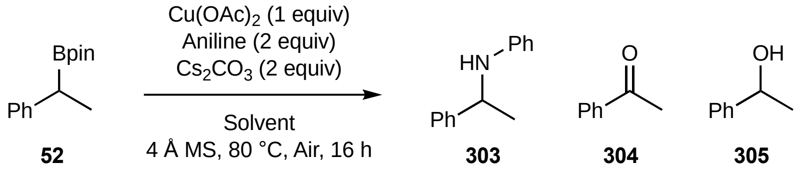


Entry	Base	Yield			
		52	**303**	**304**	**305**
1	Et_3N	0%	9%	21%	<5%
2	Cs_2CO_3	0%	19%	31%	25%
3	Pyr	0%	0%	54%	12%
4	*t*BuOK	0%	0%	9%	55%
5	Na_2CO_3	30%	8%	24%	8%
6	KOH	0%	0%	27%	78%
7	KF	0%	6%	43%	18%
8	CsF	0%	13%	47%	23%
9	$NaHCO_3$	0%	0%	36%	18%
10	$NaOSiMe_3$	0%	0%	19%	15%
11	No Base	0%	0%	56%	26%

Table 12: Effect of organic and inorganic bases on the amination of boronic ester **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.05 M.

A range of inorganic bases were screened (Table 12, entry 4-10), and results suggested the presence of a caesium counter-cation was advantageous. The use of Cs_2CO_3 and CsF led to the formation the amine **303** in the highest yields. Instead, reactions using of stronger bases such as *t*BuOK and KOH gave alcohol **305** in increased yields. This is similar to the trend observed by Hu and co-workers in their report.[175] The absence of base in the reaction led to a comparable yield of ketone **304** to when pyridine is present, but with increased alcohol **305** formation. Additionally, an absence of base appears to shut down the amine formation.

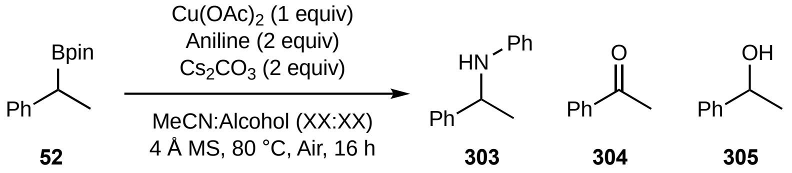
A higher water content led to a reduction in the formation of amine **303** and ketone **304** suggesting the exclusion of water is beneficial (Table 13, entry 2 and 3). In the absence of molecular sieves (Table 13, entry 2) and the inclusion of water (Table 13, entry 3), the formation of alcohol **305** remained consistent. This suggests the addition of water promotes protodeboronation over alcohol formation. The absence of EtOH as a cosolvent, led to a decreased yield of amine **303** and increases the formation of ketone **304** (Table 13, entry 4). This suggests the inclusion of an alcohol in the reaction promotes amination and disfavour ketone formation. However, the use of EtOH as the main solvent, led to reduced yields of both the amine and ketone products (Table 13, entry 6). Interestingly, the corresponding ether product from EtOH coupling was not observed.



Entry	Solvent	MS	Yield			
			52	**303**	**304**	**305**
1	MeCN:EtOH (20:1)	Yes	0%	19%	31%	25%
2	MeCN:EtOH (20:1)	-	0%	5%	13%	21%
3	MeCN:EtOH:H_2O (20:1:0.1)	-	0%	0%	<5%	22%
4	MeCN	Yes	0%	11%	49%	24%
5	MeCN	-	0%	6%	11%	6%
6	EtOH	-	0%	<5%	19%	29%

Table 13: Effect of the solvent on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.05 M.

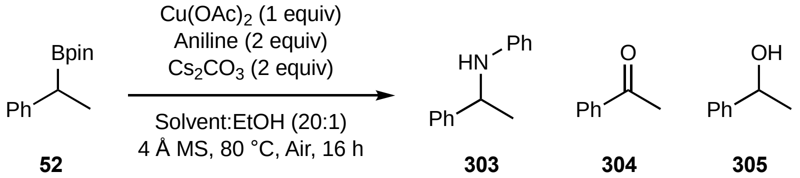
Next, the ratio of MeCN and EtOH as the reaction solvent was explored (Table 14). Generally, higher amounts of EtOH provided both amine **303** and ketone **304** in reduced yield (Table 14, entry 1). This is consistent with previous observations (see Table 13). Presumably, increasing the ratio of EtOH can promote protodeboronation and impede amine and ketone formation. Decreasing the quantity of alcohol used had a positive effect on the ketone formation overall (Table 14, entry 6). Amine formation appears limited except when using a 20:1 ratio of MeCN:EtOH (Table 14, entry 5). Switching the alcohol co-solvent did not lead to an improvement in the yield of amine **303** (Table 14, entries 7-9).



Entry	Solvent	XX:XX	Yield			
			52	**303**	**304**	**305**
1	MeCN:EtOH	1:1	0%	<5%	28%	27%
2	MeCN:EtOH	5:1	0%	5%	25%	18%
3	MeCN:EtOH	10:1	0%	7%	28%	21%
4	MeCN:EtOH	15:1	0%	<5%	29%	19%
5	MeCN:EtOH	20:1	0%	19%	31%	25%
6	MeCN:EtOH	40:1	0%	<5%	38%	22%
7	MeCN:*t*BuOH	20:1	0%	13%	31%	23%
8	MeCN:2-PrOH	20:1	0%	9%	41%	18%
9	MeCN:MeOH	20:1	0%	<5%	40%	22%

Table 14: Effect of the alcohol additive on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.05 M.

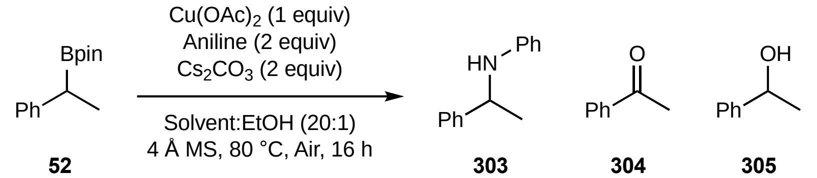
A range of non-polar aprotic solvents were screened with EtOH as a co-solvent (Table 15). However, these reactions did not lead to the formation of amine **303**. Additionally, the formation of the ketone **304** was significantly decreased. We hypothesise that the use of non-polar solvents reduces the solvation and de-nucleation of Cu(OAc)$_2$, preventing productive reaction.



Entry	Solvent	Yield			
		52	**303**	**304**	**305**
1	MeCN	0%	19%	31%	25%
2	Toluene	0%	0%	14%	27%
3	Hexane	0%	0%	<5%	25%
4	Petrol	0%	0%	19%	24%

Table 15: Effect of non-polar aprotic solvents on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.05 M.

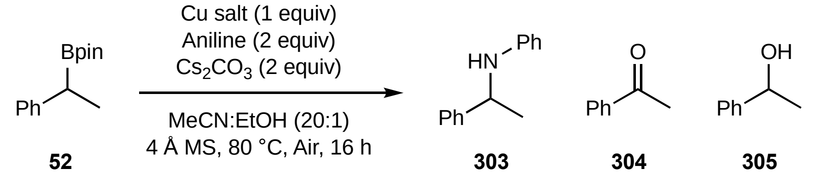
A range of polar aprotic solvents were tested (Table 16). These reactions generally gave higher yields of ketone **304** in comparison to the use of non-polar solvents. Most polar aprotic solvents resulted in a better mass balance and a considerable return of starting material **52**, suggesting protodeboronation is reduced under these conditions. MeCN, however, was the only solvent use that gave significant amounts of amine **303**.



Entry	Solvent	Yield			
		52	**303**	**304**	**305**
1	MeCN	0%	19%	31%	25%
2	DCM	>99%	0%	6%	9%
3	DMF	22%	<5%	26%	12%
4	DCE	0%	<5%	24%	11%
5	$CHCl_3$	22%	<5%	26%	12%
6	THF	0%	0%	16%	15%
7	1,4-Dioxane	0%	0%	29%	32%

Table 16: Effect of polar aprotic solvents on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.05 M.

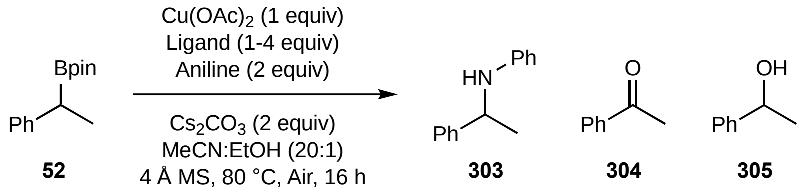
The next variable explored was the source of copper, with a range of both Cu(I) and Cu(II) salts tested (Table 17). However, only the reaction using $Cu(OAc)_2$ gave any amine **303** (Table 17, entry 1). In addition, other copper salts did not generate ketone **304** in significant yield, with the exception of $Cu(I)(MeCN)_4PF_6$ (Table 17, entry 4). However, Cu(I) salts did lead to increased amounts of alcohol **305** being formed (Table 17, entries 2-4).



Entry	Copper salt	Yield			
		52	**303**	**304**	**305**
1	$Cu(OAc)_2$	0%	19%	31%	25%
2	CuCl	0%	0%	6%	50%
3	CuI	0%	0%	<5%	51%
4	$Cu(MeCN)_4PF_6$	0%	0%	42%	40%
5	CuO	0%	0%	<5%	13%
6	$Cu(OTf)_2$	0%	0%	8%	6%

Table 17: Effect of the Cu source on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.05 M.

Ligands have been used previously in Chan-Lam reactions to aid reactivity (section 1.3.3). A ligand screen was therefore undertaken (Table 18). Mono- and bi-dentate ligands were tested, with loadings chosen to avoid saturating the Cu centre. In general, the ligands tested shut down the formation of the amine **303**, but the use of Pyridine and DMAP gave amine **303** in trace amounts (Table 18, entry 9 and 11). Increasing the loading of pyridine appeared to increase the formation of amine **303**. Pyridine-derived mono- and bi-dentate ligands appeared to promote the formation of the ketone **304**. BIPY, in particular, provided ketone **304** in a good yield. No C-N coupling was observed from diamine ligands **307** and **308**.



Entry	Ligand (equiv)	Yield			
		52	**303**	**304**	**305**
1	DPPF (1)	0%	0%	0%	0%
2	**306** (1)	0%	0%	6%	55%
3	**307** (1)	0%	0%	<5%	22%
4	**308** (1)	0%	0%	<5%	46%
5	BIPY (1)	0%	0%	57%	22%
6	**309** (1)	0%	0%	44%	16%
7	**219** (1)	0%	0%	28%	15%
8	**310** (1)	0%	0%	13%	19%
9	DMAP (2)	0%	<5%	32%	23%
10	**311** (2)	0%	0%	36%	51%
11	Pyr (1)	0%	<5%	32%	50%
12	Pyr (2)	0%	<5%	33%	14%
13	Pyr (4)	0%	<5%	29%	38%

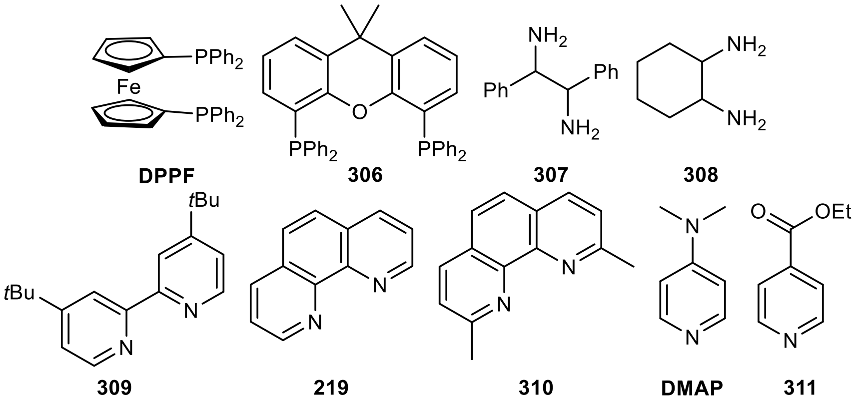
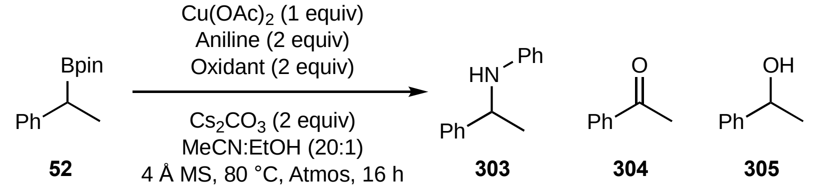


Table 18: Effects of the ligand on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.05 M.

The use of DTBP has previously been reported as a terminal oxidant in Chan-Evans-Lam reactions.[155,156] DTBP was tested alongside and in place of oxygen from air. Using DTBP under an atmosphere of air, the yield of the amine **303** was reduced and ketone **304** was slightly increased (Table 19, Entry 2). However, when under an inert atmosphere, the formation all products were considerably reduced, with no amine **303** observed (Table 19, Entry 3). This suggests that the presence of DTBP plays no positive effect on the reaction, and an inert atmosphere appears to hinder the reaction under the conditions tested.



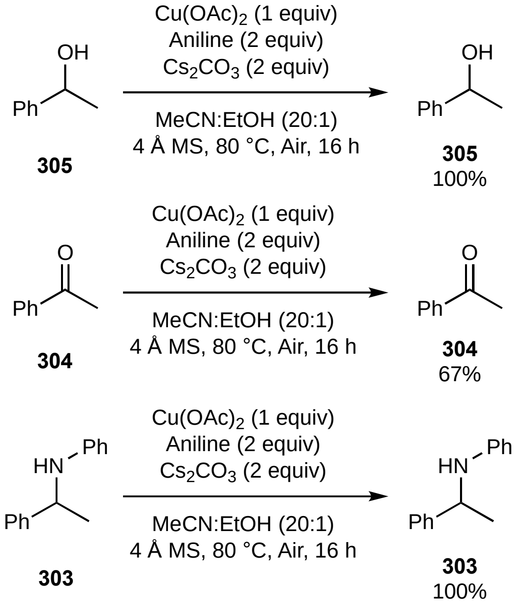
Entry	Atmos	Oxidant	Yield			
			52	**303**	**304**	**305**
1	Air	-	0%	19%	31%	25%
2	Air	$(t\text{BuO})_2$	0%	12%	43%	24%
3	N_2	$(t\text{BuO})_2$	0%	0%	12%	5%

Table 19: Effect of DTBP on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.05 M.

At this point, the findings of optimisation can be summarised as follows:

1) $Cu(OAc)_2$ appears to be the most active copper source for both amine **303** and ketone **304** formation.
2) Phosphine and nitrogen-based ligands tested appear to be beneficial for ketone **304** formation, but in general disfavour amine **303** formation.
3) The use of relatively weak inorganic bases, such as Cs_2CO_3, favours amine **303** formation and disfavour ketone **304** formation. Instead, the use of strong inorganic bases, such as KOH, favour alcohol **305** formation.
4) Generally, the use of MeCN appears to favour the formation of both the amine **303** and ketone **304** products.
5) The addition of an alcohol additive, such as EtOH, favours amine **303** formation and disfavour ketone **304** formation.
6) Employing pyridine as an additive, alongside or in the absence of a base, favours amine **303** and ketone **304** formation. In general, the use of pyridine disfavours alcohol **305** formation.

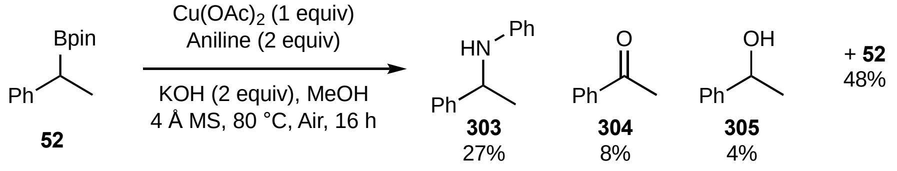
To gain an insight into the reaction conditions developed at this point, isolated samples of products **303, 304** and **305** were subjected to the reaction conditions, in the absence of boronic ester, to test the possibility of interconversion between them (Scheme 85). All products remained unaltered under the current conditions and returned only their starting materials. Interestingly, there was no oxidation of the alcohol to the corresponding ketone, despite the ability of Cu catalysts for alcohol oxidation.[177] Also, there was no observed formation of an imine or amine **303** from reaction between ketone **304** and aniline. Amine **303** also appeared to be stable to the reaction conditions.



Scheme 85: Investigating the possible interconversion of **303, 304** and **305**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.05 M.

2.3.2.2 *Further Investigation of Conditions*

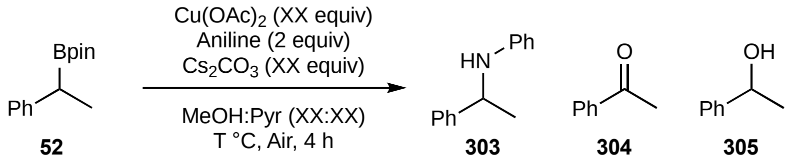
A key reaction in the investigation of conditions for the formation of amine **303** was identified whilst evaluating conditions for the optimisation of alcohol **305** (not shown in this report). A solvent screen identified MeOH as a beneficial solvent, with amine **303** formed preferentially, despite the use of KOH as base which typically leads to the formation of alcohol **305**. The high quantity of starting material returned suggests the potential for further conversion to the amine. Presumably, the starting material returned is due to a low rate of transmetallation or protodeboronation.



Scheme 86: Key result in the development of the amination conditions. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.05 M.

As a result, replacement of the MeCN:EtOH solvent system with MeOH was investigated. Despite the finding that the use of EtOH as an additive promotes amine formation, previous attempts to use MeOH produced little amine **303** (Table 12, entry 9). Interestingly, the corresponding methyl ether from MeOH coupling was not observed throughout this method development.

No amine **303** was observed when MeOH is used as the only solvent (Table 20, Entry 1). Decreasing the reaction temperature gave a greater yield of ketone **304**. Presumably, the lower temperature means less MeOH evaporates, and the reagents remain in solution (Table 20, Entry 2). Using a lower loading of Cs_2CO_3 and then addition of pyridine, led to a reasonable formation of amine **303**. The background formation of ketone and alcohol products is maintained (Table 20, Entry 3). Increasing the quantity of $Cu(OAc)_2$ significantly increased the yield of amine **303**. Watson and co-workers reported that pinacol, formed during the reaction, inhibited the catalyst activity for Chan-Lam couplings of aryl pinacol boronic esters.[138] This could explain why increasing the stoichiometry of $Cu(OAc)_2$ led to an increase in yield of **303**. Alternatively, an additional role of $Cu(OAc)_2$ could be as an oxidant, through disproportionation. As formally the loss of two electrons are required in the oxidative C-N coupling, having a higher Cu loading may maintain coupling activity for longer. It is also common for aryl Chan-Evans-Lam reactions to employ up to two equivalents of a copper species.[1] An increase in $Cu(OAc)_2$ loading, led to the formation of ketone **304** to be maintained but the yield of alcohol **305** decreased (Table 20, Entry 4).

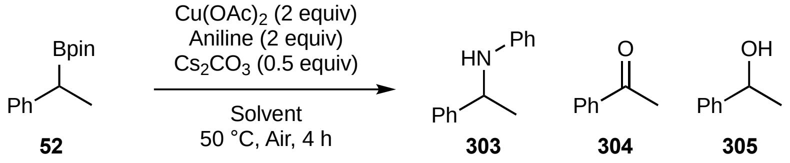


Entry	$Cu(OAc)_2$ (equiv)	Cs_2CO_3 (equiv)	MeOH:Pyr (XX:XX)	T (°C)	Yield **52**	**303**	**304**	**305**
1[a]	1	2	1:0	80	0%	0%	17%	74%
2[a]	1	2	1:0	50	0%	0%	38%	59%
3[b]	1	1	3:2	50	0%	11%	36%	34%
4[b]	2	1	3:2	50	0%	34%	40%	16%
5[b]	2	2	3:2	50	0%	16%	34%	48%
6[b]	2	0.5	3:2	50	0%	30%	32%	5%
7[b]	2	0	3:2	50	0%	6%	60%	<5%

Table 20: Effect of varying $Cu(OAc)_2$, Cs_2CO_3, MeOH:Pyr ratio and temperature on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. a) Reaction concentration of 0.05 M. b) Reaction concentration of 0.1 M.

There appears to be a correlation between the yield of alcohol **305** and the loading of Cs_2CO_3, with greater amounts of **305** formed with increased amounts of the base (Table 20, entries 3-6). This is consistent with the previous observation that stronger bases appear to favour alcohol **305** formation (Table 12, entry 6). The absence of Cs_2CO_3 leads to minimal formation of alcohol **305** and amine **303**, but formation of ketone **304** is favoured (Table 20, Entry 7). Therefore, some Cs_2CO_3 appears to be required to generate amine **303**, suggesting the role of pyridine is primarily to ligate to and de-nucleate the $Cu(OAc)_2$ rather than as a base. This also suggests that the presence of an inorganic base is not required to form ketone **304**.

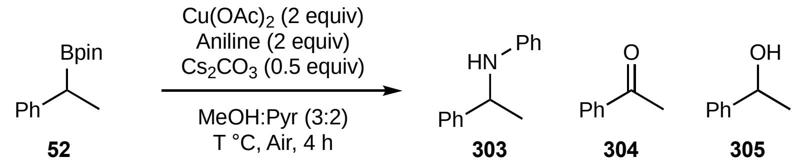
Undertaking the reaction in either MeOH or pyridine alone inhibited the formation of the amine **303** (see Table 21). The yield of ketone **304** and alcohol **305** were consistent with the previous reactions.



Entry	Solvent	Yield			
		52	**303**	**304**	**305**
1	MeOH	0%	0%	46%	37%
2	Pyr	0%	0%	38%	59%

Table 21: Effect of solvent on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.1 M.

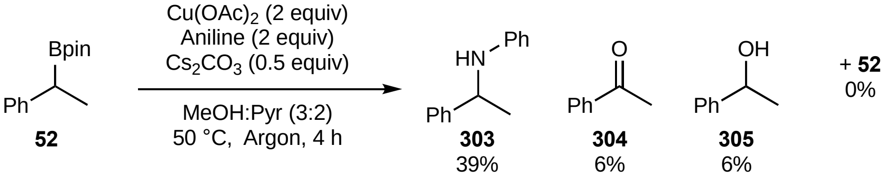
The effect of reaction temperature on yield of amine **303** was next investigated (Table 22). It appeared the formation of amine **303** was not greatly affected when changing the temperature. However, the formation of ketone **304** appeared to be favoured at lower temperatures, and the formation of alcohol **305** was significantly reduced above 40 °C. A reaction temperature of 50 °C was chosen as a compromise in the formation of by-products and synthetic applicability to some substrates.



Entry	T (°C)	Yield			
		52	**303**	**304**	**305**
1	40	0%	14%	35%	19%
2	50	0%	30%	32%	5%
3	60	0%	34%	18%	5%
4	70	0%	26%	14%	ND
5	80	0%	30%	10%	6%
6	90	0%	31%	6%	5%

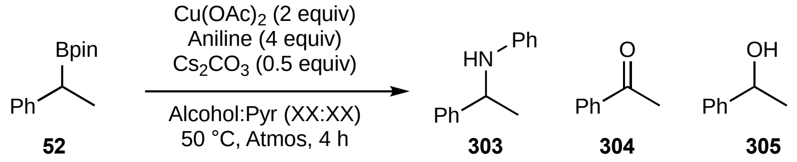
Table 22: Effect of temperature on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.1 M.

Although the use of oxygen from air as an oxidant is advantageous (due to ease of use and cost), it does not appear necessary as 2 equivalents of $Cu(OAc)_2$ are present in the reaction. Performing the reaction under an inert atmosphere significantly decreased the yield of ketone **304** (Scheme 87). This suggests that oxygen incorporated into the carbonyl is from oxygen present in the air. Additionally, the absence of air does not prevent the formation of amine **303**. The remaining mass balance was assumed to be lost to protodeboronation.



Scheme 87: The effect of an inert atmosphere on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.1 M.

To promote amination, potentially by reducing the amount of protodeboronation, the loading of aniline in the reaction was increased (Table 23). Increasing the amount of aniline generally gave an improved mass balance. When performed under air, the reaction preferentially forms ketone **304** in good yield (Table 23, entry 1). However, the formation of the amine **303** is reduced. Instead, when performing the reaction under an inert atmosphere, the yield of amine **303** was increased, and boronic ester starting material remained (Table 23, Entry 2).

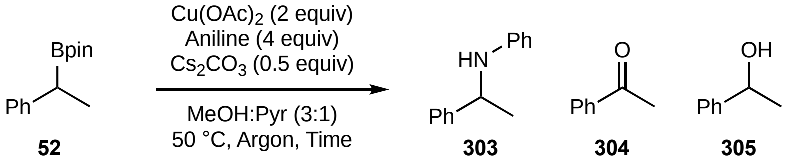


Entry	Alcohol	Alcohol:Pyr (XX:XX)	Atmos	Yield			
				52	**303**	**304**	**305**
1[a]	MeOH	3:2	Air	0%	20%	67%	15%
2[a]	MeOH	3:2	Argon	23%	48%	<5%	6%
3[b]	MeOH	3:1	Air	0%	33%	ND	14%
4[b]	MeOH	3:1	N_2	29%	58%	<5%	0%
5[b]	MeOH	3:1	Argon	51%	38%	<5%	<5%
6[b]	EtOH	3:1	Air	0%	22%	25%	9%
7[b]	EtOH	3:1	Argon	47%	15%	5%	5%

Table 23: Effect of varying pyridine quantity, concentration and alcohol under air and inert atmosphere on the amination of **52**. Yields determined using 1H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. a) Reaction concentration of 0.1 M. b) Reaction concentration of 0.125 M.

The concentration of the reaction was increased by reducing the quantity of pyridine added. This led to the formation of amine **303** in a higher yield, even in the presence of air (Table 23, Entry 3). When the reaction was under an inert atmosphere, such as nitrogen or argon, the yield of the amine **303** increased further, and some starting material **52** was also observed (Table 23, Entries 4 and 5). Replacing MeOH with EtOH led to reduced yields of amine **303** (Table 23, Entries 6 and 7). Similar trends were observed for reactions in the presence and absence of air. Performing the reaction under air increased the yield of ketone **304**, and performing the reaction under argon increased the amount of starting material **52** observed.

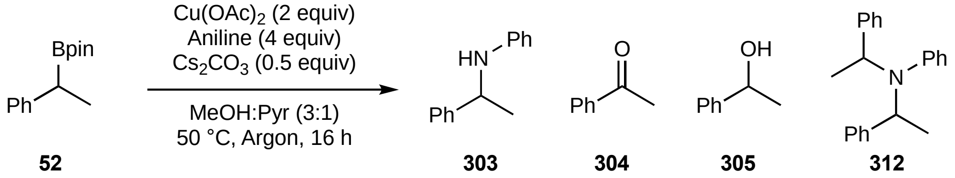
Finally, upon increasing the reaction time to allow full conversion of the starting material the yield of amine **303** was increased to 73%. Minimal formation of the ketone **304** and alcohol **305** were observed. Presumably, any ketone formed was a result of the presence of O_2 either dissolved in solvent (which were not degassed prior to use), or by leakage through the seal of the reaction flask.



Entry	Time	Yield			
		52	**303**	**304**	**305**
1	4 h	55%	43%	6%	<5%
2	8 h	30%	59%	8%	5%
3	16 h	0%	73%	13%	<5%

Table 24: Formation of amine **303** over different time periods. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.125 M.

The reaction scale was increased to 0.5 mmol, to allow the isolation of amine **303**. Retaining the reaction concentration from the optimisation, amine **303** was isolated in a significantly decreased yield over 16 h, though the amounts of ketone **304** and alcohol **305** by-products remained consistent (Table 25). It was assumed mass was lost to protodeboronation. Increasing the reaction concentration considerably improved the rate of reaction, and gave amine **303** in an excellent yield over 16 h. Pleasingly, no product from dialkylation **312** was observed.

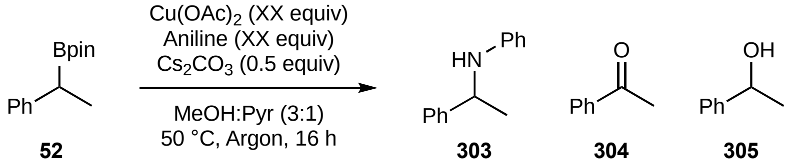


Entry	Solvent (mL)	Concentration (M)	Yield			
			303	**304**	**305**	**312**
1	4	0.125	59%	ND	ND	0%
2	1.33	0.38	73%	ND	ND	0%

Table 25: Effect of concentration on amination of **52**. Yields determined by isolation. Reactions conducted on a 0.5 mmol scale of **52**.

During method development, it appeared that the relative stoichiometry of amine, $Cu(OAc)_2$ and boronic ester played a significant role. To understand this better, the reagent stoichiometry was further investigated. Initially, changes to the stoichiometry of copper and aniline were undertaken relative to a consistent boronic ester quantity. Reactions under optimised conditions were conducted in parallel as a control.

Under the optimised conditions amine **303** was formed in excellent yield after 16 h. Some starting material was detected, but promisingly, side product formation was heavily minimised (Table 26, entry 1). The use of sub-stoichiometric quantities of $Cu(OAc)_2$ significantly reduced the formation of the amine **303** irrespective of the loading of aniline (Table 26, entries 2, 4 and 5). The quantity of unreacted starting material appears related to the loading of $Cu(OAc)_2$. Generally, 2 equivalents of $Cu(OAc)_2$ are required to consume 1 equivalent of boronic ester, irrespective of amine formation (Table 26, entries 1 and 6). This is consistent with previous Chan-Evans-Lam observations when $Cu(OAc)_2$ has been used in the absence of an alternative oxidant. When 0.5 equivalents of $Cu(OAc)_2$ are used, roughly 25% of boronic ester **52** is consumed (Table 26, entries 3 and 4). Reducing the loading of both aniline and $Cu(OAc)_2$ by half leads to approximately half the yield of amine **303** (Table 26, entry 3). Throughout these reactions the formation of alcohol **305** and ketone **304** were comparable to the optimised conditions.

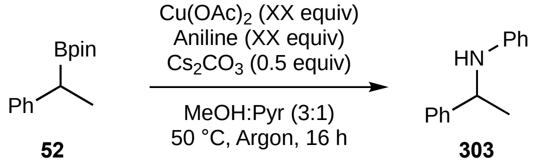


Entry	Aniline (equiv)	$Cu(OAc)_2$ (equiv)	Yield			
			52	**303**	**304**	**305**
1	4	2	14%	78%	<5%	0%
2	4	0.5	52%	7%	<5%	<5%
3	2	1	27%	38%	6%	<5%
4	2	0.5	59%	<5%	<5%	<5%
5	1	0.5	69%	5%	<5%	<5%
6	1	2	0%	38%	7%	<5%

Table 26: Effect of $Cu(OAc)_2$ and aniline loading on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.125 M.

Further reactions were performed on a 0.5 mmol scale to enable the isolation of amine **303**. Similar trends were observed at 0.5 mmol scale to that of 0.05 mmol scale. ^{1}H-NMR analysis of the crude material allowed the ratio of boronic ester **52** to product **303** to be determined. Using the optimised conditions, amine **303** was isolated in excellent yield (Table 27, entry 9).

It was found that 2 equivalents of $Cu(OAc)_2$ were needed to fully consume 1 equivalent of boronic ester **52** (Table 27, entries 2, 4 and 9). A reduced loading of $Cu(OAc)_2$ gave an increased return of starting material **52** (Table 27, entry 2). Reducing the quantity of aniline significantly decreases the yield of amine **303** formed (Table 27, entries 1, 4 and 9), but has less influence on the amount of starting material returned (Table 27, entry 2). It appears a 2:1 ratio of aniline to $Cu(OAc)_2$ gives higher yields of amine **303** than a 1:1 ratio (Table 27, entry 3 vs 7 and 4 vs 9). When increasing the loading of both aniline and $Cu(OAc)_2$, but retaining the 2:1 ratio, an increase in the conversion of boronic ester **52** and formation of amine **303** is observed (Table 27, entries 5-9).

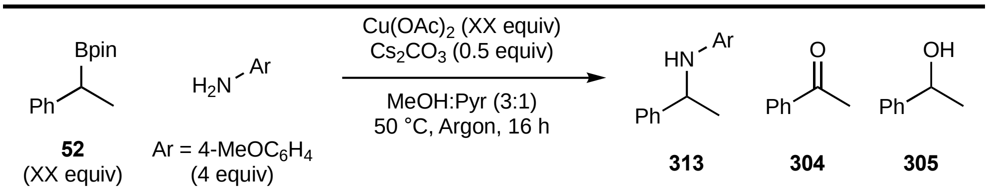


Entry	Aniline	Cu(OAc)$_2$	Crude ratio **303:52**	Yield of **303**
1	1	2	1:0.4	46%[a]
2	1	1	1:1.2	37%[a]
3	1.5	1.5	1:0.25	41%[a]
4	2	2	1:0	55%
5	2	1	1:1.2	36%[a]
6	2.5	1.25	1:0.86	47%[a]
7	3	1.5	1:0.17	67%[a]
8	3.5	1.75	1:0.45	58%
9	4	2	1:0	73%

Table 27: Effect of Cu(OAc)$_2$ and aniline loading on the amination of **52**. Yields reported are of isolated material. Reactions conducted on a 0.5 mmol scale of **52**. Reaction concentration of 0.38 M. a) Yield adjusted for the presence of **52**.

During optimisation, we chose to make the boronic ester the limiting reagent, as this is typically the synthetically more expensive reagent. There are also a wide range of commercially available anilines, which are relatively inexpensive. However, there may be occasion where the aniline is required to be the limiting reagent. We therefore decided to investigate the effect of excess boronic ester on coupling. Reactions were performed on a 0.05 mmol scale with respect to the aniline, with yields determined through ^{1}H-NMR analysis. To ease ^{1}H-NMR analysis, *p*-anisidine was used as the amine coupling partner.

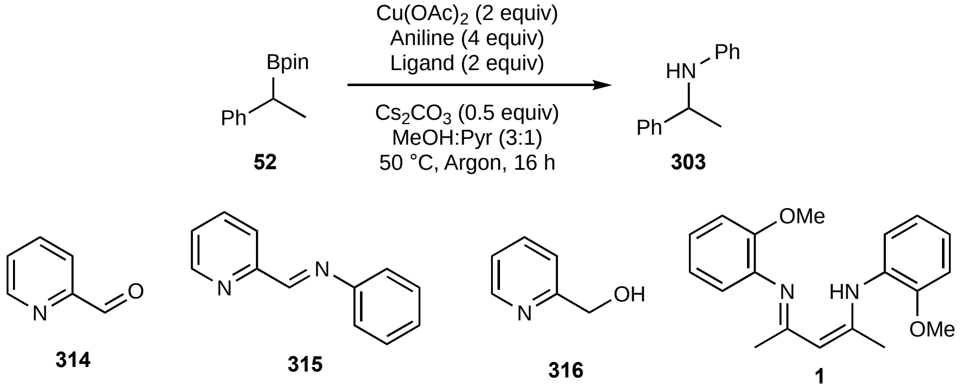
Reactions with the *p*-anisidine as the limiting reagent gave a lower yield of amine **313** in comparison with when the amine is in excess (Table 28). A 2:1 ratio of boronic ester **52** to aniline respectively (Table 28, entry 1) gave a comparable yield to that of a 1:1 ratio (Table 26, entry 6). Considering the boronic ester is in excess, the return of boronic ester starting material is relatively low. Presumably, mass is lost to protodeboronation. Decreasing the stoichiometry of boronic ester appears to have minimal effect on the yield of amine **313** (Table 28, entry 2). Consistent with previous results, reducing the amount of Cu(OAc)$_2$ reduces the formation of the amine **313** and a greater quantity of boronic ester **52** was returned (Table 28, entries 3 and 4).



Entry	**52** (equiv)	Cu(OAc)$_2$ (equiv)	Yield			
			52	**313**	**304**	**305**
1	2	2	28%[a]	35%	0%	ND
2	1.5	2	18%[a]	37%	0%	13%
3	2	1	46%[a]	12%	6%	6%
4	2	0.5	55%[a]	<5%	10%	14%

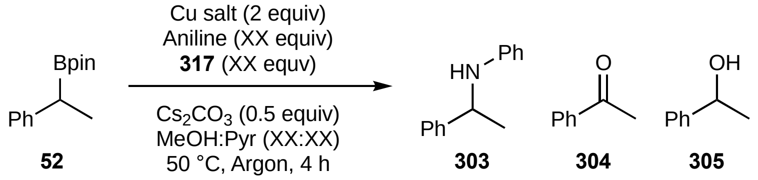
Table 28: Effect of the loading of boronic ester **52** and Cu(OAc)$_2$ on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of *p*-anisidine. a) Recovery of **52** determined from quantity of **52** added. Reaction concentration of 0.125 M.

Under the currently optimised conditions, O/N containing ligands were screened. This section of work was done in collaboration with Francesca Dennis. Ligands produced by Francesca are denoted by ‘FMD’. Previous ligands tested disfavour the formation of amine **303** (Table 18) however, pyridine is beneficial when used as an additive. Several ligands containing a pyridine scaffold were screened along with 2-methoxy diketimine (**1**). All ligands gave no observable yield of amine **303** and returned the starting material with minimal formation of side products.

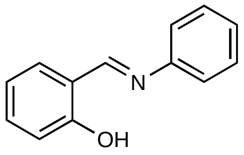


Scheme 88: Effect of various ligands on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.125 M.

Next, ligand **317** was shown to prevent the consumption of boronic ester **52** under the standard conditions (Table 29, entries 1 and 2). A copper salt screen was performed, and CuBr$_2$ was found to give a similar yield of amine **303** in the presence (Table 29, entry 3) and absence of **317** (Table 29, entry 4). Running the reaction in aniline gave an increase in yield of amine **303** and a decreased return of boronic ester **52** (Table 29, entry 5).



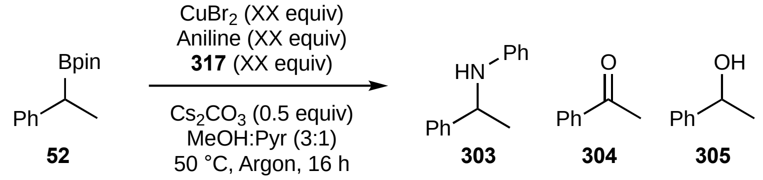
Entry	Ratio MeOH:Pyr	Aniline (equiv)	Cu salt	**317**	Yield			
					52	**303**	**304**	**305**
1	3:1	4	$Cu(OAc)_2$	-	ND	45%	0%	0%
2	3:1	4	$Cu(OAc)_2$	2	>99%	0%	0%	0%
3	3:1	4	$CuBr_2$	-	15%	43%	0%	0%
4	3:1	4	$CuBr_2$	2	40%	47%	8%	0%
5	-	45	$CuBr_2$	2	ND	57%	0%	0%



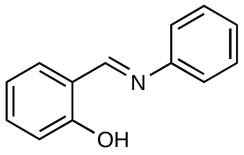
317^{FMD}

Table 29: Effect of varying solvent, copper source and ligand **317** on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.125 M.

Increasing the reaction time gave a decrease in yield of amine **303** possibly due to increased ligation preventing reactivity (Table 30, entry 1). To investigate the effect of **317** on the reaction, loadings of aniline, $CuBr_2$ and **317** were varied. Decreasing the loading of $CuBr_2$ and ligand **317** decreased the yield of amine **303** (Table 30, entries 2 and 3). Lowering the loading of ligand **317** had little effect on the yield of amine **303** suggesting $CuBr_2$ has a more significant effect (Table 30, entry 4). Decreasing the aniline loading slightly decreased the yield of amine **303** (Table 30, entry 7) and a 1:1:1 ratio of aniline:$CuBr_2$:**317** appeared to give a similar result to increased loadings (Table 30, entry 1).



Entry	Aniline (equiv)	CuBr$_2$ (equiv)	**317** (equiv)	Yield			
				52	**303**	**304**	**305**
1	4	2	2	37%	32%	<5%	0%
2	4	1	1	69%	16%	12%	0%
3	4	0.5	0.5	73%	<5%	8%	<5%
4	4	2	1	44%	28%	6%	0%
5	4	1	0.5	52%	18%	15%	0%
6	4	1	0.25	53%	12%	25%	0%
7	2	2	2	45%	24%	7%	0%
8	2	1	1	67%	<5%	14%	0%
9	1	1	1	0%	35%	5%	0%



317$^{\text{FMD}}$

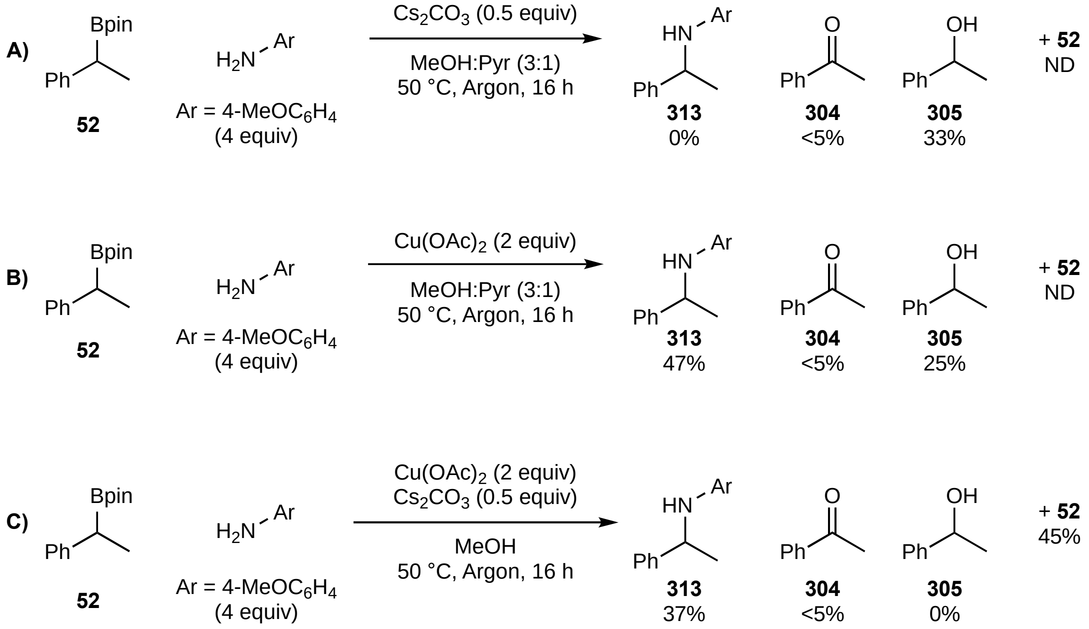
Table 30: Effect of varying the loading of aniline, CuBr$_2$ and ligand **317** on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.125 M.

2.3.3 Control Reactions

A series of control reactions were performed excluding key reagents to highlight their importance. In the absence of Cu(OAc)$_2$, no amine **303** was observed (Scheme 89A). This suggests that non-metal mediated processes are unable to form the amine product.

In the absence of Cs$_2$CO$_3$, the formation of the amine **303** was reduced, but an increase in the formation of alcohol **305** was observed (Scheme 89B). Presumably, deprotonation of aniline coordinated to Cu(OAc)$_2$ does not occur, allowing adventitious water to coordinate to Cu(OAc)$_2$ and undergo coupling instead.

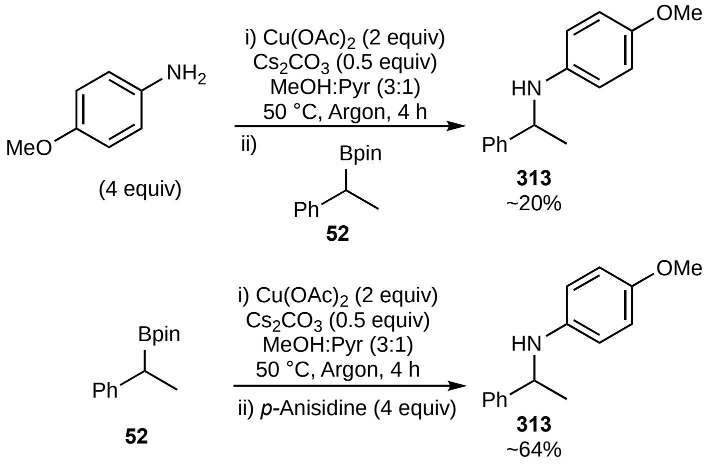
In the absence of pyridine, the yield of amine **303** is reduced but a greater quantity of boronic ester starting material was observed (Scheme 89C). This supports the previous hypothesis that pyridine helps de-nucleate Cu(OAc)$_2$, generating a greater concentration of active catalyst in solution.[1]



Scheme 89: Effect of the exclusion of reagents from the amination reaction conditions. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.125 M.

2.3.4 Preliminary Kinetics Investigation

Preliminary data was collected for the rate of consumption of boronic ester and formation of amine product **313** using ReactIR and LCMS analysis of aliquots. This work was conducted in collaboration with the Centre for Rapid Online Analysis of Reactions (ROAR) at Imperial College, London. Initial tests highlighted the importance of the order of reagent addition. The synthetic method developed (section 2.3.2.2) involved adding all reagents to the reaction vessel and initiating reaction through the addition of solvent. To improve control over the starting point of the reaction at 50 °C and measure data on the reactions kinetics, we aimed to add a key reagent to initiate the reaction. However, incubating $Cu(OAc)_2$ and *p*-anisidine for 30 minutes at 50 °C prior to addition of the boronic ester **52**, led to a significantly reduced yield of amine **313** at around 20% at 4 h. Presumably, coordination of *p*-anisidine to $Cu(OAc)_2$ generates a Cu complex that is inactive to reaction with the boronic ester. Altering the order of addition so that a solution of *p*-anisidine was added to a mixture of $Cu(OAc)_2$ and boronic ester **52**, resulted in a comparable yield of amine **313** to that of the optimised conditions.



Scheme 90: Effect of the order of addition of aniline and boronic ester on the amination of **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.5 mmol scale of **52**. Reaction concentration of 0.38 M.

Applying this finding, we were able to collect data using ReactIR which shows the consumption of *p*-anisidine and formation of amine **313** (Figure 16). Concurrently, aliquots were taken of the reaction mixture, which were analysed by LCMS to determine the concentration of amine **313** in the reaction mixture (Figure 17). A correlation between the LCMS and ReactIR data was found, suggesting ReactIR might be a suitable method by which to monitor the reaction. From LCMS analysis, amine **313** was formed in approximately 60% yield after 4 h. This is consistent with our reaction optimisation data (Table 24).

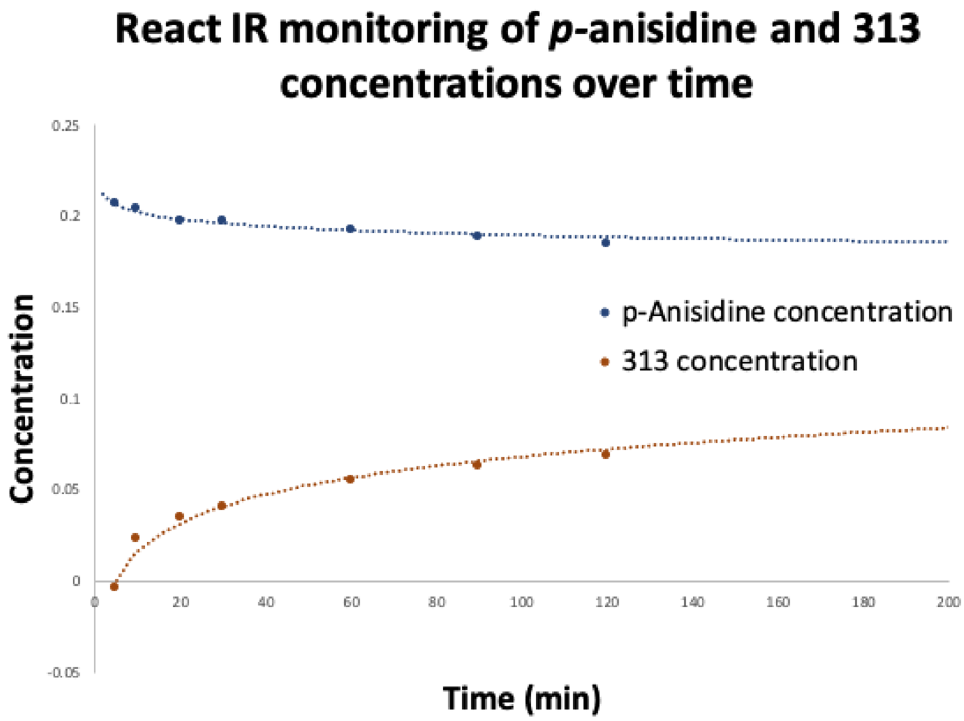


Figure 16: Change in concentration of *p*-anisidine (Blue) and amine **313** (Orange) over time as determined by React-IR.

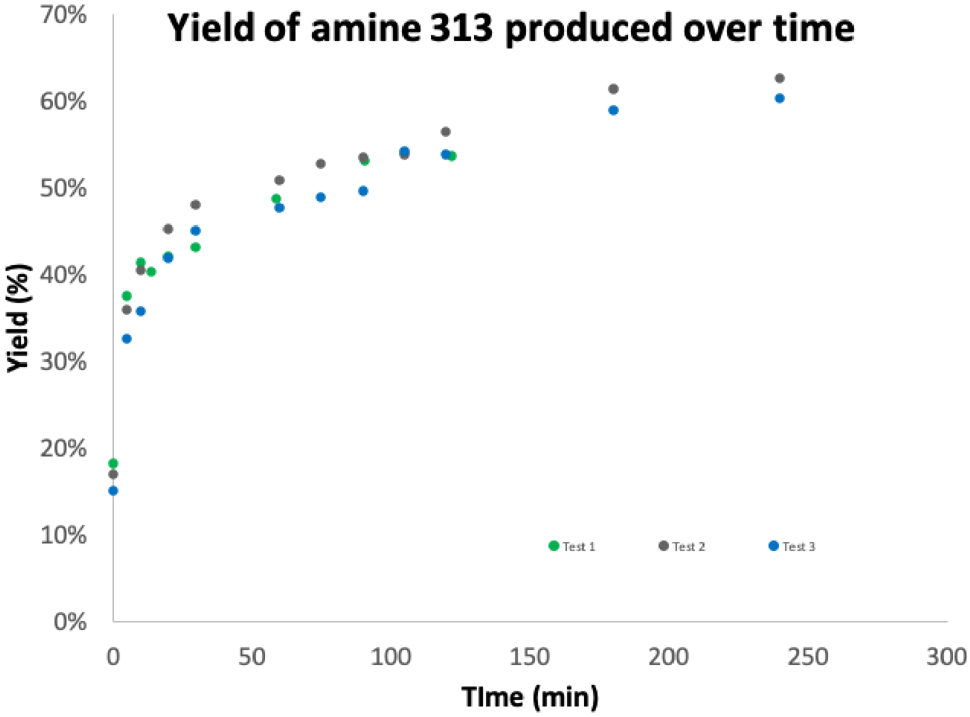


Figure 17: Change in concentration of amine **313** over time. Yields determined by LCMS, using biphenyl as an internal standard.

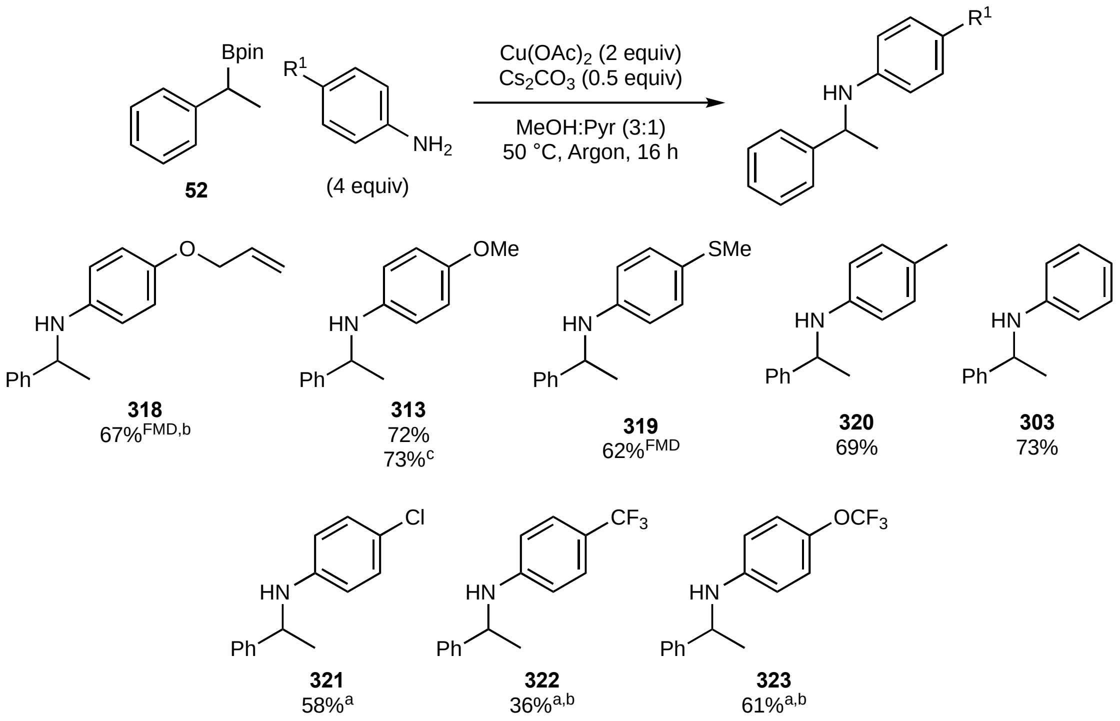
2.3.5 Scope of Reaction for the Amination of Alkylboronic Esters

This section of work was aided by Francesca. M. Dennis. Amine compounds produced and organoboron compounds supplied by Francesca are denoted by 'FMD'. The reaction was often tested by both Francesca and myself. However, the results highlighted were provided by Francesca, and are included to allow a complete discussion.

With the optimised conditions in hand, a variety of 1° and 2° amines were coupled with a range of alkyl boronic esters. Initially, reactions were carried out on 0.05 mmol scale, with a yield determined by ^{1}H-NMR analysis. During scale up, it was found that the work up procedure required consideration. First, Cu salts were removed using an extraction with ammonium hydroxide. In some cases, coelution of the amine product and boronic ester occurred during chromatographic purification. In these cases, an additional step to oxidise any remaining boronic ester using sodium perborate was carried out. The corresponding alcohol produced could then be separated from the amine product. Typically, the isolated yields obtained were comparable to NMR yield determined from the crude material. No significant loss of product was observed when employing the oxidative work up step.

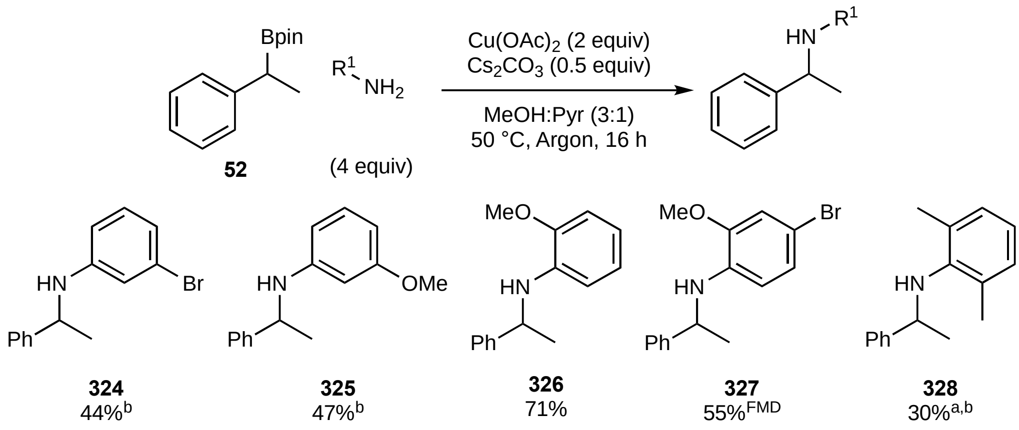
Boronic ester **52** was coupled with a variety of 1° anilines (Scheme 91). Pleasingly, throughout the scope of the reaction no production of di-alkylation was observed. This is in contrast to reports by Kuninobu and co-workers often observing dialkylation when coupling 1° benzylboronic esters and anilines.[155] The reaction could also be performed on a 1 g scale using *p*-anisidine with no decrease in the isolated yield (**313**). A range of functional groups are tolerated, including alkene (**318**), sulphides (**319**), trifluoromethyl (**322**), and trifluoromethylethers (**323**). Aryl halides are also tolerated, and importantly no products from Ullmann coupling were observed. However, the presence of an aryl bromide substituent tends to lead to a lower yield of coupling (**324** and **327**).

Electron withdrawing and donating substituents on the aniline were tolerated. However, electron deficient anilines often required higher temperatures and longer reaction times to achieve good yield. The coupling of *p*-anisidine reached a high yield after 16 h at 50 °C (**313**). However, *p*-trifluoromethyl aniline, when reacted at 65 °C for 48 h, only led to formation of **322** in modest yield. In comparison, weaker electron withdrawing substituents, such as 4-trifluoromethoxy aniline provided, a significantly higher yield of **323** at 65 °C and 48 h.



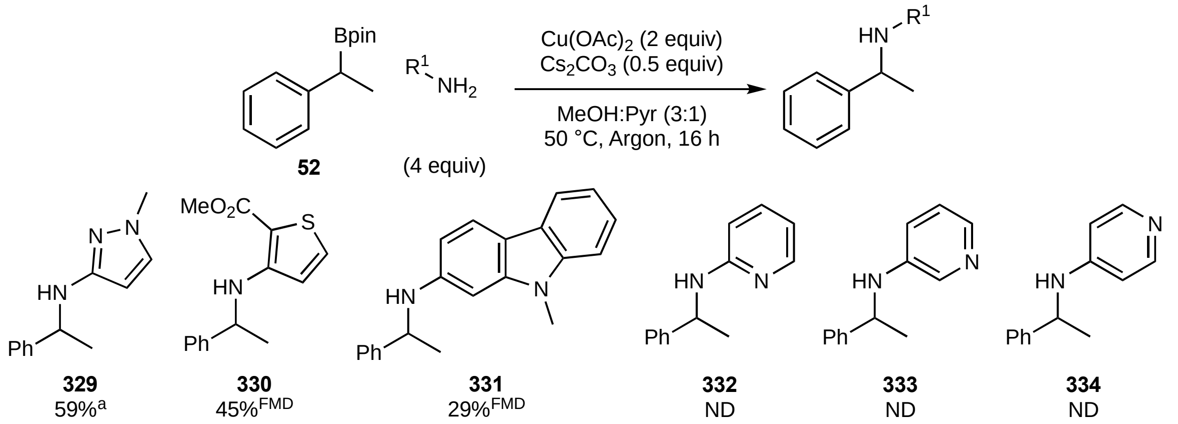
Scheme 91: Scope of *p*-substituted anilines coupled with boronic ester **52**. a) Reaction temperature of 65 °C, b) Reaction time of 48 h, c) Reaction conducted on a 1g scale.

The electronic properties of methoxy-substituted anilines appear to affect the outcome of the reaction more than steric interactions. *o*-Anisidine reacts in comparable yield to *p*-anisidine, despite the increase in steric congestion around the amine. However, *m*-anisidine only provided a moderate yield of **325** after 48 h. Also, the presence of a *p*-bromo substituent considerably decreases the yield when compared with *o*-anisidine. This is presumably due to the electron withdrawing nature of bromide substituent. Sterically demanding 2,2-dimethyl aniline gave a sluggish reaction and lower yield of **328**, even at elevated temperatures and longer reaction time. This is consistent with Chan-Evans-Lam couplings of aryl boronic acids, and Ullmann coupling, which have been found to be sensitive to the steric environment around the amine.[178]



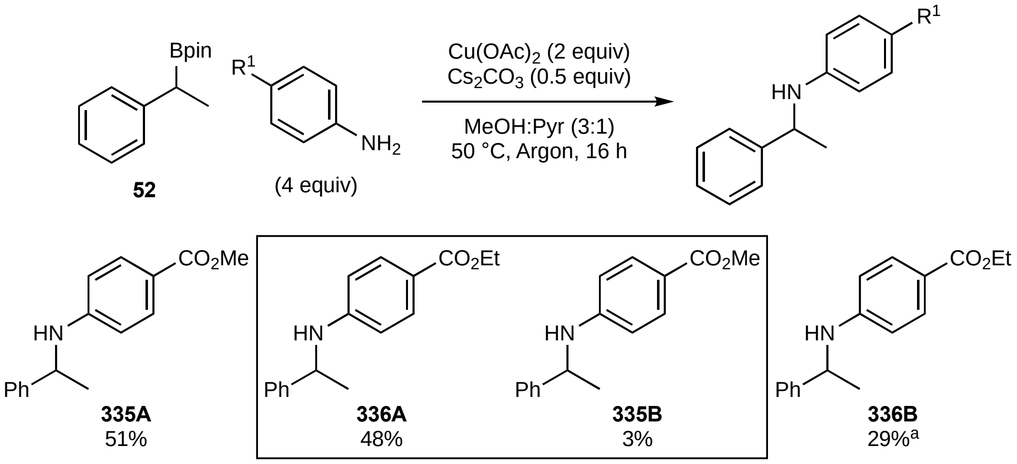
Scheme 92: Scope of *o*- and *m*- substituted anilines coupled with boronic ester **52**. a) Reaction temperature of 65 °C, b) Reaction time of 48 h.

Heteroaromatic anilines are also tolerated, with **329** and **330** formed in good yields. Issues arose when coupling pyridine-derived anilines. Although the corresponding products **332-334** were observed by NMR analysis and mass spectroscopy of the crude material, isolation was not possible. The compound appeared to be water soluble and incompatible with silica chromatography.



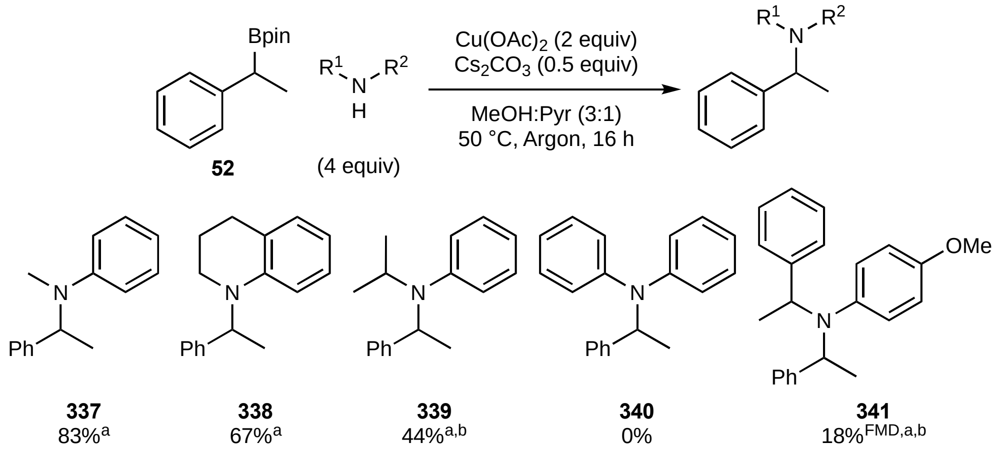
Scheme 93: Scope of heteroaryl amines coupled with boronic ester **52**. a) Reaction temperature of 65 °C.

Ester-containing anilines are compatible with the reaction conditions (Scheme 94). *p*-Methylester aniline was coupled in a good yield under the standard conditions to give amine **335A**. However, *p*-ethylester substituted aniline slowly underwent transesterification with MeOH from the solvent. An inseparable impurity of around 3% methyl ester was present (Scheme 94, **336A** and **335B**). Replacing the reaction solvent with EtOH prevented transesterification. However, the EtOH reaction solvent led to a lower yield of product **336B**.



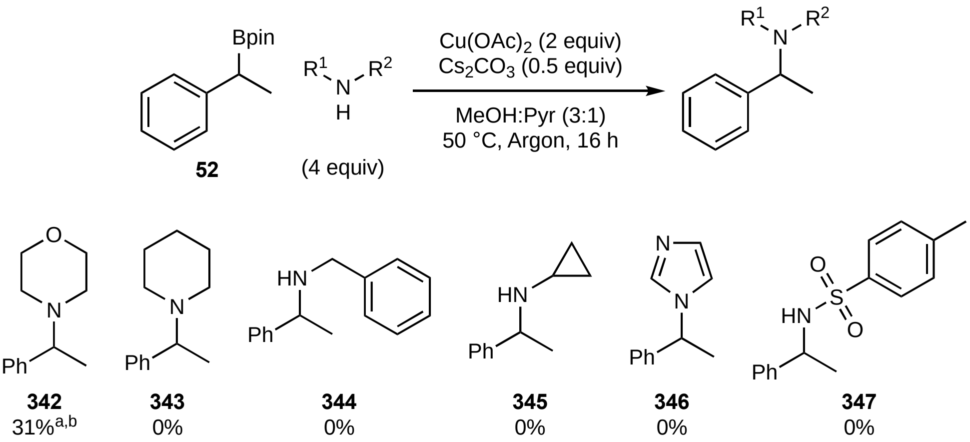
Scheme 94: *p*-Methylester and *p*-ethylester aniline coupling with boronic ester **52**. a) Reaction ran in EtOH:Pyr (3:1).

A range of 2° anilines were successfully coupled with boronic ester **52** (Scheme 95). However, there is a clear drop off in reactivity when steric hindrance is too great. *N*-Methyl aniline and cyclic aniline, tetrahydroquinoline, were coupled in good yield at 65 °C and 16 h (Scheme 95, **337** and **338**). More sterically hindered *N*-isopropyl aniline required a longer reaction time and gave a lower yield of amine **339**. However, diphenyl aniline did not undergo amination (Scheme 95, **340**). When amine **313** was re-subjected to the reaction conditions, coupling occurred in low yield to give amine **341**. This suggests that dialkylation, though possible, is challenging and explains why typically products from dialkylation are not observed.



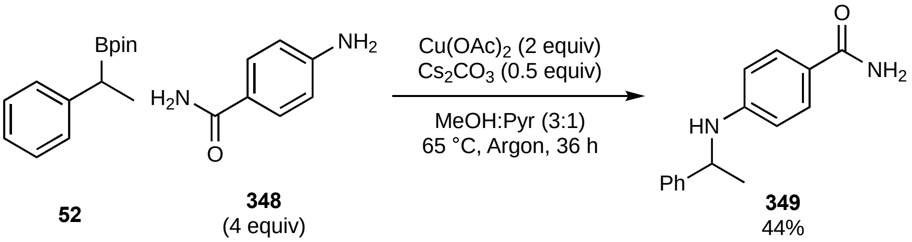
Scheme 95: Scope of 2° aniline coupling with boronic ester **52**. a) Reaction temperature of 65 °C, b) Reaction time of 48 h.

We wanted to explore the generality of these conditions with other classes of amines (Scheme 96). Morpholine was successfully coupled to give **342**, albeit in low yield. However, the coupling of piperidine, 1° alkyl amines (benzylamine and cyclopropyl amine), imidazole, and tosylamine was found to be unsuccessful.



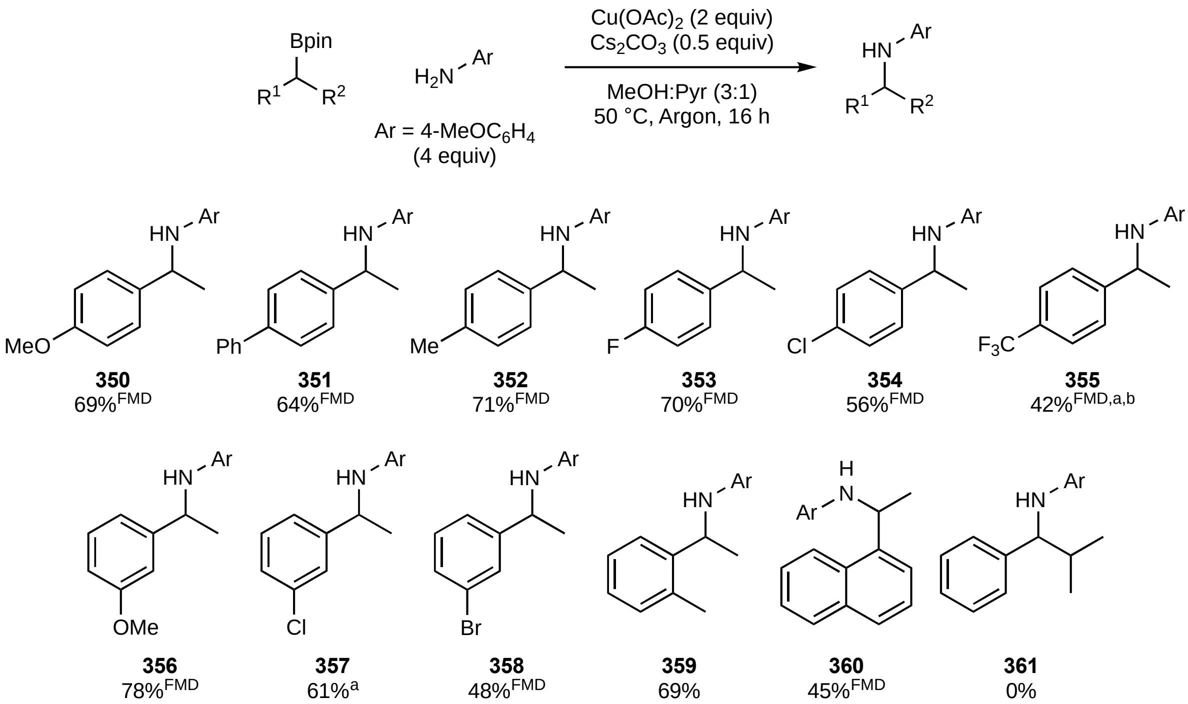
Scheme 96: Attempts to couple a range of nucleophiles with boronic ester **52**. a) Reaction temperature of 65 °C, b) Reaction time of 48 h.

The reaction of difunctional aniline **348** was carried out to see if coupling at the amine or amide group was favoured (Scheme 97). Coupling of the amine was observed exclusively, with the low yield a consequence of the electron withdrawing nature of the amide functional group. This is complementary to recent reports by Watson and co-workers.[156,158]



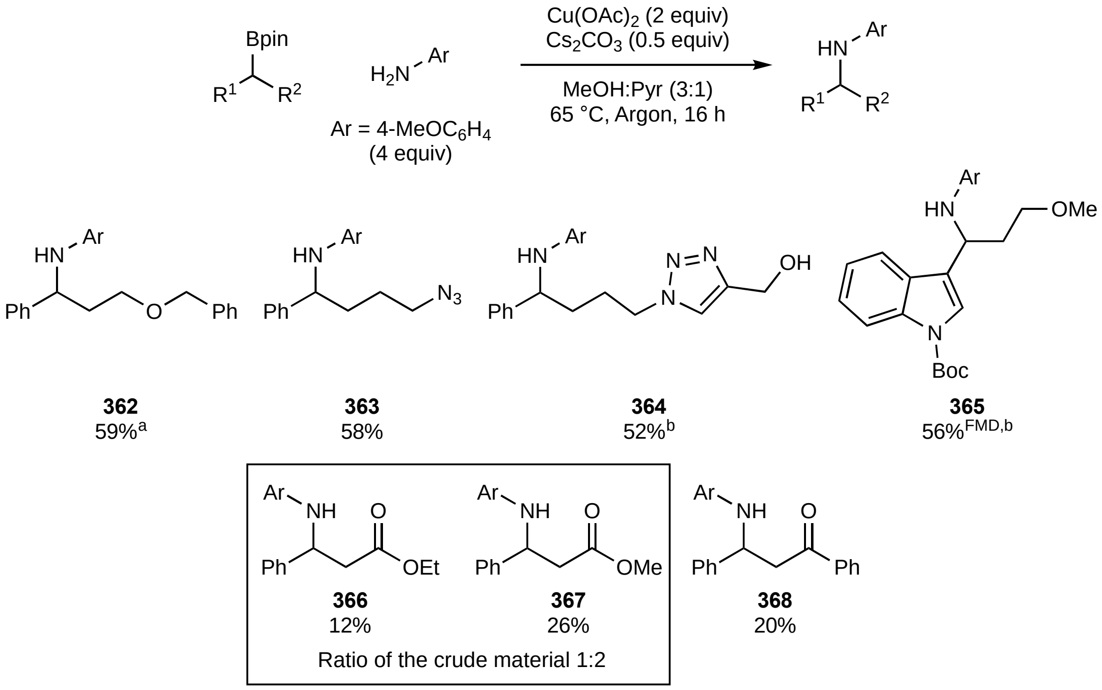
Scheme 97: Coupling of amine **348** with boronic ester **52**.

Next, the scope with respect to the boronic ester component was explored. In some cases when using aniline as the coupling reagent, the amination products were found to co-elute with the corresponding boronic ester starting material upon silica chromatography. However, *p*-anisidine-coupled products were found to be more easily purified. To minimise the need to perform an oxidative workup to remove unreacted boronic ester, *p*-anisidine was therefore used as the coupling partner (Scheme 98). 2° benzylic boronic esters with both electron withdrawing and electron donating substituents on the arene are tolerated. However, electron poor substrates required longer reaction times and higher temperatures. Aryl halides are tolerated (**353, 354, 358 and 357**), and no products from Ullmann coupling were observed. *o*-Methyl substituted boronic ester **227** reacted in comparable yield to *p*-methyl boronic ester **220** to give amines **359** and **352**. However, increased steric hindrance further, using 1-naphthyl boronic ester **228** led to a reduction in yield of amine **360**. Furthermore, no reaction was observed with a boronic ester with an isopropyl group alpha to boron (Scheme 98**, 361**). Similar findings were observed in the oxidation of boronic esters (see section 3.4).[179]



Scheme 98: Scope of the amination of 2° benzylic boronic esters with *p*-anisidine. a) Reaction temperature of 65 °C, b) Reaction time of 48 h.

The effects of increasing the alkyl chain length of the boronic ester was explored (Scheme 99). Generally, a modest decrease in yield was observed compared with α-Me boronic esters, and reaction temperature of 65 °C was required. Compatible functionalities include ether (**362**), azide (**363**), ketone (**368**), and unprotected alcohol (**364**). Heteroaromatic boronic ester **273** was also coupled in good yield to give amine **365**. β-Ester and β-keto boronic esters were also found to react to form the corresponding amines **366** and **368**. However, in both cases, the yield was modest. One possible explanation is that the products undergo decomposition through a retro-Mannich reaction. Additionally, transesterification was observed with β-ester boronic ester **285**, with an inseparable mixture of ethyl- and methyl- esters formed in a 1:2 ratio (**366** and **367)**.



362 59%[a]

363 58%

364 52%[b]

365 56%[FMD,b]

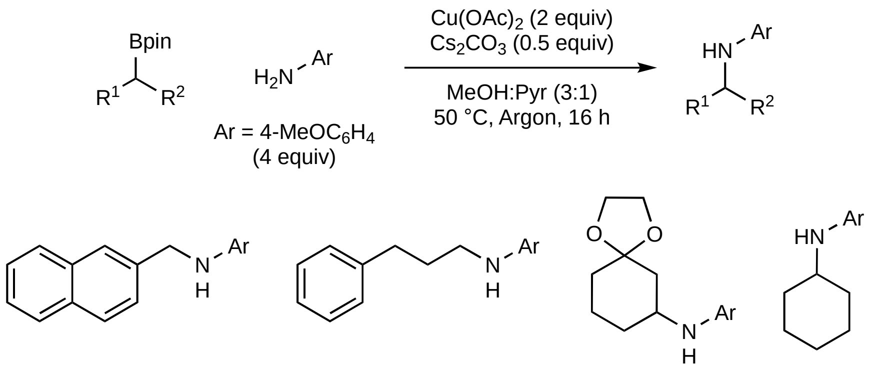
366 12%

367 26%

368 20%

Scheme 99: Scope of the amination of 2° benzylic boronic esters with *p*-anisidine. a) Reaction time of 32 h, b) Reaction time of 48 h.

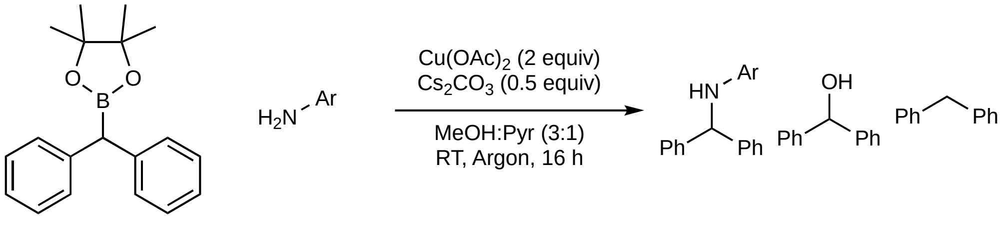
We tested 1° benzylic and a variety of non-benzylic boronic esters to explore the scope of boronic esters tolerated in the amination reaction (Scheme 100). 1° benzylic boronic ester **253** was successfully coupled to give amine **369** with only mono-substituted products observed. This is divergent from the previous report of Kuninobu and co-workers (section 2.1).[155] In comparison, 1° and 2° aliphatic boronic esters, displayed diminished reactivity. Longer reaction times and higher temperatures were required for the boronic ester to be consumed. The reactions of boronic esters **251** and **293** did not lead to any coupling product (**370** and **371**). However, cyclohexylboronic ester was successfully coupled, albeit in low yield to give amine **151B**. Presumably, the increased activity of the benzylic boronic esters is due to the favourable formation of a benzyl Cu-intermediate, stabilised by the adjacent aromatic ring. However, it could be that these substrates show a greater propensity for transmetallation, compared with aliphatic boronic esters, or require less energy to act as alkyl radical precursors.



369 62%[FMD] **370** 0% **371** 0% **151B** 11%[a]

Scheme 100: Scope of the amination of 1° benzylic and, 1° and 2° non-benzylic boronic esters with *p*-anisidine. a) Reaction temperature of 80 °C.

Next, reaction of a dibenzylic boronic ester **252** was explored (Scheme 101). Coupling was found to be successful, albeit in low yield, with comparable results obtained at both at 50 °C and room temperature. A mixture of amine **372**, alcohol **373** and protodeboronation product **374** was identified by ^{1}H-NMR analysis. The fact that full consumption of the boronic ester occurs, even at room temperature suggests an increased reactivity of this substrate. Presumably, an increased stabilisation from the two phenyl rings promotes transmetallation of the boronic ester.



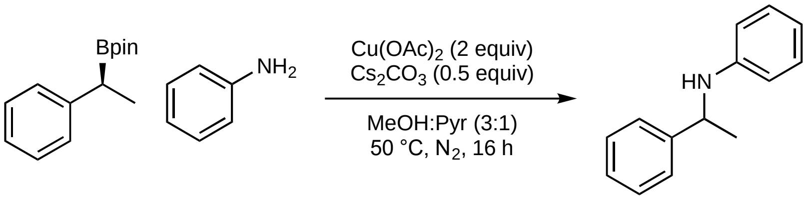
252 Ar = 4-MeOC$_6$H$_4$ (4 equiv) **372** 14% **373** 22% **374** 19%

Scheme 101: Amination of boronic ester **252**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **252**. Reaction concentration of 0.125 M.

2.3.6 Investigation Into the Mechanism of Reaction

When compared to the mechanism of arylboronic ester Chan-Evans-Lam, alkyl Chan-Evans-Lam reactions have comparatively little information available. Furthermore, little information is known about the interaction of alkylboronic esters and copper sources.

To explore whether the amination process is stereoselective, enantiomerically enriched boronic ester **(*S*)-52** was subjected to the reaction conditions (Scheme 102). The reaction gave the corresponding aminated product **303** in high yield, but with complete loss of stereochemical information. This could occur through the formation of a radical intermediate during transmetallation. Alternatively, the loss of stereochemical information could potentially be due to the configurational instability of an organocuprate intermediate. Recent reports from Knochel and co-workers suggest that alkyl Cu(I) species are configurationally unstable above -50 °C.[159]



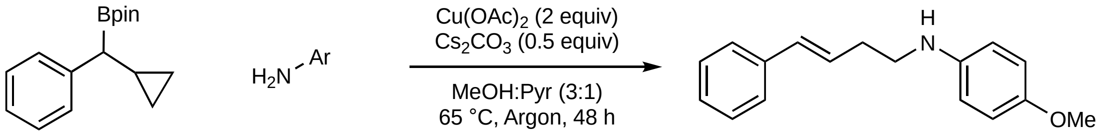
(*S*)-52
97:3 er

(4 equiv)

303
73%
50:50 er

Scheme 102: Amination of enantioenriched boronic ester **(*S*)-52**.

To gain insight into whether an alkyl radical is formed during amination, we performed a radical clock experiment using cyclopropyl boronic ester **258**. If the cyclopropane stays intact, this suggests that transmetallation occurs in a two-electron process. Instead, if opening of the cyclopropyl ring is observed, then the formation of a radical intermediate is likely to occur. Such a radical intermediate could be formed by homolytic cleavage of the C-B bond (**376**), or by H atom abstraction alpha to the boron. The resultant radical could then undergo Cu-mediated amination. Under the optimised conditions, the reaction of **258** provided only the ring opened aminated product **375** (Scheme 103). This suggests the process is likely to proceed through a radical intermediate rather than a two electron transmetalation (Figure 18). This is in contrast to the copper mediated oxidation method (section 3.4.4) where no ring opened product was observed.

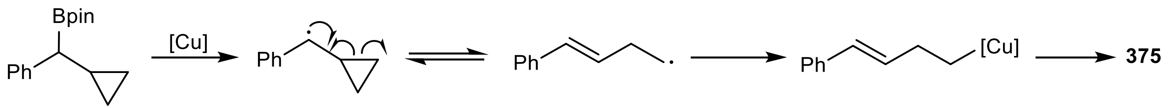


258

Ar = 4-MeOC$_6$H$_4$
(4 equiv)

375
39%^{FMD}

Scheme 103: Amination of cyclopropyl boronic ester **258**.

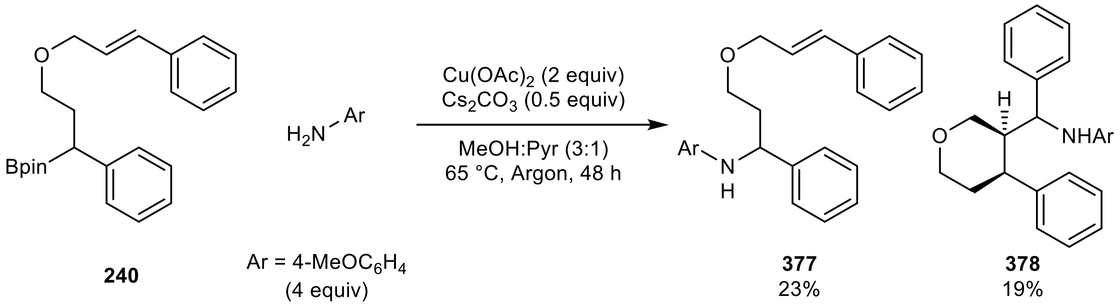


258 **376**

Figure 18: Possible mechanism for the amination of cyclopropyl boronic ester **258.**

A second radical clock experiment was performed using alkene-containing boronic ester **240**. If a radical forms at the benzylic position (where the boron is attached), intramolecular addition to the pendant alkene could occur. This would lead to the formation of a 6 membered ring through a 6-exo-trig process, giving a new benzyl radical which could then undergo amination. The standard conditions yield a mixture of linear amine **377** and pyran **378** products

(Scheme 104). The cyclised product **378** was formed as a single diastereoisomer. The phenyl and amine moieties appear to be on the same face of the ring. The relative stereochemistry of the 6-membered ring was determined by COSY and analysis of ^{1}H NMR coupling constants (Figure 20). Unfortunately, so far, efforts to grow single crystals of **378** (or derivatives) have been unsuccessful.



Scheme 104: Amination of boronic ester **240**.

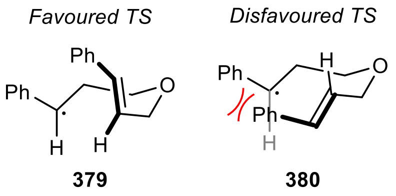


Figure 19: Proposed transition states for the formation of **378.**

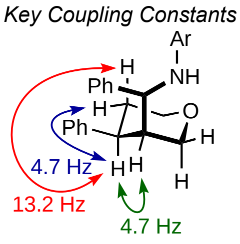
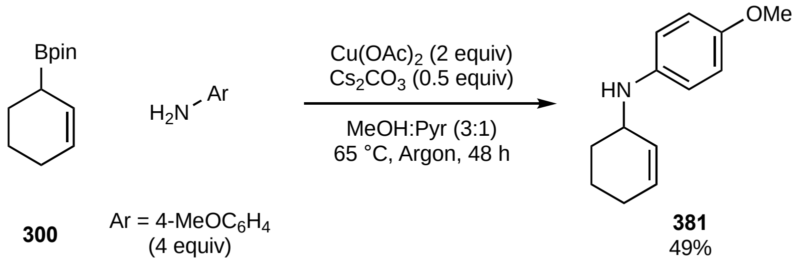


Figure 20: Key ^{1}H-NMR couplings constants used to determine the relative stereochemistry on the pyran ring.

2.3.7 Applying the Amination Conditions to Different Substrates

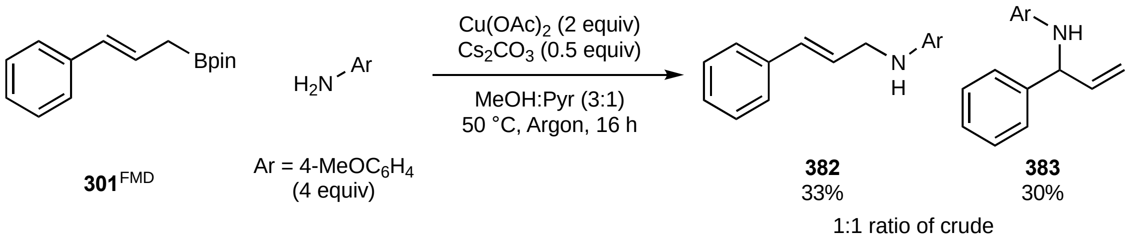
2.3.7.1 Amination of Allyl Boronic Esters

To explore the reactivity of other activated boronic esters, we subjected allylic boronic esters to the amination conditions. Symmetrical boronic ester **300** was successfully coupled to *p*-anisidine in good yield (Scheme 105). Presumably, the allylic position provides comparable stabilisation of the organocuprate intermediate to that of benzylic boronic esters.



Scheme 105: Amination of boronic ester **300**.

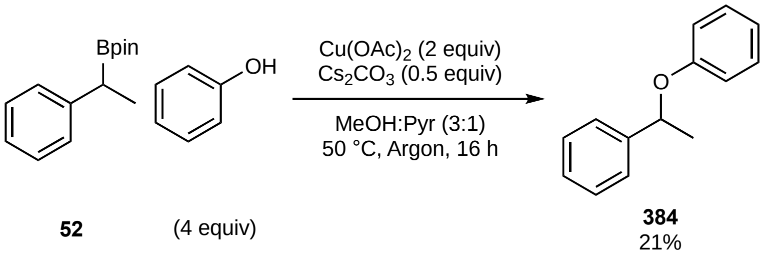
Next, the reaction of unsymmetrical allyl boronic ester **301** was explored. Coupling was found to be successful forming an inseparable mixture of amines **382** and **383** in a 1:1 ratio (Scheme 106). Currently, the reason for the formation of a mixture of regioisomers is unknown. However, it is possible that transmetallation could occur through a mixture of α and γ substitution. Alternatively, the allyl-Cu intermediate might undergo 1,3-allylic transposition prior to reductive elimination.[180]



Scheme 106: Amination of boronic ester **301**.

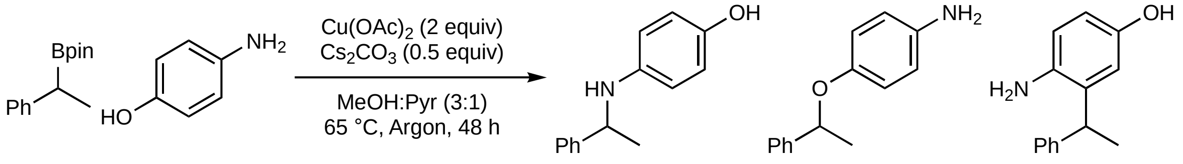
2.3.7.2 Coupling of O- and S-based Nucleophiles

Kuninobu and co-workers reported that their amination conditions could also be applied to the coupling of phenols.[155] We therefore explored whether phenol could be coupled with boronic ester **52** under our optimised conditions. On a 0.05 mmol scale, phenol was successfully coupled in low yield to give ester **384**. This provides proof of concept that alcohols can be successfully coupled. However, further optimisation would be needed to develop a more reliable method.



Scheme 107: Coupling of phenol and boronic ester **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.125 M.

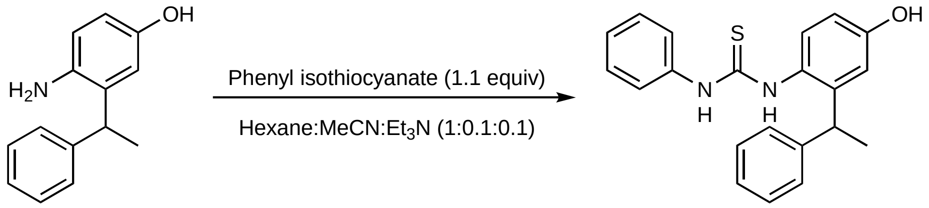
Next the preference of *O*- vs *N*-coupling was investigated by reacting aminophenol (Scheme 108). Amination occurred in a considerably higher yield than etherification however, the yield of amine **385** was moderate. Interestingly, the remainder of the mass was determined to be a product of C-C bond formation **387**, which was also isolated in a moderate yield.



52 (4 equiv) **385** 47% **386** 2% **387** 32%

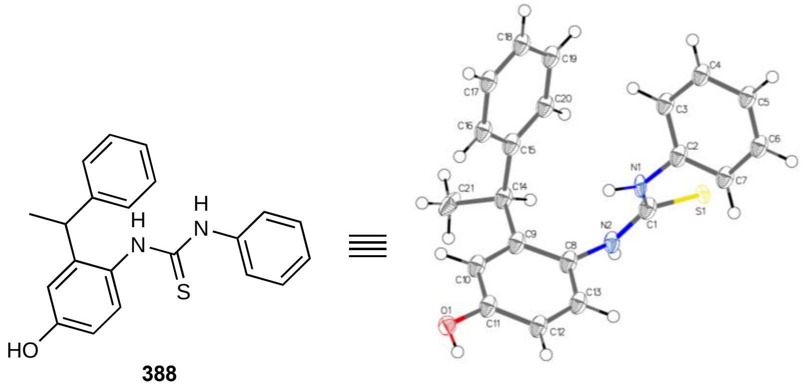
Scheme 108: Coupling of aminophenol with boronic ester **52**.

To determine the regioselectivity of arylation, X-ray crystallography was carried out on thiourea **388**, formed from the reaction of amine **387** with phenyl isothiocyanate (Scheme 109). It was found that coupling occurs exclusively ortho to the amine. Presumably, this regioisomer is formed due to the preferential co-ordination of nitrogen to copper.



387 **388** 68%

Scheme 109: Thiourea formation from amine **387**.

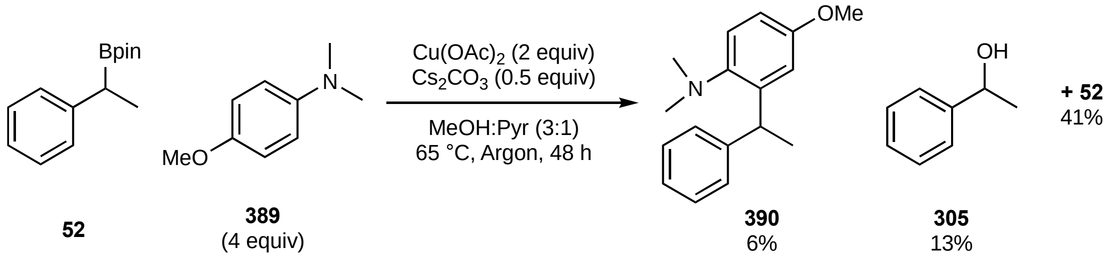


388

Figure 21: X-ray crystal structure of thiourea **388**.

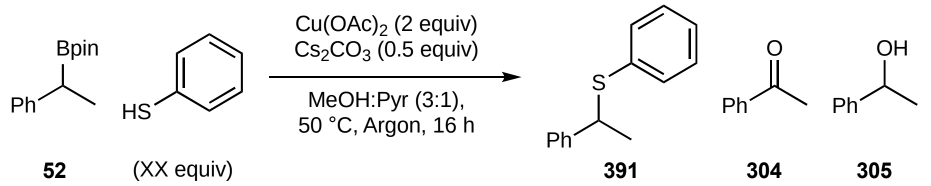
To explore the arylation further, *N,N*-dimethyl-*p*-methoxy aniline (**389**) was reacted with boronic ester **52**. It was hypothesised that due to the similar electronic profile of 3° amine **389** to aminophenol, the arylation product would form as the major product. However, a low yield of arylation product **390** was observed, along with a large return of starting material.

Presumably, there is a less favourable coordination of the dimethyl amine to copper, hindering C-C bond formation.



Scheme 110: Coupling of *N,N*-dimethyl-*p*-methoxy aniline and boronic ester **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.125 M.

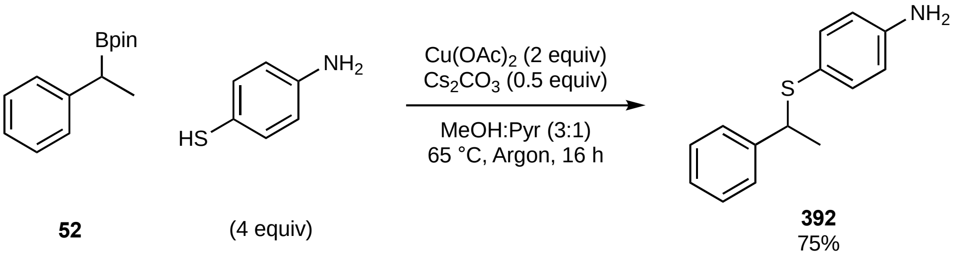
Next, we considered if C-S bond formation is possible. To the best of our knowledge, there is no current method reporting the direct C-S bond formation from alkylboron reagents. Thiophenol was reacted with boronic ester **52** to provide the thioether product **391**, albeit in a low yield. The reaction stoichiometry of boronic ester to thiol was investigated. However, it appears that the loading of thiol has little effect on the formation of thioether **391**, which is in contrast to the findings for amination.



Entry	Thiol (equiv)	Yield			
		52	**391**	**304**	**305**
1	4	64%	22%	0%	0%
2	3	55%	21%	0%	<5%
3	1	48%	26%	0%	0%

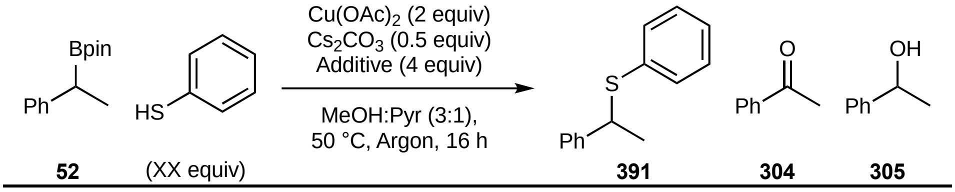
Table 31: Effect of the loading of thiol on the coupling of boronic ester **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.125 M.

The chemoselectivity of S vs N coupling was investigated using aminothiophenol (Scheme 111). Coupling occurred in excellent yield, with thioether **392** formed exclusively. Presumably, S coupling is preferential over N coupling due to the greater nucleophilicity of thiols compared with amines. Also, the low pKa of thiophenol means that deprotonation of the thiol occurs in preference to the amine under the reaction conditions. The high yield of **392**, compared with **391** (Table 31) is presumably a result that aminothiophenol is more electron rich than thiophenol. However, it could be that the presence of the amine helps break up aggregates of $Cu(OAc)_2$ leading to a greater concentration of active catalyst.



Scheme 111: Coupling of aminothiophenol with boronic ester **52**.

Finally, to investigate the considerable difference in yield between the coupling of thiol and aminothiophenol an amine additive screen was performed (Table 32). A range of 1°, 2° and 3° amines were screened. However, no products from either C-S or C-N coupling were observed.



Entry	Additive	Yield			
		52	**391**	**304**	**305**
1	**393**	77%	0%	0%	13%
2	**389**	41%	0%	0%	0%
3	**394**	84%	0%	0%	0%
4	**395**	77%	0%	0%	13%
5	**396**	75%	0%	0%	18%

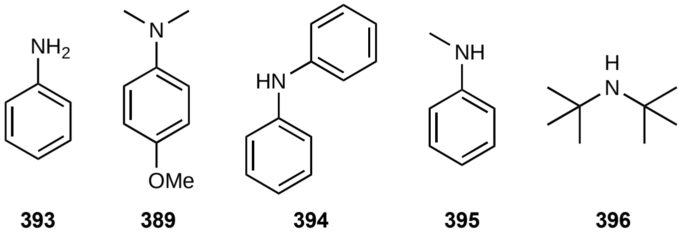
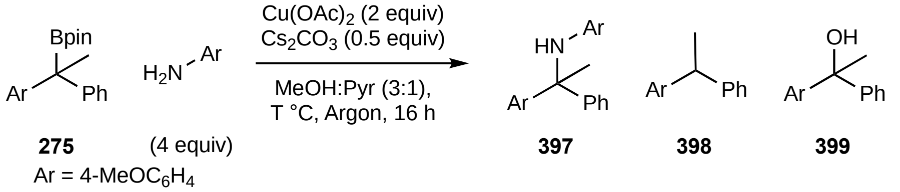


Table 32: The effect of amine additives on the coupling of thiophenol and boronic ester **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.125 M.

2.3.8 Amination of 3° Alkylboronic Esters

The use of 3° boronic esters in transition metal catalysis is limited. We were therefore interested to explore whether amination of 3° boronic esters was possible under our conditions. To our knowledge this class of organoboron reagent has not been previously reported for use in Chan-Evans-Lam aminations. Previously, copper mediated C-N bond forming examples of 3° organoboron reagents were limited to the use of cyclopropyl trifluoroborate salts.[161]

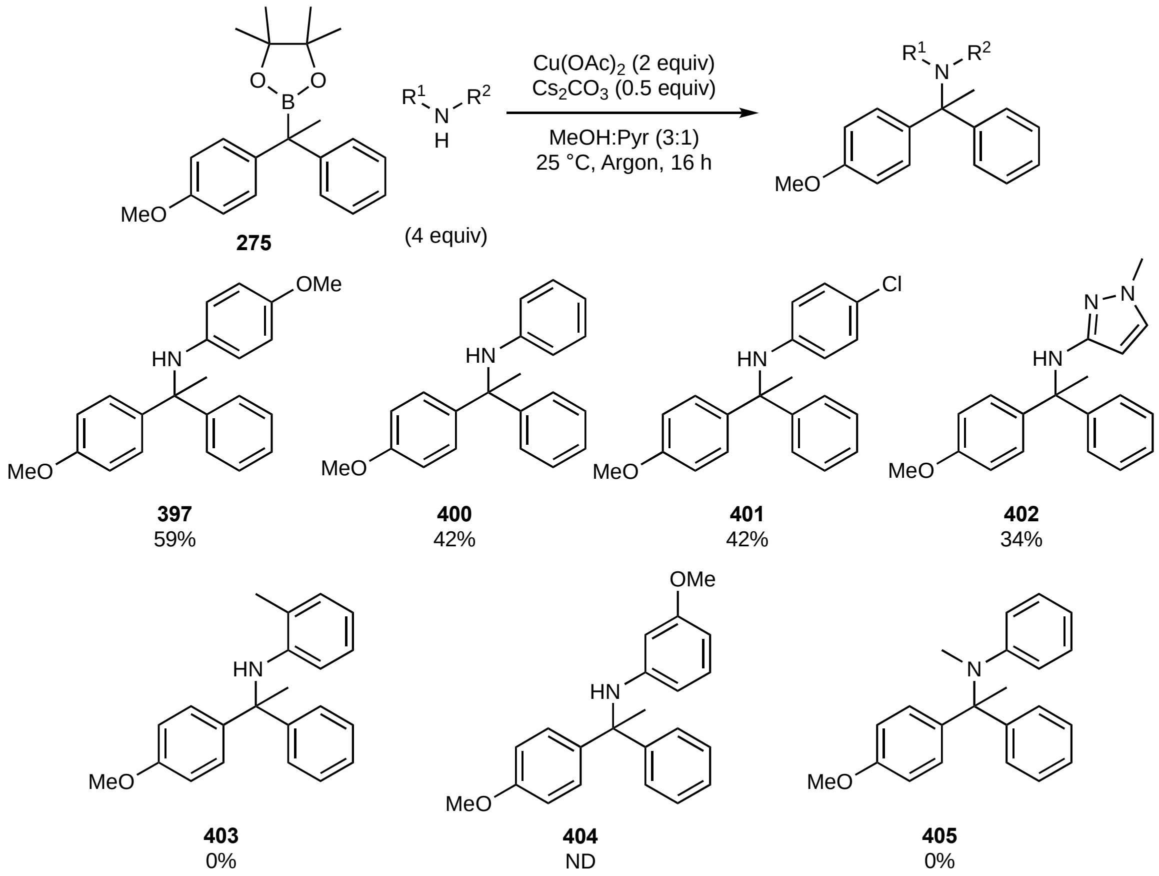
3° boronic ester **275** was coupled to *p*-anisidine in reasonable yield under the standard amination conditions (Table 33, entry 1). Due to the previous observations with dibenzylboronic ester **252** (Scheme 101), various reaction temperatures were trialled. Coupling was successful with all temperatures, however, 25 °C gave the highest yield. Consistent with the results of dibenzylboronic ester **252**, it is suspected that stabilisation from the two phenyl rings promotes transmetallation, even at a reduced temperature. Presumably, at higher temperatures an increased formation of unidentified by-products occurs.



Entry	T (°C)	Yield			
		275	**397**	**398**	**399**
1	50	0%	46%	5%	14%
2	40	0%	50%	6%	13%
3	30	0%	59%	10%	18%
4	25	0%	67%	8%	15%

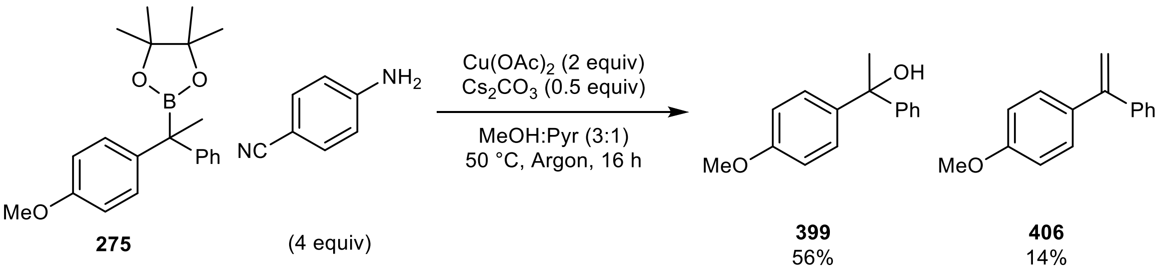
Table 33: Effect of temperature on the amination of 3° boronic ester **52**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.125 M.

Boronic ester **275** was coupled to a range of 1° anilines (Scheme 112). Functional groups tolerated include ether **397**, aryl chloride **401**, and a pyrazole **402**. No products from Ullmann coupling were observed in the reaction with *p*-chloro aniline. It was found that anilines with electron withdrawing groups gave lower yields. Increasing the reaction temperature did not increase product formation, presumably due to competing formation of side products. Only traces of product **404** were observed for *m*-methoxy aniline. *o*-Methyl aniline and 2° anilines were also not successful coupling partners, presumably due to increased steric hindrance.



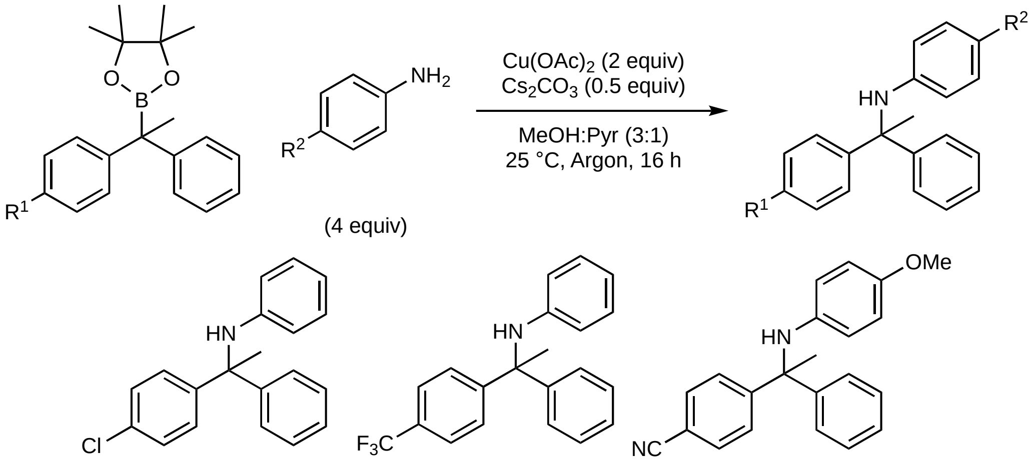
Scheme 112: Scope of anilines for the coupling of 3° boronic ester **275**.

During our investigation of anilines with electron withdrawing substituents, *p*-nitrile aniline was tested (Scheme 113). An increased temperature of 50 °C was required to reach full conversion of the boronic ester. Presumably, coordination of the electron deficient aniline to copper slows reductive elimination after transmetallation or prevents transmetallation, as no amine product was observed. However, several side-products were identified such as alcohol **399** and alkene **406**. It was later observed that after several days at room temperature, alcohol **399** underwent dehydration to form alkene **406**. This suggests the alkene could be formed during the reaction or as a product of alcohol degradation.



Scheme 113: Reaction of boronic ester **275** with *p*-cyano aniline.

Next, the scope with respect to the 3° boronic ester component was explored (Scheme 114). Functional groups tolerated include aryl halide and trifluoromethyl groups. Dibenzylic boronic esters possessing electron withdrawing functional groups such as *p*-trifluoromethyl and *p*-nitrile required an increased temperature for consumption of the boronic ester. *p*-Nitrile amine **409** was not successfully formed. The purification of these compounds was problematic such that isolation of the pure products was not obtained. However, this preliminary data displays the potential of this process.



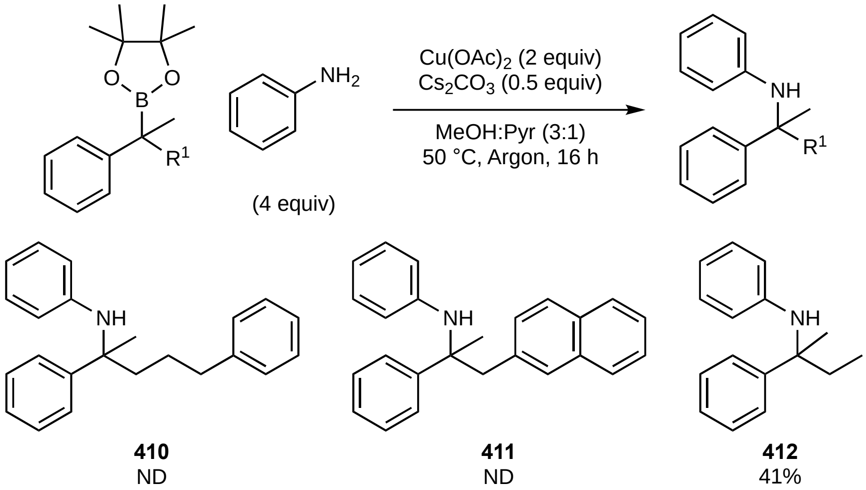
407 44%

408 25%[a]

409 0%[a]

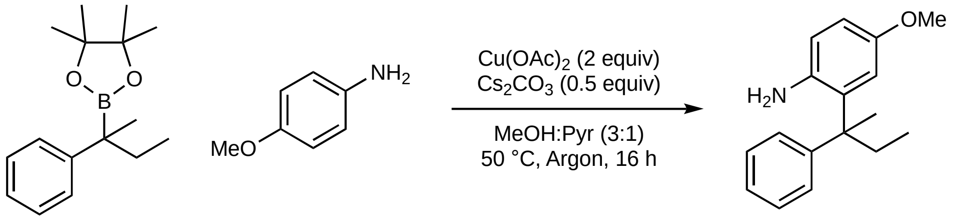
Scheme 114: Scope of amination of 3° dibenzylic boronic esters. Yields reported are a mixture of product and an unknown impurity. a) Reaction temperature of 50 °C.

To further explore the scope of 3° boronic esters, the reaction of mono-benzylic boronic esters were tested (Scheme 115). These boronic esters required an increased reaction temperature of 50 °C to access full conversion of the starting material. Amines **410**, **411** and **412** appeared to be successfully formed by NMR analysis and mass spectroscopy of the crude material. However, an inseparable mixture of products was produced for amines **410** and **411**. Despite only partial purification, the structure of amine **412** was confirmed by ^{1}H-NMR analysis.



Scheme 115: Scope of amination of monobenzylic 3° boronic esters. Yields reported are a mixture of isolated material and unknown impurity.

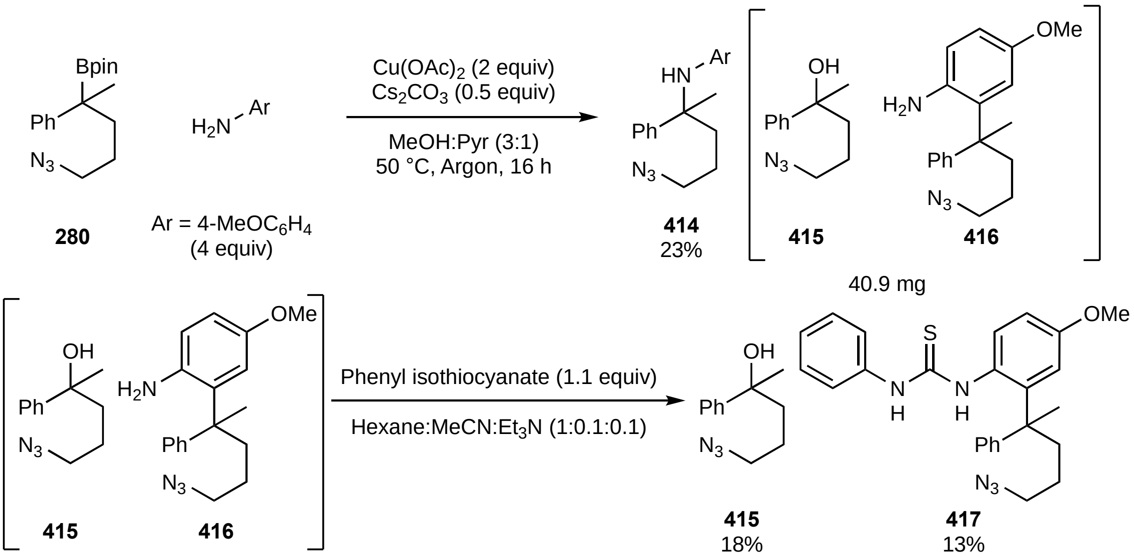
During our investigation of mono-benzylic 3° boronic esters, the coupling of *p*-anisidine and boronic ester **281** gave arylation product **413**. This is in contrast to observation of *N*-coupled product **412** observed when using aniline as the coupling partner. The regioselectivity of C-C bond formation was assigned by analogy to amine **387** (see Figure 21).



281 (4 equiv) **413** 15%

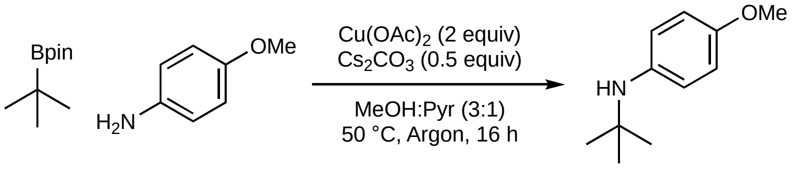
Scheme 116: Formation of amine **413** from the coupling of 3° boronic ester **281** and *p*-anisidine.

Similarly, when azide-substituted boronic ester **280** was reacted with *p*-anisidine, three products were identified (Scheme 117). Upon initial purification, a low yield of amine **414** was obtained, along with a complex mixture of products. This mixture contained predominantly alcohol **415** and arylation product **416**. Subjecting this mixture to reaction with phenyl isothiocyanate provided a separable mixture of thiourea **417** and alcohol **415**. The regioselectivity of amine **417** was assigned by analogy to amine **387** (see Figure 21).



Scheme 117: Formation of amine **414**, thiourea **416** and alcohol **415** from the coupling of 3° boronic ester **280** and *p*-anisidine.

Finally, tert-butyl pinacol boronic ester was subjected to the amination conditions. However, the formation of amine **418** was not observed. In addition, no starting material or side products were observed, and were presumed to be lost during workup.



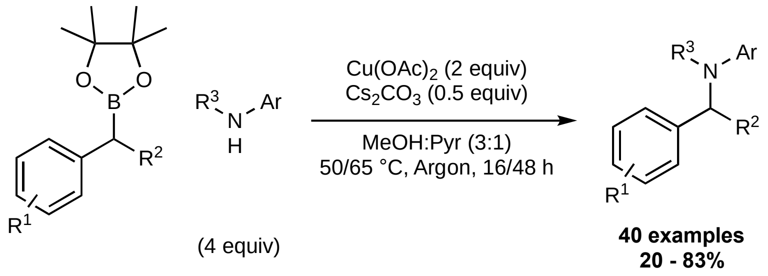
(4 equiv)

418
0%

Scheme 118: Attempted coupling of tert-butyl pinacol boronic ester and *p*-anisidine.

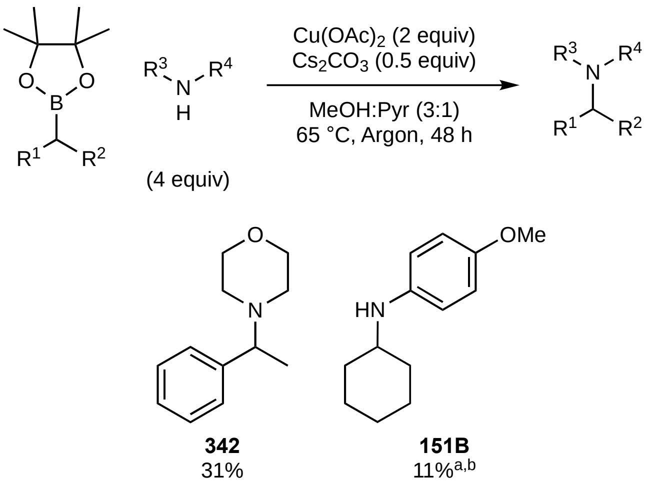
2.4 *Conclusions and Future Work*

This work was focussed on the development of a set of conditions for the amination of 2° alkylboronic esters. Benzylic boronic ester **52** was used during development due to the charge stabilisation of an organocuprate intermediate we hypothesised would form during the reaction. Through an iterative optimisation process, we have predominantly tailored our method to the coupling of a range of benzylic boronic esters and anilines. Generally, deviating from the use of benzylic boronic esters and anilines gave products in reduced yields. Whilst investigating the scope of our method we formed several noteworthy products that warrant further exploration.



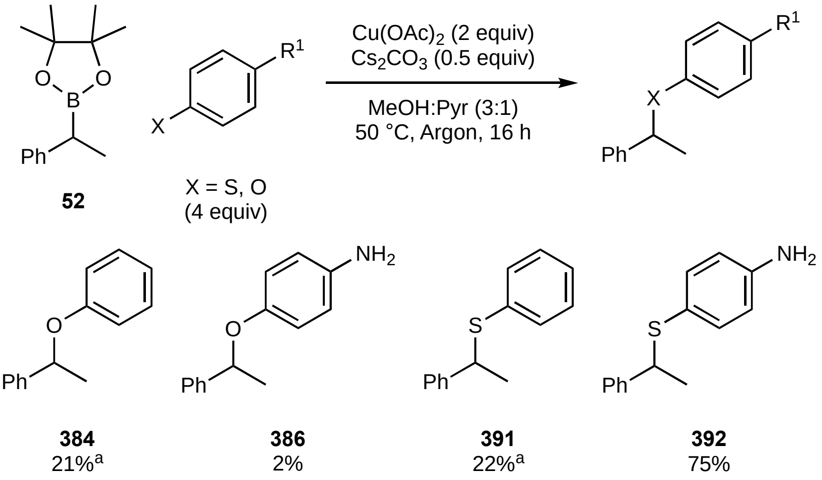
Scheme 119: Overview of alkyl boronic ester amination with substituted anilines.

To our knowledge, the successful coupling of alkylamines and alkylboronic esters is limited to the cyclopropylation of alkylamines reported by Zhu and co-workers.[149] Therefore, the coupling of morpholine to acyclic boronic ester **52**, albeit in a low yield, is a noteworthy result (Scheme 120). Presumably, issues with "non-activated" boronic esters arise due to the barrier of transmetallation. Despite this, "non-activated" cyclohexylboronic ester did undergo reaction to form amine **151B** albeit in a low yield.



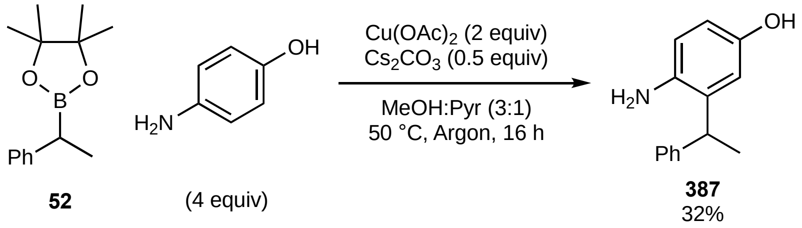
Scheme 120: Successful reaction of an alkylamine and an alkylboronic ester. a) Reaction temperature of 80 °C, b) Reaction time of 16 h.

A powerful aspect of the Chan-Evans-Lam reaction of arylboronic esters is the ability to couple different heteroatoms such as oxygen and sulfur. To our knowledge, previous examples of ether formation from 1° alkylboronic esters and phenols has been limited to a report by Kuninobu and co-workers (section 2.1).[155] Within this report the reaction of phenol and thiophenol successfully formed ether **384** and thioether **391** in low yield (Scheme 121). The reaction of phenol with 2° boronic ester **52** is complementary to the report by Kuninobu and co-workers.[155] Furthermore, to our knowledge we report the first example of a Cu-mediated coupling of sulfur nucleophiles to an alkylboronic ester. The results suggest a preference of S vs N coupling and N vs O coupling. However, the efficiency of C-S coupling requires further optimisation for unactivated thiophenols (**391** and **392**).



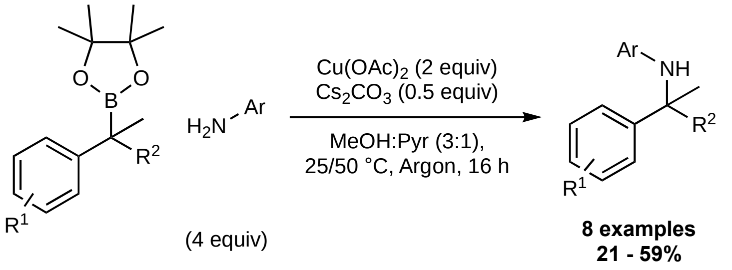
Scheme 121: Reaction of *O*- and *S*-based nucleophiles with boronic ester **52**. Yields reported are of isolated material unless otherwise stated. a) Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard; reactions conducted on a 0.05 mmol scale of **52**.

Additionally, we report several C-C bond formed acylation products analogous to **387**. To our knowledge, acylation products such as these have not been observed as products from Chan-Evans-Lam reactions of alkyl or aryl boronic esters previously. These compounds demonstrate an exciting new avenue of coupling reaction to explore.



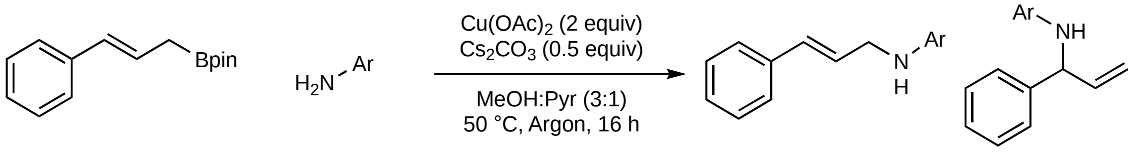
Scheme 122: C-C bond formation from reaction of **52** with aminophenol.

Through this work, 3° boronic esters and allyl boronic esters have been shown as viable coupling partners which is, to our knowledge, the first reported examples of their use in a Chan-Evans-Lam reaction. Although in its infancy, the small scope of 3° boronic esters and anilines gives great potential as a synthetic route to 3° amines that are otherwise difficult to form. Issues due to the increased propensity for protodeboronation and oxidation compared with 2° boronic esters was observed as a current limitation.



Scheme 123: Overview of 3° alkyl boronic ester amination with substituted anilines.

Although allyl boronic esters successfully formed the desired products, unsymmetrical alkene **301** lead to two different regioisomers.



301^{FMD}

Ar = 4-MeOC_6H_4
(4 equiv)

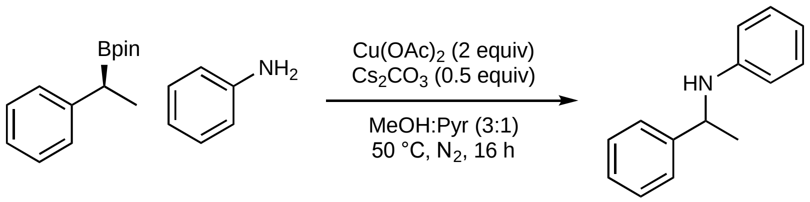
382
33%

383
30%

1:1 ratio of crude

Scheme 124: Amination of unsymmetrical boronic ester **301**.

Future work would look at the development of conditions for the formation of the noteworthy products above. Previously, reports have improved yields of arylboronic ester amination with the use of additives, ligands, and pendant coordinating groups (section 1.3.3). Products such as **342** and **151B** require reaction conditions to promote the consumption of boronic ester **52**. Whereas, products of 3° boronic esters would benefit from an increase in reaction control reducing side product formation. Coordinating groups stabilising allyl copper intermediates may alter the preference of one regioisomer over the other. Ligands observed with non-negative effects such as **317** would be a useful starting point (Table 29). Also, an investigation of the effects of different bases on the reaction of nucleophiles such as morpholine, phenol and thiophenol which have different nucleophilicities (and pKa values) should be undertaken.



(*S*)-52
97:3 er

(4 equiv)

303
73%
50:50 er

Scheme 125: Amination of enantioenriched boronic ester **(*S*)-52**.

Although the retention of stereochemistry under current conditions was unsuccessful, the stereoselective amination is of interest as a powerful synthetic method. Preliminary mechanistic results suggest the formation of a radical and account for the loss of stereochemistry. Future work would focus on the use of a chiral ligands to induce stereoselectivity to the reaction.

3 Oxidation of Alkylboronic Esters to Give Ketones

Oxidation reactions span a vast range of purposes such as the introduction of functional groups into pharmaceutical and agrochemical intermediates and, the conversion of petrochemical feedstocks to industrial chemicals. Although many methods are available, including catalytic and non-catalytic oxidations, and aerobic and anaerobic oxidations, very few methods provide selective oxidation of complex molecules that contain a diverse range of functional groups.

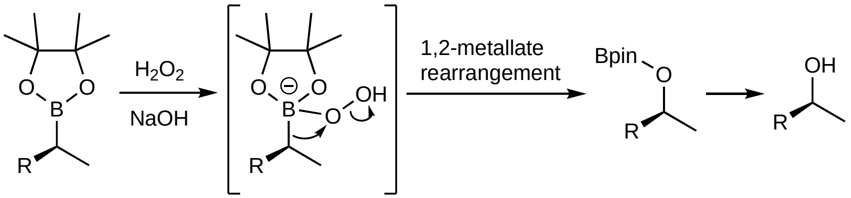
To overcome a lack of functional group tolerance, the development of new catalytic aerobic conditions is paramount. These conditions would complement established oxidation methods such as the Wacker process and the oxidation of 1°, 2° and benzylic alcohols to the corresponding aldehyde or ketone. Molecular oxygen is an ideal atom economical feedstock for the oxidation of hydrocarbons, alcohols, amines and others. However, many methods require pure O_2 which is not ideal especially in lab environments.

The oxidation of C-B bonds to the corresponding alcohol is a commonly used transformation. However, the oxidation of C-B bonds directly to the corresponding carbonyl is less widely utilised. A mild and functional group tolerant method would provide a complementary process to commonly employed methods.

3.1 *Accessing Carbonyls through C-B Bond Oxidation*

3.1.1 Background

Brown and co-workers first introduced conditions for the oxidation of boronic esters to the corresponding alcohol in 1961 (Scheme 126).[3,181] This simple stoichiometric transformation has since become the most common functionalisation of boronic esters. Additionally, Brown's conditions were proven to perform stereoselective oxidations of enantiomerically enriched boronic esters with retention of stereochemical information. Although other conditions have been documented, the method using a basic peroxide solution has been most widely adopted. General oxidation conditions proceed with addition of a peroxide anion into the empty p-orbital of the boronic ester (**419**) forming boron 'ate' complex **420**. A stereospecific 1,2-metallate rearrangement occurs, providing a B-O bond (**421**) that is hydrolysed to give the corresponding alcohol **422**.



419 **420** **421** **422**

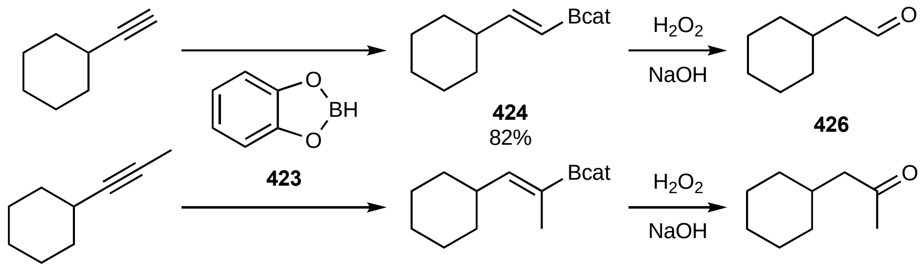
Scheme 126: Proposed mechanism of C-B bond oxidation.[3,179]

Although the oxidation of a C-B bond to an alcohol is so widely utilised, there are very limited examples of the oxidation of C-B bonds to the corresponding carbonyl.[3,179] Often in order to access higher oxidation states a second oxidation step is required from the alcohol.[182] The extra step and current alcohol oxidation methods often lower atom economy and reduce functional group tolerance.[3,179] Direct access to carbonyls from C-B bonds in one step often requires the oxidation of either an alkenyl- or α-heteroatom substituted alkylboron reagent. However, these reactants are prone to protodeboronation and are often non-trivial to prepare.

Early transition metal catalysis offers an opportunity to provide a one-step oxidation method of C-B bonds to the corresponding carbonyl. To our knowledge, current metal mediated processes are limited to the use of unfavourable chromium-based reagents.[179] This method would complement other chemoselective oxidation methods, including the oxidation of alcohol and the Wacker oxidation.

3.1.2 Alkenyl or α-Heteroatom Substituted Organoboron Oxidation

Alkyne hydroboration is a common method for the formation of alkenylboronic esters. Brown and co-workers reported conditions for the mono-hydroboration of alkynes with catecholborane (Scheme 127, **423**).[183] Terminal and internal alkynes were hydroborated successfully, with boron adding preferentially to the least hindered site (**424** and **425**). Subjecting the borylation products to standard hydrogen peroxide oxidation conditions gives the aldehyde (**426**) or ketone (**427**).

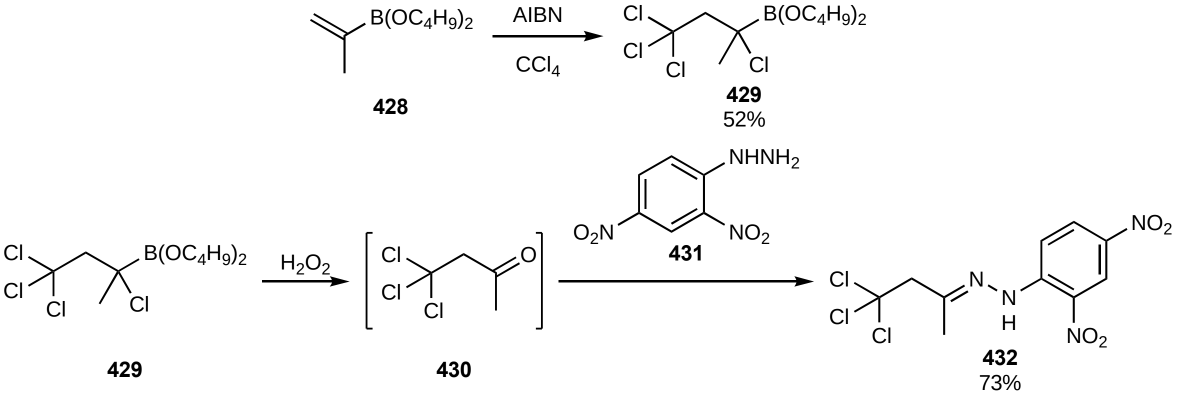


423
424 82%
426
425 86%
427 98%

Scheme 127: Oxidation of alkenyl catechol borane and tautomeristion.[183]

Utilising alkenylboronic esters, Matteson developed conditions for the proposed radical reaction of carbontetrachloride, azobisisobutyronitrile (AIBN) and unsaturated boronate **428**

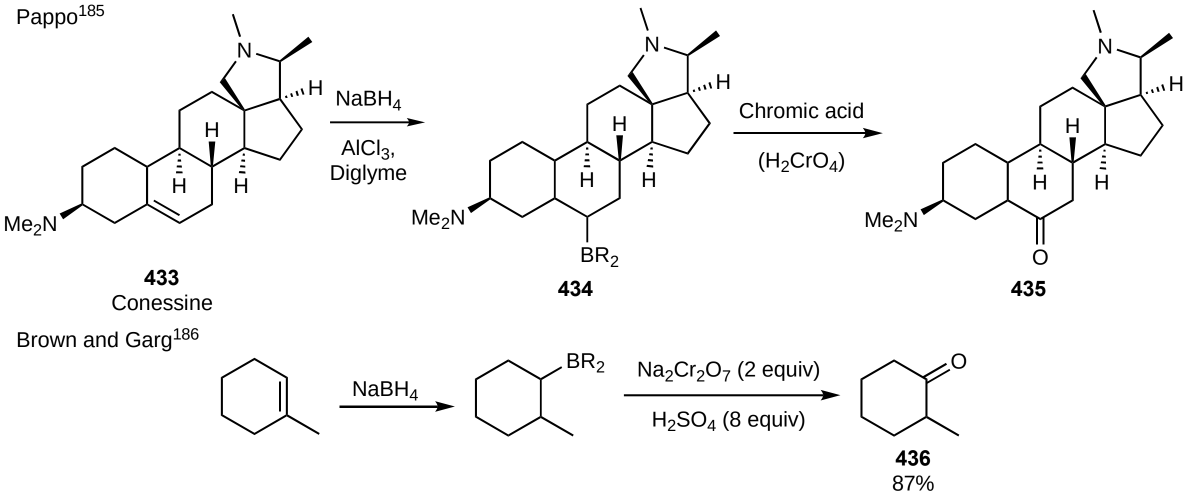
(Scheme 128).[184,185] The chlorinated product formed (**429**) was subject to standard oxidation conditions in the presence of 2,4-dinitrophenylhydrazine (**431**). The formation of the hydrazine product (**432**) indicates the formation of an aldehyde intermediate (**430**). Notably, Matteson reports the difficulties of handling and purification of α-haloalkylboronic esters. They are commonly susceptible to hydrolysis in mild bases and polymerisation upon storage.



Scheme 128: Oxidation of α-haloalkaneboronic esters and halogen elimination.[184,185]

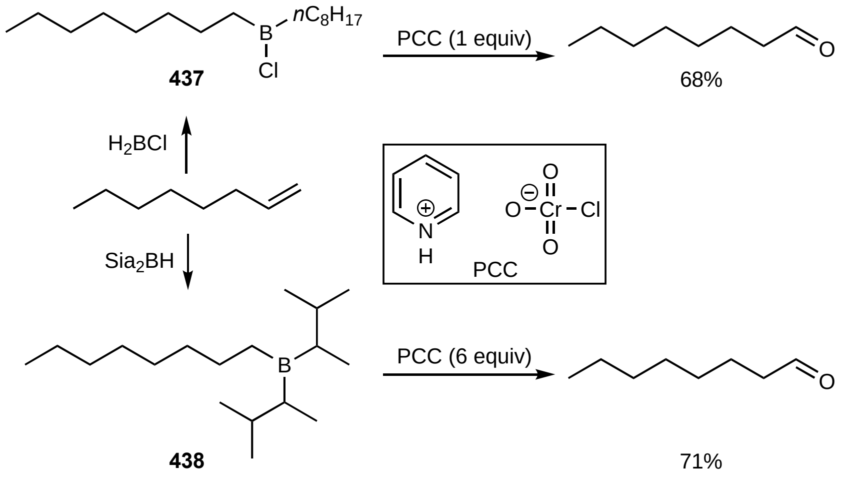
3.1.3 Chromium-mediated C-B Bond Oxidation

Whilst synthesising 18-oxygenated progesterones in 1958, Raphael Pappo reported the first example of a chromium mediated oxidation of an alkylboron species (Scheme 129).[186] Pappo utilised Brown’s hydroboration on Conessine **433**, a naturally occurring steroid, to provide intermediate borane **434**. Subjecting this intermediate to chromic acid gave the ketone product **435**. Brown and Garg further investigated Pappo’s conditions, and suggested oxidation occurred through a two-step process via the alcohol (Scheme 129).[187] Subjecting organoboronates to stoichiometric quantities of aqueous chromic acid gave both the corresponding alcohol and ketone. Addition of excess chromic acid led to complete conversion to the ketone product such as **436**. Due to aldehydes susceptibility to strongly acidic or basic conditions, oxidation of 1° boron compounds was not attempted.



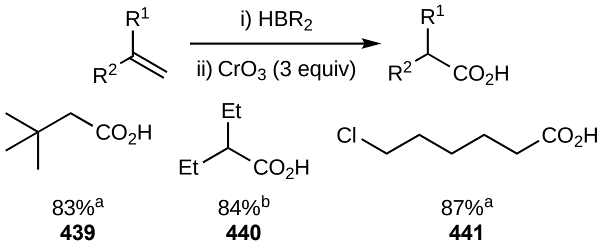
Scheme 129: Hydroboration and oxidation of Conessine[186] and alkenes. Yields measured by GC.[187]

Subsequently, Brown and co-workers endeavoured to find suitable conditions for the formation of aldehydes from organoboron reagents.[188] Pyridinium chlorochromate (PCC) was shown to be a suitable oxidant for 1° alcohols to aldehydes (Scheme 130). Several 1° selective hydroboration methods producing various types of organoboron reagents e.g. trialkylboranes, alkyldisiamylboranes and, dialkylchloroboranes were subject to successful PCC oxidation. Minor impurities from ketone formation were observed if 2° organoboron reagents were present. Dialkylchloroboranes (**437**), and alkyldisiamylboranes (**438**) gave the greatest selectivity. However, due to impurities from borylation, alkyldisiamylboranes required 6 equivalents of PCC to form 1 equivalent of aldehyde. More recently Parish and co-workers have reported pyridinium fluorochromate (PFC) as a mild and selective oxidant.[189]



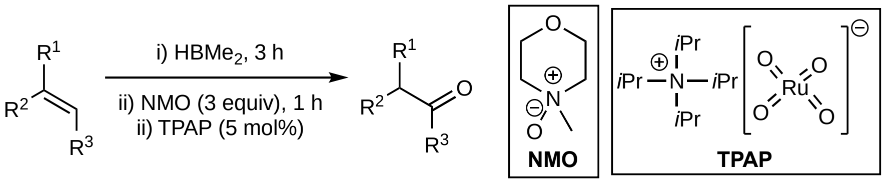
Scheme 130: PCC oxidisation of organoboron reagents.[189]

Brown and co-workers extended the Cr-mediated oxidation to the formation of carboxylic acids from 1° alkylboron reagents (Scheme 131).[190] Chromium based oxidants were tested and chromium trioxide chosen as the most active oxidant. Brown suggested a three-step process, including initial formation of the corresponding alcohol, and the subsequent oxidation to the aldehyde and carboxylic acid. Each consecutive oxidation required one equivalent of chromium trioxide, and reducing the quantity gave a mixture of all three potential products. The reaction had limited scope, including alkyl **439** and **440** and, halide **441** substituents.



Scheme 131: Hydroboration and oxidation to give carboxylic acids. a) H_2BCl b) BH_3.[190]

Although the previous examples identify the formation of alcohol intermediates, the reactions proceed as a one-pot process.[191] Complementary to this, Yates reported a two-step procedure, using tetrapropylammonium perruthenate (TPAP) and *N*-methylmopholine-*N*-oxide (NMO) (Scheme 132). The initial step of the reaction is addition of NMO, known to oxidise boranes to the corresponding alcohol. TPAP is then added to the reaction to further oxidise the alkyl borane or alcohol. Notably, alcohol formation was observed by TLC.



Scheme 132: Hydroboration and two step oxidation of alkenes using **TPAP** and **NMO**.[191]

3.2 *Complementary Oxidation Methods*

3.2.1 1°, 2° and Benzylic Alcohol Oxidation

The oxidation of 1°, 2° and benzylic alcohols are commonly used transformations and play a vital role in industrial processes.[192] There have been a number of non-catalytic and catalytic methods developed such as small molecule-based reagents (e.g. Dess-Martin periodiane and Swern oxidations) and expensive transition metal catalysts such as Pd, Ru, Rh and Ir. Currently, catalytic and small molecule-based methods often produce undesirable by-products, and catalytic systems require stoichiometric quantities of oxidants. Despite considerable advances in oxidation agents and catalysts, the utilisation of aerobic molecular oxygen as a terminal oxidant remains a challenge. Where molecular oxygen has been successful with Ru and Pd catalysts, they are often inhibited by heteroatom functionalities.[177] Transition metal catalysts are also responsible for oxidising other functional groups such as the Pd-catalysed oxidation of alkenes. The combination of an abundant metal species and molecular oxygen would provide an atom economical approach to alcohol oxidations.

More recent advances in transition metal catalysed oxidations of alcohols has identified first row metals such as copper as a potential abundant and active metal source. Copper catalysis has been reported to enable chemoselective oxidation of benzylic, allylic and aliphatic 1° alcohols to the corresponding aldehydes with a TEMPO co-catalyst.[177,193] Notably, atmospheric oxygen was used as the oxidant negating the need for high pressures of pure oxygen. Stahl and co-workers have proposed a catalytic cycle (Figure 22) for the oxidation of 1° alcohols.[193] Nitrogen chelated Cu(I) complex **442** reacts with O_2 to give a Cu(II) superoxide species **443**. This reacts with a second equivalent of Cu(I) **442** generating a peroxo bridge binuclear Cu(II) species **444**. Although the structure of the Cu_2O_2 species (**444**) is not identified, recent reports elucidate several possible structures. (For examples see ref[194,195]). The binuclear species **444** is suggested to oxidise TEMPO-H to TEMPO via hydrogen atom transfer forming Cu peroxide species **445** and Cu(I) species **442**.[193] When TEMPOH is not available, e.g. at the start of the reaction, it is proposed Cu_2O_2 **444** reacts with the alcohol substrate **447** producing copper complexes **445** and **448**. However, this process is far slower than in the presence of TEMPO. Reaction of the Cu peroxide species **445** with water produces H_2O_2 and Cu-OH species **446**. Subsequent reaction of the Cu-OH species with 1° alcohol **447** produces intermediate **448** that undergoes TEMPO mediated hydrogen abstraction providing aldehyde **449** and Cu(I) species **442**.

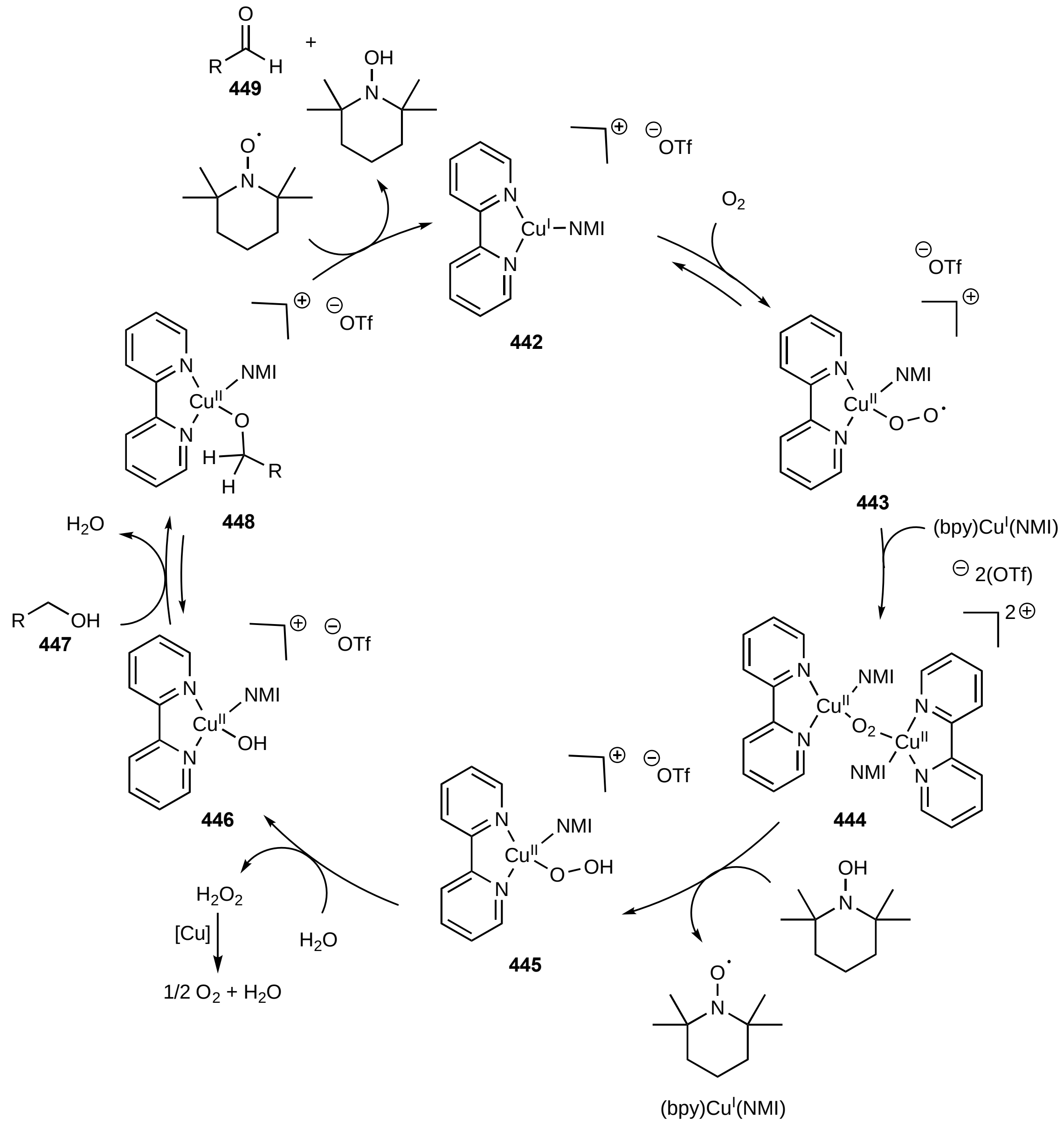
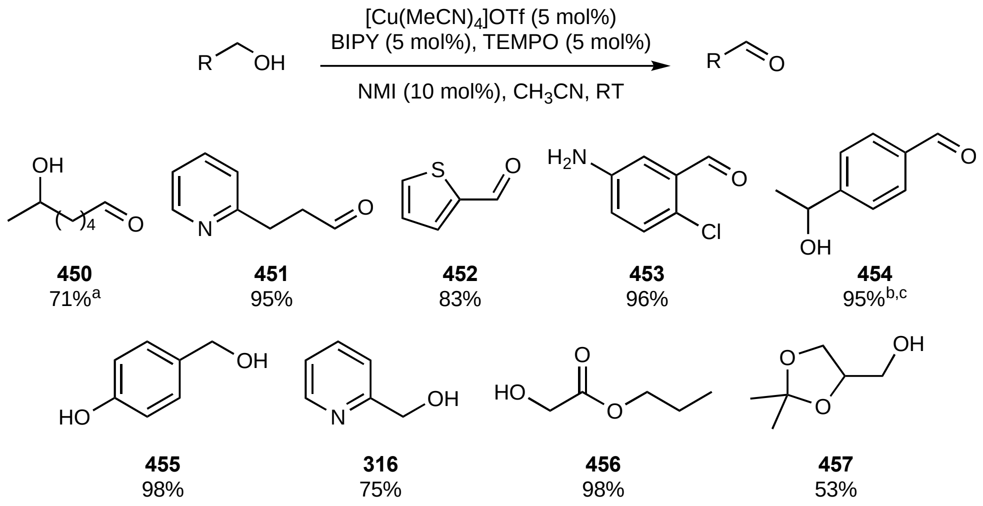


Figure 22: Proposed catalytic cycle for Cu(bpy)/TEMPO catalysed alcohol oxidation.[193]

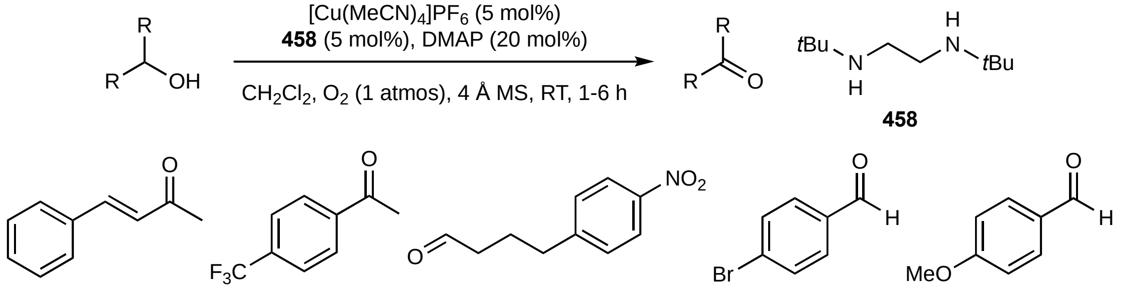
Stahl and co-workers also demonstrated the scope of 1° alcohol oxidations under their conditions (Scheme 133).[177,193] A broad range of heteroatom functionalities are tolerated including oxygen (**450**), nitrogen (**451**), sulphur (**452**) and halides (**453**). However, the presence of phenol (**455**) and neighbouring chelating heteroatoms such as pyridyl (**316**), esters (**456**) and ethers (**457**) inhibited oxidation. This inhibition is not commonly observed for small molecule oxidants. Over oxidation was observed for homobenzylic alcohols forming α-ketoaldehydes, and a complex mixture of products was formed using substrates containing a terminal alkyne. Interestingly, chemoselective oxidation of the 1° alcohol was observed when in the presence of 2° alcohols, though minor alterations to the conditions were needed to avoid the formation of mixtures of products (**454**).



Scheme 133: Scope of reaction for Cu/TEMPO 1° alcohol oxidation. a) CuBr, b) $CuBr_2$, c) dbu.[177,193]

Subsequent publications from the Stahl group address several limitations of the Cu(bpy)/TEMPO/NMI catalyst system including, slow oxidation of unactivated aliphatic alcohols and inability to oxidise 2° alcohols.[196] The use of less sterically hindered *N*-oxide co-catalysts such as 9-azabicyclo[3.3.1]nonane-*N*-oxyl (ABNO) overcame these issues. The Cu/TEMPO catalyst system displays distinctly different rates for classes of alcohols however, the Cu/ABNO system exhibits nearly identical rates across all classes.

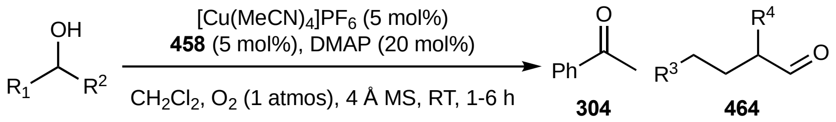
In an attempt to mimic tyrosinase, a Cu-based enzyme able to activate O_2, conditions were developed for the aerobic oxidation of alcohols without an *N*-oxide co-catalyst.[197] Oxidation of non-activated alkyl-alcohols were performed using a Cu-based catalyst, ligated with a diamine **458**, under an atmosphere of O_2 (Scheme 134). Functional groups tolerated included alkenes (**459**), nitro (**461**), halides (**462**) and protected amines. Limitations were observed when increasing the steric bulk of the substrate. However, the system is less sensitive than TEMPO based systems. 1° and 2° alcohol scaffolds (**304** and **464**) were subject to a competition experiment. When increasing the steric bulk of **464** from H to Et, the TEMPO based system drastically changes the ratio of oxidised products (Table 34, entries 1 and 2). In contrast the **458**/DMAP system only slightly alters the ratio (Table 34, entries 3 and 4). As the TEMPO system preferentially oxidises 1° alcohols the increased sterics force the opposite reactivity. A later report suggested that the reaction proceeded through initial oxidation of **458** to generate an aminoxyl radical, which affects oxidation in similar manner to TEMPO (Figure 22).[198]



458

459	**460**	**461**	**462**	**463**
91%	87%	78%	97%	95%

Scheme 134: Scope of reaction for Cu/**458** oxidation of 1° and 2° alcohols.197



Entry	Copper System	R^4	(**304**:**464**)	
1	[Cu] TEMPO	H	1.0	1.9
2		Et	8.0	1.0
3	[Cu] **458**/DMAP	H	2.6	1.0
4		Et	3.8	1.0

Table 34: Effect of sterics on the ratio of products observed from Cu/TEMPO and Cu/**458** oxidations.197

3.2.2 Tsuji-Wacker Alkene Oxidation

Chemical feedstocks from the petrochemical industry provide attractive starting materials for transformations into useful synthetic building blocks. The Wacker oxidation is a well established method for the installation of carbonyls from abundant alkene feedstocks.

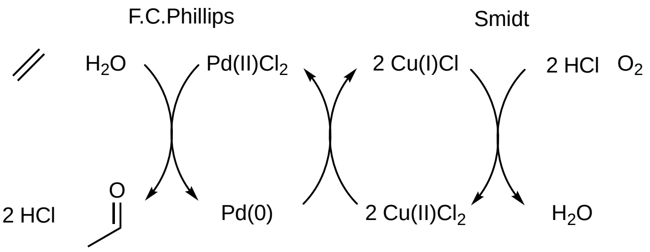
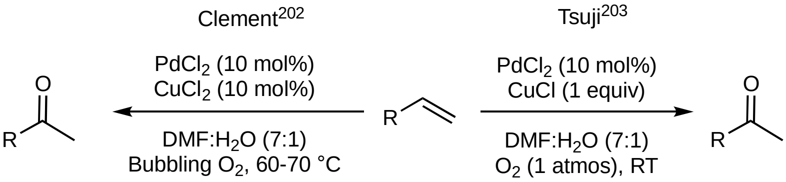


Figure 23: Combination of palladium catalysed alkene oxidation, and copper catalyst turnover.

In 1894 Francis C Phillips reported his palladium mediated conditions for the oxidation of ethylene to acetaldehyde (Figure 23).199–201 Stoichiometric quantities of $PdCl_2$ in an aqueous acidic solution mediated the reaction. The commercialisation of the process by Wacker Chemie in the 1960's was made possible by the inclusion of a copper mediated oxidation of Pd(0) to Pd(II) (Figure 23). Smidt and co-workers developed a catalytic palladium reaction including stoichiometric quantities of $CuCl_2$ with the main purpose of catalyst turnover.202 The Cu(I) species produced can then be oxidised by oxygen or air to reform the active Cu(II) oxidant species.

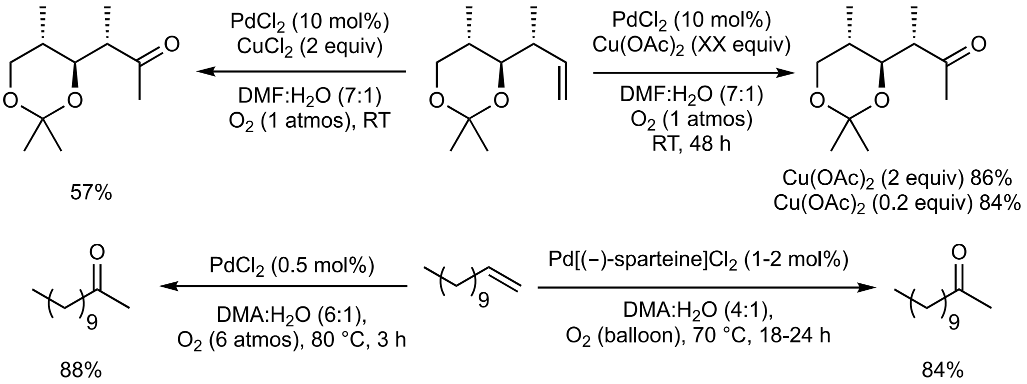
The requirement of water within the reaction gives basis for its use as an attractive reaction solvent. However, organic molecules, such as high molecular weight olefins, have varied solubility in water such that an organic co-solvent is required.[199] The Clement modification incorporates dimethylformamide (DMF) as a co-solvent, paving the way for the development of the commonly applied Tsuji-Wacker oxidation conditions (Scheme 135).[203,204] These conditions primarily oxidise α-olefins to their corresponding carbonyl compounds, preferentially forming the ketone product. The extensive use of these conditions is due to its efficiency and functional group tolerance. This includes functional groups based on oxygen (e.g. aldehydes, ketones, carboxylic acids, esters, and alcohols), nitrogen (e.g. amides, carbamates or similarly protected amines, and sulphonamides) and halogens. Functional group incompatibility arises when employing increased nucleophilic characters such as unprotected alkylamines.[199]



Scheme 135: Tsuji-Wacker oxidation conditions.

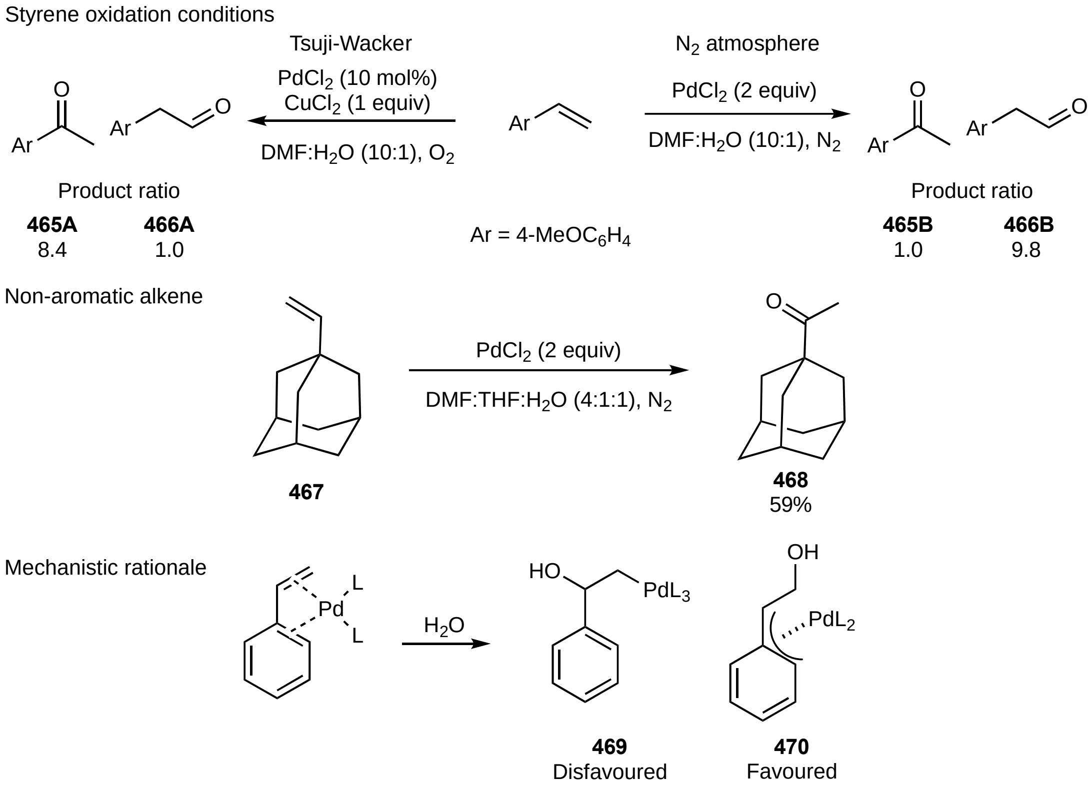
Although highly useful, the Tsuji-Wacker oxidation conditions suffer from several limitations, such as release of HCl, reduction in regioselectivity, and the use of stoichiometric quantities of copper. To overcome these issues, modifications to conditions have been made such as solvent, additive, co-oxidant, ligand and metal sources to improve reactivity and sustainability.[199–201] Recent developments within this area have focussed on new palladium catalysts that allow catalyst turnover without the need for a copper co-catalyst. These often include the extension of scope to internal alkenes and increased regioselectivity. Ligands play a big part in both regioselectivity and reactivity of the catalytic system.

The release of acidic HCl during the catalytic cycle can potentially limit functional group tolerance. $CuCl_2$ is an active participator in the formation of HCl during the catalytic cycle. Replacing $CuCl_2$ with $Cu(OAc)_2$ can considerably improve the yield for acid labile protecting groups such as acetal protections. The modification also allows reduced quantities of copper to be required within the reaction.[205] More recently, non-copper based oxidants have been explored including CrO_3, $KBrO_3$, iron(III) sulphate, Des-Martin periodinane etc.[206–209] Notably, molecular oxygen has successfully been used as the sole oxidant for catalyst regeneration. Under higher pressures of oxygen, similar conditions to the Tsuji-Wacker oxidation are successful with good catalyst turnover (Scheme 136). The inclusion of a (−)-sparteine ligated palladium complex improved catalyst re-oxidation requiring only a balloon of oxygen (Scheme 136). It is suggested that this occurs through formation of a Pd(II)-peroxo species from the oxidative addition of molecular oxygen to Pd(0). This undergoes protonolysis to regenerate the Pd(II) catalyst and hydrogen peroxide.[210,211]



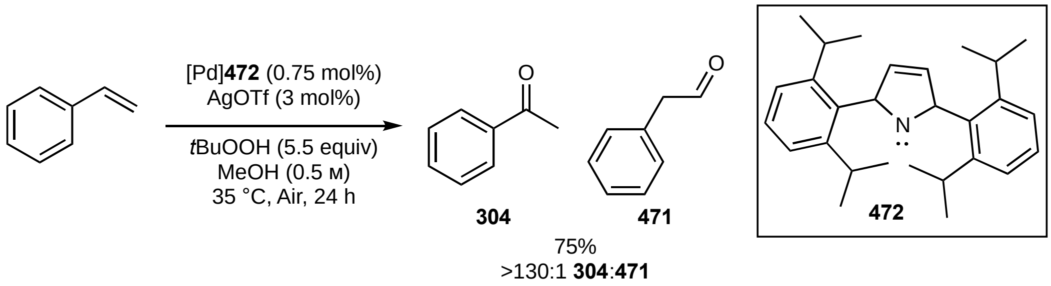
Scheme 136: Modifications to the Tsuji-Wacker oxidation, reducing copper loading and decreasing O_2 pressure.

Poor regioselectivity, to give formation of the unwanted aldehyde is a common by-product of the Wacker oxidation of terminal alkenes. Styrenes are a common substrate that suffer from poor regioselectivity (Scheme 137).[212–214] Previous reports show poor conversion or undesirable mixtures of ketone (**465**) and aldehyde (**466**). Studies undertaken have optimised conditions for the aldehyde formation and given mechanistic rationale for its formation. Under standard Tsuji-Wacker oxidation conditions, the ketone product (**465A**) is the major isomer. However, there is a notable quantity of aldehyde (**466A**) formed. Removing the external oxidant (O_2) from the system greatly increases the quantity of aldehyde formed (**466B**). The significance of the aromatic system was identified when non-aromatic analogue **467** produced solely ketone **468**. A mechanistic rational was proposed suggesting the formation of a more stable η^3-intermediate after attack of water (**470**). It was noted these conditions were dependant on the counter ion present on the starting palladium species. If a different palladium source was used selectivity decreased.[212]



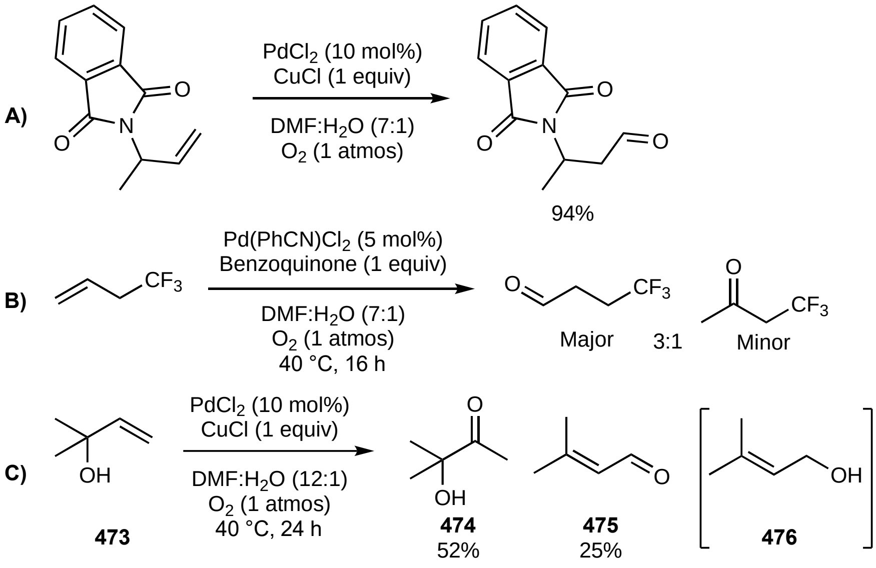
Scheme 137: Aromatic and non-aromatic alkene oxidation under O_2 and N_2 and mechanistic rationale for preferential ketone and aldehyde formation.

Many palladium complexes have been tested for improvements to selectivity and reactivity. Ligands have been shown to improve both of these areas. NHC (**472**) ligated pallidum is a prime example of a regioselective catalytic system for the oxidation of styrene's to acetophenones (Scheme 138, **304**). Its inclusion significantly improves the ratio of ketone (**304**) to aldehyde (**471**) produced. Internal olefins were also oxidised successfully, and tert-butyl hydrogen peroxide was used as the terminal oxidant.[215]



Scheme 138: Oxidation of styrene using a NHC ligated palladium catalyst.

Regioselectivity can also be altered in the presence of nearby heteroatom-based functional groups. Substrate controlled regioselectivity is most commonly observed when the reactant possesses an allylic or homoallylic heteroatom. The alterations in regioselectivity can be rationalised by directing groups mediating the position of oxidation. Groups that show a directing effect include allyl alcohols, esters, ether, and amines, whereby coordination of palladium to the heteroatom can direct the addition of the nucleophile (Scheme 139A).[216–218] Also, inductive effects, such as strongly electron withdrawing trifluoromethyl groups, can alter regioselectivity (Scheme 139B).[219] Or palladium mediated isomerisation of the starting substrate e.g. allylic alcohols (Scheme 139C, **473**).[220] The 1° alcohol moiety of the corresponding 1,3-isomerisation product **476** is subsequently oxidised under the current palladium mediated conditions to the aldehyde **475**. This method has been explored more recently by Yang and co-workers.[221]



Scheme 139: Heteroatom-based directing groups to control site of oxidation.

Conventional Tsuji-Wacker oxidation reactions rely on the strong interaction of the palladium(II) salts with a terminal alkene (**477**). In a simplified mechanistic cycle, this interaction results in a considerably more electrophilic alkene species (**478**) which is attacked by an oxygen nucleophile (usually H_2O) (Figure 24). The addition of the nucleophile generally occurs at the most substituted carbon (Markovnikov selectivity). The resultant σ-alkylpalladium species **479** undergoes ß-hydride elimination to give the enol product **480**, which tautomerises to give the ketone product **481**. The Pd(0) species then undergoes oxidation to Pd(II) often mediated by $CuCl_2$.[199–201]

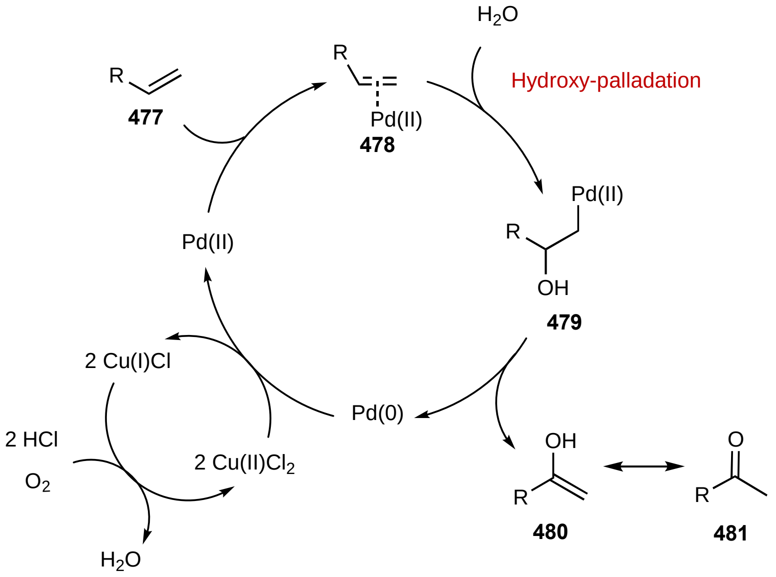
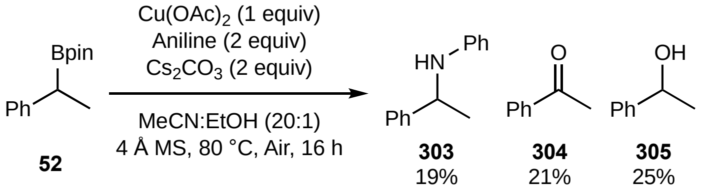


Figure 24: Simplified reaction mechanism for the Tsuji-Wacker oxidation of alkenes.

3.3 *Aims*

To our knowledge, the direct oxidation of C-B bonds directly to the corresponding carbonyls are limited to the use of unfavourable chromium-based reagents. We are interested in developing an alternative to this process, based on the initial observation of ketone formation during our investigation into the Chan-Evans-Lam reaction (section 2.3.2.1).



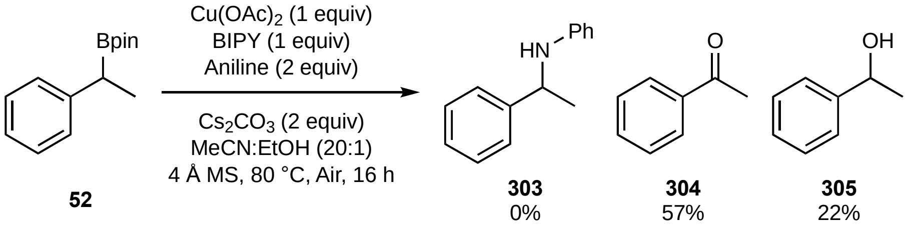
Scheme 140: Preliminary results from the optimisation of conditions for an alkyl Chan-Evans-Lam coupling.

Our aim is to optimise conditions for the oxidation reaction of boronic esters to the corresponding carbonyl. We will subsequently explore the scope of the reaction to understand if the conditions are chemoselective towards the oxidation of the C-B bond. We are also interested in generating data to help understand the mechanism of the reaction, as this will help our future development of the Chan-Evans-Lam reaction and other oxidative processes.

3.4 *Results and Discussion: Oxidation of Alkylboronic Esters*

3.4.1 Method Development for the Oxidation of Boronic Ester 52

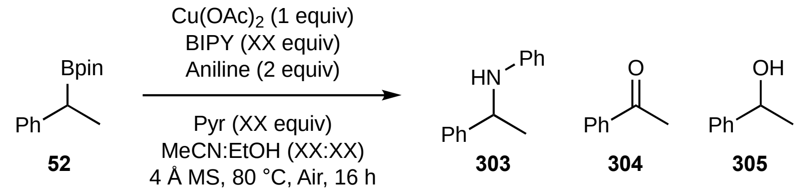
During the optimisation of conditions for the copper-mediated amination of benzylic boronic ester **52** (section 2.3.2.1) several side products were identified. This included ketone **304**, which was formed as the major product under certain conditions (Scheme 141). We decided to explore conditions for the formation of ketone **304** for two reasons. First, to better understand how the ketone side-product is formed, and how this can be avoided during amination. Second, as there are few reported direct methods to convert C-B bonds into carbonyls, we have an opportunity to develop a potentially useful methodology.



Scheme 141: Conditions identified during amination optimisation for the formation of ketone **304.**

The following trends were observed during the initial investigation of conditions from amination (section 2.3.2.1) and are summarised in below.

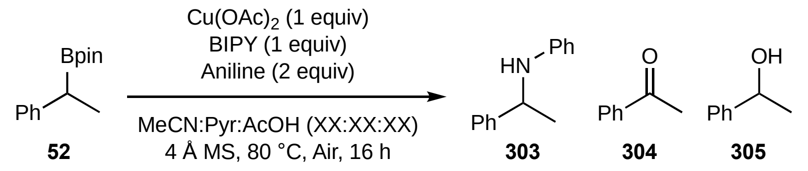
1) Reactions performed under an inert atmosphere appear to prevent the formation of ketone **304**, suggesting oxygen from the air is required for its formation.
2) The presence of inorganic bases reduced the formation of ketone **304**, but promoted formation of amine **303** and alcohol **305**.
3) Dinitrogen ligands were found to be beneficial, with the use of BIPY leading to an increased yield of ketone **304** (Scheme 141).
4) The addition of pyridine reduced the formation of alcohol **305** without lowering the yield of ketone **304** (Table 35, Entry 1).
5) MeCN was the best solvent for formation of **304**. The use of alcohol additives appears to promote transmetallation, but not the selectivity towards a specific product. For instance, in the absence of EtOH, the yield of ketone **304** decreased, but a greater amount of boronic ester **52** was returned (Table 35, entry 3).



Entry	MeCN:EtOH	Pyr (equiv)	BIPY (equiv)	Yield			
				52	**303**	**304**	**305**
1	20:1	2	-	0%	0%	54%	12%
2	20:1	70	1	0%	0%	64%	15%
3	1:0	70	1	25%	0%	45%	13%

Table 35: Effect of varying base, alcohol additive, and ligand on boronic ester oxidation. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.1 M.

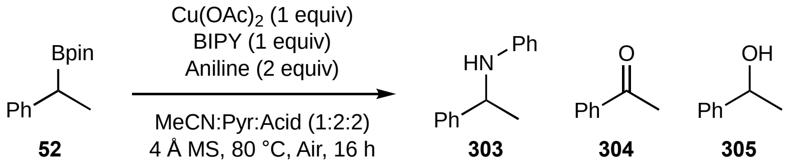
Due to the adverse effects of bases towards ketone formation, we explored whether the presence of an acid might be beneficial. Table 36 details how the addition of AcOH effects the yield of ketone **304**. The presence of AcOH decreased the yield of ketone **304** slightly. However, the yield of alcohol **305** significantly decreased. A solvent ratio of 1:2:2 MeCN:pyridine:AcOH appeared best for ketone **304** formation. In the absence of MeCN the yield of ketone **304** and alcohol **305** decreased (Table 36, entry 4). Presumably, an increase in protodeboronation accounts for the remaining mass balance.



Entry	MeCN	Pyr	AcOH	Yield			
				52	**303**	**304**	**305**
1	0.5	0.3	0.15	0%	0%	39%	<5%
2	0.2	0.25	0.15	0%	0%	40%	<5%
3	0.1	0.2	0.2	0%	0%	47%	<5%
4	0	0.3	0.2	0%	0%	33%	0%

Table 36: Effect of varying AcOH, MeCN and pyridine ratio on boronic ester oxidation. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**.

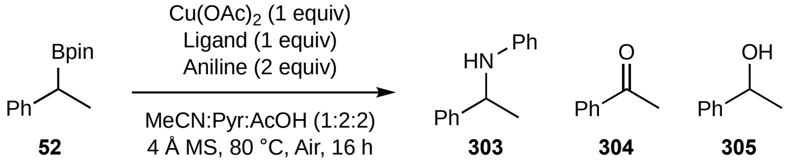
Next, a range of acids were screened (Table 37). Relatively weak acids such as imidazole, failed to hinder the formation of alcohol **305** (Table 37, Entry 2). Oxalic acid successfully prevented the formation of alcohol **305**, but let to a reduced yield of ketone **304** (Table 37, Entry 3). Benzoic acid gave similar results to AcOH, presumably due to their similar pKa and solubility. Phosphoric acid, prevented conversion of boronic ester **52** returning the starting material (Table 37, Entry 4).



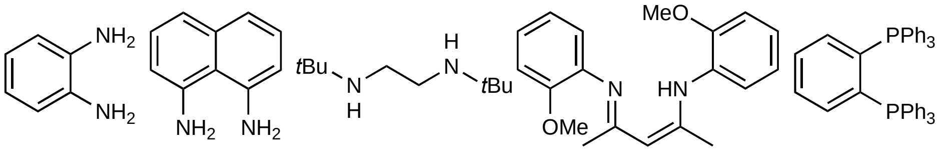
Entry	Acid	Yield			
		52	**303**	**304**	**305**
1	AcOH	0%	0%	47%	<5%
2	Imidazole	0%	0%	21%	49%
3	Oxalic acid	21%	0%	<5%	0%
5	Benzoic acid	0%	0%	40%	6%
4	Phosphoric acid	82%	0%	7%	<5%

Table 37: Effect of varying the acid on boronic ester oxidation. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**.

A ligand screen was performed using the new solvent conditions (Table 38). The use of diamine ligands generally led to the formation of ketone **304** in small amounts. However, the use of *N*,*N′*-di-*tert*-butylethylenediamine (**458**) and diketimine **1** as ligands gave good yields of ketone **304**, with the reaction using **458** giving a marginally higher yield. Additionally, little of alcohol **305** was formed in both cases. In all of the reactions, no C-N coupling from aniline or the diamine ligands was observed.



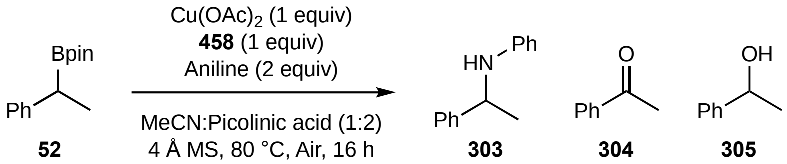
Entry	Ligand	Yield			
		52	**303**	**304**	**305**
1	BIPY	0%	0%	47%	<5%
2	**482**	0%	0%	<5%	0%
3	**483**	66%	0%	5%	6%
4	**458**	0%	0%	77%	8%
5	**1**	0%	0%	65%	0%
6	dppBz	0%	0%	52%	10%



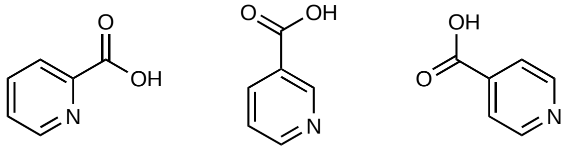
482 **483** **458** **1** **dppBz**

Table 38: Effect of varying the ligand on boronic ester oxidation. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**.

With the aim of simplifying the reaction conditions, picolinic acid was explored as a replacement for both pyridine and AcOH (Table 39). However, the use of *o*-, *m*- and *p*- picolinic acids significantly reduced the yield of ketone **304**, and in general, gave a high return of boronic ester **52**.



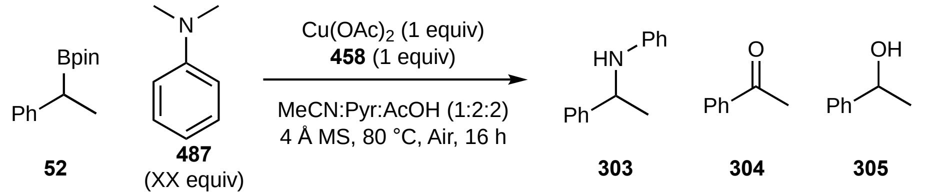
Entry	Picolinic acid	Yield			
		52	**303**	**304**	**305**
1	**484**	53%	0%	0%	0%
2	**485**	44%	0%	<5%	0%
3	**486**	8%	0%	6%	12%



484 **485** **486**

Table 39: Effect of picolinic acid as an additive on boronic ester oxidation. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**.

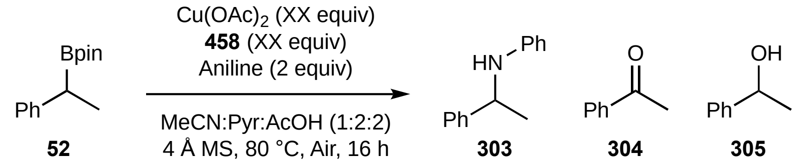
We assumed that the formation of ketone **304** did not require aniline, and so the removal or replacement of aniline was investigated (Table 40). When **458** was used as a ligand, the yield of ketone **304** decreased in reactions without aniline or the presence of dimethylaniline **487** (Table 40, Entry 1 and 2). This suggests that aniline is required in the formation of ketone **304** when using ligand **458**, though the role of aniline is not currently clear.



Entry	**487** (equiv)	Yield			
		52	**303**	**304**	**305**
1	-	0%	0%	33%	0%
2	2	82%	0%	27%	0%

Table 40: Effect of aniline on boronic ester oxidation. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**.

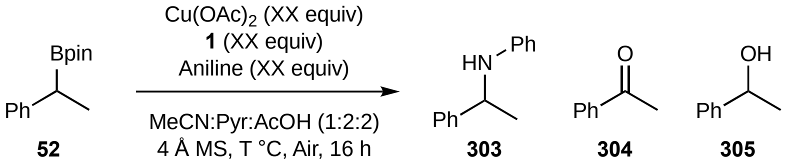
Previously, oxygen from the air has been used for the turnover of copper catalysts in Chan-Evans-Lam coupling reactions (section 1.3.3). During the investigation of conditions for amination, air was also shown to be required for ketone synthesis (Scheme 87). Therefore, the substoichiometric loadings of $Cu(OAc)_2$ were investigated under air (Table 41). Reducing the amount of $Cu(OAc)_2$ to 15 mol% gave ketone **304** in an excellent yield, suggesting oxygen is acting as a terminal oxidant (Table 41, entry 3). The amount of ligand could also be decreased to 15 mol% without decrease in the yield of ketone **304** (Table 41, entry 4).



Entry	$Cu(OAc)_2$ (equiv)	**458** (equiv)	Yield			
			52	**303**	**304**	**305**
1	0.5	1	0%	0%	67%	0%
2	0.25	1	0%	0%	69%	0%
3	0.1	1	0%	0%	59%	0%
4	15 mol%	15 mol%	0%	0%	65%	0%

Table 41: Effect of ligand **458** and $Cu(OAc)_2$ loading on boronic ester oxidation. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**.

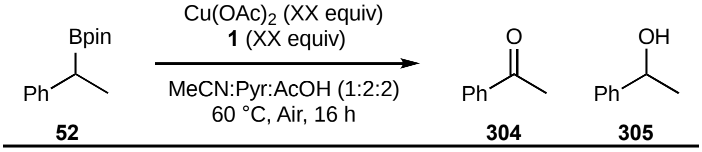
Although di-*tert*-butylethylenediamine-ligated $Cu(OAc)_2$ generates an effective catalyst, it does require aniline to provide higher yields. During the previous ligand screen diketimine (**1**) gave a moderately high yield (Table 38, entry 5) and was therefore investigated (Table 42). In the absence of aniline, the reaction using diketimine **1** gave ketone **304** in a high yield (Table 42, Entry 2). Lowering the reaction temperature had minimal effect on the yield of ketone **304** (Table 42, Entry 3 and 4). Pleasingly, using substoichiometric loadings of both Cu(OAc)$_2$ and diketimine **1** gave ketone **304** in an excellent yield (Table 42, entry 5).



Entry	Aniline (equiv)	Cu(OAc)$_2$ (equiv)	T (°C)	**1** (equiv)	Yield			
					52	**303**	**304**	**305**
1	2	1	80	1	0%	0%	64%	0%
2	-	1	80	1	0%	0%	70%	0%
3	2	1	60	1	0%	0%	68%	0%
4	-	1	60	1	0%	0%	65%	0%
5	-	15 mol%	60	15 mol%	0%	0%	74%	6%

Table 42: Effects of the loading of ligand **1**, Cu(OAc)$_2$, and aniline, and temperature on boronic ester oxidation. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**.

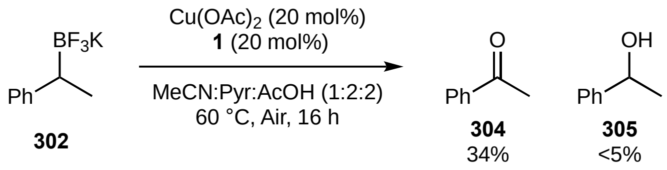
Next, molecular sieves were removed from the reaction conditions, which led to a slight increase in the yield of ketone **304** (Table 43, Entry 1). Finally, as a compromise between catalyst loading and yield, 20 mol% of Cu(OAc)$_2$ and ligand **1** was selected as the catalyst loading, as this gave a high yield of oxidation over a range of substrates.



Entry	Cu(OAc)$_2$ (mol%)	**1** (mol%)	Yield		
			52	**304**	**305**
1	15	15	0%	76%	10%
2	20	20	0%	96%	<5%

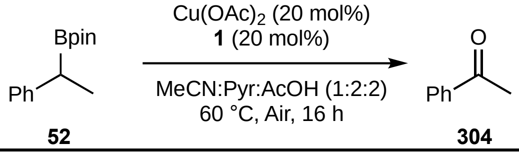
Table 43: Effect of the loading of ligand and Cu(OAc)$_2$ on boronic ester oxidation. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**.

To explore the oxidation of other organoboron reagents, the reaction of trifluoroborate **302** was investigated. Oxidation did occur, under the optimised conditions, although the reaction gave a considerably lower yield of ketone **304** compared with the reaction of boronic ester **52**. Presumably, hydrolysis of the trifluoroborate, followed by protodeboronation of the resulting boronic acid accounts for the reduced yield of **304**.



Scheme 142: Oxidation of trifluoroborate salt **302**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **302**.

The reaction scale was increased to 0.6 mmol, to allow the isolation of ketone **304**. Retaining the reaction concentration from the optimisation, ketone **304** was isolated in a significantly decreased yield over 16 h. However, the amount of alcohol **305** by-product remained consistent. It was assumed the remainder of the mass was lost as ethylbenzene due to protodeboronation. Increasing the reaction concentration led to a significantly improved yield of ketone **304** after 16 h.



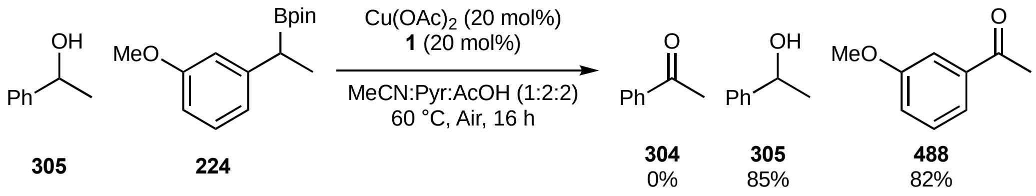
Entry	AcOH (mL)	Pyr (mL)	MeCN (mL)	Concentration (M)	**304**
1	2.4	2.4	1.2	0.1	51%
2	1.2	1.2	0.6	0.2	75%

Table 44: Effect of concentration on boronic ester oxidation. Reactions conducted on a 0.6 mmol scale of **52**.

3.4.2 Competition Experiments

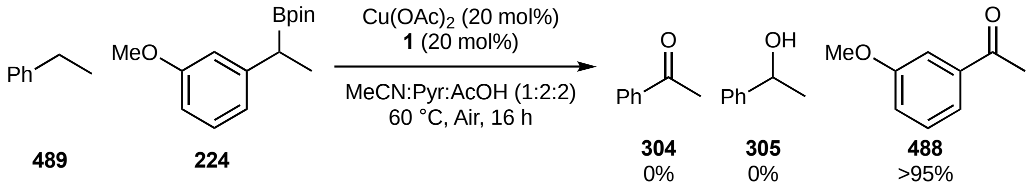
A series of competition experiments were performed to investigate the interconversion between possible reaction intermediates and ketone **304**. To do this, the by-products observed and potential intermediates were subjected to the reaction conditions in the presence of a benzylic boronic ester. The boronic ester was chosen so that the additive, acetophenone and ketone from boronic ester oxidation could be observed and quantified by ^{1}H-NMR analysis.

Chromium-mediated C-B bond oxidations have been reported to proceed by a sequential two step oxidation method via the corresponding alcohol (section 3.1.3).[187,188] We sought to determine whether alcohol **305** was a possible intermediate in our oxidation protocol (Scheme 143). Alcohol **305** was subjected to the reaction conditions in the presence of 2-methoxy substituted boronic ester **224**. No oxidation product is observed from alcohol **305** which was returned unreacted. Boronic ester **224** was converted to ketone **488** in a high yield, suggesting the oxidation process does not occur as a two-step process via the corresponding alcohol. Furthermore, subjecting alcohol **305** to the oxidation conditions in the absence of a boronic ester also returned alcohol **305** unreacted.



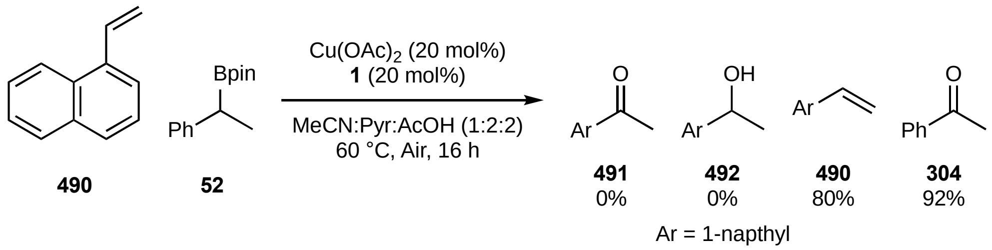
Scheme 143: Test to see if alcohol **305** reacts under the oxidation conditions. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **224**. Reaction concentration of 0.1 M.

Ethylbenzene (**489**) may be formed during the reaction through protodeboronation of boronic ester **224**. Therefore, the possibility of Cu-mediated C-H oxidation[222] of ethylbenzene was investigated (Scheme 144). Due to the volatility of ethylbenzene, any **489** present was lost during workup. However, products from the oxidation of ethylbenzene were not observed. Meanwhile, boronic ester **224** was oxidised in excellent yield, suggesting that the process does not occur through protodeboronation followed by C-H oxidation.



Scheme 144: Test to see if ethylbenzene **489** reacts under the oxidation conditions. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **224**. Reaction concentration of 0.1 M.

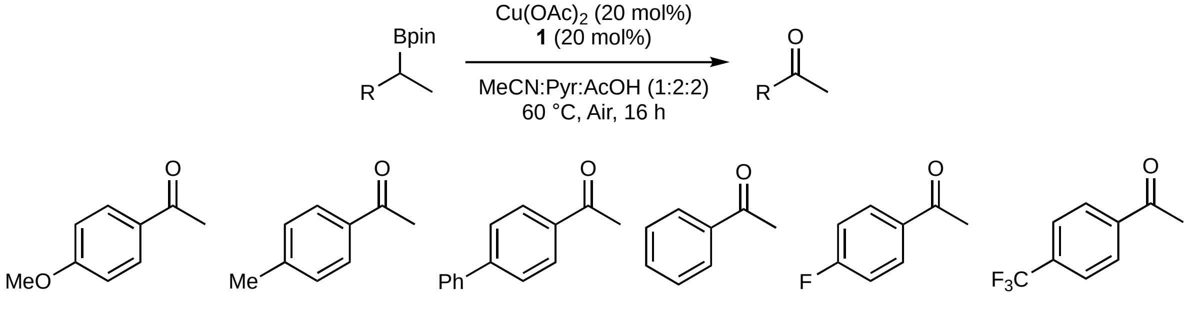
It is possible that an alkene may be formed under the reaction conditions through elimination of the boronic ester. If this occurred, Wacker oxidation (section 3.2.2)[204] could account for the formation of ketone products (Scheme 145). To investigate this possibility, alkene **490** was subjected to the oxidation conditions in the presence of boronic ester **52**. The oxidation products of alkene **490** were not observed and alkene **490** was returned in good yield. Boronic ester **52** was oxidised in excellent yield, suggesting a Wacker-type process is not occurring.



Scheme 145: Test to see if alkene **490** reacts under the oxidation conditions. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.1 M.

3.4.3 Scope of Reaction for the Oxidation of Alkylboronic Esters

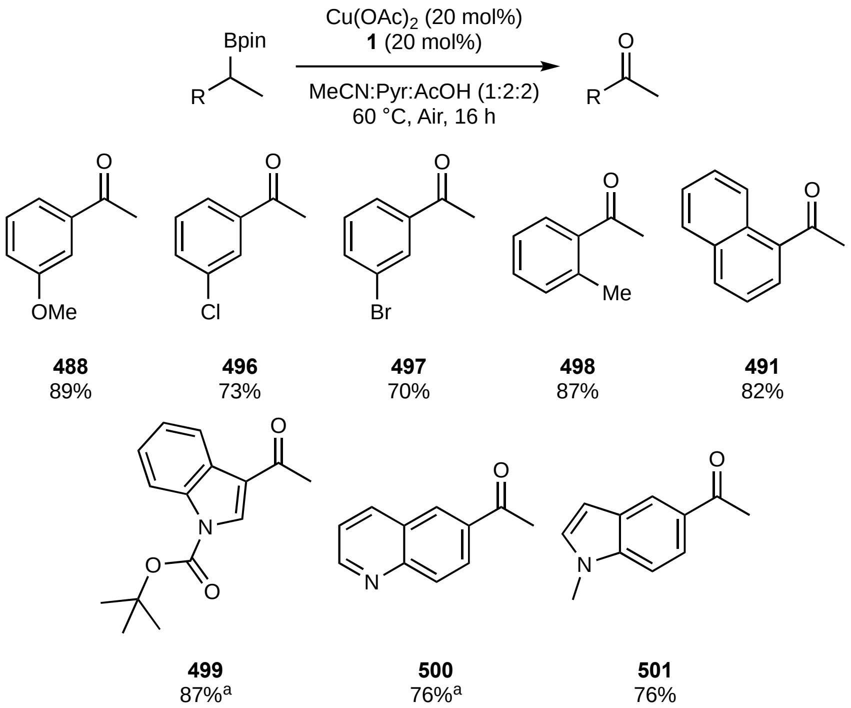
With the optimised conditions in hand, a range of *p*-substituted boronic esters were oxidised (Scheme 146). Various functional groups were tolerated including ether (**465**), aryl fluoride (**495**) and a trifluoromethyl (**460**) groups. There appears to be little influence of either electron withdrawing or electron donating substituents on the yield of oxidation.



465	**493**	**494**	**304**	**495**	**460**
86%	86%	92%	75%	69%	89%

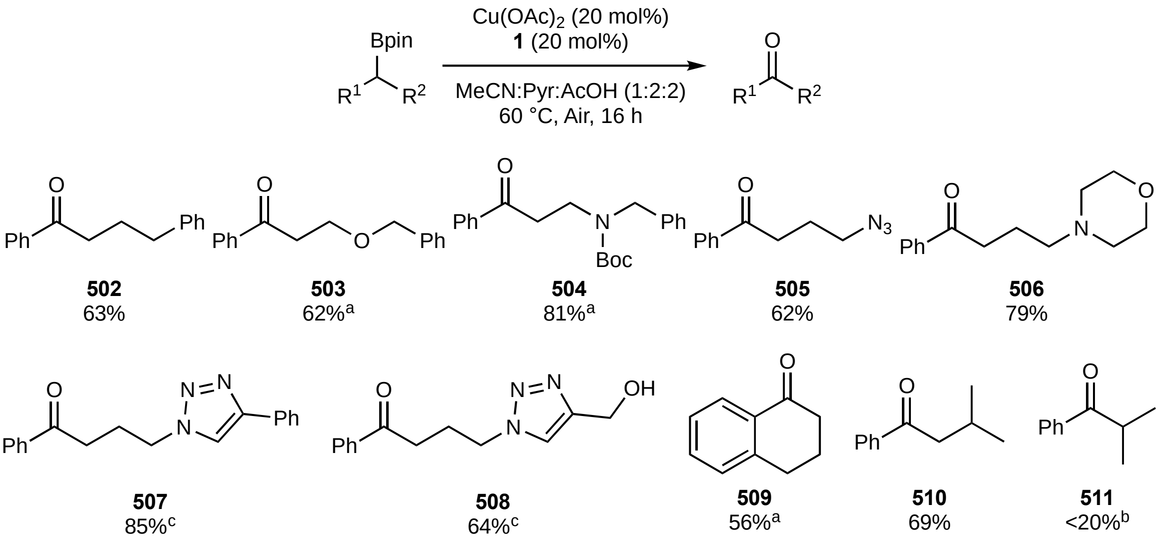
Scheme 146: Scope of oxidation of *p*-substituted benzylic boronic esters.

A variety of meta and ortho substituted benzylic boronic esters were oxidised (Scheme 147). Boronic esters containing aryl chloride and bromide substituents were reacted successfully, without transformation of the halide group. Steric hindrance is tolerated with *o*-methyl boronic ester **227** being oxidised to ketone **498** in comparable yield to the corresponding *p*-methyl boronic ester (**220)**. 1-Naphthyl boronic ester **228** was also oxidised to ketone **491** without issue. Heteroaromatic boronic esters (**265**-**267**) were also successfully oxidised (**499-501**) in excellent yield.



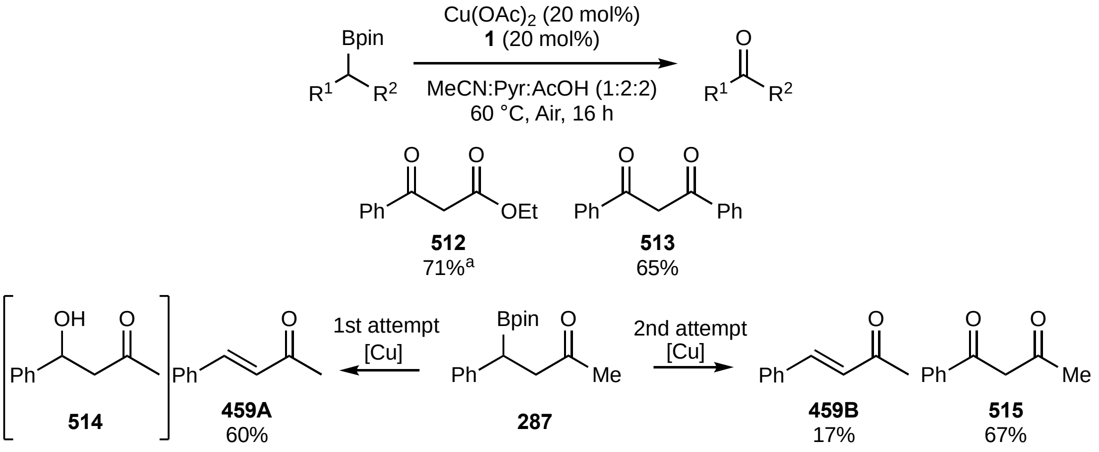
Scheme 147: Scope of oxidation of *m*- and *o*-substituted benzylic boronic esters and, heteroaryl boronic esters. a) Reaction conducted on a 0.3 mmol scale of the boronic ester.

The effect of increasing the alkyl chain length of the boronic ester was next explored (Scheme 148). Some substrates required longer reaction times and higher temperatures in comparison to the reaction of α-Me boronic esters. Compatible functional groups include ether (**503**), Boc-protected amine (**504**), azide (**505**), mopholine (**506**), and triazole (**507**). Of note, boronic ester **292** containing an unprotected alcohol was oxidised successfully, with chemoselective oxidation of the C-B bond occurring to give **508**. This is consistent with the control experiment to test if oxidation occurred via an alcohol intermediate (see Scheme 143). However, the limitation of the method in terms of sterics appears to be isopropyl-substituted boronic ester **257**, which reacted slowly with less than 20% product **511** formed after 72 h. The starting material boronic ester (**257**) was observed by NMR analysis of the crude material, but not isolated.



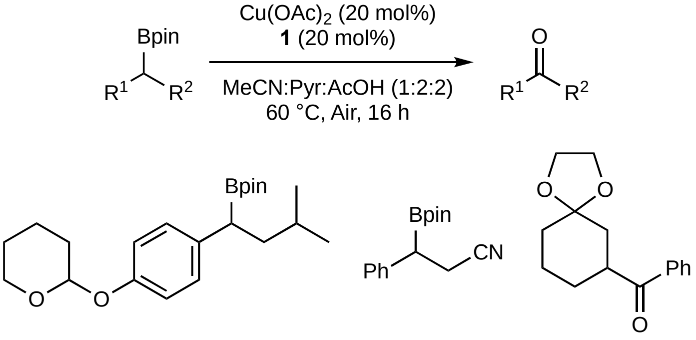
Scheme 148: Scope of oxidation of alkyl substituted benzylic boronic esters. a) Reaction time of 48 h, b) Reaction time of 72 h, c) Reaction conducted on a 0.3 mmol of the boronic ester.

β-Ester and β-keto boronic esters (**285** and **286**) were successfully oxidised in excellent yields to the corresponding ketones (**512** and **513**). However, boronic ester **287** required repeat reactions as the first attempt provided only the dehydrated α,β-unsaturated ketone **459A** in good yield (Scheme 149). A second attempt gave the desired ketone **515** in good yield and a small quantity of α,β-unsaturated ketone **459B**. Presumably, the α,β-unsaturated ketone **459** is formed from either the E1cb elimination of boronic ester **287** or the dehydration of the alcohol by-product **514**. However, β-hydride elimination of an organocuprate intermediate cannot be dismissed.



Scheme 149: Scope of oxidation of β-ester and β-keto substituted benzylic boronic esters. a) Reaction time of 24 h.

Substrates which did not undergo successful reaction include THP-protected substrate **263**, which gave a complex mixture of products, with the acid-mediated deprotection of the THP group observed (Scheme 150). The oxidation of nitrile-containing boronic ester **288** led to formation of a complex mixture of products. Reaction of acetal **294** was also unsuccessful, through traces of the corresponding ketone **516** were observed by NMR analysis and mass spectroscopy of the crude material. Presumably the steric hindrance of the cyclohexyl group in **294** limit the reactivity.

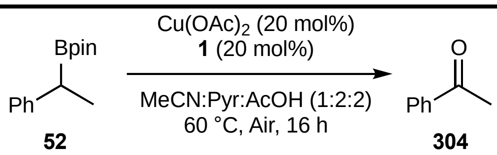


263 **288** **516** ND

Scheme 150: Attempts to oxidise alkyl substituted benzylic boronic esters.

To investigate the tolerance of our conditions further, a compatibility screen pioneered by Glorius and co-workers was performed.[223] Reactions were performed with the addition of range of additives. Each experiment was repeated three times, with an average of the three runs reported in Table 45. Pleasingly, the oxidation conditions were found to be compatible with a range of additives, providing excellent yields of ketone **304** and a >80% return of the additive.

The reaction tolerated 2° amine **303** (Table 45, entry 1), amide **517** (Table 45, entry 2), heterocycles (Table 45, entry 3 and 4), carboxylic acid **520** (Table 45, entry 5), internal alkyne **521** (Table 45, entry 6) and aryl boronic ester **522** (Table 45, entry 7). In each case, a yield of >65% of ketone **304** was observed, with >80% return of the additive. Phenyl acetylene **523** (Table 45, entry 8), Fmoc-protected amino acid **524** (Table 45, entry 9) and styrene oxide **525** (Table 45, entry 10) did not hinder the reaction however, the return of additive was significantly reduced and styrene oxide was not observed. Benzaldehyde **526** (Table 45, entry 11) and anisyl alcohol **527** (Table 45, entry 12) were returned unaltered, with no products from the oxidation of the additive observed. Amino acid, L-phenylalanine, (Table 45, entry 13) hindered the formation of the ketone product, returning a significant quantity of starting boronic ester. The amino acid **528** was presumably lost to the aqueous phase during workup.



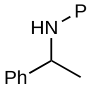
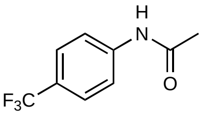
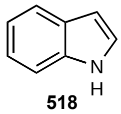
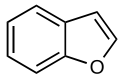
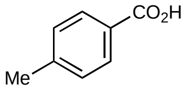
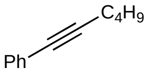
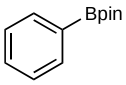
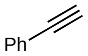
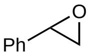
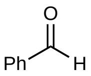
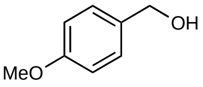
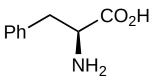
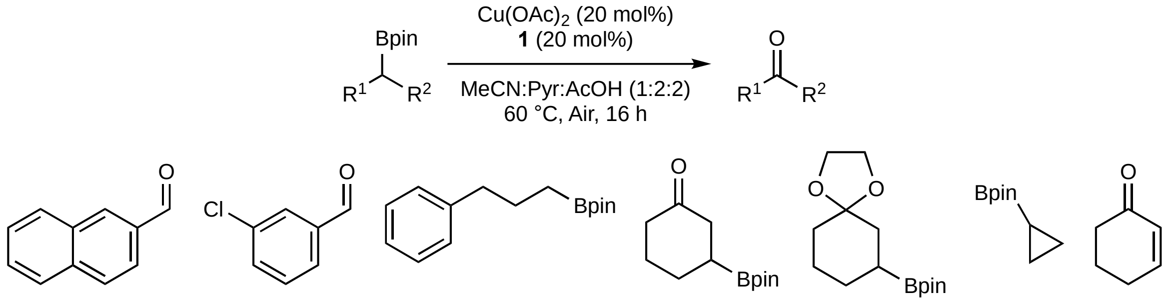
Entry	Additive	Yield		
		304	**52**	**Additive**
1	 **303**	85%	0%	84%
2	 **517**	85%	0%	90%
3	 **518**	82%	0%	90%
4	 **519**	72%	9%	84%
5	 **520**	79%	0%	80%
6	 **521**	67%	0%	86%
7	 **522**	96%	0%	96%
8	 **523**	83%	0%	46%
9	Fmoc-Phe-OH **524**	74%	0%	59%
10	 **525**	91%	0%	0%
11	 **526**	88%	0%	80%
12	 **527**	82%	0%	83%
13	 **528**	35%	52%	3%

Table 45: Compatibility test of a variety of additives on the oxidation of boronic ester **52** and recovery of the additive. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **52**. Reaction concentration of 0.1 м.

The effect of altering the boronic ester environment was explored (Scheme 151). 1° benzylic boronic esters reacted to form the corresponding aldehyde (**529** and **530**) in excellent yields. However, non-benzylic 1° and 2° boronic esters (**251, 33, 293**, and **531**) did not undergo oxidation, with starting material returned. The inability to oxidise non-benzylic boronic esters highlights a limitation of these conditions. Presumably, the reactivity benzylic boronic esters is due to the favourable formation of a benzyl Cu-intermediate, stabilised by the phenyl ring, and not due to the steric environment around boron. Finally, the oxidation of allyl boronic ester **300** gave a complex mixture of products, though traces of ketone **30** were observed by ^{1}H NMR analysis and mass spectrometry.



529 88%

530 86%

251

33

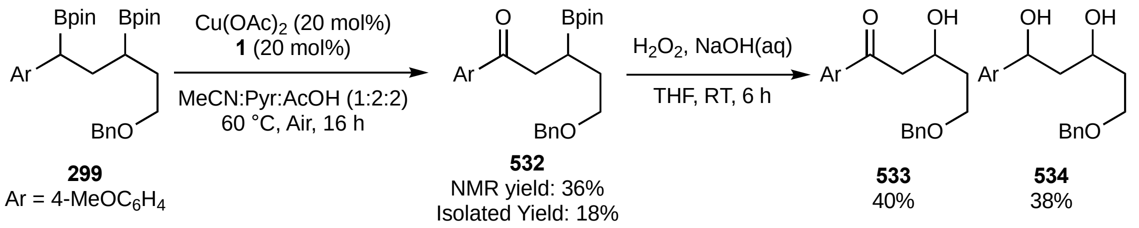
293

531

30 ND

Scheme 151: Scope of oxidation of 1° benzylic and non-benzylic boronic esters.

To explore the whether chemoselective oxidation of the benzylic and non-benzylic boronic esters could be achieved, 1,3-diboronic ester (**299**) was subjected to the reaction conditions (Scheme 152). The benzylic boronic ester of **299** was successfully oxidised to ketone **532** in moderate yield, without reaction of the non-benzylic boronic ester. However, both extended reaction times and purification of the crude material led to decomposition of ketone **532**. Although ketone **532** could be isolated, a more accurate mass balance was obtained after oxidising the non-benzylic boronic ester to the corresponding alcohol. After Cu-catalysed oxidation, the crude material was subjected to peroxide oxidisation conditions to give ketone **533** and diol **534**, which were isolated in good yield. This shows that unlike homologation chemistry,[172] the regioselectivity of the Cu-catalysed oxidation appears to be dictated by the electronics of the C−B bond undergoing functionalization rather than the steric environment at boron.

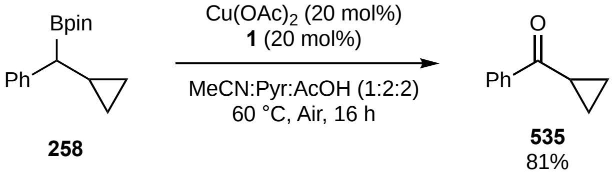


Scheme 152: Cu-catalysed oxidation of 1,3-diboronic ester **299** and H_2O_2 oxidation of intermediate **532**.

3.4.4 Insight into the Reaction Mechanism

Previous metal mediated oxidations of boronic esters have been suggested to proceed by an alcohol intermediate (section 3.1). However, the control experiments of our conditions suggest an alternative mechanism. Although information pertaining to the interactions of copper and oxygen have been reported,[194,195] little information is known about the interaction of alkylboronic esters and copper salts.

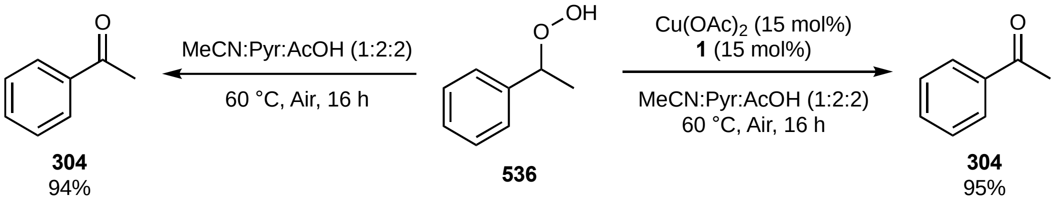
To gain insight into whether an alkyl radical is formed during oxidation, we performed a radical clock experiment using cyclopropyl boronic ester **258** (Scheme 153). If the cyclopropane stays intact, this suggests that transmetallation occurs in a two-electron process. Instead, if opening of the cyclopropyl ring is observed, then the formation of a radical intermediate is likely to occur. Such a radical intermediate could be formed by homolytic cleavage of the C-B bond, or by H atom abstraction alpha to the boron. The resultant radical could then undergo Cu-mediated oxidation. When cyclopropane **258** was subjected to the oxidation conditions, ketone **535** was formed in excellent yield with no ring opened product observed by NMR analysis or mass spectrometry of the crude material. This suggests the process is likely to proceed by a B to Cu two electron transmetallation and formation of a Cu(II) organocuprate intermediate rather than a radical intermediate. This is in contrast to the copper mediated alkyl Chan-Evans-Lam reaction (Section 2.3.6) where ring-opening of the cyclopropane was observed.



Scheme 153: Oxidation of boronic ester **258**.

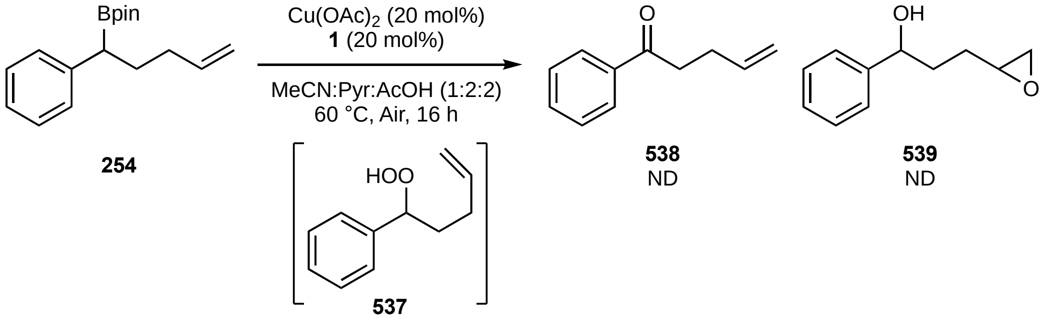
Due to the results of the competition experiments (Section 3.4.2), a peroxide intermediate was hypothesized. Independently prepared peroxide **536** reacted under the standard reaction conditions to give ketone **304** in excellent yield (Scheme 154). Interestingly, a comparable yield was obtained when reacting peroxide **536** in the absence of the copper catalyst.

Presumably if a peroxide intermediate forms, the copper catalyst does not mediate the breakdown of the peroxide. Instead, breakdown of the peroxide is likely to be mediated by the solvent mixture of pyridine and AcOH. This could be via an E2-elimination pathway. This is consistent with results obtained by Barton and co-workers for their Cu-catalysed C-H oxidation protocol, which also used a solvent mixture of pyridine and AcOH.[224]



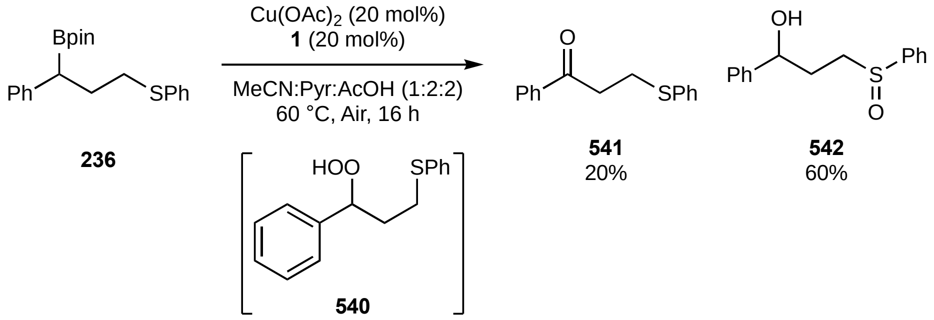
Scheme 154: Reaction of peroxide **536** in the presence and absence of $Cu(OAc)_2$. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard.

Next, to investigate whether a peroxide was formed *in situ* during oxidation, an alkene-containing boronic ester **254** was subjected to the reaction conditions. If a peroxide intermediate (**537**) is formed, we hypothesized that it could be react with the pendant alkene in an epoxidation reaction (**539**). Additionally, if a radical intermediate is formed cyclisation may occur with the alkene. When subjected to the oxidation conditions, reaction of boronic ester **254** gave a complex mixture of products. However, the ketone (**538**) was observed by 1H-NMR analysis of the crude material.



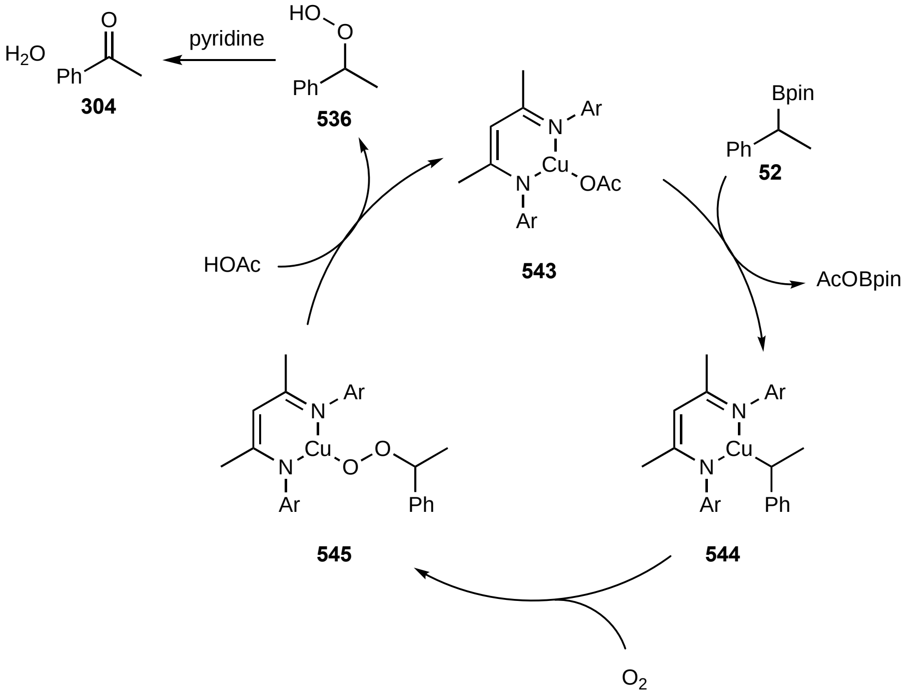
Scheme 155: Reaction of boronic ester **254** under the oxidation conditions.

It was proposed that a sulfide could act as a trap for the proposed peroxide intermediate. Boronic ester **236** containing a sulfide group as a potential reductant was designed. It was hypothesised that if a peroxide intermediate **540** is formed, it could be reduced by the sulfide to give sulfoxide **542**. Pleasingly, the oxidation of boronic ester **236** gave a mixture of sulfoxide **542** and ketone **541**. This provides compelling evidence for the formation of peroxide intermediate **540**. Presumably, elimination of peroxide **540** occurs at a slower rate than reduction of the peroxide by the sulfide.



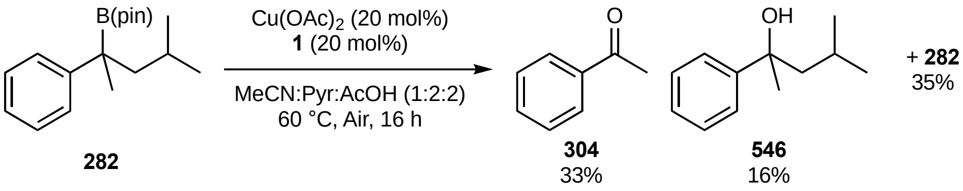
Scheme 156: Oxidation of thioether **236**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **236**. Reaction concentration of 0.1 M.

From the experimental observations above, the following mechanism is proposed (Scheme 157). Initially, denucleation and ligation of $Cu(OAc)_2$ produces copper complex **543**. This species reacts with boronic ester **52** through a B to Cu transmetalation providing alkyl Cu(II) species **544**, which can bind to O_2. Presumably this occurs through an η^1-end-on coordination of O_2, due to steric congestion around copper.[194,195] Insertion of the alkyl Cu intermediate into O_2 leads to formation of complex **545**. The peroxide can then be protonated to provide the peroxide **536**, regenerating the copper catalyst **543**. Peroxide **536** can then undergo pyridine mediated elimination to give ketone **304**.



Scheme 157: Proposed mechanism for the Cu-catalysed oxidation of benzylic boronic esters.

Finally, 3° boronic ester **282** was subjected to the reaction conditions. This gave a mixture of acetophenone **304**, alcohol **546**, and recovered boronic ester **282** (Scheme 158).



Scheme 158: Oxidation of 3° boronic ester **282**.

A report by Warren and co-workers highlights the potential for 3° peroxide decomposition to the corresponding ketone by a radical mechanism (Figure 25).[225] This is proposed to occur through initial formation of an alkoxy radical (**548**) and Cu alkoxide bond (**549)** from reaction between a Cu(I) species and a dialkyl peroxide (**547**). The alkoxy radical (**548)** readily fragments, liberating a methyl radical and forming the corresponding acetophenone **550**. The alkoxide is readily hydrolysed to give the alcohol **551**. Presumably, a similar mechanism could account for formation of acetophenone **304** from the 3° boronic ester **282**.

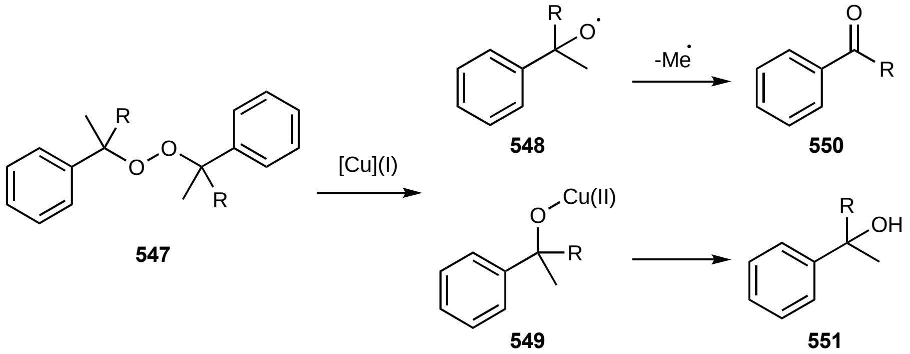
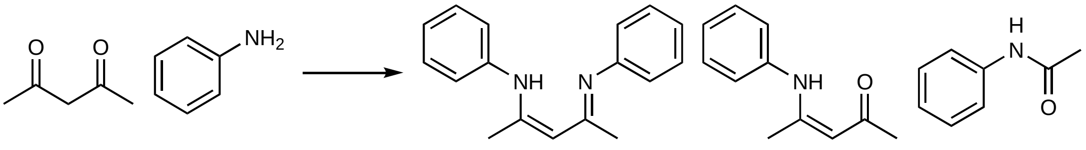


Figure 25: Suggested pathway for the formation of ketone **550** and alcohol **551** from peroxide **547.**

3.4.5 Synthesis of diketimine ligands

1,3-Diketimines have been a recognised ligand class for over half a century.[226] Recently diaryl diketimines have been of particular interest due to synthetic utility with an array of metals and their ability to be easily tailored to a reaction. Additionally, diketimines produced from 1,3-diketones and anilines are relatively cheap (**201**). A number of acid catalysed methods for their synthesis have been reported, including refluxing under Dean-Stark conditions,[226] addition of concentrated HCl in EtOH,[227] and heating in a microwave reactor.[228] Although multiple reports utilise these methods, in our hands the methods were found to be unreliable. Side products including imine **553** and amide **554** were observed in variable amounts (Scheme 159).



Scheme 159: General formation of diketimine ligand **201**, and side products **288** and **554** observed.

Presumably, the desired ligand synthesis proceeds by two sequential imine formation reactions (Figure 26). Presumably, attack of 1,3-diketone **552** by aniline forms intermediate **555**, which upon loss of water gives imine **553**. A second addition of aniline produces the desired product **201**. Although the reaction is favourable in the formation of the diketimine product **201**, it is a reversible reaction. The reversibility of the formation of imine species **553** and subsequent side product formation has been reported by Chu and co-workers.[229] They propose the addition of water to imine species **553** providing intermediate **555**. Intermediate **555** has the potential to forming acetanilide **554** irreversibly eliminating acetone.

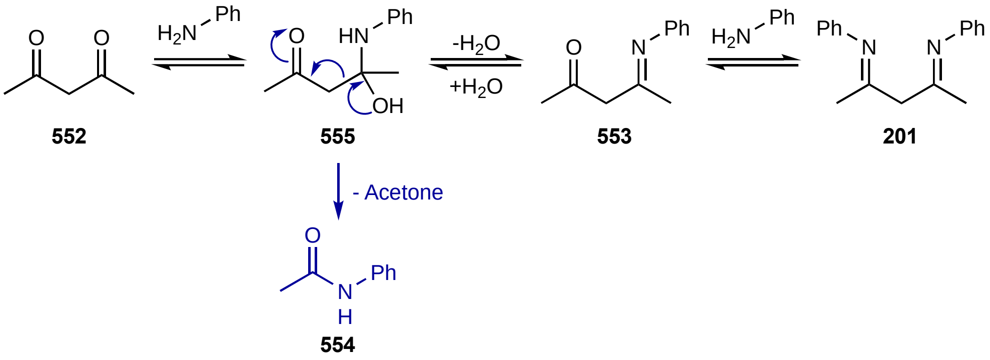
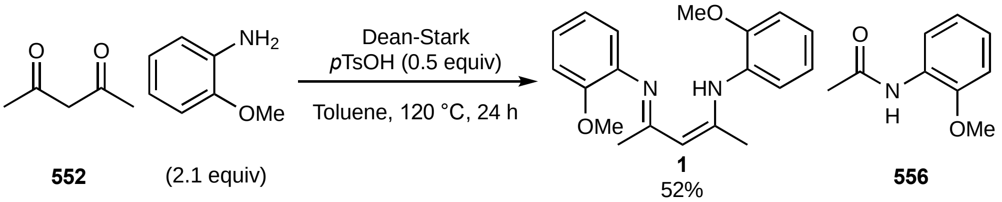


Figure 26: Simplified route to the formation of 1,3-diketimine **201** and acetanilide **554**.

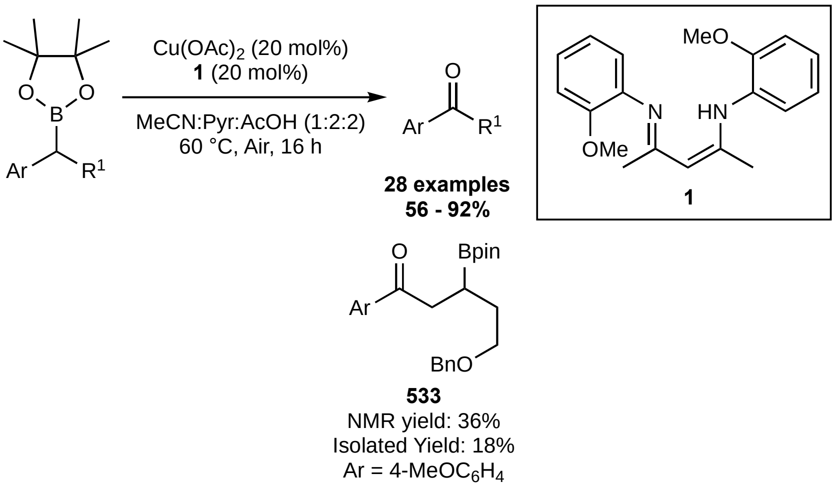
In an attempt to remove water from the reaction and prevent reversibility, water removal methods, such as Dean-Stark conditions, and the addition desiccants, including activated molecular sieves, triethoxy silane, and magnesium sulphate were trialed. However, the formation of acetanilides was observed with all methods. The most reliable conditions were found to be at reflux under Dean-Stark conditions with substoichiometric tosylic acid and excess aniline. In particular, it was found beneficial to use short reaction times. While this led to only moderate yield of **1**, this also minimised the formation of amide **556**.



Scheme 160: Conditions developed for the formation of diketimine **1** to minimise the formation of amide **556.**

3.5 *Conclusions, Limitations and Future Work*

During the method development for the amination of **52,** ketone **304** was observed. This work focussed on the development of conditions for the formation of ketone **304** and to further understand the amination reaction. To our knowledge, this is the first example of a Cu-catalysed oxidation of C-B bond directly to the corresponding carbonyl. Investigation of the scope highlighted that oxidation was limited to benzylic boronic esters.

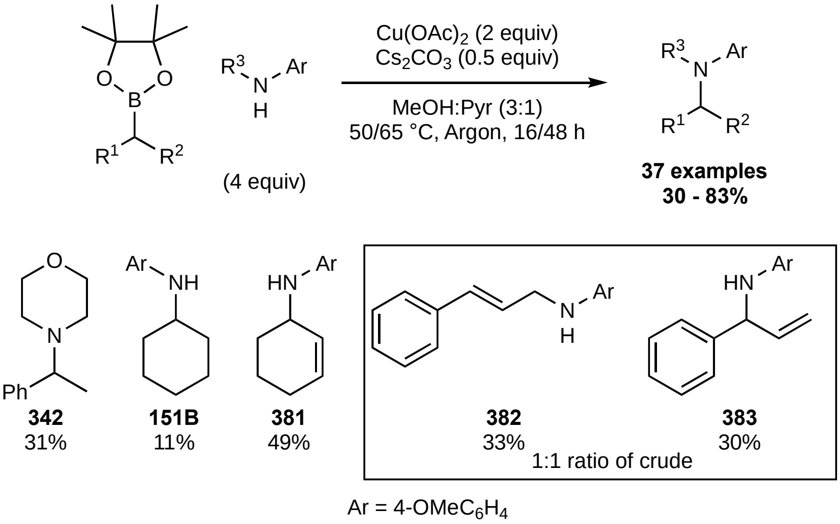


Scheme 161: Overview of benzylic boronic ester oxidation.

Future work will investigate suitable conditions for the oxidation of non-benzylic boronic esters primarily testing ligands effects. Varying the electronics and sterics of the current diketimine **1** is a potential route for exploration and would provide a rationale for further alterations. Additionally, literature reports suggest the potential for copper to perform an extra oxidation step. 1° boronic esters could therefore be directly transformed into carboxylic acids.

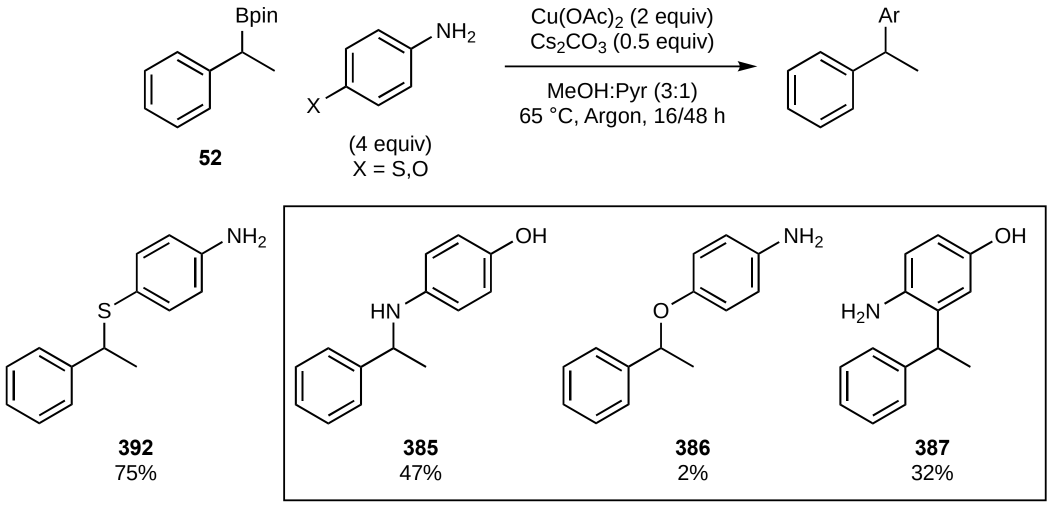
4 Conclusion

Alkyl Chan-Evans-Lam conditions have been developed to allow the coupling of 2° benzylic boronic esters and anilines. This coupling is a rare example of a transition metal mediated C-N bond formation at a 2° alkyl centre. The reaction proceeds with minimal formation of by-products and selectively forms the monoalkylated product. The conditions avoid the use of unfavourable peroxide oxidants by employing stoichiometric $Cu(OAc)_2$ under an inert atmosphere. Benzylic boronic esters were required to achieve good to excellent yields presumably due to aided transmetallation. A range of boronic esters were aminated with a range of anilines displaying the functional group tolerance of the conditions. 2° amine, morpholine, was coupled in reasonable yield at a higher temperature and longer reaction time. Allylic boronic esters were successful coupling partners, albeit with isomerisation of unsymmetrical starting materials. To our knowledge this is the second example of successful alkyl amines coupling and first example of the use of allyl boronic esters.



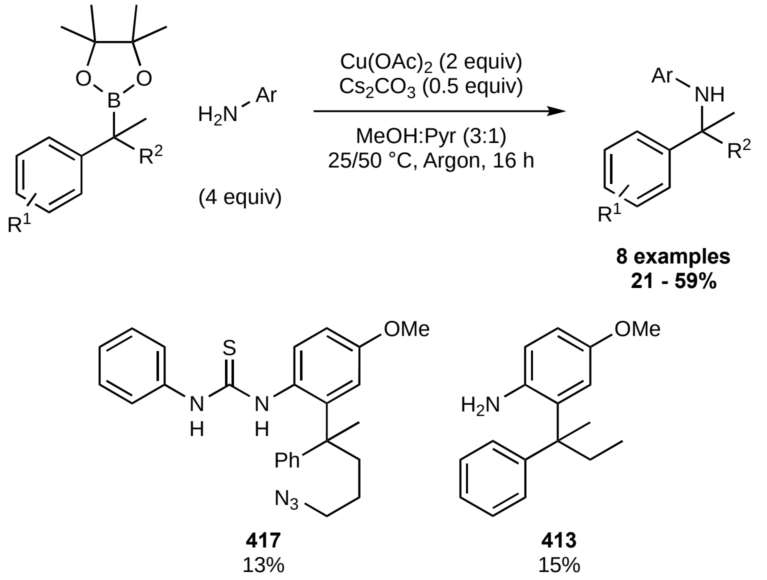
Scheme 162: Overview of the amination of 2° boronic esters.

The conditions were expanded to *O*- and *S*- heteroatom coupling with mixed results. The coupling of aminothiophenol provided the *S*- coupled product in excellent yield. However, the coupling of thiol gave significantly lower yields. To our knowledge this is the first example of an *S*-nucleophile coupling under alkyl Chan-Evans-Lam conditions. The coupling of aminophenol gave a range of products including C-N, C-O and C-C coupled products. Although heteroatom coupling is a common occurrence of aryl Chan-Evans-Lam reactions, C-C bond formation product **387** is an unexpected and potentially exciting result.



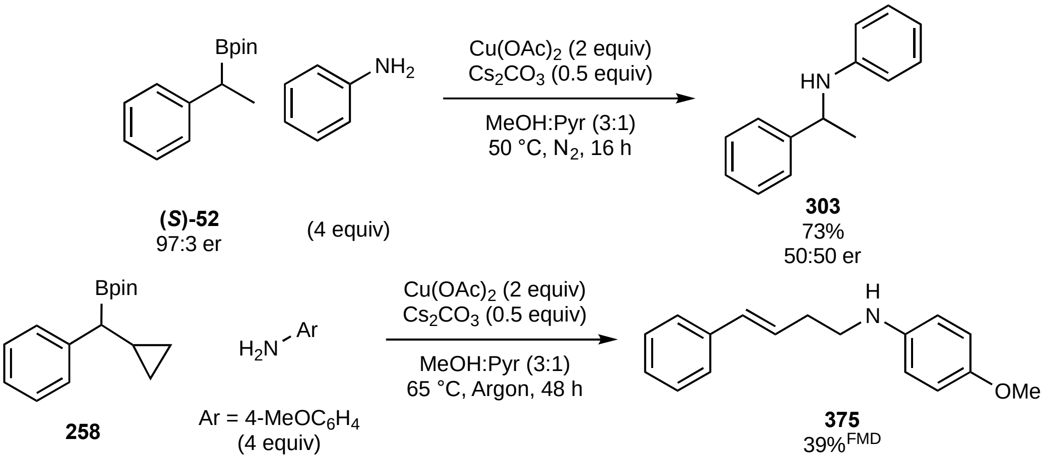
Scheme 163: Reaction of aminothiophenol and aminophenol with boronic ester **52.**

Applying our current conditions to 3° boronic esters gave 3° amines in good yield. To our knowledge, this is the second application of 3° boron reagents in Chan-Evans-Lam coupling and the first use of 3° boronic esters. C-3° amine formation demonstrates our conditions utility as reductive amination methods are unable to form these products. Lower yields were obtained due to the increased propensity for protodeboronation of 3° boronic esters and difficulty in purification. Further C-C bond formation products were observed with reaction of electron rich anilines.



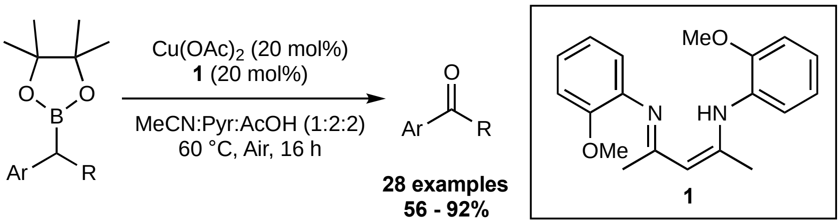
Scheme 164: Overview of reaction for the coupling of 3° boronic esters and anilines.

Preliminary investigations into the reaction mechanism indicate that amination occurs directly from the C-B bond and does not occur through any side products identified. Experimental evidence e.g. loss of stereochemical information and radical clock reactions, suggests that transmetallation proceeds through a radical pathway.



Scheme 165: Reaction of enantioenriched boronic ester **(*S*)-52** and cyclopropane **258**.

Whilst exploring the conditions and scope of the alkyl Chan-Evans-Lam reaction, our understanding of the copper mediated formation of side products from alkyl boronic esters expanded. Subsequently, conditions have been developed for a mild copper catalysed oxidation of alkyl boronic esters to the corresponding carbonyls.[179] Ambient air appears to provide oxygen to perform roles in carbonyl formation and catalyst turnover. The reaction has been demonstrated to be chemoselective for the oxidation of benzylic position boronic esters. A range of benzylic boronic esters were oxidised showing the functional group tolerance of the conditions.



Scheme 166: Overview for the oxidation of benzylic boronic esters.[179]

Preliminary mechanistic investigations suggest the reaction does not proceed via, a two-step oxidation process, C-H oxidation or Wacker type oxidation.[179] Conditions were tolerant of unprotected alcohols and suggest a direct C-B bond oxidation. To our knowledge, this is the first example of direct C-B bond oxidation under Cu-catalysed conditions. Experimental evidence suggests the mechanism proceeds by a B-to-C transmetallation, peroxide formation and rearrangement to form the corresponding carbonyl.

5 Experimental

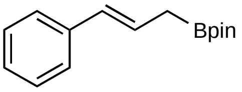
5.1 *General Experimental*

All reagents and solvents used were supplied by commercial sources without further purification unless specified. *p*-Anisidine was purified by recrystallisation from ethanol, filtered and dried *in vacuo* for 6 h. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was distilled over NaH and stored under nitrogen prior to use. All air-sensitive reactions were carried out under a nitrogen or argon atmosphere using oven-dried apparatus. Anhydrous Et_2O, THF and toluene were dried and purified by passage through activated alumina columns using a solvent purification system. All petroleum ether used was 40-60 °C petroleum ether. Thin layer chromatography (TLC) was performed on aluminium-backed plates pre-coated with silica. Compounds were visualised by exposure to UV light or by dipping the plates into solutions of vanillin or $KMnO_4$ followed by heating. All flash chromatography was carried out using silica gel mesh 40-63. It should be noted that the time taken for chromatography of boronic esters should be kept to minimum to avoid extensive decomposition and reduced yields.

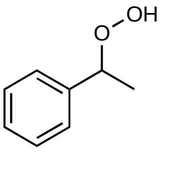
Infrared spectra were recorded on a Perkin Elmer 100 FT instrument on the neat compound. NMR spectra were recorded on Bruker Advance 400 and 500 instruments at the indicated 101, 128, 126, 377, 400 and 500 MHz as dilute solutions in the indicated deuterated solvent. NMR spectra were recorded at ambient temperature unless otherwise stated. All chemical shifts (δ) reported in parts per million (ppm) relative to residual protio-solvent (δH: $CHCl_3$ = 7.27 ppm, DMSO = 2.50 ppm or D_2O = 4.79 ppm) or the solvent itself (δC: $CDCl_3$ = 77.0 ppm or DMSO = 39.5 ppm). All multiplets are designated by the following abbreviations: s = singlet, br. s = broad singlet, d = doublet, br. d = broad doublet, dd = doublet doublet, dt = doublet triplet, td = triplet doublet, ddd = doublet doublet doublet, dtd = doublet triplet doublet, q = quartet, p = pentet, sept = septet, m = multiplet. All coupling constants (*J*) are reported in Hertz (Hz). ^{13}C NMR spectra were acquired as decoupled spectra and assignments determined using CPD experiments. ^{19}F NMR spectra acquired as decoupled spectra. High-resolution mass spectra were recorded using either quadrupole time of flight (Q-TOF) or electron ionisation (EI) by the Chemistry Mass Spectrometry Facility in the Faculty of Science, University of Sheffield. Melting points were measured using Linkam HFs91 heating stage, used in conjunction with a TC92 controller and are uncorrected.

Single crystal X-ray intensity data was collected at 100 K on a Bruker D8 Venture diffractometer equipped with a Photon 100 CMOS detector using a CuKα microfocus X-ray source from crystals mounted in fomblin oil on a MiTiGen microloop and cooled in a stream of cold N_2. Data were corrected for absorption using empirical methods (SADABS)[230] based upon symmetry equivalent reflections combined with measurements at different azimuthal angles.[231] The crystal structures were solved and refined against F^2 values using ShelXT[232] for solution and ShelXL[233] for refinement accessed via the Olex2 program.[234] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions with idealized geometries and then refined by employing a riding model and isotropic displacement parameters.

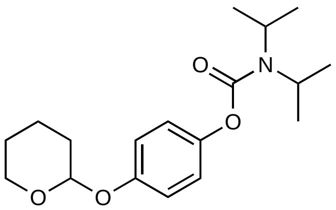
5.2 *Compounds Supplied by Members of The Partridge Group*



301



536

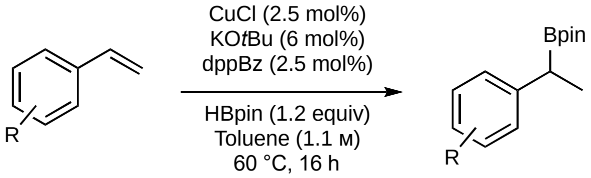


557

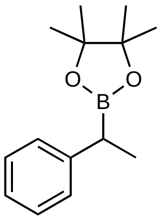
5.3 *Preparation of Boronic Esters*

5.3.1 Cu-Catalysed Hydroboration of Alkenes

General Procedure 1: Cu-Catalysed Hydroboration of Styrene and Styrene Derivatives.



Using a variation of the procedure of Yun and co-workers,[162] an oven dried flask was charged with CuCl (2.5 mol%), *t*BuOK (6 mol%) and dppBz (2.5 mol%), and purged with N_2. Anhydrous toluene (1.1 M) was added, and the mixture was stirred at room temperature for 10 min. Pinacolborane (1.2 equiv) was added and the mixture was stirred for 10 min. The corresponding alkene (1 equiv) was added and the mixture heated to 60 °C for 16 h. Upon completion (as determined by TLC) the mixture was cooled to room temperature, passed through a bed of Celite eluting with EtOAc (10 mL), and concentrated *in vacuo*. The crude material was purified by flash chromatography to give the corresponding boronic ester.



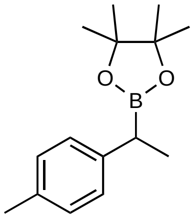
52

(±)-4,4,5,5-Tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane (52). The title compound was prepared according to General Procedure **1** using CuCl (0.022 g, 0.22 mmol), *t*BuOK (0.059 g, 0.53 mmol), dppBz (0.097 g, 0.22 mmol), pinacolborane (1.5 mL, 10 mmol) and styrene (1.0 mL, 8.7 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **52** (1.65 g, 83%) as a colourless oil. The data were consistent with the literature.[162]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (4H, m, Ar**H**), 7.19-7.08 (1H, m, Ar**H**), 2.45 (1H, q, *J* = 7.5 Hz, C**H**), 1.34 (3H, d, *J* = 7.5 Hz, CHC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 128.3 (2 × CH), 127.8 (2 × CH), 125.1 (CH), 83.3 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 17.0 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.5.



220

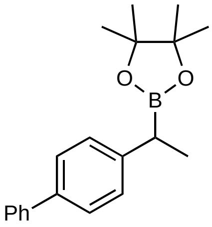
(±)-4,4,5,5-Tetramethyl-2-(1-*p*-tolylethyl)-1,3,2-dioxaborolane (220).

The title compound was prepared according to General Procedure **1** using CuCl (0.010 g, 0.10 mmol), *t*BuOK (0.028 g, 0.25 mmol), dppBz (0.047 g, 0.11 mmol), pinacolborane (0.73 mL, 5.0 mmol) and 4-methylstyrene (0.55 mL, 4.2 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **220** (0.647 g, 65%) as a colourless oil. The data were consistent with the literature.[162]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.05 (2H, d, *J* = 8.1 Hz, Ar**H**), 2.40 (1H, q, *J* = 7.6 Hz, C**H**), 2.31 (3H, s, ArC**H$_3$**), 1.31 (3H, d, *J* = 7.6 Hz, CHC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (C), 134.4 (C), 129.0 (2 × CH), 127.6 (2 × CH), 83.2 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 21.0 (CH_3), 17.0 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.6.



221

(±)-2-(1-[1,1'-Biphenyl]-4-ylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (221).

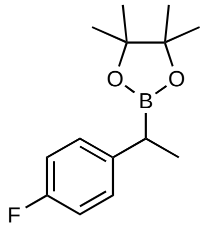
The title compound was prepared according to General Procedure **1** using CuCl (0.004 g, 0.04 mmol), *t*BuOK (0.011 g, 0.098 mmol), dppBz (0.019 g, 0.043 mmol), pinacolborane (0.60 mL, 4.0 mmol) and 4-vinylbiphenyl (0.30 mL, 1.7 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **221** (0.416 g, 83%) as a white solid. The data were consistent with the literature.[235]

m.p. = 72-73 °C (petroleum ether); literature = 60 °C (not specified).[236]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (2H, m, Ar**H**), 7.54-7.47 (2H, m, Ar**H**), 7.46-7.39 (2H, m, Ar**H**), 7.35-7.27 (3H, m, Ar**H**), 2.49 (1H, q, *J* = 7.5 Hz, C**H**), 1.37 (3H, d, *J* = 7.5 Hz, CHC**H$_3$**), 1.24 (6H, s, 2 × CC**H$_3$**), 1.23 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (C), 141.2 (C), 137.9 (C), 128.6 (2 × CH), 128.1 (2 × CH), 127.0 (2 × CH), 126.9 (2 × CH), 126.8 (CH), 83.3 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 17.1 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.5.



222

(±)-2-(1-(4-Fluorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (222).

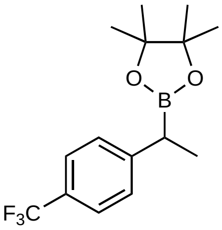
The title compound was prepared according to General Procedure **1** using CuCl (0.010 g, 0.10 mmol), *t*BuOK (0.027 g, 0.24 mmol), dppBz (0.045 g, 0.10 mmol), pinacolborane (0.67 mL, 4.6 mmol) and 4-fluorostyrene (0.48 mL, 3.9 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **222** (0.726 g, 73%) as a colourless oil. The data were consistent with the literature.[162]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.14 (2H, m, Ar**H**), 6.98-6.91 (2H, m, Ar**H**), 2.42 (1H, q, J = 7.5 Hz, C**H**), 1.31 (3H, d, J = 7.5 Hz, CHC$\mathbf{H_3}$), 1.22 (6H, s, 2 × CC$\mathbf{H_3}$), 1.21 (6H, s, 2 × CC$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9 (C, d, $J_{C\text{-}F}$ = 242.3 Hz), 140.5 (C, d, $J_{C\text{-}F}$ = 2.8 Hz), 129.0 (2 × CH, d, $J_{C\text{-}F}$ = 7.6 Hz), 115.0 (2 × CH, d, $J_{C\text{-}F}$ = 20.9 Hz), 83.4 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 17.2 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.5.

^{19}F NMR (377 MHz, $CDCl_3$) δ -119.0.



223

(±)-2-[1-(4-Trifluoromethylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (223).

The title compound was prepared according to General Procedure **1** using CuCl (0.003 g, 0.03 mmol), *t*BuOK (0.008 g, 0.071 mmol), dppBz (0.014 g, 0.031 mmol), pinacolborane (0.23 mL, 1.5 mmol) and 4-(trifluoromethyl)styrene (0.25 mL, 1.3 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **223** (0.359 g, 96%) as a white solid. The data were consistent with the literature.[237]

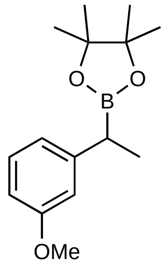
m.p. 53-54 °C (petroleum ether); no literature value available.[237]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, d, J = 8.2 Hz, Ar**H**), 7.32 (2H, d, J = 8.2 Hz, Ar**H**), 2.51 (1H, q, J = 7.5 Hz, C**H**), 1.35 (3H, d, J = 7.5 Hz, CHC$\mathbf{H_3}$), 1.22 (6H, s, 2 × CC$\mathbf{H_3}$), 1.21 (6H, s, 2 × CC$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ149.3 (C), 128.8-127.6 (CCF_3, m), 128.0 (2 × CH), 125.2 (2 x CH, q, $J_{C\text{-}F}$ = 3.6 Hz), 124.5 (C, q, $J_{C\text{-}F}$ = 271.4 Hz), 83.5 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 16.7 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.3.

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.2.


224

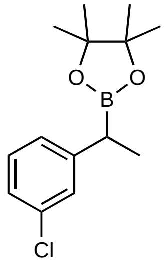
(±)-2-(1-(3-Methoxyphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (224).

The title compound was prepared according to General Procedure **1** using CuCl (0.009 g, 0.09 mmol), *t*BuOK (0.024 g, 0.21 mmol), dppBz (0.040 g, 0.090 mmol), pinacolborane (0.35 mL, 2.4 mmol) and 3-vinylanisole (0.50 mL, 3.6 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **224** (0.94 g, 99%) as a colourless oil. The data were consistent with the literature.[235]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.23-7.15 (1H, m, Ar**H**), 6.86-6.77 (2H, m, Ar**H**), 6.74-6.66 (1H, m, Ar**H**), 3.80 (1H, s, C**H**$_3$), 2.43 (1H, q, *J* = 7.5 Hz, C**H**), 1.33 (3H, d, *J* = 7.5 Hz, CHC**H**$_3$), 1.23 (6H, s, 2 × CC**H**$_3$), 1.22 (6H, s, 2 × CC**H**$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 159.5 (C), 146.6 (C), 129.2 (CH), 120.3 (CH), 113.4 (CH), 110.5 (CH), 83.3 (2 × C), 55.0 (CH$_3$), 24.6 (2 × CH$_3$), 24.6 (2 × CH$_3$), 17.0 (CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$) δ 33.4.


225

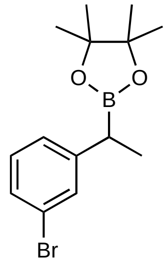
(±)-2-(1-(3-Chlorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (225).

The title compound was prepared according to General Procedure **1** using CuCl (0.010 g, 0.10 mmol), *t*BuOK (0.026 g, 0.23 mmol), dppBz (0.044 g, 0.099 mmol), pinacolborane (0.60 mL, 4.8 mmol) and 3-chlorostyrene (0.50 mL, 3.9 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **225** (0.880 g, 88%) as a colourless oil. The data were consistent with the literature.[162]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.23-7.15 (2H, m, Ar**H**), 7.14-7.06 (2H, m, Ar**H**), 2.42 (1H, q, *J* = 7.4 Hz, C**H**), 1.32 (3H, d, *J* = 7.4 Hz, CHC**H**$_3$), 1.22 (6H, s, 2 × CC**H**$_3$), 1.21 (6H, s, 2 × CC**H**$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 147.1 (C), 134.0 (C), 129.4 (CH), 127.8 (CH), 126.0 (CH), 125.3 (CH), 83.5 (2 × C), 24.6 (2 × CH$_3$), 24.6 (2 × CH$_3$), 16.8 (CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$) δ 33.3.


226

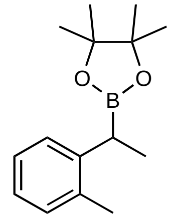
(±)-2-[1-(3-Bromophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (226).

The title compound was prepared according to General Procedure **1** using CuCl (0.007 g, 0.07 mmol), *t*BuOK (0.018 g, 0.16 mmol), dppBz (0.030 g, 0.067 mmol), pinacolborane (0.48 mL, 3.3 mmol) and 3-bromostyrene (0.36 mL, 2.7 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **226** (0.724 g, 82%) as a colourless oil. The data were consistent with the literature.[236]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.14 (2H, m, Ar**H**), 7.14-7.06 (2H, m, Ar**H**), 2.42 (1H, q, *J* = 7.4 Hz, C**H**), 1.32 (3H, d, *J* = 7.4 Hz, CHC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4 (C), 130.8 (C), 129.8 (CH), 128.2 (CH), 126.5 (CH), 122.4 (CH), 83.5 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 16.8 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.3.



227

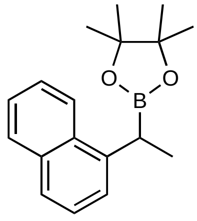
(±)-4,4,5,5-Tetramethyl-2-[1-(2-methylphenyl)ethyl]-1,3,2-dioxaborolane (227).

The title compound was prepared according to General Procedure **1** using CuCl (0.011 g, 0.11 mmol), *t*BuOK (0.029 g, 0.26 mmol), dppBz (0.047 g, 0.11 mmol), pinacolborane (0.74 mL, 5.1 mmol) and 2-methylstyrene (0.55 mL, 4.3 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **227** (0.743 g, 74%) as a colourless oil. The data were consistent with the literature.[235]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.18 (1H, m, Ar**H**), 7.18-7.10 (2H, m, Ar**H**), 7.09-7.02 (1H, m, Ar**H**), 2.59 (1H, q, *J* = 7.5 Hz, C**H**), 2.32 (1H, s, C**H$_3$**), 1.33 (3H, d, *J* = 7.5 Hz, CHC**H$_3$**), 1.23 (6H, s, 2 × CC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (C), 135.6 (C), 130.0 (CH), 127.1 (CH), 126.0 (CH), 125.0 (CH), 83.3 (2 × C), 24.6 (2 × CH), 24.6 (2 × CH), 19.9 (CH_3), 16.3 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7.



228

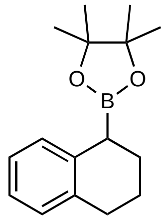
(±)-4,4,5,5-Tetramethyl-2-[1-(1-naphthalen-1-yl)ethyl]-1,3,2-dioxaborolane (228).

The title compound was prepared according to General Procedure **1** using CuCl (0.005 g, 0.05 mmol), *t*BuOK (0.014 g, 0.12 mmol), dppBz (0.023 g, 0.052 mmol), pinacolborane (0.35 mL, 2.4 mmol) and 1-vinylnaphthalene (0.30 mL, 2.0 mmol). Flash chromatography (4% Et_2O/petroleum ether) of the crude material gave boronic ester **228** (0.505 g, 88%) as a colourless oil. The data were consistent with the literature.[162]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.09 (1H, m, Ar**H**), 7.87-7.82 (1H, m, Ar**H**), 7.70-7.66 (1H, m, Ar**H**), 7.52-7.38 (4H, m, Ar**H**), 3.13 (1H, q, *J* = 7.5 Hz, C**H**), 1.51 (3 H, d, *J* = 7.5 Hz, CHC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4 (C), 133.9 (C), 132.0 (C), 128.7 (CH), 125.8 (2 × CH), 125.3 (CH), 125.2 (CH), 124.2 (CH), 124.1 (CH), 83.4 (2 × C), 24.7 (2 × CH_3), 24.5 (2 × CH_3), 16.4 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.4.



229

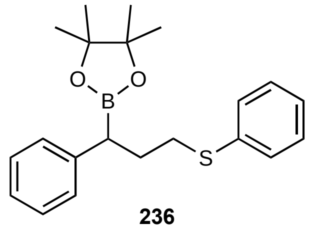
(±)-4,4,5,5-Tetramethyl-2-(1,2,3,4-tetrahydronaphthalen-1-yl)-1,3,2-dioxaborolane (229).

The title compound was prepared according to General Procedure **1** using CuCl (0.009 g, 0.09 mmol), *t*BuOK (0.026 g, 0.23 mmol), dppBz (0.043 g, 0.096 mmol), pinacolborane (0.67 mL, 4.6 mmol) and 1,2-dihydronaphthalene (0.499 mL, 3.83 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **229** (0.750 g, 75%) as a colourless oil. The data were consistent with the literature.[238]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-6.98 (4H, m, Ar**H**), 2.84-2.71 (2H, m, C**H_2**), 2.66-2.49 (1H, m, C**H**), 1.97-1.81 (3H, m, C**H_2**), 1.80-1.65 (1H, m, C**H_2**), 1.25 (6H, s, 2 × CC**H_3**), 1.24 (6H, s, 2 × CC**H_3**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 (C), 136.6 (C), 129.3 (CH), 129.3 (CH), 125.3 (CH), 124.7 (CH), 83.3 (2 × C), 29.7 (CH_2), 25.1 (CH_2), 24.7 (2 × CH_3), 24.6 (2 × CH_3), 22.7 (CH_2).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.6.



236

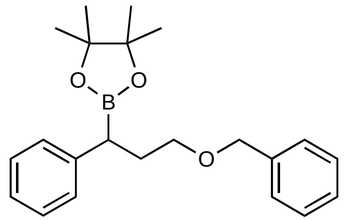
(±)-4,4,5,5-Tetramethyl-2-[1-phenyl-3-(phenylsulfanyl)propyl]-1,3,2-dioxaborolane (236).

The title compound was prepared according to a modification of General Procedure **1** using CuCl (0.0055 g, 0.055 mmol), *t*BuOK (0.0149 g, 0.133 mmol), dppBz (0.0247 g, 0.0552 mmol), pinacolborane (0.39 mL, 2.7 mmol) and 3-(phenylsulfanyl)prop-1-en-1-yl benzene[239] (0.500 g, 2.21 mmol). After stirring the mixture at 60 °C for 24 h, further pinacol borane (0.30 mL, 1.9 mmol) was added and the mixture was stirred at 60 °C for 2 h prior to filtration. Flash chromatography (7% EtOAc/hexane) of the crude material gave boronic ester **236** (0.105 g, 13%) as a colourless oil.[179]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.12 (10H, m, Ar**H**), 2.94-2.80 (2H, m, C**H_2**S), 2.54-2.46 (1H, m, C**H**CH_2), 2.24-2.12 (1H, m, CHC**H_A**H_B), 2.08-1.96 (1H, m, CHCH_A**H_B**), 1.22 (1H, s, 6H, s, 2 × CC**H_3**), 1.19 (1H, s, 6H, s, 2 × CC**H_3**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (C), 136.8 (C), 128.7 (2 × CH), 128.5 (2 × CH), 128.4 (4 × CH), 125.5 (CH), 125.4 (CH), 83.5 (2 × C), 32.4 (CH_2), 31.9 (CH_2), 24.6 (2 × CH_3), 24.6 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2.



234

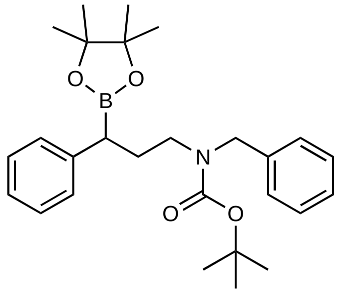
(±)-2-[3-(Benzyloxy)-1-phenylpropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (234).

The title compound was prepared according to General Procedure **1** using CuCl (0.0055 g, 0.056 mmol), *t*BuOK (0.0150 g, 0.134 mmol), dppBz (0.0250 g, 0.0560 mmol), pinacolborane (0.39 mL, 2.7 mmol) and 3-(benzyloxy)prop-1-en-1-yl]benzene[240] (0.500 g, 2.23 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **234** (0.206 g, 26%) as a colourless oil.[179]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (4H, d, Ar**H**), 7.30-7.27 (1H, m, Ar**H**), 7.26-7.19 (4H, m, Ar**H**), 7.16-7.11 (1H, m, Ar**H**), 4.53-4.42 (2H, m, C**H₂**), 3.50-3.35 (2H, m, $CH_2C\mathbf{H_2}$), 2.52-2.46 (1H, m, C**H**CH_2), 2.27-2.17 (1H, m, $CHC\mathbf{H_A}CH_B$), 1.98-1.89 (1H, m, $CHCH_AC\mathbf{H_B}$), 1.18 (6H, s, 2 × $C\mathbf{H_3}$), 1.15 (6H, s, 2 × $CC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8 (C), 138.6 (C) 128.4 (2 × CH), 128.3 (2 × CH), 127.7 (2 × CH), 127.4 (CH), 125.2 (CH), 83.3 (2 × C), 72.8 (CH_2), 69.4 (CH_2), 32.4 (CH_2), 24.6 (2 × CH_3), 24.5 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2.



235

(±)-*tert*-Butyl *N*-benzyl-*N*-[3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]carbamate (235).

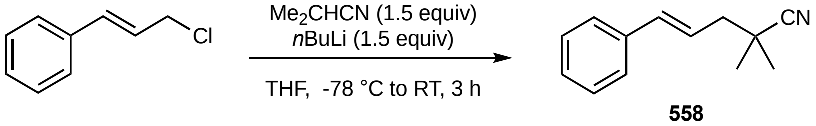
The title compound was prepared according to a modification of General Procedure **1** using CuCl (0.0040 g, 0.039 mmol), *t*BuOK (0.0100 g, 0.0386 mmol), dppBz (0.0170 g, 0.0386 mmol), pinacolborane (0.30 mL, 1.9 mmol) and *tert*-butyl *N*-benzyl-*N*-[(2*E*)-3-phenylprop-2-en-1-yl]carbamate[179] (0.500 g, 1.55 mmol). After stirring the mixture at 60 °C for 24 h, further pinacol borane (0.30 mL, 1.9 mmol) was added and the mixture was stirred at 60 °C for 24 h prior to filtration. Flash chromatography (10% EtOAc/petroleum ether) of the crude material gave boronic ester **235** (0.396 g, 57%) as a colourless oil.[179]

^{1}H NMR (500 MHz, DMSO, 80 °C) δ 7.32-7.27 (2H, m, Ar**H**), 7.25-7.20 (3H, m, Ar**H**), 7.17-7.14 (2H, m, Ar**H**), 7.13-7.09 (3H, m, Ar**H**), 4.38-4.28 (2H, m, $C\mathbf{H_2}Ph$), 3.10-3.07 (2H, m, $CH_2C\mathbf{H_2}N$), 2.23-2.16 (1H, m, C**H**), 2.01-1.91 (1H, m, $CHC\mathbf{H_A}CH_B$), 1.82-1.71 (1H, m, $CHCH_AC\mathbf{H_B}$), 1.38 (9H, s, 3 × $C(O)OCC\mathbf{H_3}$), 1.14 (6H, s, 2 × $BOCC\mathbf{H_3}$), 1.12 (6H, s, 2 × $BOCC\mathbf{H_3}$).

^{13}C NMR (126 MHz, DMSO, 80 °C) δ 154.5 (C), 142.2 (C), 138.3 (C), 127.8 (2 × CH), 127.7 (2 × CH), 127.6 (2 × CH), 126.8 (2 × CH), 126.4 (CH), 124.7 (CH), 82.7 (2 × C), 78.3 (C), 49.3 (CH_2), 45.7 (CH_2), 29.8 (CH_2), 27.7 (3 × CH_3), 24.0 (2 × CH_3), 23.9 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.9.

(*E*)-2,2-Dimethyl-5-phenylpent-4-enenitrile (558)

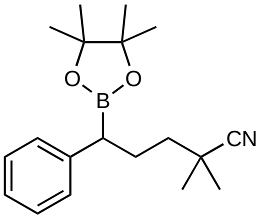


558

Using a variation of the procedure of Hultzsch and co-workers,[241] to a Schlenk flask under inert atmosphere, THF (12 mL) and isobutyronitrile (1.1 mL, 13 mmol) were added and the mixture was cooled to –78 °C. *n*BuLi (2.5 ᴍ in cyclohexane, 5.0 mL, 13 mmol) was added dropwise and the mixture was stirred at **–**78 °C for 10 min. Cinnamyl chloride (1.1 mL, 8.1 mmol) was added dropwise, and the mixture was stirred at **–**78 °C for 30 min and then room temperature for 3 h. The mixture was cooled to 0 °C, and saturated aqueous NH_4Cl (20 mL) and Et_2O (15 mL) were added. The mixture was extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography (5% Et_2O/petroleum ether) of the crude material gave nitrile **558** (0.310 g, 21%) as a yellow oil. The data were consistent with the literature.[241]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.39 (2H, m, Ar**H**), 7.36-7.31 (2H, m, Ar**H**), 7.28-7.26 (1H, m, Ar**H**), 6.53 (1H, d, *J* = 15.7 Hz, ArC**H**), 6.27 (1H, dt, *J* = 15.6, 7.5 Hz, C**H**CH_2), 2.45 (2H, dd, *J* = 7.5, 1.2 Hz, CHC$\mathbf{H_2}$), 1.40 (6H, s, 2 × C$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7 (C), 134.8 (CH), 128.6 (2 × CH), 127.7 (CH), 126.3 (2 × CH), 124.8 (C), 123.5 (CH), 44.3 (CH_2), 32.6 (C), 26.3 (2 × CH_3).



237

(±)-2,2-Dimethyl-5-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanenitrile (237)

The title compound was prepared according to a modification of General Procedure **1** using CuCl (0.0063 g, 0.064 mmol), *t*BuOK (0.0085 g, 0.076 mmol), dppBz (0.0283 g, 0.0634 mmol), pinacolborane (0.22 mL, 1.5 mmol) and alkene **558** (0.235 g, 1.27 mmol). After stirring the mixture at 60 °C for 24 h, further pinacol borane (0.22 mL, 1.5 mmol) was added, and the mixture was stirred at 60 °C for 24 h prior to filtration. Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave *boronic ester* **237** (0.012 g, 3%) as a colourless oil.

IR 2977, 2234 (CN), 1367, 1324, 1141 cm^{-1}.

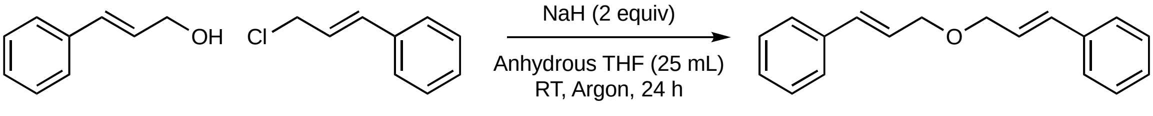
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (2H, m, Ar**H**), 7.22-7.18 (2H, m, Ar**H**), 7.18-7.13 (1H, m, Ar**H**), 2.29-2.22 (1H, m, BC**H**), 2.06-1.96 (1H, m, CHC$\mathbf{H_A}$$CH_B$), 1.91-1.81 (1H, m, CHCH$_A$C**H$_B$**), 1.52-1.42 (2H, m, C**H$_2$**C), 1.32 (3H, s, NCCC**H$_3$**), 1.29 (3H, s, NCCC**H$_3$**), 1.22 (6H, s, 2 × OCC**H$_3$**), 1.19 (6H, s, 2 × OCC**H$_3$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 142.2 (C), 128.4 (2 × CH), 128.3 (2 × CH), 125.5 (CH), 125.1 (C), 83.4 (2 × C), 40.4 (CH$_2$), 32.2 (C), 27.6 (CH$_2$), 26.7 (CH$_3$), 26.4 (CH$_3$), 24.6 (2 × CH$_3$), 24.5 (2 × CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$) δ 33.0.

HRMS (Q-TOF) Exact mass calcd for $[C_{19}H_{28}BNO_2Na]^+$ $[M+Na]^+$**:** 336.2111, found: 336.2105.

((1E,1'E)-Oxybis(prop-1-ene-3,1-diyl))dibenzene (239)

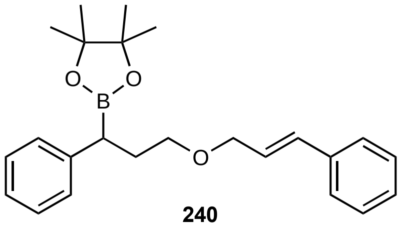


239

Cinnamyl alcohol (1.54 mL, 12.0 mmol) was added to sodium hydride (60% wt in paraffin oil, 0.960 g, 24.0 mmol) in anhydrous THF (25 mL) under argon at 0 °C, and the mixture was stirred for 10 min. Cinnamyl chloride (1.67 mL, 12.0 mmol) was added dropwise, and the mixture was stirred at room temperature for 24 h. MeOH (20 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO$_4$), filtered, and concentrated in *vacuo*. The crude material was purified by flash chromatography (1% EtOAc/petroleum ether) to give ether **239** (2.12 g, 71%) as a yellow oil. The data were consistent with the literature.[242]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46-7.40 (4H, m, Ar**H**), 7.37-7.31 (4H, m, Ar**H**), 7.30-7.26 (2H, m, Ar**H**), 6.67 (2H, d, J = 15.9 Hz, 2 × ArC**H**=CH), 6.35 (2H, dt, J = 15.9, 6.0 Hz, 2 × ArCH=C**H**), 4.23 (4H, dd, J = 6.0, 1.4 Hz, 2 × C**H$_2$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 136.7 (2 × C), 132.6 (2 × CH), 128.5 (4 × CH), 127.7 (2 × CH), 126.5 (4 × CH), 126.0 (2 × CH), 70.7 (2 × CH$_2$).



240

(±)-4,4,5,5-Tetramethyl-2-(1-phenyl-3-{[(2*E*)-3-phenylprop-2-en-1-yl]oxy}propyl)-1,3,2-dioxaborolane (240)

The title compound was prepared according to a modification of General Procedure **1** using CuCl (0.040 g, 0.40 mmol), *t*BuOK (0.054 g, 0.480 mmol), dppBz (0.179 g, 0.400 mmol), pinacolborane (0.58 mL, 4.0 mmol) and ether **239** (1.00 g, 3.78 mmol). The mixture was stirred at 60 °C for 24 h. The crude material was purified by column chromatography (2% EtOAc/petroleum ether) to give *boronic ester* **240** (0.326 g, 22%) as a colourless oil which solidified upon standing.

m.p. 59-61 °C (petroleum ether).

IR 2977, 2931, 1745, 1358, 1141 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42-7.37 (2H, m, Ar**H**), 7.35-7.29 (2H, m, Ar**H**), 7.27-7.21 (5H, m, Ar**H**), 7.17-7.10 (1H, m, Ar**H**), 6.58 (1H, d, J = 16.0 Hz, C**H**=CHCH$_2$), 6.29 (1H, dt, J = 16.0, 6.0 Hz, CH=C**H**CH$_2$), 4.11 (2H, d, J = 6.0 Hz, CH=CHC**H$_2$**), 3.52-3.38 (2H, m, CH$_2$C**H$_2$**O), 2.52-2.45 (1H, m, BC**H**), 2.27-2.16 (1H, m, C**H$_A$**H$_B$CH$_2$O), 1.99-1.89 (1H, m, CH$_A$**H$_B$**CH$_2$O), 1.19 (6H, s, 2 × C**H$_3$**), 1.17 (6H, s, 2 × C**H$_3$**).

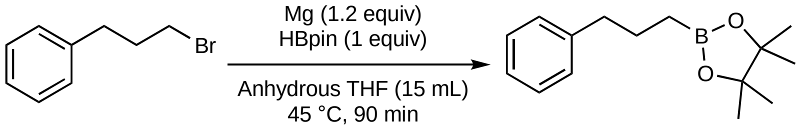
^{13}C NMR (101 MHz, CDCl$_3$) δ 142.8 (C), 136.8 (C), 132.1 (CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 127.5 (CH), 126.5 (CH), 126.4 (2 × CH), 125.2 (CH), 83.3 (2 × C), 71.3 (CH$_2$), 69.4 (CH$_2$), 32.4 (CH$_2$), 24.6 (2 × CH$_3$), 24.5 (2 × CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$) δ 32.7.

HRMS (Q-TOF) Exact mass calcd for [$C_{24}H_{32}BO_3$]$^+$ [M+H]$^+$: 379.2445, found: 379.2439.

5.3.2 Borylation of 1° and 2° Alkyl bromides

(±)-4,4,5,5-Tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (251)



251

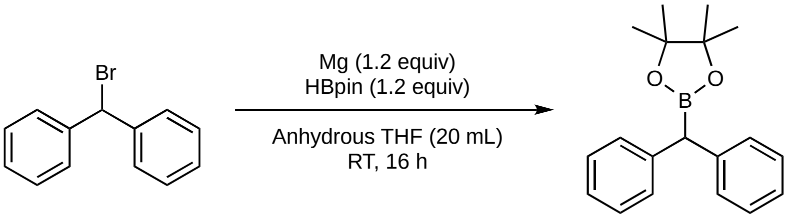
An oven dried two-neck flask fitted with a condenser was charged with magnesium turnings (0.140 g, 5.50 mmol) and purged with argon. Anhydrous THF (15 mL) was added followed by pinacolborane (0.70 ml, 4.2 mmol). 1-Bromo-3-phenylpropane (0.70 ml, 4.6 mmol) was added dropwise over 5 min and the mixture was stirred at 25 °C. After 30 min 1-bromo-3-phenylpropane (0.70 ml, 4.6 mmol) was added and the mixture heated at 45 °C for 90 min. The mixture was cooled to room temperature, diluted with hexane, and quenched with aqueous HCl (0.1 м, 10 mL). The mixture was separated and the organic phase was dried (MgSO$_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (10% EtOAc/petroleum ether) to give the boronic ester **251** (1.48 g, 82%) as a colourless oil. The data were consistent with the literature.[243]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30-7.25 (2H, m, Ar**H**), 7.21-7.14 (3H, m, Ar**H**), 2.65-2.58 (2H, m, ArC**H$_2$**), 1.79-1.69 (2H, m, C**H$_2$**), 1.25 (12H, s, 4 x C**H$_3$**), 0.87-0.81 (2H, m, BC**H$_2$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 142.7 (C), 128.5 (2 × CH), 128.1 (2 × CH), 125.5 (CH), 82.9 (2 × C), 38.6 (CH$_2$), 26.1 (CH$_2$), 24.8 (4 × CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$) δ 34.0.

2-Benzhydryl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (252)



252

Two iodine crystals were added to magnesium (0.298 g, 12.2 mmol) in anhydrous THF (20 mL) under argon, and the mixture was stirred for 10 min. Pinacolborane (1.78 mL, 12.2 mmol) was added dropwise and the mixture stirred for 10 min. Bromodiphenylmethane (2.50 g, 10.2 mmol) was added dropwise and the mixture was stirred for 16 h. The mixture was cooled to 0 °C, aqueous HCl (1 M, 20 mL) added, and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The crude material was purified by flash chromatography (5% EtOAc/petroleum ether) to give boronic ester **252** (2.37 g, 79%) as a white solid. The data were consistent with the literature.[244]

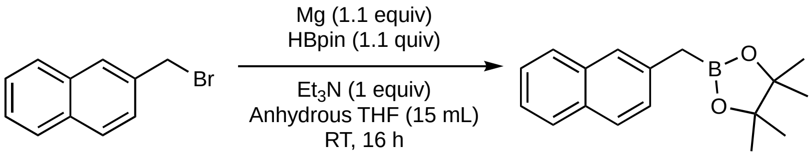
m.p. 77-78 °C (petroleum ether); no literature value available.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.26 (8H, m, Ar**H**), 7.19-7.15 (2H, m, Ar**H**), 3.87 (1H, s, C**H**), 1.24 (12H, s, 4 × C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1 (2 × C), 129.1 (4 × CH), 128.4 (4 × CH), 125.6 (2 × CH), 83.7 (2 × C), 24.6 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.6.

4,4,5,5-Tetramethyl-2-(naphthalen-2-ylmethyl)-1,3,2-dioxaborolane (253)



253

An oven dried two-neck flask fitted with a condenser was charged with magnesium turnings (0.0596 g, 2.47 mmol) and purged with N_2. Anhydrous THF (15 mL), pinacolborane (0.36 mL, 2.5 mmol) and Et_3N (0.32 mL, 2.3 mmol) were added, and the mixture was stirred for 10 min. A solution of 2-(bromomethyl)naphthalene (0.500 g, 2.26 mmol) in THF (15 mL) was added dropwise over 15 min, and the mixture was stirred for 16 h. Hexane (20 mL) and aqueous HCl (0.1 M, 30 mL) were added, and the mixture extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The crude material was purified by flash chromatography (4% Et_2O/petroleum ether) to give boronic ester **253** (0.268 g, 44%) as a colourless oil. The data were consistent with the literature.[245]

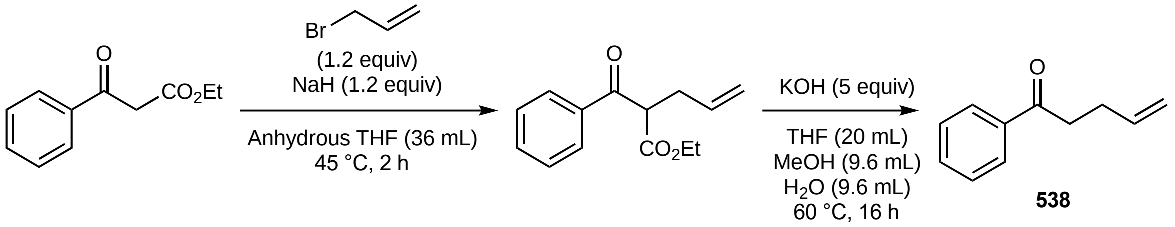
m.p. 70-71 °C (petroleum ether); literature = 67-69 °C (not specified).[246]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.73 (3H, m, Ar**H**), 7.64-7.62 (1H, m, Ar**H**), 7.43-7.33 (3H, m, Ar**H**), 2.47 (2H, s, C**H**$_{\mathbf{2}}$), 1.24 (12H, s, 4 × C**H**$_{\mathbf{3}}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3 (C), 133.8 (C), 131.5 (C), 128.2 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.6 (CH), 125.7 (CH), 124.7 (CH), 83.5 (2 × C), 24.7 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.9.

(±)-1-Phenylpent-4-en-1-one (538).

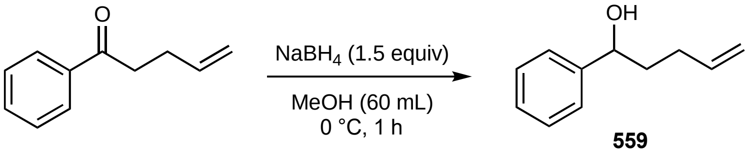


Ethyl benzoylacetate (2.00 g, 10.4 mmol) was added slowly to a mixture of NaH (60% wt in paraffin oil, 0.500 g, 12.5 mmol) and anhydrous THF (36 mL) at 0 °C. The mixture was stirred for 30 min until gas evolution stopped. Allyl bromide (1.51 g, 12.5 mmol) was added dropwise and the mixture heated to 45 °C for 2 h. The mixture was cooled to room temperature, and methanol (9.6 mL) and water (9.6 mL) were added. Potassium hydroxide (2.92 g, 52.0 mmol) was added, and the mixture was heated to 60 °C for 16 h. The mixture was cooled to room temperature, and extracted with aqueous HCl (1 M, 30 mL) and EtOAc (40 mL). The combined organic layers were washed with brine (3 × 20mL), dried ($MgSO_4$), and concentrated in *vacuo*. The crude material was filtered through a plug of silica eluting with Et_2O to give ketone **538** (1.36 g, 72%) as an orange oil. The material was used without further purification. The data were consistent with the literature.[247]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.92 (2H, m, Ar**H**), 7.61-7.53 (1H, m, Ar**H**), 7.52-7.42 (2H, m, Ar**H**), 5.99-5.85 (1H, m, C**H**=CH_2), 5.16-5.05 (1H, m, CH=C**H**$_{\mathbf{A}}$H$_B$), 5.06-4.99 (1H, m, CH=CH$_A$**H**$_{\mathbf{B}}$), 3.14-3.04 (2H, m, COC**H**$_{\mathbf{2}}$), 2.56-2.45 (2H, m, COCH$_2$C**H**$_{\mathbf{2}}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4 (C), 137.3 (CH), 136.9 (C) 133.1 (CH), 128.3 (2 × CH), 128.0 (2 × CH), 115.3 (CH_2), 37.7 (CH_2), 28.1 (CH_2).

(±)-1-Phenylpent-4-en-1-ol (559)

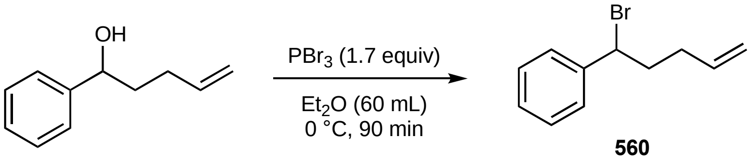


$NaBH_4$ (0.425 g, 11.2 mmol) was added portion-wise to a mixture of ketone **538** (1.20 g, 7.49 mmol) in methanol (60 mL) at 0 °C, and the mixture was stirred for 1 h. The mixture was warmed to room temperature, water (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The crude material was filtered through a plug of silica eluting with Et_2O to give alcohol **559** (1.12 g, 93%) as a yellow oil. The material was used without further purification. The data were consistent with the literature.[248]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (4H, m, Ar**H**), 7.33-7.28 (1H, m, Ar**H**), 5.91-5.79 (1H, m, C**H**=CH_2), 5.09-5.02 (1H, m, CH=C$\mathbf{H_A}$$H_B$), 5.02-4.96 (1H, m, CH=CH$_A$$\mathbf{H_B}$), 4.75-4.67 (1H, m, OC**H**), 2.25-2.05 (2H, m, OCHCH$_2$C$\mathbf{H_2}$), 1.99-1.86 (2H, m, OCHC$\mathbf{H_2}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6 (C), 138.2 (CH), 128.45 (2 × CH), 127.6 (CH), 125.9 (2 × CH), 114.9 (CH_2), 74.0 (CH), 38.0 (CH_2), 30.0 (CH_2).

(±)-(1-Bromo-pent-4-enyl)benzene (560).

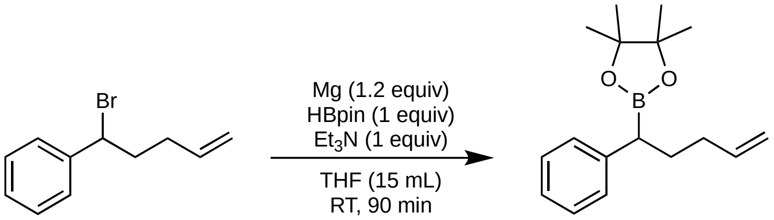


PBr_3 (1.1 mL, 12 mmol) was added dropwise to alcohol **559** (1.12 g, 6.90 mmol) in Et_2O (2.5 mL) at 0 °C, and the mixture was stirred for 90 min. Saturated aqueous NH_4Cl (20 mL) was added slowly, and the mixture was warmed to room temperature and extracted with Et_2O (2 × 40 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL), dried ($MgSO_4$), and concentrated in *vacuo*. The crude material was filtered through a plug of silica eluting with Et_2O to give bromide **560** (1.54 g, 99%) as a yellow oil. The material was used without further purification. The data were consistent with the literature.[249]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.30 (5H, m, Ar**H**), 5.87-5.74 (1H, m, C**H**=CH_2), 5.13-5.01 (2H, m, CH=C$\mathbf{H_2}$), 5.05-4.90 (1H, m, BrC**H**), 2.43-2.38 (1H, m, BrCHC$\mathbf{H_A}$$H_B$), 2.29-2.13 (3H, m, BrCHCH$_A$$\mathbf{H_B}$, $\mathbf{CH_2}$CH=CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (C), 136.6 (CH), 128.7 (2 × CH), 128.3 (CH), 127.3 (2 × CH), 115.9 (CH_2), 54.8 (CH), 38.9 (CH_2), 32.1 (CH_2).

(±)-4,4,5,5-Tetramethyl-2-(1-phenylpent-4-en-1-yl)-1,3,2-dioxaborolane (254).



254

An oven dried two-neck flask fitted with a condenser was charged with magnesium turnings (0.207 g, 8.58 mmol) and purged with N_2. Anhydrous THF (15 mL), pinacolborane (1.0 mL, 7.1 mmol) and Et_3N (1.0 mL, 7.2 mmol) were added. Bromide **560** (1.58 g, 7.02 mmol) was added dropwise in THF (15 mL) over 15 min and the mixture was heated at 65 °C for 16 h. The mixture was cooled to room temperature, hexane (20 mL) and aqueous HCl (0.1 M, 30 mL) were added, and the mixture extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The crude material was purified by flash chromatography (2% EtOAc/petroleum ether) to give *boronic ester* **254** (0.900 g, 47%) as a colourless oil.

IR 3063, 2978, 1639, 1321, 1142 cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.19 (4H, m, Ar**H**), 7.17-7.11 (1H, m, Ar**H**), 5.88-5.75 (1H, m, C**H**=CH_2), 5.04-4.92 (2H, m, CH=C$\mathbf{H_2}$), 2.38-2.31 (1H, m, BC**H**), 2.09-1.99 (2H, m, C$\mathbf{H_2}$CH=CH_2), 1.99-1.90 (1H, m, BCHC$\mathbf{H_A}$$H_B$), 1.82-1.70 (1H, m, BCHC$H_A$$\mathbf{H_B}$), 1.22 (6H, s, 2 × C$\mathbf{H_3}$), 1.20 (6H, s, 2 × C$\mathbf{H_3}$).

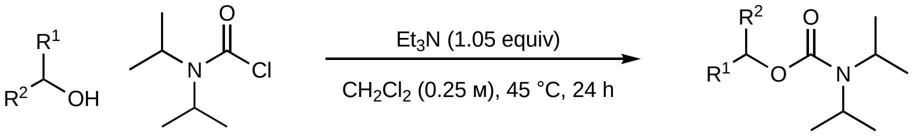
^{13}**C NMR** (101 MHz, $CDCl_3$) δ 143.1 (C), 138.7 (CH), 128.4 (2 × CH), 128.26 (2 × CH), 125.17 (CH), 114.65 (CH_2), 83.26 (2 × C), 33.29 (CH_2), 31.74 (CH_2), 24.62 (2 × CH_3), 24.56 (2 × CH_3).

^{11}**B NMR** (128 MHz, $CDCl_3$) δ 33.3.

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{26}BO_2]^+$ $[M+H]^+$: 273.2026, found: 273.2023.

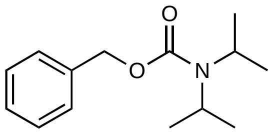
5.3.3 Preparation of Carbamates

General Procedure 2: Carbamate formation from 1° and 2° Alcohols.



(1.05 equiv)

N,N-Diisopropylcarbamoyl chloride (1.05 equiv) was added to a mixture of corresponding alcohol (1 equiv) and Et_3N (1.05 equiv) in CH_2Cl_2 (0.25 M). The mixture was stirred at 45 °C for 24 h, cooled to room temperature, washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The crude material was purified by flash chromatography to give the corresponding carbamate.



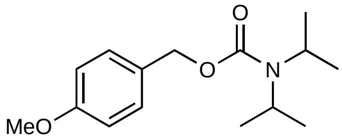
256

Benzyl *N,N*-diisopropylcarbamate (256)

The title compound was prepared according to General Procedure **2** using *N,N*-diisopropylcarbamoyl chloride (3.32 g, 20.3 mmol), benzyl alcohol (2.0 mL, 19 mmol) and Et_3N (2.8 mL, 20 mmol). Flash chromatography (10% EtOAc/petroleum ether) of the crude material gave carbamate **256** (4.23 g, 93%) as a colourless oil. The data were consistent with the literature.[250]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (4H, m, Ar**H**), 7.34-7.29 (1H, m, Ar**H**), 5.15 (2H, s, C$\mathbf{H_2}$), 4.23-3.71 (2H, m, 2 × C**H**), 1.23 (6H, s, 2 × C$\mathbf{H_3}$), 1.22 (6H, s, 2 × C$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (C), 137.1 (C), 128.4 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 66.5 (CH_2), 45.8 (br, 2 × CH), 20.7 (4 × CH_3).



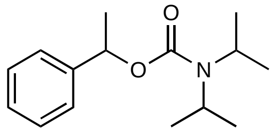
297

4-Methoxybenzyl *N,N*-diisopropylcarbamate (297)

The title compound was prepared according to General Procedure **2** using *N,N*-diisopropylcarbamoyl chloride (3.76 g, 23.0 mmol), 4-methoxybenzyl alcohol (2.7 mL, 22 mmol) and Et_3N (3.2 mL, 23 mmol). Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave carbamate **297** (3.93 g, 67%) as an amorphous solid. The data were consistent with the literature.[251]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, d, J = 8.6 Hz, Ar**H**), 6.89 (2H, d, J = 8.6 Hz, Ar**H**), 5.07 (2H, s, C$\mathbf{H_2}$), 4.22-3.94 (1H, m, C**H**), 3.88-3.67 (4H, m, C**H**, C$\mathbf{H_3}$), 1.24-1.15 (12H, m, 4 × C$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C), 155.6 (C), 129.7 (2 × CH), 129.2 (C), 113.7 (2 × CH), 66.2 (CH_2), 55.2 (CH_3), 46.1 (br, 2 × CH), 21.4 (2 × CH_3), 20.6 (2 × CH_3).



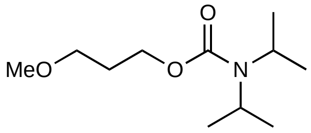
274

(±)-1-Phenylethyl *N,N*-diisopropyl carbamate (274)

The title compound was prepared according to General Procedure **2** using *N,N*-diisopropylcarbamoyl chloride (2.85 g, 17.4 mmol), (±)-1-phenylethanol (2.0 mL, 17 mmol) and Et_3N (2.4 mL, 17 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave carbamate **274** (2.95 g, 71%) as a colourless oil. The data were consistent with the literature.[252]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.29 (4H, m, Ar**H**), 7.32-7.23 (1H, m, Ar**H**), 5.85 (1H, q, J = 6.6 Hz, ArC**H**), 4.26-3.62 (2H, m, 2 × C**H**N), 1.56 (3H, d, J = 6.6 Hz, ArCHC$\mathbf{H_3}$), 1.22 (12H, s, 4 × C$\mathbf{H_3}$CHN).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (C), 142.8 (C), 128.4 (2 × CH), 127.4 (CH), 126.0 (2 × CH), 72.7 (CH), 46.3 (br, 2 × CH), 22.9 (CH_3), 21.4 (2 × CH_3), 20.6 (2 × CH_3).



270

3-Methoxypropyl *N,N*-diisopropylcarbamate (270)

The title compound was prepared according to General Procedure **2** using *N,N*-diisopropylcarbamoyl chloride (3.96 g, 24.2 mmol), 3-methoxypropan-1-ol (2.2 mL, 23 mmol) and Et_3N (3.4 mL, 24 mmol). Flash chromatography (10% EtOAc/petroleum ether) of the crude material gave *carbamate* **270** (3.88 g, 77%) as a yellow oil.

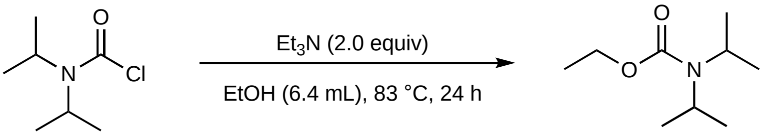
IR 2969, 2932, 1687, 1435, 1289 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (2H, t, *J* = 6.4 Hz, C(O)OC**H$_2$**), 4.13-3.55 (2H, m, 2 × CH_3C**H**), 3.47 (2H, t, *J* = 6.4 Hz, C**H$_2$**OCH_3), 3.34 (3H, s, OC**H$_3$**), 1.92 (2H, p, *J* = 6.4 Hz, OCH_2C**H$_2$**), 1.25-1.15 (12H, m, 4 × CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (C), 69.6 (CH_2), 61.7 (CH_2), 58.6 (CH_3), 46.3 (br, 2 × CH), 29.4 (CH_2), 20.9 (4 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{11}H_{24}NO_3]^+$ $[M+H]^+$: 218.1756, found: 218.1751.

Ethyl *N,N*-diisopropylcarbamate (264)



264

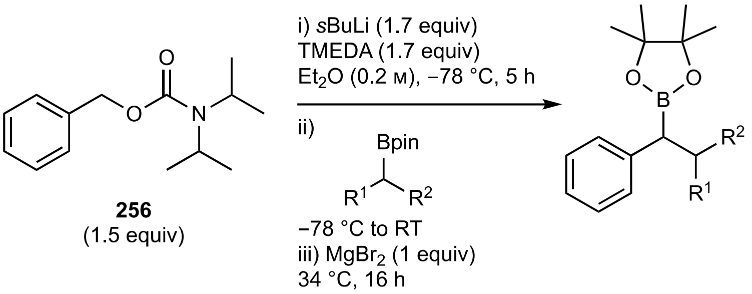
N,N-Diisopropylcarbamoyl chloride (2.01 g, 12.3 mmol) was added to a mixture of Et_3N (3.4 mL, 24 mmol) in ethanol (6.4 mL, 110 mmol). The mixture was stirred at 83 °C for 24 h, cooled to room temperature, and concentrated *in vacuo.* Et_2O (25 mL) was added, washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* Flash chromatography (10 % EtOAc/petroleum ether) of the crude material gave carbamate **264** (1.98 g, 94%) as a colourless oil. The data were consistent with the literature.[253]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (2H, q, *J* = 7.1 Hz, C**H$_2$**), 4.06-3.66 (2H, m, 2 × CH_3C**H**), 1.27 (3H, t, *J* = 7.1 Hz, CH_2C**H$_3$**), 1.22 (6H, s, 2 × CHC**H$_3$**), 1.20 (6H, s, 2 × CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (C), 60.4 (CH_2), 46.1 (br, 2 × CH), 21.0 (4 × CH_3), 14.7 (CH_3).

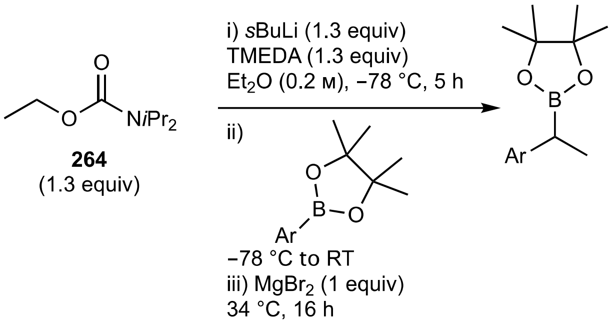
5.3.4 Lithiation Borylation Reactions

General Procedure 3: Lithiation-Borylation of Carbamate 256 with Boronic Esters.



Using a modification of the procedure by Aggarwal, Crudden and co-workers,[8] a Schlenk flask containing carbamate **256** (1.5 equiv) was backfilled with nitrogen three times. TMEDA (1.7 equiv) and anhydrous Et_2O (0.2 м) were added and the mixture was cooled to **–**78 °C. *s*BuLi (1.7 equiv) was added dropwise and the mixture was stirred at **–**78 °C for 4 h. The boronic ester (1 equiv) was added dropwise, and the mixture was stirred at **–**78 °C for 1 h. A solution of $MgBr_2$ in Et_2O[i] (1 equiv) was added dropwise and the mixture was stirred at 34 °C for 16 h. The mixture was cooled to room temperature, and saturated aqueous NH_4Cl (20 mL) and Et_2O (15 mL) were added. The mixture was extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The mixture was purified by flash chromatography to give the boronic ester.

General Procedure 4: Lithiation-Borylation of Carbamate 264 with Heteroaryl Boronic Esters.



Using a modification of the procedure by Aggarwal and co-workers,[166] a Schlenk flask containing carbamate **264** (1.3 equiv) was backfilled with nitrogen three times. TMEDA (1.3 equiv) and anhydrous Et_2O (0.2 м) were added, and the mixture was cooled to –78 °C. *s*BuLi (1.3 equiv) was added dropwise and the mixture was stirred at **–**78 °C for 4 h. The

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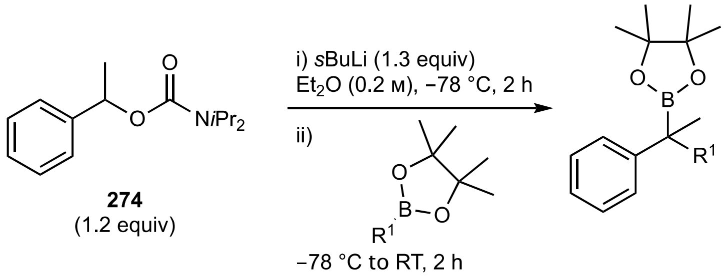
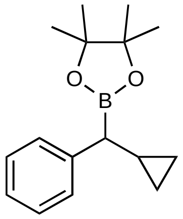
[i] Freshly prepared before use, by the following procedure: A flask was charged with Mg turnings (1.1 equiv) and purged with N_2. Et_2O (3 mL) followed by 1,2-dibromoethane (1 equiv) were added, and the mixture was stirred at room temperature for 2 h.

boronic ester (1 equiv) was added dropwise, and the mixture was stirred at –78 °C for 1 h. A solution of $MgBr_2$ in Et_2O[i] (1 equiv) was added dropwise and the mixture was stirred at 34 °C for 16 h. The mixture was cooled to room temperature, and H_2O (20 mL) and Et_2O (15 mL) were added. The mixture was extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

General Procedure 5: Lithiation-Borylation of Carbamate 274 with Boronic Esters.



Using a modification of the procedure by Aggarwal and co-workers,[168] a Schlenk flask containing carbamate **274** (1.2 equiv) was backfilled with nitrogen three times. Anhydrous Et_2O (0.2 M) was added, and the mixture was cooled to –78 °C. *s*BuLi (1.3 equiv) was added dropwise and the mixture was stirred at –78 °C for 1 h. The boronic ester (1 equiv) was added dropwise, and the mixture was stirred at –78 °C for 1 h and then at room temperature for 2 h. H_2O (20 mL) and Et_2O (15 mL) were added, and the mixture extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*.



258

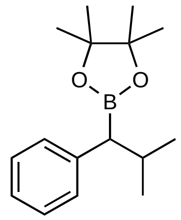
(±)-2-(Cyclopropylphenylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (258)

The title compound was prepared according to General Procedure **3** using carbamate **256** (1.08 g, 4.59 mmol), TMEDA (0.69 mL, 4.6 mmol), *s*BuLi (1.3 M in cyclohexane, 3.2 mL, 4.3 mmol) and cyclopropyl pinacol boronic ester (0.5 mL, 2.7 mmol). Flash chromatography (1% Et_2O/petroleum ether) of the crude material gave boronic ester **258** (0.67 g, 96 %) as a colourless oil. The data were consistent with the literature.[238]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (1H, m, Ar**H**), 7.19-7.11 (1H, m, Ar**H**), 1.77-1.69 (1H, m, C**H**), 1.24 (6H, s, 2 × C**H$_3$**), 1.23 (6H, s, 2 × C**H$_3$**), 1.20-1.11 (1H, m, C**H**CH_2), 0.63-0.53 (1H, m, CHC**H$_2$**), 0.53-0.43 (1H, m, CHC**H$_2$**), 0.30-0.21 (1H, m, CHC**H$_2$**), 0.14-0.07 (1H, m, CHC**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (C), 128.2 (2 × CH), 128.2 (2 × CH), 125.2 (CH), 83.3 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 13.1 (CH), 5.0 (CH_2), 4.7 (CH_2).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.4.



257

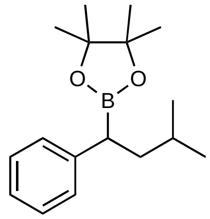
(±)-4,4,5,5-Tetramethyl-2-(2-methyl-1-phenylpropyl)-1,3,2-dioxaborolane (257)

The title compound was prepared according to General Procedure **3** using carbamate **256** (1.00 g, 4.25 mmol), TMEDA (0.64 mL, 4.3 mmol), *s*BuLi (1.3 M in cyclohexane, 3.2 mL, 4.3 mmol), isopropyl pinacol boronic ester[254] (0.430 g, 2.50 mmol), and $MgBr_2$ (1.38 g, 7.50 mmol). Flash chromatography (5% Et_2O/petroleum ether) of the crude material gave boronic ester **257** (0.554 g, 85%) as a colourless oil. The data were consistent with the literature.[255]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.18 (4H, m, Ar**H**), 7.16-7.10 (1H, m, Ar**H**), 2.18-2.06 (1H, m, C**H**CH_3), 2.00-1.95 (1H, m, BC**H**), 1.21 (6H, s, 2 × C$\mathbf{H_3}$), 1.19 (6H, s, 2 × C$\mathbf{H_3}$), 1.06-1.01 (3H, m, C$\mathbf{H_3}$), 0.76-0.71 (3H, m, C$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2 (C), 129.0 (2 × CH), 128.1 (2 × CH), 125.1 (CH), 83.1 (2 × C), 30.9 (CH), 24.6 (2 × CH_3), 24.5 (2 × CH_3), 23.1 (CH_3), 21.9 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2.



259

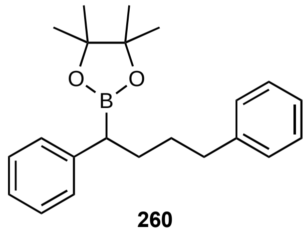
(±)-4,4,5,5-Tetramethyl-2-(3-methyl-1-phenylbutyl)-1,3,2-dioxaborolane (259)

The title compound was prepared according to General Procedure **3** using carbamate **256** (1.00 g, 4.25 mmol), TMEDA (0.64 mL, 4.3 mmol), *s*BuLi (1.3 M in cyclohexane, 3.2 mL, 4.3 mmol), isobutyl pinacol boronic ester[254] (0.460 g, 2.50 mmol), and $MgBr_2$ (1.38 g, 7.50 mmol). Flash chromatography (1% Et_2O/petroleum ether) of the crude material gave boronic ester **259** (0.300 g, 46%) as a colourless oil. The data were consistent with the literature.[16]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.20 (4H, m, Ar**H**), 7.16-7.10 (1H, m, Ar**H**), 2.47-2.39 (1H, m, C**H**), 1.74-1.60 (2H, m, CHC$\mathbf{H_2}$), 1.53-1.41 (1H, m, C**H**CH_2), 1.20 (6H, s, 2 × C$\mathbf{H_3}$), 1.18 (6H, s, 2 × C$\mathbf{H_3}$), 0.91-0.85 (6H, m, 2 × C$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (C), 128.3 (2 × CH), 128.2 (2 × CH), 125.0 (CH), 83.2 (2 × C), 41.4 (CH_2), 26.8 (CH), 24.6 (4 × CH_3), 23.0 (CH_3), 22.1 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.7.



260

(±)-2-(1,4-Diphenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (260)

The title compound was prepared according to General Procedure **3** using carbamate **256** (0.746 g, 3.17 mmol), TMEDA (0.48 mL, 3.2 mmol), *s*BuLi (1.3 M in cyclohexane, 2.4 mL, 3.2 mmol), and boronic ester **251** (0.459 g, 1.87 mmol). Flash chromatography (20% Et_2O/petroleum ether) of the crude material gave boronic ester **260** (0.40 g, 69%) as a white solid. The data were consistent with the literature.[256]

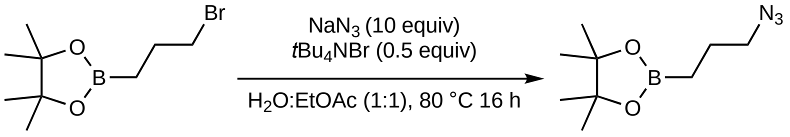
m.p. 40-42 °C (petroleum ether); no literature value available.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.13 (10H, m, Ar**H**), 2.69-2.54 (2H, m, C**H_2**), 2.38-2.31 (1H, m, C**H**CH_2), 1.99-1.85 (1H, m, CHC**H_2**), 1.80-1.67 (1H, m, CHC**H_2**), 1.66-1.56 (2H, m, C**H_2**), 1.22 (6H, s, 2 × C**H_3**), 1.19 (6H, s, 2 × C**H_3**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (C), 142.7 (C), 128.3 (2 × CH), 128.2 (2 × CH), 128.2 (2 × CH), 125.5 (CH), 125.1 (CH), 83.3 (2 × C), 35.9 (CH_2), 32.3 (CH_2), 31.1 (CH_2), 24.6 (2 × CH_3), 24.6 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.3.

2-(3-Azidopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (561)



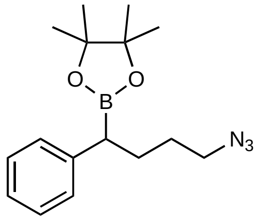
561

Using a modification of the procedure by Aggarwal and co-workers,[257] 2-(3-bromopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.7 mL, 3.3 mmol) was added to a mixture of sodium azide (2.16 g, 33.2 mmol) and tetrabutylammonium bromide (0.535 g, 1.66 mmol) in H_2O (8.5 mL) and EtOAc (8.5 mL). The mixture was stirred at 80 °C for 16 h. The mixture was cooled to room temperature, extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (100% Et_2O) to give the boronic ester **561** (0.668 g, 95%) as a colourless oil. The data were consistent with the literature.[257]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (2H, t, *J* = 7.0 Hz, C**H_2**N), 1.72 (2H, tt, *J* = 7.0 Hz, 7.7 Hz, C**H_2**CH_2N), 1.26 (12H, s, 4 × C**H_3**), 0.85 (2H, t, *J* = 7.7 Hz, BC**H_2**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 83.2 (2 × C), 53.4 (CH_2), 24.8 (4 × CH_3), 23.5 (CH_2).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7.



261

(±)-2-(4-Azido-1-phenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (261)

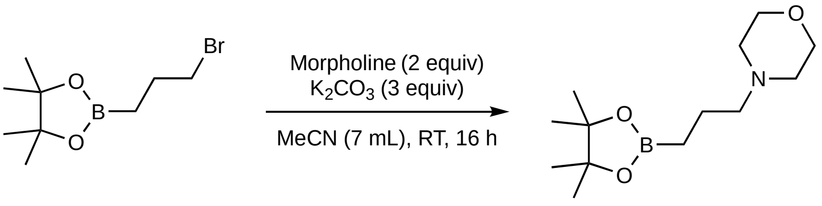
The title compound was prepared according to General Procedure **3** using carbamate **256** (1.14 g, 4.83 mmol), TMEDA (0.72 mL, 4.8 mmol), *s*BuLi (1.3 м in cyclohexane, 3.7 mL, 4.8 mmol), and boronic ester **561** (0.600 g, 2.84 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **261** (0.479 g, 56%) as a colourless oil.[179]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.29-7.24 (2H, m, Ar**H**), 7.24-7.12 (3H, m, Ar**H**), 3.27-3.21 (2H, m, C**H$_2$**N$_3$), 2.34-2.27 (1H, m, C**H**CH$_2$), 1.98-1.86 (1H, m, CHC**H$_A$**H$_B$), 1.78-1.69 (1H, m, CHCH$_A$**H$_B$**), 1.62-1.54 (2H, m, CHCH$_2$C**H$_2$**), 1.22 (6H, s, 2 × C**H$_3$**), 1.20 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 142.5 (C), 128.4 (2 × CH), 128.3 (2 × CH), 125.4 (CH), 83.4 (2 × C), 51.4 (CH$_2$), 29.5 (CH$_2$), 28.3 (CH$_2$), 24.6 (2 × CH$_3$), 24.5 (2 × CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$) δ 33.4.

4-[3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]morpholine (562)



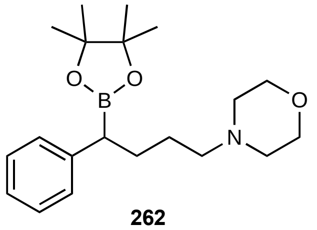
562

2-(3-Bromopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.58 mL, 2.7 mmol) and morpholine (0.48 mL, 5.5 mmol) was added to a mixture of K$_2$CO$_3$ (1.14 g, 8.22 mmol) in MeCN (7 mL). The mixture was stirred at room temperature for 16 h. Water (20 mL) was added and the mixture extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (MgSO$_4$), filtered, and concentrated *in vacuo.* The crude material was purified by passing through a plug of silica eluting with Et$_2$O giving the boronic ester **562** (0.670 g, 96%) as a colourless oil.[179]

^{1}H NMR (400 MHz, CDCl$_3$) δ 3.74-3.67 (4H, m, 2 × OC**H$_2$**), 2.48-2.38 (4H, m, 2 × NC**H$_2$**), 2.34-2.26 (2H, m, NC**H$_2$**), 1.67-1.51 (2H, m, BCH$_2$C**H$_2$**), 1.24 (12H, s, 4 × C**H$_3$**), 0.81-0.71 (2H, m, BC**H$_2$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 83.0 (2 × C), 67.0 (2 × CH$_2$), 61.4 (CH$_2$), 53.7 (2 × CH$_2$), 24.8 (2 × CH$_3$), 24.8 (2 × CH$_3$), 20.9 (CH$_2$).

^{11}B NMR (128 MHz, CDCl$_3$) δ 33.9.



262

(±)-4-[4-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]morpholine (262)

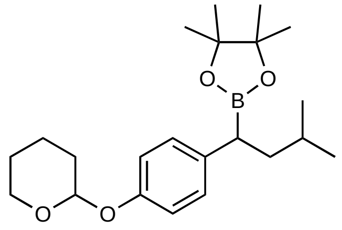
The title compound was prepared according to a modification of General Procedure **3**, using carbamate **256** (0.940 g, 4.00 mmol), TMEDA (0.60 mL, 4.0 mmol), *s*BuLi (1.3 M in cyclohexane, 2.9 mL, 4.0 mmol) and boronic ester **562** (0.600 g, 2.35 mmol). The mixture was worked up using H$_2$O (20 mL) and Et$_2$O (15 mL), instead of saturated aqueous NH$_4$Cl. Flash chromatography (50% EtOAc/petroleum ether) of the crude material gave boronic ester **262** (0.487 g, 60%) as a white solid.[179]

m.p. 45-47 °C (50% EtOAc/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.22 (2H, m, Ar**H**), 7.22-7.18 (2H, m, Ar**H**), 7.15-7.10 (1H, m, Ar**H**), 3.72-3.65 (4H, m, 2 × OC$\mathbf{H_2}$), 2.42-2.26 (7H, m, 3 × NC$\mathbf{H_2}$ + C**H**) 1.90-1.80 (1H, m, CHC$\mathbf{H_A}$H$_B$), 1.73-1.62 (1H, m, CHCH$_A$$\mathbf{H_B}$), 1.50-1.41 (2H, m, NCH$_2C\mathbf{H_2}$), 1.21 (6H, s, 2 × C$\mathbf{H_3}$), 1.19 (6H, s, 2 × C$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0 (C), 128.3 (2 × CH), 128.3 (2 × CH), 125.2 (CH), 83.3 (2 × C), 67.0 (2 × CH_2), 59.0 (CH_2), 53.7 (2 × CH_2), 30.3 (CH_2), 26.0 (CH_2), 24.6 (2 × CH_3), 24.6 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2.



263

(±)-4,4,5,5-tetramethyl-2-{3-methyl-1-[4-(oxan-2-yloxy)phenyl]butyl}-1,3,2-dioxaborolane (263)

The title compound was prepared according to a modification of General Procedure **3**, using carbamate **557** (0.941 g, 2.81 mmol), TMEDA (0.49 mL, 3.3 mmol), *s*BuLi (1.3 M in cyclohexane, 2.5 mL, 3.3 mmol) and isobutyl pinacol boronic ester^{254} (0.344 g, 1.87 mmol). The mixture was worked up using H_2O (20 mL) and Et_2O (15 mL), instead of saturated aqueous NH_4Cl. Flash chromatography (2% Et_2O/petroleum ether) of the crude material gave *boronic ester* **263** (0.597 g, 85%) as a colourless oil.

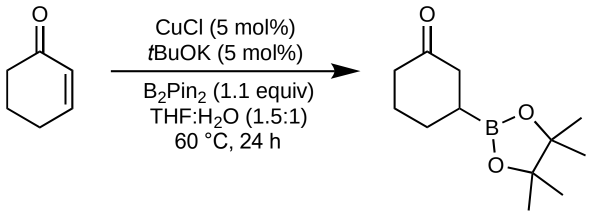
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (2H, d, J = 7.7 Hz, Ar**H**), 6.95 (2H, d, J = 7.7 Hz, Ar**H**), 5.45-5.33 (1H, m, OC**H**), 4.05-3.91 (1H, m, C$\mathbf{H_A}$H$_B$O), 3.71-3.56 (1H, m, CH$_A$$\mathbf{H_B}$O), 2.45-2.33 (1H, m, BC**H**), 2.09-1.94 (1H, m, OCHC$\mathbf{H_A}$H$_B$), 1.90-1.80 (2H, m, OCHCH$_2$C$\mathbf{H_2}$), 1.72-1.54 (5H, m, OCHCH$_A$$\mathbf{H_B}$,OCH$_2C\mathbf{H_2}$ and BCHC$\mathbf{H_2}$), 1.54-1.41 (1H, m, C**H**CH$_3$), 1.27-1.14 (12H, m, 4 × CC$\mathbf{H_3}$), 0.95-0.80 (6H, m, 2 × CHC$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7 (C), 136.4 (C), 129.1 (2 × CH), 116.3 (2 × CH), 96.6 (CH), 83.1 (2 × C), 62.1 (CH_2), 41.6 (CH_2), 30.5 (CH_2), 26.7 (CH), 25.2 (CH_2), 24.6 (4 × CH_3), 23.0 (CH_3), 22.1 (CH_3), 19.0 (CH_2).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.4.

HRMS (Q-TOF) Exact mass calcd for $[C_{22}H_{35}BO_4Na]^+$ $[M+Na]^+$: 397.2526, found: 397.2521.

(±)-3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexanone (33)[258]



33

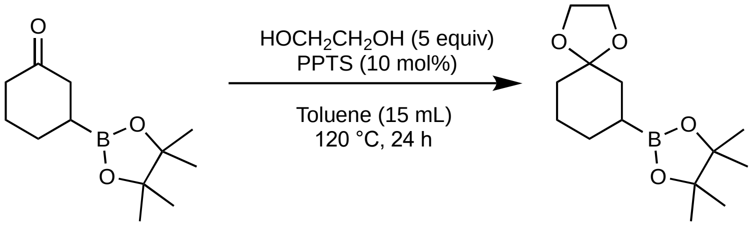
Using a modification of the procedure by Yun and co-workers,[258] an oven dried flask was charged with CuCl (0.0800 g, 0.851 mmol), *t*BuOK (0.0950 g, 0.851 mmol), and purged with argon. THF (10 mL) was added, and the mixture stirred at room temperature for 10 min. A solution of bis(pinacolato)diboron (2.03 g, 8.01 mmol) in THF (4 mL) was added, and the mixture was stirred for 10 min. 2-Cyclohexene-1-one (0.70 mL, 7.3 mmol) and water (9 mL) were added, and the reaction stirred at 60 °C for 24 h. The mixture was diluted with EtOAc (40 mL), washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (50% EtOAc/petroleum ether) to give boronic ester **33** (1.22 g, 76%) as a colourless oil. The data were consistent with the literature.[259]

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41-2.24 (4H, m, 2 x C$\mathbf{CH_2}$), 2.12-2.02 (1H, m, C**H**), 1.92-1.84 (1H, m, CCH$_2$C$\mathbf{H_A}$H$_B$), 1.81-1.68 (1H, m, CCH$_2$CH$_A$$\mathbf{H_B}$), 1.68-1.57 (1H, m, CHC$\mathbf{H_A}H_BCH_2$), 1.51-1.40 (1H, m, CHCH$_A$$\mathbf{H_B}CH_2$), 1.24 (12H, s, 4 × C$\mathbf{H_3}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.3 (C), 83.4 (2 × C), 42.5 (CH_2), 41.8 (CH_2), 28.4 (CH_2), 26.5 (CH_2), 24.7 (2 × CH_3), 24.7 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2.

(±)-2-{1,4-Dioxaspiro[4.5]decan-7-yl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (293).



33 **293**

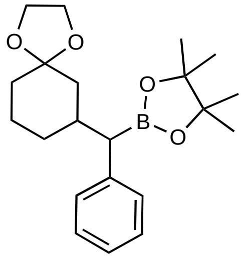
Boronic ester **33** (1.47 g, 6.56 mmol) was added to a mixture of pyridinium *p*-toluenesulfonate (0.165 g, 0.656 mmol) and ethylene glycol (1.8 mL, 33 mmol) in toluene (15 mL). The mixture was stirred at 120 °C under Dean-Stark conditions for 24 h. The mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with ether (2 × 40 mL). The combined organic layers were washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (10% EtOAc/petroleum ether) to give *boronic ester* **293** (1.04 g, 60%) as a clear yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97-3.90 (4H, m, 2 × OC**H₂**), 1.79-1.49 (8H, m, BC**H,** 2 x CC**H₂,** CCH_2C**H₂,** CHC**H**$_A$H$_B$CH₂), 1.36-1.27 (1H, m, 1H, m, CHCH$_A$**H**$_B$CH₂), 1.23 (12H, s, 4 × C**H₃**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 108.9 (C), 82.9 (2 × C), 64.2 (CH_2), 64.0 (CH_2), 35.7 (CH_2), 35.4 (CH_2), 26.3 (CH_2), 24.8 (2 × CH_3), 24.7 (2 × CH_3), 24.5 (CH_2).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7.

HRMS (Q-TOF) Exact mass calcd for $[C_{14}H_{26}BO_4]^+$ $[M+H]^+$: 269.1924 found: 269.1919



294

(±)-2-({1,4-Dioxaspiro[4.5]decan-7-yl}(phenyl)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (294).

The title compound was prepared according to General Procedure **3** using carbamate **256** (0.756 g, 3.21 mmol), TMEDA (0.48 mL, 3.2 mmol), *s*BuLi (1.3 M in cyclohexane, 2.5 mL, 3.2 mmol), and boronic ester **293** (0.498 g, 1.86 mmol). Flash chromatography (10% EtOAc/petroleum ether) of the crude material gave *boronic ester* **294** (0.579 g, 87%) as a yellow oil.

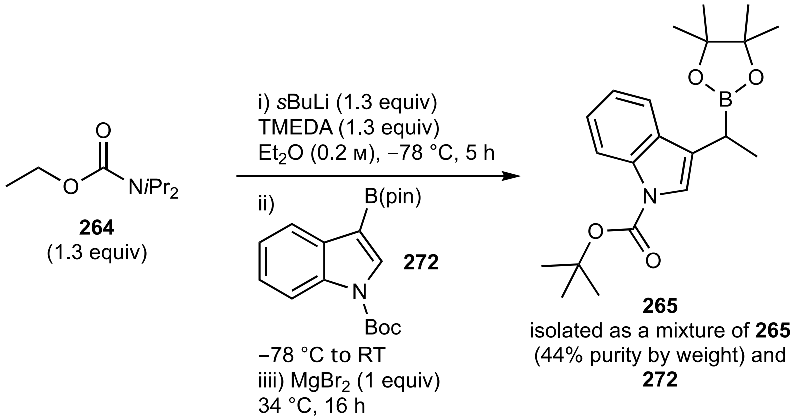
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.18 (4H, m, Ar**H**), 7.16-7.09 (1H, m, Ar**H**), 3.89-3.74 (4H, m, 2 × OC**H₂**), 2.20-2.09 (1H, m, BC**H**), 1.87-1.20 (9H, m**,** ArCHC**H,** 2 x CC**H₂,** CCH_2C**H₂,** CHC**H₂**CH₂), 1.19 (6H, s, 2 × C**H₃**), 1.17 (6H, s, 2 × C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0 (C), 129.1 (2 × CH) , 128.1 (2 × CH), 125.2 (CH), 109.4 (C), 83.2 (2 × C), 64.1 (CH_2), 63.9 (CH_2), 40.4 (CH_2), 37.9 (CH), 34.9 (CH_2), 32.1 (CH_2), 24.6 (2 × CH_3), 24.5 (2 × CH_3), 23.3 (CH_2).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.9.

HRMS (Q-TOF) Exact mass calcd for $[C_{21}H_{31}BO_4Na]^+$ $[M+Na]^+$: 381.2213, found: 381.2208.

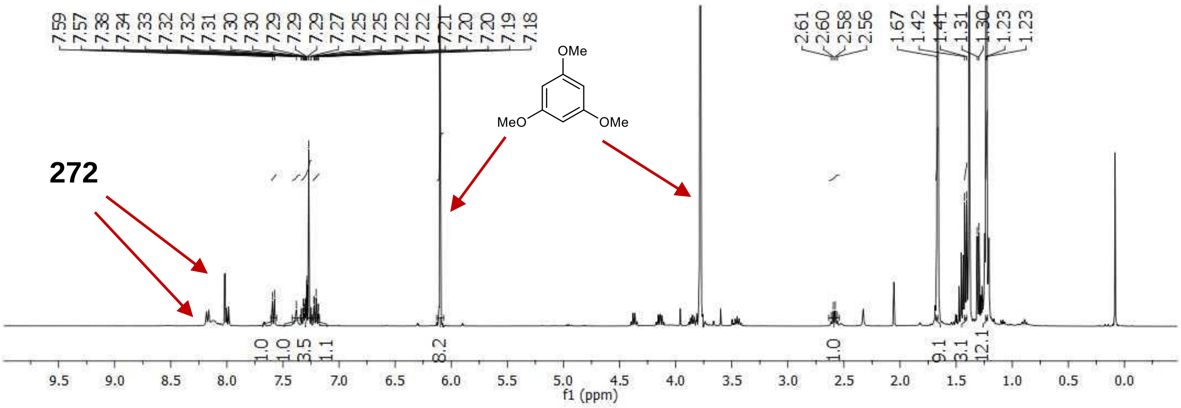
(±)-*tert*-Butyl 3-[1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl]-1*H*-indole-1-carboxylate (265).



The title compound was prepared according to General Procedure **4** using carbamate **264** (0.329 g, 1.90 mmol), TMEDA (0.29 mL, 1.9 mmol), *s*BuLi (1.3 м in cyclohexane, 1.5 mL, 1.9 mmol), and boronic ester **272** (0.500 g, 1.46 mmol in Et$_2$O 5 mL) to give a crude mixture containing **265** and **272** (0.657 g) as a orange oil. Through ^{1}H NMR analysis of the mixture (9.1 mg of sample with 5.3 mg of 1,3,5-trimethoxybenzene added as an internal standard), the purity of the boronic ester **265** was determined to 44% by weight. The material was used without further purification.[179]

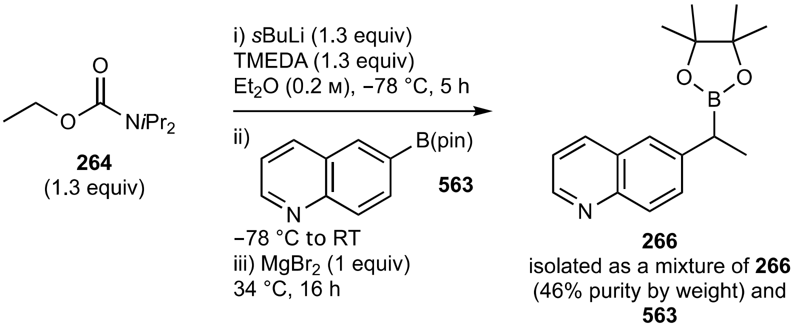
Characteristic data for **265**:

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61-7.56 (1H, m, Ar**H**), 7.42-7.34 (1H, m, Ar**H**), 7.34-7.24 (2H, m, Ar**H**), 7.24-7.18 (1H, m, Ar**H**), 2.59 (1H, q, J = 7.5 Hz, C**H**), 1.67 (9H, s, 3 × COCC**H$_3$**), 1.42 (3H, d, J = 7.5 Hz, CHC**H$_3$**), 1.24-1.22 (12H, m, 4 × BOCC**H$_3$**).



HRMS (Q-TOF) Exact mass calcd for $[C_{21}H_{30}BNO_4Na]^+$ $[M+Na]^+$**:** 394.2166, found: 394.2176.

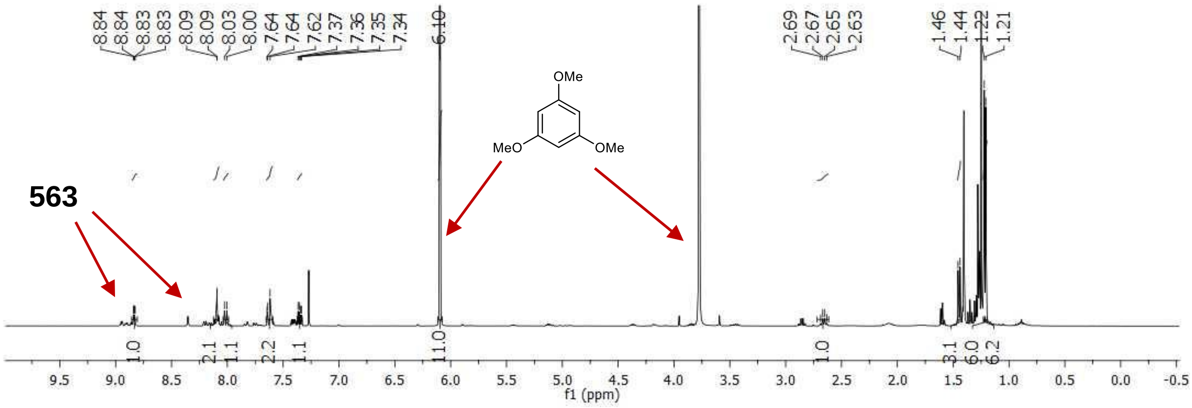
(±)-6-[1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl]quinoline (266).



The title compound was prepared according to General Procedure **4** using carbamate **264** (0.442 g, 2.55 mmol), TMEDA (0.38 mL, 2.6 mmol), *s*BuLi (1.3 м in cyclohexane, 2.0 mL, 2.6 mmol), and boronic ester **563** (0.500 g, 1.96 mmol in Et_2O 5 mL). The crude material was subjected to flash chromatography (17% EtOAc/petroleum ether) to give an inseparable mixture of **266** and **563** (0.198 g) as a yellow oil. Through ^{1}H NMR analysis of the mixture (10.6 mg of sample with 10.6 mg of 1,3,5-trimethoxybenzene added), the purity of the boronic ester **266** was determined to 46% by weight. The material was used without further purification.[179]

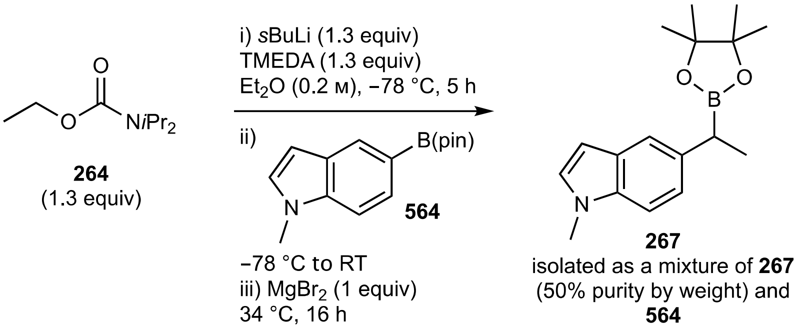
Characteristic data for **266**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86-8.81 (1H, m, Ar**H**) 8.12-8.07 (1H, m, Ar**H**), 8.04-7.99 (1H, m, Ar**H**), 7.65-7.59 (2H, m, Ar**H**), 7.37-7.33 (1H, m, Ar**H**), 2.66 (1H, q, J = 7.5 Hz, C**H**), 1.45 (3H, d, J = 7.5 Hz, CHC**H₃**), 1.22 (6H, s, 2 × CC**H₃**), 1.21 (6H, s, 2 × CC**H₃**).



HRMS (EI) Exact mass calcd for $[C_{17}H_{23}BO_2]^+$ $[M+H]^+$: 284.1822, found: 284.1816.

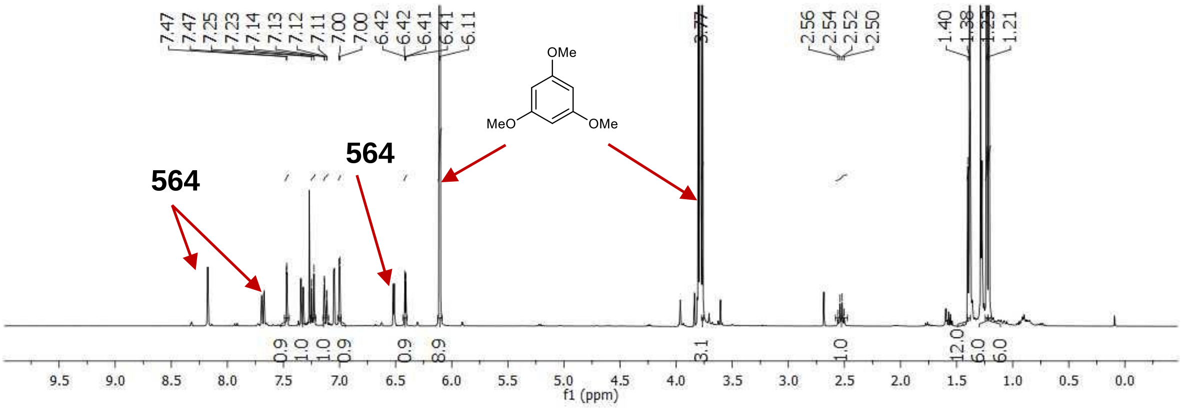
(±)-1-Methyl-5-[1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl]-1*H*-indole (267).



The title compound was prepared according to General Procedure **4** using carbamate **264** (0.440 g, 2.54 mmol), TMEDA (0.38 mL, 2.5 mmol), *s*BuLi (1.3 м in cyclohexane, 2.0 mL, 2.6 mmol), and boronic ester **564** (0.500 g, 1.95 mmol in Et_2O 5 mL). The crude material was subjected to flash chromatography (2% EtOAc/petroleum ether) to give an inseparable mixture of **267** and **564** (0.495 g) as a brown amorphous solid. Through ^{1}H NMR analysis of the mixture (10.2 mg of sample with 9.0 mg of 1,3,5-trimethoxybenzene added), the purity of the boronic ester **267** was determined to 50% by weight. The material was used without further purification.[179]

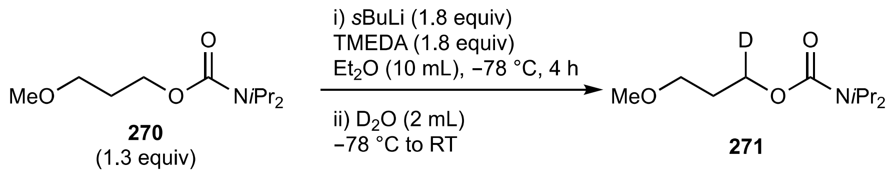
Characteristic peaks for **267**:

^{1}H NMR ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.24 (1H, d, *J* = 8.4 Hz, Ar**H**), 7.12 (1H, dd, *J* = 8.4, 1.5 Hz, Ar**H**), 7.00 (1H, d, *J* = 3.1 Hz, Ar**H**), 6.42 (1H, d, *J* = 3.1 Hz, Ar**H**), 3.77 (3H, s, NC**H$_3$**) 2.53 (1H, q, *J* = 7.5 Hz, C**H**), 1.41-1.37 (3H, m, CHC**H$_3$**), 1.23 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).



HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{25}BNO_2]^+$ $[M+H]^+$**:** 286.1978, found: 286.1973.

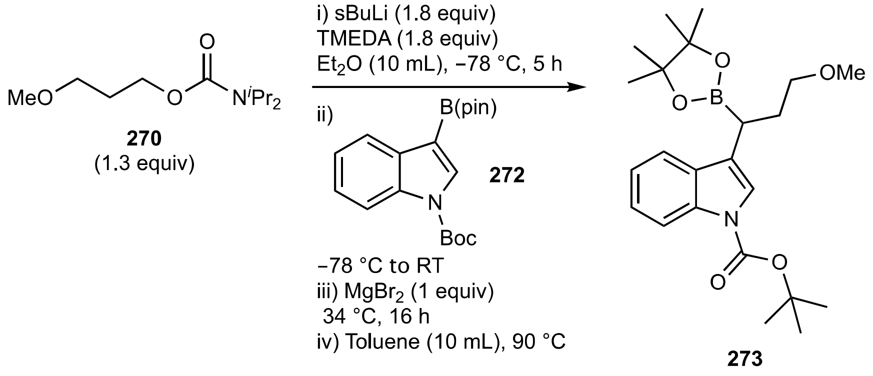
(±)-3-Methoxy(1-$^2H_1$)propyl *N,N*-bis(propan-2-yl)carbamate (271).



A Schlenk flask containing carbamate **270** (0.576 g, 2.65 mmol) was backfilled with nitrogen three times. TMEDA (0.55 mL, 3.7 mmol) and anhydrous Et$_2$O (10.2 mL) were added, and the mixture was cooled to –78 °C. *s*BuLi (1.3 м in cyclohexane, 2.8 mL, 3.7 mmol) was added dropwise, and the mixture was stirred at **–**78 °C for 4 h. D$_2$O (2 mL) was added dropwise, and the mixture was warmed to room temperature and stirred for 1 h. H$_2$O (20 mL) was added, and the mixture extracted with Et$_2$O (3 × 15 mL). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated *in vacuo* to give *carbamate* **271** (0.564 g, 97%). The crude material was analysed by ^{1}H NMR spectroscopy, which showed 100% deuterium incorporation.

^{1}H NMR (400 MHz, CDCl$_3$) δ 4.19-4.04 (1H, m, OC**H**), 3.90-3.79 (1H, m, NC**H**), 3.63-3.51 (1H, m, NC**H**), 3.47-3.40 (2H, m, C**H$_2$**OCH$_3$), 3.31-3.28 (3H, m, OC**H$_3$**), 1.92-1.75 (2H, m, OCH$_2$C**H$_2$**), 1.26-1.07 (12H, m, 4 × CHC**H$_3$**).

(±)-*tert*-Butyl 3-[3-methoxy-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]-1*H*-indole-1-carboxylate (273).



Using a modification of the procedure by Aggarwal and co-workers,[168] a Schlenk flask containing carbamate **270** (0.576 g, 2.65 mmol) was backfilled with nitrogen three times. TMEDA (0.55 mL, 3.7 mmol) and anhydrous Et$_2$O (10 mL) were added, and the mixture was cooled to –78 °C. *s*BuLi (1.3 м in cyclohexane, 2.8 mL, 3.7 mmol) was added dropwise, and the mixture was stirred at –78 °C for 4 h. Boronic ester **272** (0.700 g, 2.04 mmol) was added dropwise, and the mixture was stirred at –78 °C for 1 h. A solution of MgBr$_2$ in Et$_2$O[i] (0.378 g, 2.04 mmol, 1.0 м) was added dropwise, and the mixture was stirred at 34 °C for 18 h. Toluene (10 mL) was added and mixture stirred at 90 °C for 18 h. Upon cooling the room temperature,

H_2O (20 mL) and Et_2O (15 mL) were added, and the mixture extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (5% EtOAc/petroleum ether) to give *boronic ester* **273** (0.422 g, 50%) as a colourless oil.

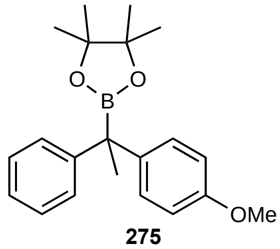
IR 2977, 2930, 1729, 1452, 1368, 1142 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H, Ar**H**), 7.66-7.61 (1H, m, Ar**H**), 7.41 (1H, s, Ar**H**), 7.31-7.27 (1H, m, Ar**H**), 7.24-7.17 (1H, m, Ar**H**), 3.48-3.36 (2H, m, $C\mathbf{H_2}OCH_3$), 3.33 (3H, s, $OC\mathbf{H_3}$), 2.66-2.57 (1H, m, BC**H**), 2.25-2.14 (1H, m, $BCHC\mathbf{H_A}CH_B$), 2.05-1.93 (1H, m, $BCHCH_AC\mathbf{H_B}$), 1.66 (9H, s, 3 × $C(O)OCC\mathbf{H_3}$), 1.22 (6H, s, 2 × $BOCC\mathbf{H_3}$), 1.21 (6H, s, 2 × $BOCC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8 (C), 135.6 (C), 130.7 (C), 124.0 (CH), 122.3 (C), 122.0 (CH), 121.5 (CH), 119.6 (CH), 115.0 (CH), 83.5 (2 × C), 83.0 (C), 72.0 (CH_2), 58.5 (CH_3), 31.0 (CH_2), 28.2 (3 × CH_3), 24.7 (4 × CH_3), 18.4 (BCH).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7.

HRMS (Q-TOF) Exact mass calcd for $[C_{23}H_{34}BNO_5Na]^+$ $[M+Na]^+$: 438.2428, found: 438.2422.



275

(±)-2-[1-(4-Methoxyphenyl)-1-phenylethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (275).

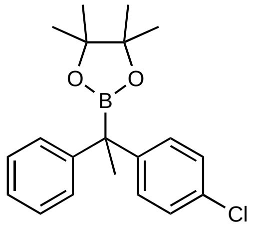
The title compound was prepared according to General Procedure **5** using carbamate **274** (1.60 g, 6.42 mmol), *s*BuLi (1.3 M in cyclohexane, 5.6 mL, 7.3 mmol) and 4-methoxyphenylboronic acid pinacol ester (1.00 g, 4.27 mmol) added in Et_2O (2 mL). Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave boronic ester **275** (1.25 g, 87 %) as a white solid. The data were consistent with the literature.[168]

m.p. 64-66 °C (petroleum ether); no literature value available.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.24 (2H, m, Ar**H**), 7.25-7.20 (2H, m, Ar**H**), 7.20-7.15 (3H, m, Ar**H**), 6.86-6.80 (2H, m, Ar**H**), 3.81 (3H, s, $OC\mathbf{H_3}$), 1.68 (3H, s, $BCC\mathbf{H_3}$), 1.22 (12H, s, 4 × $OCC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (C), 148.1 (C), 139.4 (C), 129.4 (2 × CH), 128.4 (2 × CH), 127.9 (2 × CH), 125.3 (CH), 113.3 (2 × CH), 83.7 (2 × C), 55.1 (CH_3), 25.9 (CH_3), 24.4 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.6.



276

(±)-2-[1-(4-Chlorophenyl)-1-phenylethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (276)

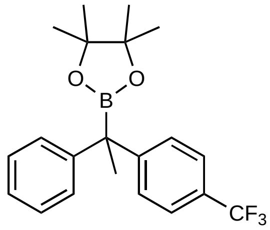
The title compound was prepared according to General Procedure **5** using carbamate **274** (1.25 g, 5.03 mmol), *s*BuLi (1.3 м in cyclohexane, 4.2 mL, 5.5 mmol) and 4-chlorophenylboronic acid pinacol ester (1.00 g, 4.19 mmol) added in Et_2O (2 mL). Flash chromatography (4% EtOAc/petroleum ether) of the crude material gave boronic ester **276** (1.38 g, 96%) as an off white solid. The data were consistent with the literature.[168]

m.p. 74-75 °C (petroleum ether); no literature value available.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (1H, m, Ar**H**), 7.26-7.15 (8H, m, Ar**H**), 1.67 (3H, s, BCC**H₃**), 1.21 (6H, s, 2 × OCC**H₃**), 1.21 (6H, s, 2 × OCC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (C), 146.2 (C), 131.1 (C), 129.9 (2 × CH), 128.4 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 125.6 (CH), 83.9 (2 × C), 25.7 (CH_3), 24.5 (2 × CH_3), 24.4 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.1.



277

(±)-2-[1-(4-Trifluoromethylphenyl)-1-phenylethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (277)

The title compound was prepared according to General Procedure **5** using carbamate **274** (0.551 g, 2.21 mmol), *s*BuLi (1.3 м in cyclohexane, 1.8 mL, 2.4 mmol) and 4-trifluoromethlphenylboronic acid pinacol ester (0.500 g, 1.84 mmol) added in Et_2O (2 mL). Flash chromatography (4% EtOAc/petroleum ether) of the crude material gave *boronic ester* **277** (0.575 g, 83 %) as an off white solid.

m.p. 65-66 °C (petroleum ether).

IR 2977, 2932, 1616, 1317, 1113 cm^{-1}

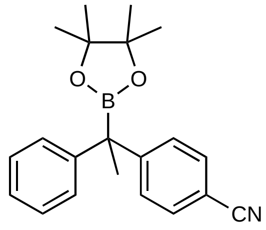
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.49 (2H, m, Ar**H**), 7.36-7.28 (4H, m, Ar**H**), 7.22-7.18 (3H, m, Ar**H**), 1.71 (3H, s, BCC**H₃**), 1.22 (6H, s, 2 × OCC**H₃**), 1.21 (6H, s, 2 × OCC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2 (C), 146.6 (C), 128.8 (2 × CH), 128.4 (2 × CH), 128.2 (2 × CH), 127.6 (C, q, $J_{C\text{-}F}$ = 32.2 Hz), 125.8 (CH), 124.8 (2 × CH, q, $J_{C\text{-}F}$ = 3.8 Hz), 124.4 (CF_3, q, $J_{C\text{-}F}$ = 271.6 Hz), 84.0 (2 × C), 25.6 (CH_3), 24.5 (2 × CH_3), 24.4 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.3.

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.2.

HRMS (Q-TOF) Exact mass calcd for $[C_{21}H_{25}BF_3O_2]^+$ $[M+H]^+$: 377.1900, found: 377.1894.



278

(±)-4-[1-Phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl]benzonitrile (278).

The title compound was prepared according to General Procedure **5** using carbamate **274** (1.31 g, 5.25 mmol), *s*BuLi (1.3 M in cyclohexane, 4.4 mL, 5.7 mmol) and 4-cyanophenylboronic acid pinacol ester (1.01 g, 4.41 mmol) added in Et$_2$O (2 mL). Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave *boronic ester* **278** (1.02 g, 69 %) as an off white solid.

m.p. 98-100 °C (petroleum ether).

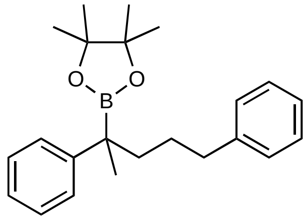
IR 2977, 2227, 1687, 1321, 1143 cm^{-1}

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58-7.51 (2H, m, Ar**H**), 7.38-7.28 (4H, m, Ar**H**), 7.24-7.16 (3H, m, Ar**H**), 1.69 (3H, s, BCC**H$_3$**), 1.21 (6H, s, 2 × OCC**H$_3$**), 1.20 (6H, s, 2 × OCC**H$_3$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 153.5 (C), 146.1 (C), 131.8 (2 × CH), 129.3 (2 × CH), 128.3 (2 × CH), 128.3 (2 × CH), 126.0 (CH), 119.3 (C), 109.0 (C), 84.1 (2 × C), 25.4 (CH$_3$), 24.4 (2 × CH$_3$), 24.4 (2 × CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$) δ 33.4.

HRMS (Q-TOF) Exact mass calcd for [C$_{21}$H$_{25}$BNO$_2$]$^+$ [M+H]$^+$: 334.1978, found: 334.1973.



279

(±)-2-(2,5-Diphenylpentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (279).

The title compound was prepared according to General Procedure **5** using carbamate **274** (1.07 g, 4.28 mmol), *s*BuLi (1.3 M in cyclohexane, 3.8 mL, 4.9 mmol) and boronic ester **251** (0.704 g, 2.86 mmol) added. Flash chromatography (1% EtOAc/petroleum ether) of the crude material gave boronic ester **279** (0.938 g, 94%) as a colourless oil.

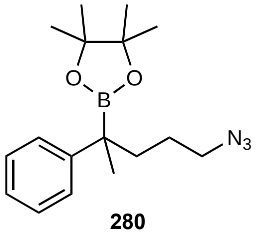
IR 2976, 2933, 2857, 1495, 1311, 1143 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35-7.25 (6H, m, Ar**H**), 7.20-7.13 (4H, m, Ar**H**), 2.68-2.56 (2H, m, ArC**H$_2$**), 1.96-1.86 (1H, m, BCC**H$_A$**CH$_B$), 1.82-1.74 (1H, m, BCCH$_A$C**H$_B$**), 1.61-1.53 (2H, m, ArCH$_2$C**H$_2$**), 1.36 (3H, s, BCC**H$_3$**), 1.22 (6H, s, 2 × OCC**H$_3$**), 1.22 (6H, s, 2 × OCC**H$_3$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 147.2 (C), 142.8 (C), 128.3 (2 × CH), 128.2 (2 × CH), 128.0 (2 × CH), 126.8 (2 × CH), 125.5 (CH), 125.0 (CH), 83.3 (2 × C), 39.2 (CH$_2$), 36.7 (CH$_2$), 29.7 (C), 27.5 (CH$_2$), 24.6 (2 × CH$_3$), 24.6 (2 × CH$_3$), 21.6 (CH$_3$).

^{11}B NMR (128 MHz, CDCl$_3$) δ 33.9.

HRMS (Q-TOF) Exact mass calcd for [C$_{23}$H$_{35}$BNO$_2$]$^+$ [M+NH$_4$]$^+$: 368.2761, found: 368.2755.



280

(±)-2-(5-Azido-2-phenylpentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (280)

The title compound was prepared according to General Procedure **5** using carbamate **274** (1.19 g, 4.77 mmol), *s*BuLi (1.3 M in cyclohexane, 4.2 mL, 5.4 mmol) and boronic ester **561** (0.700 g, 3.32 mmol). Flash chromatography (1% EtOAc/petroleum ether) of the crude material gave *boronic ester **280*** (0.540 g, 52%) as a colourless oil.

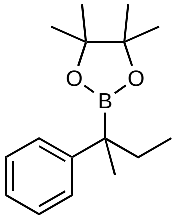
IR 2977, 2932, 2092, 1350, 1312, 1145 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (4H, m, Ar**H**), 7.18-7.12 (1H, m, Ar**H**), 3.25-3.17 (2H, m, C$\mathbf{H_2}$N), 1.88-1.72 (2H, m, C$\mathbf{H_2}$$CH_2$N), 1.55-1.42 (2H, m, C$\mathbf{CH_2}$), 1.36 (3H, s, BCC$\mathbf{H_3}$), 1.22 (6H, s, 2 × OCC$\mathbf{H_3}$), 1.21 (6H, s, 2 × OCC$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4 (C), 128.2 (2 × CH), 126.8 (2 × CH), 125.3 (CH), 83.5 (2 × C), 52.1 (CH_2), 36.5 (CH_2), 24.9 (CH_2), 24.6 (2 × CH_3), 24.5 (2 × CH_3), 21.3 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7.

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{26}BN_3O_2Na]^+$ $[M+Na]^+$: 338.2016, found: 338.2017.



281

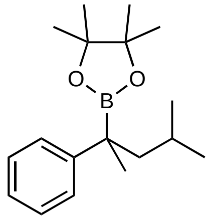
(±)-2-(2-Phenylbut-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (281)

The title compound was prepared according to General Procedure **5** using carbamate **274** (1.92 g, 7.69 mmol), *s*BuLi (1.3 M in cyclohexane, 6.4 mL, 8.3 mmol) and ethylboronic acid pinacol ester (1.00 g, 6.41 mmol). Flash chromatography (4% EtOAc/petroleum ether) of the crude material gave boronic ester **281** (1.51 g, 91%) as a yellow oil. The data were consistent with the literature.[168]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (4H, m, Ar**H**), 7.17-7.11 (1H, m, Ar**H**)), 1.89 (1H, dq, *J* = 14.7, 7.4 Hz, C$\mathbf{CH_A}$$H_B$), 1.72 (1H, dq, *J* = 14.7, 7.4 Hz, C$CH_A$$\mathbf{H_B}$), 1.34 (3H, s, BCC$\mathbf{H_3}$), 1.22 (6H, s, 2 × OCC$\mathbf{H_3}$), 1.22 (6H, s, 2 × OCC$\mathbf{H_3}$), 0.84 (3H, t, *J* = 7.4 Hz, CH_2C$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3 (C), 128.0 (2 × CH), 126.9 (2 × CH), 124.9 (CH), 83.2 (2 × C), 31.9 (CH_2), 24.6 (4 × CH_3), 21.0 (CH_3), 10.0 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7.



282

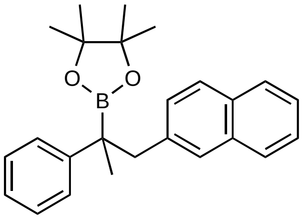
(±)-4,4,5,5-Tetramethyl-2-(4-methyl-2-phenylpentan-2-yl)-1,3,2-dioxaborolane (282).

The title compound was prepared according to General Procedure **5** using carbamate **274** (1.63 g, 6.52 mmol), *s*BuLi (1.3 M in cyclohexane, 5.4 mL, 7.1 mmol) and isobutyl pinacol boronic ester[254] (1.00 g, 5.43 mmol). Flash chromatography (17% EtOAc/petroleum ether) of the crude material gave boronic ester **282** (1.32 g, 85%) as a yellow oil.[179]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (2H, m, Ar**H**), 7.30-7.24 (2H, m, Ar**H**), 7.15-7.10 (1H, m, Ar**H**), 1.86-1.77 (1H, m, C**H**), 1.68-1.56 (2H, m, C**H₂**), 1.37 (3H, s, BCC**H₃**), 1.18 (6H, s, 2 × OCC**H₃**), 1.17 (6H, s, 2 × OCC**H₃**), 0.90 (3H, d, *J* = 6.5 Hz, CHC**H₃**), 0.80 (3H, d, *J* = 6.5 Hz, CHC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7 (C), 127.9 (2 × CH), 126.9 (2 × CH), 124.9 (CH), 83.2 (2 × C), 48.0 (CH_2), 25.8 (CH), 24.6 (2 × CH_3), 24.5 (CH_3), 24.5 (2 × CH_3), 24.0 (CH_3), 21.0 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.4.



283

(±)-4,4,5,5-Tetramethyl-2-[1-(naphthalen-2-yl)-2-phenylpropan-2-yl]-1,3,2-dioxaborolane (283)

The title compound was prepared according to General Procedure **5** using carbamate **274** (1.01 g, 4.03 mmol), *s*BuLi (1.3 M in cyclohexane, 3.5 mL, 4.6 mmol) and boronic ester **253** (0.721 g, 2.69 mmol) added in Et_2O (4 mL). Flash chromatography (1% EtOAc/petroleum ether) of the crude material gave *boronic ester* **283** (0.949 g, 95%) as an amorphous white solid.

IR 2976, 2929, 1345, 1313, 1142 cm^{-1}.

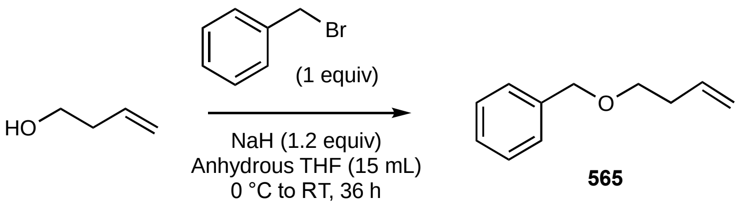
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.78 (1H, m, Ar**H**), 7.75-7.69 (1H, m, Ar**H**), 7.69-7.63 (1H, m, Ar**H**), 7.55 (1H, s, Ar**H**), 7.47-7.41 (2H, m, Ar**H**), 7.41-7.38 (2H, m, Ar**H**), 7.36-7.30 (2H, m, Ar**H**), 7.25-7.19 (1H, m, Ar**H**), 7.17-7.12 (1H, m, Ar**H**), 3.43 (1H, d, *J* = 13.1 Hz, C**H$_A$**CH$_B$), 3.13 (1H, d, *J* = 13.1 Hz, CH$_A$C**H$_B$**), 1.36 (3H, s, BCC**H₃**), 1.27 (6H, s, 2 × OCC**H₃**), 1.21 (6H, s, 2 × OCC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4 (C), 137.4 (C), 133.1 (C), 131.9 (C), 129.3 (CH), 128.7 (CH), 128.0 (2 × CH), 127.5 (2 × CH), 127.1 (2 × CH), 126.7 (CH), 125.5 (CH), 125.3 (CH), 125.0 (CH), 83.5 (2 × C), 45.8 (CH_2), 24.7 (2 × CH_3), 24.5 (2 × CH_3), 20.5 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.5.

HRMS (Q-TOF) Exact mass calcd for $[C_{25}H_{30}BO_2]^+$ $[M+H]^+$: 373.2339, found: 373.2333.

[(But-3-en-1-yloxy)methyl]benzene (565)



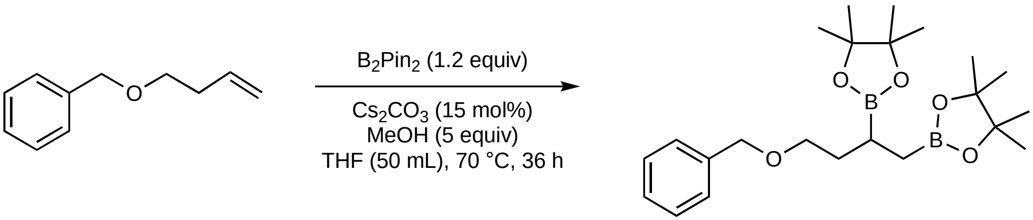
565

An oven dried flask was charged with NaH (60% wt in paraffin oil, 2.01 g, 50.4 mmol) and anhydrous THF (15 mL) and, cooled to 0 °C. 3-Butene-1-ol (3.00 g, 42.0 mmol) was added dropwise and stirred at 0 °C for 30 min. Benzyl bromide (5.0 mL, 42 mmol) was added dropwise, warmed to room temperature and stirred for 36 h. The mixture was quenched with saturated aqueous NH_4Cl (20 mL), Et_2O (20 mL) added and the organic phase was washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The crude material was purified by column chromatography (6% EtOAc/Petroleum ether) to give alkene **565** (6.01 g, 88%) as a yellow oil. The data were consistent with the literature.[260]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.34 (4H, m, Ar**H**), 7.33-7.28 (1H, m, Ar**H**), 5.86 (1H, ddt, *J* = 17.1, 10.2, 6.7 Hz, CH_2=C**H**), 5.12 (1H, ddd, *J* = 17.1, 1.6 Hz, C$\mathbf{H_A}$$H_B$=CH), 5.06 (1H, ddd, *J* = 10.2, 1.6 Hz, C$H_A$$\mathbf{H_B}$=CH), 4.54 (2H, s, ArC$\mathbf{H_2}$), 3.55 (2H, t, *J* = 6.8 Hz, CH_2C$\mathbf{H_2}$O), 2.40 (2H, tdd, *J* = 6.8, 6.7, 1.4 Hz, C$\mathbf{H_2}$$CH_2$O).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5 (C), 135.2 (CH), 128.4 (2 × CH), 127.6 (2 × CH), 127.5 (CH), 116.4 (CH_2), 72.9 (CH_2), 69.6 (CH_2), 34.2 (CH_2).

(±)-2-[4-(Benzyloxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (296).



565 **296**

Cs_2CO_3 (0.600 g, 1.84 mmol), bis(pinacolato)diboron (3.75 g, 14.8 mmol) and alkene **565** (2.00 g, 12.3 mmol) were added to a mixture of MeOH (2.5 mL, 61.5 mmol) in THF (50 mL). A condenser was fitted, flushed with N_2, and the mixture was stirred at 70 °C for 36 h. The mixture was cooled to room temperature and water was added (25 mL). The mixture was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The crude material was purified by flash chromatography (10% EtOAc/petroleum ether) to give boronic ester **296** (3.05 g, 60%

yield) as a colourless oil. There are inconsistencies with the literature report for ^{1}H and ^{13}C NMR data.[261]

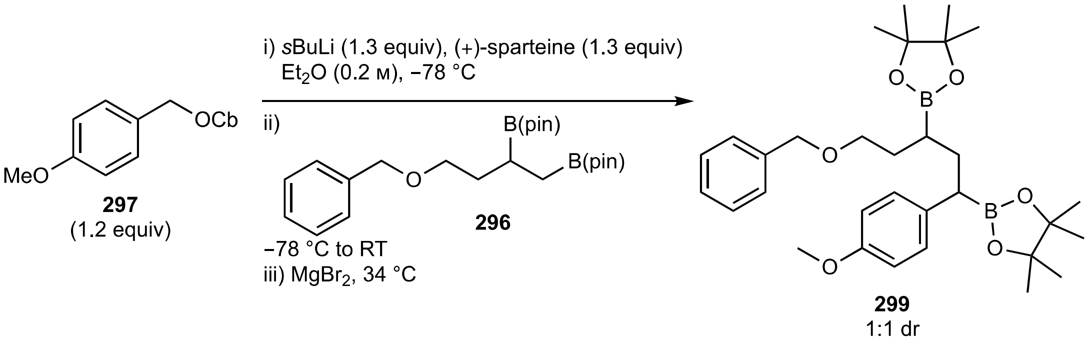
^{1}H NMR Observed: (400 MHz, CDCl$_3$) δ 7.37-7.29 (4H, m, Ar**H**), 7.28-7.22 (1H, m, Ar**H**), 4.50 (2H, s, ArC**H$_2$**), 3.51-3.45 (2H, m, OC**H$_2$**CH$_2$), 1.87-1.77 (1H, m, OCH$_2$C**H$_A$**CH$_B$), 1.73-1.63 (1H, m, OCH$_2$CH$_A$C**H$_B$**), 1.25-1.18 (25H, m, BC**H** and 8 × C**H$_3$**)), 0.95-0.79 (2H, m, BC**H$_2$**). **Reported:** (400 MHz, CDCl$_3$) δ 7.50-7.09 (m, 5H), 4.48 (s, 2H), 3.47 (t, J = 7.0 Hz, 2H), 1.86-1.59 (m, 2H), 1.21 (s, 12H), 1.19 (s, 12H), 0.94-0.74 (m, 3H).

^{13}C NMR Observed: (101 MHz, CDCl$_3$) δ 138.9 (C), 128.2 (2 × CH), 127.6 (2 × CH), 127.3 (CH), 82.8 (2 × C), 82.8 (2 × C), 72.6 (CH$_2$), 69.7 (CH$_2$), 33.4 (CH$_2$), 25.0 (2 × CH$_3$), 24.9 (2 × CH$_3$), 24.8 (2 × CH$_3$), 24.7 (2 × CH$_3$). **Reported:** (100 MHz, CDCl$_3$) δ 138.92, 128.34, 127.76, 127.42, 82.99, 82.96, 72.75, 69.77, 33.44, 31.67, 25.10, 24.97, 24.87, 24.79, 22.74, 14.21.

^{11}B NMR (128 MHz, CDCl$_3$) δ 34.0.

HRMS (Q-TOF) Exact mass calcd for $[C_{23}H_{39}B_2O_5]^+$ $[M+H]^+$**:** 417.2984, found: 417.2986.

(±)-2-[5-(Benzyloxy)-1-(4-methoxyphenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (299).



Using a modification of the procedure by Aggarwal and co-workers,[172] a Schlenk flask containing carbamate **297** (0.477 g, 1.80 mmol) and (+)-sparteine (0.456 g, 1.95 mmol) was backfilled with nitrogen three times. Anhydrous Et$_2$O (0.2 м) was added and the mixture was cooled to –78 °C. *s*BuLi (1.3 м in cyclohexane, 1.5 mL, 2.0 mmol) was added dropwise, and the mixture was stirred at **–**78 °C for 4 h. Boronic ester **296** (0.624 g, 1.50 mmol) was added dropwise, and the mixture was stirred at **–**78 °C for 1 h. A solution of MgBr$_2$ in Et$_2$O[i] (1.5 mmol) was added dropwise and the mixture was stirred at 34 °C for 18 h. The mixture was cooled to room temperature, and saturated aqueous NH$_4$Cl (20 mL) and Et$_2$O (15 mL) were added. The mixture was extracted with Et$_2$O (3 × 15 mL), and the combined organic layers were dried (MgSO$_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (1:5 EtOAc/petroleum ether) to give boronic ester **299** (0.691 g, 86%, dr = 1:1) as a colourless oil.[179]

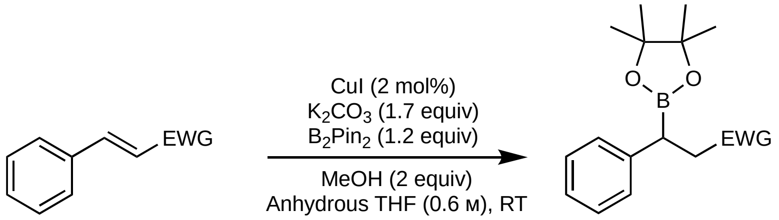
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (4H, m, Ar**H**), 7.28-7.23 (1H, m, Ar**H**), 7.11 (2H, dd, *J* = 8.7, 3.2 Hz, Ar**H**), 6.79 (2H, dd, *J* = 8.7, 2.3 Hz, Ar**H**), 4.51-4.43 (2H, m, ArC**H₂**O), 3.77 (3H, s, OC**H₃**), 3.47-3.35 (2H, m, OC**H₂**CH₂), 2.38-2.27 (1H, m, ArC**H**), 2.00-1.64 (4H, m, ArCHBC**H₂**, OCH₂C**H₂**), 1.22-1.16 (24H, m, 8 × CC**H₃**), 1.09-0.95 (1H, m, OCH₂CH₂C**H**B).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (C), 138.9 (C), 138.8 (C), 135.5 (C), 135.1 (C), 129.5 (CH), 129.3 (CH), 128.3 (2 × CH), 127.7 (2 × CH), 127.6 (CH), 127.3 (CH), 113.7 (2 × CH), 113.5 (2 × CH), 83.1 (2 × C), 82.8 (2 × C), 72.7 (CH_2), 72.7 (CH_2), 69.9 (CH_2), 69.9 (CH_2), 69.7 (CH_3), 55.2 (CH_2), 55.1 (CH_2), 34.2 (CH_2), 33.9 (CH_2), 31.3 (CH_2), 31.0 (CH_2), 30.3 (CH), 24.9 (2 × CH_3), 24.8 (2 × CH_3), 24.6 (2 × CH_3), 24.6 (2 × CH_3).

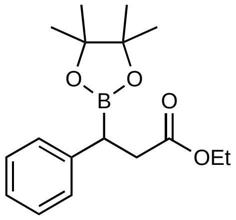
^{11}B NMR (128 MHz, $CDCl_3$) δ 33.1.

5.3.5 Cu-Catalysed 1,4-Borylation

General Procedure 6: Cu-Catalysed 1,4-Borylation of Michael Acceptors.



Using a modification of the procedure by Zeng and co-workers,[171] an oven dried flask was charged with CuI (2 mol%), K_2CO_3 (1.7 equiv) and purged with N_2. Anhydrous THF (0.6 м in total) was added, and the mixture was stirred at room temperature for 10 min. A solution of bis(pinacolato)diboron (1.2 equiv) in anhydrous THF (0.2 м) was added and the mixture was stirred for 10 min. The alkene (1 equiv) was added followed by methanol (2 equiv), and the mixture stirred at room temperature. Upon completion (as determined by TLC) the mixture was diluted with EtOAc (40 mL), washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The crude material was purified by flash chromatography to give the boronic ester.



285

(±)-Ethyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (285).

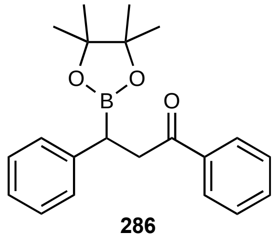
The title compound was prepared according to General Procedure **6** using CuI (0.023 g, 0.12 mmol), K_2CO_3 (1.40 g, 10.1 mmol), bis(pinacolato)diboron (1.81 g, 7.14 mmol), ethyl cinnamate (1.0 mL, 6.0 mmol), THF (10 mL) and methanol (0.32 ml, 12 mmol), stirring for 24 h. The crude material was purified by flash chromatography (10% EtOAc/petroleum ether) to give the boronic ester **285** (1.48 g, 82%) as a white solid. The data were consistent with the literature.[171]

m.p. 47-49 °C (petroleum ether). No literature value available.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.20 (4H, m, Ar**H**), 7.19-7.13 (1H, m, Ar**H**), 4.17-4.06 (2H, m, $CH_3C\mathbf{H_2}$), 2.89 (1H, dd, *J* = 16.0, 9.9 Hz, $CC\mathbf{H_A}H_B$), 2.74 (1H, dd, *J* = 9.9, 6.0 Hz, C**H**), 2.66 (1H, dd, *J* = 16.0, 6.0 Hz, $CCH_A\mathbf{H_B}$), 1.25-1.21 (9H, m, 2 × $C\mathbf{CH_3}$, $CH_2C\mathbf{H_3}$), 1.18 (6H, s, 2 × $C\mathbf{H_3}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C), 141.4 (C), 128.4 (2 x CH), 128.1 (2 × CH), 125.6 (CH), 83.5 (2 × C), 60.3 (CH_2), 37.3 (CH_2), 24.7 (2 × CH_3), 24.7 (2 × CH_3), 14.2 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.9.



286

(±)-1,3-Diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one (286).

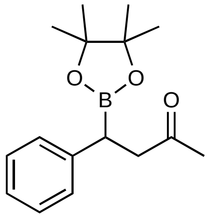
The title compound was prepared according to General Procedure **6** using CuI (0.038 g, 0.20 mmol), K_2CO_3 (2.35 g, 17.0 mmol), bis(pinacolato)diboron (3.05 g, 12.0 mmol), chalcone (2.08 g, 10.0 mmol), THF (15 mL) and methanol (0.8 ml, 20 mmol), stirring for 16 h. The crude material was purified by flash chromatography (5% EtOAc/hexane) to give boronic ester **286** (1.99 g, 72%) as a white solid. The data were consistent with the literature.[171]

m.p. 79-81 °C (*n*-pentane); literature: 75-77 °C (not specified).[171]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-7.97 (2H, m, Ar**H**), 7.60-7.52 (1H, m, Ar**H**), 7.51-7.44 (2H, m, Ar**H**), 7.38-7.27 (4H, m, Ar**H**), 7.24-7.17 (1H, m, Ar**H**), 3.60 (1H, dd, *J* = 18.3, 10.9 Hz, $CC\mathbf{H_A}H_B$), 3.46 (1H, dd, *J* = 18.3, 5.0 Hz, $CCH_A\mathbf{H_B}$), 2.85 (1H, dd, *J* = 10.9, 5.0 Hz, C**H**), 1.29 (6H, s, 2 × $CC\mathbf{H_3}$), 1.21 (6H, s, 2 × $CC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6 (C), 141.9 (C), 136.7 (C), 132.9 (CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.0 (2 × CH), 125.5 (CH), 83.3 (2 × C), 43.2 (CH_2), 24.5 (2 × CH_3), 24.5 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.9.

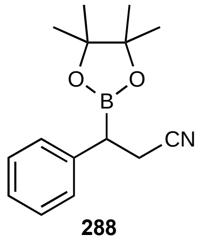


287

(±)-4-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-one (287)

The title compound was prepared according to General Procedure **6** using CuI (0.038 g, 0.20 mmol), K_2CO_3 (2.35 g, 17.0 mmol), bis(pinacolato)diboron (3.05 g, 12.0 mmol), 4-phenyl-3-buten-2-one (1.46 g, 9.99 mmol), THF (15 mL) and methanol (0.8 ml, 20 mmol), stirring for 16 h. The crude material was purified by flash chromatography (5% EtOAc/hexane) to give boronic ester **287** (1.83 g, 67%) as a colourless oil. The data were consistent with the literature.[171]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33-7.24 (4H, m, Ar**H**), 7.22-7.16 (1H, m, Ar**H**), 3.09 (1H, dd, *J* = 18.3, 10.8 Hz, C**H**CH$_2$), 2.89 (1H, dd, *J* = 18.3, 5.3 Hz, CHC**H$_A$**CH$_B$), 2.69 (1H, dd, *J* = 10.8, 5.3 Hz, CHCH$_A$C**H$_B$**), 2.19 (3H s, C(O)C**H$_3$**), 1.27 (6H, s, 2 × OCC**H$_3$**), 1.22 (6H, s, 2 × OCC**H$_3$**).
^{13}C NMR (101 MHz, CDCl$_3$) δ 208.3 (C), 141.6 (C), 128.4 (2 × CH), 128.1 (2 × CH), 125.5 (CH), 83.3 (2 × C), 47.5 (CH$_2$), 29.5 (CH$_3$), 24.5 (2 × CH$_3$), 24.5 (2 × CH$_3$).
^{11}B NMR (128 MHz, CDCl$_3$) δ 32.8.

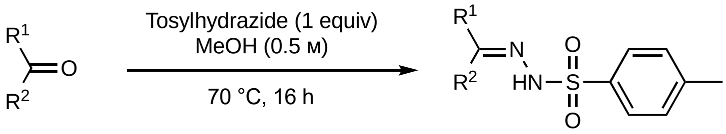

288

(±)-3-Phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanenitrile (288)

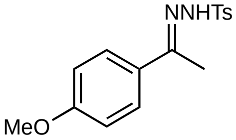
The title compound was prepared according to General Procedure **6** using CuI (0.038 g, 0.20 mmol), K$_2$CO$_3$ (2.35 g, 17.0 mmol), bis(pinacolato)diboron (3.05 g, 12.0 mmol), cinnamonitrile (1.25 mL, 9.95 mmol), THF (15 mL) and methanol (0.8 ml, 20 mmol), stirring for 16 h. The crude material was purified by flash chromatography (5% EtOAc/hexane) to give boronic ester **288** (1.44 g, 56%) as a colourless oil. The data were consistent with the literature.[262]
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35-7.29 (2H, m, Ar**H**), 7.26-7.20 (3H, m, Ar**H**), 2.83-2.74 (1H, m, C**H**), 2.72-2.60 (2H, m, C**H$_2$**), 1.26 (6H, s, 2 × CC**H$_3$**), 1.23 (6H, s, 2 × CC**H$_3$**).
^{13}C NMR (101 MHz, CDCl$_3$) δ 139.4 (C), 128.9 (2 × CH), 128.2 (2 × CH), 126.7 (CH), 119.5 (C), 84.4 (2 × C), 24.6 (2 × CH$_3$), 24.5 (2 × CH$_3$), 20.7 (CH$_2$).
^{11}B NMR (128 MHz, CDCl$_3$) δ 32.5.

5.3.6 Borylation using Tosylhydrazones

General Procedure 7: Formation of Tosylhydrazones from Ketones and Aldehydes.



The corresponding carbonyl (1 equiv) was added to tosylhydrazide (1 equiv) in MeOH (0.5 м) and refluxed for 16 h. The precipitate was collected and washed with petroleum ether (3 × 20 mL) to provide the tosylhydrazone. This was used without further purification.



241

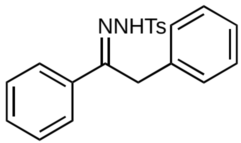
4-Methyl-2-[1-(4-methoxyphenyl)ethylidene]hydrazide benzenesulfonic acid (241)

The title compound was prepared according to General Procedure **7** using 4-methoxyacetophenone (1.11 g, 7.39 mmol) and tosylhydrazide (1.39 g, 7.46 mmol) to give hydrozone **241** (2.19 g, 93%) as a white solid. The data were consistent with the literature.[263]

m.p. 175-177 °C (petroleum ether). Literature = 178–180 °C (no solvent given)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.62 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.32 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.87 (2H, d, *J* = 8.9 Hz, Ar**H**), 3.83 (3H, s, OC**H$_3$**), 2.42 (3H, s, ArC**H$_3$**), 2.14 (3H, s, NCC**H$_3$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 160.9 (C), 152.8 (C), 144.1 (C), 135.4 (C), 129.7 (C), 129.6 (2 × CH), 128.1 (2 × CH), 127.8 (2 × CH), 113.7 (2 × CH), 55.3 (CH$_3$), 21.6 (CH$_3$), 13.3 (CH$_3$).

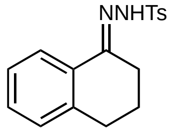


243

4-Methyl-2-(1,2-diphenylethylidene)hydrazide benzenesulfonic acid (243)

The title compound was prepared according to General Procedure **7** using 1,2-diphenylethanone (0.521 g, 2.66 mmol) and tosylhydrazide (0.494 g, 2.65 mmol) to give hydrozone **243** (0.682 g, 71%) as a white solid. The data were consistent with the literature.[264]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75-7.65 (4H, m, Ar**H**), 7.51-7.47 (1H, m, Ar**H**), 7.41-7.31 (3H, m, Ar**H**), 7.26-7.17 (4H, m, Ar**H**), 6.99-6.93 (2H, m, Ar**H**), 4.02 (2H, s, C**H$_2$**), 2.43 (3H, s, C**H$_3$**).

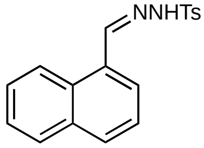


242

N'-(3,4-Dihydronaphthalen-1(2*H*)-ylidene)-4-methylbenzenesulfonohydrazide (242)

The title compound was prepared according to General Procedure **7** using α-tetralone (0.40 mL, 3.01 mmol) and tosylhydrazide (0.564 g, 3.03 mmol) to give hydrozone **242** (0.792 g, 83%) as a white solid. The data were consistent with the literature.[263]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03-7.96 (1H, m, Ar**H**), 7.94 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.61 (1H, s, N**H**), 7.33 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.28-7.16 (2H, m, Ar**H**), 7.13-7.07 (1H, m, Ar**H**), 2.72 (2H, t, *J* = 6.1 Hz, NCC**H$_2$**), 2.46 (2H, t, *J* = 6.5 Hz, ArC**H$_2$**), 2.42 (3H, s, C**H$_3$**), 1.90 (2H, tt, *J* = 6.5, 6.1 Hz, NCCH$_2$C**H$_2$**).



244

4-Methyl-2-(1-naphthalenylmethylene)hydrazide benzenesulfonic acid (244).

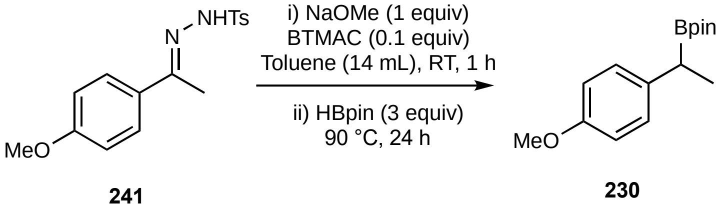
The title compound was prepared according to General Procedure **7** using 1-naphthalenecarboxaldehyde (1.0 mL, 7.4 mmol) and tosylhydrazide

(1.40 g, 7.52 mmol) to give hydrozone **244** (2.20 g, 92%) as a white solid. The data were consistent with the literature.[265]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64-8.57 (1H, m, Ar**H**), 8.37 (1H, s, C**H**), 7.98-7.92 (3H, m, Ar**H,** N**H**), 7.91-7.85 (2H, m, Ar**H**), 7.76-7.71 (1H, m, Ar**H**), 7.61-7.50 (2H, m, Ar**H**), 7.50-7.44 (1H, m, Ar**H**), 7.36-7.30 (2H, m, Ar**H**), 2.41 (3H, s, C**H₃**).

5.3.6.1 Borylation of Tosylhydrazone 230

(±)-2-(1-(4-Methoxyphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (230).



241 **230**

Using a modification of the procedure of Wang and co-workers,[163] an oven dried Schlenk flask was charged with tosylhydrazide **241** (1.30 g, 4.10 mmol), sodium methoxide (0.220 g, 4.10 mmol) and BTMAC (0.0800 g, 0.410 mmol), and the flask was evacuated and backfilled with argon three times. Toluene (14 mL) was added and the mixture was stirred for 1 h. Pinacolborane (1.5 mL, 10 mmol) was added, and the mixture was stirred at 90°C for 24 h. The mixture was cooled to room temperature, and EtOAc:petroleum ether (1:1, 14 mL) and a few drops of methanol were added. The mixture was filtered through a bed of silica washing with EtOAc:petroleum ether (1:1, 10 mL) and concentrated *in vacuo*. Pentane (0.5 mL) was added, and the mixture was left to stand for 2 h. The resulting material was filtered, washed with pentane (3 × 10 mL), and concentrated *in vacuo.* The crude material was purified by column chromatography (7% EtOAc/petroleum ether) to give boronic ester **230** (0.348 g, 33%) as a colourless oil. The data were consistent with the literature.[163]

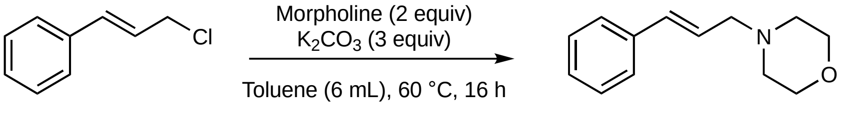
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.12 (2H, m, Ar**H**), 6.85-6.80 (2H, m, Ar**H**), 3.79 (3H, s, OC**H₃**), 2.38 (1H, q, J = 7.5 Hz, C**H**) 1.31 (3H, d, J = 7.5 Hz, CHC**H₃**) 1.22 (6H, s, 2 × CC**H₃**), 1.19 (6H, s, 2 × CC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (C), 137.0 (C), 128.6 (2 × CH), 113.7 (2 × CH), 83.2 (2 × C), 55.1 (CH_3), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 17.4 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.5.

5.3.7 Synthesis of Miscellaneous Compounds

4-[(*E*)-3-Phenylprop-2-en-1-yl]morpholine (*N*-cinnamylmorpholine) (566).



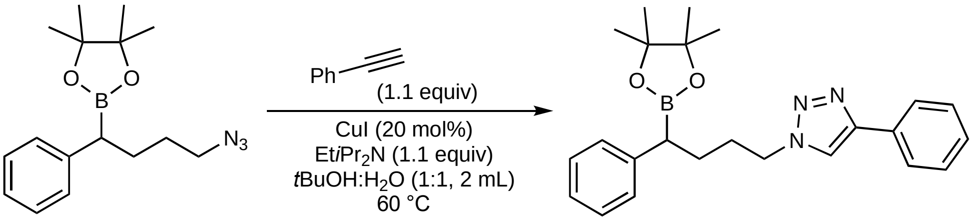
566

Cinnamyl chloride (1.0 mL, 7.4 mmol) and morpholine (1.3 mL, 15 mmol) was added to a mixture of K_2CO_3 (3.05 g, 22.1 mmol) in toluene (6 mL). The mixture was stirred at 60 °C for 16 h. Aqueous HCl (1 м) was added until acidic and the mixture washed with Et_2O (2 × 20 mL). Aqueous NaOH (2.5 м) was added to the aqueous phase until basic and extracted with Et_2O (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated to give alkene **566** (1.20 g, 80%) as a colourless oil. The data were consistent with the literature.[266]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.36 (2H, m, Ar**H**), 7.35-7.30 (2H, m, Ar**H**), 7.27-7.21 (1H, m, Ar**H**), 6.55 (1H, d, *J* = 15.9 Hz, ArC**H**=CH), 6.27 (1H, dt, *J* = 15.9, 6.8 Hz, ArCH=C**H**), 3.80-3.72 (4H, m, 2 × OC**H₂**), 3.17 (2H, dd, *J* = 6.8, 1.2 Hz, CHC**H₂**), 2.58-2.44 (4H, m, 2 × NC**H₂**CH₂).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (C), 133.4 (CH), 128.6 (2 × CH), 127.6 (CH), 126.3 (2 × CH), 126.1 (CH), 67.0 (2 × CH_2), 61.5 (CH_2), 53.7 (2 × CH_2).

(±)-4-Phenyl-1-[4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]-1*H*-1,2,3-triazole (291).



261 **291**

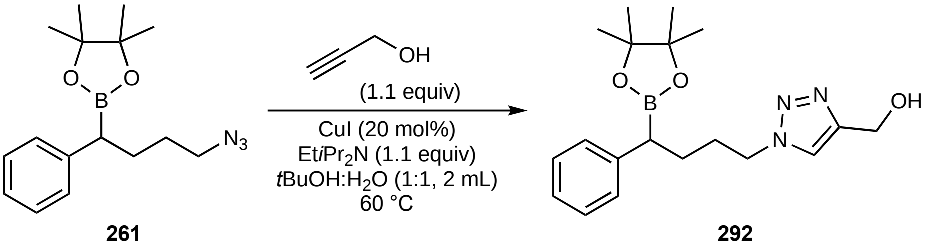
Using a modification of the procedure by Frost and co-workers,[267] boronic ester **261** (0.325 g, 1.08 mmol), phenyl acetylene (0.13 mL, 1.2 mmol), CuI (41.0 mg, 0.216 mmol) and Et*i*Pr_2N (0.21 mL, 1.2 mmol) were stirred in a mixture of *t*BuOH (1 mL) and H_2O (1 mL) at 60 °C for 16 h. The mixture was cooled to room temperature, and Et_2O (10 mL) and saturated aqueous NH_4Cl (10 mL) were added. The mixture was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The crude material was purified by flash chromatography (30%→40% EtOAc/petroleum ether) to give boronic ester **291** (0.310 g, 71%) as an amorphous white solid.[179]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.80 (2H, m, Ar**H**), 7.66 (1H, s, NC**H**), 7.45-7.40 (2H, m, Ar**H**), 7.36-7.31 (1H, m, Ar**H**), 7.29-7.24 (3H, m, Ar**H**), 7.21-7.13 (2H, m, Ar**H**), 4.40-4.33 (2H, m, NC**H₂**), 2.36-2.29 (1H, m, BC**H**), 1.98-1.86 (3H, m, BCHC$\mathbf{H_A}$CH_B and C$\mathbf{H_2}$CH_2N), 1.79-1.70 (1H, m, BCHCH_AC$\mathbf{H_B}$), 1.21 (6H, s, 2 × CC$\mathbf{H_3}$), 1.18 (6H, s, 2 × CC$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6 (C), 142.2 (C), 130.7 (C), 128.8 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.0 (CH), 125.7 (2 × CH), 125.6 (CH), 119.3 (CH), 83.5 (2 × C), 50.3 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 24.6 (2 × CH_3), 24.6 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.0.

(±)-{1-[4-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]-1*H*-1,2,3-triazol-4-yl}methanol (292).



Using a modification of the procedure by Frost and co-workers,[267] boronic ester **261** (0.250 g, 0.830 mmol), propargyl alcohol (0.0510 g, 0.913 mmol), CuI (0.0320 g, 0.166 mmol) and Et*i*Pr_2N (0.16 mL, 0.91 mmol) were stirred in a mixture of *t*BuOH (1 mL) and H_2O (1 mL) at 60 °C for 16 h. The mixture was cooled to room temperature, and Et_2O (10 mL) and saturated aqueous NH_4Cl (10 mL) were added. The mixture was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The crude material was purified by flash chromatography (100% EtOAc) to give boronic ester **292** (0.144 g, 49%) as a white solid.[179]

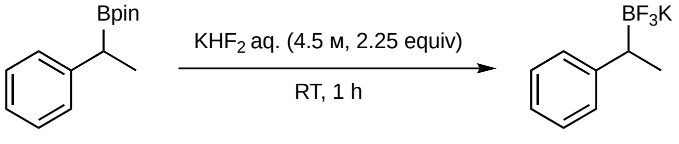
m.p. 70-71 °C (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (1H, s, Ar**H**), 7.30-7.23 (2H, s, Ar**H**), 7.19-7.14 (3H, s, Ar**H**), 4.78 (2H, s, C$\mathbf{H_2}$OH), 4.35-4.27 (2H, m, C$\mathbf{H_2}$N), 2.33-2.26 (1H, m, C**H**), 1.92-1.81 (3H, m, CHC$\mathbf{H_A}$CH_B, C$\mathbf{H_2}$CH_2N), 1.74-1.68 (1H, m, CHCH_AC$\mathbf{H_B}$), 1.21 (6H, m, 2 × CC$\mathbf{H_3}$), 1.18 (6H, m, 2 × CC$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4 (C), 142.2 (C), 128.5 (2 × CH), 128.3 (2 × CH), 125.6 (CH), 121.3 (CH), 83.5 (2 × C), 56.7 (CH_2O), 50.3 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 24.6 (2 × CH_3), 24.6 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.8.

Potassium (±)-1-phenylethyltrifluoroborate (302)



52 **302**

Using a modification of the procedure by Aggarwal and co-workers,[174] KHF_2 (0.757 g, 9.69 mmol) in H_2O (2.2 mL) was added dropwise to a stirred solution boronic ester **52** (1.02 g, 4.39 mmol) in MeOH (20 mL), and the mixture was stirred for 30 min. The mixture was concentrated *in vacuo*, MeOH (6 mL) and H_2O (6 mL) were added, and the mixture was concentrated. This process was repeated 9 times. Acetone (15 mL) was added, the liquid phase decanted, and the insoluble material was washed with acetone (3 × 10 mL). The combined washings were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give trifluroborate **302** (0.835 g, 90%) as a white solid. The data were consistent with the literature.[174]

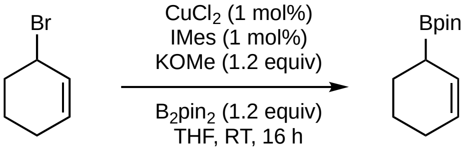
^{1}H NMR (400 MHz, D_2O) δ 7.32-7.24 (4H, m, Ar**H**), 7.17-7.10 (1H, m, Ar**H**), 1.97-1.85 (1H, m, C**H**), 1.21-1.15 (3H, m, C**H₃**).

^{13}C NMR (101 MHz, D_2O) δ 153.9 (C), 128.2 (2 × CH), 127.6 (CH), 127.4 (2 × CH), 15.8 (CH_3).

^{11}B NMR (128 MHz, D_2O) δ 0.33 (q, *J* = 14.9 Hz).

^{19}F NMR (377 MHz, D_2O) δ -143.7 (q, *J* = 14.9 Hz).

(±)-2-(Cyclohex-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (300)



300

Using a modification of the procedure by Marder and co-workers,[173] a solution of $CuCl_2$ (9.7 mg, 0.072 mmol), IMes (2.4 mg, 0.071 mmol) in THF (15 mL) was stirred for 10 min. B_2pin_2 (2.21 g, 8.70 mmol) and KOMe (0.606 g, 8.64 mmol) were added and the mixture was stirred for 10 min. 3-Bromocyclohexene (0.83 mL, 7.2 mmol) was added and the mixture was stirred for 16 h. The mixture was diluted with Et_2O (20 mL), filtered through a plug of Celite, and concentrated *in vacuo*. The crude material was purified by flash chromatography (5% Et_2O/petroleum ether) to give the boronic ester **300** (0.633 g, 42%) as a colourless oil. The data were consistent with the literature.[173]

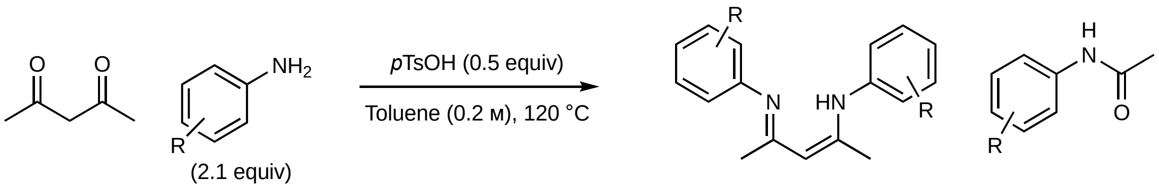
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78-5.63 (2H, m, **H**C=C**H**), 2.02-1.97 (2H, m, CH=CHC**H₂**), 1.83-1.72 (2H, m, CHCH₂C**H₂**), 1.72-1.59 (3H, m, C**H₂**C**H**B), 1.25 (12H, s, 4 × C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 127.6 (CH), 126.1 (CH), 83.1 (2 × C), 25.0 (CH_2), 24.8 (2 × CH_3), 24.7 (2 × CH_3), 24.1 (CH_2), 22.5 (CH_2).

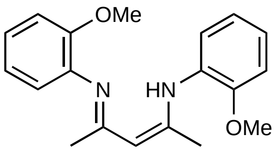
^{11}B NMR (128 MHz, $CDCl_3$) δ 33.3.

5.4 *Preparation of Ligands*

General Procedure 8: Diketimine and Acetamide Formation



Acetyl acetone (1 equiv) was added to a solution of *p*-toluenesulfonic acid (0.5 equiv) in toluene (0.2 м). The corresponding aniline (2.1 equiv) was added, and the mixture was stirred at 120 °C under Dean-Stark conditions for 24 h or 48 h. The mixture was cooled to room temperature, diluted with Et_2O (40 mL), washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by recrystallisation.



1

2-((2-Methoxyphenyl)amino)-4-((2-methoxyphenyl)imino)-2-pentene (1).

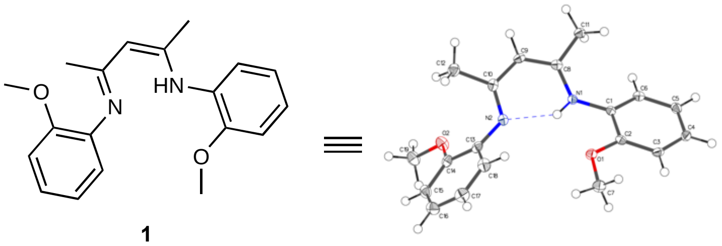
The title compound was prepared according to General Procedure **8** using acetyl acetone (0.35 mL, 3.4 mmol), *p*-toluenesulfonic acid (0.320 g, 1.75 mmol) and *o*-anisidine (0.81 ml, 7.2 mmol) heating for 24 h. Recrystallisation of the crude material from hexane (100 mL) gave diketimine **1** (0.540 g, 52%) as a light yellow solid. The data were consistent with the literature.[268]

m.p. 135-136 °C (hexane); literature = 129-130 °C (4:1 methanol:hexane).[268]

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.72 (1H, s, N**H**), 7.03-6.98 (4H, m, Ar**H**), 6.95-6.84 (4H, m, Ar**H**), 4.93 (1H, s, C**H**), 3.79 (6H, s, 2 × C**H_3**O), 1.99 (6H, s, 2 × C**H_3**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0 (2 × C), 151.3 (2 × C), 135.3 (2 × C), 123.6 (2 × CH), 123.1 (2 × CH), 120.5 (2 × CH), 111.4 (2 × CH), 97.9 (2 × CH_3), 55.7 (2 × CH_3), 21.1 (CH).

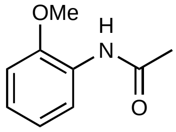
Crystals suitable for X-ray diffraction were obtained through recrystallisation of **1** from hexane.



1

Crystal Data for $C_{19}H_{22}N_2O_2$ (M =310.38 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 12.6590(9) Å, b = 17.1958(12) Å, c = 7.6942(5) Å, β = 101.985(4)°, V = 1638.4(2) Å^3, Z =

4, T = 100.38 K, μ(MoKα) = 0.082 mm^{-1}, $Dcalc$ = 1.258 g/cm^3, 20813 reflections measured (3.288° ≤ 2Θ ≤ 55.108°), 3730 unique (R_{int} = 0.0415, R_{sigma} = 0.0544) which were used in all calculations. The final R_1 was 0.0604 (I > 2σ(I)) and wR_2 was 0.1066 (all data).



556

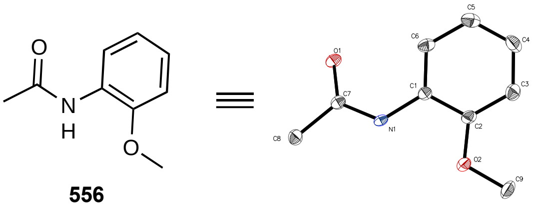
N-(2-Methoxyphenyl)acetamide (556)

The title compound was prepared according to General Procedure **8** using acetyl acetone (0.70 mL, 6.8 mmol), *p*-toluenesulfonic acid (0.650 g, 3.42 mmol) and *o*-anisidine (1.6 ml, 14 mmol) heating for 48 h. Recrystallisation of the crude material from hexane (300 mL) gave acetamide **556** (0.766 g, 68%) as a light yellow solid. The data were consistent with the literature.[269]

m.p. 130-132 °C (hexane). Literature 128-130 °C (no solvent given).[269]

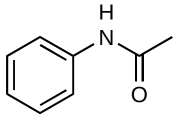
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42-8.31 (1H, m, Ar**H**), 7.77 (1H, s, N**H**), 7.11-7.01 (1H, m, Ar**H**), 7.01-6.92 (1H, m, Ar**H**), 6.92-6.84 (1H, m, Ar**H**), 3.89 (3H, s, OC**H$_3$**), 2.21 (3H, s, CC**H$_3$**).

Crystals suitable for X-ray diffraction were obtained through recrystallisation of **556** from hexane.



556

Crystal Data for $C_9H_{11}NO_2$ (M =165.19 g/mol): orthorhombic, space group Pbca (no. 61), a = 9.8639(9) Å, b = 9.4358(10) Å, c = 18.366(2) Å, V = 1709.4(3) Å^3, Z = 8, T = 100 K, μ(MoKα) = 0.091 mm^{-1}, $Dcalc$ = 1.284 g/cm^3, 6242 reflections measured (4.436° ≤ 2Θ ≤ 55.28°), 1967 unique (R_{int} = 0.0479, R_{sigma} = 0.0467) which were used in all calculations. The final R_1 was 0.0497 (I > 2σ(I)) and wR_2 was 0.1349 (all data).



554

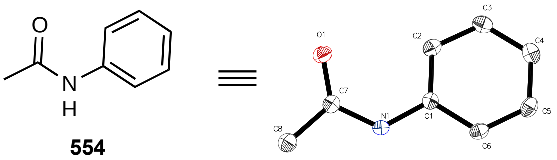
N-Phenylacetamide (554)

The title compound was prepared according to General Procedure **8** using acetyl acetone (0.45 mL, 4.4 mmol), *p*-toluenesulfonic acid (0.417 g, 2.19 mmol) and aniline (0.84 ml, 9.2 mmol) heating for 48 h. Recrystallisation of the crude material from hexane (200 mL) gave acetamide **554** (0.522 g, 88%) as a light yellow solid. The data were consistent with the literature.[269]

m.p. 112-114 °C (hexane). Literature 113-115 °C (no solvent given).[269]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.48 (2H, m, Ar**H**), 7.39-7.29 (3H, m, 2 × Ar**H** and N**H**), 7.15-7.08 (1H, m, Ar**H**), 2.18 (3H, s, C**H$_3$**).

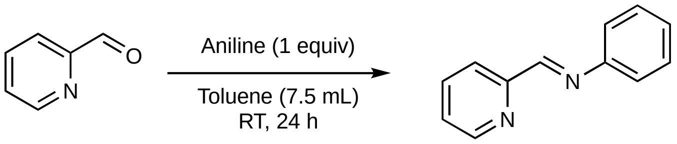
Crystals suitable for X-ray diffraction were obtained through recrystallisation of **556** from hexane.



554

Crystal Data for C_8H_9NO (M =135.16 g/mol): orthorhombic, space group Pbca (no. 61), a = 9.3724(16) Å, b = 7.7953(12) Å, c = 19.574(3) Å, V = 1430.1(4) Å^3, Z = 8, T = 100 K, μ(MoKα) = 0.084 mm^{-1},D_{calc} = 1.256 g/cm^3, 17932 reflections measured (6.018° ≤ 2Θ ≤ 55.106°), 1643 unique (R_{int} = 0.0952, R_{sigma} = 0.0543) which were used in all calculations. The final R_1 was 0.0455 (I > 2σ(I)) and wR_2 was 0.1070 (all data).

2-(Phenyliminomethyl)pyridine (315)



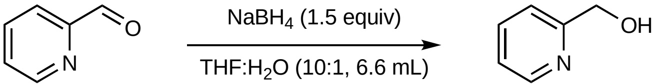
315

2-Pyridinecarboxaldehyde (1.13 g, 10.5 mmol) was added to aniline (0.96 mL, 11 mmol) in toluene (7.5 mL) and stirred for 24 h. The solvent was removed, and crude material dried under high vacuum to give imine **315** (1.91 g, >99%) as a yellow oil. This material was used without further purification. The data were consistent with the literature.[270]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76-8.70 (1H, m, Ar**H**), 8.62 (1H, s, NC**H**), 8.28-8.18 (1H, m, Ar**H**), 7.87-7.78 (1H, m, Ar**H**), 7.47-7.35 (3H, m, Ar**H**), 7.32-7.29 (3H, m, Ar**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6 (CH), 154.5 (C), 150.9 (C), 149.7 (CH), 136.7 (CH), 129.2 (2 × CH), 126.7 (CH), 125.1 (CH), 121.9 (CH), 121.1 (2 × CH).

Pyridin-2-ylmethanol (316)



316

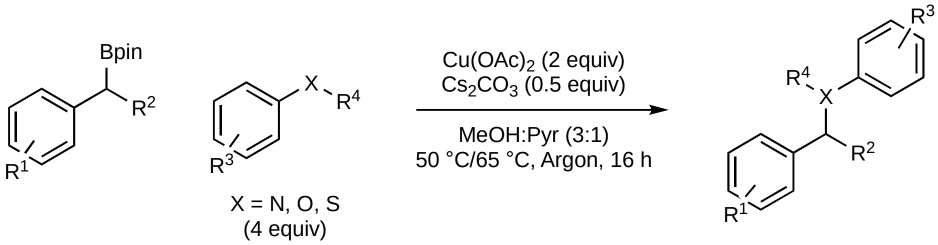
A solution of 2-pyridinecarboxaldehyde (0.50 mL, 5.3 mmol) in THF (6 mL) and H_2O (0.6 mL) was cooled to 0 °C, and $NaBH_4$ (0.301 g, 7.96 mmol) was added portion wise. The mixture was stirred for 3 h, warmed to room temperature and saturated aqueous NH_4Cl (5 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo* to give alcohol **316** (0.296 g, 52%) as a yellow oil. The material was used without further purification. The data were consistent with the literature.[271]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59-8.53 (1H, m, Ar**H**), 7.73-7.64 (1H, m, Ar**H**), 7.30-7.17 (2H, m, Ar**H**), 4.77 (2H, s, C**H$_2$**), 4.06 (1H, s, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C), 148.5 (CH), 136.7 (CH), 122.6 (CH), 120.5 (CH), 64.1 (CH_2).

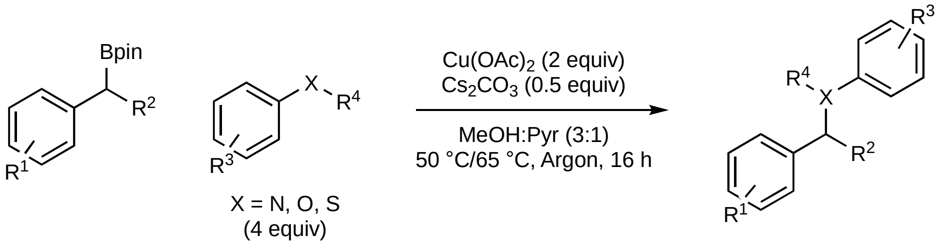
5.5 *Cu Mediated C-X (X = N, O, S) Bond Formation*

General Procedure 9: Cu-Mediated Coupling of N-, O- and S-Nucleophiles and Alkylboronic Acid Pinacol Esters.



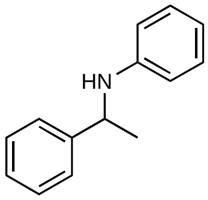
A flask containing the corresponding boronic ester (0.50 mmol, 1 equiv), aniline (2.00 mmol, 4 equiv), $Cu(OAc)_2$ (0.182 g, 1.00 mmol) and Cs_2CO_3 (0.0820 g, 0.252 mmol) was purged with argon. Methanol (1.0 mL) and pyridine (0.33 mL) were added, and the mixture was stirred at 50 °C or 65 °C until the reaction was complete (as determined by TLC). The mixture was cooled to room temperature, NH_4OH (10 % w/v, 10 mL) was added, and the mixture was extracted with Et_2O (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography.

General Procedure 10: Cu-Mediated Coupling of N-, O- and S-Nucleophiles and Alkylboronic Acid Pinacol Ester with an Oxidative Workup.



A flask containing the corresponding boronic ester (0.50 mmol, 1 equiv), aniline (2.00 mmol, 4 equiv), $Cu(OAc)_2$ (0.182 g, 1.00 mmol) and Cs_2CO_3 (0.082 g, 0.25 mmol) was purged with argon. Methanol (1.0 mL) and pyridine (0.33 mL) were added, and the mixture was stirred at 50 °C or 65 °C until the reaction was complete (as determined by TLC). The mixture was cooled to room temperature, NH_4OH (10 % w/v, 10 mL) was added, and the mixture was extracted with Et_2O (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. THF (1 mL), H_2O (1 mL) and sodium perborate (0.382 g, 2.50 mmol) were added, and the mixture stirred at room temperature for 1 h. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The crude material was purified by column chromatography.

5.5.1 Scope with respect to amine for the amination of boronic ester 52



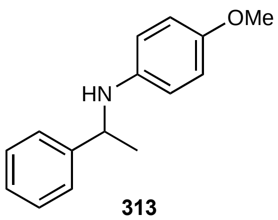
303

(±)-N-(1-Phenylethyl)aniline (303)

The title compound was prepared according to General Procedure **10** using boronic ester **52** (0.116 g, 0.501 mmol) and aniline (0.18 mL, 2.0 mmol) heating at 50 ºC for 16 h. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave amine **303** (0.0719 g, 73%) as a brown oil. The data were consistent with the literature.[272]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (2H, m, Ar**H**), 7.36-7.30 (2H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 7.14-7.06 (2H, m, Ar**H**), 6.69-6.61 (1H, m, Ar**H**), 6.56-6.48 (2H, m, Ar**H**), 4.50 (1H, q, *J* = 6.7 Hz, C**H**), 4.05 (1H, s, N**H**), 1.53 (3H, d, *J* = 6.7 Hz, CHC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (C), 145.2 (C), 129.1 (2 × CH), 128.6 (2 × CH), 126.8 (CH), 125.8 (2 × CH), 117.2 (CH), 113.2 (2 × CH), 53.4 (CH), 25.0 (CH_3).



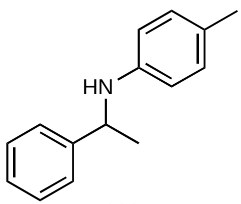
313

(±)-4-Methoxy-*N*-(1-phenylethyl)aniline (313)

The title compound was prepared according to General Procedure **9** using boronic ester **52** (0.116 g, 0.501 mmol) and *p*-anisidine (0.246 g, 2.00 mmol) heating at 50 ºC for 16 h. Flash chromatography (4% EtOAc/petroleum ether) of the crude material gave amine **313** (0.0823 g, 72%) as a yellow oil. The data were consistent with the literature.[272]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.39 (2H, m, Ar**H**), 7.39-7.33 (2H, m, Ar**H**), 7.39-7.33 (1H, m, Ar**H**), 6.75 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.52 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.46 (1H, q, *J* = 6.7 Hz, C**H**), 3.82 (1H, s, N**H**), 3.74 (3H, s, OC**H₃**), 1.54 (3H, d, *J* = 6.7 Hz, CHC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (C), 145.4 (C), 141.5 (C), 128.5 (2 × CH), 126.8 (CH), 125.8 (2 × CH), 114.7 (2 × CH), 114.5 (2 × CH), 55.7 (CH_3), 54.2 (CH), 25.1 (CH_3).



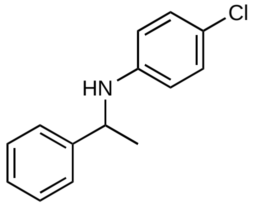
320

(±)-4-Methyl-*N*-(1-phenylethyl)aniline (320)

The title compound was prepared according to General Procedure **10** using boronic ester **52** (0.116 g, 0.499 mmol) and *p*-toluidine (0.216 g, 2.00 mmol) heating at 50 ºC for 16 h. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave amine **320** (0.0729 g, 69%) as a brown oil. The data were consistent with the literature.[272]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (2H, m, Ar**H**), 7.35-7.29 (2H, m, Ar**H**), 7.25-7.18 (1H, m, Ar**H**), 6.91 (2H, d, *J* = 8.3 Hz, Ar**H**), 6.45 (2H, d, *J* = 8.3 Hz, Ar**H**), 4.47 (1H, q, *J* = 6.7 Hz, C**H**), 3.92 (1H, s, N**H**), 2.20 (3H, s, CC**H₃**), 1.51 (3H, d, *J* = 6.7 Hz, CHC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4 (C), 145.0 (C), 129.6 (2 × CH), 128.6 (2 × CH), 126.8 (CH), 126.3 (C), 125.8 (2 × CH), 113.3 (2 × CH), 53.6 (CH), 25.1 (CH_3), 20.3 (CH_3).



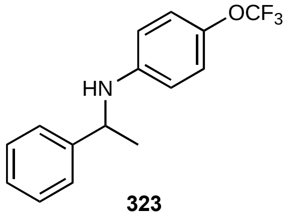
321

(±)-4-Chloro-*N*-(1-phenylethyl)aniline (321)

The title compound was prepared according to General Procedure **10** using boronic ester **52** (0.116 g, 0.501 mmol) and 4-chloroaniline (0.256 g, 2.01 mmol) heating at 65 ºC for 16 h. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave amine **321** (0.0672 g, 58%) as a brown oil. The data were consistent with the literature.[272]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (4H, m, Ar**H**), 7.27-7.21 (1H, m, Ar**H**), 7.10-7.01 (2H, m, Ar**H**), 6.52-6.32 (2H, m, Ar**H**), 4.45 (1H, q, *J* = 6.7 Hz, C**H**), 4.06 (1H, s, N**H**), 1.52 (3H, d, *J* = 6.7 Hz, CHC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8 (C), 144.7 (C), 128.9 (2 × CH), 128.7 (2 × CH), 127.0 (CH), 125.8 (2 × CH), 121.8 (C), 114.4 (2 × CH), 53.6 (CH), 25.0 (CH_3).



323

(±)-*N*-(1-phenylethyl)-4-(trifluoromethoxy)aniline (323)

The title compound was prepared according to General Procedure **9** using boronic ester **52** (0.116 g, 0.499 mmol) and 4-(trifluoromethoxy)aniline (0.27 mL, 2.0 mmol) heating at 65 ºC for 48 h. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave *amine* **323** (0.0853g, 61%) as a yellow oil.

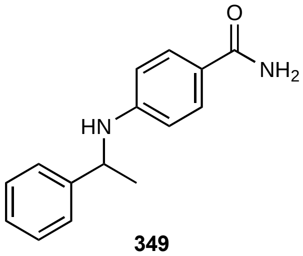
IR 3420, 2968, 1613, 1512, 1248, 1153 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (4H, m, Ar**H**), 7.27-7.24 (1H, m, Ar**H**), 6.95 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.46 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.45 (1H, q, *J* = 6.9 Hz, C**H**), 4.10 (1H, s, N**H**), 1.53 (3H, d, *J* = 6.9 Hz, C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.0 (C), 144.7 (C), 140.3 (C, q, $J_{C\text{-}F}$ = 1.9 Hz), 128.7 (2 × CH), 127.1 (CH), 125.7 (2 × CH), 122.2 (2 × CH), 120.64 (CF_3, q, $J_{C\text{-}F}$ = 255.2 Hz), 113.4 (2 × CH), 53.7 (CH), 25.0 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ -58.5.

HRMS (Q-TOF) Exact mass calcd for $[C_{15}H_{15}F_3NO]^+$ $[M+H]^+$: 282.1106, found: 282.1095.



349

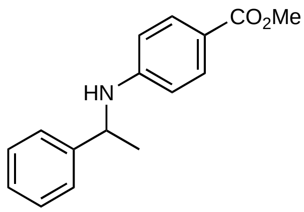
(±)-4-[(1-Phenylethyl)amino]benzamide (349)

The title compound was prepared according to a modification of General Procedure **10** using boronic ester **52** (0.117 g, 0.502 mmol) and 4-aminobenzamide (0.272 g, 2.01 mmol) heating at 65 °C for 36 h. The mixture was cooled to room temperature, Et_2O (5 mL) was added and passed through a plug of celite. Flash chromatography (3% MeOH/DCM) of the crude material gave a mixture of amine **349** and pinacol (1:0.3, 0.0623 g). THF (1 mL), H_2O (1 mL) and sodium periodate (0.060 g, 0.281 mmol) were added, and the mixture was stirred at room temperature for 16 h. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo.* Flash chromatography (3% MeOH/DCM) of the crude material gave amine **349** (0.0526 g, 44%) as an off white solid. The data were consistent with the literature.[273]

m.p 153-155 °C (CH_2Cl_2). No literature value.

^{1}H NMR (400 MHz, DMSO) δ 7.53 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.46 (1H, s, N**H**), 7.39-7.33 (2H, m, Ar**H**), 7.33-7.25 (2H, m, Ar**H**), 7.22-7.14 (1H, m, Ar**H**), 6.81 (1H, s, N**H**), 6.72-6.66 (1H, m, N**H**), 6.47 (2H, d, *J* = 8.6 Hz, Ar**H**), 4.54 (1H, q, *J* = 6.8 Hz, C**H**), 1.42 (3H, d, *J* = 6.8 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, DMSO) δ 168.4 (C), 150.8 (C), 146.1 (C), 129.3 (2 × CH), 128.8 (2 × CH), 127.0 (CH), 126.3 (2 × CH), 121.4 (C), 111.9 (2 × CH), 52.2 (CH), 24.9 (CH_3).



335

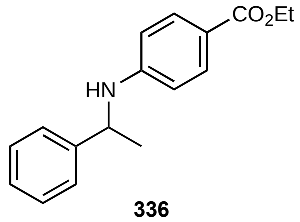
(±)-Methyl-4-((1-phenylethyl)amino)benzoate (335)

The title compound was prepared according to General Procedure **9** using boronic ester **52** (0.117 g, 0.503 mmol) and 4-methoxycarbonylaniline (0.302 g, 2.01 mmol) heating at 65 ºC for 48 h. Flash chromatography (10% EtOAc/petroleum ether) of the crude material gave amine **335** (0.0648 g, 53%) as a white solid. The data were consistent with the literature.[274]

m.p. 101-103 °C (Petroleum ether). No literature value.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.8 Hz, Ar**H**), 7.35-7.33 (4H, m, Ar**H**), 7.27-7.22 (1H, m, Ar**H**), 6.48 (2H, d, *J* = 8.8 Hz, Ar**H**), 4.57 (1H, q, *J* = 6.6, C**H**), 4.48 (1H, s, N**H**), 4.48 (3H, s, OC**H$_3$**), 1.56 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (C), 150.9 (C), 144.1 (C), 131.4 (2 x CH), 128.8 (2 x CH), 127.1 (CH), 125.7 (2 x CH), 118.3 (C), 112.1 (2 x CH), 53.0 (CH), 51.5 (CH_3), 24.7 (CH_3).



336

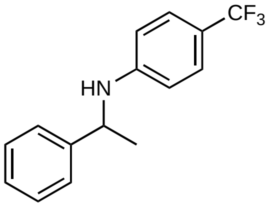
(±)-Ethyl-4-((1-phenylethyl)amino)benzoate (336)

The title compound was prepared according to a modification of General Procedure **9** using boronic ester **52** (0.116 g, 0.500 mmol) and 4-ethoxycarbonylaniline (0.330 g, 2.00 mmol). Ethanol (1 mL) and pyridine (0.3 mL) were added and heated at 65 ºC for 48 h. Flash chromatography (10% EtOAc/petroleum ether) of the crude material gave amine **336** (0.0390 g, 29%) as a white solid. The data were consistent with the literature.[273]

m.p. 85-86 °C ($CHCl_3$). No literature value.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.8 Hz, Ar**H**), 7.36-7.31 (4H, m, Ar**H**), 7.26-7.22 (1H, m, Ar**H**), 6.48 (2H, d, *J* = 8.8 Hz, Ar**H**), 4.57 (1H, q, *J* = 6.6 Hz, C**H**), 4.47 (1H, s, N**H**), 4.29 (2H, q, *J* = 7.1 Hz, C**H₂**CH₃), 1.56 (3H, d, *J* = 6.6 Hz, CHC**H₃**), 1.33 (3H, t, *J* = 7.1 Hz, CH₂C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (C), 150.8 (C), 144.2 (C), 131.3 (2 x CH), 128.8 (2 x CH), 127.1 (CH), 125.7 (2 x CH), 118.8 (C), 112.1 (2 x CH), 60.1 (CH_2), 53.0 (CH), 24.7 (CH_3), 14.4 (CH_3).



322

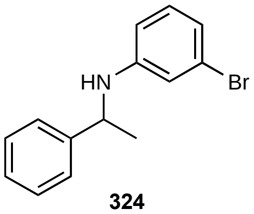
(±)-*N*-(1-Phenylethyl)-4-(trifluoromethyl)aniline (322)

The title compound was prepared according to General Procedure **10** using boronic ester **52** (0.116 g, 0.501 mmol), 4-trifluoromethylaniline (0.25 mL, 2.0 mmol) heating at 65 ºC for 48 h. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave amine **322** (0.0479 g, 36%) as a colourless oil. The data were consistent with the literature.[275]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.34 (6H, m, Ar**H**), 7.32-7.27 (1H, m, Ar**H**), 6.57-6.53 (2H, m, Ar**H**), 4.55 (1H, q, *J* = 6.7 Hz, C**H**), 4.42 (1H, s, N**H**), 1.58 (3H, d, *J* = 6.7 Hz, CHC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6 (C), 144.2 (C), 128.8 (2 x CH), 127.2 (CH), 126.4 (2 x CH, q, $J_{C\text{-}F}$ = 3.8 Hz), 125.7 (2 x CH), 125.0 (CF_3, q, $J_{C\text{-}F}$ = 270.4 Hz), 118.6 (C, q, $J_{C\text{-}F}$ = 32.5 Hz), 112.4 (2 x CH), 53.2 (CH), 24.8 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ -61.1.



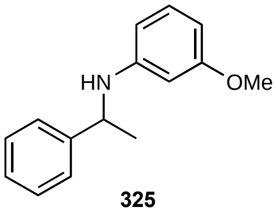
324

(±)-3-Bromo-*N*-(1-phenylethyl)aniline (324)

The title compound was prepared according to General Procedure **10** using boronic ester **52** (0.116 g, 0.501 mmol) and 3-bromoaniline (0.344 g, 2.00 mmol) heating at 65 ºC for 16 h. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave amine **324** (0.0613 g, 44%) as a brown oil. The data were consistent with the literature.[276]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (4H, m, Ar**H**), 7.29-7.23 (1H, m, Ar**H**), 6.96-6.90 (1H, m, Ar**H**), 6.78-6.74 (1H, m, Ar**H**), 6.70-6.67 (1H, m, Ar**H**), 6.44-6.37 (1H, m, Ar**H**), 4.47 (1H, q, *J* = 6.6 Hz, C**H**), 4.10 (1H, s, N**H**), 1.53 (3H, d, *J* = 6.6 Hz, CHC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4 (C), 144.4 (C), 130.4 (CH), 128.7 (2 × CH), 127.1 (CH), 125.7 (2 × CH), 123.0 (C), 120.0 (CH), 116.0 (CH), 111.8 (CH), 53.3 (CH), 24.8 (CH_3).



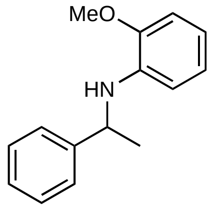
325

(±)-3-Methoxy-*N*-(1-phenylethyl)aniline (325)

The title compound was prepared according to General Procedure **10** using boronic ester **52** (0.120 g, 0.519 mmol) and *m*-anisidine (0.251 g, 2.04 mmol) heating at 50 ºC for 48 h. Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave amine **325** (0.0552 g, 47%) as a yellow oil. The data were consistent with the literature.[277]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (2H, m, Ar**H**), 7.36 – 7.30 (2H, m, Ar**H**), 7.26 – 7.20 (1H, m, Ar**H**), 7.01 (1H, dd, *J* = 8.1, 8.0 Hz, Ar**H**), 6.23 (1H, dd, *J* = 8.1, 2.1 Hz, Ar**H**), 6.16 (1H, dd, *J* = 8.0, 1.8 Hz, Ar**H**), 6.08 (1H, dd, *J* = 2.1, 1.8 Hz, Ar**H**), 4.49 (1H, q, *J* = 6.7 Hz, C**H**), 4.11 (1H, s, N**H**), 3.70 (3H, s, OC**H₃**), 1.53 (3H, d, *J* = 6.7 Hz, C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6 (C), 148.6 (C), 145.1 (C), 129.8 (CH), 128.6 (2 × CH), 126.9 (CH), 125.8 (2 × CH), 106.4 (CH), 102.4 (CH), 99.3 (CH), 54.9 (CH_3), 53.5 (CH), 24.9 (CH_3).



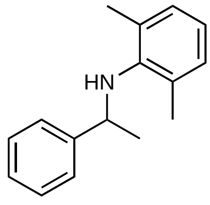
326

(±)-2-Methoxy-*N*-(1-phenylethyl)aniline (326)

The title compound was prepared according to General Procedure **10** using boronic ester **52** (0.116 g, 0.499 mmol) and *o*-anisidine (0.23 mL, 2.0 mmol) heating at 50 ºC for 16 h. Flash chromatography (4% EtOAc/petroleum ether) of the crude material gave amine **326** (0.0801 g, 71%) as a colourless oil. The data were consistent with the literature.[278]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (2H, m, Ar**H**), 7.36-7.30 (2H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 6.81-6.76 (1H, m, Ar**H**), 6.75-6.69 (1H, m, Ar**H**), 6.66-6.59 (1H, m, Ar**H**), 6.39-6.33 (1H, m, Ar**H**), 4.65 (1H, s, N**H**), 4.50 (1H, q, *J* = 6.6 Hz, C**H**), 3.91 (3H, s, OC**H₃**), 1.57 (3H, d, *J* = 6.6 Hz, CHC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5 (C), 145.4 (C), 137.2 (C), 128.6 (2 × CH), 126.7 (CH), 125.8 (2 × CH), 121.1 (CH), 116.3 (CH), 111.0 (CH), 109.2 (CH), 55.4 (CH_3), 53.3 (CH), 25.2 (CH_3).



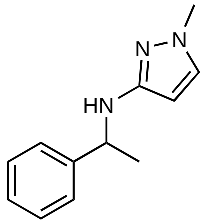
328

(±)-N-(1-Phenylethyl)-2,6-dimethylbenzenamine (328)

The title compound was prepared according to General Procedure **10** using boronic ester **52** (0.116 g, 0.501 mmol) and 2,6-dimethylaniline (0.25 mL, 2.0 mmol) heating at 65 ºC for 48 h. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave amine **328** (0.0339 g, 30%) as a red oil. The data were consistent with the literature.[279]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (4H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 6.96 (2H, d, *J* = 7.4 Hz, Ar**H**), 6.79 (1H, t, *J* = 7.4 Hz, Ar**H**), 4.33 (1H, q, *J* = 6.7 Hz, C**H**), 3.21 (1H, s, N**H**), 2.28 (6H, s, 2 × CC**H₃**), 1.52 (3H, d, *J* = 6.7 Hz, CHC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3 (C), 144.9 (C), 129.4 (2 × C), 128.8 (2 × CH), 128.4 (2 × CH), 126.9 (CH), 126.1 (2 × CH), 121.5 (CH), 56.7 (CH_3), 22.6 (CH), 18.9 (2 × CH_3).



329

(±)-1-Methyl-*N*-(1-phenylethyl)-1*H*-pyrazol-3-amine (329)

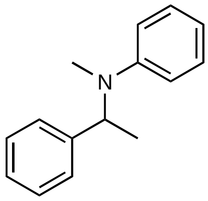
The title compound was prepared according to General Procedure **9** using boronic ester **52** (0.116 g, 0.499 mmol) and 1-methyl-1*H*-pyrazol-3-amine (0.194 g, 2.01 mmol) heating at 65 ºC for 16 h. Flash chromatography (1:1→2:1 EtOAc/petroleum ether) of the crude material gave *amine* **329** (0.0589 g, 59%) as a colourless oil.

IR 3293, 2967, 2926, 1550, 1501 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.37 (2H, m, Ar**H**), 7.35-7.30 (2H, m, Ar**H**), 7.26-7.20 (1H, m, Ar**H**), 7.00 (1H, d, *J* = 2.3 Hz, Ar**H**), 5.29 (1H, d, *J* = 2.3 Hz, Ar**H**), 4.46 (1H, q, *J* = 6.7 Hz, NC**H**), 4.07 (1H, s, N**H**), 3.68 (3H, s, NC**H₃**), 1.50 (3H, d, *J* = 6.7 Hz, CHC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C), 145.6 (C), 130.8 (CH), 128.4 (2 × CH), 126.8 (CH), 126.0 (2 × CH), 91.3 (CH), 54.7 (CH), 38.4 (CH_3), 24.5 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{12}H_{16}N_3]^+$ $[M+H]^+$: 202.1344, found: 202.1339.



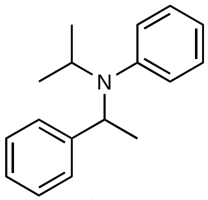
337

(±)-*N*-methyl-*N*-(1-phenylethyl)aniline (337)

The title compound was prepared according to General Procedure **9** using boronic ester **52** (0.116 g, 0.501 mmol) and *N*-methylaniline (0.22 mL, 2.0 mmol) heating at 65 ºC for 16 h. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave amine **337** (0.0877 g, 83%) as a yellow oil. The data were consistent with the literature.[280]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (4H, m, Ar**H**), 7.33-7.27 (3H, m, Ar**H**), 6.92-6.87 (2H, m, Ar**H**), 6.81-6.75 (1H, m, Ar**H**), 5.18 (1H, q, *J* = 6.9 Hz, C**H**), 2.73 (3H, s, NC**H₃**), 1.60 (3H, d, *J* = 6.9 Hz, CHC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2 (C), 142.8 (C), 129.2 (2 × CH), 128.4 (2 × CH), 126.9 (2 × CH), 126.8 (CH), 116.6 (CH), 113.0 (2 × CH), 56.5 (CH), 31.8 (CH_3), 16.3 (CH_3).



339

(±)-*N*-(1-Phenylethyl)-*N*-(propan-2-yl)aniline (339)

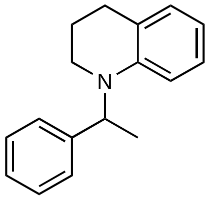
The title compound was prepared according to General Procedure **10** using boronic ester **52** (0.116 g, 0.498 mmol) and *N*-isopropylaniline (0.29 mL, 2.0 mmol) heating at 65 ºC for 48 h. Flash chromatography (100% pentane) of the crude material gave *amine* **339** (0.0525 g, 44%) as a colourless oil.

IR 2670, 2931, 1595, 1500, 1263 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.40 (2H, m, Ar**H**), 7.38-7.30 (2H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 7.20-7.11 (2H, m, Ar**H**), 6.85-6.74 (3H, m, Ar**H**), 4.79 (1H, q, *J* = 6.9 Hz, ArC**H**), 3.89 (1H, sept, *J* = 6.7 Hz, C**H**(CH_3)$_2$), 1.53 (3H, d, *J* = 6.9 Hz, NCHC**H₃**), 1.20 (3H, d, *J* = 6.7 Hz, CH(C**H₃**CH_3)), 1.16 (3H, d, *J* = 6.7 Hz, CH(CH_3C**H₃**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0 (C), 144.9 (C), 128.3 (2 × CH), 128.3 (2 × CH), 126.8 (CH), 126.3 (2 × CH), 119.5 (2 × CH), 118.4 (CH), 54.1 (CH), 48.7 (CH), 20.4 (CH_3), 20.3 (CH_3), 19.4 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{22}N]^+$ $[M+H]^+$: 240.1752, found: 240.1747.



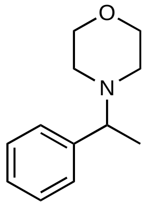
338

(±)-1-(1-Phenylethyl)-1,2,3,4-tetrahydroquinoline (338)

The title compound was prepared according to General Procedure **10** using boronic ester **52** (0.116 g, 0.499 mmol) and 1,2,3,4-tetrahydroquinoline (0.266 g, 2.00 mmol) heating at 65 °C for 16 h. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave amine **338** (0.0789 g, 67%) as a colourless oil. The data were consistent with the literature.[281]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.33 (4H, m, Ar**H**), 7.29-7.24 (1H, m, Ar**H**), 7.08-7.03 (1H, m, Ar**H**), 7.03-6.98 (1H, m, Ar**H**), 6.75-6.69 (1H, m, Ar**H**), 6.63-6.57 (1H, m, Ar**H**), 5.16 (1H, q, J = 6.9 Hz, C**H**), 3.21-3.14 (1H, m, NC$\mathbf{H_A}$CH_B), 3.10-3.02 (1H, m, NCH_AC$\mathbf{H_B}$), 2.86-2.74 (2H, m, ArC$\mathbf{H_2}$), 1.94-1.85 (2H, m, NCH_2C$\mathbf{H_2}$), 1.61 (3H, d, J = 6.9 Hz, C$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6 (C), 142.7 (C), 129.2 (CH), 128.4 (2 × CH), 127.1 (CH), 126.9 (2 × CH), 126.7 (CH), 122.8 (C), 115.4 (CH), 110.6 (CH), 54.6 (CH), 42.5 (CH_2), 28.5 (CH_2), 22.2 (CH_2), 16.0 (CH_3).



342

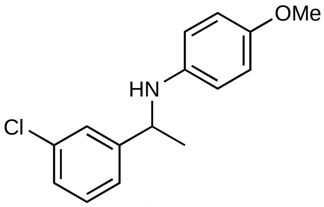
(±)-4-(1-Phenylethyl)morpholine (342)

The title compound was prepared according to General Procedure **9** using boronic ester **52** (0.116 g, 0.502 mmol) and morpholine (0.18 mL, 2.0 mmol) heating at 65 °C for 48 h. Flash chromatography (5→10% EtOAc/petroleum ether) of the crude material gave amine **342** (0.0301 g, 31%) as a yellow oil. The data were consistent with the literature.[282]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.29 (4H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 3.73-3.66 (4H, m, 2 × OC$\mathbf{H_2}$), 3.31 (1H, q, J = 6.6 Hz, C**H**), 2.56-2.44 (2H, m, 2 × NC$\mathbf{H_A}$$H_B$), 2.41-2.34 (2H, m, 2 × NC$H_A$$\mathbf{H_B}$), 1.36 (3H, d, J = 6.6 Hz, C$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 128.3 (2 × CH), 127.6 (2 × CH), 127.0 (CH), 67.2 (2 × CH_2), 65.4 (CH), 51.3 (2 × CH_2), 19.8 (CH_3).

5.5.2 Scope with respect to boronic ester for the amination of benzylic boronic esters.

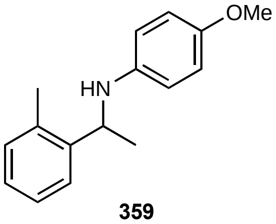

357

(±)-*N*-[1-(3-Chlorophenyl)ethyl]-4-methoxyaniline (357)

The title compound was prepared according to General Procedure **9** using boronic ester **225** (0.133 g, 0.497 mmol) and *p*-anisidine (0.247 g, 2.00 mmol), heating at 65 °C for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **357** (0.0792 g, 61%) as an orange oil. The data were consistent with the literature.[283]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 (1H, s, Ar**H**), 7.27-7.24 (2H, m, Ar**H**), 7.24-7.19 (1H, m, Ar**H**), 6.71 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.46 (2H, d, *J* = 8.8 Hz, Ar**H**), 4.38 (1H, q, *J* = 6.7 Hz, C**H**), 3.77 (1H, s, N**H**), 3.71 (3H, s, OC**H$_3$**), 1.49 (3H, d, *J* = 6.7 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 152.1 (C), 147.9 (C), 141.2 (C), 134.5 (C), 129.9 (CH), 127.0 (CH), 126.1 (CH), 124.1 (CH), 114.8 (2 × CH), 114.5 (2 × CH), 55.7 (CH$_3$), 54.0 (CH), 25.1 (CH$_3$).

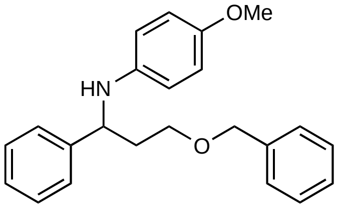

359

(±)-4-Methoxy-*N*-(1-*o*-tolylethyl)aniline (359)

The title compound was prepared according to General Procedure **9** using boronic ester **227** (0.120 g, 0.487 mmol) and *p*-anisidine (0.251 g, 2.04 mmol) heating at 50 °C for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **359** (0.0809 g, 69%) as a brown oil. The data were consistent with the literature.[278]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46-7.40 (1H, m, Ar**H**), 7.20-7.10 (3H, m, Ar**H**), 6.70 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.42 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.62 (1H, q, *J* = 6.6 Hz, C**H**), 3.77 (1H, s, N**H**), 3.70 (3H, s, OC**H$_3$**), 2.44 (3H, s, CC**H$_3$**), 1.47 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 151.8 (C), 143.0 (C), 141.6 (C), 134.6 (C), 130.6 (CH), 126.6 (CH), 126.5 (CH), 124.6 (CH), 114.8 (2 × CH), 114.1 (2 × CH), 55.7 (CH$_3$), 50.4 (CH), 23.1 (CH$_3$), 19.0 (CH$_3$).


362

(±)-*N*-[3-(Benzyloxy)-1-phenylpropyl]-4-methoxyaniline (362)

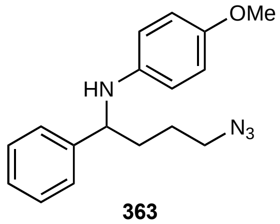
The title compound was prepared according to General Procedure **9** using boronic ester **234** (0.177 g, 0.501 mmol), *p*-anisidine (0.247 g, 2.02 mmol) heating at 65 °C for 32 h. Flash chromatography (8% EtOAc/petroleum ether) of the crude material gave *amine* **362** (0.103 g, 59%) as an orange oil.

IR 3385, 3028, 2857, 1510, 1235 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (9H, m, Ar**H**), 7.25-7.19 (1H m, Ar**H**), 6.67 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.42 (2H, d, *J* = 8.9 Hz, **ArH**), 4.61 (1H, s, N**H**), 4.51 (2H, s, ArC**H₂**), 4.49-4.45 (1H, m, C**H**), 3.69 (3H, s, C**H₃**), 3.63-3.52 (2H, m, CH_2C**H₂**O), 2.12-2.05 (2H, m, CHC**H₂**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6 (C), 144.0 (C), 141.9 (C), 138.1 (C), 128.5 (2 × CH), 128.4 (2 × CH), 127.7 (2 × CH), 127.7 (CH), 126.8 (CH), 126.4 (2 × CH), 114.6 (2 × CH), 114.3 (2 × CH), 73.2 (CH_2), 68.1 (CH_2), 57.8 (CH_3), 55.7 (CH), 38.3 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_{23}H_{26}NO_2]^+$ $[M+H]^+$: 348.1964, found: 348.1958.



363

(±)-*N*-(4-Azido-1-phenylbutyl)-4-methoxyaniline (363)

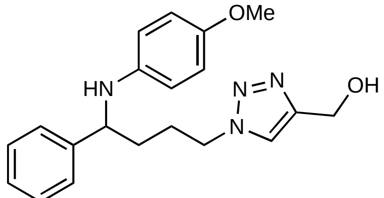
The title compound was prepared according to General Procedure **9** using boronic ester **261** (0.151 g, 0.500 mmol), *p*-anisidine (0.247 g, 2.01 mmol) heating at 65 ºC for 16 h. Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave *amine* **363** (0.0869 g, 59%) as a brown oil.

IR 3396, 2930, 2093, 1509, 1451, 1233 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (4H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 6.70 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.49 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.32-4.23 (1H, m, C**H**), 3.70 (3H, s, C**H₃**), 3.34-3.25 (2H, m, NCHC**H₂**), 1.96-1.81 (2H, m, C**H₂**CH_2N), 1.77-1.69 (1H, m, C**H$_A$**H_BN), 1.66-1.59 (1H, m, CH_A**H$_B$**N).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (C), 143.6 (C), 141.3 (C), 128.7 (2 × CH), 127.1 (CH), 126.4 (2 × CH), 114.8 (2 × CH), 114.6 (2 × CH), 58.6 (CH_3), 55.7 (CH), 51.2 (CH_2), 35.7 (CH_2), 25.8 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{21}N_4O]^+$ $[M+H]^+$: 297.1715, found: 297.1717.



364

(±)-(1-{4-[(4-methoxyphenyl)amino]-4-phenylbutyl}-1*H*-1,2,3-triazol-4-yl)methanol (364)

The title compound was prepared according to a modification of General Procedure **9** using boronic ester **292** (0.0899 g, 0.252 mmol), *p*-anisidine (0.124 g, 1.00 mmol), $Cu(OAc)_2$ (0.0910 g, 0.501 mmol) and Cs_2CO_3 (0.0410 g, 0.126 mmol), methanol (0.5 mL) and pyridine (0.17 mL). The mixture was stirred at 65 °C for 48 h. Flash chromatography (2%→5% EtOAc/petroleum ether) of the crude material gave *amine* **364** (0.0457 g, 52%) as an off white solid.

m.p. 135-136 °C ($CHCl_3$).

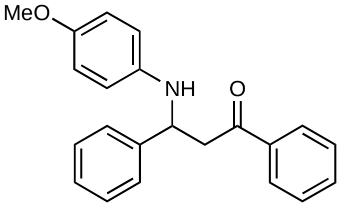
IR: 3333, 3207, 2928, 2858, 1737, 1513, 1234 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, s, Ar**H**), 7.35-7.28 (4H, m, Ar**H**), 7.26-7.20 (1H, m, Ar**H**), 6.68 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.48 (2H, d, *J* = 8.8 Hz, Ar**H**), 4.78 (2H, s, C**H₂**O), 4.38-

4.32 (2H, m, C**H$_2$**N), 4.29-4.24 (1H, m, C**H**), 3.69 (3H, s, C**H$_3$**), 2.10-2.02 (1H, m, CHC**H$_A$**H$_B$), 1.96-1.89 (1H, m, CHCH$_A$**H$_B$**), 1.85-1.75 (2H, m, C**H$_2$**CH$_2$N).

^{13}C NMR (101 MHz, CDCl$_3$) δ 152.4 (C), 147.7 (C), 142.9 (C), 140.6 (C), 128.7 (2 × CH), 127.3 (CH), 126.4 (2 × CH), 121.5 (CH), 115.1 (2 × CH), 114.8 (2 × CH), 58.8 (CH), 56.6 (CH$_2$), 55.7 (CH$_3$), 50.0 (CH$_2$), 35.0 (CH$_2$), 27.1 (CH$_2$).

HRMS (Q-TOF) Exact mass calcd for [C$_{20}$H$_{25}$N$_4$O$_2$]$^+$ [M+H]$^+$: 353.1978, found: 353.1972.



368

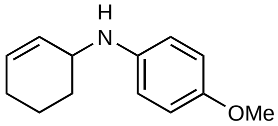
3-[(4-Methoxyphenyl)amino]-1,3-diphenylpropan-1-one (368)

The title compound was prepared according to General Procedure **9** using boronic ester **286** (0.169 g, 0.503 mmol), *p*-anisidine (0.249 g, 2.02 mmol) heating at 65 ºC for 24 h. Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave a mixture of amine **368** (0.0338 g, 20%) as an amorphous solid. The data were consistent with the literature.[284]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94-7.90 (2H, m, Ar**H**), 7.61-7.54 (1H, m, Ar**H**), 7.48-7.43 (4H, m, Ar**H**), 7.37-7.31 (2H, m, Ar**H**), 7.26-7.22 (1H, m, Ar**H**), 6.69 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.53 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.93 (1H, dd, *J* = 7.8, 5.0 Hz, C**H**), 3.69 (3H, s, C**H$_3$**), 3.50 (1H, dd, *J* = 16.2, 5.0 Hz, C**H$_A$**H$_B$), 3.41 (1H, dd, *J* = 16.2, 7.8 Hz, CH$_A$**H$_B$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 198.4 (C), 152.3 (C), 143.2 (C), 141.2 (C), 136.7 (C), 133.4 (CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 127.3 (CH), 126.4 (2 × CH), 115.3 (2 × CH), 114.7 (2 × CH), 55.7 (CH and CH$_3$), 46.4 (CH$_2$).

5.5.3 Amination of Allyl Boronic Esters



381

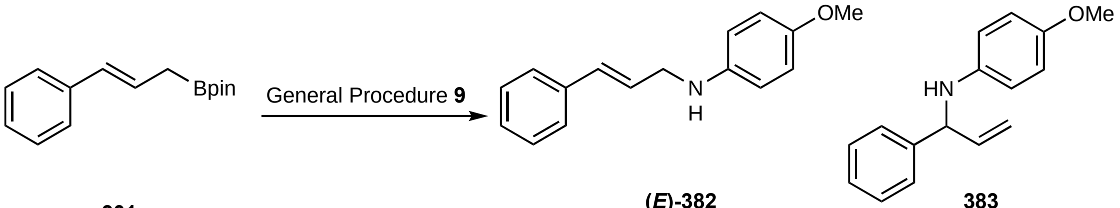
(±)-*N*-(4-Methoxybenzyl)cyclohex-2-enamine (381)

The title compound was prepared according to General Procedure **9** using boronic ester **300** (0.104 g, 0.501 mmol) and *p*-anisidine (0.247 g, 2.00 mmol), heating at 65 ºC for 48 h. Flash chromatography (3% EtOAc/petroleum ether) of the crude material gave amine **381** (0.0498 g, 49%) as an yellow oil. The data were consistent with the literature.[285]

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.79 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.61 (2H, d, *J* = 9.0 Hz, Ar**H**), 5.88-5.79 (1H, m, CHC**H**=CH), 5.80-5.72 (1H, m, CHCH=C**H**), 3.92 (1H, s, NC**H**), 3.76 (3H, s, C**H$_3$**), 3.34 (1H, s, N**H**), 2.13-1.99 (2H, m, CH=CHC**H$_2$**), 1.95-1.85 (1H, m, NCHC**H$_A$**H$_B$), 1.81-1.69 (1H, m, NCHCH$_2$C**H$_A$**H$_B$), 1.67-1.52 (2H, m, NCHCH$_2$CH$_A$**H$_B$** and NCHCH$_A$**H$_B$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 152.0 (C), 141.3 (C), 129.9 (CH), 128.9 (CH), 115.0 (2 × CH), 114.9 (2 × CH), 55.8 (CH$_3$), 49.0 (CH), 29.0 (CH$_2$), 25.2 (CH$_2$), 19.8 (CH$_2$).

(±)-*N*-(4-Methoxyphenyl)-1-phenyl-2-propenylamine (383) and (*E*)-*N*-cinnamyl-4-methoxybenzenamine ((*E*)-382)



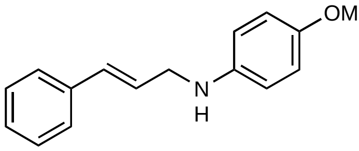
301

(*E*)-382
33%

383
30%

Ratio before purificaton 1.1:1

The title compounds were prepared according to General Procedure **9** using boronic ester **301** (0.126 g, 0.516 mmol) and *p*-anisidine (0.250 g, 2.03 mmol) heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine (*E)*-**382** (0.0404 g, 33%) and amine **383** (0.0368 g, 30%) as yellow oils. The data were consistent with the literature.[286]

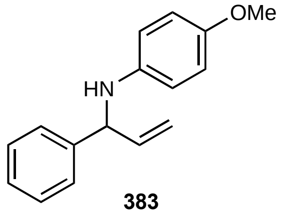


(*E*)-382

(*E*)-*N*-Cinnamyl-4-methoxybenzenamine ((*E*)-382)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (4H, m, Ar**H**), 7.26-7.22 (1H, m, Ar**H**), 6.82-6.80 (2H, m, Ar**H**), 6.70-6.68 (2H, m, Ar**H**), 6.63 (1H, d, *J* = 15.9 Hz, ArC**H**), 6.35 (1H, dt, *J* = 15.9, 5.9 Hz, ArCH=C**H**), 3.91 (2H, d, *J* = 5.9 Hz, C$\mathbf{H_2}$), 3.76 (3H, s, C$\mathbf{H_3}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7 (C), 141.6 (C), 136.8 (C), 131.8 (CH), 128.6 (2 × CH), 127.5 (2 × CH), 127.0 (CH), 126.3 (CH), 114.9 (2 × CH), 114.9 (2 × CH), 55.8 (CH_3), 47.6 (CH_2).



383

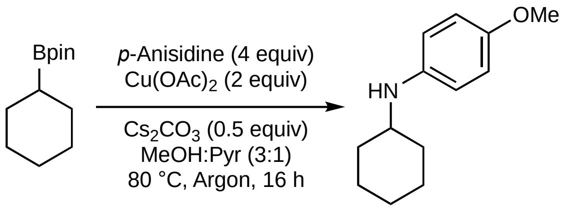
(±)-*N*-(4-Methoxyphenyl)-1-phenyl-2-propenylamine (383)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (5H, m, Ar**H**), 6.75-6.73 (2H, m, Ar**H**), 6.59-6.57 (2H, m, Ar**H**), 6.09-6.00 (1H, ddd, *J* = 17.1, 10.2, 6.0 Hz, CH_2=C**H**), 5.28 (1H, d, *J* = 17.1 Hz, CH=C$\mathbf{H_A}$$H_B$), 5.22 (1H, d, *J* = 10.2 Hz, CH=C$H_A$$\mathbf{H_B}$), 4.86 (1H, d, *J* = 6.0 Hz, NC**H**), 3.73 (3H, s, C$\mathbf{H_3}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.2 (C), 142.1 (C), 141.4 (C), 139.5 (CH), 128.7 (2 × CH), 127.4 (2 × CH), 127.1 (2 × CH), 115.9 (CH), 114.9 (CH_2), 114.7 (2 × CH), 61.8 (CH), 55.7 (CH_3).

5.5.4 Amination of Cyclohexylboronic ester

(±)-*N*-Cyclohexyl-4-methoxyaniline (151B)



151B

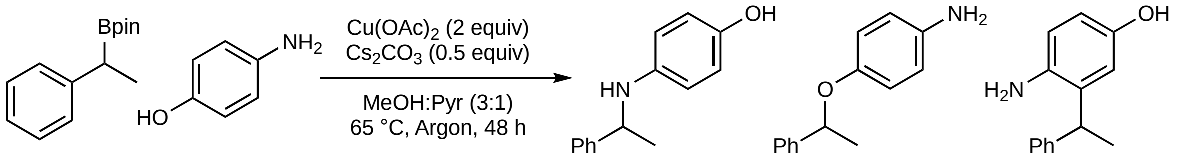
Methanol (1.0 mL) and pyridine (0.33 mL) were added to a flask containing cyclohexylboronic acid pinacol ester (0.106 g, 0.503 mmol), *p*-anisidine (0.248 g, 2.03 mmol), Cu(OAc)$_2$ (0.182 g, 1.00 mmol) and Cs$_2$CO$_3$ (0.0820 g, 0.252 mmol) and the mixture was stirred at 80 °C for 16 h. The mixture was cooled to room temperature, NH$_4$OH (10 % w/v, 10 mL) was added, and the mixture was extracted with Et$_2$O (3 x 10 mL). The combined organic phases were dried (MgSO$_4$), filtered, and concentrated *in vacuo*. Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave amine **151B** (0.0114 g, 11%) as an orange oil. The data were consistent with the literature.[287]

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.77 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.58 (2H, d, *J* = 8.2 Hz, Ar**H**), 3.75 (3H, s, OC$\mathbf{H_3}$), 3.21-3.13 (1H, m, NC**H**), 2.08-2.02 (2H, m, 2 × CHC$\mathbf{H_A}$H$_B$), 1.80-1.69 (2H, m, 2 × CHCH$_2$C$\mathbf{H_A}$H$_B$), 1.69-1.63 (1H, m, CHCH$_2$CH$_2$C$\mathbf{H_A}$H$_B$), 1.40-1.31 (2H, m, 2 × CHCH$_2$CH$_A$$\mathbf{H_B}$), 1.27 (1H, s, N**H**), 1.25-1.18 (1H, m, CHCH$_2$CH$_2$CH$_A$$\mathbf{H_B}$), 1.18-1.08 (2H, m, 2 × CHCH$_A$$\mathbf{H_B}$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 151.9 (C), 141.6 (C), 114.9 (2 × CH), 114.8 (2 × CH), 55.8 (CH$_3$), 52.8 (CH), 33.6 (2 × CH$_2$), 26.0 (CH$_2$), 25.1 (2 × CH$_2$).

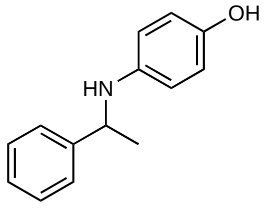
5.5.5 C-O and C-S Coupling of Alkylboronic Ester 52

(±)-4-[(1-Phenylethyl)amino]phenol (385), (±)-4-(1-phenylethoxy)aniline (386) and (±)-4-amino-3-(1-phenylethyl)phenol (387)



52 (4 equiv) **385** 47% **386** 2% **387** 32%

The title compounds were prepared according to General Procedure **9** using boronic ester **52** (0.116 g, 0.500 mmol) and 4-aminophenol (0.218 g, 2.00 mmol) heating at 65 °C for 48 h. Flash chromatography (20% EtOAc/petroleum ether) of the crude material gave amine **385** (0.0499 g, 47%), *amine* **386** (0.0023 g, 2%) and *amine* **387** (0.0338 g, 32%) as red oils.



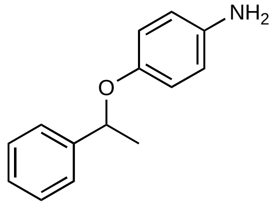
385

(±)-4-[(1-Phenylethyl)amino]phenol (385)

The data were consistent with the literature.[288]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (4H, m, Ar**H**), 7.25-7.21 (1H, m, Ar**H**), 6.62 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.43 (2H, d, *J* = 8.8 Hz, Ar**H**), 4.41 (1H, q, *J* = 6.7 Hz, C**H**), 2.19 (1H, s, N**H**), 1.50 (3H, d, *J* = 6.7 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4 (C), 145.4 (C), 141.6 (C), 128.6 (2 × CH), 126.8 (CH), 125.9 (2 × CH), 116.0 (2 × CH), 114.7 (2 × CH), 54.3 (CH), 25.1 (CH_3).



386

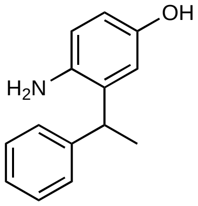
(±)-4-(1-Phenylethoxy)aniline (386)

IR 3446, 3360, 2920, 2850, 1624, 1508, 1230 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (4H, m, Ar**H**), 7.27-7.21 (1H, m, Ar**H**), 6.70 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.56 (2H, d, *J* = 8.7 Hz, Ar**H**), 5.17 (1H, q, *J* = 6.5 Hz, C**H**), 3.44 (2H, s, N**H$_2$**), 1.60 (3H, d, *J* = 6.5 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1 (C), 143.6 (C), 139.9 (C), 128.5 (2 × CH), 127.3 (CH), 125.7 (2 × CH), 117.4 (2 × CH), 116.3 (2 × CH), 76.87 (CH), 24.3 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{14}H_{16}NO]^+$ $[M+H]^+$: 214.1232, found: 214.1226.



387

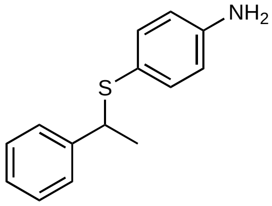
(±)-4-Amino-3-(1-phenylethyl)phenol (387)

IR 3363, 2966, 2929, 1600, 1498, 1450, 1214 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (2H, m, Ar**H**), 7.23-7.18 (3H, m, Ar**H**), 6.82 (1H, d, *J* = 2.7 Hz, Ar**H**), 6.60 (1H, dd, *J* = 8.4, 2.7 Hz, Ar**H**), 6.55 (1H, d, *J* = 8.4 Hz, Ar**H**), 4.09 (1H, q, *J* = 7.2 Hz, C**H**), 1.59 (3H, d, *J* = 7.2 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8 (C), 145.3 (C), 137.5 (C), 132.1 (C), 128.7 (2 × CH), 127.5 (2 × CH), 126.4 (CH), 117.6 (CH), 114.6 (CH), 113.8 (CH), 40.1 (CH), 21.7 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{14}H_{16}NO]^+$ $[M+H]^+$: 214.1232, found: 214.1226.



392

(±)-4-[(1-phenylethyl)thio]-benzenamine (392)

The title compound was prepared according to General Procedure **9** using boronic ester **52** (0.116 g, 0.500 mmol) and 4-aminothiophenol (0.250 g, 2.00 mmol) heating at 65 ºC for 16 h. Flash chromatography (10% EtOAc/petroleum ether) of the crude material gave *thioether* **392** (0.0863 g, 75%) as a colourless oil.

IR 3362, 3026, 1618, 1595, 1493 cm^{-1}

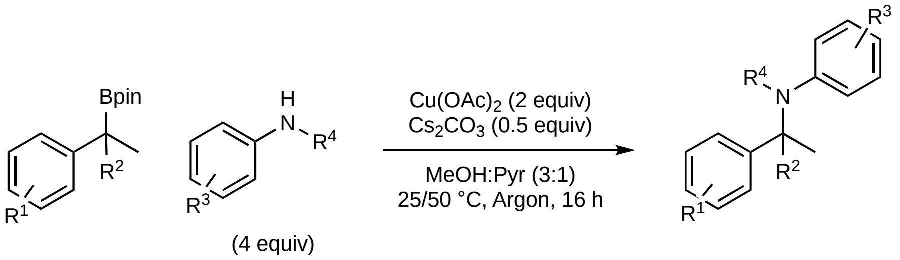
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.20 (5H, m, Ar**H**), 7.11 (2H, d, *J* = 8.6 Hz, Ar**H**), 6.54 (2H, d, *J* = 8.6 Hz, Ar**H**), 4.13 (1H, q, *J* = 7.0 Hz, C**H**), 3.70 (2H, s, N**H$_2$**), 1.60 (3H, d, *J* = 7.0 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6 (C), 143.5 (C), 136.4 (2 × CH), 128.2 (2 × CH), 127.3 (2 × CH), 126.8 (CH), 122.0 (C), 115.1 (2 × CH), 49.2 (CH), 21.6 (CH_3).

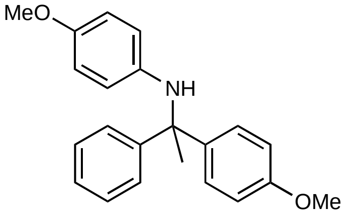
HRMS (Q-TOF) Exact mass calcd for $[C_{14}H_{16}NS]^+$ $[M+H]^+$: 230.1003, found: 230.0998.

5.5.6 Amination of 3° Alkylboronic Esters

General Procedure 11: Cu-Mediated Coupling of N-Nucleophiles and 3° Alkylboronic Esters.



A flask containing the corresponding boronic ester (0.50 mmol, 1 equiv), aniline (2.00 mmol, 4 equiv), $Cu(OAc)_2$ (0.182 g, 1.00 mmol) and Cs_2CO_3 (0.0820 g, 0.252 mmol) was purged with argon. Methanol (1.0 mL) and pyridine (0.33 mL) were added, and the mixture was stirred at 25 °C or 50 °C for 16 h. NH_4OH (10% w/v, 10 mL) was added, and the mixture was extracted with Et_2O (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography.



397

(±)-4-Methoxy-*N*-[1-(4-methoxyphenyl)-1-phenylethyl]aniline (397)

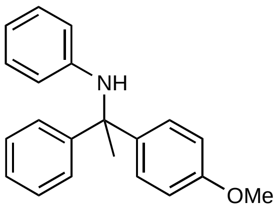
The title compound was prepared according to General Procedure **11** using boronic ester **275** (0.168 g, 0.498 mmol) and *p*-anisidine (0.246 g, 2.00 mmol) heating at 25 °C. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave *amine* **397** (0.0977 g, 59%) as a yellow oil.

IR 3396, 2991, 2932, 2833, 1608, 1507, 1237 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.43 (2H, m, Ar**H**), 7.37 (2H, d, *J* = 8.8 Hz, Ar**H**), 7.35-7.29 (2H, m, Ar**H**), 7.26-7.20 (1H, m, Ar**H**), 6.85 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.64 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.41 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.03 (1H, s, N**H**), 3.80 (3H, s, OC**H$_3$**), 3.70 (3H, s, OC**H$_3$**), 2.03 (3H, s, CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (C), 152.4 (C), 147.7 (C), 139.8 (C), 139.7 (C), 128.3 (2 × CH), 128.0 (2 × CH), 126.8 (2 × CH), 126.6 (CH), 118.2 (2 × CH), 114.2 (2 × CH), 113.6 (2 × CH), 62.2 (C), 55.6 (CH_3), 55.2 (CH_3), 26.7 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{22}H_{23}NO_2]^+$ $[M]^+$: 333.1729, found: 333.1719.



400

(±)-*N*-[1-(4-methoxyphenyl)-1-phenylethyl]aniline (400)

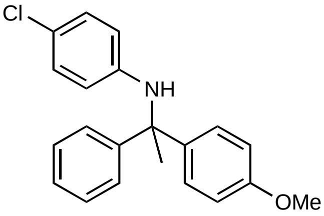
The title compound was prepared according to General Procedure **11** using boronic ester **275** (0.169 g, 0.499 mmol) and aniline (0.18 mL, 2.0 mmol) heating at 25 °C. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave *amine* **400** (0.0642 g, 42%) as a yellow oil.

IR 3409, 2989, 2834, 1599, 1497, 1249 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 8.8 Hz, Ar**H**), 7.38-7.30 (4H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 7.07-7.00 (2H, m, Ar**H**), 6.86 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.68-6.63 (1H, m, Ar**H**), 6.47-6.41 (2H, m, Ar**H**), 4.36 (1H, s, N**H**), 3.80 (3H, s, OC**H₃**), 2.10 (3H, s, CC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (C), 147.3 (C), 146.0 (C), 139.3 (C), 128.6 (2 × CH), 128.4 (2 × CH), 128.0 (2 × CH), 126.8 (2 × CH), 126.7 (CH), 117.4 (CH), 116.0 (2 × CH), 113.6 (2 × CH), 61.9 (C), 55.2 (CH_3), 26.6 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{21}H_{21}NONa]^+$ $[M+Na]^+$: 326.1521, found: 326.1536.



401

(±)-4-Chloro-*N*-[1-(4-methoxyphenyl)-1-phenylethyl]aniline (401)

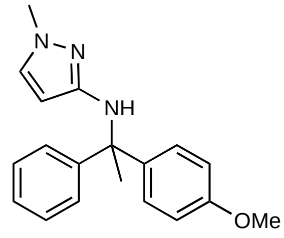
The title compound was prepared according to General Procedure **11** using boronic ester **275** (0.170 g, 0.501 mmol) and 4-chloroaniline (0.257 g, 2.01 mmol) heating at 25 °C. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave *amine* **401** (0.0710 g, 42%) as a yellow oil.

IR: 3473, 3383, 3006, 1601, 1493, 1247 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.40 (2H, m, *J* = 8.9 Hz, Ar**H**), 7.37-7.31 (4H, m, Ar**H**), 7.27-7.23 (1H, m, Ar**H**), 6.97 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.86 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.35 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.39 (1H, s, N**H**), 3.81 (3H, s, OC**H₃**), 2.07 (3H, s, CC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (C), 146.8 (C), 144.5(C), 138.7 (C), 128.5 (2 × CH), 128.5 (2 × CH), 128.0 (2 × CH), 126.9 (CH), 126.7 (2 × CH), 122.2 (C), 117.0 (2 × CH), 113.7 (2 × CH), 62.0 (C), 55.2 (CH_3), 26.9 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{21}H_{20}ClNONa]^+$ $[M+Na]^+$: 360.1131, found: 360.1135.



402

(±)-*N*-[1-(4-Methoxyphenyl)-1-phenylethyl]-1-methyl-1*H*-pyrazol-3-amine (402)

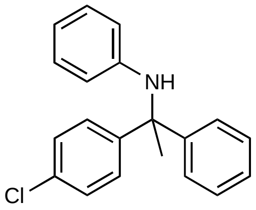
The title compound was prepared according to General Procedure **11** using boronic ester **275** (0.169 g, 0.501 mmol) and 1-methyl-1*H*-pyrazol-3-amine (0.194 g, 2.00 mmol) heating at 25 °C. Flash chromatography (1:5 EtOAc/petroleum ether) of the crude material gave *amine* **402** (0.0522 g, 34%) as a yellow oil.

IR 3267, 2933, 2835, 1547, 1509, 1249 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.45 (2H, m, Ar**H**), 7.39 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.33-7.28 (2H, m, Ar**H**), 7.25-7.19 (1H, m, Ar**H**), 6.92 (1H, d, *J* = 2.3 Hz, Ar**H**), 6.84 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.84 (1H, d, *J* = 2.3 Hz, Ar**H**), 4.58 (1H, s, N**H**), 3.79 (3H, s, OC**H$_3$**), 3.68 (3H, s, NC**H$_3$**), 2.00 (3H, s, CC**H$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1 (C), 155.0 (C), 147.7 (C), 139.6 (C), 130.3 (CH), 128.2 (2 × CH), 128.0 (2 × CH), 126.7 (2 × CH), 126.5 (CH), 113.4 (2 × CH), 94.0 (CH), 61.8 (C), 55.2 (CH_3), 38.3 (CH_3), 27.7 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{19}H_{22}N_3O]^+$ $[M+H]^+$: 308.1763, found: 308.1757.



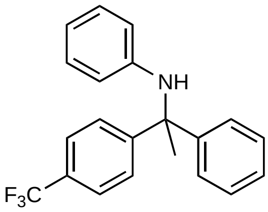
407

(±)-*N*-[1-(4-chlorophenyl)-1-phenylethyl]aniline (407)

The title compound was prepared according to General Procedure **11** using boronic ester **276** (0.171 g, 0.499 mmol) and aniline (0.18 mL, 2.0 mmol) heating at 25 °C. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave *amine* **407** (0.0681 g, 44%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.41 (4H, m, Ar**H**), 7.37-7.28 (5H, m, Ar**H**), 7.08-7.03 (2H, m, Ar**H**), 6.73-6.66 (1H, m, Ar**H**), 6.47-6.42 (2H, m, Ar**H**), 4.34 (1H, s, N**H**), 2.11 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8 (C), 145.6 (C), 145.4 (C), 132.6 (C), 128.7 (2 × CH), 128.5 (6 × CH), 127.1 (CH), 126.6 (2 × CH), 117.8 (CH), 116.1 (2 × CH), 62.1 (C), 26.7 (CH_3).



408

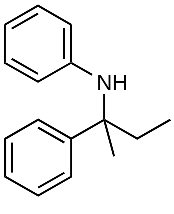
(±)-*N*-{1-phenyl-1-[4-(trifluoromethyl)phenyl]ethyl}aniline (408)

The title compound was prepared according to General Procedure **11** using boronic ester **277** (0.189 g, 0.502 mmol) and aniline (0.18 mL, 2.0 mmol) heating at 50 °C. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave *amine* **408** (0.0432 g, 25%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.48 (4H, m, Ar**H**), 7.34 (2H, d, *J* = 7.7 Hz, Ar**H**), 7.28-7.23 (2H, m, Ar**H**), 7.20-7.16 (1H, m, Ar**H**), 7.00-6.93 (2H, m, Ar**H**), 6.64-6.57 (1H, m, Ar**H**), 6.34 (2H, d, *J* = 7.7 Hz, Ar**H**), 4.27 (1H, s, N**H**), 2.05 (3H, s, C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7 (C), 146.5 (C), 145.5 (C), 129.0 (C, q, $J_{C\text{-}F}$ = 32.6 Hz), 128.7 (2 × CH), 128.6 (2 × CH), 127.4 (2 × CH), 127.2 (CH), 126.6 (2 × CH), 125.4 (2 × CH, q, $J_{C\text{-}F}$ = 3.7 Hz), 124.2 (CF_3, q, $J_{C\text{-}F}$ = 271.8 Hz,), 118.0 (CH), 116.2 (2 × CH), 62.4 (C), 26.6 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.3.

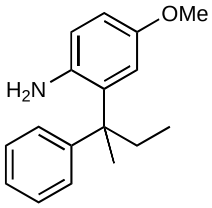


412

(±)-*N*-(2-phenylbutan-2-yl)aniline (412)

A mixture of the title compound and an unknown impurity was prepared according to General Procedure **11** using boronic ester **281** (0.130 g, 0.500 mmol) and aniline (0.18 mL, 2.0 mmol) heating at 50 °C. Flash chromatography (1% EtOAc/petroleum ether) of the crude material gave amine **412** (0.0466 g, approx. 41%) in low purity as a yellow oil. The data were consistent with the literature.[289]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.45 (2H, m, Ar**H**), 7.36-7.30 (2H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 7.04-6.95 (2H, m, Ar**H**), 6.65-6.56 (1H, m, Ar**H**), 6.38-6.30 (2H, m, Ar**H**), 4.01 (1H, s, N**H**), 1.92 (2H, q, *J* = 7.4, C**H₂**), 1.63 (3H, s, CC**H₃**), 0.83 (3H, t, *J* = 7.4 Hz, CH_2C**H₃**).



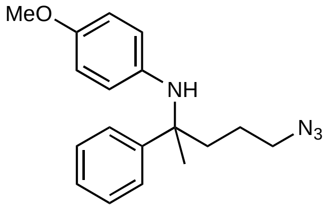
413

(±)-4-Methoxy-2-(2-phenylbutan-2-yl)aniline (413).

The title compound was prepared according to General Procedure **11** using boronic ester **281** (0.131 g, 0.504 mmol) and *p*-anisidine (0.247 g, 2.00 mmol) heating at 50 °C. Flash chromatography (3% EtOAc/petroleum ether) of the crude material gave *amine* **413** (0.0191 g, 15%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (4H, m, Ar**H**), 7.24-7.18 (1H, m, Ar**H**), 7.06 (1H, d, *J* = 2.9 Hz, Ar**H**), 6.67 (1H, dd, *J* = 8.5, 2.9 Hz, Ar**H**), 6.49 (1H, d, *J* = 8.5 Hz, Ar**H**), 3.82 (3H, s, OC**H₃**), 2.89 (2H, s, N**H₂**), 2.41 (1H, dq, *J* = 14.7, 7.4 Hz, C**H$_A$**H$_B$), 2.02 (1H, dq, *J* = 14.7, 7.4 Hz, CH$_A$**H$_B$**), 1.60 (3H, s, CC**H₃**), 0.69 (3H, dd, *J* = 7.4, 7.4 Hz, CH_2C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3 (C), 148.5 (C), 138.3 (C), 134.2 (C), 128.6 (2 × CH), 126.5 (2 × CH), 126.1 (CH), 118.0 (CH), 115.1 (CH), 111.1 (CH), 55.6 (CH_3), 45.8 (C), 31.1 (CH_2), 25.8 (CH_3), 9.2 (CH_3).



414

(±)-*N*-(5-Azido-2-phenylpentan-2-yl)-4-methoxyaniline (414)

The title compound was prepared according to General Procedure **11** using boronic ester **280** (0.159 g, 0.503 mmol) and *p*-anisidine (0.246 g, 2.00 mmol) heating at 25 °C. Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave *amine* ***414*** (0.0365 g, 23%) as a yellow oil. A mixture of *alcohol* **415** and *amine* **416** (40.9 mg) were also collected.

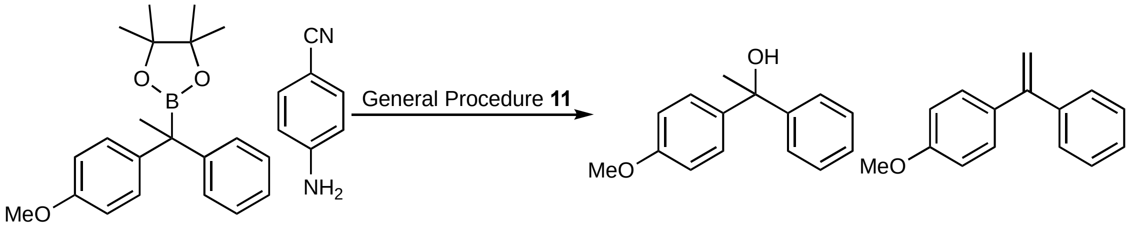
IR 3390, 2932, 2831, 2093, 1508, 1235, cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.45 (2H, m, Ar**H**), 7.39-7.32 (2H, m, Ar**H**), 7.27-7.23 (1H, m, Ar**H**), 6.62 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.31 (2H, d, *J* = 8.8 Hz, Ar**H**), 3.69 (4H, s, N**H**, OC**H$_3$**), 3.26-3.12 (2H, m, C**H$_2$**N), 2.01-1.88 (2H, m, C**H$_2$**CH_2N), 1.61 (3H, s, CC**H$_3$**), 1.55-1.47 (2H, m, CC**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (C), 146.2 (C), 139.7 (C), 128.5 (2 × CH), 126.5 (CH), 126.2 (2 × CH), 117.0 (2 × CH), 114.3 (2 × CH), 58.3 (C), 55.6 (CH_3), 51.6 (CH_2), 40.6 (CH_2), 26.3 (CH_3), 23.5 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_{18}H_{23}N_4O]^+$ $[M+H]^+$: 311.1872, found: 311.1866.

(±)-1-(4-Methoxyphenyl)-1-phenylethan-1-ol (399) and 1-Methoxy-4-(1-phenylvinyl)benzene (406)

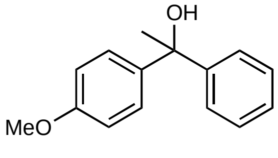


275

399
51%

406
15%

The title compounds were prepared according to General Procedure **11** using boronic ester **275** (0.170 g, 0.503 mmol) and 4-aminobenzonitrile (0.237 g, 2.01 mmol) heating at 50 °C. Flash chromatography (8% EtOAc/petroleum ether) of the crude material gave alkene **406** (0.0163 g, 15%) and alcohol **399** (0.0586 g, 51%) as yellow oils.



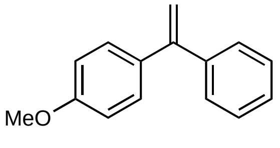
399

(±)-1-(4-Methoxyphenyl)-1-phenylethan-1-ol (399)

The data were consistent with the literature.[290]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.38-7.30 (4H, m, Ar**H**), 7.27-7.22 (1H, m, Ar**H**), 6.86 (2H, d, *J* = 8.9 Hz, Ar**H**), 3.80 (3H, s, OC**H$_3$**), 2.15 (1H, s, O**H**), 1.95 (3H, s, CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (C), 148.2 (C), 140.3 (C), 128.1 (2 × CH), 127.1 (2 × CH), 126.8 (CH), 125.7 (2 × CH), 113.4 (2 × CH), 75.9 (C), 55.2 (CH_3), 31.0 (CH_3).



406

1-Methoxy-4-(1-phenylvinyl)benzene (406)

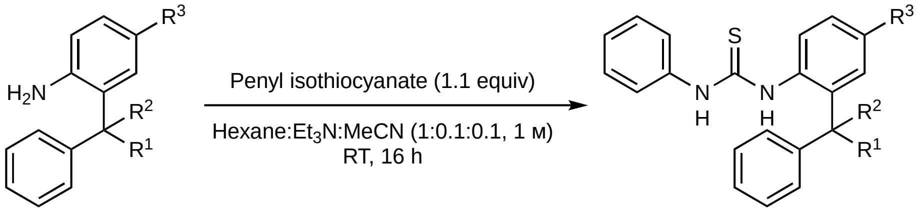
The data were consistent with the literature.[291]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38-7.31 (5H, m, Ar**H**), 7.29 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.88 (2H, d, *J* = 8.7 Hz, Ar**H**), 5.41 (1H, d, *J* = 1.3 Hz, C=C**H$_A$**H$_B$), 5.37 (1H, d, *J* = 1.3 Hz, C=CH$_A$**H$_B$**), 3.84 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 159.3 (C), 149.5 (C), 141.8 (C), 134.0 (C), 129.4 (2 × CH), 128.3 (2 × CH), 128.1 (CH), 127.6 (2 × CH), 113.5 (2 × CH), 112.9 (CH$_2$), 55.3 (CH$_3$).

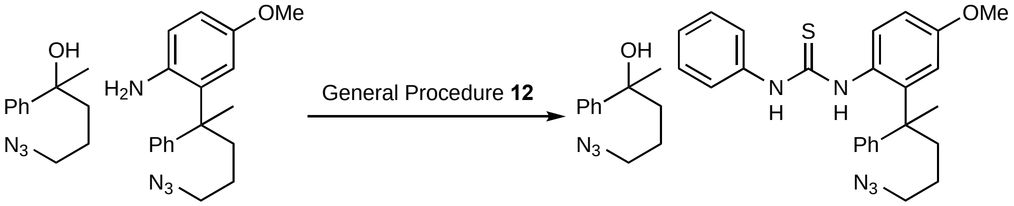
5.6 *Preparation of Thioureas*

General Procedure 12: Formation of Thioureas From Phenyl Isothiocyanate.



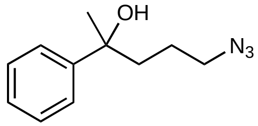
Phenyl isothiocyanate (1.1 equiv) was added to a solution of the corresponding amine (1 equiv) in hexane:Et$_3$N:MeCN (1:0.1:0.1, 0.1 M), and the mixture was stirred for 16 h at room temperature. The precipitate was washed with hexane (2 × 5 mL) to provide the pure thiourea.

(±)-5-Azido-2-phenylpentan-2-ol (415) and (±)-1-[2-(5-azido-2-phenylpentan-2-yl)-4-methoxyphenyl]-3-phenylthiourea (417)



415 **416** **415** **417**

The title compounds were prepared according to General Procedure **12** using a mixture of alcohol **415** and amine **416** (40.9 mg) and, phenyl isothiocyanate (18.9 mg, 0.140 mmol). The precipitate was collected and washed with hexane (2 × 5 mL) to give *thiourea* **417** (16.0 mg). Flash chromatography (petroleum ether→20% EtOAc/petroleum ether) of the mother liquor gave *alcohol* **415** (18.1 mg).



415

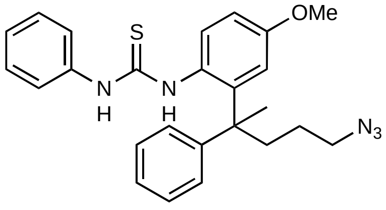
(±)-5-Azido-2-phenylpentan-2-ol (415)

IR 3420, 2930, 2092, 1602, 1146, 1260 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.39 (2H, m, Ar**H**), 7.40-7.33 (2H, m, Ar**H**), 7.29-7.24 (1H, m, Ar**H**), 3.26-3.19 (2H, m, C**H_2**N_3), 1.95-1.83 (2H, m, C**H_2**CH_2N_3), 1.80 (1H, s, O**H**), 1.64-1.57 (4H, m, CH_3, CC**H_A**H_B), 1.53-1.38 (1H, m, CCH_A**H_B**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (C), 128.3 (2 × CH), 126.7 (CH), 124.6 (2 × CH), 74.3 (C), 51.6 (CH_2), 41.1 (CH_2), 30.5 (CH_3), 23.7 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_{11}H_{15}N_3ONa]^+$ $[M+Na]^+$: 228.1113, found: 228.1107.



417

(±)-1-[2-(5-azido-2-phenylpentan-2-yl)-4-methoxyphenyl]-3-phenylthiourea (417)

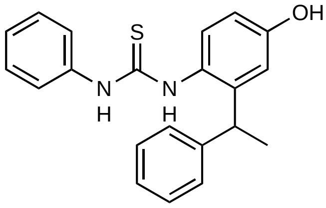
m.p. 150-151 °C (hexane)

IR 3334, 3170, 2959, 2096, 1508, 1214 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, s, N**H**), 7.35-7.29 (1H, m, Ar**H**), 7.26-7.21 (2H, m, Ar**H**), 7.18-7.13 (2H, m, Ar**H**), 7.04 (6H, m, Ar**H**), 6.90-6.87 (1H, m, Ar**H**), 6.38 (1H, s, Ar**H**), 3.90 (3H, s, OC**H_3**), 3.38-3.28 (1H, m, C**H_A**H_BN), 3.28-3.18 (1H, m, CH_A**H_B**N), 2.23-2.03 (2H, m, C**H_2**CH_2N_3), 1.57 (3H, s, CC**H_3**), 1.44-1.31 (2H, m, CC**H_2**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7 (C), 158.5 (C), 148.2 (C), 145.1 (C), 136.8 (C), 131.9 (CH), 129.6 (CH), 128.8 (4 × CH), 126.6 (2 × CH), 126.3 (2 × CH), 125.4 (CH), 123.8 (C), 115.4 (CH), 110.8 (CH), 55.5 (CH_3), 51.9 (CH_2), 45.5 (C), 36.1 (CH_2), 27.8 (CH_3), 24.8 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_{25}H_{28}N_5OS]^+$ $[M+H]^+$: 446.2015, found: 446.2009.



388

(±)-3-[4-Hydroxy-2-(1-phenylethyl)phenyl]-1-phenylthiourea (388)

The title compound was prepared according to General Procedure **12** using amine **387** (33.8 mg, 0.158 mmol) and phenyl isothiocyanate (23.8 mg, 0.176 mmol) to give *thiourea **388*** (37.2 mg, 68%).

m.p. 155-157 °C (hexane)

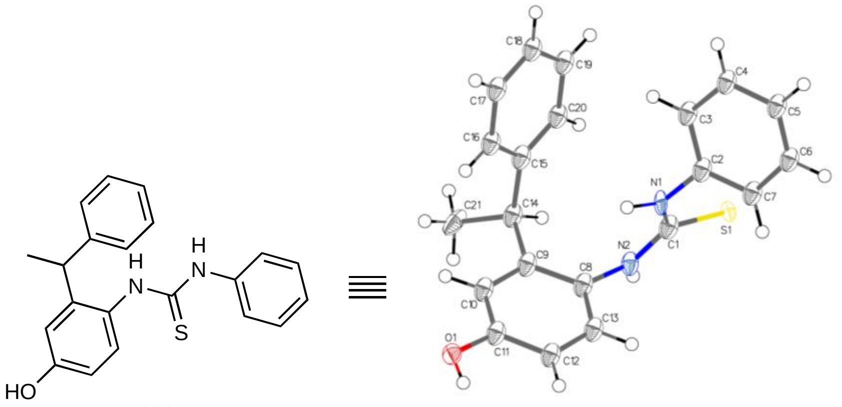
IR 3339, 3152, 2967, 1747, 1533, 1275 cm^{-1}.

^{1}H NMR (400 MHz, CD_3CN) δ 7.73 (1H, s, N**H**), 7.33-7.23 (8H, m, Ar**H**), 7.21-7.15 (2H, m, Ar**H**), 7.09-7.06 (1H, m, Ar**H**), 6.79 (1H, s, Ar**H**), 6.73-6.68 (1H m, Ar**H**), 4.33 (1H, q, $J = 7.2$ Hz, C**H**), 1.55 (3H, d, $J = 7.2$ Hz, CHC**H_3**).

^{13}C NMR (101 MHz, CD_3CN) δ 182.8 (C), 157.9 (C), 147.0 (C), 146.4 (C), 131.6 (CH), 129.6 (C), 129.4 (4 × CH), 128.5 (4 × CH), 127.1 (CH), 126.9 (C), 126.8 (CH), 115.5 (CH), 114.8 (CH), 40.4 (CH), 21.6 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{21}H_{21}N_2OS]^+$ $[M+H]^+$: 349.1375, found: 349.1369.

Crystals suitable for X-ray diffraction were obtained through recrystallisation of **388** from hexane and slow evaporation.

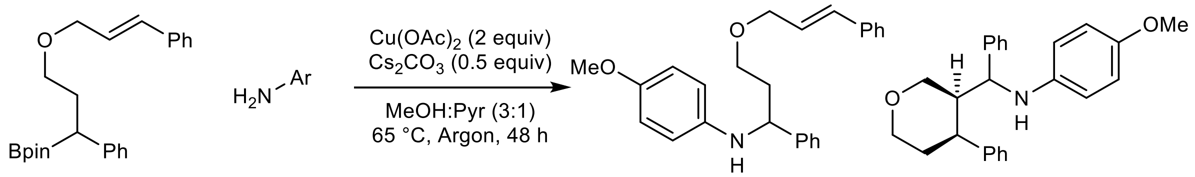


388

Crystal Data for $C_{21}H_{20}N_2OS$ (M =348.45 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 9.9812(6) Å, b = 12.5463(7) Å, c = 14.3653(9) Å, β = 97.872(3)°, V = 1781.97(18) Å^3, Z = 4, T = 100.01 K, μ(CuKα) = 1.688 mm^{-1}, $Dcalc$ = 1.299 g/cm^3, 19833 reflections measured (9.398° ≤ 2Θ ≤ 133.59°), 3096 unique (R_{int} = 0.1953, R_{sigma} = 0.1111) which were used in all calculations. The final R_1 was 0.2461 (I > 2σ(I)) and wR_2 was 0.4694 (all data).

5.7 *Exploring the Mechanism of Amination of Alkyl Boronic Esters*

(±)-4-Methoxy-*N*-(1-phenyl-3-{[(2*E*)-3-phenylprop-2-en-1-yl]oxy}propyl)aniline (377) and (±)-4-methoxy-*N*-[phenyl(4-phenyloxan-3-yl)methyl]aniline (378)



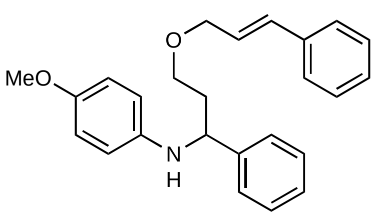
240

Ar = 4-MeOC$_6$H$_4$
(4 equiv)

377
23%

378
19%

The title compound was prepared according to General Procedure **9** using boronic ester **240** (0.189 g, 0.499 mmol) and *p*-anisidine (0.247 g, 2.01 mmol) heating at 65 °C for 48 h. Flash chromatography (3%→5% EtOAc/petroleum ether) of the crude material gave *amine* **377** (0.0426 g, 23%) as an orange oil and *amine* **378** (0.0349 g, 19%) as a yellow oil.



377

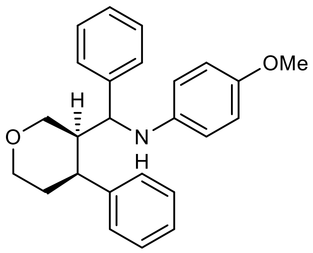
4-Methoxy-*N*-(1-phenyl-3-{[(2*E*)-3-phenylprop-2-en-1-yl]oxy}propyl)aniline (377)

IR: 3381, 2854, 1600, 1512, 1451, 1235 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40-7.36 (4H, m, Ar**H**), 7.36-7.29 (4H, m, Ar**H**), 7.29-7.25 (1H, m, Ar**H**), 7.25-7.20 (1H, m, Ar**H**), 6.68 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.62 (1H, d, *J* = 15.9 Hz, ArC**H**=CH), 6.47 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.30 (1H, dt, *J* = 15.9, 5.9 Hz, ArCH=C**H**), 4.59 (1H, s, N**H**), 4.51-4.45 (1H, m, NC**H**), 4.15 (2H, d, *J* = 5.9 Hz, CH=CHC$\mathbf{H_2}$), 3.69 (3H, s, C$\mathbf{H_3}$), 3.64-3.58 (1H, m, OC$\mathbf{H_A}$CH$_B$CH$_2$), 3.58-3.52 (1H, m, OCH$_A$C$\mathbf{H_B}$ CH$_2$), 2.12-2.05 (2H, m, OCH$_2$C$\mathbf{H_2}$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 151.7 (C), 144.0 (C), 142.0 (C), 136.6 (C), 132.4 (CH), 128.6 (4 × CH) , 127.7 (CH), 126.9 (CH), 126.5 (2 × CH), 126.4 (2 × CH), 126.0 (CH), 114.7 (2 × CH), 114.4 (2 × CH), 71.6 (CH$_2$), 68.0 (CH$_2$), 57.9 (CH), 55.7 (CH$_3$), 38.4 (CH$_2$).

HRMS (Q-TOF) Exact mass calcd for $[C_{25}H_{28}NO_2]^+$ [M+H]$^+$: 374.2120, found: 374.2115.



378

4-Methoxy-*N*-[phenyl(4-phenyloxan-3-yl)methyl]aniline (378)

IR: 3400, 2849, 1601, 1511, 1495, 1238 cm^{-1}.

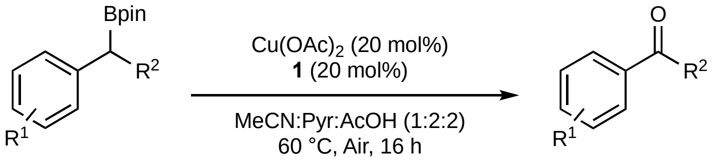
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39-7.34 (2H, m, Ar**H**), 7.31-7.28 (3H, m, Ar**H**), 7.24-7.18 (2H, m, Ar**H**), 7.15-7.10 (1H, m, Ar**H**), 7.07-7.02 (2H, m, Ar**H**), 6.64 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.26 (2H, d, *J* = 8.9 Hz, Ar**H**), 5.61 (1H, br. d, J = 6.2 Hz, N**H**), 4.34 (1H, dd, J = 11.5, 4.7 Hz, CH$_2$C$\mathbf{H_A}$H$_B$O), 4.26 (1H, br. d, J = 6.2 Hz, NC**H**), 4.20 (1H, d, J = 12.2 Hz, CHC$\mathbf{H_A}$H$_B$O), 3.69 (3H, s, OC$\mathbf{H_3}$), 3.65 (1H, ddd, J = 13.1 11.5, 2.3 Hz, CH$_2$CH$_A$$\mathbf{H_B}$O), 3.60 (1H, dd, J = 12.2, 3.3 Hz, CHCH$_A$$\mathbf{H_B}$O), 3.29 (1H, dt, J = 13.2, 4.7 Hz, **CH**CH$_2$CH$_2$), 2.87 (1H, dtd, J = 13.2, 13.1, 4.7 Hz, C$\mathbf{H_A}$H$_B$CH$_2$O), 1.95 (1H, br. s, C**H**CH$_2$O), 1.68 (1H, br. d, J = 13.1 Hz, CH$_A$$\mathbf{H_B}CH_2$O).

^{13}C NMR (101 MHz, CDCl$_3$) δ 151.0 (C), 143.7 (C), 143.0 (C), 141.0 (C), 128.7 (2 × CH), 128.3 (2 × CH), 127.8 (2 × CH), 126.7 (3 × CH), 126.4 (CH), 114.7 (2 × CH), 113.3 (2 × CH), 69.1 (CH$_2$), 68.6 (CH$_2$), 56.9 (CH), 55.7 (CH$_3$), 45.9 (CH), 44.6 (CH), 26.9 (CH$_2$).

HRMS (Q-TOF) Exact mass calcd for $[C_{25}H_{28}NO_2]^+$ [M+H]$^+$: 374.2120, found: 374.2115.

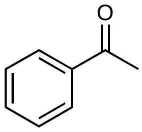
5.8 *Cu-Catalysed Oxidation of Alkyl Boronic Esters*

General Procedure 13: Cu-Catalysed Oxidation of Alkylboronic Acid Pinacol Ester



Pyridine (1.2 mL) and acetic acid (1.2 mL) were added to a mixture of the corresponding boronic ester (0.6 mmol, 1 equiv), $Cu(OAc)_2$ (21.7 mg, 0.119 mmol) and diketimine **1** (37.2 mg, 0.120 mmol) in MeCN (0.6 mL). The mixture was stirred at 60 °C until completion (as determined by TLC), cooled to room temperature. Water was added (10 mL), and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography.

5.8.1 Scope of Oxidation of Benzylic Boronic Esters



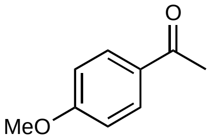
304

Acetophenone (304)

The title compound was prepared according to General Procedure **13** using boronic ester **52** (0.139 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et_2O/petroleum ether) to give ketone **304** (0.0544 g, 75%) as a colourless oil. The data were consistent with the literature.[292]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.86 (2H, m, Ar**H**), 7.60-7.51 (1H, m, Ar**H**), 7.51-7.39 (2H, m, Ar**H**), 2.60 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1 (C), 137.2 (C), 133.0 (CH), 128.6 (2 × CH), 128.3 (2 × CH), 26.6 (CH_3).



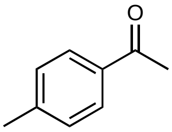
465

4-Methoxyacetophenone (465)

The title compound was prepared according to General Procedure **13** using boronic ester **230** (0.157 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et_2O/petroleum ether) to give ketone **465** (0.0775 g, 86%) as a colourless oil. The data were consistent with the literature.[292]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, J = 9.0 Hz, Ar**H**), 6.94 (2H, d, J = 9.0 Hz, Ar**H**), 3.88 (3H, s, C**H$_3$**), 2.57 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.9 (C), 163.4 (C), 130.6 (2 × CH), 130.3 (C), 113.6 (2 × CH), 55.4 (CH_3), 26.3 (CH_3).



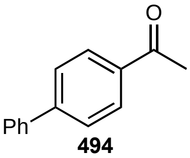
493

4-Methylacetophenone (493)

The title compound was prepared according to General Procedure **13** using boronic ester **220** (0.148 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et$_2$O/petroleum ether) to give ketone **493** (0.0700 g, 86%) as a yellow oil. The data were consistent with the literature.[293]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90-7.83 (2H, m, Ar**H**), 7.30-7.22 (1H, m, Ar**H**), 2.58 (3H, s, C**H**$_3$), 2.42 (3H, 2s, C**H**$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 197.9 (C), 143.9 (C), 134.7 (C), 129.2 (2 × CH), 128.4 (2 × CH), 26.5 (CH$_3$), 21.6 (CH$_3$).



494

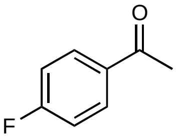
4-Phenylacetophenone (494)

The title compound was prepared according to General Procedure **13** using boronic ester **221** (0.185g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et$_2$O/petroleum ether) to give ketone **494** (0.108 g, 92%) as a white solid. The data were consistent with the literature.[294]

m.p. 121-122 °C (petroleum ether); literature = 121-122 °C (hexane).[295]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05 (2H, d, J = 8.4 Hz, Ar**H**), 7.70 (2H, d, J = 8.4 Hz, Ar**H**), 7.67-7.62 (2H, m, Ar**H**), 7.52-7.46 (2H, m, Ar**H**), 7.44-7.39 (1H, m, Ar**H**), 2.65 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 197.8 (C), 145.8 (C), 139.9 (C), 135.8 (C), 128.9 (2 × CH), 128.9 (2 × CH), 128.2 (CH), 127.3 (2 × CH), 127.2 (2 × CH), 26.7 (CH$_3$).



495

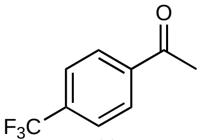
4-Fluoroacetophenone (495)

The title compound was prepared according to General Procedure **13** using boronic ester **222** (0.150 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et$_2$O/petroleum ether) to give ketone **495** (0.0568 g, 69%) as a yellow oil. The data were consistent with the literature.[294]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03-7.96 (2H, m, Ar**H**), 7.19-7.10 (2H, m, Ar**H**), 2.60 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 196.5 (C), 165.7 (C, d, $J_{C\text{-}F}$ = 254.7 Hz), 133.5 (C, d, $J_{C\text{-}F}$ = 3.1 Hz), 130.9 (2 × CH, d, $J_{C\text{-}F}$ = 9.4 Hz), 115.6 (2 × CH, d, $J_{C\text{-}F}$ = 21.9 Hz), 26.5 (CH$_3$).

^{19}F NMR (377 MHz, CDCl$_3$) δ -105.3.



460

4-Trifloromethylacetophenone (460)

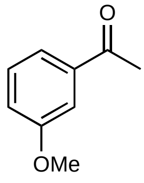
The title compound was prepared according to General Procedure **13** using boronic ester **223** (0.180 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et$_2$O/petroleum ether) to give ketone **460** (0.100 g, 89%) as a white solid. The data were consistent with the literature.[296]

m.p. 28-29 °C (petroleum ether); literature: 30-33 °C (solvent not specified).[297]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.75 (2H, d, *J* = 8.1 Hz, Ar**H**), 2.66 (1H, s, C$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0 (C), 139.7 (C), 134.4 (C, q, $J_{C\text{-}F}$ = 32.7), 128.6 (2 × CH), 125.7 (2 × CH, q, $J_{C\text{-}F}$ = 3.7), 123.6 (2 × C, q, $J_{C\text{-}F}$ = 272.7), 26.8 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ -63.1.

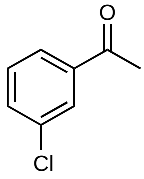

488

3-Methoxyacetophenone (488)

The title compound was prepared according to General Procedure **13** using alkyl boronic ester **224** (0.157 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by column chromatography (10% Et_2O/petroleum ether) to give ketone **488** (0.0800 g, 89%) as a yellow oil. The data were consistent with the literature.[298]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.52 (1H, m, Ar**H**), 7.51-7.48 (1H, m, Ar**H**), 7.42-7.34 (1H, m, Ar**H**), 7.16-7.09 (1H, m, Ar**H**), 3.86 (3H, s, OC$\mathbf{H_3}$), 2.60 (3H, s, ArC$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0 (C), 159.8 (C), 138.5 (C), 129.5 (CH), 121.1 (CH), 119.6 (CH), 112.3 (CH), 55.4 (CH_3), 26.7 (CH_3).

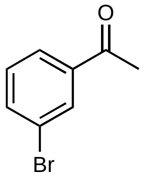

496

3-Chloroacetophenone (496)

The title compound was prepared according to General Procedure **13** using boronic ester **225** (0.160 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et_2O/petroleum ether) to give ketone **496** (0.0680 g, 73%) as a colourless oil. The data were consistent with the literature.[299]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.88 (1H, m, Ar**H**), 7.84-7.79 (1H, m, Ar**H**), 7.54-7.49 (1H, m, Ar**H**), 7.42-7.36 (1H, m, Ar**H**), 2.58 (1H, s, C$\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7 (C), 138.5 (C), 134.8 (C) 132.9 (CH), 129.9 (CH), 128.3 (CH), 126.3 (CH), 26.6 (CH_3).

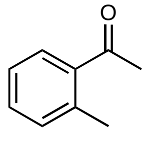

497

3-Bromoacetophenone (497)

The title compound was prepared according to General Procedure **13** using boronic ester **226** (0.187 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et_2O/petroleum ether) to give ketone **497** (0.0837 g, 70%) as a colourless oil. The data were consistent with the literature.[300]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.11-8.05 1H, m, Ar**H**), 7.91-7.85 (1H, m, Ar**H**), 7.73-7.66 (1H, m, Ar**H**), 7.38-7.32 (1H, m, Ar**H**), 2.60 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 196.7 (C), 138.7 (C), 136.0 (CH), 131.4 (CH), 130.2 (CH), 126.8 (CH), 122.9 (C), 26.6 (CH$_3$).



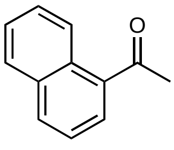
498

2-Methylacetophenone (498)

The title compound was prepared according to General Procedure **13** using boronic ester **227** (0.148 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et$_2$O/petroleum ether) to give ketone **498** (0.0704 g, 87%) as a colourless oil. The data were consistent with the literature.[301]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75-7.68 (1H, m, Ar**H**), 7.43-7.36 (1H, m, Ar**H**), 7.30-7.24 (2H, m, Ar**H**), 2.60 (3H, s, C**H**$_3$), 2.54 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 201.8 (C), 138.4 (C), 137.6 (C), 132.0 (CH), 131.5 (CH), 129.4 (CH), 125.7 (CH), 29.5 (CH$_3$), 21.6 (CH$_3$).



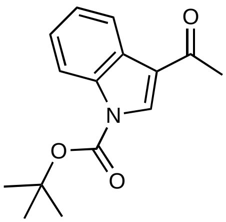
491

1-Acetonaphthone (491)

The title compound was prepared according to General Procedure **13** using boronic ester **228** (0.170 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et$_2$O/petroleum ether) to give ketone **491** (0.084 g, 82%) as a colourless oil. The data were consistent with the literature.[301]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.80-8.73 (1H, m, Ar**H**), 8.04-7.98 (1H, m, Ar**H**), 7.98-7.92 (1H, m, Ar**H**), 7.92-7.85 (1H, m, Ar**H**), 7.66-7.58 (1H, m, Ar**H**), 7.58-7.48 (2H, m, Ar**H**), 2.76 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 201.8 (C), 135.5 (C), 134.0 (C), 133.0 (CH), 130.1 (C), 128.7 (CH), 128.4 (CH), 128.0 (CH), 126.4 (CH), 126.0 (CH), 124.3 (CH), 30.0 (CH$_3$).



499

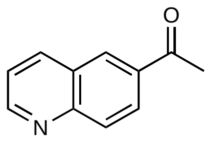
tert-Butyl 3-acetylindole-1-carboxylate (499)

The title compound was prepared according to General Procedure **13** using boronic ester **265** (44% purity by weight, 0.253 g, 0.300 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% EtOAc/petroleum ether) to give ketone **499** (0.0674 g, 87%) as a white solid. The data were consistent with the literature.[302]

m.p. 145-147 °C (petroleum ether); literature: 145-146 °C (solvent not specified).[302]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.41-8.36 (1H, m, Ar**H**), 8.24 (1H, s, Ar**H**), 8.15-8.10 (1H, m, Ar**H**), 7.42-7.33 (2H, m, Ar**H**), 2.58 (3H, s, COC**H**$_3$), 1.72 (9H, s, 3 × CC**H**$_3$).

^{13}C NMR (101 MHz, CDCl$_3$) δ 193.9 (C), 149.2 (C), 135.5 (C), 132.4 (CH), 127.4 (C), 125.5 (CH), 124.4 (CH), 122.7 (CH), 120.7 (C), 114.9 (CH), 85.4 (C), 28.1 (3 × CH$_3$), 27.7 (CH$_3$).



500

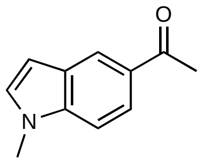
6-Acetylquinoline (500)

The title compound was prepared according to General Procedure **13** using boronic ester **266** (46% purity by weight, 0.150 g, 0.244 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (20% EtOAc/petroleum ether) to give ketone **500** (0.0307 g, 76%) as a pale yellow solid. The data were consistent with the literature.[303]

m.p. 77-78 °C (petroleum ether); literature: 77.0-77.5 °C (hexane/CH$_2$Cl$_2$).[304]

^{1}H NMR (400 MHz, CDCl3) δ 9.05-9.00 (1H, m, Ar**H**), 8.46 (1H, s, Ar**H**), 8.32-8.26 (2H, m, Ar**H**), 8.20-8.14 (1H, m, Ar**H**), 7.53-7.47 (1H, m, Ar**H**), 2.75 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 197.4 (C), 152.6 (CH), 150.1 (C), 137.5 (CH), 134.9 (C), 130.1 (CH), 129.8 (CH), 127.7 (CH), 127.5 (C), 122.0 (CH), 26.8 (CH$_3$).



501

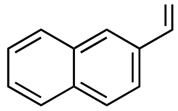
1-Methyl-5-[1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl]indole (501)

The title compound was prepared according to General Procedure **13** boronic ester **267** (50% purity by weight, 0.193 g, 0.341 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (5% EtOAc/petroleum ether) to give ketone **501** (0.0447 g, 76%) as a yellow solid. The data were consistent with the literature.[305]

m.p. 97-98 °C (petroleum ether); no literature value available.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.33-8.29 (1H, m, Ar**H**), 7.95-7.89 (1H, m, Ar**H**), 7.38-7.33 (1H, m, Ar**H**), 7.15-7.11 (1H, m, Ar**H**), 6.64-6.60 (1H, m, Ar**H**), 3.84 (3H, s, NC**H$_3$**), 2.68 (3H, s, CC**H$_3$**).

^{13}C NMR (101 MHz, CDCl$_3$) δ 198.3 (C), 139.1 (C), 130.4 (CH), 129.5 (C), 127.9 (CH), 123.2 (CH), 121.8 (CH), 109.1 (CH), 103.0 (CH), 33.0 (CH$_3$), 26.6 (CH$_3$).



529

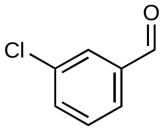
2-Naphthaldehyde (529)

The title compound was prepared according to General Procedure **13** using boronic ester **253** (0.161 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (5% EtOAc/petroleum ether) to give aldehyde **529** (0.0826g, 88%) as a yellow solid. The data were consistent with the literature.[306]

m.p. 57-59 °C (petroleum ether), literature: 59 °C (solvent not specified).[307]

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 10.18 (1H, s, CH), 8.36 (1H, s, ArH), 8.06-7.91 (4H, m, ArH), 7.70-7.57 (2H, m, ArH).

^{13}**C NMR** (101 MHz, $CDCl_3$) δ 192.3 (CH), 136.5 (C), 134.6 (CH), 134.1 (C), 132.7 (C), 129.5 (CH), 129.1 (CH), 129.1 (CH), 128.1 (CH), 127.1 (CH), 122.8 (CH).

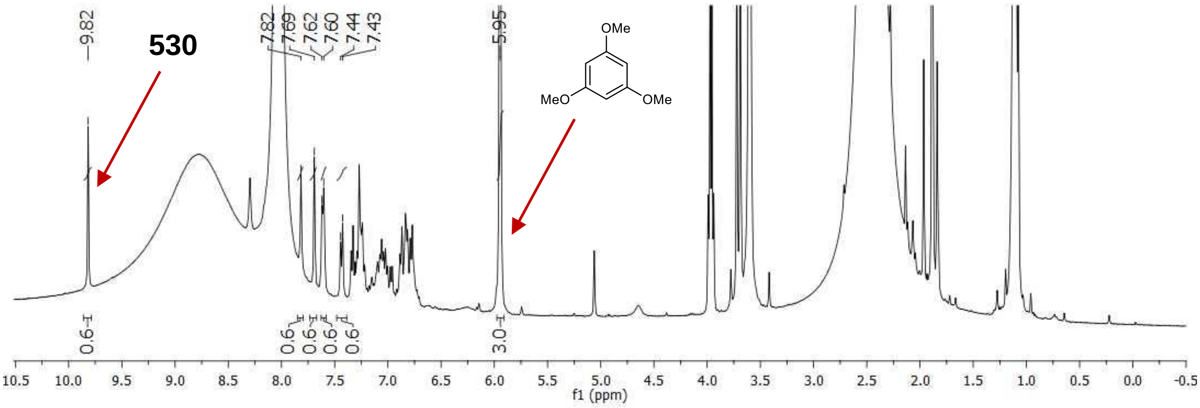


530

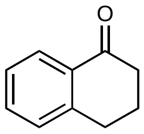
3-Chlorobenzaldehyde (530)

The title compound was prepared according to General Procedure **13** using 2-(3-chlorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.0142 g, 0.0619 mmol), heating at 60 °C for 16 h. Using 1,3,5-trimethoxybenzene (0.0156 g, 0.0927 mmol), ^{1}H NMR analysis showed that ketone **530** was formed in 86% yield. (Unfortunately, on preparative scale, this product co-eluted with grease/plasticiser from the commercial solvent during flash chromatography, and so an isolated yield could not be accurately determined). The data were consistent with the literature.[308]

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 9.82 (1H, s, C**H**), 7.85-7.80 (1H, m, Ar**H**), 7.73-7.67 (1H, m, Ar**H**), 7.63-7.58 (1H, m, Ar**H**), 7.48-7.39 (1H, m, Ar**H**).



HRMS (EI) Exact mass calcd for $[C_7H_5ClO]^+$ $[M]^+$ 140.0023, found: 140.0024.



509

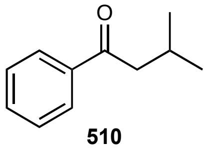
1-Tetralone (509)

The title compound was prepared according to General Procedure **13** using boronic ester **229** (0.155 g, 0.600 mmol), heating at 60 °C for 48 h. The crude material was purified by flash chromatography (10% Et_2O/petroleum ether) to give ketone **509** (0.0490 g, 56%) as a brown oil. The data were consistent with the literature.[309]

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.07-8.02 (1H, m, Ar**H**), 7.51-7.45 (1H, m, Ar**H**), 7.36-7.29 (1H, m, Ar**H**), 7.29-7.24 (1H, m, Ar**H**), 3.02-2.95 (2H, m, COC$\mathbf{H_2}$), 2.70-2.65 (2H, m, ArC$\mathbf{H_2}$), 2.21-2.11 (2H, m, ArCH$_2$C$\mathbf{H_2}$).

^{13}**C NMR** (101 MHz, $CDCl_3$) δ 198.4 (C), 144.5 (C), 133.4 (CH), 132.6 (C), 128.8 (CH), 127.2 (CH), 126.6 (CH), 39.2 (CH_2), 29.7 (CH_2), 23.3 (CH_2).

Isovalerophenone (510)



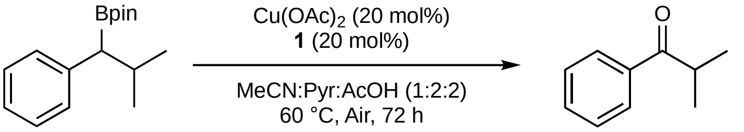
510

The title compound was prepared according to General Procedure **13** using boronic ester **259** (0.165 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et_2O/petroleum ether) to give ketone **510** (0.0674 g, 69%) as a colourless oil. The data were consistent with the literature.[310]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.93 (2H, m, Ar**H**), 7.60-7.53 (1H, m, Ar**H**), 7.51-7.44 (2H, m, Ar**H**), 2.85 (2H, d, *J* = 6.8 Hz, C$\mathbf{H_2}$), 2.31 (1H, nonet, *J* = 6.8 Hz, C**H**), 1.01 (d, *J* = 6.8 Hz, 2 × C$\mathbf{H_2}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2 (C), 137.5 (C), 132.8 (CH), 128.5 (2 × CH), 128.1 (2 × CH), 47.5 (CH_2), 25.2 (CH), 22.8 (2 × CH_3).

Isobutyrophenone (511)

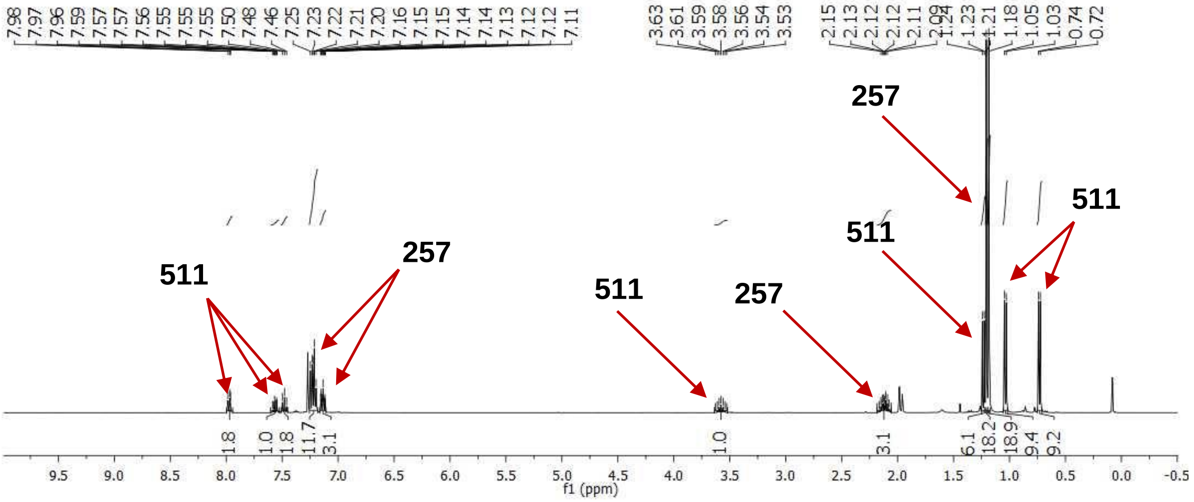


257

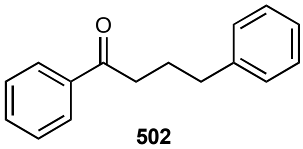
Iolated as a 1:3 mixture of **511** and **257**

The title compound was prepared according to General Procedure **13** using boronic ester **257** (0.156 g, 0.600 mmol), heating at 60 °C for 72 h. The crude material was purified by flash chromatography (2% Et_2O/petroleum ether) to give an inseparable mixture of ketone **511** and boronic ester **257** (0.0940 g, 1:3 **511:257**, 19% of **511** and 57% of **257**). The data were consistent with the literature.[311]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.94 (2H, m, Ar**H**), 7.60-7.54 (1H, m, Ar**H**), 7.51-7.45 (2H, m, Ar**H**), 3.57 (1H, sept, *J* = 6.9 Hz, C**H**), 1.23 (6H, d, *J* = 6.8 Hz, 2 × C$\mathbf{H_3}$).



HRMS (Q-TOF) Exact mass calcd for $[C_{10}H_{13}O]^+$ $[M+H]^+$ 149.0966, found: 149.0917.



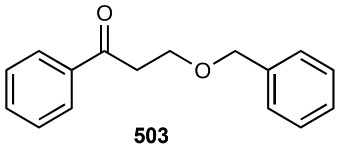
502

1,4-Diphenylbutan-1-one (502)

The title compound was prepared according to General Procedure **13** using boronic ester **260** (0.202 g, 0.600 mmol), heating at 60 °C for 48 h. The crude material was purified by flash chromatography (2% Et_2O/petroleum ether) to give ketone **502** (0.0850 g, 63%) as a yellow oil. The data were consistent with the literature.[312]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.90 (2H, m, Ar**H**), 7.59-7.53 (1H, m, Ar**H**), 7.49-7.42 (2H, m, Ar**H**), 7.34-7.28 (2H, m, Ar**H**), 7.24-7.19 (3H, m, Ar**H**), 3.03-2.96 (2H, m, CC**H₂**), 2.78-2.70 (2H, m, C**H₂**), 2.15-2.05 (2H, m, ArC**H₂**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (C), 141.7 (C), 136.9 (C), 132.9 (CH), 128.5 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.0 (2 × CH), 125.9 (CH), 37.7 (CH_2), 35.2 (CH_2), 25.7 (CH_2).



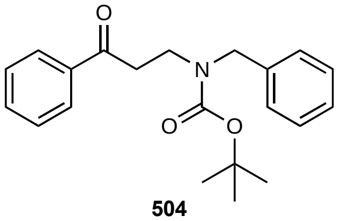
503

3-(Benzyloxy)-1-phenylpropan-1-one (503)

The title compound was prepared according to General Procedure **13** using boronic ester **234** (0.211 g, 0.599 mmol), heating at 60 °C for 48 h. The crude material was purified by flash chromatography (5% EtOAc/petroleum ether) to give ketone **503** (0.0890 g, 62%) as a colourless oil. The data were consistent with the literature.[313]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.97 (2H, m, Ar**H**), 7.61-7.55 (1H, m, Ar**H**), 7.51-7.45 (2H, m, Ar**H**), 7.38-7.33 (4H, d, Ar**H**), 7.33-7.28 (1H, m, Ar**H**), 4.58 (2H, s, C**H₂**Ph), 3.95 (2H, t, J = 6.6 Hz, CH_2C**H₂**O), 3.32 (2H, t, J = 6.6 Hz, C(O)C**H₂**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3 (C), 138.1 (C), 136.9 (C), 133.1 (CH), 128.5 (2 × CH), 128.3 (2 × CH), 128.1 (2 × CH), 127.6 (2 × CH), 127.6 (CH), 73.3 (CH_2), 65.6 (CH_2), 38.8 (CH_2).



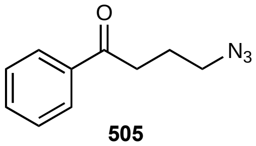
504

tert-Butyl *N*-benzyl-*N*-(3-oxo-3-phenylpropyl)carbamate (504)

The title compound was prepared according to a modification of General Procedure **13** using boronic ester **235** (0.135 g, 0.299 mmol), $Cu(OAc)_2$ (10.9 mg, 0.06 mmol) and diketimine **1** (18.6 mg, 0.06 mmol), acetonitrile (0.6 mL), pyridine (1.2 mL) and acetic acid (1.2 mL), heating at 60 °C for 48 h. The crude material was purified by flash chromatography (5% EtOAc/petroleum ether) to give ketone **504** (0.0820 g, 81%) as a colourless oil.[179]

^{1}H NMR (500 MHz, DMSO, 80 °C) δ 7.93-7.88 (2H, m, Ar**H**), 7.65-7.59 (1H, m, Ar**H**), 7.54-7.47 (2H, m, Ar**H**), 7.36-7.31 (2H, m, Ar**H**), 7.28-7.22 (3H, m, Ar**H**), 4.44 (2H, s, C**H₂**Ph), 3.52 (2H, t, *J* = 7.0 Hz, C**H₂**N), 3.20 (2H, t, *J* = 7.0 Hz, COC**H₂**), 1.38 (9H, s, 3 × C**H₃**).

^{13}C NMR (126 MHz, DMSO, 80 °C) δ 198.3 (C), 154.5 (C), 138.2 (C), 136.4 (C), 132.6 (2 × CH) , 128.2 (2 × CH), 128.0 (2 × CH), 127.4 (2 × CH), 126.8 (CH), 126.6 (CH), 78.7 (C), 49.7 (CH_2), 42.3 (CH_2), 36.9 (CH_2), 27.6 (3 × CH_3).



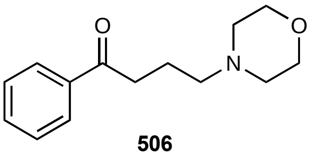
505

(5-Azidopent-1-en-2-yl)benzene (505)

The title compound was prepared according to General Procedure **13** using boronic ester **261** (0.181 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (10% Et_2O/petroleum ether) to give ketone **505** (0.0710 g, 62%) as a yellow oil. The data were consistent with the literature.[314]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.92 (2H, m, Ar**H**), 7.62-7.56 (1H, m, Ar**H**), 7.52-7.45 (2H, m, Ar**H**), 3.44 (2H, t, *J* = 6.6 Hz, C**H₂**N_3), 3.11 (2H, t, *J* = 7.0 Hz, COC**H₂**), 2.06 (2H, tt, *J* = 7.0, 6.6 Hz, $COCH_2$C**H₂**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9 (C), 136.7 (C), 133.2 (CH), 128.7 (2 × CH), 128.0 (2 × CH), 50.9 (CH_2), 35.2 (CH_2), 23.3 (CH_2).



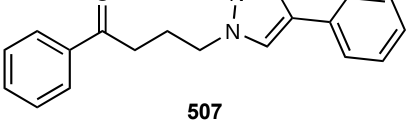
506

4-(Morpholin-4-yl)-1-phenylbutan-1-one (506)

The title compound was prepared according to General Procedure **13** using boronic ester **262** (0.207 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (100% EtOAc) to give ketone **506** (0.110 g, 79%) as a yellow oil. The data were consistent with the literature.[315]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.94 (2H, m, Ar**H**), 7.59-7.51 (1H, m, Ar**H**), 7.50-7.42 (2H, m, Ar**H**), 3.70-3.62 (4H, m, 2 × CH_2), 3.06-2.97 (2H, m, COC**H₂**), 2.49-2.38 (6H, m, 3 × NC**H₂**), 2.00-1.91 (2H, m, NCH_2C**H₂**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9 (C), 137.1 (C) 132.9 (CH), 128.5 (2 ×CH), 128.0 (2 × CH), 66.8 (2 × CH_2), 58.0 (CH_2), 53.5 (2 × CH_2), 36.1 (CH_2), 21.1 (CH_2).



507

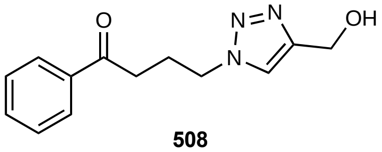
1-Phenyl-4-(4-phenyl-1,2,3-triazol-1-yl)butan-1-one (507)

The title compound was prepared according to a modification of General Procedure **13** using boronic ester **291** (0.121 g, 0.300 mmol), $Cu(OAc)_2$ (10.9 mg, 0.06 mmol) and diketimine **1** (18.6 mg, 0.06 mmol), acetonitrile (0.6 mL), pyridine (1.2 mL) and acetic acid (1.2 mL), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (50% EtOAc/petroleum ether) to give ketone **507** (0.0740 g, 85%) as a light yellow solid.[179]

m.p. 106-108 °C (pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.91 (2H, m, Ar**H**), 7.89-7.78 (3H, m, Ar**H**), 7.63-7.55 (1H, m, Ar**H**), 7.53-7.39 (4H, m, Ar**H**), 7.39-7.31 (1H, m, Ar**H**), 4.56 (2H, t, J = 6.8 Hz, C**H_2**N), 3.08 (2H, t, J = 6.8 Hz, C(O)C**H_2**), 2.43 (2H, p, J = 6.8 Hz, C**H_2**CH_2N).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7 (C), 147.9 (C), 136.4 (C), 133.4 (CH), 130.5 (C), 128.8 (2 × CH), 128.7 (2 × CH), 128.2 (CH), 128.0 (2 × CH), 125.7 (2 × CH), 119.7 (CH), 49.5 (CH_2), 34.6 (CH_2), 24.6 (CH_2).



508

4-[4-(Hydroxymethyl)-1,2,3-triazol-1-yl]-1-phenylbutan-1-one (508)

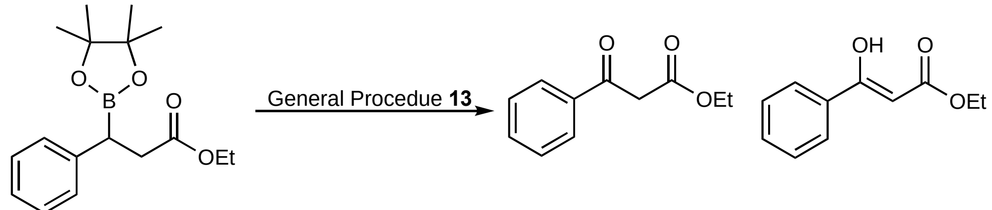
The title compound was prepared according to General Procedure **13** using boronic ester **292** (0.107 g, 0.300 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (75% EtOAc/petroleum ether → 100% EtOAc) to give ketone **508** (0.0467 g, 64%) as a white solid.[179]

m.p. 87-89 °C (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.88 (2H, m, Ar**H**), 7.64-7.53 (2H, m, Ar**H**), 7.52-7.42 (2H, m, Ar**H**), 4.84-4.77 (2H, m, C**H_2**O), 4.50 (2H, t, J = 6.8 Hz, C**H_2**N), 3.04 (2H, t, J = 6.8 Hz, C**H_2**CO), 2.67-2.51 (1H, s, O**H**), 2.37 (2H, p, J = 6.8 Hz, C**H_2**CH_2N).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (C), 147.7 (C), 136.4 (C), 133.4 (CH), 128.7 (2 × CH), 128.0 (2 × CH), 121.7 (CH), 56.6 (CH_2), 49.4 (CH_2), 34.6 (CH_2), 24.5 (CH_2).

Ethyl benzoylacetate (512)



285 **Keto-512** **Enol-512**

71% yield
4:1 ratio keto:enol observed by NMR

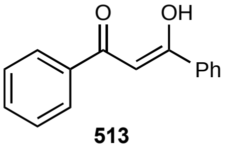
The title compound was prepared according to General Procedure **13** using boronic ester **285** (0.183 g, 0.600 mmol), heating at 60 °C for 24 h. The crude material was purified by flash chromatography (4% Et_2O/petroleum ether) to give ketone **512** (0.0820 mg, 71%) as a yellow oil. A 4:1 keto:enol tautomeric ratio was observed by NMR analysis. The data were consistent with the literature.[316]

Keto tautomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.93 (2H, m, Ar**H**), 7.65-7.57 (1H, m, Ar**H**), 7.47-7.38 (2H, m, Ar**H**), 4.32-4.19 (2H, m, $\mathrm{C\mathbf{H_2}CH_3}$), 4.00 (2H, s, $\mathrm{C C\mathbf{H_2}}$), 1.29-1.23 (3H, m, $\mathrm{CH_2C\mathbf{H_3}}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6 (C), 167.5 (C), 136.0 (C), 133.7 (CH), 128.8 (2 × CH), 128.5 (2 × CH), 61.5 (CH_2), 46.0 (CH_2), 14.1 (CH_3).

Enol tautomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.59 (1H, s, O**H**), 7.82-7.77 (2H, m, Ar**H**), 7.52-7.47 (3H m, Ar**H**), 5.68 (1H, s, C**H**), 4.32-4.19 (2H, m, $\mathbf{CH_2CH_3}$), 1.37-1.32 (3H, m, $\mathrm{CH_2C\mathbf{H_3}}$)

^{13}C NMR (101 MHz, $CDCl_3$) δ173.2 (C), 171.5 (C), 133.5 (C), 131.2 (CH), 128.6 (2 × CH), 126.1 (2 × CH), 87.4 (CH), 60.3 (CH_2), 14.3 (CH_3).



513

1,3-Diphenylpropane-1,3-dione (513)

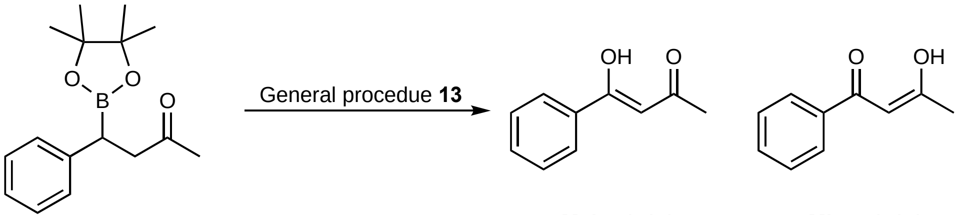
The title compound was prepared according to General Procedure **13** using boronic ester **286** (0.202 g, 0.600 mmol), heating at 60 °C for 48 h. The crude material was purified by flash chromatography (2% Et_2O/petroleum ether) to give ketone **513** (0.0880 g, 65%) as a light yellow solid. The data were consistent with the literature.[317]

m.p. 74-75 °C (petroleum ether); literature = 74-76 °C (unspecified).[318]

^{1}H NMR (400 MHz, $CDCl_3$) δ 16.90 (1H, s, O**H**), 8.04-7.98 (4H, m, ArH) 7.60-7.55 (2H, m, ArH), 7.54-7.47 (2H, m, ArH), 6.88 (1H, s, CH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.8 (C), 135.5 (C), 132.5 (CH), 128.7 (2 × CH), 127.2 (2 × CH), 93.1 (CH).

Phenylbutane-1,3-dione (515)



287 **Major (515)** **Minor (515)**

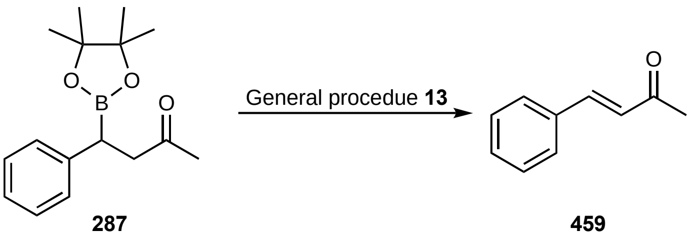
65% yield
7:1 ratio observed by NMR

The title compound was prepared according to General Procedure **13** using boronic ester **287** (0.165 g, 0.600 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (5% EtOAc/petroleum ether) to give ketone **515** (0.0650 g, 67%) as a white solid. The data were consistent with the literature.[319]

m.p. 57-59 °C (petroleum ether); literature = 57-58 °C (petroleum ether).[320]

^{1}H NMR (400 MHz, $CDCl_3$) δ 16.17 (1H, s, O**H**), 7.92-7.82 (2H, m, Ar**H**), 7.57-7.51 (1H, m, Ar**H**), 7.51-7.43 (2H, m, Ar**H**), 6.19 (1H, s, C**H**, major), 4.12 (1H, s, C**H**, minor), 2.32 (1H, s, C**H$_3$**, minor), 2.22 (3H, s, C**H$_3$**, major).
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8 (C), 183.3 (C), 134.9 (C), 133.8 (CH, minor), 132.3 (CH), 128.8 (CH, minor), 128.6 (2 × CH), 127.0 (2 × CH), 96.7 (CH), 54.8 (CH_3, minor), 25.9 (CH_3).

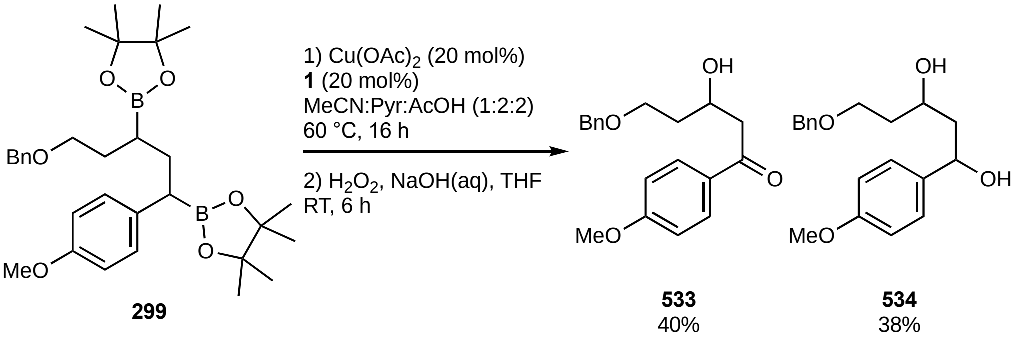
4-Phenyl-3-buten-2-one (459)



The title compound was prepared according to General Procedure **13** using boronic ester **287** (0.165 g, 0.602 mmol), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (5% EtOAc/petroleum ether) to give ketone **459** (0.0527 g, 60%) as an amorphous solid. The data were consistent with the literature.[321]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.55 (2H, m, Ar**H**), 7.52 (1H, d, J = 16.2 Hz, OCC**H**=CH), 7.43-7.39 (3H, m, Ar**H**), 6.73 (1H, d, J = 16.2 Hz, OCCH=C**H**), 2.40 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (C), 143.4 (CH), 134.4 (C), 130.5 (CH), 129.0 (2 × CH), 128.2 (2 × CH), 127.1 (CH), 27.5 (CH_3).

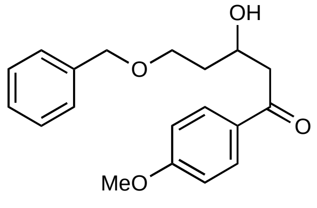
5.8.2 Oxidation of Diboronic Ester 299

(±)-5-(Benzyloxy)-3-hydroxy-1-(4-methoxyphenyl)pentan-1-one (533) and (±)-5-(benzyloxy)-1-(4-methoxyphenyl)pentane-1,3-diol (534).



According to a modification of General Procedure **13**, boronic ester **299** (0.161 g, 0.300 mmol) was reacted with $Cu(OAc)_2$ (10.9 mg, 0.06 mmol) and diketimine **1** (18.6 mg, 0.06 mmol), acetonitrile (0.6 mL), pyridine (1.2 mL) and acetic acid (1.2 mL), heating at 60 °C for 16 h. The mixture was cooled to room temperature, water was added (10 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine

(3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was diluted into THF (3 mL) and a solution of NaOH (12.0 mg, 0.30 mmol) and H_2O_2 (30% w/w, 0.6 mL, 0.02 mmol) in H_2O (0.6 mL) was added dropwise. The mixture was stirred at room temperature for 6 h, water was added (10 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (20% EtOAc/CH_2Cl_2) to give ketone **533** (0.0374 g, 40%) as a yellow oil and alcohol **534** (0.0358 g, 38%, d.r. = 1:1) as a light yellow oil.[179]

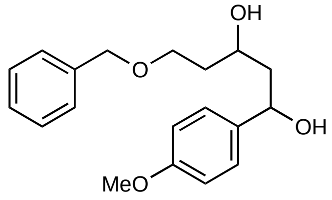


533

(±)-5-(Benzyloxy)-3-hydroxy-1-(4-methoxyphenyl)pentan-1-one (533)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.37-7.33 (4H, m, Ar**H**), 7.32-7.28 (1H, m, Ar**H**), 6.94 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.54 (2H, s, ArC**H₂**O), 4.46-4.39 (1H, m, C**H**), 3.88 (3H, s, C**H₃**), 3.75-3.69 (2H, m, OC**H₂**CH₂), 3.16-3.08 (2H, m, C**H₂**CO), 1.93-1.84 (2H, m, OCH₂C**H₂**), 1.61 (1H, s, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9 (C), 163.7 (C), 138.1 (C), 130.4 (2 × CH), 129.9 (C), 128.4 (2 × CH), 127.7 (2 × CH), 127.7 (CH), 113.8 (2 × CH), 73.2 (CH_2), 67.9 (CH_2), 66.8 (CH), 55.5 (CH_3), 44.7 (CH_2), 36.2 (CH_2).

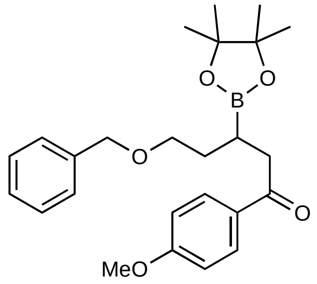


534

(±)-5-(Benzyloxy)-1-(4-methoxyphenyl)pentane-1,3-diol (534)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (7H, m, Ar**H**), 6.91-6.86 (2H, m, Ar**H**), 5.04-4.90 (1H, m, ArC**H**OH), 4.56-4.51 (2H, m, PhC**H₂**), 4.21-4.08 (1H, m, OCH₂CH₂C**H**), 3.82-3.80 (3H, m, C**H₃**), 3.78-3.64 (2H, m, OC**H₂**), 2.01-1.69 (4H, m, C**H₂**CHOHC**H₂**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (C), 158.7 (C), 137.7 (C), 137.6 (C), 136.8 (C), 136.8 (C), 128.5 (2 × CH), 128.5 (2 × CH), 127.8 (CH), 127.8 (CH), 127.7 (2 × CH), 127.7 (2 × CH), 126.9 (2 × CH), 126.8 (2 × CH), 113.7 (2 × CH), 113.7 (2 × CH), 74.4 (CH), 73.4 (CH_2), 73.2 (CH_2), 72.3 (CH), 71.1 (CH), 69.6 (CH), 69.5 (CH_2), 68.8 (CH_2), 55.3 (CH_3), 45.7 (CH_2), 44.7 (CH_2), 36.8 (CH_2), 36.1 (CH_2).



532

(±)-5-(Benzyloxy)-1-(4-methoxyphenyl)-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-1-one (532).

The title compound was prepared according to a modification of General Procedure **13** using boronic ester **299** (0.161 g, 0.300 mmol), $Cu(OAc)_2$ (10.9 mg, 0.06 mmol) and diketimine **1** (18.6 mg, 0.06 mmol), acetonitrile (0.6 mL), pyridine (1.2 mL) and acetic acid

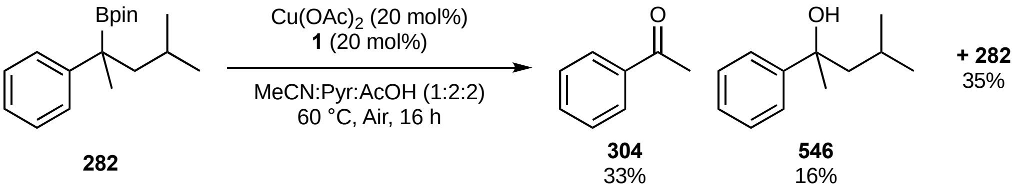
(1.2 mL), heating at 60 °C for 16 h. The crude material was purified by flash chromatography (20% EtOAc/Petroleum ether) to give ketone **532** (0.0230 g, 18%) as a light yellow oil.[179]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.37-7.24 (5H, m, Ar**H**), 6.91 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.52-4.49 (2H, m, ArC**H$_2$**O), 3.87 (3H, s, OC**H$_3$**), 3.57-3.51 (2H, m, OC**H$_2$**CH$_2$), 3.14-3.09 (2H, m, C**H$_2$**CO), 1.93-1.83 (1H, m, OCH$_2$C**H$_A$**CH$_B$), 1.77-1.67 (1H, m, OCH$_2$CH$_A$C**H$_B$**), 1.55-1.46 (1H, m, BC**H**), 1.24 (6H, m, 2 × CC**H$_3$**), 1.22 (6H, m, 2 × C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7 (C), 163.2 (C), 138.7 (C), 130.3 (2 × CH), 130.1 (C), 128.3 (2 × CH), 127.7 (2 × CH), 127.4 (CH), 113.5 (2 × CH), 82.9 (2 × C), 72.8 (CH_2), 69.7 (CH_2), 55.4 (CH_3), 40.3 (CH_2), 30.3 (CH_2), 24.7 (2 × CH_3), 24.7 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.4.

5.8.3 Reaction of 3° Boronic Ester 282



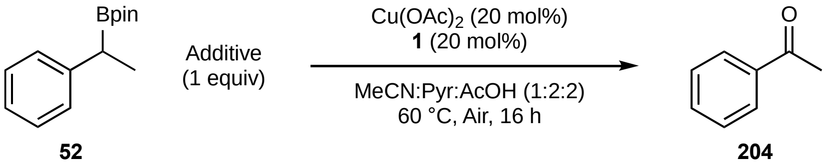
According to General Procedure **13**, boronic ester **282** (0.173 g, 0.600 mmol) was reacted at 60 °C for 16 h. The crude material was purified by flash chromatography (5% EtOAc/Petroleum ether) to give boronic ester **282** (0.0608g, 35%) as a clear oil, ketone **304** (0.0235g, 33%) as a yellow oil and alcohol **546** (0.0172g, 16%) as a yellow oil. Data of ketone **304** and boronic ester **282** can be seen above. The data for alcohol **281** are below and were consistent with the literature.[322]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (2H, m, Ar**H**), 7.38-7.32 (2H, m, Ar**H**), 7.27-7.21 (1H, m, Ar**H**), 2.18 (1H, s, O**H**), 1.84-1.77 (1H, m, C**H$_A$**CH$_B$), 1.75-1.69 (1H, m, CH$_A$C**H$_B$**), 1.67-1.60 (1H, m, C**H**CH$_3$), 1.57 (3H, s, CC**H$_3$**), 0.89 (3H, d, *J* = 6.6 Hz , CHC**H$_3$**), 0.77 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3 (C), 128.1 (2 × CH), 126.4 (CH), 124.8 (2 × CH), 75.2 (C), 52.7 (CH_2), 31.3 (CH_3), 24.4 (2 × CH_3), 24.4 (CH_3).

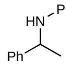
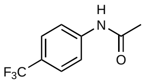
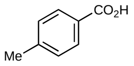
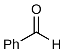
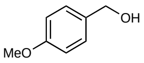
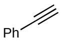
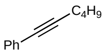
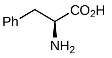
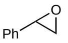
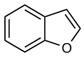
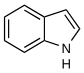
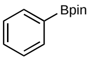
5.8.4 Additive Compatibility Test for the Oxidation of Benzylic Boronic Esters

General Procedure 14*: *Cu-Catalysed Oxidation of Alkylboronic Acid Pinacol Ester 52 in the Presence of an Additive.



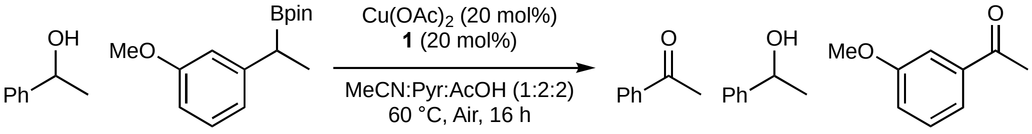
Pyridine (0.2 mL) and acetic acid (0.2 mL) were added to a solution of boronic ester **52** (11. 6 mg, 0.05 mmol), additive (0.05 mmol), $Cu(OAc)_2$ (1.8 mg, 0.010 mmol), diketimine **1** (3.1 mg, 0.01 mmol) in MeCN (0.1 mL). The mixture was stirred at 60 °C for 16 h. The mixture was cooled to room temperature, 1,3,5-trimethoxybenzene (amount recorded as an internal standard), Et_2O (1 mL) and H_2O (2 mL), were added. The organic phase was separated and concentrated *in vacuo*. The mixture was analysed by ^{1}H NMR spectroscopy to determine the amount of ketone **304**, and amounts of additive and boronic ester **52** returned.

The values reported in the manuscript are the mean of three runs.

Entry	Additive	Yield of **304**				Returned **52**				Returned **Additive**			
		1	2	3	Mean	1	2	3	Mean	1	2	3	Mean
1		88%	82%	84%	85%	0%	0%	0%	0%	>95%	73%	82%	84%
2		76%	>95%	84%	85%	0%	0%	0%	0%	91%	88%	90%	90%
3		74%	84%	80%	79%	0%	0%	0%	0%	82%	83%	76%	80%
4		81%	93%	90%	88%	0%	0%	0%	0%	72%	82%	85%	80%
5		89%	76%	82%	82%	0%	0%	0%	0%	92%	80%	78%	83%
6		79%	86%	85%	83%	0%	0%	0%	0%	32%	45%	60%	46%
7		57%	72%	71%	67%	0%	0%	0%	0%	84%	95%	79%	86%
8		39%	20%	45%	35%	53%	77%	25%	52%	10%	0%	0%	3%
9	Fmoc-Phe-OH	76%	78%	67%	74%	0%	0%	0%	0%	69%	58%	49%	59%
10		>95%	88%	89%	91%	0%	0%	0%	0%	0%	0%	0%	0%
11		70%	77%	69%	72%	26%	<5%	<5%	9%	84%	81%	86%	84%
12		76%	96%	74%	82%	0%	0%	0%	0%	94%	79%	98%	90%
13		93%	97%	98%	96%	0%	0%	0%	0%	99%	93%	97%	96%

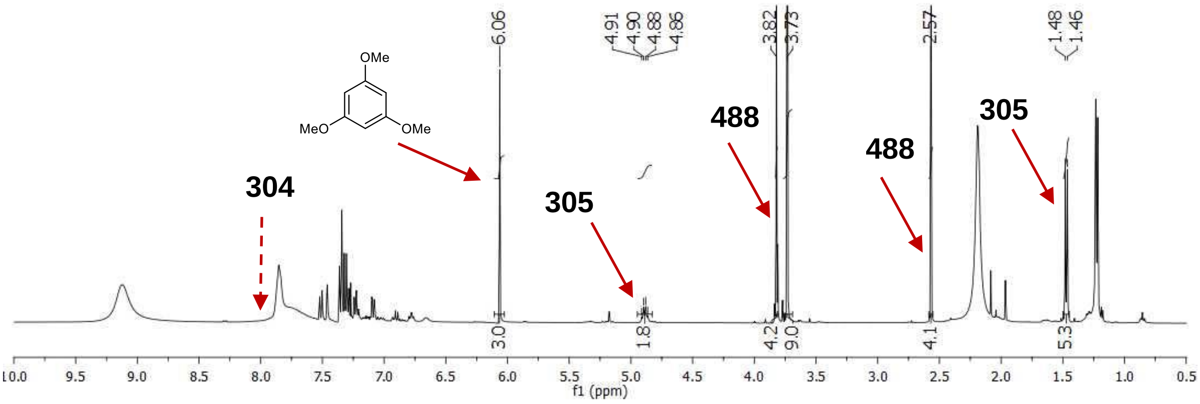
5.9 *Exploring the Mechanism of Cu-Catalysed Oxidation*

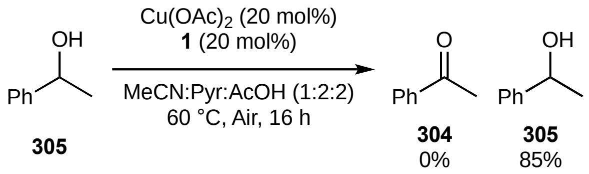
5.9.1.1 Competition and Control Experiments



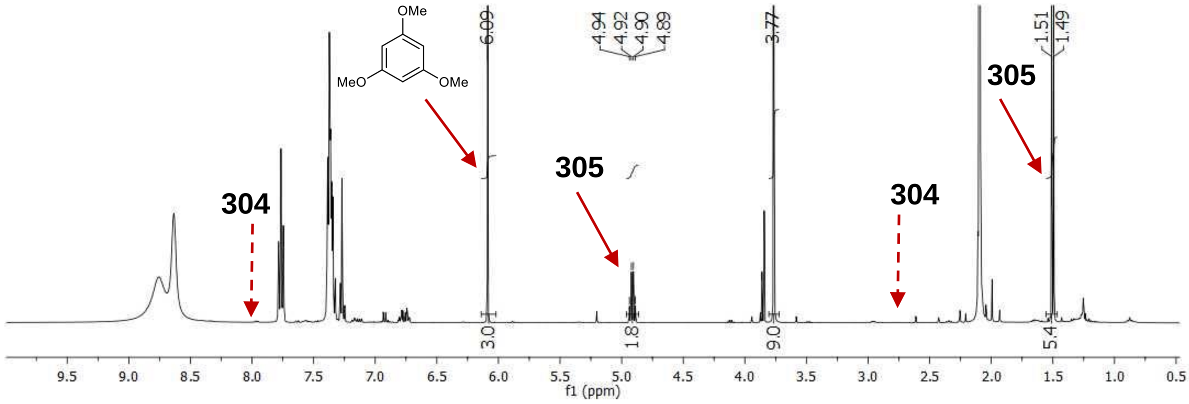
305 **224** **304** 0% **305** 85% **488** 82%

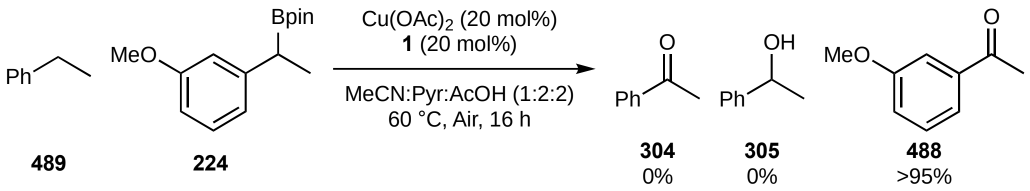
Pyridine (0.2 mL) and acetic acid (0.2 mL) were added to a solution of alcohol **305** (7.1 mg, 0.058 mmol), boronic ester **224** (13.1 mg, 0.0500 mmol), Cu(OAc)$_2$ (1.8 mg, 0.010 mmol), diketimine **1** (3.1 mg, 0.01 mmol) in MeCN (0.1 mL). The mixture was stirred at 60 °C for 16 h. The mixture was cooled to room temperature, 1,3,5-trimethoxybenzene (4.8 mg, 0.029 mmol, as an internal standard), Et$_2$O (1 mL) and H$_2$O (2 mL), were added. The organic phase was separated and concentrated *in vacuo*. The mixture was analysed by ^{1}H NMR spectroscopy, which showed alcohol **305** remained (85% NMR yield) and ketone **304** was not observed, and boronic ester **224** was converted into ketone **488** (82% NMR yield).



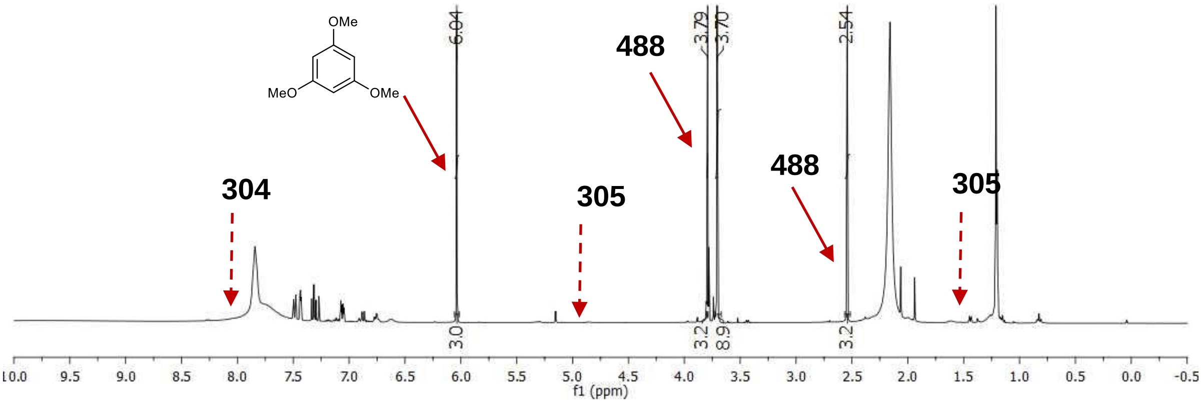


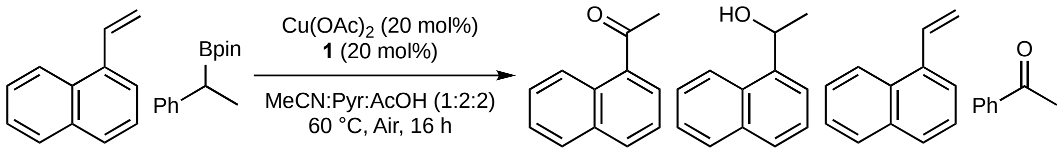
Pyridine (0.2 mL) and acetic acid (0.2 mL) were added to a solution of alcohol **305** (7.6 mg, 0.062 mmol), $Cu(OAc)_2$ (1.8 mg, 0.010 mmol), diketimine **1** (3.1 mg, 0.010 mmol) in MeCN (0.1 mL). The mixture was stirred at 60 °C for 17 h. The mixture was cooled to room temperature, 1,3,5-trimethoxybenzene (5.6 mg, 0.033 mmol, as an internal standard), Et_2O (1 mL) and H_2O (2 mL), were added. The organic phase was separated and concentrated *in vacuo*. The mixture was analysed by ^1H NMR spectroscopy, which showed alcohol **305** remained (93% NMR yield) and ketone **304** was not observed.





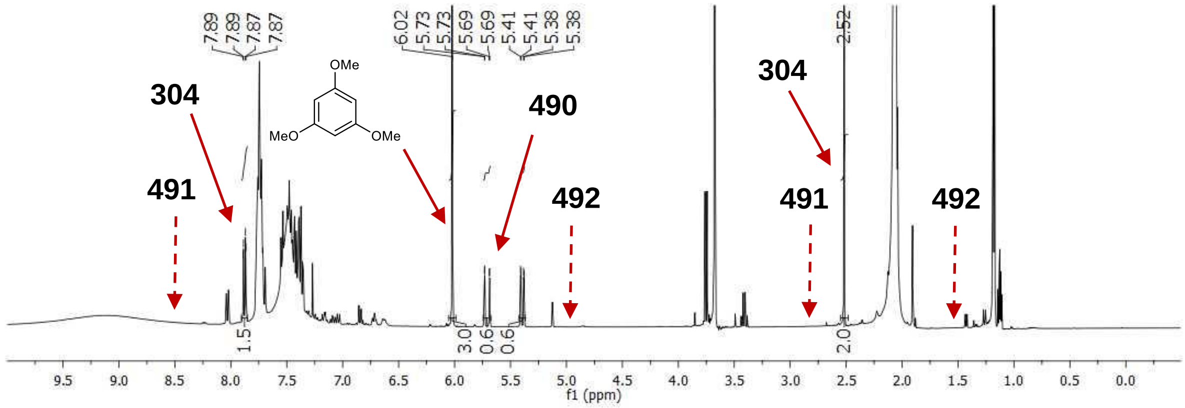
Pyridine (0.2 mL) and acetic acid (0.2 mL) were added to a solution of alkane **489** (4.9 mg, 0.046 mmol), boronic ester **224** (13.9 mg, 0.0530 mmol), Cu(OAc)$_2$ (1.8 mg, 0.010 mmol), diketimine **1** (3.1 mg, 0.010 mmol) in MeCN (0.1 mL). The mixture was stirred at 60 °C for 16 h. The mixture was cooled to room temperature, 1,3,5-trimethoxybenzene (8.1 mg, 0.048 mmol, as an internal standard), Et$_2$O (1 mL) and H$_2$O (2 mL), were added. The organic phase was separated and concentrated *in vacuo*. The mixture was analysed by ^{1}H NMR spectroscopy, which showed boronic ester **224** was converted into ketone **488** (>95% NMR yield). Alkane **489** could not be quantified due to its volatility, and alcohol **305** and ketone **304** were not observed.



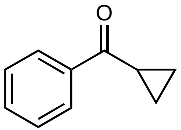


490 **52** **491** 0% **492** 0% **490** 80% **304** 92%

Pyridine (0.2 mL) and acetic acid (0.2 mL) were added to a solution of 1-vinylnaphthalene **490** (8.9 mg, 0.058 mmol), boronic ester **52** (14.7 mg, 0.0633 mmol), Cu(OAc)$_2$ (1.8 mg, 0.010 mmol), diketimine **1** (3.1 mg, 0.010 mmol) in MeCN (0.1 mL). The mixture was stirred at 60 °C for 16 h. The mixture was cooled to room temperature, 1,3,5-trimethoxybenzene (13.0 mg, 0.0773 mmol, as an internal standard), Et$_2$O (1 mL) and H$_2$O (2 mL), were added. The organic phase was separated and concentrated *in vacuo*. The mixture was analysed by ^{1}H NMR spectroscopy, which showed boronic ester **52** was converted into ketone **304** (92% NMR yield). Alkene **490** was returned in 80%, and alcohol **492** and ketone **491** were not observed.



5.9.1.2 Reaction of Cyclopropyl Boronic Ester 258



535

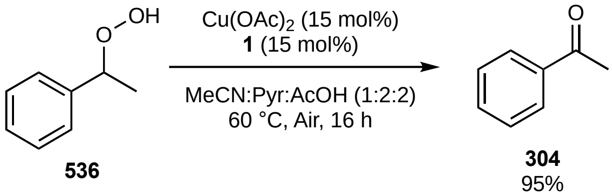
Cyclopropyl phenyl ketone (535)

The title compound was prepared according to General Procedure 13 using boronic ester **258** (0.155 g, 0.600 mmol), heating at 60 °C for 16 h. ^{1}H NMR analysis mass spectrometry of the crude reaction mixture did not show the presence of possible products arising from ring-opening of the cyclopropane. The crude material was purified by flash chromatography (4% Et$_2$O/petroleum ether) to give ketone **535** (0.0710 g, 81%) as a colourless oil. The data were consistent with the literature.[323]

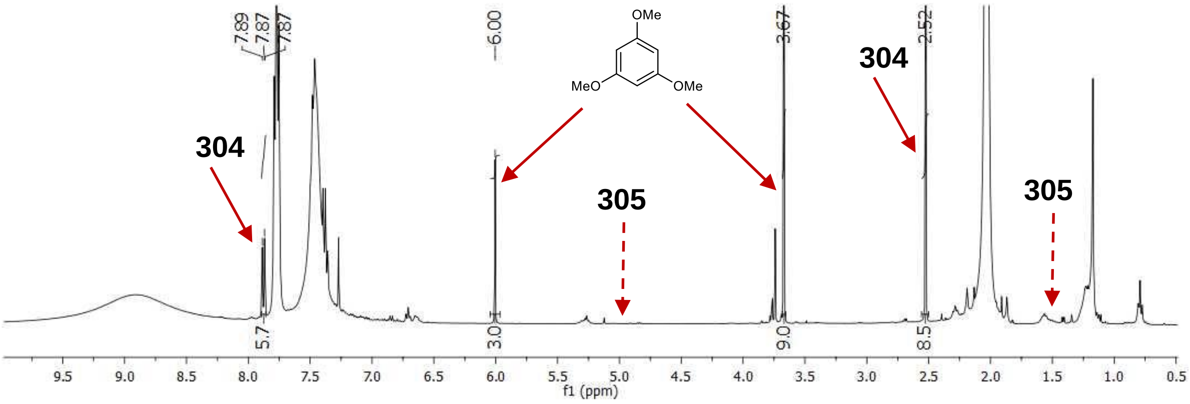
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.10-7.99 (2H, m, Ar**H**), 7.65-7.54 (1H, m, Ar**H**), 7.54-7.44 (2H, m, Ar**H**), 2.76-2.65 (1H, m, C**H**), 1.31-1.23 (2H, m, C**H$_2$**), 1.11-1.02 (2H, m, C**H$_2$**).

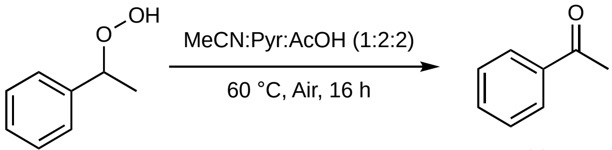
^{13}C NMR (101 MHz, CDCl$_3$) δ 200.7 (C), 138.0 (C), 132.8 (CH), 128.5 (2 × CH), 128.0 (2 × CH), 17.2 (CH), 11.7 (2 × CH$_2$).

5.9.1.3 Decomposition of Peroxide 536



Pyridine (0.6 mL) and acetic acid (0.6 mL) were added to a solution of peroxide **536**[322] (18.0 mg, 0.130 mmol), $Cu(OAc)_2$ (3.5 mg, 0.0020 mmol), diketimine **1** (6.1 mg, 0.0020 mmol) in MeCN (0.4 mL). The mixture was stirred at 60 °C for 16 h. The mixture was cooled to room temperature, 1,3,5-trimethoxybenzene (7.4 mg, 0.044 mmol, as an internal standard), Et_2O (2 mL) and H_2O (2 mL) were added. The organic phase was separated and concentrated *in vacuo*. The mixture was analysed by ^{1}H NMR spectroscopy which showed the consumption of peroxide **536** and the formation of ketone **304** (95% NMR yield).

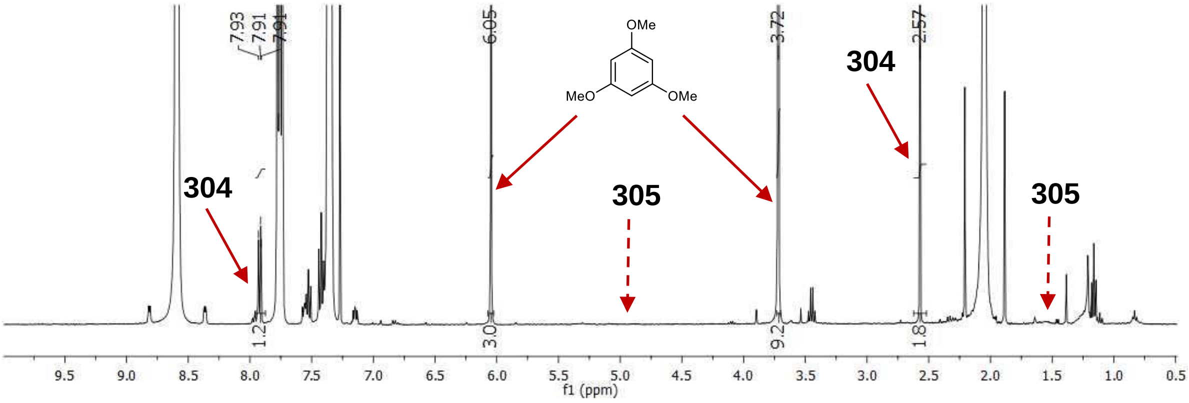




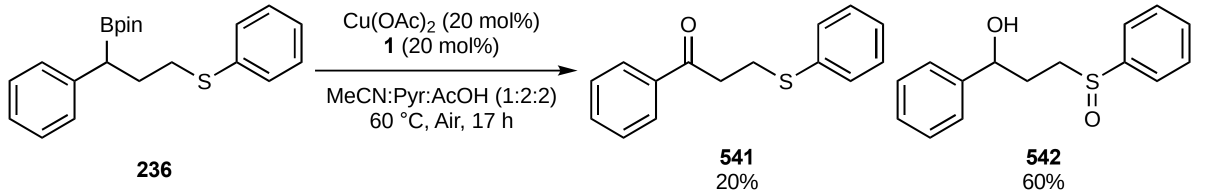
536

304
94%

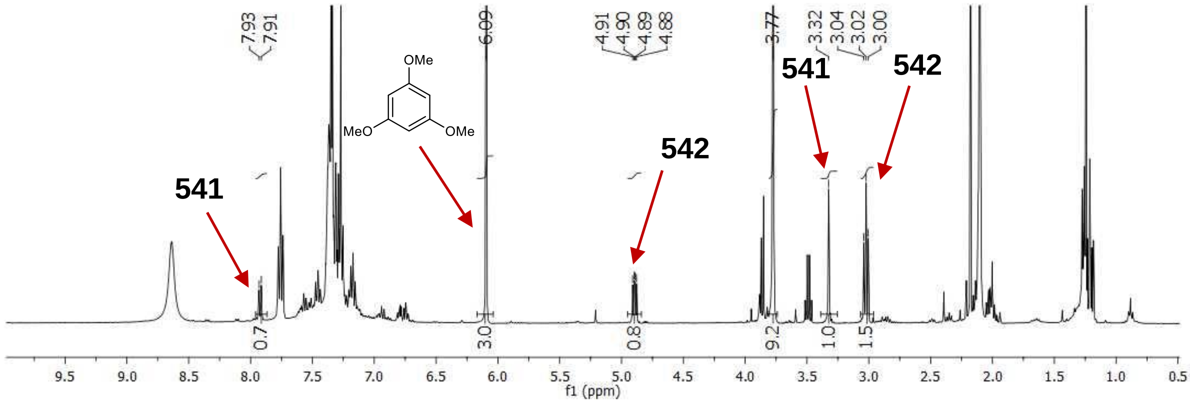
Pyridine (0.6 mL) and acetic acid (0.6 mL) were added to a solution of peroxide **536**[322] (9.8 mg, 0.071 mmol) in MeCN (0.4 mL). The mixture was stirred at 60 °C for 16 h. The mixture was cooled to room temperature, 1,3,5-trimethoxybenzene (4.7 mg, 0.028 mmol, as an internal standard), Et_2O (2 mL) and H_2O (2 mL) were added. The organic phase was separated and concentrated *in vacuo*. The mixture was analysed by ^1H NMR spectroscopy which showed the consumption of peroxide **536** and the formation of ketone **304** (94% NMR yield).

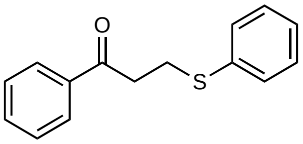


5.9.1.4 Reaction of Sulfide-substituted Boronic Ester 236



Pyridine (0.2 mL) and acetic acid (0.2 mL) were added to a solution of boronic ester **236** (18.1 mg, 0.0511 mmol), $Cu(OAc)_2$ (1.8 mg, 0.010 mmol), diketimine **1** (3.1 mg, 0.01 mmol) in MeCN (0.1 mL). The mixture was stirred at 60 °C for 17 h. The mixture was cooled to room temperature, 1,3,5-trimethoxybenzene (6.7 mg, 0.040 mmol, as an internal standard), Et_2O (1 mL) and H_2O (2 mL), were added. The organic phase was separated and concentrated *in vacuo*. The mixture was analysed by ^{1}H NMR spectroscopy, which showed the formation of ketone **541** (20% NMR yield) and alcohol **542** (60% NMR yield). Flash chromatography of the crude mixture (10% Et_2O/hexane) gave a sample of alcohol **542** as a pale yellow oil for characterisation.[179]



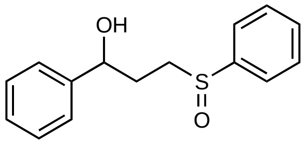


541

1-Phenyl-3-(phenylsulfanyl)propan-1-one (541)

Characteristic peaks for ketone **541**. The data are consistent with the literature.[324]

^{1}H NMR (400 MHz, CDCl3) δ 7.95-7.91 (2H, m, Ar**H**), 3.35-3.32 (4H, m, C$\mathbf{H_2}$C$\mathbf{H_2}$).



542

(±)-3-(Benzenesulfinyl)-1-phenylpropan-1-ol (542)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (9H, m, Ar**H**), 7.22-7.15 (1H, m, Ar**H**), 4.93-4.87 (1H, m, C**H**), 3.07-2.98 (2H, m, SC$\mathbf{H_2}$), 2.20-2.07 (1H, m, CHC$\mathbf{H_A}$CH$_B$), 2.07-2.00 (1H, m, CHCH$_A$C$\mathbf{H_B}$), 1.99 (1H, s, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (C), 136.1 (C), 129.2 (2 × CH), 128.9 (2 × CH), 128.6 (2 × CH), 127.8 (CH), 126.0 (CH), 125.8 (2 × CH), 73.1 (CH), 38.1 (CH_2), 30.0 (CH_2).

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