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Amination of Alkylboronic Esters

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Alkylboronic esters are high value chemical building blocks which can be used to make complex, C-sp^3 rich molecules. The ability to convert the C–B bond in a range of C–C and C-heteroatom bond-forming reactions, in addition to their broad functional group compatibility, gives alkylboronic esters significant synthetic utility. Methods to convert boronic esters into amines have particular interest, due to the wide prevalence of nitrogen-based functional groups in biologically active compounds, functional materials, and catalysts. In this review, we explore different methods for the amination of alkylboronic esters. These can be split into three distinct classes based on the mechanism of reaction: amination through 1,2-metallate rearrangement, amination using nucleophilic 'ate' complexes, and oxidative amination reactions such as alkyl variants of the Chan-Lam reaction.

Introduction

Boronic acids and their derivatives are powerful chemical building blocks in organic synthesis.[1] This is due to the combination of their stability under ambient conditions, broad functional group compatibility, complementary reactivity, and generally wide commercial availability. Alkylboronic esters, in particular, are finding much use as building blocks in the synthesis of C-sp^3 rich molecules.[2–4] Methodologies for their further reaction traditionally have focused on C–C bond forming reactions, and oxidation to the corresponding alcohol. In recent years, significant attention has been spent on the conversion of alkyl C–B bonds into C–N bonds. Due to the prevalence of nitrogen-based functional groups in biologically relevant molecules, functional materials and catalysts, methods which combine the beneficial properties of boron reagents with the ability to form amines are of high value.

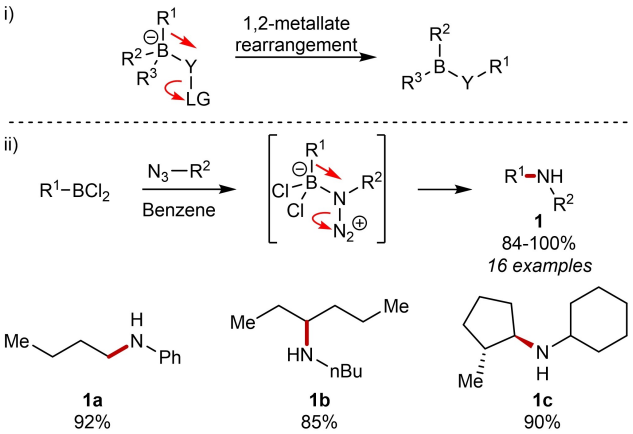
This review will explore methods reported for the amination of alkylboronic esters. This will be split into three distinct reaction pathways: amination through 1,2-metallate rearrangements, amination using nucleophilic 'ate' complexes, and oxidative amination reactions such as alkyl variants of the Chan-Lam reaction.

Discussion

1,2-Metallate Rearrangements

The 1,2-metallate rearrangement is one of the key reaction pathways through which organoboron compounds react (Scheme 1).[5,6] Classic examples include the oxidation to alcohol using hydrogen peroxide, Matteson homologation and related lithiation-borylation chemistry,[7,8] and Zweifel olefinations.[9] These reactions all involve formation of a tetrahedral boron 'ate' complex, where one substituent has a leaving group on the atom attached to boron. A 1,2-metallate rearrangement can occur with one of the three other groups undergoing migration with concomitant loss of the leaving group. The mechanism is stereospecific, requiring an anti-periplanar alignment of the σ orbital of the boron-migrating group bond and the σ* orbital of the boron-leaving group bond.

Amination reactions of organoboron reagents involving a 1,2-metallate rearrangement have been extensively studied.[10] They all involve reaction of a nitrogen-based nucleophile which has a leaving group attached, analogous to hydrogen peroxide



Scheme 1. i) Mechanism of 1,2-metallate rearrangement. ii) Reaction of alkyl dichloroboranes with azides to give alkyl amines.

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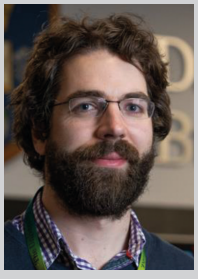
oxidation. For reaction to be successful, the nucleophiles need to:

- be reactive enough to form a boron 'ate' complex with the boron reagent.
- have a leaving group suitable to facilitate 1,2-metallate rearrangement.

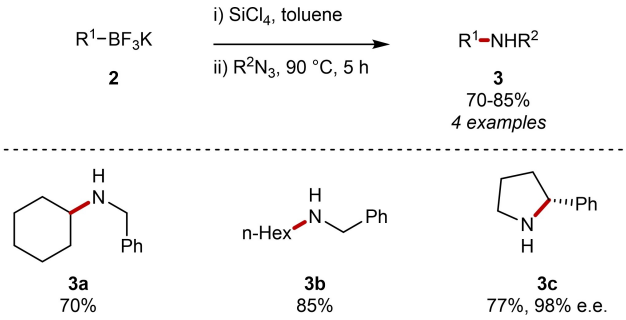
In the context of alkylboronic esters, which are relatively weak electrophiles (compared with boranes and dihaloboranes) and can be sterically hindered (depending on the diol backbone and/or the carbon group attached to boron), their ability to form a boron 'ate' complex can limit the type of amine formed. In particular, the direct formation of *N*-tertiary amines requires a *N*-tertiary nucleophile, which are inherently sterically hindered, and the intermediacy of a zwitterionic 'ate' complex. So far there are no reported examples of *N*-tertiary amines being formed from boronic esters through a 1,2-metallate rearrangement to the best of our knowledge. Furthermore, some methods reported for the amination of alkylboronic acids have been found to be unreactive using the corresponding boronic esters, presumably due to reduced ability of the amination reagents to form the key 'ate' complex intermediate.[11–14]

The amination of boron reagents through a 1,2-metallate rearrangement using azides as the nitrogen-based nucleophile, first reported by H. C. Brown and coworkers, demonstrates the balance of reactivity needed between the boron and amination reagents (Scheme 1).[15] In this reaction, N_2 acts as the leaving group during 1,2-metallate rearrangement. To balance the relatively mild nucleophilicity of the azide, a strongly electrophilic dichloroborane boron reagent was required. These reactions were found to be stereospecific, demonstrated by the amination of norbornyl and 2-methylcyclopentyl dichloroboranes (**1c**). This work has inspired other researchers to develop similar amination methods starting from alkylboronic esters, which are not sufficiently reactive to undergo amination directly with azides and so require first transformation into the corresponding dihaloborane.

Matteson and Kim reported the amination of potassium trifluoroborate salts **2**, derived from the corresponding DICHED boronic ester, using $SiCl_4$ and azides (Scheme 2). It was proposed that $SiCl_4$ acts to defluorinate the trifluoroborate salt, and the resulting difluoroborane reacts with the azide to give the corresponding amine product **3**. While only a few examples of this method were reported, it was shown that intramolecular amination was successful, giving pyrrolidine **3c** in excellent yield and enantioselectivity.



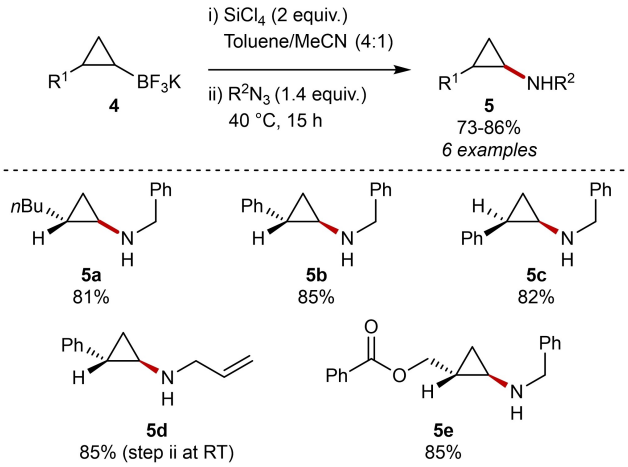
Dr Ben Partridge graduated in 2007 with an MSci in Chemistry with Industrial Experience from the University of Bristol. He stayed at Bristol for his PhD, working with Prof. Varinder Aggarwal FRS, before moving to the University of California, Berkeley in 2011 for a postdoc with Prof. John Hartwig. From 2013 he worked as a postdoctoral researcher with Prof. Hon Wai Lam at the University of Edinburgh and the University of Nottingham. He was appointed as Lecturer of Organic Chemistry at the University of Sheffield in June 2016. His research interests include organoboron chemistry, catalysis and asymmetric synthesis.



Scheme 2. Amination of trifluoroborate salts, derived from DICHED boronic esters, using $SiCl_4$ and azides.

Pietruszka and Solduga have reported that cyclopropane trifluoroborate salts **4**, derived from enantiomerically enriched TADDOL boronic esters, are also suitable substrates for amination using $SiCl_4$ and azides (Scheme 3).[16] This method involves the sequential addition of $SiCl_4$, reported to form the corresponding dichloroborane, followed by the azide. Acetonitrile was used as a co-solvent with toluene to aid solubility of the trifluoroborate salt. While the amination step could be carried out at room temperature, heating the mixture at 40 °C led to a more efficient reaction. The reaction was found to be stereospecific for both *trans*- and *cis*-cyclopropane trifluoroborate salts (**5b**, **5c**). While *trans*-cyclopropane with a benzoyl ester was successfully aminated (**5e**), the corresponding *cis*-cyclopropane substrate decomposed under the reaction conditions. This was proposed to occur through intramolecular reaction of the carbonyl with the highly electrophilic dichloroborane intermediate.

Aggarwal and co-workers demonstrated that amination using azides could be applied to the reaction of benzylic tertiary potassium trifluoroborate salts **6**, formed from the correspond-



Scheme 3. Amination of cyclopropane potassium trifluoroborate salts using $SiCl_4$ and azides.

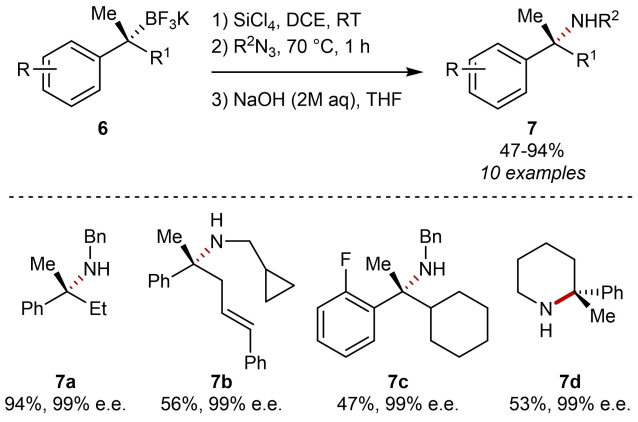
ing tertiary boronic esters (Scheme 4).[17] The trifluoroborate salt required an initial treatment with $SiCl_4$, proposed to generate an intermediate difluoroborane, before reaction with the azide. These reactions gave the corresponding C-tertiary amines **7** in good to excellent yield and with complete stereospecificity. An intramolecular reaction to give piperidine **7d**, and application of the method in the total synthesis of Igmesine was also reported. The method was reported subsequently to be successful in the reaction of an aliphatic tertiary potassium trifluoroborate salt.[18]

As an alternative to using azide as the aminating reagent, the use of hydroxylamine derivatives and *N*-chloroamine reagents has been reported. Again, H. C. Brown and coworkers pioneered the initial work in this area. This includes amination of triaryl boranes, formed through hydroboration, to form primary amines in moderate yield.[19] However, stereoelectronic factors hinder the amination of trialkylboranes using hydroxylamine *O*-sulfonic acid (HSA). The reaction was found to be limited to the amination of only 2 out of 3 alkyl groups, and a variety of other monoalkylboranes did not react. To overcome this, conversion of the borane (formed through hydroboration) first into an alkylboronic ester **8** and then into the corresponding borinic acid **9** was carried out. The borinic ester was found to react efficiently with HSA to give the primary amine product **10** (Scheme 5).[20] While this protocol involves multiple steps, a range of amines **10** were formed in good to excellent yield. Key to this design was the addition of a methyl group to boron, which displays poor migratory aptitude in 1,2-metallate rearrangements compared with other alkyl groups. The approach was later adapted to the amination of alkylboronic ester formed through Matteson homologation reactions.[21]

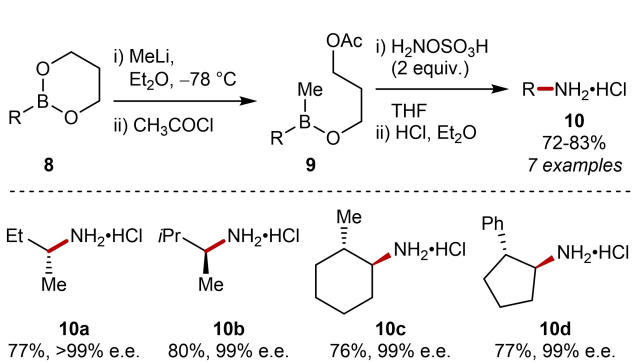
Fernandez, et al. reported that the amination of catechol esters **11** could be achieved, by first converting to the corresponding trialkylborane **12** and then reacting with HSA (Scheme 6).[22] Borane formation was achieved through treatment of the boronic ester with either methylmagnesium chloride or diethylzinc. The reaction of the borane with HSA gave the primary amine product (**13a**) stereospecifically. To access *N*-secondary and *N*-tertiary amines (**13b** and **13c**), chloro-alkylamines were used as the aminating reagent, formed through treatment of the corresponding amine with sodium hypochlorite. Interestingly, secondary amines (**13b**) were formed with only a modest loss of stereochemical information. However, the formation of a *N*-tertiary amine **13c** gave racemic material, consistent with a radical reaction pathway[23] rather than a 1,2-metallate rearrangement.

Significantly, Morken and co-workers reported in 2012 a direct method for the amination of alkylboronic esters without requiring pre-functionalisation of the boron reagent.[24] This used MeO-NH_2, deprotonated using nBuLi, as the aminating reagent (Scheme 7). This protocol was successfully applied to the amination of primary and secondary boronic esters (**15**), though *tert*-butyl boronic ester was found to be unreactive (**15f**). Allyl boronic esters also underwent successful amination (**15d**). Importantly, enantiomerically enriched boronic esters were found to react with 100% enantiospecificity (**15c**) which is consistent with operation of a 1,2-metallate rearrangement. This method has used by Aggarwal and co-workers in the total synthesis Kalkitoxin.[25]

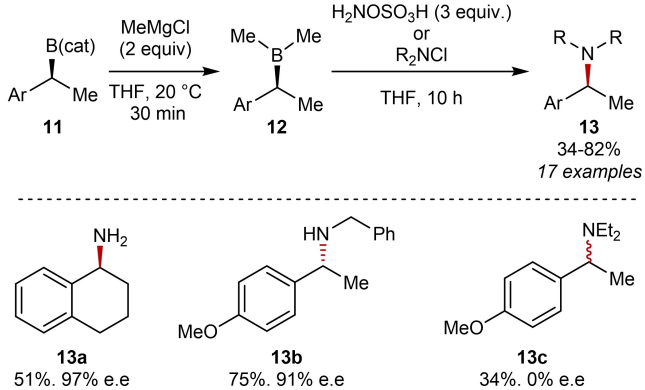
Subsequently, Morken and coworkers provided a modified procedure that uses *t*BuOK as a base (Scheme 8), thereby avoiding the use of *n*BuLi and simplifying the reaction protocol.[26] It is suggested that under these conditions the base can deprotonate a MeO–NH_2 – boronic ester adduct, rather than forming an anionic nitrenoid species. These milder conditions were found to be successful for the amination of



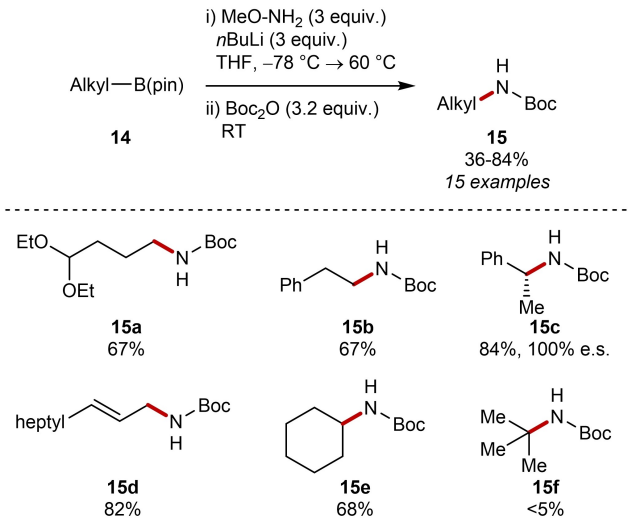
Scheme 4. Amination of tertiary trifluoroborate salts using $SiCl_4$ and azides.



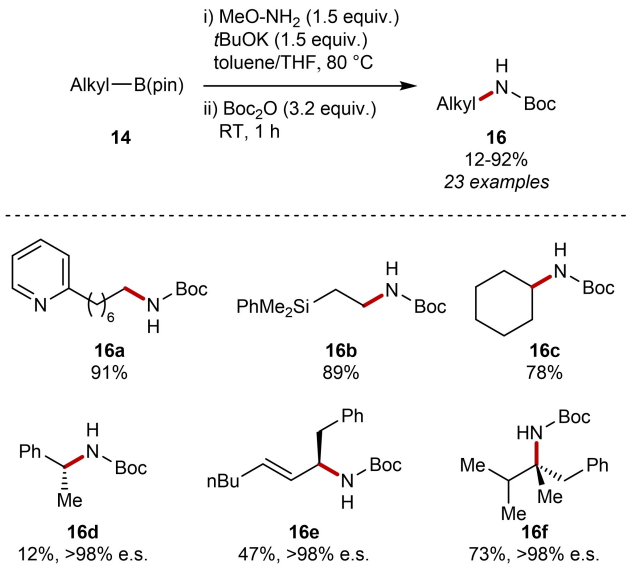
Scheme 5. Conversion of alkylboronic esters into amines via the corresponding borinic acid.



Scheme 6. Conversion of alkylboronic esters into amines via the corresponding triarykylborane.



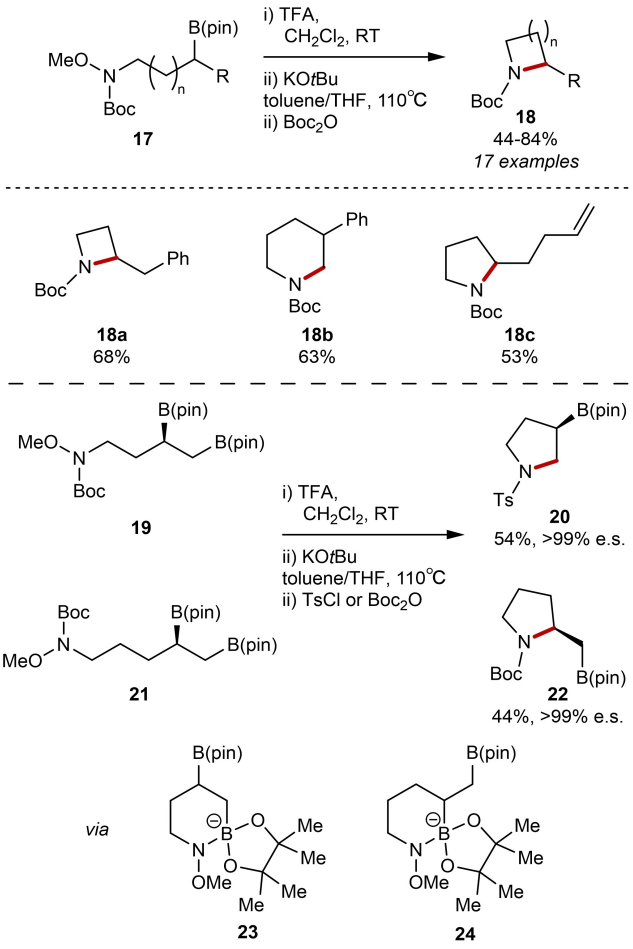
Scheme 7. Amination of alkylboronic esters using MeO-NH_2 and nBuLi.



Scheme 8. Amination of alkylboronic esters using MeO-NH_2 and *t*BuOK.

primary, secondary and tertiary boronic esters (**16**). The reaction of enantiomerically enriched boronic esters, including tertiary boronic esters, was found to be stereospecific. The reaction of benzylic boronic esters were generally low in yield (**16 d**), in contrast to the conditions in Scheme 7, due to competing protodeboronation. Interestingly, Tortosa and co-workers have found that this method can used to selectively mono-aminate a spirocyclic 1,2-diboronic ester.[27]

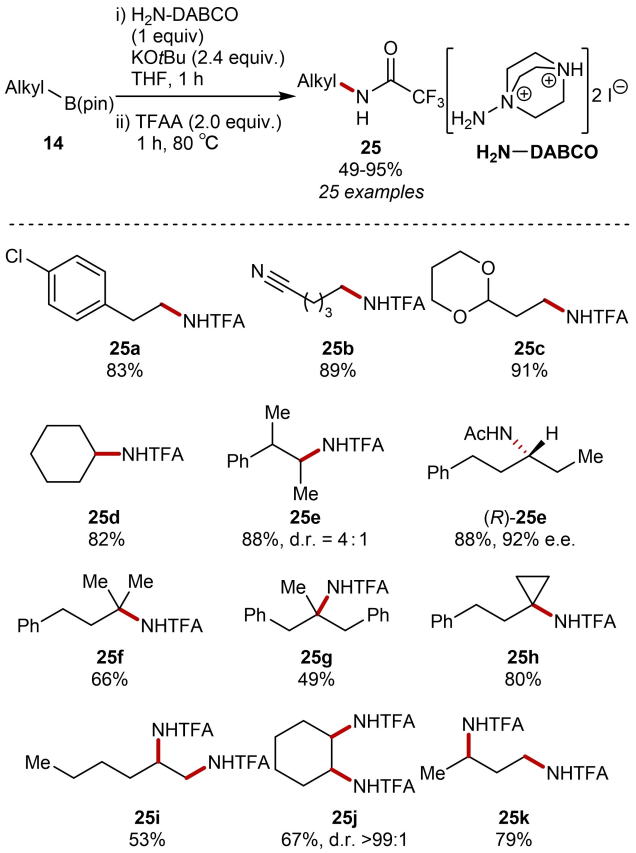
Morken and co-workers demonstrated that their amination procedure could be adapted towards intramolecular amination leading to the formation of azacylic products **18** (Scheme 9).[28] This protocol starts with the deprotection of a Boc-methoxyamine group, followed by amination and subsequent protection of the secondary amine. Using this method, a variety of azetidines, pyrrolidines and piperidines were successfully prepared. Interestingly, the intramolecular amination could be



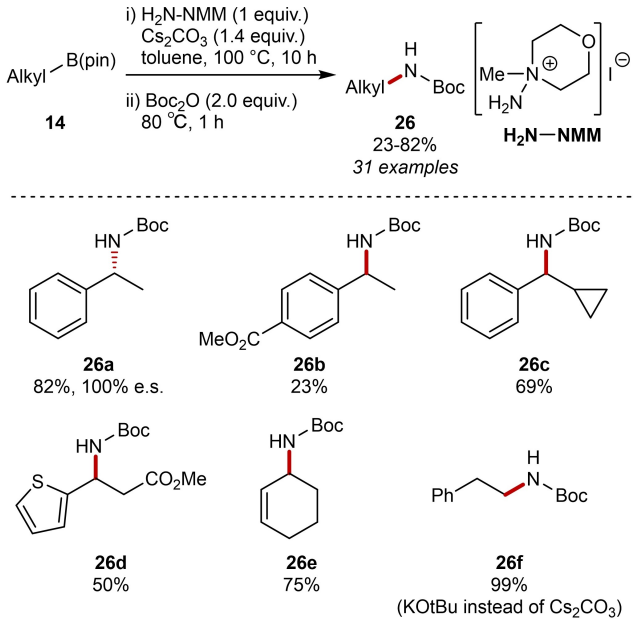
Scheme 9. Intramolecular amination of boronic esters and diboronic esters using methoxyamine derivatives.

successfully applied to 1,2-diboronic esters resulting in pyrrolidine and piperidine boronic esters (**20** and **22**). By varying the chain length, the site selectivity of the reaction was tested. For both boronic esters **19** and **21**, the corresponding pyrrolidine products were formed. The selectivity presumably arises due to the preference for either the formation or rate of 1,2-metallate rearrangement of a 6-membered 'ate' complex intermediate (**23** and **24**). Finally, by using enantiomerically enriched boronic esters, the intramolecular amination was found to be stereospecific.

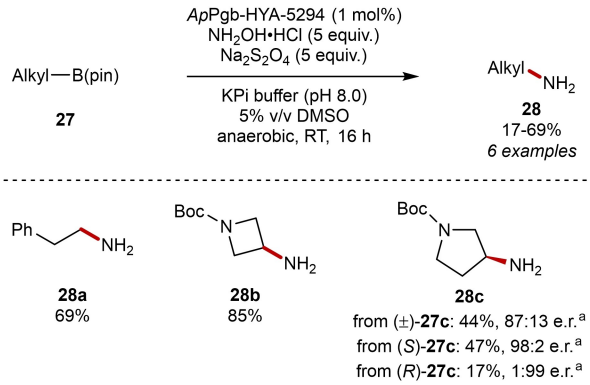
Liu and co-workers reported that the aminoazanium salt of DABCO can act as an efficient amination reagent for pinacolboronic esters (Scheme 10).[29] Unlike methoxyamine which requires fresh preparation, the H_2N-DABCO reagent is reported to be a stable solid that can be stored for several months. The reagent was found to successfully aminate a range of primary, secondary and tertiary aliphatic boronic esters to give amines **25** in good to excellent yield. For diastereomeric boronic esters, the amine products were obtained with the same d.r. as the starting material (**25 d**). In addition, an enantiomerically enriched boronic ester was aminated with 100% enantiospecificity (**25 e**). 1,2- and 1,3-diboronic esters were also subjected to



Scheme 10. Amination of aliphatic and diboronic esters using H_2N-DABCO.



Scheme 11. Amination of alkylboronic esters using H_2N-NMM.



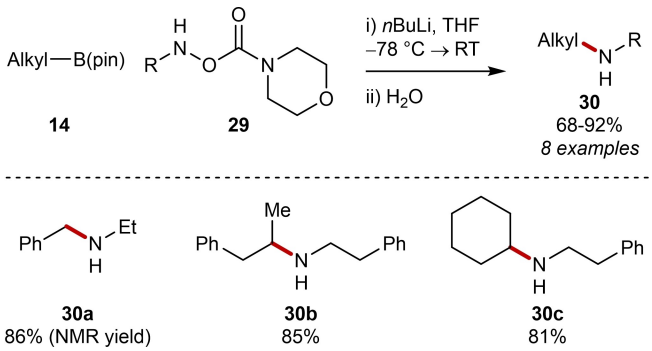
Scheme 12. Amination of alkylboronic esters using a nitrene transferase and hydroxylamine. [a] Reaction using *Ap*Pgb-HYA-5294 (2.5 mol%), $NH_2OH{\cdot}HCl$ (3 equiv.), $Na_2S_2O_4$ (1 equiv.), 5% v/v EtOH.

the reaction conditions, giving the corresponding diamine products (**25 i**–**25 k**).

Liu and co-workers found that when using H_2N-DABCO as an aminating reagent with benzylic boronic esters, protodeboronation occurred predominantly.[30] To overcome this, they found that a combination of H_2N-NMM and Cs_2CO_3 as base led to amination in high yield (Scheme 11). The use a milder base than KO*t*Bu was found to be key to reduce protodeboronation. A range of benzylic and allylic boronic esters underwent amination successfully (**26**). Substrates with electron withdrawing groups on the aromatic ring reacted in lower yield (**26 b**) due to higher proportions of protodeboronation being observed. Primary and secondary aliphatic boronic esters were also successfully reacted (**26 f**), but required the use of KO*t*Bu as base for good yields. Consistent with a stereospecific 1,2-metallate rearrangement mechanism, the reaction with an enantiomerically enriched boronic ester was found to occur in 100% stereospecificity.

Arnold, Alfonso and co-workers have developed an enzyme-catalysed amination of alkylboronic esters, using an engineered protoglobin nitrene transferase (Scheme 12).[31] This uses hydroxylamine as the amine source, which is proposed to react with the heme group of the enzyme to form a nitrene intermediate. It is proposed that the nitrene reacts with the boronic ester through a stereospecific 1,2-metallate rearrangement. A small selection of both primary and secondary alkylboronic esters were successfully reacted in modest to good yield. Interestingly, racemic boronic ester **27 c** reacted to give enantiomerically enriched amine (***S*)-28 c** with an e.r. of 87:13, presumably through a through a kinetic resolution. When (***S*)-27 c** and (***R*)-27 c** were reacted individually, both products were obtained with excellent enantiospecificity. However, the reaction of (***S*)-27 c** proceeded in higher yield than that of (***R*)-27 c**, consistent with the results obtained with racemic material.

Dong and co-workers have developed a class of nitrenoid reagent **29**, derived from hydroxylamines, to perform *N*-insertion reactions into C–B bonds (Scheme 13).[32] The advantage of these conditions is that the aminoborane intermediate can be obtained and undergo subsequent Matteson homologation. While the report focused on the reaction of arylboronic esters, the method was found to be suitable for reaction of primary and secondary alkylboronic esters to give the corresponding dialkylamine products **30** in good to excellent yield.



Scheme 13. Amination of alkylboronic esters using a nitrenoid reagents.

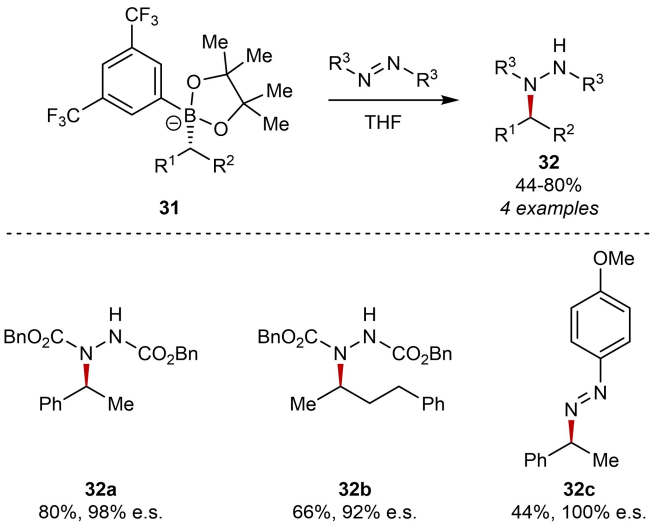
'Ate' Complex Reactions

In the amination reactions above which react through a 1,2-metallate rearrangement, the boronic ester acts as an electrophile and reacts with nucleophilic amine sources. Complementary to this, if the boronic ester is converted into an 'ate' complex, it can act as a nucleophile and react with electrophilic amination reagents. This approach has been only reported for a few examples, outlined below.

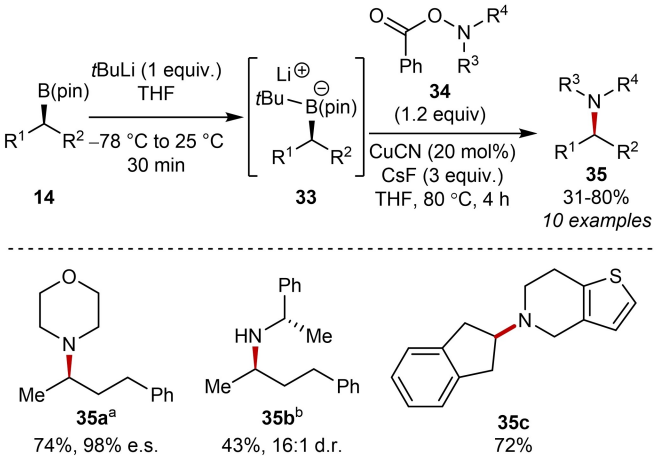
Aggarwal and co-workers showed that nucleophilic 'ate' complexes **31** can be generated through the reaction of alkylboronic esters with aryl lithium reagents, which can subsequently be reacted with a range of electrophiles with inversion of stereochemistry.[33] Specifically for this review, the reaction with azodicarboxylate reagents led to formation of hydrazine products **32** (Scheme 14). The choice of aryl lithium was found to be important to control the stereoselectivity of the reaction, with the use of 3,5-$(CF_3)_2C_6H_3Li$ needed to give good to excellent levels of enantiospecificity in the reaction. Furthermore, the 'ate' complex could be reacted with diazonium salts to give the corresponding azo product **32 c** with complete enantiospecificity. This approach has also been used for the reaction of azodicarboxylates with allylboron 'ate' complexes, which occurs through an S_E2' mechanism.[34]

Morken and co-workers have reported that alkylboronic esters activated by an alkyllithium, to give 'ate' complex **33**, can undergo transmetallation with CuCN and react with a range of electrophiles.[35] *tert*-Butyllithium was found to be suitable for activating the primary and secondary boronic esters. Its success is attributed to the fact that the *tert*-butyl group is sufficiently electron donating to promote transmetallation, but sterically hindered enough to prevent its own transfer to Cu. The authors also note that 'ate' complex formation between the boronic ester and *t*BuLi is both kinetically fast and irreversible, which allow the tolerance of epoxides, alkyl halides and silyl ethers in the reaction (though these functional groups are not shown in examples of amination reactions). Cu-catalysed amination of these 'ate' complexes was achieved through reaction with electrophilic benzoyloxyamine reagents **34**, to give the corresponding secondary or tertiary amine products **35** in modest to excellent yield (Scheme 15). Impressively, the reaction was found to occur with excellent enantiospecificity. It was found that CsF was needed to improve reaction efficiency, with Li–Cs ion exchange proposed to occur to generate a more reactive Cs-based 'ate' complex.

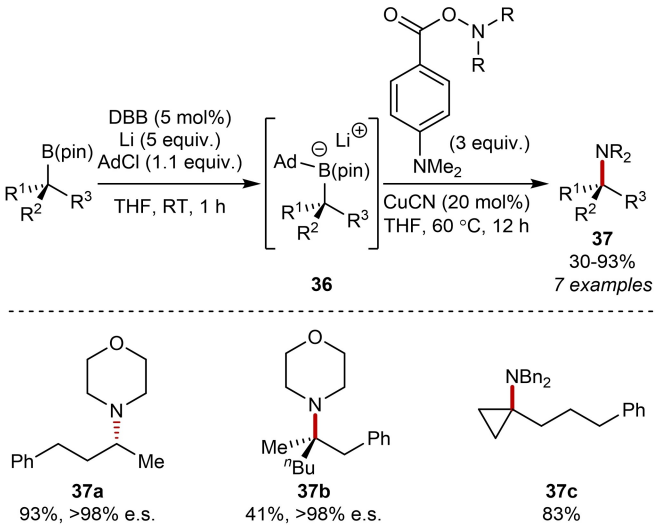
Expanding on these results, Morken and co-workers have used adamantyllithium as an activator to enable to the Cu-catalysed amination of tertiary alkylboronic esters (Scheme 16).[36] Despite having two tertiary carbon groups in boron 'ate' complex **36**, the non-adamantyl preferentially undergoes amination. DFT calculations suggested that there is a 2.3 kcal/mol energy difference between the transition states for the transmetallation of adamantyl vs *tert*-butyl group to CuCN. The authors propose that this arises due to the greater flexibility of *tert*-butyl group compared to adamantyl, allowing it to undergo more pyramidalization during transmetallation. The conditions were applied to the amination of several secondary and tertiary boronic esters, with *N*-tertiary amines **37** formed in modest to excellent yield. Due to the difficulty in



Scheme 14. Reaction of nucleophilic 'ate' complexes with nitrogen electrophiles.

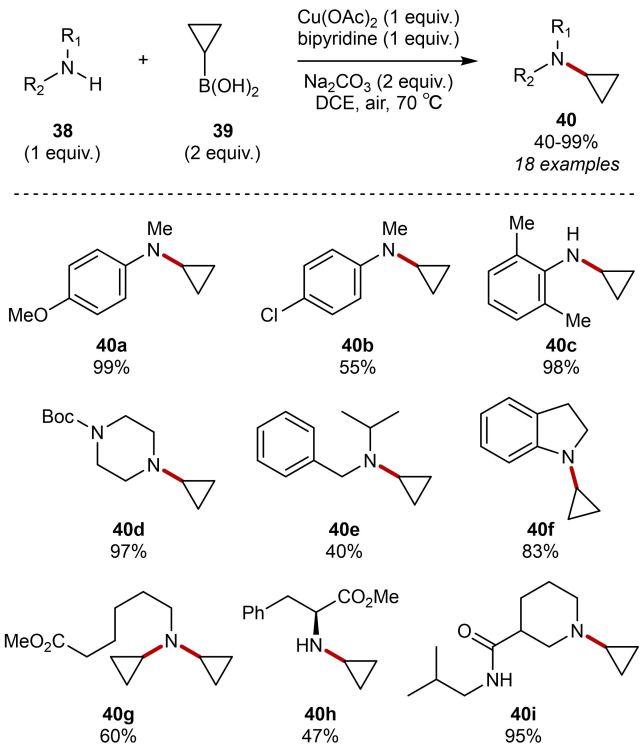


Scheme 15. Cu-catalysed amination of boron 'ate' complex with benzoyloxyamines using *t*-BuLi as an activator. a) 50 mol% styrene was added. b) p-$MeNC_6H_4COONHR$ used as the amination reagent, and 40 mol% PPh_3 added.



Scheme 16. Cu-catalysed amination of boron 'ate' complex with benzoyloxy-amines using adamantyllithium as an activator. Ad = adamantyl, DBB = 4,4′-di-*tert*-butylbiphenyl.

preparing C-tertiary amines in general, being able to obtain these with > 98% enantiospecificity is particularly impressive.



Scheme 17. Chan-Lam amination using cyclopropylboronic acid and a range of amines.

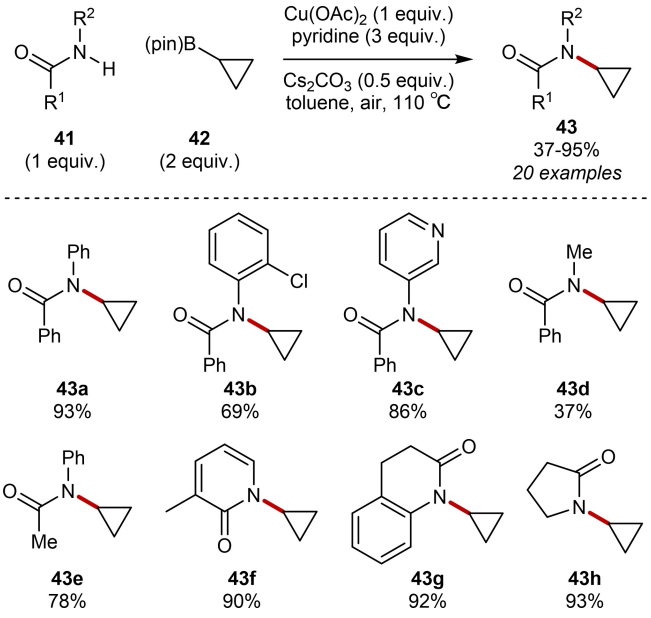
Chan-Lam and Oxidative Amination Reactions

The Chan-Lam amination is the Cu-catalysed oxidative coupling of nitrogen-based nucleophiles with boronic acid reagents.[37–39] First developed for the amination of arylboronic acids, the adaptation of this approach to alkylboron reagents has taken longer to realise. The potential advantage of this approach is the typically mild reaction conditions under which both boron reagents and Cu-catalysis operate. Furthermore, an alkyl variant of the Chan-Lam reaction would overcome issues with other transition metal catalysed amination reactions, such as those experienced by the Buchwald-Hartwig amination.

Initial success towards the alkyl Chan-Lam reaction has involved the amination of boronic acids, in particular cyclopropyl[40–43] and methyl boronic acids.[44] The use of alkylboronic acids in the Chan-Lam reaction has been previously reviewed,[37,38] and so only a select number of examples will be summarised below. The Chan-Lam coupling of cyclopropyl potassium trifluoroborate with phenols and azaheterocycles has also been reported,[45] but will not be reviewed in detail.

A representative example of an alkyl Chan-Lam reaction with cyclopropyl boronic acid is the amination reaction reported by Zhu and co-workers (Scheme 17).[41] This involves heating the amine and boronic acid in the presence of a Cu-catalyst, derived from $Cu(OAc)_2$ and bipyridine, and a base under air. Amination was found to be successful in modest to excellent yield across a range of primary and secondary amines (**40**). For the reaction of primary amines, an excess of boronic acid was used to achieve efficient dialkylation of the amine (**40 g**). In substrates containing both amines and amides, alkylation of the amine group occurred chemoselectively (**40 i**). Notable functional groups that are tolerated include amides, aryl halides, esters, ketones, and nitro groups.

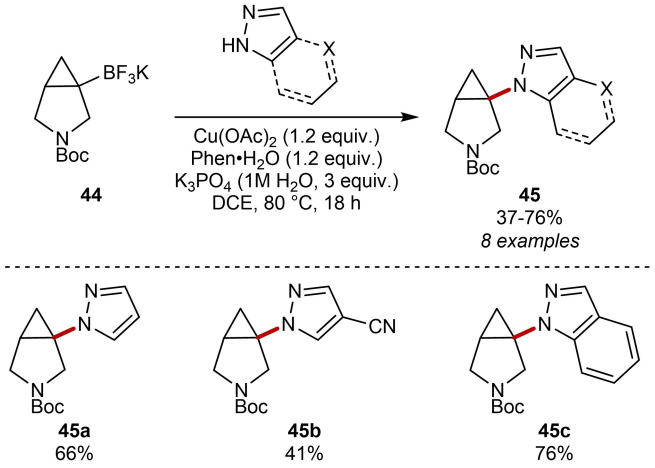
The Cu-catalysed amidation of cyclopropyl pinacol boronic ester was reported by Taillefer and co-workers (Scheme 18).[46] Using a combination of $Cu(OAc)_2$, pyridine as a ligand and Cs_2CO_3 as a base, a range of secondary amides could be



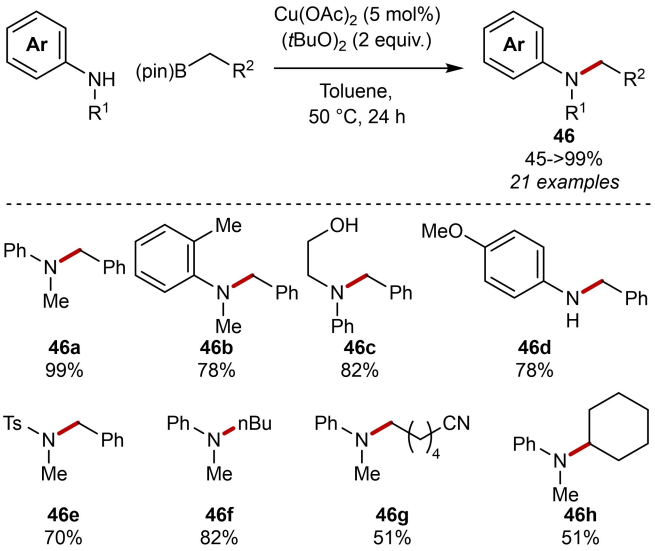
Scheme 18. Chan-Lam amidation of cyclopropyl boronic ester with acyclic and cyclic amides.

cyclopropylated when heated at 110 °C. The corresponding tertiary amide products **43** were formed in moderate to excellent yield. Substrates with an aromatic substituent on either or both of the carbonyl or nitrogen groups were mainly explored. However, pyrrolidinone was also a suitable substrate in this chemistry (**43 h**).

Harris and co-workers reported that bicyclic cyclopropyl potassium trifluoroborate salt **44** can undergo Chan-Lam coupling reactions with pyrazole and benzopyrazole substrates (Scheme 19).[47] The boron reagents were made from the corresponding alkenylboronic esters, through a Simmons-Smith cyclopropanation followed by trifluoroborate formation. The complex pyrazole products **45** were formed in good to excellent yield, though coupling of pyrazoles with electron withdrawing substituents was less efficient (**45 b**). This method is a rare example of a Chan-Lam reaction using a tertiary alkylboron reagent. Furthermore, apart from this report, the Chan-Lam amination of substituted cyclopropyl boron reagents has only been reported as isolated reactions in the patent literature to the best of our knowledge.[48,49]



Scheme 19. Chan-Lam coupling of tertiary potassium trifluoroborate salts with pyrazoles.



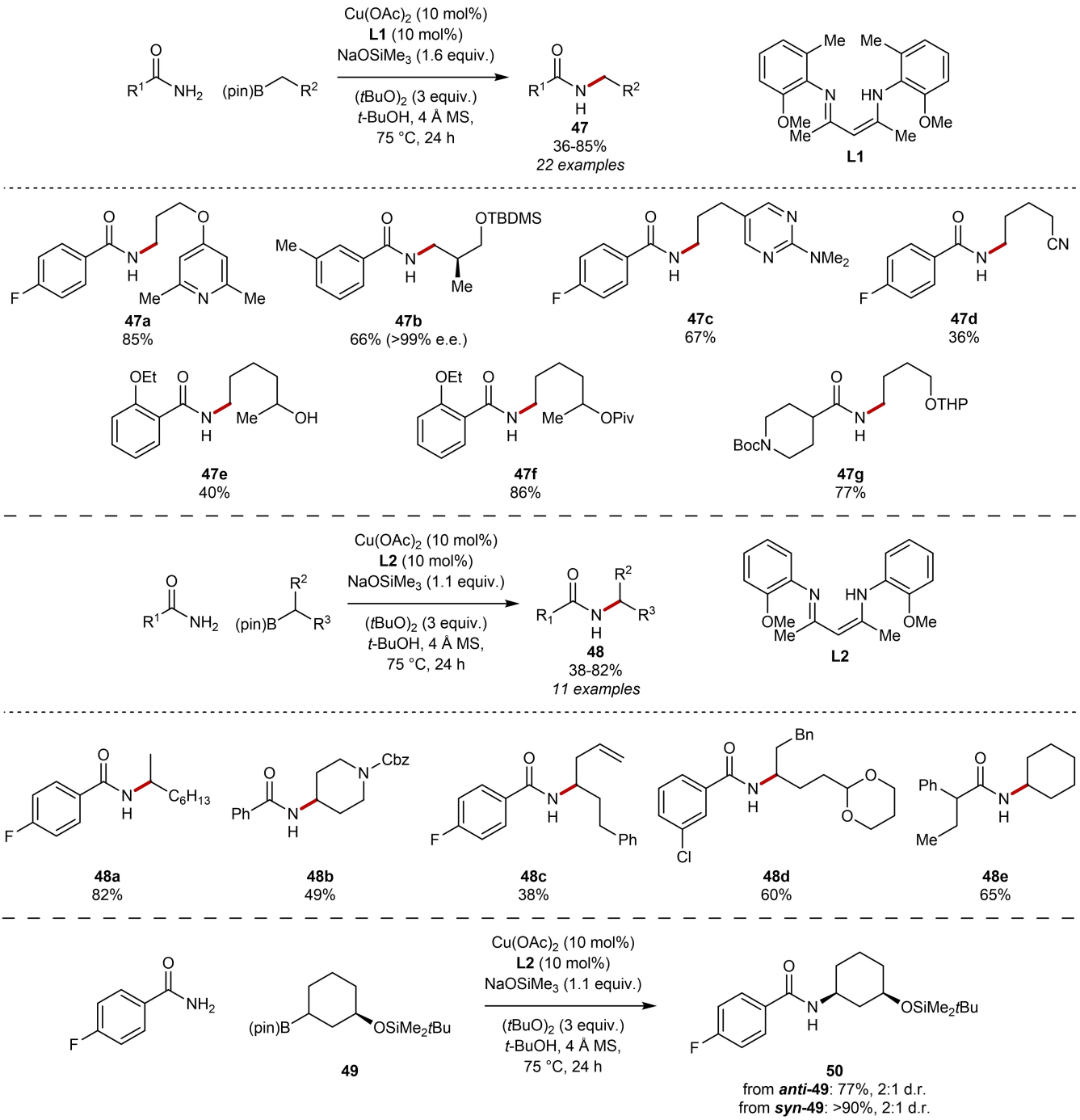
Scheme 20. Chan-Lam coupling of alkylboronic esters with anilines.

Kuninobu and co-workers reported that primary benzylic and aliphatic boronic esters could be coupled with anilines (Scheme 20).[50] The reaction conditions use $Cu(OAc)_2$ as a pre-catalyst and di-*tert*-butylperoxide as the terminal oxidant. A range of primary boronic esters and cyclohexylboronic ester were successfully coupled with anilines to give alkylated anilines **46**. While secondary anilines were mainly explored, the reaction with primary anilines occurred to give mono-alkylation as the major product (**46 d**). Increasing the stoichiometry of boronic ester allowed formation of the corresponding dialkylation product in good yield. The reaction was found to proceed chemoselectively at the amine when using a substrate also containing an alcohol (**46 c**). The coupling of *N*-methyl tosylamine (**46 e**), phthalimide and phenols was also successful under these conditions.

Watson and co-workers have reported the coupling of primary amides with alkylboronic acids[51] and subsequently primary and secondary aliphatic boronic esters (Scheme 21).[52] Both reports use substoichiometric loadings of $Cu(OAc)_2$ as a catalyst and di-*tert*-butylperoxide as the terminal oxidant. Also, key to success was the use of a mild siloxide base in the reaction. The reaction of boronic esters required the use of anionic NacNac ligands to generate a Cu-catalyst, with **L1** used for coupling primary boronic esters and **L2** used with secondary boronic esters. The reaction was found to be compatible with a broad range of functional groups, including *N*-heterocycles, alcohols, alkenes, esters, acetals and nitriles. Coupling of both benzamides and alkylamides could be carried out, with moderate to excellent yields of amide products (**47** and **48**) obtained. The reaction was found to retain stereochemical information at pendent stereogenic centres (**47 b**). However, boronic esters ***anti*-49** and ***syn*-49** underwent stereoconvergent amidation to give amide **50**, indicating a configurationally unstable intermediate is formed during the reaction.

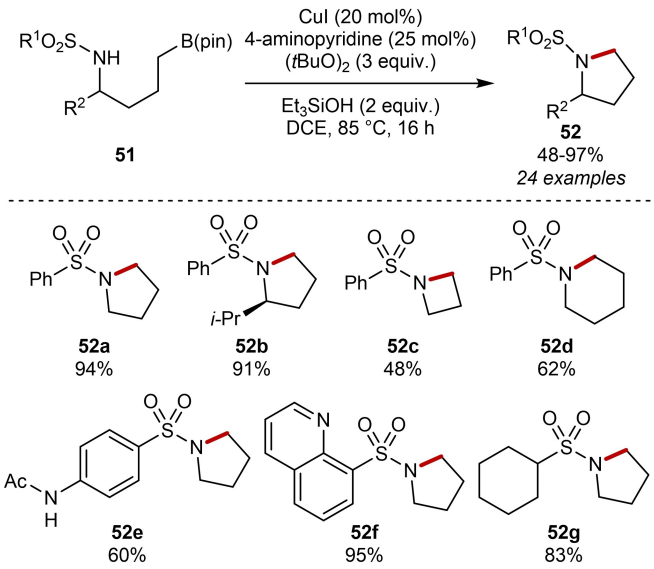
Kim and Lee reported the Chan-Lam coupling of secondary sulfonamides with primary alkylboronic esters.[53] The catalyst used was derived from CuI and 4-aminopyridine as a ligand. It was also found that di-*tert*-butylperoxide, as the terminal oxidant, and a silanol additive were required for efficient reaction. Interestingly, the intramolecular coupling could be used to generate a range of 4-, 5- and 6-membered rings (**52**) in good to excellent yield (Scheme 22). Apart from an isolated example,[54] this to the best of our knowledge is the first report of an intramolecular Chan-Lam methodology. An intermolecular variant was also reported, though this process generally occurs to give sulfonamides **53** in lower yields (Scheme 23). The conditions also require the addition of a combination of $NaOSiMe_3$ and NaOtBu as bases and $NaIO_4$, which presumably consumes pinacol through oxidative cleavage. The methods were found to tolerate a broad range of functional groups, including alkenes, amides, aryl halides, nitro groups, and heteroaromatic rings.

Partridge and co-workers reported conditions for the coupling of anilines with secondary and tertiary benzylic esters (Scheme 24).[55] Stoichiometric loadings of $Cu(OAc)_2$ were used

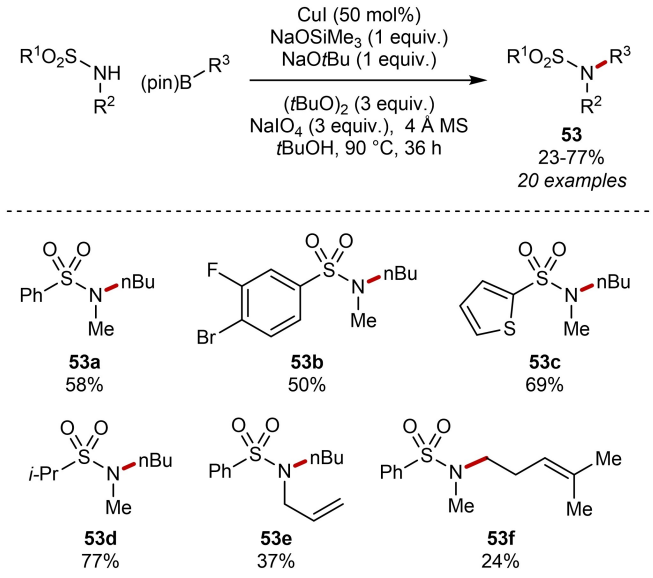


Scheme 21. Cu-catalysed amidation of primary alkyl boronic esters and secondary alkyl boronic esters.

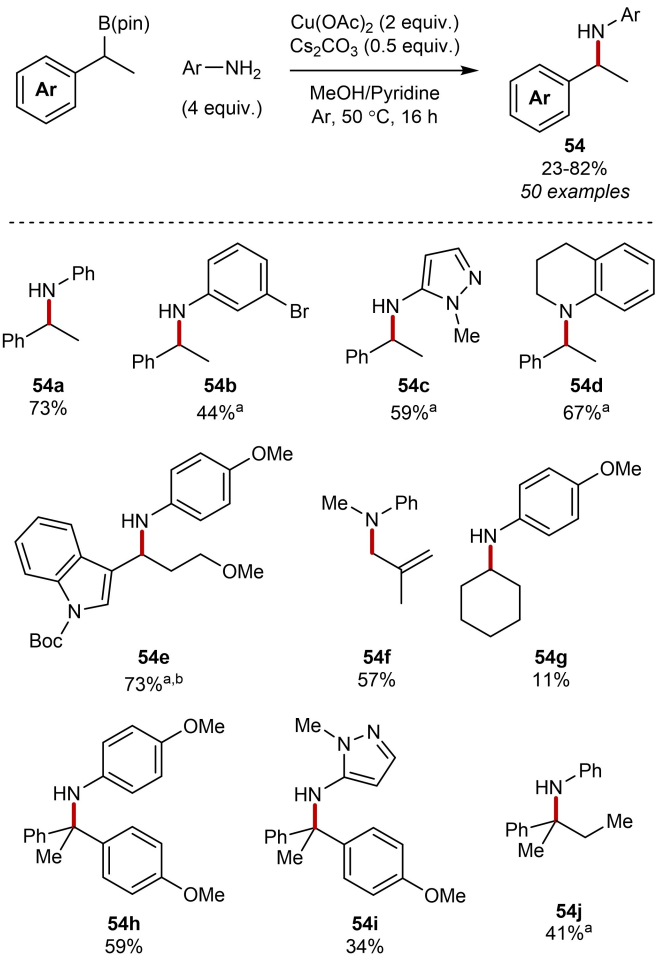
as both catalyst and terminal oxidant, with an excess of aniline required to achieve suitable yields. Reactions were run under an inert atmosphere to minimise formation of oxidative side products, related to the incorporation of O_2, observed previously by the group.[56] A wide range of anilines, containing a broad diversity of functional groups, were reacted successfully. However, anilines with electron withdrawing groups typically reacted in lower yield and require higher reaction temperatures and prolonged reaction times (**54b**). The boronic ester scope includes the reaction of primary and secondary benzylic boronic esters, and allyl boronic esters (**54f**). For benzylic boronic esters, the reaction of substrates with electron withdrawing group on the aromatic ring were less efficient. Cyclohexylboronic ester, however, only reacted in low yield (**54g**). Interestingly, tertiary boronic esters were found to successfully undergo amination in modest to good yield to give interesting C-tertiary amine products (**54h**–**54j**). The authors suggested that the boronic ester acts as alkyl radical precursor in the reaction. This is based on a radical clock experiment, and the finding that amination



Scheme 22. Intramolecular Chan-Lam coupling using sulfonamide-containing boronic esters.



Scheme 23. Intermolecular Chan-Lam coupling of sulfonamides with alkylboronic esters.

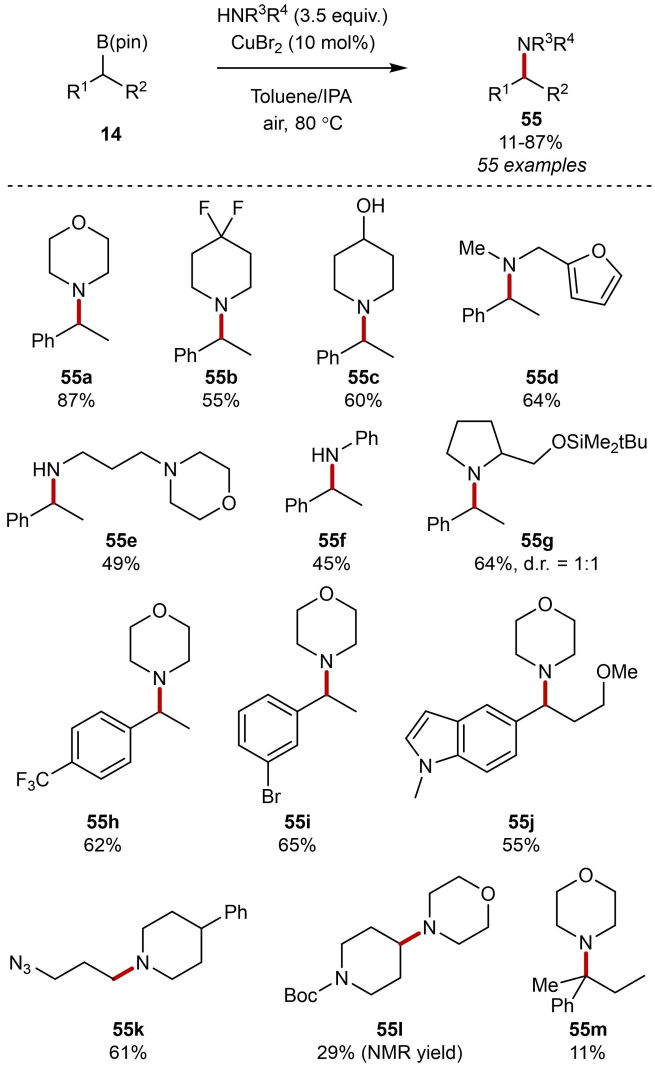


Scheme 24. Chan-Lam amination of secondary and tertiary benzylic boronic esters with anilines. a) Reaction conducted at 65 °C. b) Reaction time of 48 h.

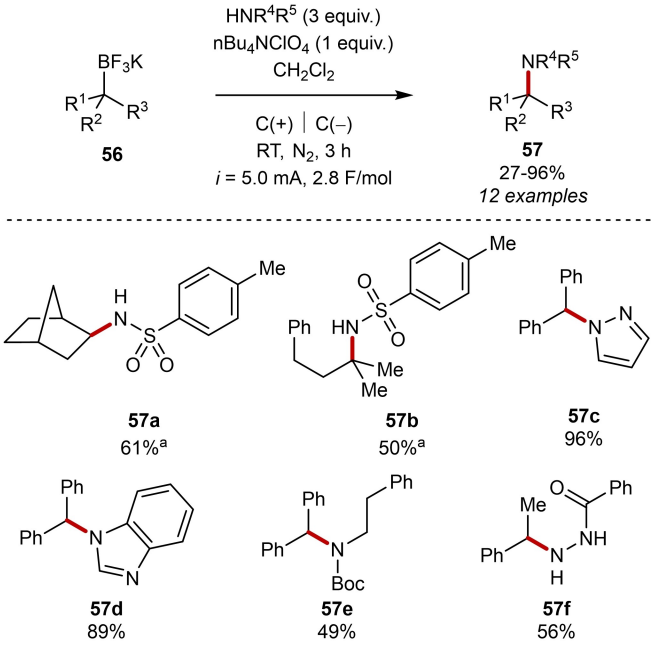
with stereoablation occurred when using an enantiomerically enriched boronic ester.

Partridge and coworkers subsequently reported their second generation conditions for the coupling of aliphatic amines with alkylboronic esters (Scheme 25).[57] This required $CuBr_2$ as a catalyst, in substoichiometric loadings, with O_2 from the air as the terminal oxidant. Unlike the authors' previous report,[55] amination occurred preferentially under air, generally giving <10% oxidation side products. The scope of amines used included cyclic and acyclic secondary alkyl amines (**55a–d**), and a smaller selection of primary amines (**55e**), which reacted in lower yield typically. Anilines reacted in modest yield (**55f**), especially in comparison to the previously reported conditions (Scheme 24). A range of primary and secondary benzylic boronic esters, and primary aliphatic boronic esters (**55k**) were reacted in good to excellent yield. A secondary aliphatic boronic ester (**55l**) also reacted in modest yield, but tertiary boronic esters only gave small quantities of amine product (**55m**). The reaction was found to be stereoablative when using enantiomerically enriched boronic esters, and the reaction of chiral amines gave diastereomeric products without stereocontrol. The authors propose that the boronic ester acts as an alkyl radical precursor formed upon reaction with an aminyl radical, generated *in situ* by reaction of the amine with $CuBr_2$. Evidence to support this proposal includes a radical clock experiment, TEMPO-trapping experiments, and EPR spectroscopy analysis of the reaction mixture.

Chung, Lee and co-workers have developed an anodic oxidation of alkyl potassium trifluoroborate salts, prepared from the corresponding pinacol boronic esters (Scheme 26).[58] The reaction is proposed to proceed through two consecutive single oxidations of the trifluoroborate salt to give a carbocation intermediate, which can trapped by a range of nucleophiles, including nitrogen-based nucleophiles. Alkyl trifluoroborate salts (**56**) where chosen for this study as they can be oxidised



Scheme 25. Cu-catalysed amination of alkylboronic esters with aliphatic amines.



Scheme 26. Anodic oxidative coupling of alkyl trifluoroborate salts with a range of nitrogen-based nucleophiles. [a] nBu_4NPF_6 used as electrolyte instead of nBu_4NClO_4.

directly under electrochemical conditions. This is unlike the corresponding alkylboronic esters which are only readily oxidised after conversion into a boronate intermediate though addition of a coordinating base.[59] Several secondary and tertiary trifluoroborate salts were reacted successfully in modest to excellent yield with nitrogen-based nucleophiles, including sulfonamides (**57a**–**57b**), a phosphoramidite, azoles (**57c**–**57d**), carbamates (**57e**), and an acylhydrazide (**57f**).

Summary and Outlook

In this review, we have summarised different methods for the amination of alkylboronic esters. These generally occur through one of three distinct pathways: 1) stereospecific amination through a 1,2-metallate rearrangement, 2) amination through reaction of a nucleophilic boron 'ate' complex, and 3) oxidative coupling reactions. These methods are complementary to each other, and have their own individual strengths and weaknesses.

Methods for amination of boronic esters through 1,2-metallate rearrangement are stereospecific. However, they are predominantly limited to the formation of primary amines.

Amination reactions through reaction of a boron 'ate' complex have been used to form hard to make C-secondary and C-tertiary amines with excellent enantiospecificity. However, the methods are perhaps limited in their functional group tolerance due to the use of an organolithium reagent for activation of the boronic ester.

Finally, oxidative coupling reactions, such as the alkyl Chan-Lam amination, allow the coupling of the widest range nitrogen-containing groups, including amines, amides, sulfonamides and *N*-heteroaryl groups, and exhibit excellent functional group tolerance. However, these reactions have been found to be stereoablative, due to the alkylboron reagent acting as a radical precursor.

Due to the importance of controlled synthesis of amines and nitrogen-containing molecules, we expect further efforts will address some of these limitations, and expand the breadth of products that can be made from alkylboronic esters.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: amines · boron · boronic esters · catalysis · nitrogen

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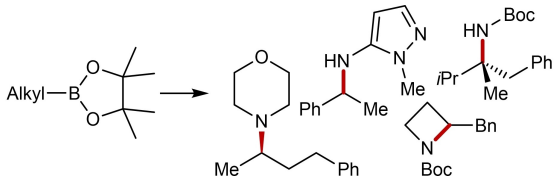
REVIEW



This review explores methods to convert alkylboronic esters into alkyl amines, high value motifs found in bioactive molecules, materials, and catalysts. Three distinct reaction pathways are discussed: amination through 1,2-metallate rearrangements, amination using nucleophilic 'ate' complexes, and alkyl variants of the Chan-Lam reaction.

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