# Cu-Catalysed Coupling of Aliphatic Amines with Alkylboronic Esters

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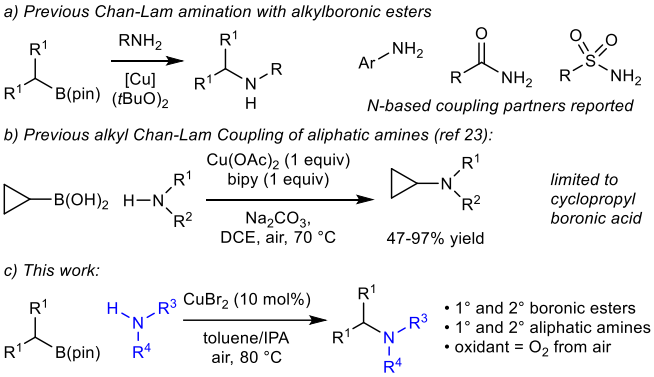
**Abstract**

We report a Cu-catalysed oxidative coupling of aliphatic amines with benzylic and aliphatic boronic esters to give high value alkyl amines, products found widely in applications from medicinal chemistry to materials science. This operationally simple reaction, which can be performed on gram scale, runs under mild conditions and exhibits broad functional group tolerance. The terminal oxidant of the reaction is $O_2$ from the air, avoiding the need for additional chemical oxidants. Investigation into the reaction mechanism suggests that the boronic ester is activated by an aminyl radical, formed through oxidation of the amine by the Cu catalyst, to give a key alkyl radical intermediate. To demonstrate its utility and potential for late-stage functionalization, we showcase the method as the final step in the total synthesis of a TRPV1 antagonist.

**Keywords:** amination, amines, boron, Chan-Lam, copper

Methods to form C-N bonds are of high synthetic value due to the wide prevalence of N-based functional groups in biologically active compounds, functional materials, and catalysts. Advances in transition metal catalysis have made methods to form of $Csp^2$-N bonds become synthetically reliable and routinely used.[1–9] However, perhaps the preparation of alkyl amines is now a greater synthetic challenge.[10] Traditional methods to make alkyl amines, such as alkylation reactions and reductive amination[11,12] often suffer from poor selectivity and the need for protecting group strategies. Other methods to form alkyl amines, such as hydrogenation[13] and biocatalysis[14–16] strategies are excellent particularly for process chemistry applications, but are less easily applied in discovery chemistry settings. A practical and reliable cross coupling method for the formation of alkyl amines is therefore desirable, comparable to versatility of the Buchwald-Hartwig reaction for the formation of aryl amines.[17]

Our approach to this challenge has been to develop an alkyl variant of the Chan-Lam amination, the oxidative coupling of an organoboron reagent with an *N*-based nucleophile. We and others have made some progress in this field (scheme 1),[18–24] but there is room for improvement particularly in the scope of reaction of both amine and boron coupling partners. Herein, we describe conditions for the Cu-catalysed amination of alkylboronic esters with aliphatic amines, coupling partners that have previously been found challenging in alkyl Chan-Lam reactions.[23] Importantly, our method uses $O_2$ from air (at atmospheric pressure) as the terminal oxidant, rather than a peroxide-based oxidant (which may pose an additional safety risk), making the reaction easy to perform.[25]




**Scheme 1:** Previous examples of Chan-Lam amination with alkylboron reagents.

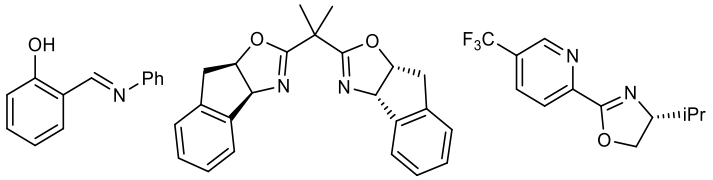
## Discussion:

We initially found that by heating boronic ester **1** with $CuBr_2$ in neat morpholine, amine **2** was formed in quantitative yield (Table 1, entry 1). While this provided proof of concept, it was clear that we needed to reduce the loading of amine and identify a suitable solvent to generate a more general procedure. After investigating a range of Cu-salts and ancillary ligands, we identified that conducting the reaction under air using a combination of $CuBr_2$ and N,O-ligand **L1** in toluene gave amine **2** in high yield (entry 2).[26] While ketone **3** and alcohol **4** side products were also observed, unlike our previous findings[18,27] these were only formed in moderate amounts. A survey of ligands, including chiral ligands **L2** and **L3**, gave little improvement (entry 3-4). Investigation of the reaction solvent led to improved results. While the use of many solvents led to formation of amine **2** in good yield (see SI for more details), amination was not sufficiently selective with ketone **3** and alcohol **4** side products formed in significant levels. The presence of these side products can make product isolation for some substrates challenging, and so more selective conditions are desirable. A 1:1 mixture of toluene/isopropanol was found to give a high yield of amine **2** with minimal oxidation side products (entry 5). Under these conditions, the loading of $CuBr_2$ could be reduced to 10 mol% without loss of yield. However, a compromise is needed between loading of amine and yield of **2** (entries 6-7). A control experiment with $CuBr_2$ but without ligand suggested that the presence of **L1** had minimal effect on the reaction (entry 8). We therefore believe the likely effect of ligands, such as **L1**-**L3**, is to aid solubilisation of $CuBr_2$, rather than generate discrete Cu complexes that act as a catalyst. This perhaps explains why all reactions we have conducted using chiral ligands have generated **2** as a racemate. Other control experiments showed that $CuBr_2$ is required for amination to occur (entry 9). Under an inert atmosphere only trace amounts of amine **2** was formed (entry 10), suggesting that $O_2$ is the terminal oxidant in the reaction. By switching the limiting reagent to morpholine (entry 11), and using an excess of boronic ester **1**, amine **2** was still formed albeit in moderate yield. Finally, our best conditions (entry 8) were successfully performed on gram scale, with amine **2** isolated in excellent yield (scheme 2).

**Table 1:** Evaluation of reaction conditions on the yield of amine **2**.[a]


1 2 3 4

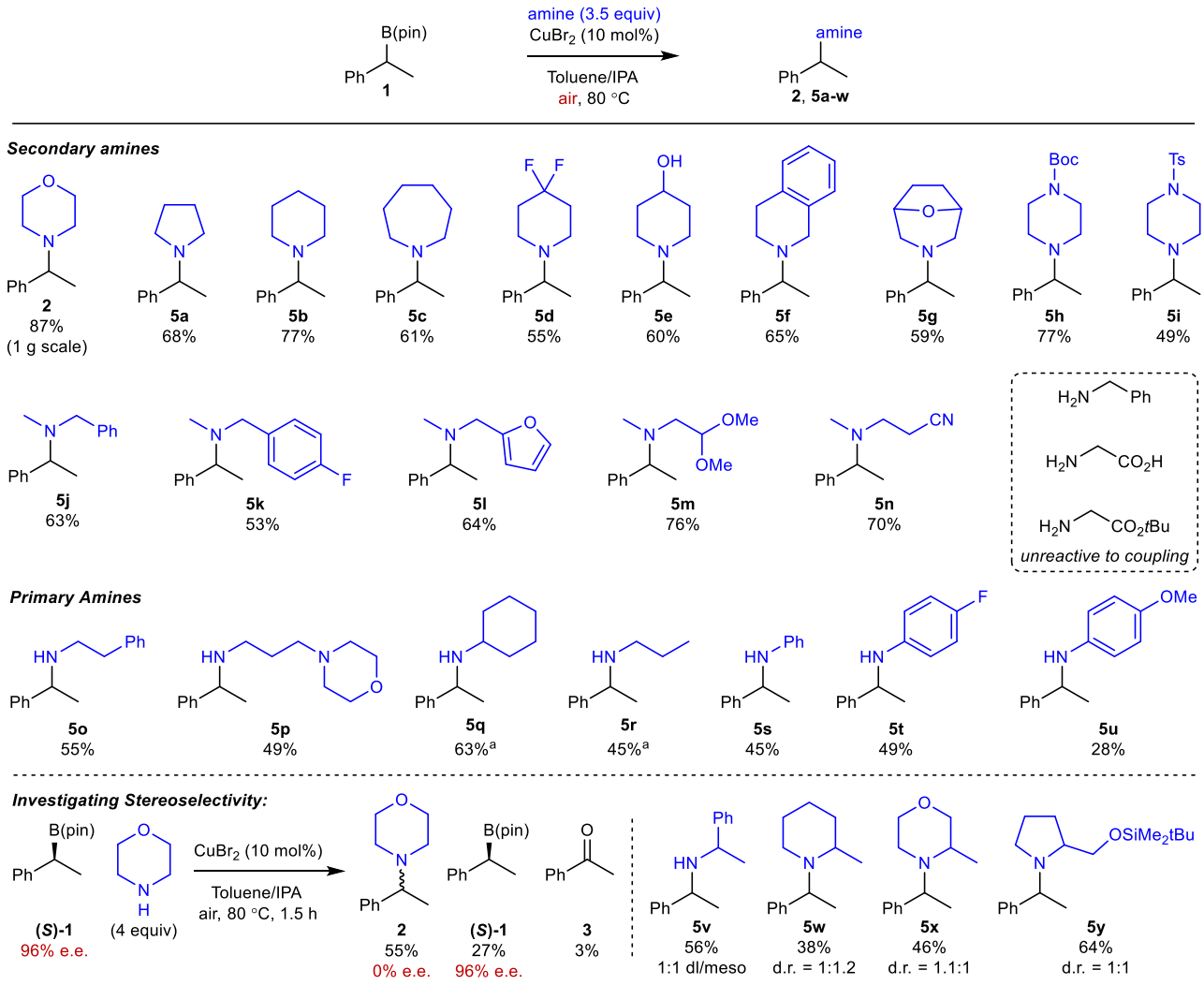
| Entry | $CuBr_2$ mol% | L (mol%) | Amine equiv. | solvent | Yield | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 1 | 2 | 3 | 4 |
| 1[b] | 100 | - | 40 | - | <5% | >95% | <5% | - |
| 2[c] | 25 | L1 (25) | 4 | toluene | <5% | 81% | 9% | 10% |
| 3[d] | 25 | L2 (25) | 40 | - | <5% | 95%[e] | - | - |
| 4[d] | 25 | L3 (25) | 40 | - | <5% | 67%[e] | - | - |
| 5 | 25 | L1 (25) | 4 | toluene/IPA (1:1) | <5% | 95% | <5 | 2% |
| 6 | 10 | L1 (10) | 4 | toluene/IPA (1:1) | <5% | 95% | 3% | - |
| 7 | 10 | L1 (10) | 3 | toluene/IPA (1:1) | <5% | 79% | 6% | - |
| 8 | 10 | - | 3.5 | toluene/IPA (1:1) | <5% | 95% | 0% | - |
| 9 | 0 | - | 3.5 | toluene/IPA (1:1) | <5% | <5% | 4% | 58% |
| 10[b] | 10 | - | 3.5 | toluene/IPA (1:1) | 93% | 3% | 0% | 0% |
| 11[f] | 10 | - | 1 | toluene/IPA (1:1) | 20%[g] | 46% | 35%[g] | 12%[g] |




L1 L2 L3

a) Reactions performed using 0.5 mmol of boronic ester **1** unless otherwise stated. Yields determined by $^1H$ NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. b) reaction carried out under an inert atmosphere. c) reaction carried out at 60 °C. d) reaction carried out at 40 °C. e) formed as a racemate. f) reaction using morpholine as the limiting reagent and 3.5 equivalents of boronic ester **1**. g) yield based on amount of boronic ester **1** instead of the limiting reagent. IPA = isopropyl alcohol.

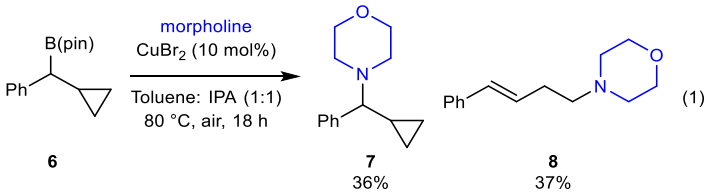
We next looked to explore the scope and limitations of our reaction conditions (scheme 2). Pleasingly, a broad range of secondary amines could be coupled in good to excellent yield with boronic ester **1**. This includes simple cyclic amines such as pyrrolidine, piperidine and azepane (**5a**-**5c**). Substituted piperidines (**5d**-**5e**) and mono-protected piperazines (**5i**-**5k**) were also tolerated well. The coupling of amines of relevance to medicinal chemistry including difluoropiperidine (**5d**)[28] and bicyclic amine (**5h**)[29] was successful. Acyclic secondary amines could also be reacted successfully (**5l**-**5p**), though the yield is typically a slightly lower. Pleasingly, the reaction conditions are also successful when coupling primary aliphatic amines (**5q**-**5s**), the first time these have been reported in an alkyl Chan-Lam reaction with boronic esters. The yield of reactions with these amines are generally lower, which correlates with the lower nucleophilicity of primary versus secondary amines. Anilines can also be successfully coupled (**5t**-**5v**), although the yield is typically lower than with our previously reported conditions.[30] Unfortunately, the coupling of benzylamine, and α-amino acids and esters was not successful. In the case of amino acids (and corresponding ester), presumably coordination of both the carbonyl and amine to Cu leading to inactive complexes. Overall, the process shows excellent functional group tolerance, including groups such as acetals, alcohols, nitriles, sulfonamides and tertiary amines.



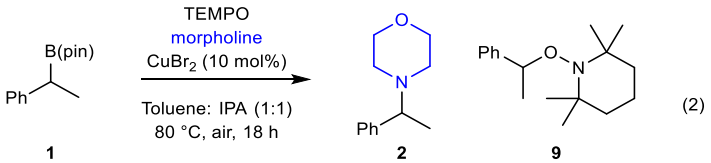

**Scheme 2:** Scope of amines in the amination of boronic ester **1**. Reactions were conducted on a 0.5 mmol scale. Yields reported are of isolated material of the corresponding product unless otherwise stated. a) Yield determined by 1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

We were keen to test the stereoselectivity of the reaction. However, attempts to use enantiomerically enriched boronic ester **(*S*)-1** only resulted in the formation of racemic product. To investigate this further, we stopped the reaction early allowing the isolation of unreacted boronic ester **1**. Chiral HPLC analysis confirmed that the boronic ester had not undergone racemisation under the reaction conditions. Furthermore, we explored whether the reaction is diastereoselective when coupling chiral amines (**5w**-**5z**). In each case, essentially a 1:1 d.r. of the respective product was observed. Attempts to use amines with larger substituents at the 2-position were unsuccessful, presumably due reaching the reaction's limit of steric congestion.

The stereoablative nature of the amination reaction is consistent with the formation of an alkyl radical intermediate. However, we cannot rule out at this stage the formation of an alkyl copper intermediate, which have been reported to be configurationally unstable above −50 °C.[31] To probe the possibility of a radical intermediate, we performed the amination of cyclopropane **6** in a radical clock experiment (eq 1). This resulted in a mixture of two amines, amine **7** with the cyclopropane intact and amine **8** in which the cyclopropane ring has opened. This suggests a radical intermediate is formed, with recombination occurring on a similar timescale to cyclopropane ring opening.[32]




**6** **7** 36% **8** 37%




**1** **2** **9**

TEMPO (0.1 equiv): 77% 10%
TEMPO (1.0 equiv): 10% 73%

To gather further evidence, we performed experiments in which we added TEMPO, known to form adducts with alkyl radicals,[33] to our reaction. Adduct **9** was observed in each case, suggesting that the boronic ester acts as an alkyl radical precursor. When 1 equivalent of TEMPO was used, the major product from the reaction was adduct **9**. However, when 10 mol% of both TEMPO and $CuBr_2$ were added, amine **2** still was formed in high yield along with 10% of adduct **9**. This suggests that TEMPO does not irreversibly inhibit the copper catalyst.

While formation of alkyl radicals from alkylboronic esters has been previously reported, this typically requires prior formation of a boron 'ate' complex through coordination of an alkoxide, pyridine or aryl lithium.[34–38] However, such an 'ate' complex was not observed by $^{1}H$ or $^{11}B$ NMR spectroscopy when analysing mixtures of boronic ester **1** with morpholine in the presence of isopropanol.[26]

To investigate this further, we conducted a series of cyclic voltammetry experiments. Boronic ester **1** showed a high oxidation potential ($E_{on}$ >1.44 V) in MeCN (figure 1a).[39] The voltammogram of $CuBr_2$ does not change in the presence of the boronic ester, suggesting there is not a direct interaction between **1** and the Cu salt. However, cyclic voltammetry of a mixture of morpholine and **1** does show the formation of a new peak (oxidation potential of $E_{pc}$ = 1.25 V; figure 1b). Given that this is greater than the oxidation potential of morpholine ($E_{pc}$ = 0.81 V), we suggest this could arise from a new species generated upon interaction of **1** and a morpholine radical, which can be oxidised at a lower potential than the boronic ester without activation. Aminyl radicals have been reported to react with trialkylboranes[40–42] and alkylboronic esters[43,44] leading to the formation of alkyl radicals.

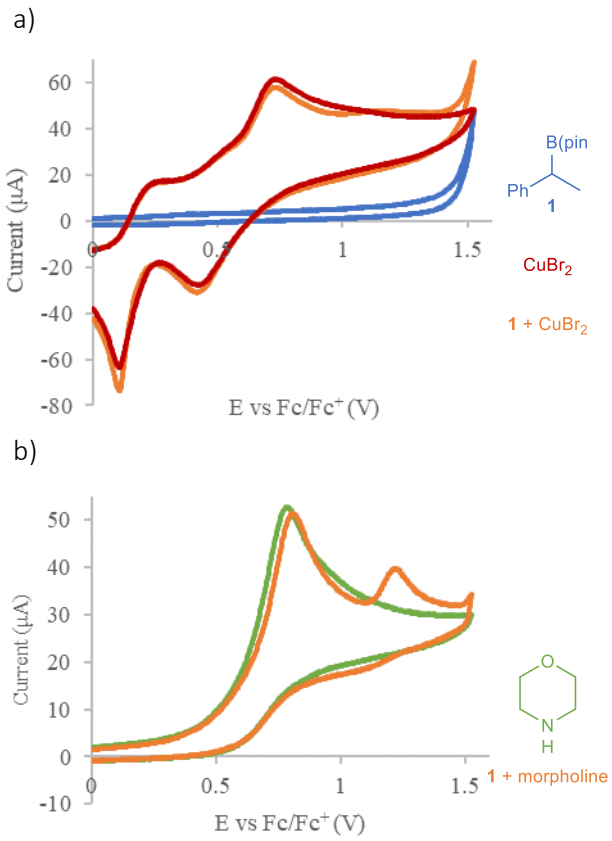



**Figure 1:** Cyclic voltammetry experiments, conducted in MeCN under $N_2$ using $n$Bu$_4$NPF$_6$ as the electrolyte, of a) boronic ester **1** and $CuBr_2$, and b) boronic ester **1** and morpholine.

To further understand the nature of the radical intermediates formed during the amination reaction, EPR studies were performed using 5,5-dimethyl-1-pyrroline N-oxide (DMPO) as a spin trap. Analysis of a solution of $CuBr_2$ in toluene:IPA (1:1) showed an intense, broad EPR signal at around 3150 G. This signal did not change upon addition of boronic ester **1** suggesting that the electronic structure of Cu does not change in the presence of the boronic ester. This is consistent with the cyclic voltammetry data above (Figure 1a). When a mixture of morpholine and $CuBr_2$ was analysed, a different EPR signal was observed, presumably in part due to ligation of morpholine to Cu (Figure S1). When $CuBr_2$ with morpholine, or $CuBr_2$ with boronic ester **1**, samples were measured in the presence of DMPO, the Cu(II) EPR signal disappears, presumably due to reduction of Cu(II) to Cu(I) (Figure S2). Reduction and regeneration of the Cu(II) signals are observed in the reaction mixtures of $CuBr_2$ with morpholine, or $CuBr_2$ with boronic ester **1** and morpholine, even in the absence of DMPO (Figure S3). However, this process is slow (Figure S3). This implies that Cu(II) reduction and regeneration is part of the catalytic cycle and this process is enhanced in the presence of DMPO (Figure S2). No DMPO-adduct signals were detected for $CuBr_2$ with boronic ester **1** (Figure 2A, red trace). However, for $CuBr_2$ with morpholine a new signal is observed (Figure 2A, black trace) which increases steadily with time (Figure 2B). This spectrum is consistent with literature data for aminyl-radical adducts of DMPO.[45] When a mixture of $CuBr_2$ with morpholine and boronic ester **1** was measured with DMPO, complex EPR spectra were observed due to multiple DMPO-adducts (Figure 2C).[46,47] We could model the spectra as a mixture of three components (Figure S4): (1) a DMPO-morpholine radical adduct, with the same parameters as the species found in the absence **1**, and which is the dominant species (2) a carbon-centred DMPO-R adduct, and (3) an unknown radical with triplet-of-doublets spectrum that increases for more than 12 hours. The spectrum of this unknown radical is possibly due to decomposition of the primary DMPO-adducts, but is not consistent with the oxidation product DMPOX which is often seen in DMPO spin trapping experiments.[48] While the exact identity of the DMPO-R species cannot be uniquely determined from this data, a benzylic radical would be consistent with the TEMPO-trapping experiment above (eq 2).

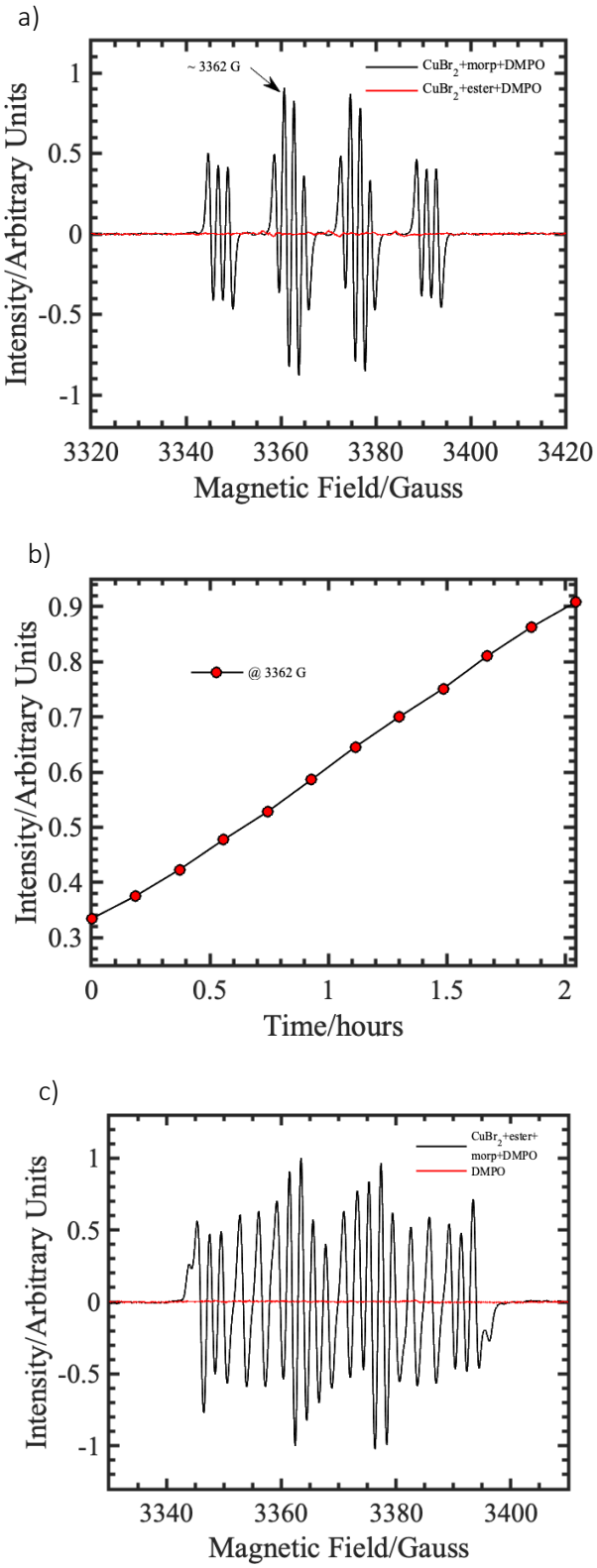
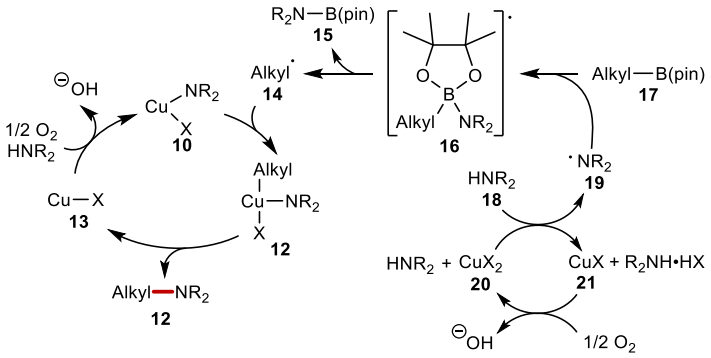



**Figure 2:** Data from EPR experiments, performed in solutions of toluene:IPA (1:1) at 80 °C.a) EPR spectra for $CuBr_2$ + morpholine + DMPO (black trace) and $CuBr_2$ + boronic ester **1** + DMPO (red trace); b) Plot of EPR signal intensity at 3362 G versus time for a solution of $CuBr_2$ + morpholine + DMPO; c) EPR spectra of a mixture of $CuBr_2$ + morpholine + boronic ester **1** + DMPO collected ~ 100 minutes after mixing (black trace) and of DMPO (red trace) as a negative control.

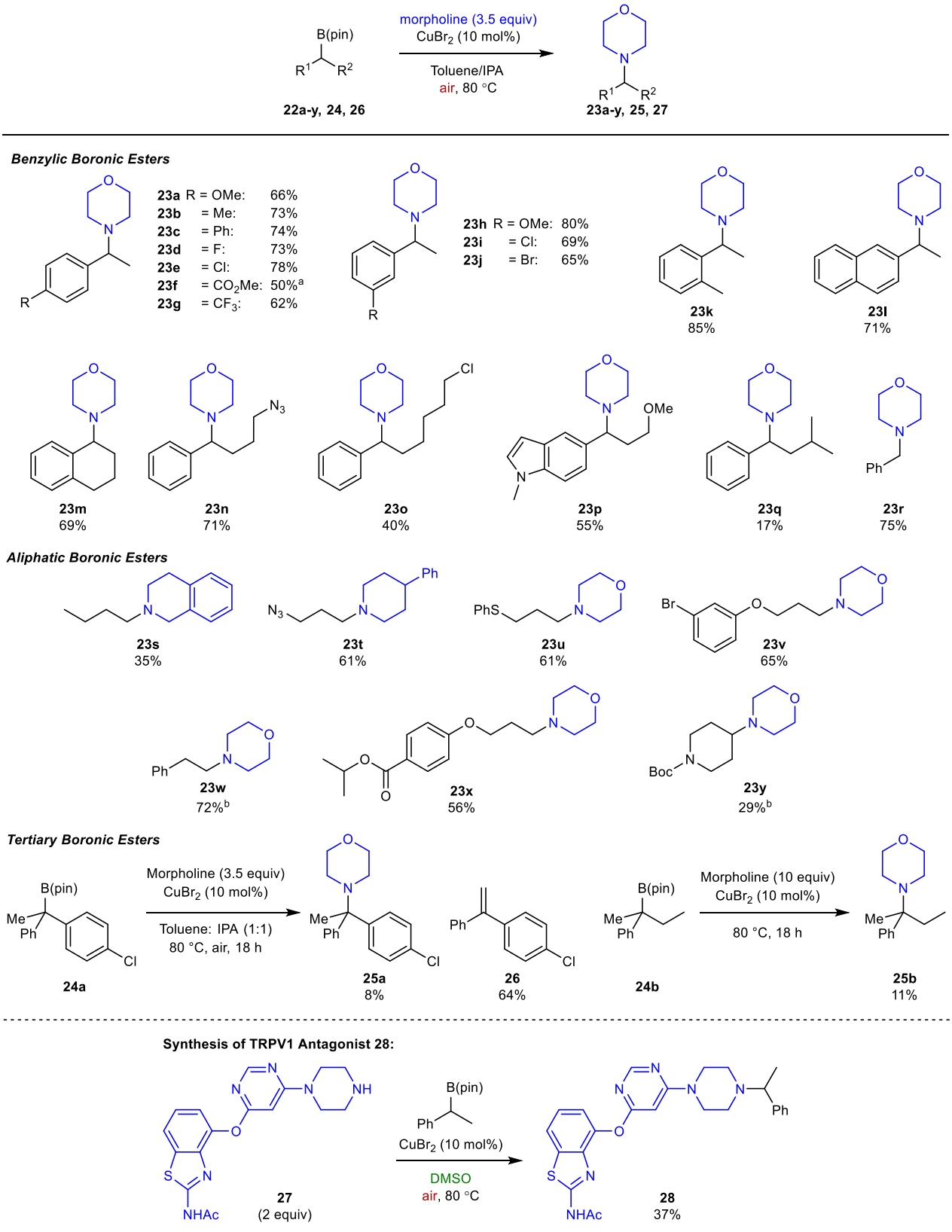
Based on the experimental data above, we tentatively propose a reaction mechanism outlined in Scheme 3. This involves oxidation of the amine **18** by a Cu(II) complex **20**,[49] to generate an aminyl radical **19** and Cu(I) complex **21**. Aminyl radical **19** can then combine with alkylboronic ester **17** to give intermediate **16**, which can undergo homolytic bond cleavage to generate alkyl radical **14** and boronate **15**. The alkyl radical **14** can

then combine with an amino Cu(II) complex **10**, leading to a Cu(III) complex **12** that can undergo reductive elimination to give the alkyl amine product **12** and a Cu(I) complex **13**. Re-oxidation of Cu(I) complexes **13** and **21** by $O_2$ from air regenerates Cu(II) complexes **10** and **20** respectively. The fact that two equivalents of amine are consumed in the proposed mechanism presumably explains why the yield of amination is reduced with lower amine loadings or when the amine is the limiting reagent. Further investigations into elucidating this complex reaction mechanism are ongoing.




**Scheme 3:** Proposed mechanism for Cu-catalysed amination reaction.

We have also explored the scope of reaction with respect to the boronic ester (scheme 4). A range of secondary benzylic boronic esters were successfully reacted with morpholine in good to excellent yield. Varying the electronics of the substitutes on the aryl ring of the boronic ester did not lead to great variation in yield. However, the reaction of boronic esters with more electron donating MeO- (**23a**) or electron withdrawing $CF_3$- (**23g**) substituents showed a small reduction in yield, in part to a small increase in corresponding alcohol and ketone side products observed in the crude reaction mixture. Methyl ester-containing boronic ester was also successfully reacted (**23f**), though a change of reaction solvent to PrOAc was made to avoid formation of the corresponding isopropyl ester trans-esterification side product, which was observed when using the standard IPA/toluene solvent system. However, the yield of amination is reduced compared with our standard conditions, in part due to larger quantities of alcohol and ketone side products observed when using the alternative reaction solvent. Importantly, aryl bromides and chlorides (**23e, 23i, 23j, 23v**) were tolerated, with no products from Ullmann-Goldberg amination observed. In addition, functional groups including azides, ethers and indole were also tolerated. Pleasingly, an alkyl chloride was also tolerated, with no products of amination through nucleophilic substitution observed in the reaction mixture (**23o**). A primary benzylic boronic ester was also successfully coupled in high yield (**23r**).




**Scheme 4:** Scope of amination with respect to the boronic ester substrate. Reactions were conducted using 0.5 mmol of boronic ester unless otherwise stated. Yields reported are of isolated material of the corresponding product. [a] Using PrOAc as reaction solvent instead of IPA/Toluene. [b] Yield determined by 1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

The amination reaction was also successful with primary and secondary aliphatic boronic esters. Primary alkylboronic esters could be coupled (**23s**-**23x**) in good yield, though with slightly reduced efficiency compared with benzylic boronic esters. While less reactive still, we could also form the amination product **23y** from a secondary aliphatic boronic ester.

Subjecting tertiary boronic esters **24a** and **24b** to our reaction conditions did lead to formation of a C-tertiary amines **25a** and **25b**, albeit in lower yield compared to our previous results when coupling anilines.[30] In reaction of **24a**, the corresponding alkene **25** was formed as the major product from the mixture. Unfortunately, tert-butyl boronic ester was found to be unreactive under these reaction conditions.

Finally, we wanted to apply our amination reaction as the final step in the synthesis of a complex molecule, to simulate how the method could be used in a discovery chemistry scenario. We targeted amine **28**, a TRVP1 inhibitor which is a potential treatment for chronic pain.[52] Due to the poor solubility of **27** in most organic solvents, we required the use of DMSO as reaction solvent in which **27** was partially soluble. Despite this, and without further optimisation, amine **28** could be isolated successfully, and in a yield that would allow the material to be tested for its biological activity. We therefore believe our method could find application in settings such as medicinal chemistry, and allow chemists to develop structure-activity relationships through the coupling of a common advanced amine or boronic ester intermediates.

**Conclusions:**

In conclusion, we have developed conditions for the Cu-catalyzed amination of alkylboronic esters with aliphatic amines. This method expands the scope of the alkyl Chan-Lam reaction, enabling, the coupling of both primary and secondary alkyl amines with aliphatic boronic esters for the first time. Of note, the method uses oxygen from air as the terminal oxidant for the reaction, without need for additional chemical oxidants. The reaction conditions tolerate a broad range of functional groups, and have been applied successfully as the final step in the synthesis of a TRVP1 inhibitor. Mechanistic studies suggest that the reaction proceeds via an alkyl radical intermediate, generated from the boronic ester upon activation by an aminyl radical. The investigation of related Cu-catalyzed oxidative couplings of alkylboron reagents is ongoing, and will be reported in due course.

**Acknowledgements:**

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**References:**

(1) Heravi, M. M.; Kheilkordi, Z.; Zadsirjan, V.; Heydari, M.; Malmir, M. Buchwald-Hartwig Reaction: An Overview. *J. Organomet. Chem.* **2018**, *861*, 17–104. https://doi.org/https://doi.org/10.1016/j.jorganchem.2018.02.023.

(2) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116* (19), 12564–12649. https://doi.org/10.1021/acs.chemrev.6b00512.

(3) Beletskaya, I. P.; Cheprakov, A. V. The Complementary Competitors: Palladium and Copper in C–N Cross-Coupling Reactions. *Organometallics* **2012**, *31* (22), 7753–7808. https://doi.org/10.1021/om300683c.

(4) Qiao, J. X.; Lam, P. Y. . Copper-Promoted Carbon-Heteroatom Bond Cross-Coupling with Boronic Acids and Derivatives. *Synthesis (Stuttg).* **2011**, No. 6, 829–856. https://doi.org/10.1055/s-0030-1258379.

(5) Monnier, F.; Taillefer, M. Copper-Catalyzed C(Aryl)–N Bond Formation. In *Topics in Organometallic Chemistry*; Taillefer, M., Ma, D., Eds.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2013; pp 173–

204. https://doi.org/10.1007/3418_2013_69.

(6) Munir, I.; Zahoor, A. F.; Rasool, N.; Naqvi, S. A. R.; Zia, K. M.; Ahmad, R. Synthetic Applications and Methodology Development of Chan–Lam Coupling: A Review. *Mol. Divers.* **2019**, *23* (1), 215–259. https://doi.org/10.1007/s11030-018-9870-z.

(7) West, M. J.; Fyfe, J. W. B.; Vantourout, J. C.; Watson, A. J. B. Mechanistic Development and Recent Applications of the Chan–Lam Amination. *Chem. Rev.* **2019**, *119* (24), 12491–12523. https://doi.org/10.1021/acs.chemrev.9b00491.

(8) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. Copper Catalysed Ullmann Type Chemistry: From Mechanistic Aspects to Modern Development. *Chem. Soc. Rev.* **2014**, *43* (10), 3525–3550. https://doi.org/10.1039/C3CS60289C.

(9) Monnier, F.; Taillefer, M. Catalytic C□C, C□N, and C□O Ullmann-Type Coupling Reactions. *Angew. Chemie Int. Ed.* **2009**, *48* (38), 6954–6971. https://doi.org/10.1002/anie.200804497.

(10) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. *Chem. Rev.* **2020**, *120* (5), 2613–2692. https://doi.org/10.1021/acs.chemrev.9b00462.

(11) Abdel-Magid, A. F.; Mehrman, S. J. A Review on the Use of Sodium Triacetoxyborohydride in the Reductive Amination of Ketones and Aldehydes. *Org. Process Res. Dev.* **2006**, *10* (5), 971–1031. https://doi.org/10.1021/op0601013.

(12) Afanasyev, O. I.; Kuchuk, E.; Usanov, D. L.; Chusov, D. Reductive Amination in the Synthesis of Pharmaceuticals. *Chem. Rev.* **2019**, *119* (23), 11857–11911. https://doi.org/10.1021/acs.chemrev.9b00383.

(13) Cabré, A.; Verdaguer, X.; Riera, A. Recent Advances in the Enantioselective Synthesis of Chiral Amines via Transition Metal-Catalyzed Asymmetric Hydrogenation. *Chem. Rev.* **2022**, *122* (1), 269–339. https://doi.org/10.1021/acs.chemrev.1c00496.

(14) Patil, M. D.; Grogan, G.; Bommarius, A.; Yun, H. Oxidoreductase-Catalyzed Synthesis of Chiral Amines. *ACS Catal.* **2018**, *8* (12), 10985–11015. https://doi.org/10.1021/acscatal.8b02924.

(15) Simić, S.; Zukić, E.; Schmermund, L.; Faber, K.; Winkler, C. K.; Kroutil, W. Shortening Synthetic Routes to Small Molecule Active Pharmaceutical Ingredients Employing Biocatalytic Methods. *Chem. Rev.* **2022**, *122* (1), 1052–1126. https://doi.org/10.1021/acs.chemrev.1c00574.

(16) Sangster, J. J.; Marshall, J. R.; Turner, N. J.; Mangas-Sanchez, J. New Trends and Future Opportunities in the Enzymatic Formation of C−C, C−N, and C−O Bonds. *ChemBioChem* **2022**, *23* (6), e202100464. https://doi.org/https://doi.org/10.1002/cbic.202100464.

(17) Campos, K. R.; Coleman, P. J.; Alvarez, J. C.; Dreher, S. D.; Garbaccio, R. M.; Terrett, N. K.; Tillyer, R. D.; Truppo, M. D.; Parmee, E. R. The Importance of Synthetic Chemistry in the Pharmaceutical Industry. *Science (80-. ).* **2019**, *363* (6424), eaat0805. https://doi.org/10.1126/science.aat0805.

(18) Grayson, J. D.; Dennis, F. M.; Robertson, C. C.; Partridge, B. M. Chan–Lam Amination of Secondary and Tertiary Benzylic Boronic Esters. *J. Org. Chem.* **2021**, *86* (14), 9883–9897. https://doi.org/10.1021/acs.joc.1c00976.

(19) Mori-Quiroz, L. M.; Shimkin, K. W.; Rezazadeh, S.; Kozlowski, R. A.; Watson, D. A. Copper-Catalyzed Amidation of Primary and Secondary Alkyl Boronic Esters. *Chem. Eur. J.* **2016**, *22* (44), 15654–15658. https://doi.org/10.1002/chem.201603677.

(20) Racine, E.; Monnier, F.; Vors, J.-P.; Taillefer, M. Direct N-Cyclopropylation of Secondary Acyclic Amides Promoted by Copper. *Chem. Commun.* **2013**, *49* (67), 7412–7414. https://doi.org/10.1039/C3CC42575D.

(21) Sueki, S.; Kuninobu, Y. Copper-Catalyzed N - and O -Alkylation of Amines and Phenols Using Alkylborane Reagents. *Org. Lett.* **2013**, *15* (7), 1544–1547. https://doi.org/10.1021/ol400323z.

(22) Kim, D. S.; Lee, H. G. Formation of the Tertiary Sulfonamide C(Sp3)–N Bond Using Alkyl Boronic Ester via Intramolecular and Intermolecular Copper-Catalyzed Oxidative Cross-Coupling. *J. Org. Chem.* **2021**, *86* (23), 17380–17394. https://doi.org/10.1021/acs.joc.1c01759.

(23) Bénard, S.; Neuville, L.; Zhu, J. Copper-Promoted N-Cyclopropylation of Anilines and Amines by Cyclopropylboronic Acid. *Chem. Commun.* **2010**, *46* (19), 3393–3395. https://doi.org/10.1039/B925499D.

(24) Singh, K.; Kumar, M.; Pavadai, E.; Naran, K.; Warner, D. F.; Ruminski, P. G.; Chibale, K. Synthesis of New Verapamil Analogues and Their Evaluation in Combination with Rifampicin against Mycobacterium Tuberculosis and Molecular Docking Studies in the Binding Site of Efflux Protein Rv1258c. *Bioorg. Med. Chem. Lett.* **2014**, *24* (14), 2985–2990. https://doi.org/https://doi.org/10.1016/j.bmcl.2014.05.022.

(25) A video showing our reaction set up and tips to help solve problems can be viewed at: https://digitalmedia.sheffield.ac.uk/id/1_isl6hrng

(26) For more information, see the supporting information.

(27) Grayson, J. D.; M. Partridge, B. Mild Cu-Catalyzed Oxidation of Benzylic Boronic Esters to Ketones. *ACS Catal.* **2019**, *9* (5), 4296–4301. https://doi.org/10.1021/acscatal.9b00992.

(28) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61* (14), 5822–5880. https://doi.org/10.1021/acs.jmedchem.7b01788.

(29) Zask, A.; Kaplan, J.; Verheijen, J. C.; Richard, D. J.; Curran, K.; Brooijmans, N.; Bennett, E. M.; Toral-Barza, L.; Hollander, I.; Ayral-Kaloustian, S.; Yu, K. Morpholine Derivatives Greatly Enhance the Selectivity of Mammalian Target of Rapamycin (MTOR) Inhibitors. *J. Med. Chem.* **2009**, *52* (24), 7942–7945. https://doi.org/10.1021/jm901415x.

(30) Grayson, J. D.; Dennis, F. M.; Robertson, C. C.; Partridge, B. M. Chan–Lam Amination of Secondary and Tertiary Benzylic Boronic Esters. *J. Org. Chem.* **2021**, *86* (14), 9883–9897. https://doi.org/10.1021/acs.joc.1c00976.

(31) Skotnitzki, J.; Morozova, V.; Knochel, P. Diastereoselective Copper-Mediated Cross-Couplings between Stereodefined Secondary Alkylcoppers with Bromoalkynes. *Org. Lett.* **2018**, *20* (8), 2365–2368. https://doi.org/10.1021/acs.orglett.8b00699.

(32) Halgren, T. A.; Roberts, J. D.; Horner, J. H.; Martinez, F. N.; Tronche, C.; Newcomb, M. Kinetics and Equilibrium Constants for Reactions of α-Phenyl-Substituted Cyclopropylcarbinyl Radicals. *J. Am. Chem. Soc.* **2000**, *122* (13), 2988–2994. https://doi.org/10.1021/ja991114h.

(33) Bagryanskaya, E. G.; Marque, S. R. A. Scavenging of Organic C-Centered Radicals by Nitroxides. *Chem. Rev.* **2014**, *114* (9), 5011–5056. https://doi.org/10.1021/cr4000946.

(34) Lima, F.; Kabeshov, M. A.; Tran, D. N.; Battilocchio, C.; Sedelmeier, J.; Sedelmeier, G.; Schenkel, B.; Ley, S. V. Visible Light Activation of Boronic Esters Enables Efficient Photoredox C(Sp 2 )-C(Sp 3 ) Cross-Couplings in Flow. *Angew. Chemie Int. Ed.* **2016**, *55* (45), 14085–14089. https://doi.org/10.1002/anie.201605548.

(35) Lennox, A. J. J.; Nutting, J. E.; Stahl, S. S. Selective Electrochemical Generation of Benzylic Radicals Enabled by Ferrocene-Based Electron-Transfer Mediators. *Chem. Sci.* **2018**, *9* (2), 356–361. https://doi.org/10.1039/C7SC04032F.

(36) Corcé, V.; Ollivier, C.; Fensterbank, L. Boron{,} Silicon{,} Nitrogen and Sulfur-Based Contemporary Precursors for the Generation of Alkyl Radicals by Single Electron Transfer and Their Synthetic

Utilization. *Chem. Soc. Rev.* **2022**, *51* (4), 1470–1510. https://doi.org/10.1039/D1CS01084K.

(37) Shu, C.; Noble, A.; Aggarwal, V. K. Photoredox-Catalyzed Cyclobutane Synthesis by a Deboronative Radical Addition–Polar Cyclization Cascade. *Angew. Chemie Int. Ed.* **2019**, *58* (12), 3870–3874. https://doi.org/https://doi.org/10.1002/anie.201813917.

(38) Pillitteri, S.; Ranjan, P.; Van der Eycken, E. V; Sharma, U. K. Uncovering the Potential of Boronic Acid and Derivatives as Radical Source in Photo(Electro)Chemical Reactions. *Adv. Synth. Catal.* **2022**, *n/a* (n/a). https://doi.org/https://doi.org/10.1002/adsc.202200204.

(39) MeCN was used as a solvent to enable solubility of the $n$Bu$_4$NPF$_6$ electrolyte, which was insoluble in toluene/IPA (1:1). When the standard reaction was performed using MeCN as solvent, amination was successful with amine **2** formed in 78% yield. See the supporting information for details.

(40) Davies, A. G.; Hook, S. C. W.; Roberts, B. P. Homolytic Displacement at a Metal Centre by the Dimethylamino Radical. *J. Organomet. Chem.* **1970**, *22* (3), c37–c38. https://doi.org/https://doi.org/10.1016/S0022-328X(00)87698-6.

(41) Davies, A. G.; Hook, S. C. W.; Roberts, B. P. The Reaction of N-Chlorodimethylamine with Tributylborane and with Dibutyl(Dimethylamino) Borane. *J. Organomet. Chem.* **1970**, *23* (1), C11–C13. https://doi.org/https://doi.org/10.1016/S0022-328X(00)92783-9.

(42) Sharefkin, J. G.; Banks, H. D. The Reaction of Organoboranes with N-Chlorodialkylamines. A New Synthesis of Primary Alkyl Chlorides from Olefins by Hydroboration. *J. Org. Chem.* **1965**, *30* (12), 4313–4314. https://doi.org/10.1021/jo01023a506.

(43) Speckmeier, E.; Maier, T. C. ART–An Amino Radical Transfer Strategy for C(Sp 2 )–C(Sp 3 ) Coupling Reactions, Enabled by Dual Photo/Nickel Catalysis. *J. Am. Chem. Soc.* **2022**, *144* (22), 9997–10005. https://doi.org/10.1021/jacs.2c03220.

(44) Wang, Z.; Wierich, N.; Zhang, J.; Daniliuc, C. G.; Studer, A. Alkyl Radical Generation from Alkylboronic Pinacol Esters through Substitution with Aminyl Radicals. *J. Am. Chem. Soc.* **2023**, *145* (16), 8770–8775. https://doi.org/10.1021/jacs.3c01129.

(45) Chen, C.; Veregin, R. P.; Harbour, J. R.; Hair, M. L.; Issler, S. L.; Tromp, J. Photochemistry of Zinc Oxide in Heptane: Detection by Oxygen Uptake and Spin Trapping. *J. Phys. Chem.* **1989**, *93* (6), 2607–2609. https://doi.org/10.1021/j100343a071.

(46) Buettner, G. R. Spin Trapping: ESR Parameters of Spin Adducts 1474 1528V. *Free Radic. Biol. Med.* **1987**, *3* (4), 259–303. https://doi.org/https://doi.org/10.1016/S0891-5849(87)80033-3.

(47) Huang, Z.; Shanmugam, M.; Liu, Z.; Brookfield, A.; Bennett, E. L.; Guan, R.; Vega Herrera, D. E.; Lopez-Sanchez, J. A.; Slater, A. G.; McInnes, E. J. L.; Qi, X.; Xiao, J. Chemical Recycling of Polystyrene to Valuable Chemicals via Selective Acid-Catalyzed Aerobic Oxidation under Visible Light. *J. Am. Chem. Soc.* **2022**, *144* (14), 6532–6542. https://doi.org/10.1021/jacs.2c01410.

(48) Bilski, P.; Reszka, K.; Bilska, M.; Chignell, C. F. Oxidation of the Spin Trap 5,5-Dimethyl-1-Pyrroline N-Oxide by Singlet Oxygen in Aqueous Solution. *J. Am. Chem. Soc.* **1996**, *118* (6), 1330–1338. https://doi.org/10.1021/ja952140s.

(49) Kauffmann, T.; Albrecht, J.; Berger, D.; Legler, J. "Dimerization" of Organic Nitrogen Compounds via Copper-Containing Intermediates. *Angew. Chemie Int. Ed. English* **1967**, *6* (7), 633–634. https://doi.org/https://doi.org/10.1002/anie.196706331.

(50) Sorin, G.; Martinez Mallorquin, R.; Contie, Y.; Baralle, A.; Malacria, M.; Goddard, J.-P.; Fensterbank, L. Oxidation of Alkyl Trifluoroborates: An Opportunity for Tin-Free Radical Chemistry. *Angew. Chemie Int. Ed.* **2010**, *49* (46), 8721–8723. https://doi.org/10.1002/anie.201004513.

(51) Lane, C. F. The Reaction between Trialkylboranes and Copper(II) Salts. An Unusual Electron-Transfer Oxidation-Reduction. *J. Organomet. Chem.* **1971**, *31* (3), 421–431.

https://doi.org/https://doi.org/10.1016/S0022-328X(00)86250-6.

(52) Wang, H.-L.; Katon, J.; Balan, C.; Bannon, A. W.; Bernard, C.; Doherty, E. M.; Dominguez, C.; Gavva, N. R.; Gore, V.; Ma, V.; Nishimura, N.; Surapaneni, S.; Tang, P.; Tamir, R.; Thiel, O.; Treanor, J. J. S.; Norman, M. H. Novel Vanilloid Receptor-1 Antagonists: 3. The Identification of a Second-Generation Clinical Candidate with Improved Physicochemical and Pharmacokinetic Properties. *J. Med. Chem.* **2007**, *50* (15), 3528–3539. https://doi.org/10.1021/jm070191h.