Cu-Catalysed Coupling of Aliphatic Amines with Alkylboronic Esters

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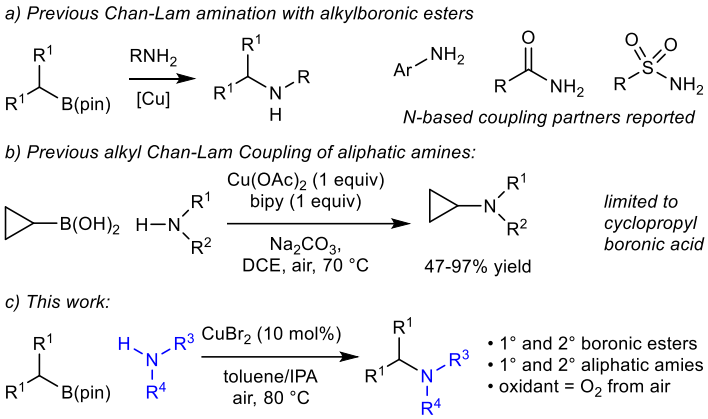
Abstract

We report a Cu-catalysed oxidative coupling of aliphatic amines with alkylboronic 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 excellent 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 the intermediacy of an alkyl radical, generated from the boronic ester upon activation through an amino radical transfer process. To demonstrate its utility and potential for late-stage functionalization, we showcase the method as the final step in the total synthesis of a TRPV 1 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, 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 the is room for improvement particularly in the scope of reaction to both amine and boron coupling partners. Herein, we describe conditions for the Chan-Lam amination of alkylboronic esters with aliphatic amines, coupling partners that have previously been found challenging in alkyl Chan-Lam reactions. Importantly, our method uses O_2 from air (at atmospheric pressure) as the terminal oxidant, rather than a peroxide-based oxidant, reducing the risk and making the reaction easy to perform.[25]

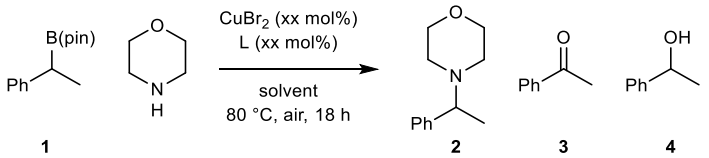


Scheme 1: Previous examples of Chan-Lam amination with alkylboron reagents.

Discussion:

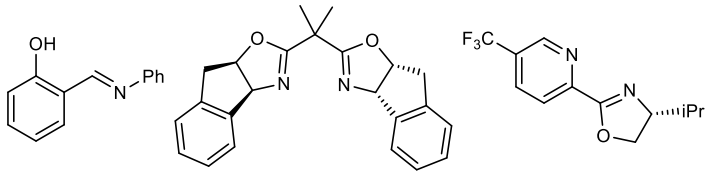
We initially found that by heating boronic ester **1** with $CuBr_2$ in neat morpholine, amine **2** was formed in quantitative yield (Table 1, entry 1). While this provided proof of concept, it was clear that we needed to reduce the loading of amine and identify a suitable solvent to generate a more 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 modest 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, with a 1:1 mixture of toluene/isopropanol giving 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 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 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

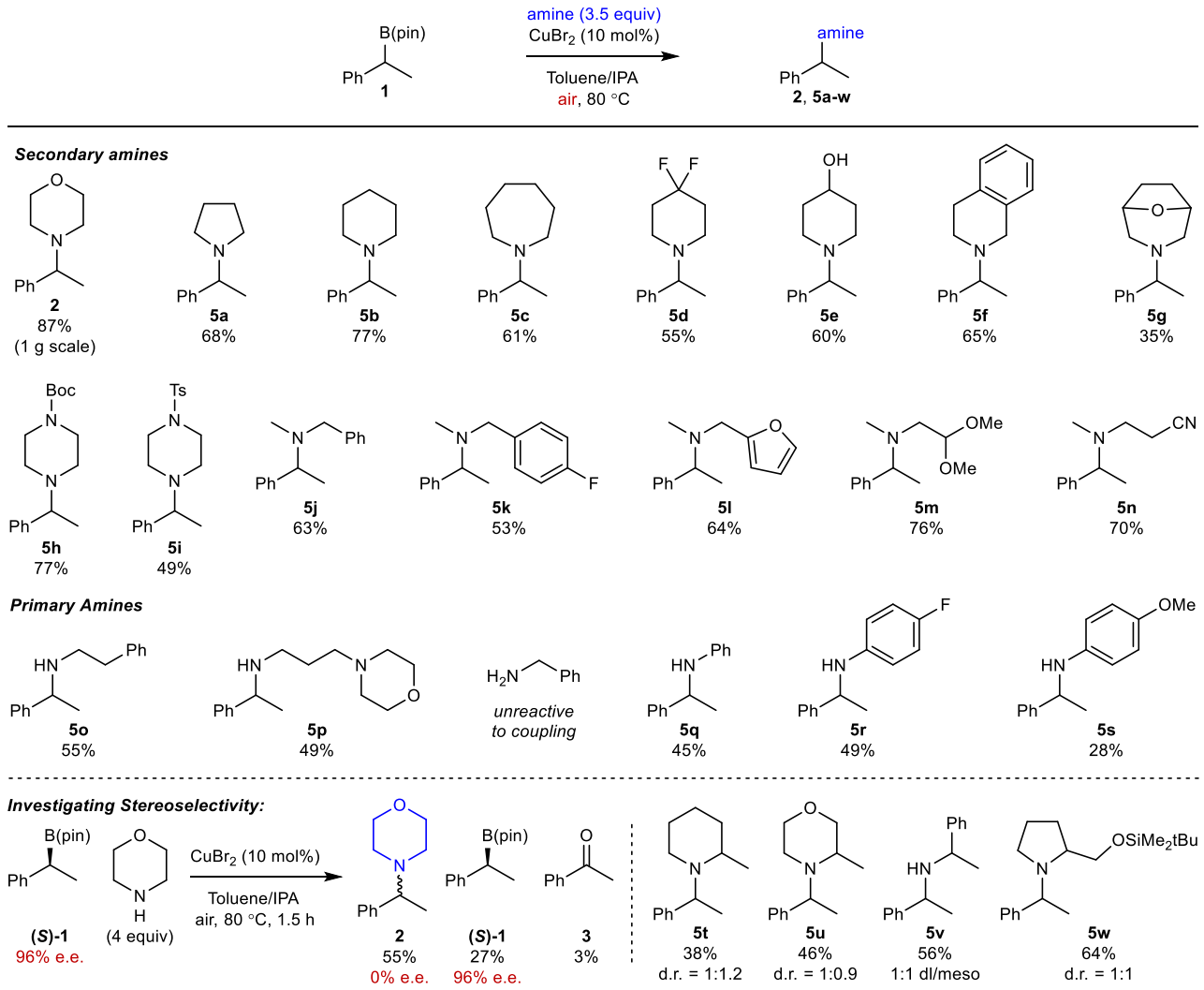
Entry	$CuBr_2$ mol%	L (mol%)	Amine equiv.	solvent	Yield			
					1	2	3	4
1[b]	100	-	40	-	<5%	>95%	<5%	-
2[c]	25	L1 (25)	4	toluene	<5%	81%	9%	10%
3[d]	25	L2 (25)	40	-	<5%	95%[e]	-	-
4[d]	25	L3 (25)	40	-	<5%	67%[e]	-	-
5	25	L1 (25)	4	toluene/IPA (1:1)	<5%	95%	<5	2%
6	10	L1 (10)	4	toluene/IPA (1:1)	<5%	95%	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.

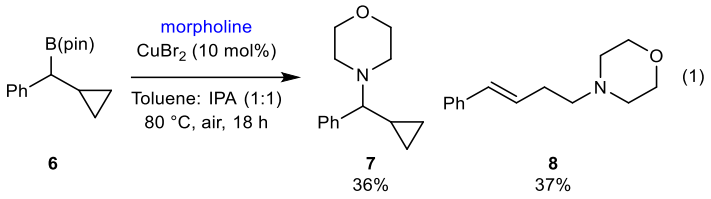
We next looked to explore the scope and limitations of our reaction conditions (scheme 2). Pleasingly, a broad range of secondary amines could be coupled in good to excellent yield with boronic ester **1**. This includes simple cyclic amines such as pyrrolidine, piperidine and azepane (**5a**-**5c**). Substituted piperidines (**5d**-**5e**) and mono-protected piperazines (**5i**-**5k**) were also tolerated well. The coupling of amines of particular relevance to medicinal chemistry including fluoropiperidine (**5d**)[28] and bicyclic amine (**5h**),[29] albeit in low yield, 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. However, the coupling of benzylamine was not successful. 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**), however the yield is typically lower than with our previously reported conditions.[30] Overall, the process shows excellent functional group tolerance, including groups such as acetals, alcohols, nitriles, and sulfonamides.



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.

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 a radical intermediate. However, we cannot rule out at this stage the formation of an alkyl copper intermediate, which are thought 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]



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.[33–37] 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).[38] 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. This type of interaction was recently proposed by Speckmeier and Maier[39] as a way to generate alkyl radicals from alkyl boronic esters. While the mechanism of this oxidation is currently unclear, given the reduction potential of O_2 has been estimated as +1.21 V (in MeCN)[40] it should be feasible under aerobic conditions our reaction. Further investigations into elucidating this complex reaction mechanism are ongoing.

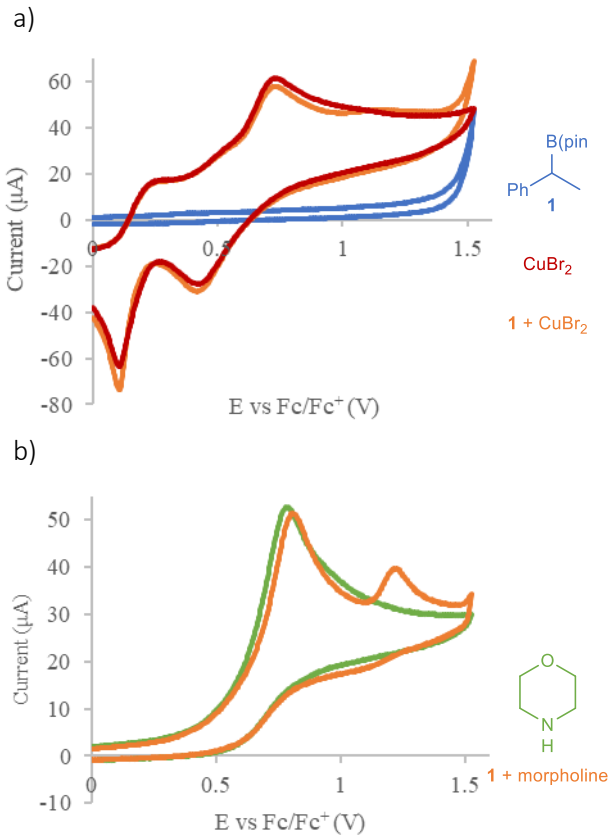
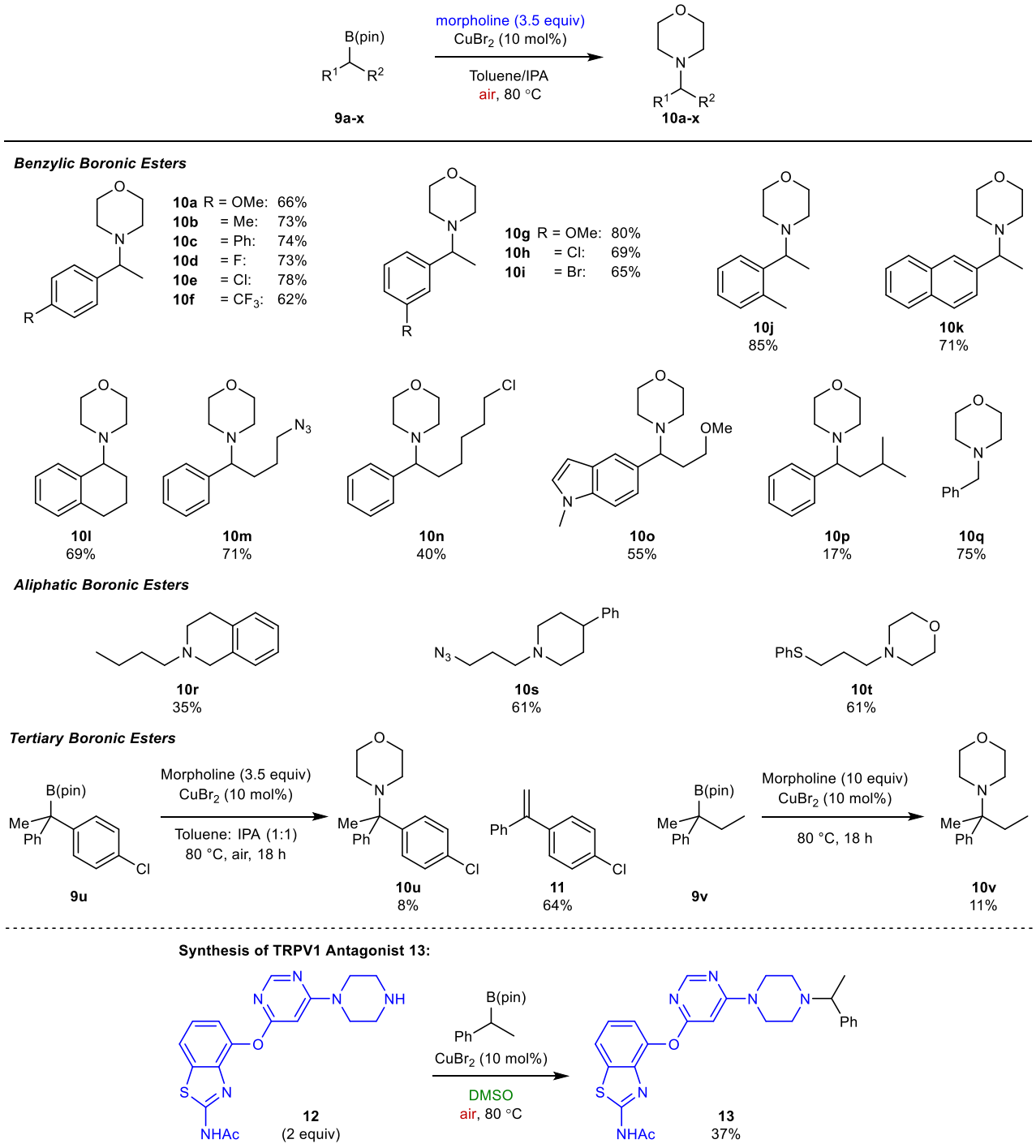


Figure 1: Cyclic voltammetry experiments, conducted in MeCN under N_2, of a) boronic ester **1** and $CuBr_2$, and b) boronic ester **1** and morpholine.

We have also explored the scope of reaction with respect to the boronic ester (scheme 3). A range of secondary 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 terms of yield. However, the more electron donating MeO- (**10a**) and electron withdrawing CF_3- (**10f**) groups 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. Importantly, aryl bromides and chlorides (**10e, 10h, 10i**) 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 (**10n**). A primary benzylic boronic ester was also successfully coupled in high yield (**10q**).



Scheme 3: Scope of amination with respect to the boronic ester substrate. Reactions were conducted on a 0.5 mmol scale. Yields reported are of isolated material of the corresponding product.

We could extend the amination reaction to aliphatic boronic esters. In particular, primary boronic esters could be coupled successfully (**10r**-**10u**), though the efficiency of the reaction is slightly reduced compared with benzylic boronic esters.

Subjecting tertiary boronic esters **9v** and **9w** to our reaction conditions did lead to formation of a C-tertiary amines **10v** and **10w**, albeit in lower yield compared to our previous results when coupling anilines.[30] In reaction of **9v**, the corresponding alkene **11** was formed as the major product from the mixture.

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 **13**, a TRVP 1 inhibitor which is a potential treatment for chronic pain.[41] Due to the poor solubility of **12** in most organic solvents, we required the use of DMSO as reaction solvent in which **12** was partially soluble. Despite this, and without further optimisation, amine **13** 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-catalysed Chan-Lam amination of alkylboronic esters with aliphatic amines. This method expands the scope to the coupling of both primary and secondary amines, and uses oxygen from air as the terminal oxidant for the reaction. The reaction conditions tolerate a broad range of functional groups, and have been applied successfully to the synthesis of a TRVP 1 inhibitor. Mechanistic studies suggest that the reaction proceeds via an alkyl radical intermediate, generated from the boronic ester upon activation through an amino radical transfer process. The investigation of related Cu-catalysed oxidative couplings of alkylboron reagents is ongoing, and will be reported in due course.

Acknowledgements:

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References:

[1] M. M. Heravi, Z. Kheilkordi, V. Zadsirjan, M. Heydari, M. Malmir, *J. Organomet. Chem.* **2018**, *861*, 17–104.

[2] P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649.

[3] I. P. Beletskaya, A. V Cheprakov, *Organometallics* **2012**, *31*, 7753–7808.

[4] J. X. Qiao, P. Y. . Lam, *Synthesis (Stuttg).* **2011**, 829–856.

[5] F. Monnier, M. Taillefer, in *Top. Organomet. Chem.* (Eds.: M. Taillefer, D. Ma), Springer Berlin Heidelberg, Berlin, Heidelberg, **2013**, pp. 173–204.

[6] I. Munir, A. F. Zahoor, N. Rasool, S. A. R. Naqvi, K. M. Zia, R. Ahmad, *Mol. Divers.* **2019**, *23*, 215–259.

[7] M. J. West, J. W. B. Fyfe, J. C. Vantourout, A. J. B. Watson, *Chem. Rev.* **2019**, *119*, 12491–12523.

[8] C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev.* **2014**, *43*, 3525–3550.

[9] F. Monnier, M. Taillefer, *Angew. Chemie Int. Ed.* **2009**, *48*, 6954–6971.

[10] A. Trowbridge, S. M. Walton, M. J. Gaunt, *Chem. Rev.* **2020**, *120*, 2613–2692.

[11] A. F. Abdel-Magid, S. J. Mehrman, *Org. Process Res. Dev.* **2006**, *10*, 971–1031.

[12] O. I. Afanasyev, E. Kuchuk, D. L. Usanov, D. Chusov, *Chem. Rev.* **2019**, *119*, 11857–11911.

[13] A. Cabré, X. Verdaguer, A. Riera, *Chem. Rev.* **2022**, *122*, 269–339.

[14] M. D. Patil, G. Grogan, A. Bommarius, H. Yun, *ACS Catal.* **2018**, *8*, 10985–11015.

[15] S. Simić, E. Zukić, L. Schmermund, K. Faber, C. K. Winkler, W. Kroutil, *Chem. Rev.* **2022**, *122*, 1052–1126.

[16] J. J. Sangster, J. R. Marshall, N. J. Turner, J. Mangas-Sanchez, *ChemBioChem* **2022**, *23*, e202100464.

[17] K. R. Campos, P. J. Coleman, J. C. Alvarez, S. D. Dreher, R. M. Garbaccio, N. K. Terrett, R. D. Tillyer, M. D. Truppo, E. R. Parmee, *Science (80-.).* **2019**, *363*, eaat0805.

[18] J. D. Grayson, F. M. Dennis, C. C. Robertson, B. M. Partridge, *J. Org. Chem.* **2021**, *86*, 9883–9897.

[19] L. M. Mori-Quiroz, K. W. Shimkin, S. Rezazadeh, R. A. Kozlowski, D. A. Watson, *Chem. - A Eur. J.* **2016**, *22*, 15654–15658.

[20] E. Racine, F. Monnier, J.-P. Vors, M. Taillefer, *Chem. Commun.* **2013**, *49*, 7412–7414.

[21] S. Sueki, Y. Kuninobu, *Org. Lett.* **2013**, *15*, 1544–1547.

[22] D. S. Kim, H. G. Lee, *J. Org. Chem.* **2021**, *86*, 17380–17394.

[23] S. Bénard, L. Neuville, J. Zhu, *Chem. Commun.* **2010**, *46*, 3393–3395.

[24] K. Singh, M. Kumar, E. Pavadai, K. Naran, D. F. Warner, P. G. Ruminski, K. Chibale, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2985–2990.

[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] J. D. Grayson, B. M. Partridge, *ACS Catal.* **2019**, *9*, 4296–4301.

[28] N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880.

[29] A. Zask, J. Kaplan, J. C. Verheijen, D. J. Richard, K. Curran, N. Brooijmans, E. M. Bennett, L. Toral-Barza, I. Hollander, S. Ayral-Kaloustian, K. Yu, *J. Med. Chem.* **2009**, *52*, 7942–7945.

[30] J. D. Grayson, F. M. Dennis, C. C. Robertson, B. M. Partridge, *J. Org. Chem.* **2021**, *86*, 9883–9897.

[31] J. Skotnitzki, V. Morozova, P. Knochel, *Org. Lett.* **2018**, *20*, 2365–2368.

[32] T. A. Halgren, J. D. Roberts, J. H. Horner, F. N. Martinez, C. Tronche, M. Newcomb, *J. Am. Chem. Soc.* **2000**, *122*, 2988–2994.

[33] F. Lima, M. A. Kabeshov, D. N. Tran, C. Battilocchio, J. Sedelmeier, G. Sedelmeier, B. Schenkel, S. V Ley, *Angew. Chemie Int. Ed.* **2016**, *55*, 14085–14089.

[34] A. J. J. Lennox, J. E. Nutting, S. S. Stahl, *Chem. Sci.* **2018**, *9*, 356–361.

[35] V. Corcé, C. Ollivier, L. Fensterbank, *Chem. Soc. Rev.* **2022**, *51*, 1470–1510.

[36] C. Shu, A. Noble, V. K. Aggarwal, *Angew. Chemie Int. Ed.* **2019**, *58*, 3870–3874.

[37] S. Pillitteri, P. Ranjan, E. V Van der Eycken, U. K. Sharma, *Adv. Synth. Catal.* **2022**, *n/a*, DOI https://doi.org/10.1002/adsc.202200204.

[38] MeCN was used as a solvent solubilise the electrolyte. 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.

[39] E. Speckmeier, T. C. Maier, *J. Am. Chem. Soc.* **2022**, DOI 10.1021/jacs.2c03220.

[40] M. L. Pegis, J. A. S. Roberts, D. J. Wasylenko, E. A. Mader, A. M. Appel, J. M. Mayer, *Inorg. Chem.* **2015**, *54*, 11883–11888.

[41] H.-L. Wang, J. Katon, C. Balan, A. W. Bannon, C. Bernard, E. M. Doherty, C. Dominguez, N. R. Gavva, V. Gore, V. Ma, N. Nishimura, S. Surapaneni, P. Tang, R. Tamir, O. Thiel, J. J. S. Treanor, M. H. Norman, *J. Med. Chem.* **2007**, *50*, 3528–3539.