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Mild Cu-Catalyzed Oxidation Of Benzylic Boronic Esters To Ketones

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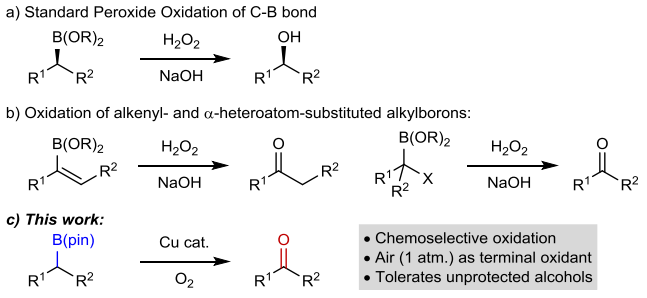
ABSTRACT: The oxidation of benzylic boronic esters directly to the ketone is reported. This mild Cu-catalyzed method uses an ambient atmosphere of air as the terminal oxidant and is notably chemoselective. Oxidation of the C-B bond occurs selectively, even in the presence of unprotected alcohols. Initial investigation suggests the reaction proceeds through an alkylboron to Cu transmetallation, peroxide formation, and rearrangement to give the carbonyl.

KEYWORDS: Boron, catalysis, copper, ketones, oxidation

Organoboron reagents are versatile synthetic building blocks used in a broad range of applications from medicinal chemistry to materials science.[1] Recent advances mean that alkylboronic esters can be readily prepared and transformed through a growing number of C-C and C-heteroatom bond-forming processes.[2] Oxidation of such boronic esters using basic H_2O_2 to give the corresponding alcohol is widely used (Scheme 1),[3] including in the synthesis of complex natural products.[4] If access to the carbonyl in one step is desired,[5] oxidation of either an alkenyl- or α-heteroatom-substituted alkylboron is required. However, respectively these reagents are susceptible to protodeboronation and are often non-trivial to prepare. The oxidation of alkylboronic acids to the carboxylic acid has been achieved using chromic acid.[6] However, mild and direct conditions for boronic ester-to-carbonyl oxidation are desirable to increase functional group tolerance and improve sustainability.

Herein, we report a mild Cu-catalyzed oxidation of alkylboronic esters. This highly functional group tolerant reaction oxidizes the C-B bond selectively to give the corresponding carbonyl, using air as the terminal oxidant. Furthermore, oxidation of the boronic ester is highly chemoselective, even in the presence of unprotected alcohols. Our method therefore complements other chemoselective oxidation methods, including Wacker oxidation[7] and the selective oxidation of primary,[8] secondary[9] and benzylic alcohols.[10]

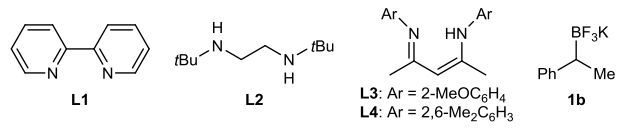


Scheme 1: Oxidation of alkylboronic esters. pin = pinacol.

As part of ongoing investigations into the transformation of alkylboronic esters, we evaluated the effect of various conditions on the oxidation of benzylic boronic ester **1a**. Initial findings showed that **1a** could be oxidized to give a mixture of ketone **2** and alcohol **3** in the presence of $Cu(OAc)_2$, bipyridine (**L1**) and aniline under air at ambient pressure (Table 1, entry 1). Key to the efficient formation of **2** was the use of a solvent mixture of MeCN, AcOH and pyridine.[11-13] Evaluation of other ligands in place of **L1** showed that dinitrogen ligands best promoted ketone formation (entries 2-4). Diamine **L2** gave **2** in high yield alongside **3** as a side product. Though the yield of **2** was lower when using diimine ligands **L3** and **L4**, these reactions selectively gave ketone **2** with only traces of alcohol **3** observed. The absence of aniline from the reaction mixture had a negative effect when using **L2** (entry 5) but a beneficial effect when using **L3** (entry 6). Pleasingly, the loading of both $Cu(OAc)_2$ and **L3** could be lowered, and the temperature decreased to 60 °C (entry 7). Presumably, at lower temperatures, decomposition of **1a** through protodeboronation is reduced, leading to a higher yield of **2**, even at substoichiometric catalyst loadings. A catalyst loading of 20 mol% was chosen as it gave consistently high yields across a range of substrates. Finally, the reaction could be run in the absence of molecular sieves without decrease in yield (entry 8). Reaction of trifluoroborate salt **1b** under these conditions gave **2** selectively, but in low yield (entry 9).

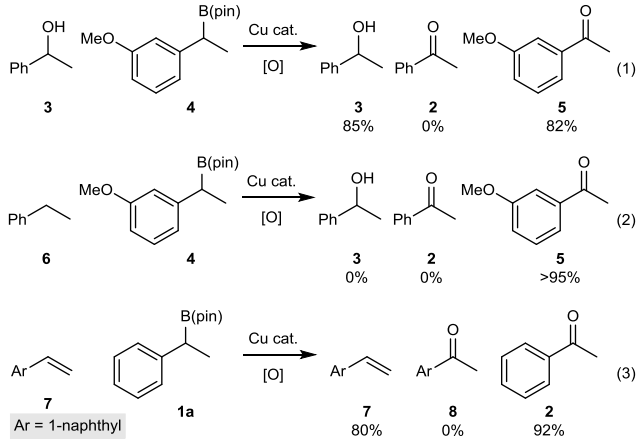
Table 1. Evaluation of Reaction Conditions[a]

Entry	L	Catalyst loading[b]	Additive (equiv.)	T (°C)	Yield of **2**[c]	Yield of **3**[c]
1	**L1**	100 mol%	aniline (2)	80	47%	2%
2	**L2**	100 mol%	aniline (2)	80	77%	8%
3	**L3**	100 mol%	aniline (2)	80	64%	<5%
4	**L4**	100 mol%	aniline (2)	80	61%	<5%
5	**L2**	100 mol%	-	80	33%	<5%
6	**L3**	100 mol%	-	80	70%	<5%
7	**L3**	15 mol%	-	60	74%	<5%
8[d]	**L3**	20 mol%	-	60	96%	<5%
9[d,e]	**L3**	20 mol%	-	60	34%	<5%

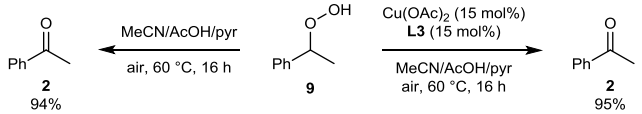


[a] Reactions conducted using 0.05 mmol of **1a**. [b] Loading of both $Cu(OAc)_2$ and ligand (1:1 ratio). [c] Determined by ^1H NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard. [d] Without 4 Å MS. [e] Reaction using **1b** in place of **1a**. pyr = pyridine, MS = molecular sieves.

Intrigued by the mechanism of ketone formation, we performed several competition experiments (see equations 1-3). We considered the possibility of sequential oxidation of the boronic ester to the alcohol and then ketone, given the precedent of Cu-catalyzed oxidation of alcohols.[14] To test this, a 1:1 mixture of boronic ester **4** and alcohol **3** were subjected to our standard oxidation conditions (eq 1). ^1H NMR analysis of the crude showed that boronic ester **4** had been oxidized to ketone **5** but alcohol **3** was recovered unreacted. Also, subjecting alcohol **3** to the reaction conditions in the absence of boronic ester, resulted in recovery of **3**.[12] This suggests that sequential oxidation of the boronic ester to the ketone, via the alcohol, does not occur. Similar competition experiments with ethylbenzene (eq 2) and 2-vinylnaphthalene (eq 3) also gave selective oxidation of the boronic ester to ketone. This suggests that the reaction does not proceed through either protodeboronation followed by benzylic oxidation[15] or elimination then Wacker oxidation.[7]

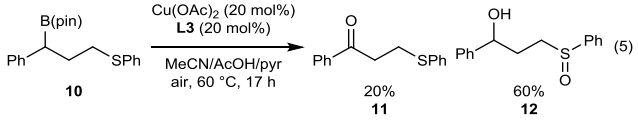


Next, we hypothesized that a peroxide may be an intermediate in the reaction. Peroxide **9** was independently prepared, and subjected to both our reaction conditions and the solvent mixture without catalyst (Scheme 2). In both cases ketone **2** was formed in high yield. This suggests that while the Cu-catalyst may be required to form a peroxide, breakdown of the peroxide to the ketone is mediated by a mixture of pyridine and acetic acid, presumably through an E2-like elimination process.[16]

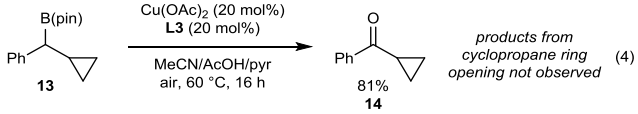


Scheme 2. Reaction of peroxide **9**. Yields determined by ^1H NMR analysis of the crude reaction using 1,3,5-trimethoxybenzene as an internal standard.

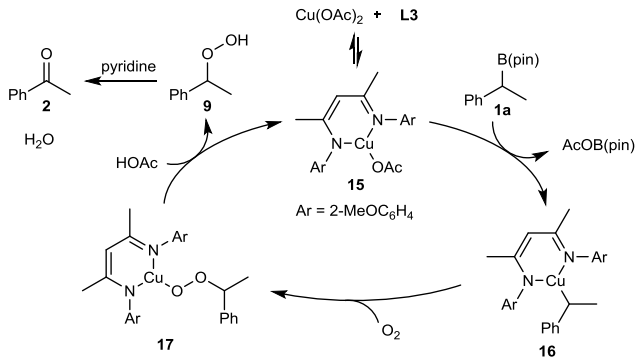
In an attempt to trap a peroxide intermediate *in situ*, boronic ester **10** was prepared with a sulfide group that could act as a reductant. Under our oxidation conditions, **10** reacted to give a mixture of ketone **11** and alcohol **12** (eq 5). The presence of both the alcohol and sulfoxide groups in alcohol **12** provides strong evidence that a peroxide is formed during the reaction pathway.



Next, we performed a radical clock experiment using cyclopropyl boronic ester **13** to test if a radical mechanism was under operation (eq 4). Ketone **14** was isolated in 81% yield, with possible products from opening of the cyclopropane not observed by either mass spectrometry or NMR analysis of the crude mixture. This suggests that peroxide formation is unlikely to occur through the combination of O_2 with a benzylic radical intermediate (potentially formed through either homolytic C-B bond cleavage or H-abstraction alpha to B). Instead, we propose that B-to-Cu transmetallation[17] leads to an alkyl Cu(II) species, that can combine with O_2 to form a peroxide.[15e] Presumably, initial binding of O_2 to Cu occurs through an η^1-end-on coordination due to steric congestion at Cu.[18] However, the process of insertion of O_2 into the Cu-C bond requires further study.



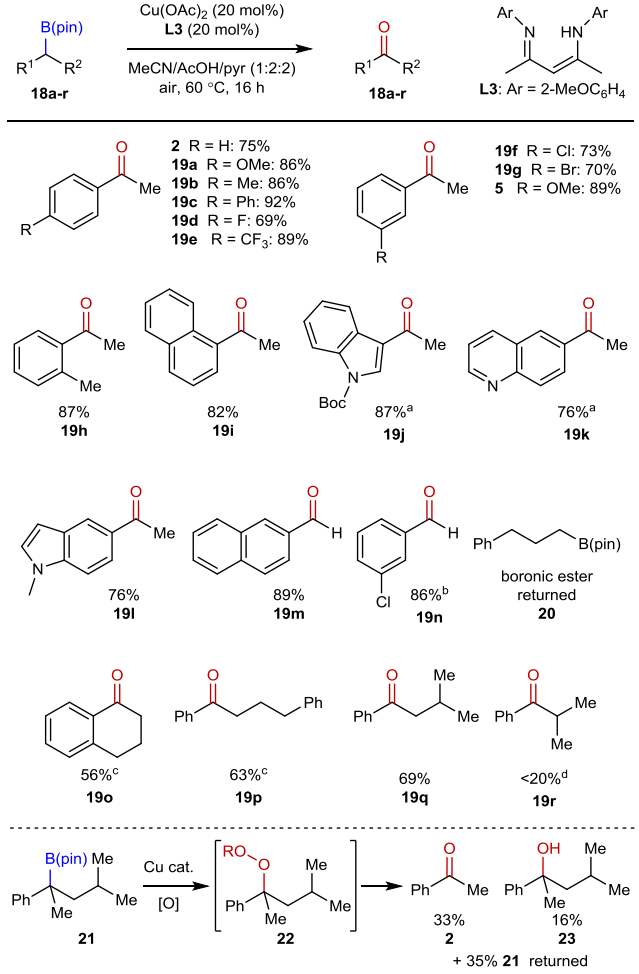
Given these results, we propose the following reaction mechanism (Scheme 3). Cu complex **15**, which forms through ligation of **L3** with $Cu(OAc)_2$, facilitates B-to-Cu transmetallation to give intermediate **16**. The combination of O_2 with **16** leads to the formation of a peroxide species **17**, which can be protonated by AcOH to form peroxide **9** and regenerate Cu complex **15**. Ketone **2** is formed through pyridine-mediated elimination of peroxide **9**.



Scheme 3. Proposed mechanism for the Cu-catalyzed oxidation reaction.

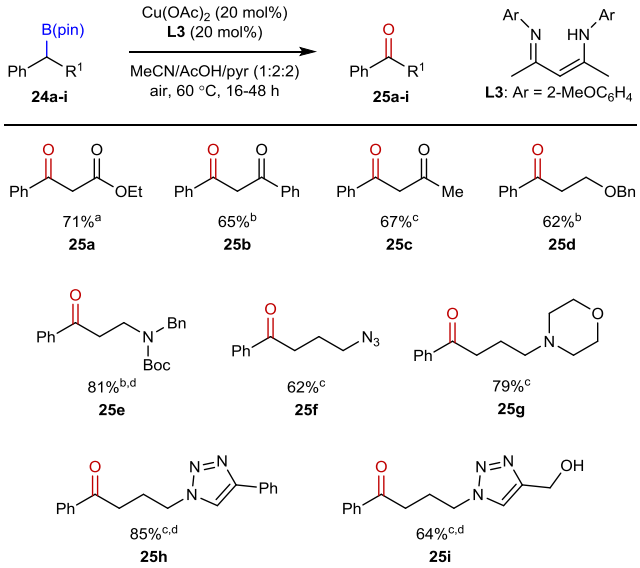
Scheme 4 presents the oxidation of various benzylic boronic esters. The reaction was found to be mild and functional group tolerant. Compatible functionality includes aryl halide, methyl ether, and trifluoromethyl groups. Steric hindrance from ortho-methyl (**19h**) and 1-naphthyl (**19i**) groups is tolerated without issue. Heterocycle-containing boronic esters were also oxidized successfully (**18j**-**18l**). Primary benzylic boronic esters reacted to give the corresponding aldehyde (**19m-n**). However, a current limitation is that non-benzylic boronic esters do

not react, with primary alkylboronic ester **20** returned unreacted. The alkyl chain could be extended beyond Me, with tetralone (**19o**), phenylpropyl (**19p**) and isobutyl chains tolerated (**19q**). The more sterically hindered isopropyl-substituted boronic ester **18r** reacted slowly, with 10-20% of **19r** observed after 72 h. Reaction of tertiary boronic ester **21** under our conditions proceeded, albeit slowly. The products, acetophone and alcohol **23**, were presumably formed through decomposition of alkylperoxide **22**.[19]



Scheme 4. Oxidation of various alkylboronic esters. Reactions were conducted on a 0.60 mmol scale. Yields reported are of isolated material. [a] Reaction conducted on a 0.30 mmol scale. [b] Reaction conducted on a 0.05 mmol, and the yield determined by ^{1}H NMR analysis of the crude reaction using 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction time of 48 h. [d] Reaction time of 72 h.

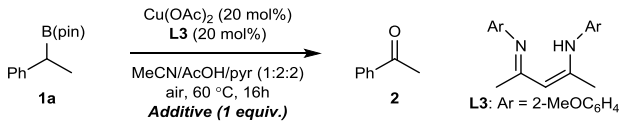
We next explored the reaction of more complex boronic esters (Scheme 5). Boronic esters containing ester (**24a**), ketone (**24b-24c**), and ether (**24d**) functionality reacted in good yield. Nitrogen functionality is also tolerated, as shown by substrates containing Boc-protected amine (**25e**), azide (**25f**), morpholine (**25g**) and triazole groups (**25h**). Reaction of boronic ester **24i** demonstrates that oxidation of the C-B bond occurs selectively, even in the presence of an unprotected alcohol. Some substrates did require longer reaction times to achieve good conversion.

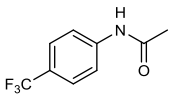


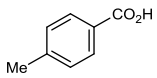
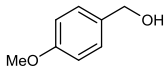
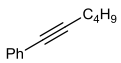
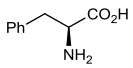
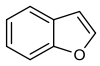
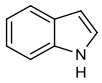
Scheme 5. Oxidation of difunctional alkylboronic esters, with the newly formed ketone highlighted in red. Reactions were conducted on a 0.60 mmol scale. Yields reported are of isolated material. [a] Reaction time of 24 h. [b] Reaction time of 48 h. [c] Reaction time of 16 h. [d] 0.30 mmol scale.

To further explore the compatibility of our method, we oxidized boronic ester **1a** in the presence of a variety of additives (Table 2).[20] Pleasingly, the conditions were compatible with secondary amine, amide, carboxylic acid, aldehyde and alcohol functionality without decrease in yield of ketone **2** and a ≥80% recovery of the additive (entries 1-6). In the cases of benzaldehyde and anisyl alcohol, no oxidation of the additive to the corresponding benzoic acid was observed by NMR or mass spectroscopy analysis. Alkynes are also tolerated (entries 7 and 8). In the presence of phenyl acetylene, oxidation of **1a** preceded in high yield but the additive was returned in only 46%. In comparison, the yield of **2** was reduced to 67% in the presence of 1-phenyl-1-hexyne, despite the alkyne being returned unreacted. An amino acid reduced the efficiency of oxidation, with significant portion of starting material **1a** returned (entry 9). The corresponding Fmoc-protected amino acid was compatible, albeit with small amount of additive decomposition (entry 10). Styrene oxide did not interfere with the oxidation reaction but decomposed under the reaction conditions (entry 11). The heterocycles benzofuran and indole were also found to be compatible without significant decrease in yield of **2** (entries 12 and 13).

Table 2. Examining Functional Group Compatibility[a]

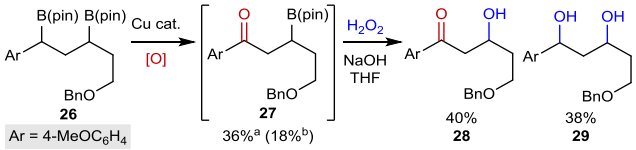


Entry	Additive	Yield of **2**[b]	Returned **1a**[b]	Returned Additive[b]
1		85%	0%	84%
2		85%	0%	90%

3		79%	0%	80%
4		88%	0%	80%
5		82%	0%	83%
6		83%	0%	46%
7		67%	0%	86%
8		35%	52%	3%
9	Fmoc-Phe-OH	74%	0%	59%
10		91%	0%	0%
11		72%	9%	84%
12		82%	0%	90%

[a] Reactions conducted using 0.05 mmol of **1a** and 0.05 mmol of additive. [b] Values reported are the average of 3 experiments, and determined by ^{1}H NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard.

Finally, we trialed 1,3-diboronic ester **26** under our oxidation conditions (Scheme 6). We found that the benzylic boronic ester was selectively oxidized to give ketone **27** in 36% yield after 16 h. Unfortunately, decomposition of **27** over time led to a reduced yield and prohibited extending the reaction time. Although **27** could be isolated, to more accurately determine the mass balance after Cu-catalyzed oxidation, the crude mixture was subjected to oxidation using basic H_2O_2. This gave both ketone **28** and diol **29**, formed from the remaining diboronic ester **26**. This shows that unlike homologation chemistry,[21] the regioselectivity of our method appears to be dictated by the electronics of the C-B bond undergoing functionalization rather than the steric environment at boron.



Scheme 6. Cu-catalyzed oxidation of 1,3-diboronic ester **26**. Cu cat. conditions: $Cu(OAc)_2$ (20 mol%), **L3** (20 mol%), MeCN/AcOH/pyr (1:2:2), air, 60 °C, 16 h. The reaction was conducted on a 0.30 mmol scale and yields reported are of isolated material. [a] Yield determined by ^{1}H NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard from a 0.05 mmol scale reaction. [b] Isolated yield.

In conclusion, we report a mild Cu-catalyzed oxidation of alkylboronic esters to the corresponding ketone. The mild conditions use ambient air as the terminal oxidant, and chemoselective oxidation of the C-B bond is achieved even in the presence of unprotected alcohols. Experimental evidence suggests that the mechanism of reaction proceeds by B-to-Cu transmetallation, peroxide formation, and rearrangement to give the ketone. Further oxidative transformations of alkylboronic esters are in development and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests

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(11) AcOH was important to improve selectivity of oxidation to the ketone; in its absence, greater proportions of alcohol **3** were observed. Pyridine is likely to play a dual role; acting both as a base and as a coordinating ligand to help break up Cu aggregates.

(12) See supporting information for more details.

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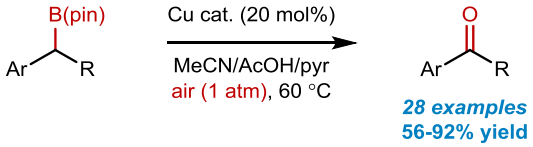

- ***Chemoselective oxidation***
- ***Terminal oxidant = O_2 from air***
- ***Functional group tolerant***