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Copper Catalysis

Copper-Catalyzed Oxyboration of Unactivated Alkenes

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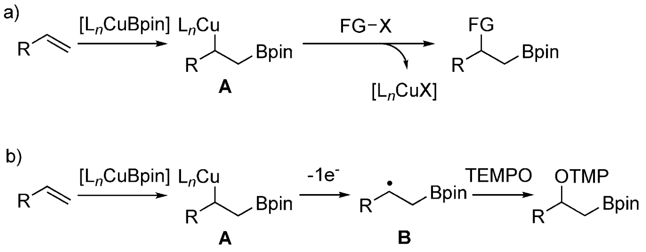
Abstract: The first regiodivergent oxyboration of unactivated terminal alkenes is reported, using copper alkoxide as a catalyst, bis(pinacolato)diboron [$(Bpin)_2$] as a boron source, and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as an oxygen source. The reaction is compatible with various functional groups. Two regioisomers are selectively produced by selecting the appropriate ligands on copper. The products may be used as a linchpin precursor for various other functionalizations, and net processes such as carbooxygenation, aminooxygenation, and dioxygenation of alkenes can be achieved after C–B bond transformations. Mechanistic studies indicate that the reaction involves the following steps: 1) Transmetalation between CuO*t*Bu and $(Bpin)_2$ to generate a borylcopper species; 2) regiodivergent borylcupration of alkenes; 3) oxidation of the thus-generated C–Cu bond to give an alkyl radical; 4) trapping of the resulting alkyl radical by TEMPO.

Organoboron compounds are synthetically versatile in organic chemistry and their efficient synthesis has been a subject of interest for several decades. Among various preparation methods of organoboron compounds, borylative difunctionalization of alkenes is a particulary attractive approach, because both a boron atom and another useful functionality can be simultaneously introduced to readily available starting materials. The transition metal-catalyzed borylative difunctionalization of alkenes has been intensively studied, including diboration,[1] silaboration,[2] carboboration,[3] and aminoboration.[4] To our knowledge, however, there is no report on oxyboration of alkenes. Considering the prevalence of oxygen functionalities in a variety of organic molecules, oxyboration of alkenes should be a valuable synthetic method. Herein, we report the first catalytic intermolecular oxyboration of unactivated terminal alkenes using copper catalysis. The key to success was a combination of two distinct properties of copper-containing species in a catalytic cycle: the nucleophilic property of the borylcopper(I) species in the borylcupration of alkenes, and the one-electron redox-active property of alkylcopper species **A** in the outer-sphere generation of alkyl radical **B**, which was trapped by (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as an oxygen atom source (Scheme 1 b). The novel biphasic mechanism complements previous copper-catalyzed borylative difunctionalizations of unactivated alkenes through two-electron pathways (Scheme 1 a).[5] Appropriate selection of the ligand on the copper catalyst enables a switch in regioselectivity[6] and allows this method to be used as a linchpin for the synthesis of various oxygenated vicinally difunctionalized compounds.



Scheme 1. a) Previous copper-catalyzed borylative difunctionalization of alkenes; b) this work: successive borylcupration–one-electron oxidation pathway. FG = functional group; TMP = 2,2,6,6-tetramethylpiperidin-1-yl.

Alkylcopper(I) species **A**, generated through the borylcupration of an alkene, can act as a two-electron donor nucleophile (Scheme 1 a),[5] and therefore we began our investigation by seeking an adequate two-electron oxidant for alkylcopper(I) intermediate **A** in the copper-catalyzed oxyboration of **1 a** (Table 1, entries 1–4). This reaction, however, did not afford the desired products **2 a** or **3 a**. 4-Phenylbutylboronic acid pinacol ester, perhaps generated through borylcupration of **1 a** followed by inadvertent protonation, was instead produced in 66 % yield (Table 1, entry 2), indicating that two-electron oxygenation of the C–Cu^I bond of **A** was slower than protonation. Consequently, we investigated one-electron oxidants to convert the C–Cu^I bond to a C–O bond in a step-wise manner through one-electron oxidation of alkylcopper(I) **A** to alkylcopper(II), homolysis of alkylcopper(II) to alkyl radical **B** to regenerate Cu^I, and trapping of **B** by an oxygen atom radical (Scheme 1 b). Although the use of molecular oxygen as an oxidant afforded no desired product (Table 1, entry 5), the reaction with TEMPO proceeded efficiently to give **2 a** in 66 % yield with high regioselectivity (entry 6).[7] The ligand on the copper catalyst was responsible for both the reactivity and regioselectivity: diphosphine ligands other than Xantphos derivatives afforded both a low yield and low selectivity (Table 1, entries 7 and 8; see also the Supporting information for details). Modifi-

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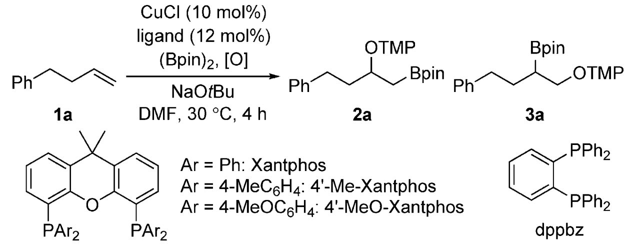
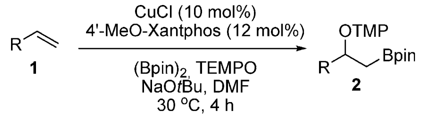
Table 1. Optimization of oxyboration of a terminal alkene.

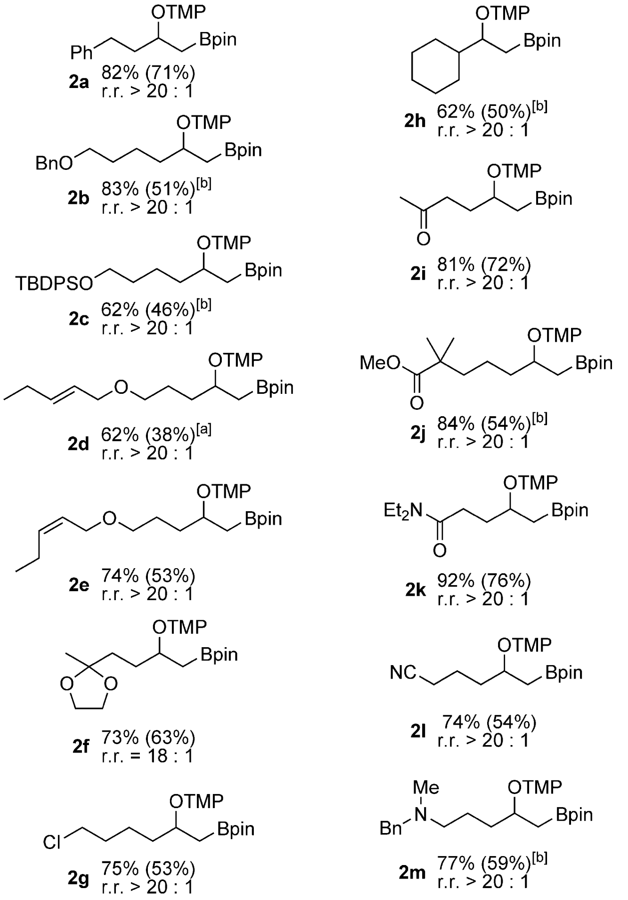


Entry	Ligand	[O]	Yield [%][a]	**2a**/**3a**
1	Xantphos	TBHP	0	–
2	Xantphos	TBP	0	–
3	Xantphos	oxaziridine	0	–
4	Xantphos	$(PhCOO)_2$	0	–
5	Xantphos	O_2	0	–
6	Xantphos	TEMPO	66	>20:1
7	dppf	TEMPO	19	2.3:1
8	dppbz	TEMPO	20	2.5:1
9	4′-Me-Xantphos	TEMPO	68	>20:1
10	4′-MeO-Xantphos	TEMPO	76	>20:1
11[b]	4′-MeO-Xantphos	TEMPO	82 (71)	>20:1

General reaction conditions: **1a** (0.10 mmol), $(Bpin)_2$ (0.20 mmol), oxidant (0.20 mmol), CuCl (10 mol%), ligand (12 mol%), NaO*t*Bu (0.15 mmol), DMF (1.0 mL), 30 °C, 4 h. Yields and regioisomeric ratio (**2a**:**3a**) were determined by ^1H NMR using *t*BuOMe as an internal standard. [a] Combined yield of **2a** and **3a**; yield of isolated **2a** is given in parentheses. [b] 0.25 mmol scale; $(Bpin)_2$ (0.72 mmol), and TEMPO (0.70 mmol) were used.

Table 2. Substrate scope of 4′-MeO-Xantphos-ligated CuCl-catalyzed oxyboration of alkenes.





2a 82% (71%) r.r. > 20 : 1

2b 83% (51%)[b] r.r. > 20 : 1

2c 62% (46%)[b] r.r. > 20 : 1

2d 62% (38%)[a] r.r. > 20 : 1

2e 74% (53%) r.r. > 20 : 1

2f 73% (63%) r.r. = 18 : 1

2g 75% (53%) r.r. > 20 : 1

2h 62% (50%)[b] r.r. > 20 : 1

2i 81% (72%) r.r. > 20 : 1

2j 84% (54%)[b] r.r. > 20 : 1

2k 92% (76%) r.r. > 20 : 1

2l 74% (54%) r.r. > 20 : 1

2m 77% (59%)[b] r.r. > 20 : 1

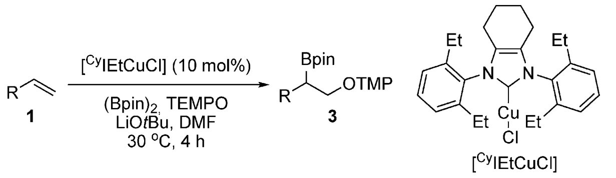
Conditions: **1** (0.25 mmol), $(Bpin)_2$ (0.72 mmol), TEMPO (0.70 mmol), CuCl (10 mol%), 4′-MeO-Xantphos (12 mol%), NaO*t*Bu (0.38 mmol), DMF (2.5 mL), 30 °C, 4 h. Yields and regioisomeric ratio (r.r. = **2**/**3**) were determined by ^1H NMR using *t*BuOMe as an internal standard. Combined yields of isolated **2** and **3** are given in parentheses. [a] Xantphos was used instead of 4′-MeO-Xatphos. [b] $(Bpin)_2$ (0.66 mmol) and TEMPO (0.63 mmol) were added dropwise over the course of 20 min.

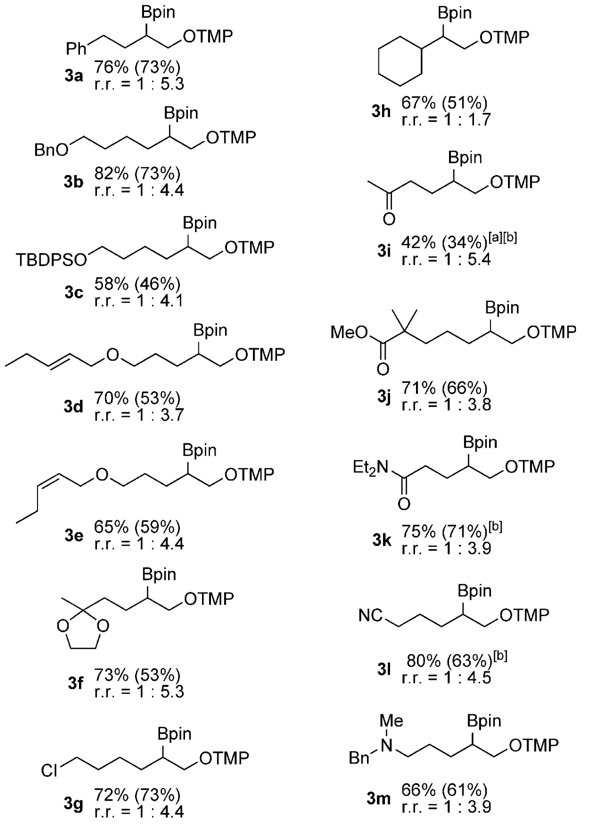
cation of the substituents on the phosphorus atom of Xantphos derivatives increased the reactivity while maintaining the high regioselectivity, and 4′-MeO-Xantphos was revealed to be the best ligand (Table 1, entry 10). The yield was further improved to 82% by increasing the amounts of bis(pinacolato)diboron [$(Bpin)_2$] and TEMPO (entry 11).

The optimized conditions were applicable to a variety of terminal alkenes (Table 2). In most cases, excellent regioselectivity (**2**/**3** > 20:1) was obtained. Due to the instability of the products under purification by silica-gel column chromatography, the products were isolated with gel-permeation chromatography and the yields of isolated product were diminished by approximately 10–25% compared with the NMR yields. The developed oxyboration reaction exhibited high functional group tolerance. Ether-containing alkenes and a ketal-containing alkene all reacted to give the corresponding products (**2b**–**f**) in moderate to high yields. Notably, the oxyboration reaction was completely selective to the terminal double bond over the internal double bond (**2d**, **2e**). A potentially reactive alkyl chloride moiety was intact under the reaction conditions (**2g**). The reaction even proceeded regioselectively with sterically demanding vinyl cyclohexane to give **2h**. Various carbonyl groups and a nitrile functional group were tolerated (**2i**–**l**). The reaction of an alkene bearing a strongly coordinating amino group afforded **2m** in good yield without poisoning the copper catalyst.

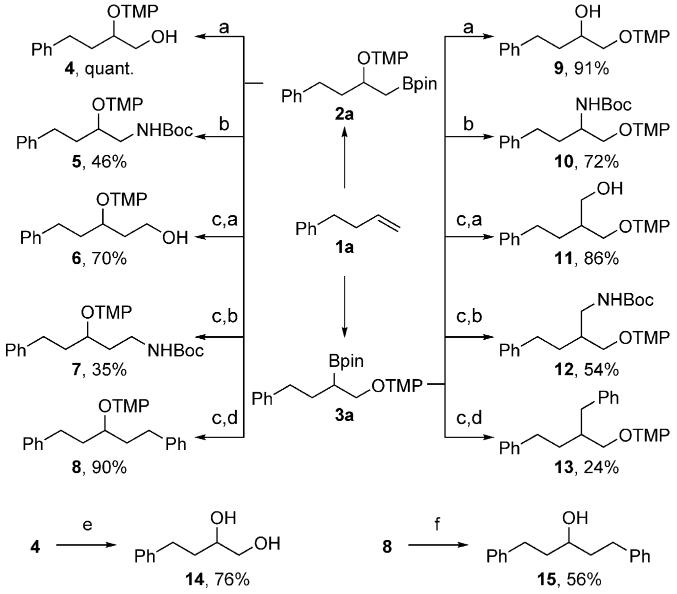
When [IMesCuCl] was utilized as the catalyst instead of 4′-MeO-Xantphos-ligated CuCl for the oxyboration of **1a**, the regioselectivity switched, preferentially affording internally borylated **3a** as a major product over **2a** [57% combined yield, **2a**/**3a** = 1:2.5; IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]. This result encouraged us to further investigate the reaction conditions toward catalyst-controlled regiodivergence. Among various N-heterocyclic carbene (NHC)-ligated copper catalysts studied, [^{Cy}IEtCuCl] was the best catalyst in terms of reactivity and selectivity (76% yield, **2a**/**3a** = 1:5.3; Table 3).[8] The functional group compatibility was similarly broad to 4′-MeO-Xantphos-ligated copper catalyst conditions, although the regioselectivity was generally moderate (Table 3). Ether, acetal, and chloroalkyl functionalities were tolerated under the reaction conditions (**3b**–**g**). Carbonyl and nitrile functionalities were also compatible, affording **3i**–**l** in good NMR yields. Isolation of **3i**, **3k**, and **3l** was particularly difficult, however, due to

Table 3. Substrate scope of [^{Cy}IEtCuCl]-catalyzed oxyboration of alkenes.





Conditions: **1** (0.25 mmol), $(Bpin)_2$ (0.66 mmol), TEMPO (0.63 mmol), [^{Cy}IEtCuCl] (10 mol%), LiO*t*Bu (0.38 mmol), DMF (2.5 mL), 30 °C, 4 h. $(Bpin)_2$ and TEMPO were added dropwise over the course of 20 min. Yields and regioisomeric ratio (r.r. = **2**:**3**) were determined by ^{1}H NMR using *t*BuOMe as an internal standard. Combined yields of isolated **2** and **3** are given in parentheses. [a] [IPrCuCl] was used instead of [^{Cy}IEtCuCl]. $(Bpin)_2$ and TEMPO were added dropwise over the course of 50 min. [b] Yield of isolated product after oxidation with $NaBO_3{\cdot}H_2O$ (1.25 mmol). TBDPS = *tert*-butyldiphenylsilyl.

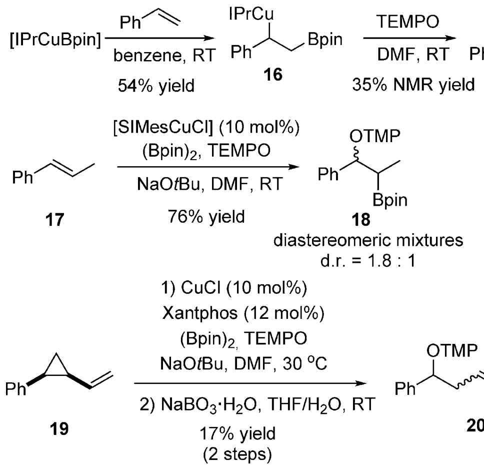


Scheme 2. Conversion of the oxyboration product. Reagents and conditions: a) $NaBO_3{\cdot}H_2O$, THF/H_2O, RT; b) $MeONH_2$, *n*BuLi, THF, −78 °C to RT; Boc_2O, NEt_3, THF, RT; c) bromochloromethane, *n*BuLi, THF, −78 °C to 60 °C; d) bromobenzene, $Pd(dba)_2$ (5 mol%), RuPhos (7.5 mol%), NaO*t*Bu, toluene/H_2O, 80 °C; e) Zn, AcOH, THF, 70 °C; f) Zn, AcOH, THF, 60 °C.

their instability under gel-permeation chromatography and other purification conditions, and thus they were isolated after conversion to the corresponding secondary alcohols by treatment with $NaBO_3{\cdot}H_2O$ without purification of the oxyboration products.

Due to the wide substrate scope, regiodivergence, and versatility of the organoboron compounds, the products are useful precursors for diverse vicinally functionalized molecules. Therefore, we examined the conversion of the C–B bond into other functionalities (Scheme 2). Oxidation of **2a** and **3a** by $NaBO_3{\cdot}H_2O$ efficiently produced alcohol products **4** and **9**, respectively. Notably, the two-step oxyboration–oxidation sequence realized selective introduction of two distinct oxygen functionalities on either side of the C=C double bond. Amination of the C–B bond was also possible with $MeONH_2$ and *n*BuLi,[9] giving aminooxygenation products **5** and **10**. Matteson's homologation in the presence of bromochloromethane and *n*BuLi successfully introduced sp^3 carbon functionalities, producing borylmethyl oxygenation intermediates.[10] The homologated products were directly subjected to oxidation, amination, and Pd-catalyzed cross-coupling[11] conditions without purification, giving a variety of 1,3-difunctionalized compounds, **6**, **7**, **8**, **11**, **12**, and **13**. The OTMP group could be converted into the corresponding alcohol in the presence of Zn and AcOH (**4**→**14**, **8**→**15**). Overall, the copper-catalyzed regiodivergent oxyboration followed by conversion of the C–B bond enabled rapid access to diverse patterns of oxygenative difunctionalization products, which are difficult to access by other means, from terminal alkenes.

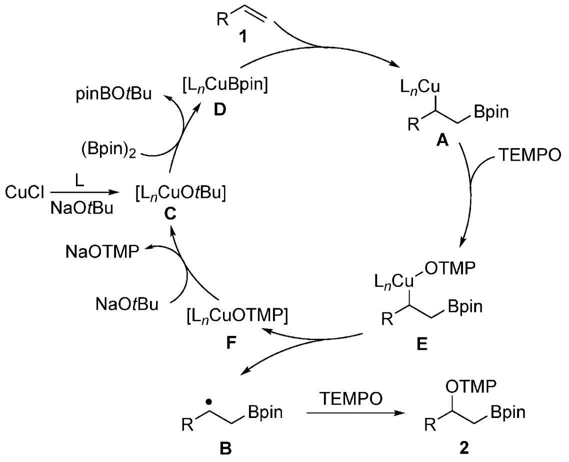
To gain insight into the reaction mechanism, following reactions were conducted (Scheme 3). Due to difficult handling of alkylcopper species derived from unactivated alkenes, we prepared the isolable β-borylalkylcopper **16** from styrene, following a procedure reported by Sadighi and co-workers,[12] and treated this possible intermediate with 2 equivalents of TEMPO. As expected, the oxygenation proceeded to give oxyboration product **2n** in 35% yield. When [^{Cy}IEtCuCl]-catalyzed oxyboration was applied to styrene under the conditions given in Table 3, **2n** was produced in 65% yield as the sole regioisomer. Based on this observation and the following results for the reaction with β-methylstyrene (**17**), we postulated that a radical species derived from **16** might be involved in the C-oxygenation step. In borylcupration of internal alkenes, *syn* addition of the boron and copper atoms to a C=C double bond proceeds. Subsequent protonation[13] or amination[4a] of the C–



Scheme 3. Mechanistic studies.

Cu bond occurs with stereoretention, giving the *syn* adducts exclusively. In contrast, the present oxyboration of **17** produced a 1.8:1 diastereomeric mixture of products **18**. This result can be explained by considering that C-oxygenation of an organocopper intermediate is a radical coupling process between a radical generated from the alkylcopper(II) species and TEMPO. This proposed mechanism is further supported by a following radical clock experiment. When the vinylcyclopropane **19** was subjected to the oxyboration reaction followed by oxidation of the C–B bond, the ring-opened product **20** was obtained in 17% yield. This observation is also in accordance with the involvement of alkyl radical species in the C-oxygenation process.

These experimental results, combined with previous observations by other researchers,[14] led us to propose the following catalytic cycle (Scheme 4). First, copper(I) alkoxide **C** generated from CuCl and NaO*t*Bu forms borylcopper(I) species **D** by transmetalation with $(Bpin)_2$. Insertion of the terminal C=C double bond into the thus-generated borylcopper(I) produces β-borylalkylcopper(I) **A**. One-electron oxidation of Cu^I to Cu^{II} with TEMPO results in the generation of alkylcopper(II) species **E**, which affords outer-sphere alkyl radical **B** and Cu^IOTMP **F** through homolytic cleavage of the unstable C–Cu^{II} bond of **E**. The radical intermediate **B** is trapped by a second equivalent of TEMPO to afford oxyboration product **2**. Because a stoichiometric amount of NaO*t*Bu is necessary for high product yield, CuO*t*Bu **C** needs to be regenerated from **F** and NaO*t*Bu. The regioselectivity shown in Scheme 4 is for L = Xantphos, alhough the mechanism should be basically the same for the reaction with an NHC ligand, except for the regioselectivity of the borylcupration step.



Scheme 4. Proposed catalytic cycle.

In summary, we have developed the first oxyboration of unactivated alkenes promoted by a copper catalyst. Key to the success of this reaction was the use of both nucleophilic and redox-active properties of copper catalysis. The regioselectivity of the reaction was controlled by the ligands: β-oxygenated terminal alkylboronates **2** were obtained with 4′-MeO-Xantphos-ligated CuCl as catalyst, whereas β-oxygenated internal alkylboronates **3** were obtained with [^{Cy}IEtCuCl]. Conversions of the C–B bond produced molecules with diverse vicinal substitution patterns, which are difficult to access by other means. Preliminary mechanistic studies revealed that the reaction involves the borylcupration of alkenes, one-electron oxidation of the resulting alkylcopper(I) species to give an alkyl radical species, and C–O bond formation with TEMPO through radical coupling. Copper-catalyzed borylative C-radical generation will be applicable to other bond-forming reactions. Further investigation of these applications is ongoing in our laboratory.

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Keywords: alkenes · copper · difunctionalization · boration · radical reactions

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COMMUNICATION

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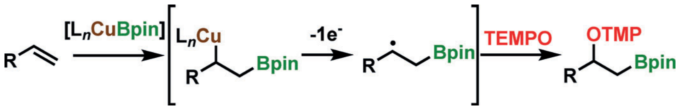

The first oxyboration of alkenes has been realized using copper alkoxide as a catalyst, $(Bpin)_2$ as a boron source, and TEMPO as an oxygen source. The oxyboration proceeds through a unique mechanism involving both nucleophilic and one-electron redox-active properties of copper catalysis. Regiodivergent oxyboration of alkenes is enabled by selecting appropriate ligands on copper.