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Direct Synthesis of Alkenylboronates from Alkenes and Pinacol Diboron via Copper Catalysis

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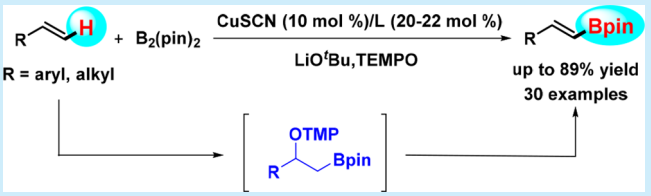
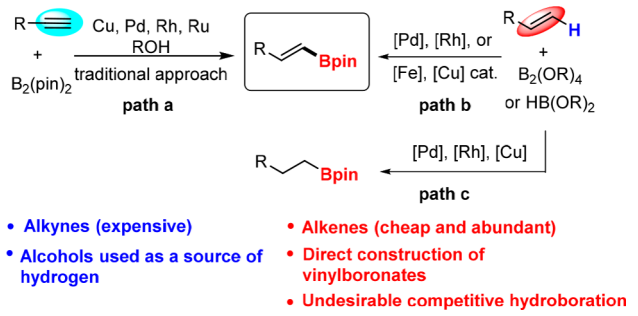
Supporting Information

ABSTRACT: We report an efficient approach for the direct synthesis of alkenylboronates using copper catalysis. The Cu/TEMPO catalyst system (where TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) exhibits both excellent reactivity and selectivity for the synthesis of alkenylboronates, starting from inexpensive and abundant alkenes and pinacol diboron. This approach allows for the direct functionalization of both aromatic and aliphatic terminal alkenes. Mechanistic experiments suggest that the alkenylboronates arise from oxyboration intermediates.



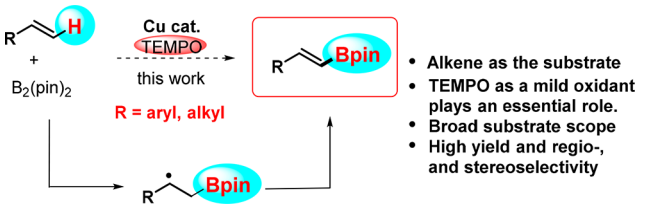
Alkenylboronates are versatile building blocks that are widely employed in academia and the pharmaceutical industry.[1] These fundamentally and practically important species can be readily transformed to a series of functional groups such as C−C, C−O, C−N, C−F, C−Br, and C−I bonds by transition-metal-catalyzed cross-coupling reactions.[2,3] Given the significance of alkenylboronates, effective approaches for preparing alkenylboronates are highly desirable. Traditionally, alkenylboronates are synthesized through transition-metal-catalyzed (i.e., Pd, Cu, Rh, and Ru) hydroboration of alkynes (Scheme 1, path a)[4−6] and from multistep boron-Wittig reaction of aldehydes.[7] The starting materials required for these approaches are more expensive and less readily available than their alkene counterparts. Consequently, the direct borylation of alkenes is attractive for both economical and practical reasons.[8−16]

Scheme 1. Common Approaches to Alkenylboronates



While there are significant advantages to the direct borylation of alkenes, a major challenge that has long been recognized is the undesired hydroboration of alkenes that leads to alkylboronate side-products (Scheme 1, path c).[6c,8] In recent years, examples of transition-metal-catalyzed dehydrogenative borylation of alkenes by β−H elimination have emerged (Scheme 1, path b).[9a,b,10a−d,11a,12,14−16] Notably, because of the inexpensive and environmentally benign aspects of copper catalysis, investigations of Cu-catalyzed borylation of alkynes and alkenes have been a trending topic in the past decade.[6a,c,17] However, to our knowledge, there are no examples of Cu-catalyzed methods that operate through radical-based pathways to furnish alkenylboronates starting from alkene precursors. As such, we envisioned a Cu-catalyzed radical pathway to access alkenylboronates using readily acccessible alkenes as substrates instead of alkynes (Scheme 2), thus giving rise to a novel system with broad substrate scope and good reactivity (Scheme 2). Herein, we detail a new approach for the direct synthesis of alkenylboronates from alkenes and pinacol diboron via copper catalysis by using TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) as a mild oxidant. Note that our new approach is compatible with both aliphatic and aromatic alkenes.

Scheme 2. A Radical-Based Strategy for Synthesizing Alkenylboronates



To test our hypothesis, we examined the borylation of 2-vinylnaphthalene (**1a**) using the Cu/TEMPO system. The choice of TEMPO as the mild oxidant is based on our previous

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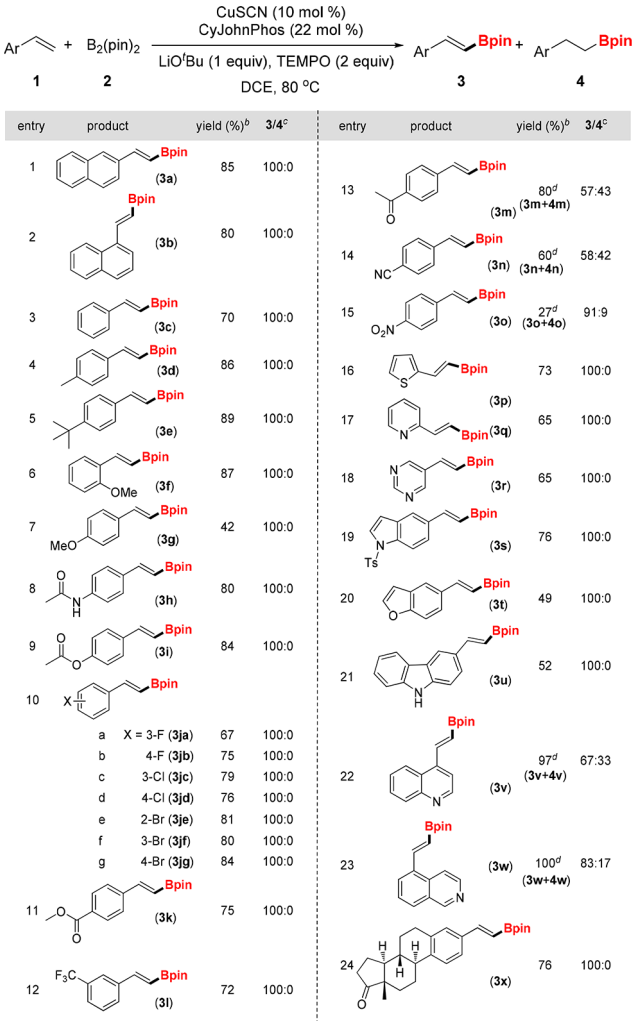
studies.[18] Initially, to our delight, alkenylboronate **3a** and hydroboration side-product **4a** were obtained in a combined 24% yield in a ratio of 61:39 (**3a**/**4a**, in DMF, Table S1 in the Supporting Information, entry 1).[19] In the absence of TEMPO, alkenylboronate **3a** is not formed, suggesting that TEMPO plays a significant role in the current direct borylation process. Surprisingly, a significant solvent effect was observed during the evaluation of solvents (Table S1, entries 1−10).[19] DCE was found to be the most effective solvent, providing **3a** in high chemoselectivity (**3a:4a** = 92:8) (Table S1, entry 10).[19] Further optimization of the reaction parameters resulted in the use of a combination of CuSCN and CyJohnPhos, which produced alkenylboronate **3a** in 85% yield with exclusive chemoselectivity, regioselectivity, and stereoselectivity (**3a:4a** = 100:0) (Table S1, entry 14).[19] Moreover, only the *E*-stereoisomer of **3a** was formed. We reasoned that the observed stereoselectivity is thermodynamically controlled. The optimal condition for the current borylation of alkenes is the use of 10 mol % CuSCN/22 mol % CyJohnPhos, LiO^tBu (1 equiv), TEMPO (2 equiv), and $B_2(pin)_2$ (2 equiv) in DCE solvent at 80 °C (Table S1, entry 14).[19]

With this protocol established, we explored the generality and limitations of our Cu-catalyzed borylation of aromatic terminal alkenes with $B_2(pin)_2$ (Table 1). To our delight, a wide range of aromatic and heteroaromatic terminal alkenes smoothly transformed to provide alkenylboronates in high chemoselectivities and stereoselectivities. Electron-rich aromatic alkenes with alkyl (**1d**, **1e**), ether (**1f**, **1g**), amide (**1h**), and acyloxy (**1i**) substitutions underwent efficient and selective borylation with $B_2(pin)_2$ to afford the desired aromatic alkenylboronates in up to 89% yield, 100:0 ratio of **3**/**4**, and as single *E*-stereoisomers (**3a**−**3i**). Notably, varying the size of the substituents from methyl (**1d**) to *tert*-butyl (**1e**) displayed good compatibility. In addition, inductively electron-withdrawing groups on aromatic rings were also well-tolerated, with the desired products formed in good selectivities and high yields. For example, styrenes substituted with F, Cl, and Br atoms at various positions of the phenyl ring performed well to furnish exclusively **3ja**−**3jg** in up to 84% yield (Table 1, entry 10). Substrate **1l** with the trifluoromethyl substitution also worked well (Table 1, entry 12). However, strongly electron-withdrawing groups such as 4-keto-(**1m**), 4-cyano-(**1n**), and 4-nitro-(**1o**) groups on the phenyl ring drastically influenced both the chemoselectivity and reactivity. In these reactions, competitive hydroborylation was a major side-reaction (Table 1, entries 13−15). To our surprise, the scope of this method smoothly extended to heteroaromatic alkenes with excellent chemoselectivity and high yields. For example, 2-vinylthiophene (**1p**), 2-vinylpyridine (**1q**), 5-vinylpyrimidine (**1r**), 5-vinyl-*N*-Ts-indole (**1s**), 5-vinylbenzofuran (**1t**), and 3-vinyl-9*H*-carbazole (**1u**) underwent efficient borylation in up to 76% yield, 100:0 ratio of **3**/**4**, and as single *E*-stereoisomers (Table 1, entries 16−21). However, while 4-vinylquinoline (**1v**) and 5-vinylisoquinoline (**1w**) exhibited high reactivity, lower levels of chemoselectivities were observed (97%−100% combined yields of **3** and **4**; Table 1, entries 22 and 23). Finally, to demonstrate utility in organic synthesis, a more complex alkene containing the estrone (**1x**) motif was examined. The reaction proceeded smoothly to afford the corresponding product **3x** in 76% yield with complete chemoselectivity (100:0 ratio of **3**/**4**), thus providing a promising approach for late-stage modification of bioactive compounds.

Table 1. Dehydrogenative Borylation of Various Terminal Aryl Alkenes[a]



[a]Conditions: **1a** (0.3 mmol, 1 equiv), $B_2(pin)_2$ (2 equiv), LiO^tBu (1 equiv), TEMPO (2 equiv), CuSCN (10 mol %), CyJohnPhos (22 mol %), 80 °C, DCE (2 mL). The corresponding reaction time is shown in the Supporting Information. [b]Isolated yield. [c]The ratio of **3**/**4** was determined by ^{1}H NMR spectroscopy analysis. [d]Total yield of **3** and **4** after chromatographic purification.

Inspired by the above results, we turned our attention to more challenging unactivated aliphatic alkenes. We chose **5a** as the model substrate to test the borylation of aliphatic alkenes (Table S2 in the Supporting Information).[19] We found that the choice of ligand has a significant effect on the formation of aliphatic alkenylboronates. By surveying a series of ligands, we found XantPhos to be particularly promising and completely inhibited the competitive hydroborylation (Table S2, entry 1).[19] By further examining other parameters of the reaction conditions, efficient and selective borylation smoothly occurred to provide **6a** in 93% yield and 87:13 *E*/*Z* ratio in the presence of CuSCN (10 mol %), Xantphos (20 mol %), ^{t}BuOLi (2.5 equiv), and TEMPO (2.1 equiv) in CH_3CN at 100 °C (Table S2, entry 4).[19] We also found that the reaction temperature strongly influenced the generation of alkenylboronates (Table S2, entries 1−5).[19] Various aliphatic alkenes containing a long alkyl chain (**6b**) or cyclohexyl (**6c**), silylether (**6d**), ether (**6e**), and ester (**6f**) groups (Scheme 3) performed

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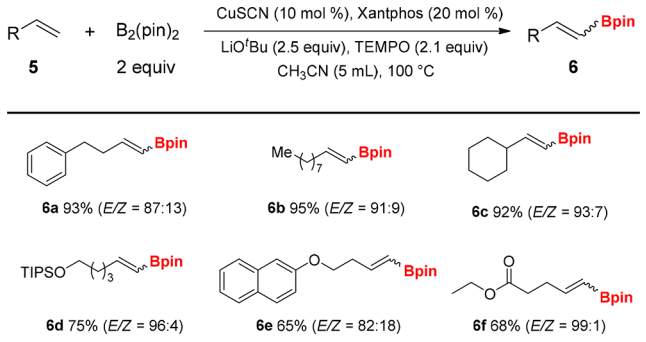
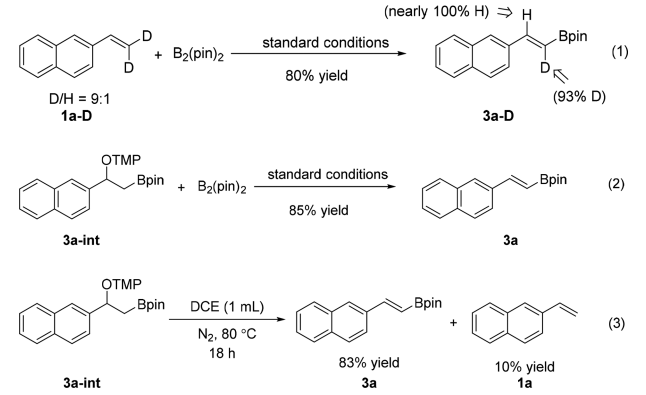
Scheme 3. Scope of Aliphatic Alkenes



well under the optimal conditions to furnish the borylated products in up to 95% yield with excellent regioselectivity and stereoselectivity. In all cases, the *E*-stereoisomer is exclusively formed (determined by ^{1}H NMR analysis).

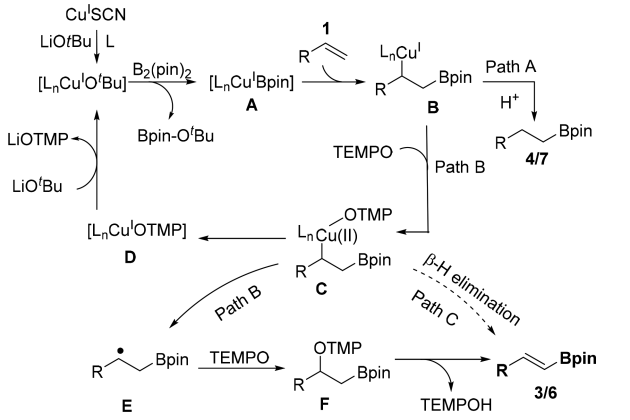
To gain insight into the reaction mechanism, a series of mechanistic studies was performed. First, we synthesized a deuterium-labeled 2-vinylnaphthalene **1a-D**[20] to test whether the alkenylboronate product is formed through a β-H elimination pathway (eq 1). In this case, deuterium is not



incorporated into the β-position of alkenylboronate **3a-D** (nearly 100% H at the β-position, 93% D at the α-position of alkenylboronate). Thus, a Cu-catalyzed β-H elimination pathway is effectively ruled out. Second, we obtained a reaction profile for the Cu-catalyzed borylation of **1a** under the standard conditions. We found that substrate **1a** was quickly consumed and a new intermediate was formed, followed by gradual generation of product **3a** (Figure S1).[19] The new signal suggests that this intermediate is a key component of this reaction. We trapped it and determined its structure to be oxyborylated **3a-int** by ^{1}H NMR, ^{13}C NMR spectra, and HRMS. Two additional control experiments were performed: (1) intermediate **3a-int** was subjected to the standard reactions conditions, which gave rise to the borylated product **3a** in 85% yield (eq 2); (2) direct heating of **3a-int** in DCE at 80 °C also led to the formation of **3a** in 83% yield, along with 10% yield of terminal alkene **1a** (eq 3). These unexpected results suggest that alkenylboronate product **3a** can be derived from intermediate **3a-int** by direct heating without any external reagents.

On the basis of our mechanistic studies and previous report,[21] a tentative reaction mechanism for this Cu-catalyzed alkene borylation is proposed. As shown in Scheme 4, CuSCN first reacts with LiO^{t}Bu to produce the active L$_n$Cu(I)O^{t}Bu complex, followed by transmetalation with pinacol diboron to

Scheme 4. Plausible Reaction Mechanism



generate L$_n$Cu(I)Bpin **A** and pinBO^{t}Bu. Next, alkene **1** inserts into the Cu-Bpin bond to form β-boryl alkyl copper(I) **B**, which can undergo two competing pathways. We considered that the electronic properties of the R groups can significantly influence both the reactivity and chemoselectivity in this step.[22] In addition, the optimized combination of CuSCN, ligand, and solvent plays a key role in suppressing the hydroborylation process. Intermediate **B** then reacts with TEMPO to form the C−Cu(II) complex **C**, which can undergo homolytic cleavage to provide alkyl radical **E** and L$_n$Cu(I)OTMP **D**. Complex **D** is treated with LiO^{t}Bu to regenerate the active L$_n$Cu(I)O^{t}Bu. Alkyl radical **E** is trapped by a second equivalent of TEMPO to afford oxyboration intermediate **F**, which is thermally transformed to alkenylboronate. TEMPOH is observed by GC analysis, which provides support for this proposed mechanism.[19] Over the course of the reaction, the starting material is never completely consumed, even under prolonged reaction time. A plausible explanation for this is that intermediate **F** provides terminal alkenes in low yields upon heating (see eq 3).

In summary, the results described herein show that the Cu−TEMPO catalyst system exhibits both excellent reactivity and selectivity for the direct synthesis of alkenylboronates using inexpensive and abundant alkenes as starting materials. Not only are aromatic terminal alkenes accommodated, but aliphatic terminal alkenes are also compatible in forming the corresponding products in high yields with excellent chemoselectivity, regioselectivity, and stereoselectivity. The competitive hydroborylation of alkenes is efficiently suppressed in our newly reported system. Detailed mechanistic studies revealed that the reaction undergoes a radical pathway and TEMPO plays a significant role in this transformation. Mechanistic support suggests that the formation of alkenylboronate comes from oxyboration intermediate **F**. We were able to rule out a β-H elimination pathway. Furthermore, the diverse transformations of alkenylboronates in the literature[23] suggest that these reactions could find widespread applications in both academia and industry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03599.

Experimental details and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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(22) If a strong electron-rich group is attached at the *para* position of phenyl ring, the insertion step becomes sluggish, resulting in low yield, for example, substrate **1g** (Table 1, entry 7). On the other hand, strong electron-deficient aromatic groups (R) are prone to leading to competitive protonation of alkyl copper complex **B** to form

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hydroborylation side-product **4a,** in which a small amount of water in solvent probably provides the proton source. Substrates **1m−1o** and **1v−1w** verify this phenomenon (Table 1, entries 13−15, 22, 23).

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