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Copper-catalyzed borofunctionalization of styrenes with B₂pin₂ and CO†

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The construction of structurally complexed and high-value chemical molecules from simple and readily available feedstocks is a long-standing challenge to chemists. Here, we describe a copper-catalyzed borofunctionalization of styrenes with B₂pin₂ and carbon monoxide. A set of new sodium cyclic borates were obtained with NaO^tBu as the base. These unique sodium cyclic borates can be easily converted into a variety of multifunctional β-boryl vinyl esters, boryl carbonates, β-boryl aldehydes, and boryl vinyl ether. In addition, the procedure also features good functional group tolerance and utilizes CO as the C1 source.

Introduction

The use of carbon monoxide (CO) as a cheap and abundant C1 building block for the synthesis of a wide range of value-added chemicals is of great importance, and it has received increasing attention from both academia and industry.¹ For decades, carbonylation has been considered as one of the most direct and effective pathways to introduce carbonyl groups into various molecules.² The simultaneous incorporation of two different functional groups into π-systems is one of the most capable tools for the construction of complexed molecular motifs.³ Transition-metal-catalyzed borofunctionalization of π-systems serves as a novel and practical strategy for the installation of both boron and carbon groups across the unsaturated bonds, thus enabling the rapid assembly of molecular complexity.⁴ The resulting organoboron compounds allow a variety of highly efficient transformations to other functionalized molecules with ease.⁵

Copper catalysis has emerged as one of the most powerful tools to install boron groups across C–C unsaturated bonds in recent years.⁶ Furthermore, this method offers tremendous versatility enabled by difunctionalization of the unsaturated C–C bonds by the addition of an electrophile. Among these, the catalytic borocarbonylation of alkenes,⁷ which has received less attention, represents an unconventional approach for borylative difunctionalization by the incorporation of CO in the reactions.

The general mechanism for carbonylative borofunctionalization of alkenes (Fig. 1a) involves alkyl copper intermediate **I**,⁸ which was generated *via* migratory insertion of alkene and Cu–Bpin species, followed by CO insertion and the interception of

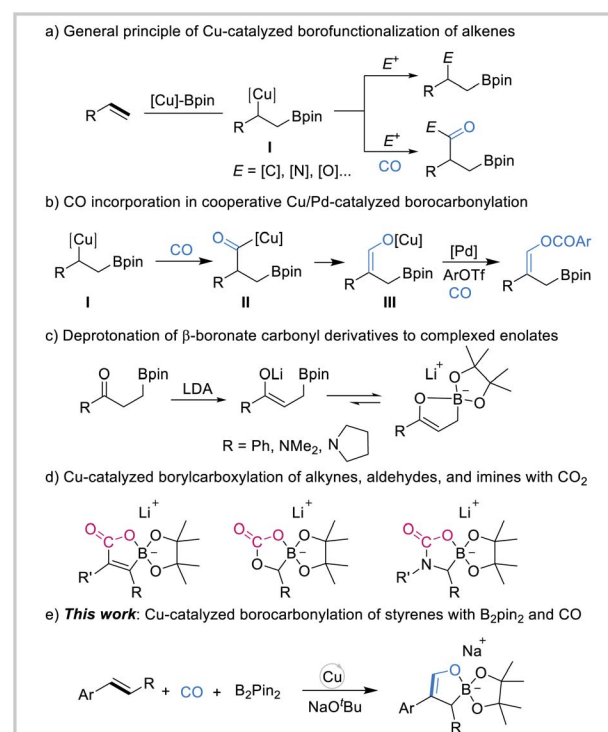


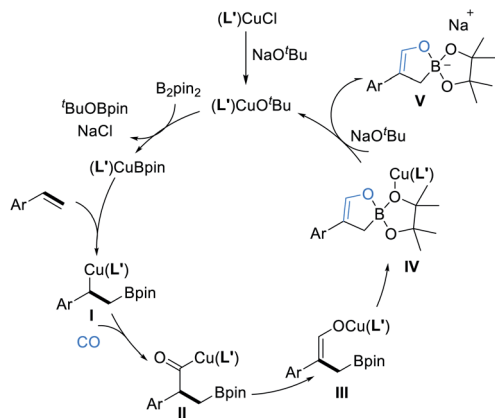
Fig. 1 (a) General principle of Cu-catalyzed borofunctionalization of alkenes. (b) CO incorporation in cooperative Cu/Pd-catalyzed borocarbonylation. (c) Deprotonation of β-boronate carbonyl derivatives to complexed enolates. (d) Cu-catalyzed borylcarboxylation of alkynes, aldehydes, and imines with CO₂. (e) Cu-catalyzed borofunctionalization of styrenes with B₂pin₂ and CO (this work).

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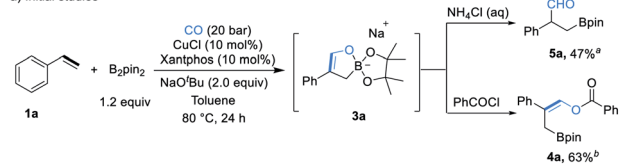
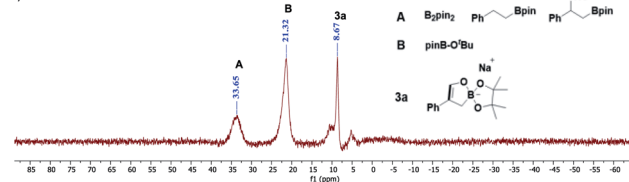


Scheme 1 Proposed catalytic cycle for borofunctionalization.

an electrophile to produce the boryl-functionalized carbonyl-based product. Recently, in our developed palladium/copper-catalyzed carbonylative four-component reaction, we demonstrated that CO can also insert into the alkyl copper intermediate **I** to form acyl copper intermediate **II**, which then undergoes isomerization to form the vinyl alkoxide copper species **III**. In the presence of the palladium catalyst, aryl triflates were carbonylated to give the corresponding β -boryl vinyl esters (Scheme 1b).^{7f}

In the 1990s, Whiting and co-workers studied and proposed that β -boronate carbonyl derivatives can be readily deprotonated in the presence of lithium diisopropylamide (LDA), affording intramolecularly complexed enolates (Fig. 1c).⁹ Recently, Hou's group reported a novel route for the efficient synthesis of a new class of lithium borate compounds enabled by Cu-catalyzed borylative difunctionalization of alkynes, aldehydes, and imines with CO₂ (Fig. 1d).¹⁰ These cyclic borate compounds might be of great interest as potential synthetically useful synthons. However, due to the lack of efficient and versatile synthetic methods, the availability of cyclic borate intermediates or products remains quite limited. During the course of our studies on the use of CO as the C1 source for organic synthesis, we became interested in the synthesis of cyclic borate intermediates by using CO as the starting material.

a) Initial studies

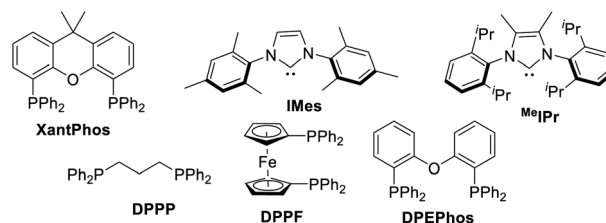
b) ¹¹B NMRScheme 2 Initial studies and ¹¹B NMR analysis after reaction. ^aNMR yield. ^bGC yield.

Herein, we report a Cu-catalyzed multi-component borofunctionalization of styrenes with bis(pinacolato)diboron (B₂pin₂) and CO (Fig. 1e). This procedure has enabled the efficient synthesis of a novel class of sodium cyclic borate intermediates.

We propose the catalytic cycle shown in Scheme 1 to realize this multi-component borofunctionalization reaction. A (L')CuCl catalyst first reacts with NaO'Bu and B₂pin₂ to give an active (L')Cu-Bpin species.¹¹ Subsequently, borocupration of the alkene substrate affords the β -boroalkylcopper intermediate **I**, followed by CO insertion of the organocopper intermediate **I** to generate the acyl-copper intermediate **II**, which undergoes isomerization to the O-bound copper enolate species **III**.¹² Migration of the (L')Cu unit from the resulting vinyl alkoxide copper to a pinacol boronate oxygen atom and intramolecular B-O bond formation would form the cyclic borate intermediate **IV**. Finally, ligand exchange between copper complex **IV** and NaO'Bu regenerates the (L')CuO'Bu species for the next catalytic cycle and releases the final sodium cyclic borates **V**.

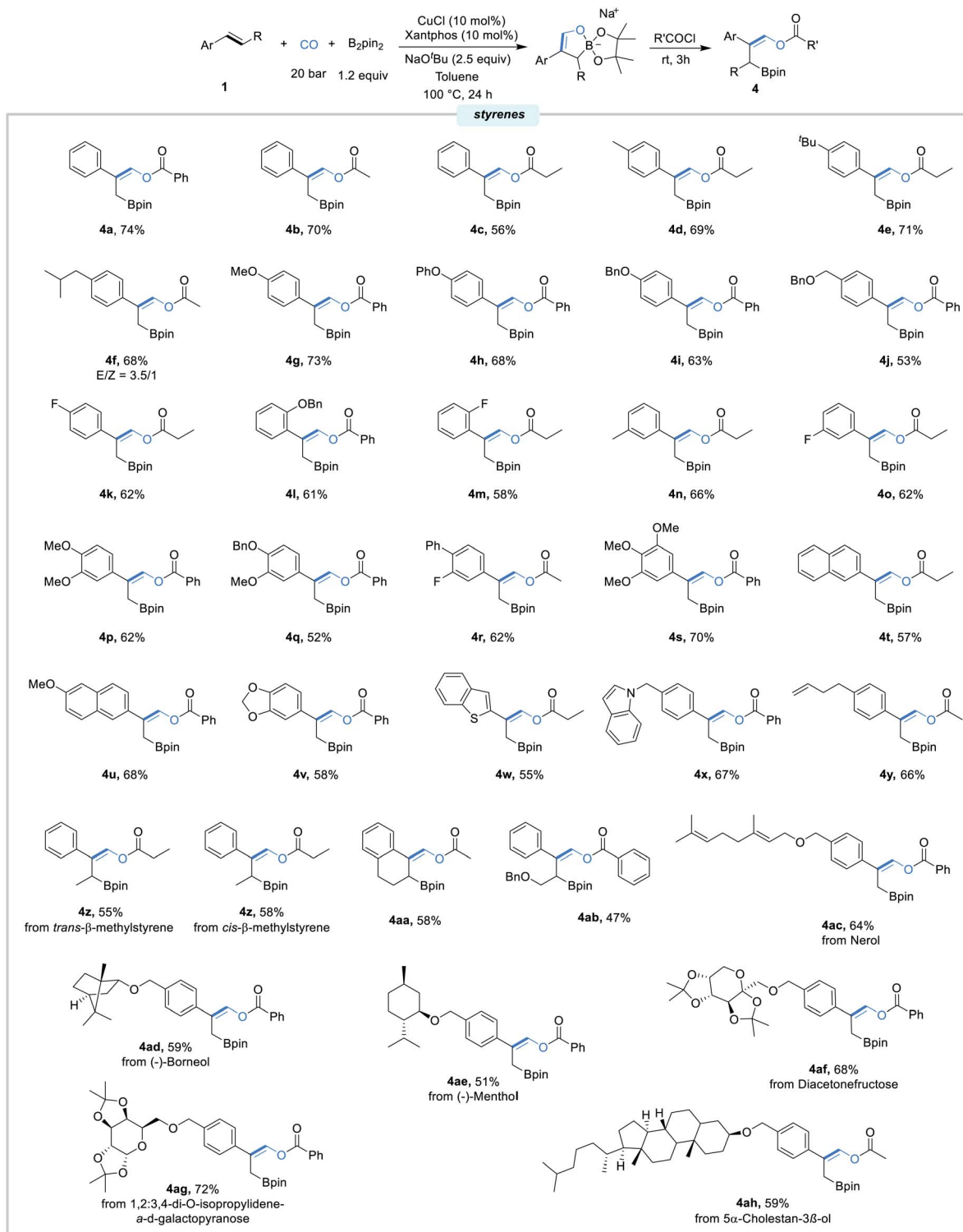
Table 1 Investigation of reaction conditions^a

Entry	Variations from the standard conditions	Yield of 4a (%)
1	None	84 (74) ^b
2	CuCN instead of CuCl	80
3	^{Me} IPrCuCl instead of CuCl/xantphos	21
4	^{Me} IPrCuCl instead of CuCl	33
5	IMesCuCl instead of CuCl/xantphos	12
6	DPPP instead of xantphos	61
7	DPPF instead of xantphos	65
8	DPEphos instead of xantphos	42
9	LiO'Bu instead of NaO'Bu	Trace
10	KO'Bu instead of NaO'Bu	Trace
11	NaOMe instead of NaO'Bu	<10
12	1.5 equiv. of NaO'Bu instead of 2.5 equiv.	46
13	THF instead of toluene	18
14	80 °C instead of 100 °C	76
15	10 bar CO instead of 20 bar	79



^a Standard conditions: **1a** (0.2 mmol, 1.0 equiv.), B₂pin₂ (0.24 mmol, 1.2 equiv.), CuCl (10 mol%), ligand (10 mol%), NaO'Bu (0.5 mmol, 2.5 equiv.), CO (20 bar), toluene (1.0 mL), 100 °C, 24 h; yields are determined by GC analysis using hexadecane as the internal standard. ^b Isolated yield.





Scheme 3 Substrate scope. Standard conditions: **1** (0.2 mmol, 1.0 equiv.), B_2pin_2 (0.24 mmol, 1.2 equiv.), CuCl (10.0 mol%), xantphos (10.0 mol%), NaO^tBu (0.5 mmol, 2.5 equiv.), CO (20 bar), toluene (1.0 mL), 100 °C, 24 h; acid chlorides (0.4 mmol, 2.0 equiv.), rt, 3 h; isolated yields. Otherwise noted, the products are with only *E* configuration.

Results and discussion

Initial studies were focused on different work-up methods after the reaction and confirm the possible intermediates, as the cyclic borate is not stable and attempts on purification and

crystallization were all failed. Firstly, under the conditions attempted, we quenched the reaction by addition of a saturated aqueous NH_4Cl solution, and the desired β-boryl aldehyde product **5a** was formed in 47% NMR yield (Scheme 2a), however, it was isolated in dramatically decreased yield due to its poor



stability during purification by silica gel column chromatography. We then turned our attention to use acid chlorides, in this case, the desired β -boryl vinyl ester **4a** was obtained in 63% GC yield and it can be isolated through chromatography. On the basis of preliminary findings, reported in the literature,^{10,13} and analysis of the ¹¹B NMR spectrum (Scheme 2b & ESI†), we proposed that sodium cyclic borate **3a** was afforded as the product under the catalytic system.

From this result, the reaction conditions were optimized by further reaction with benzoyl chloride for 3 h. After intensive investigations, we found reaction conditions under which the β -boryl vinyl ester **4a** can be obtained in 84% GC yield and isolated in 74% yield when xantphos/CuCl was used as the catalyst in the presence of NaO^tBu (2.5 equiv.) as the base under a 20 bar CO atmosphere (Table 1, entry 1). Using CuCN as the copper precursor gave a similar yield (Table 1, entry 2). NHC-based copper catalysts such as ^{Me}IPrCuCl and IMesCuCl afforded much lower yields of the desired product (Table 1, entries 3–5). The use of other bidentate ligands DPPP, DPPF, and DPEphos instead of xantphos did not improve the yield (Table 1, entries 6–8). Only a trace product was detected when other bases, such as LiO^tBu and KO^tBu were used, and very low yield (<10%) of the product was obtained with NaOMe (Table 1, entries 9–11). Reducing the amount of NaO^tBu to 1.5 equivalents led to a decreased yield to 46% (Table 1, entry 12). Changing the solvent to THF only gave **4a** in 18% yield (Table 1, entry 13). Decreasing temperature to 80 °C or lowering CO pressure to 10 bar led to slightly lower yields (Table 1, entries 14 and 15).

With the best conditions in hand, we next evaluated the scope of this borofunctionalization reaction under the optimal reaction conditions. As shown in Scheme 3, styrenes bearing different electron-donating or electron-withdrawing groups at the *para*, *meta*, or *ortho* position were all successfully converted

into the desired products **4a–4o** in moderate to good yields. Di- and tri-substituted styrenes can also proceed efficiently to give the corresponding β -boryl vinyl esters **4p–4s** in 52–70% yields. Delightfully, the reaction worked well with styrenes containing 2-vinylnaphthalene, 2-MeO-6-vinylnaphthalene, 5-vinylbenzo[d][1,3]dioxole, and 5-vinylbenzo[b]thiophene, delivering products **4t–4w** in reasonable yields. Gratifyingly, functionalized styrenes were also tolerated, providing the desired products **4x** and **4y**. Moreover, more challenging internal styrenes were proved to be compatible with the catalytic system, giving the corresponding products **4z–4ab** in moderate yields. Furthermore, nerol, (–)-borneol, (–)-menthol, diacetonefructose, 1,2:3,4-di-*O*-isopropylidene- α -*D*-galactopyranose, and 5 α -cholestan-3 β -ol derived styrenes were all proceeded smoothly here, furnishing products **4ac–4ah** in good yields.

In addition, the sodium cyclic borates could react with chloroformates to form boryl-functionalized carbonates **6a** and **6b** in 71% yield and 60% yield, respectively (Table 2a). The reaction of **3l** with trimethyloxonium tetrafluoroborate (Me₃OB⁺F₄, 1.5 equiv.) occurred smoothly at ambient temperature, affording boryl vinyl ether **7** in 46% yield with 5 : 1 *E/Z* ratio (Table 2b). It is important to mention that electrophiles such as MeI and allylic chloride were tested as well but no reaction occurred. After quenching the reaction with a saturated aqueous NHCl₄ solution after completion of the reaction under the optimal reaction conditions, β -boryl aldehydes **5b** (64% yield) and **5c** (49% yield) can be isolated by silica gel column chromatography (Table 2c). Instead of saturated aqueous NHCl₄, a saturated deuterium water (D₂O) solution of NHCl₄ was used for the work-up and 51% of benzylic hydrogen was deuterated and only 14% aldehyde hydrogen was deuterated (Table 2c and **5d**).

Conclusions

In summary, we have developed a new strategy for the preparation of sodium cyclic borate intermediates from readily available starting materials. By one-pot borofunctionalization of styrenes, B₂pin₂, CO, and NaO^tBu in the presence of the xantphos/CuCl catalyst, a new family of cyclic borate compounds was easily generated with good functional group tolerance. The reaction may serve as an attractive method for the synthesis of cyclic borates, as it uses CO as the C1 source and a relatively cheap copper catalyst. Moreover, cyclic borates are potential versatile reagents for organic synthesis. It is expected that this protocol will prompt further exploration of novel catalytic systems for the carbonylative reaction using CO as the C1 source towards the synthesis of valuable chemicals.

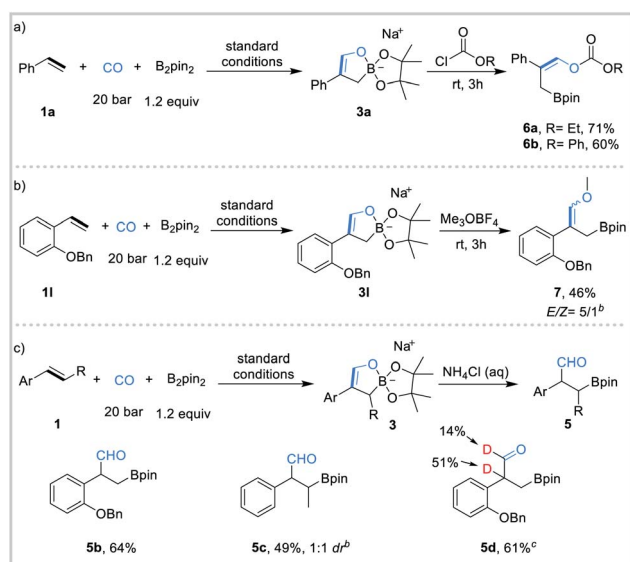
Author contributions

XFW directed this project. YY and FPW performed all the experiments. YY prepared the draft and XFW revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

Table 2 Transformations of the sodium cyclic borates^a



^a 0.2 mmol scale, isolated yields. ^b Determined by ¹H NMR. ^c Quenched with a saturated NHCl₄ (D₂O) solution.



Acknowledgements

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