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Copper-Catalyzed Asymmetric Borylallylation of Vinyl Arenes

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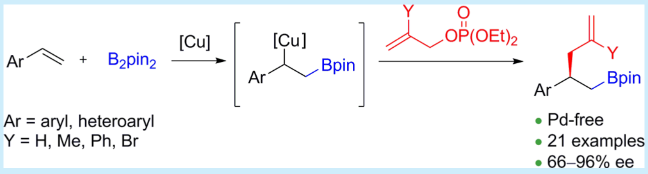
Supporting Information

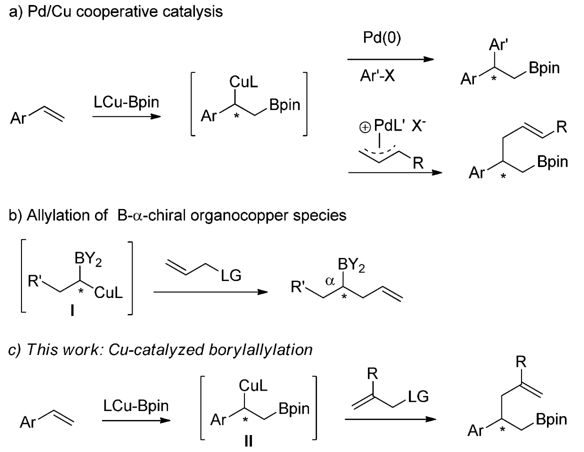
ABSTRACT: A copper-catalyzed, enantioselective method for the borylallylation of vinyl arenes is reported. The reaction produces enantioenriched and functionalized organoboron compounds by sequentially incorporating boryl and allyl groups onto the C═C bond of vinyl arenes. Copper-catalyzed borylative coupling of vinyl arenes with allyl phosphates successfully proceeds in a regio- and enantioselective manner in the absence of a palladium cocatalyst.



The installation of different functional groups onto C−C unsaturated bonds in a single process is a powerful method for the preparation of complex organic molecules.[1] In recent years, organocopper intermediates generated by borylcupration of unsaturated substrates with bis(pinacolato)-diboron (B_2pin_2) have been discovered to be useful organometallic reagents for the formation of various C−C bonds through addition,[2] substitution,[3] and coupling reactions with electrophiles.[4] In these multicomponent reactions, borylated organocopper intermediates were generated in situ from alkenes, allenes, and alkynes in the presence of a copper catalyst.

Recently, palladium and copper cooperative catalysis has been applied to coupling reactions of such organocopper intermediates with aryl halides.[5] The dual catalysis was also applied to the enantioselective allylboration of vinyl arenes by Liao and co-workers using *tert*-butyl allyl carbonates as electrophiles (Scheme 1, a).[6] Transition-metal-catalyzed allylation methods are considered valuable transformations due to the versatility of the olefin functional group incorporated in the allylation.[7] In particular, copper-catalyzed allylic substitution[8] could be a good candidate for a series of tandem reactions of in situ generated organocopper intermediates. While a copper-catalyzed hydroallylation of styrenes has been reported,[9] copper-catalyzed borylative coupling of simple styrenes with allylic electrophiles has not yet been reported without cooperative palladium catalysis. To date, only copper-catalyzed borylallylations of allenes, alkynes, and vinyl boronates have been reported.[10] Herein, we report an enantioselective borylallylation of vinyl arenes catalyzed by a chiral phosphine−copper catalyst that provides access to functionalized alkylboranes.

Scheme 1. Catalytic Allylation Methods



Our group recently reported the copper-catalyzed allylation of enantioenriched α-boryl organocopper species (**I**).[11] Given the similar steric factors of α-boron organocopper species and β-boryl organocopper species (**II**), we envisioned that catalytic borylallylation could be achieved by copper catalysis in the absence of palladium. Upon applying our previous reaction conditions[12] developed for α-boron organocopper species (**I**) to simple styrene (**1a**) with allyl phosphate, however, the desired product was obtained in poor NMR yield and ee (30%, 3% ee) along with the protonated side product. Therefore, we screened a series of reaction conditions to optimize the borylallylation of styrene (Table 1). After extensive investigation starting with a racemic ligand (dppbz, Figure 1), we found that the desired product **3aa** could be obtained in 84−87% yield when CuBr or CuCl was used as precatalyst with LiOMe as the base and allyl phosphate (**2a**) in dimethylacetamide (DMA) solvent. The use of other bases or solvents or other allylic electrophiles resulted in low NMR yields or substantial formation of side products resulting from C−H borylation (**3a′**) and protoborylation (**3a″**).[13] Next, we screened a variety of chiral ligands for their effectiveness (entries 3−10). Among the screened ligands, Josiphos-type ligands and QuinoxP ligand gave promising yields of the desired product **3aa** in good ee (entries 7−10). Finally, we

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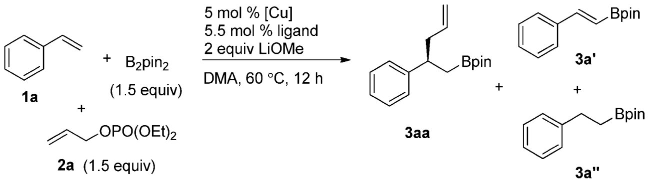
Table 1. Optimization



entry	[Cu]	ligand	conv[a] (%)	NMR yield[a] (%) 3aa	NMR yield[a] (%) 3a′ + 3a″	ee[b] of 3aa (%)
1	CuBr	dppbz	94	87 (80)[c]	<2	
2	CuCl	dppbz	92	84	<2	
3	CuBr	(*R*)-Segphos	90	50	3	75
4	CuBr	Duanphos	100	98 (95)[c]	<2	77
5	CuBr	(*S*,*S*)-BPE	43	43	38	56
6	CuBr	(*R*,*R*)-Walphos	70	48	<2	18 (*S*)
7	CuBr	(*R*,*S*)-*t*-Bu-Josiphos	100	55	19	89
8[d]	CuBr	(*R*,*S*)-Josiphos	92	73	3	87
9[d]	CuBr	(*R*,*R*)-QuinoxP	97	77 (73)[c]	2	88
10[d]	CuCl	(*R*,*R*)-QuinoxP	97	78 (74)[c]	2	90

[a] Determined by ^{1}H NMR analysis using DMF as an internal standard. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Isolated yield of the corresponding hydroxy product via oxidation using $NaBO_3$. [d] Reaction temperature was 40 °C instead of 60 °C.

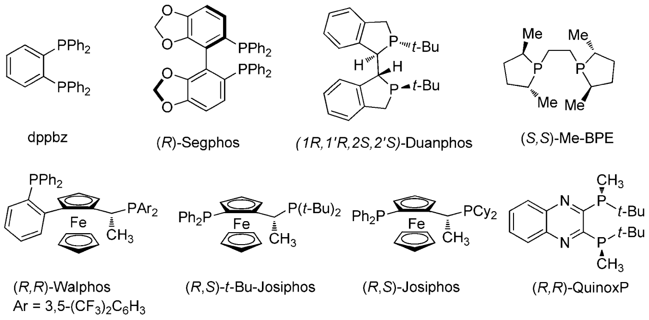
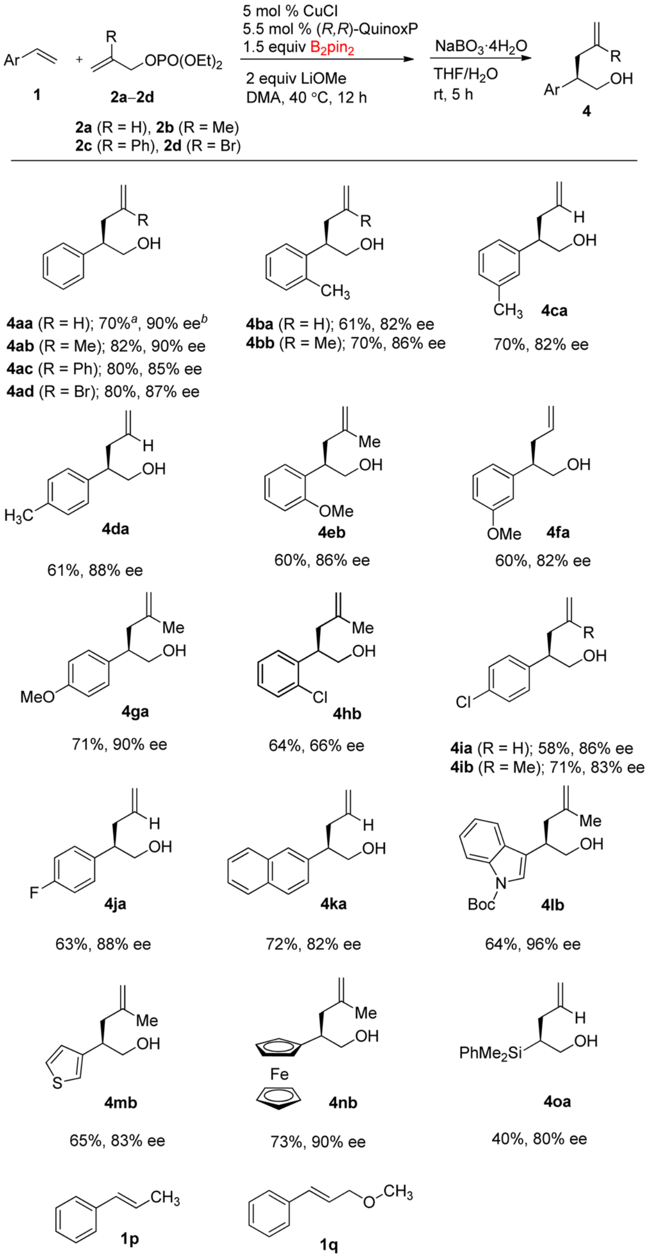


Figure 1. Ligand structure.

chose CuCl/QuinoxP in DMA (entry 10) as an optimized set of reaction conditions.

Having identified optimized conditions, we next investigated the substrate scope of the borylallylation (Scheme 2). Reactions of styrene (**1a**) with different allylic electrophiles (**2a–d**) proceeded to give good yields of borylallylated products with good enantioselectivities. Substituted allylic electrophiles (**2b–d**) provided improved yields of the products compared to allyl phosphate **2a**, presumably due to less competing side reaction with the active Cu–Bpin catalyst. In particular, the use of Br-substituted allylic phosphate (**2d**) led to the desired compound containing a vinyl bromide, which could be further utilized in a variety of other organic transformations.[14] *o*-, *m*-, and *p*-methyl and -methoxy-substituted styrenes were all reactive (**1b–g**), but slightly decreased ee values were observed in the *ortho*- and *meta*-substituted cases. Substrates (**1e–j**) with an electron-donating- or electron-withdrawing substituent were suitable substrates in the borylallylation. However, the vinyl arene (**1h**) with an *o*-Cl exhibited relatively low enantioselectivity compared to other *ortho*-substituted vinyl arenes. The reaction of vinyl naphthalene and other heteroaromatic vinyl arenes gave the desired products in good yields and ee. In particular, 3-vinyl indole (**1l**) and vinyl ferrocene substrate (**1n**) afforded the corresponding products **4lb** and **4nb** in 96% and 90% ee, respectively. The reaction of a vinylsilane gave product **4oa** in 40% yield and 80% ee. Finally, we found that internal alkene substrates (**1p** and **1q**) did not afford the desired coupled products due to competitive reactions of the borylcopper catalyst with allyl phosphate.

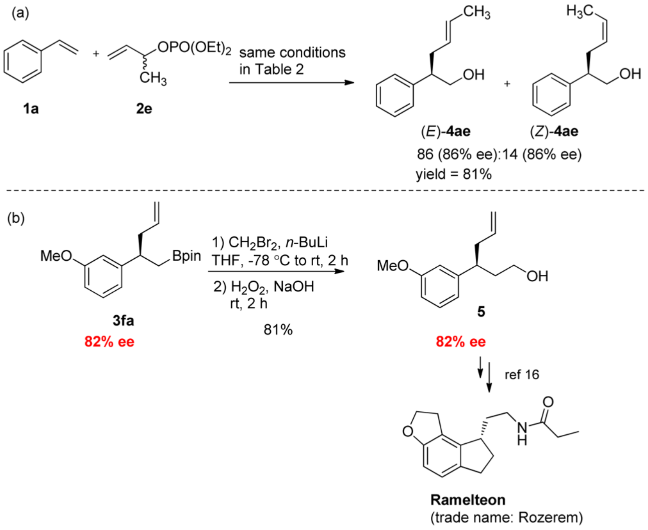
Scheme 2. Substrate Scope in Asymmetric Borylallylation[a]



[a] Isolated yield. [b] Determined by HPLC analysis on a chiral stationary phase.

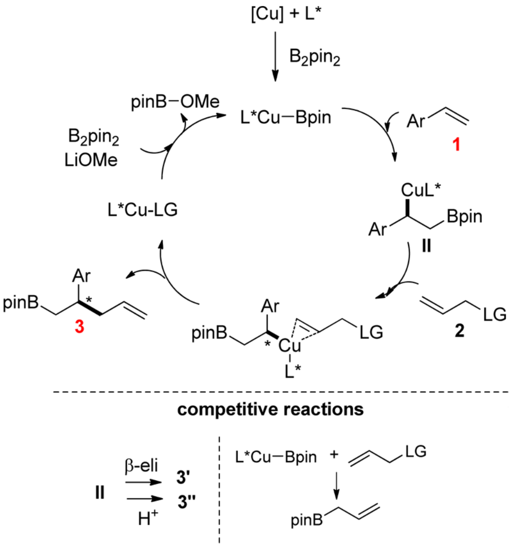
This three-component coupling was also effective with secondary allylic phosphate **2e** (Scheme 3, a), affording the corresponding allylation products (*E*)- and (*Z*)-**4ae** in a 6:1 ratio in 86% ee. These results indicate the S_N2'-substitution occurs without much influence of the stereogenic center of the allylic phosphate. However, 1,2-disubstituted internal allylic

Scheme 3. Borylallyation with Allyl Phosphate 2e and Application of Product 3



phosphates with increased steric demand at the terminal olefin carbon were not efficient (see the Supporting Information for details). In a brief application, the borylallylated product **3fa** was homologated[15] without erosion of the ee to a known intermediate in the synthesis of ramelteon[16] (Scheme 3, b).

Scheme 4. Proposed Catalytic Cycle and Competitive Reaction Pathways



A proposed catalytic cycle for this reaction is shown in Scheme 4. The active catalyst L*Cu−Bpin reacts with vinyl arene to form the borylcuprated intermediate **II**, which undergoes S_N2'-allylic substitution with an allylic electrophile to yield the desired product (**3**). A catalyst regeneration step completes the catalytic cycle. Other undesired products can form from intermediate **II** by side reactions and direct boryl substitution of the allylic electrophile with the Cu−Bpin catalyst.

In conclusion, we have described a copper-catalyzed, enantioselective method for the borylallylation of vinyl arenes in the absence of a palladium cocatalyst. Enantioenriched and functionalized organoboron compounds can be efficiently obtained by sequentially incorporating boryl and allyl groups onto the C=C bond of vinyl arenes in a regio- and enantioselective manner. Efforts to develop more widely applicable borylallylation protocols are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03022.

Experimental procedures, characterization of products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(12) A combination of 5 mol % of CuCl, 5.5 mol % of (*R*,*R*)-Walphos, and 2 equiv of LiO*t*-Bu was used in THF at 40 °C. Compounds **3a** and **3a″** were produced in 30% and 11% NMR yields, respectively.

(13) See the Supporting Information for details and Scheme 4.

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