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Copper(I)-Catalyzed Enantioselective 1,6-Borylation of α,β,γ,δ-Unsaturated Phosphonates

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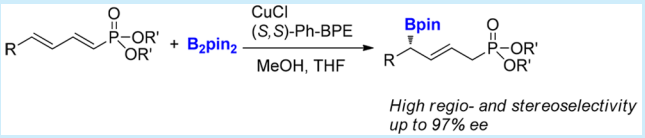
Supporting Information

ABSTRACT: Copper(I)-catalyzed asymmetric 1,6-borylation of 1,3-dienylphosphonates was achieved using (*S*,*S*)-Ph-BPE as a chiral ligand. Regio-, stereo-, and enantioselective borylation successfully proceeded to afford phosphonate-containing allylboronates, with high enantioselectivity up to 97% ee. Further applications of the resulting products generated a valuable phosphonate analogue of γ-butyrolactone.



Optically active phosphonate derivatives play an important role as a bioisostere of a carboxylic acid in drug synthesis[1] and a probe for designing antibodies.[2] In particular, chiral allyl phosphonate derivatives are observed in pharmacologically interesting compounds, such as antibiotics rhizocticin (**1**) and plumbemycin (**2**) and an analogue of cidoforvir (**3**) (Figure 1).[3]

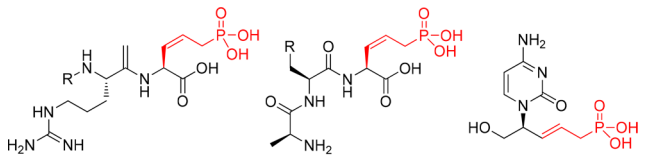


Figure 1. Examples of biologically active chiral allyl phosphonate derivatives.

Asymmetric conjugate addition to Michael acceptors is a powerful method for construction of optically active building blocks.[4] Among them, enantioselective 1,4-borylation of α,β-unsaturated acceptors is one of the most well-established areas in organic chemistry[5] due to the applicability of C−B bonds to various functional groups such as C−O, C−N, and C−C bonds.[6] Successful examples of asymmetric 1,4-borylation of electron-deficient alkenes have been reported with transition metals[7,8] and organocatalysts[9] in past years. On the other hand, enantioselective 1,6-borylation of extended Michael acceptors has been underdeveloped, due to difficulty in controlling regio-, stereo-, and enantioselectivity.[10] For that reason, to the best of our knowledge, limited examples were reported using a copper catalyst.[11,12] In 2013, Kobayashi and co-workers succeeded in Cu(II)-catalyzed asymmetric 1,6-borylation of cyclic dienones in water, with good enantioselectivity up to 89% ee.[11a] However, acyclic dienones and dienoates predominantly afforded β-borylated products via 1,4-addition, and δ-selective borylation was possible only with β,β-disubstituted cyclic substrates. In 2014 and 2018, 1,6-borylations of acyclic α,β,γ,δ-unsaturated carbonyl compounds with a small amount of copper catalyst were reported by Lam and co-workers, which afforded (*E*) or (*Z*)-allylboronates with high enantioselectivity up to 96% ee.[11b,c]

In recent years, our laboratory has been engaged in the development of copper-catalyzed 1,4-borylation of α,β-unsaturated acceptors.[7a−d] Despite the promising reactivity of unsaturated phosphonates to access interesting compounds, regio- and enantioselective borylation of these compounds with copper catalysts has not been achieved.[13] Herein, we report a copper-catalyzed enantioselective 1,6-borylation of dienylphosphonates.

We initiated our investigation by examining the reaction of (1*E*,3*E*)-pentadienylphosphonate (**1a**) with bis(pinacolato) diboron (B_2pin_2), in the presence of a catalytic amount of copper and racemic ligand and MeOH as a protic additive (Table 1). Racemic DPEphos ligand (Figure 2) displayed excellent regio- and stereoselectivity affording only (*E*)-**2a** in good yield (entry 1). When the IMes−CuCl complex was used, a mixture of (*Z*)-**2a** and (*E*)-**2a** was obtained, with (*Z*)-**2a** formed as the major product (entry 2). Based on these racemic results, we screened various chiral bisphosphine ligands. (*R*,*S*)-Josiphos, the representative ligand in our previous copper catalyzed asymmetric conjugate borylation of various electron-deficient alkenes[7a−c] afforded (*E*)-**2a** in good enantioselectivity, but with moderate regioselectivity (entry 3). Mandyphos ligand displayed a poor *E*/*Z* ratio and enantioselectivity (entry 4). Changing the ligand to Me-Duphos or MeO-BIPHEP allowed better regioselectivity, but the enantiomeric excess was disappointing (entries 5 and 6). Finally, (*S*,*S*)-Ph-BPE predominantly produced (*E*)-allylic boronate **2a** in 72% good yield with high 90% ee (entry 7).

With the optimized reaction conditions in hand, we next investigated the 1,6-borylation of various 1,3-dienylphosphonates (Scheme 1). Products were isolated after oxidation, due

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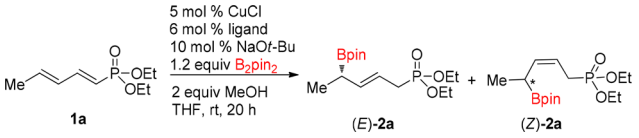
Table 1. Optimization of Reaction Conditions



entry	ligand	(*E*)-**2a**:(*Z*)-**2a**[a]	NMR yield (%)[b]	ee (%)[c]
1	DPEphos	>99:<1	87	–
2	IMes-CuCl	20:80	17	–
3	(*R*,*S*)-Josiphos	77:23	63	86
4	(*R*,*R*,*S*,*S*)-Mandyphos	41:59	34	8
5	(*S*,*S*)-Me-Duphos	91:9	86	55
6	(*R*)-MeO-BIPHEP	>99:<1	87	13
7	(*S*,*S*)-Ph-BPE	96:4	83 (72)[d]	90

[a]Determined by ^{1}H NMR analysis. [b]NMR yield of (*E*)-**2a**, determined by ^{1}H NMR analysis using DMF as an internal standard. [c]Ee of (*E*)-**2a**, determined by chiral HPLC analysis. See the Supporting Information for details. [d]Isolated yield.

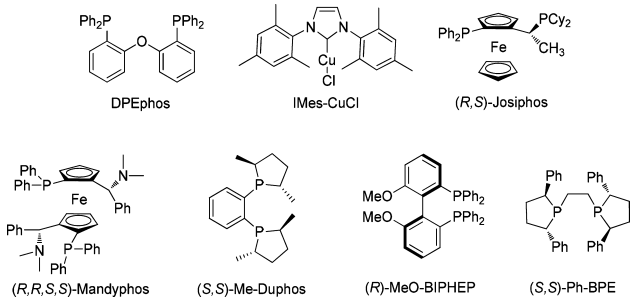
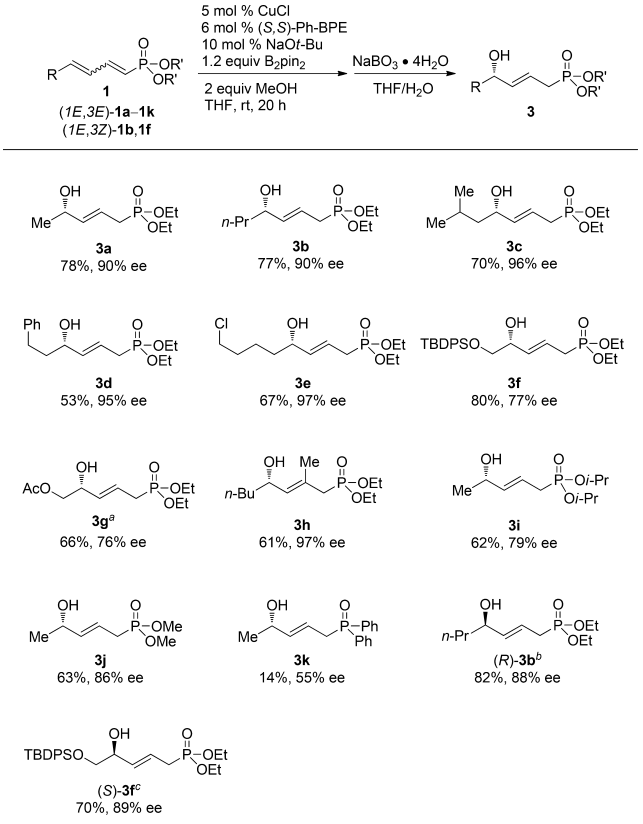


Figure 2. Ligand structure.

to instability of phosphonate-containing allylboronates to silica gel chromatography. Corresponding allylic alcohol products bearing methyl (**3a**), *n*-propyl (**3b**), isobutyl (**3c**), and CH_2CH_2Ph (**3d**) at the δ carbon were obtained with high enantioselectivities. The absolute configuration of **3a** was confirmed by comparing its optical rotation value with the value of **3a** synthesized from (L)-ethyl lactate.[14,15] The chloro group was compatible with the catalytic system as well, affording the desired product (**3e**) in 67% yield with 97% ee. Conversely, moderate ee was observed for silyl ether and ester containing products **3f** and **3g**. β,β-Disubstituted dienylphosphonate (**1h**) provided a δ-addition product (**3h**) in moderate yield with high enantiomeric excess. However, changing the substituent of phosphonates from ethyl to other groups, such as isopropyl (**3i**) and methyl (**3j**), did not improve the enantioselectivity. In addition, standard catalytic conditions were not effective for dienyl-diphenylphosphine oxide, as the desired product (**3k**) was afforded in poor yield and enantioselectivity. Changing the geometry of **1b** and **1f** from (*E*) to (*Z*) resulted in formation of the final products (**3b** and **3f**), with exact opposite absolute configuration and similar enantioselectivities.[16]

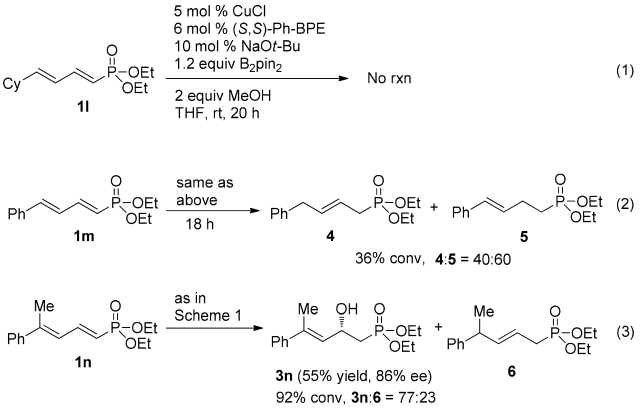
The catalytic system was also sensitive to the substituent at the δ position (Scheme 2). The dienylphosphonate bearing a cyclohexyl substituent at the δ-carbon (**1l**) did not produce either the 1,6-borylated product under the optimized reaction conditions or 1,4-borylated product, as was the case in the borylation of $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compounds by the Lam group[11b] (Scheme 2, eq 1). Deborylated products (**4** and **5**) were observed with a phenyl-containing substrate (**1m**)

Scheme 1. Substrate Scope in Asymmetric 1,6-Borylation



[a]20 mol % NaO*t*-Bu was used. [b](1*E*,3*Z*)-**1b** was used. [c](1*E*,3*Z*)-**1f** was used.

Scheme 2. Limitation of 1,6-Borylation



(Scheme 2, eq 2). Adding steric hindrance to the δ-position led to the 1,4-addition product (**3n**) in moderate yield, but with good enantioselectivity with a small amount of deborylated product **6** (Scheme 2, eq 3).

To demonstrate the synthetic utility of the phosphonate-containing allyl boronic ester, we performed its allylation with diverse aldehydes (Scheme 3). We screened various Lewis acid catalysts, and $ZnBr_2$ was the most effective Lewis acid catalyst among them, generating corresponding product **7a** with good regioselectivity.[17] Reaction of (*E*)-**2a** with isovaleraldehyde, 3-phenylpropionaldehyde, hexanal, and cyclohexanecarboxaldehyde allowed the desired product **7b**–**7e** with excellent regioselectivities. Also, the enantioselectivity was maintained without erosion during the reaction. As a further application to

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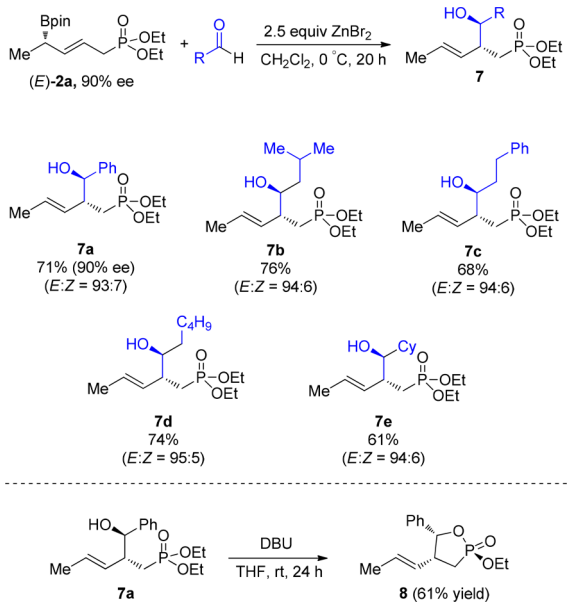
Scheme 3. Addition of (*E*)-2a into Various Aldehydes[a]



[a]Reactions were carried out with 2.5 equiv of $ZnBr_2$, and *E*/*Z* ratio was determined by NMR analysis of a crude reaction mixture.

synthesize biologically useful intermediates, cyclization of **7a** produced 1,2-oxaphospholane-2-oxide **8**.[18]

In conclusion, we have developed a copper-catalyzed asymmetric 1,6-borylation of 1,3-dienylphosphonates with B_2pin_2. We found that the (*S*,*S*)-Ph-BPE ligand is efficient in producing *δ*-borylated allylphosphonates with high regio- and enantioselectivity. Also, further transformation of the resulting product provides a synthetic method for cyclic phosphonate compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03532.

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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