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Cu-Catalyzed Asymmetric Borylative Cyclization of Cyclohexadienone-Containing 1,6-Enynes

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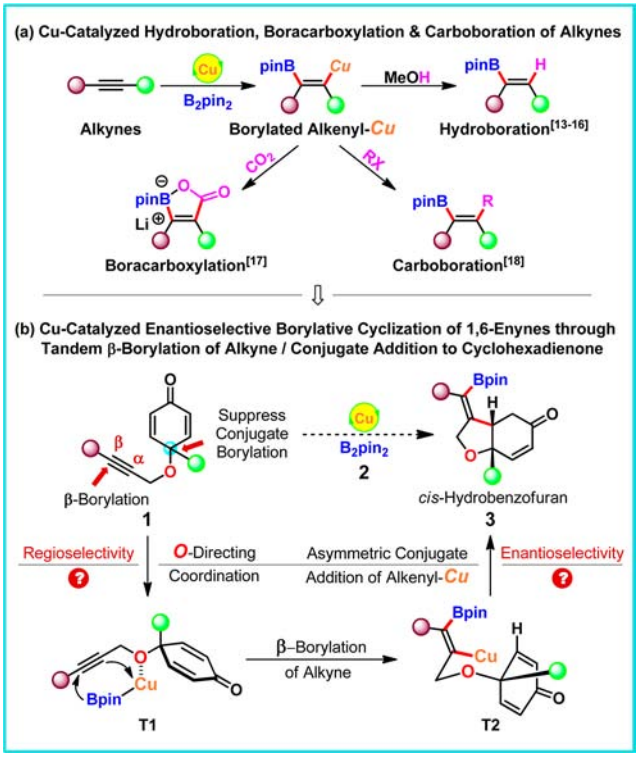
Supporting Information

ABSTRACT: The first Cu-catalyzed asymmetric borylative cyclization of cyclohexadienone-containing 1,6-enynes is achieved through a tandem process: selective *β*-borylation of propargylic ether and subsequent conjugate addition to cyclohexadienone. The reaction proceeds with excellent regioselectivity and enantioselectivity to afford an optically pure *cis*-hydrobenzofuran framework bearing alkenylboronate and enone substructures. Furthermore, the resulting bicyclic products could be converted to bridged and tricyclic ring structures. This method extends the realm of Cu-catalyzed asymmetric tandem reactions using bis(pinacolato)diboron (B_2pin_2).

Transition-metal-catalyzed C−B bond formation[1] always fascinates organometallic chemists, due to its fundamental scientific interest and great applications in organic synthesis.[2] Because of the economic attractiveness and excellent functional group tolerance, copper catalysis[3] has recently attracted renewed attention, particularly in the field of Cu-catalyzed borylative addition to C═O,[4] C═N,[5] C═C,[6−8] and C≡C[9,13−16] bonds with B_2pin_2. In some cases, the copper intermediate generated in this borylation process could subsequently react with certain electrophiles. So far, Cu-catalyzed asymmetric borylative tandem reactions are limited to borylation/alkylation,[10] conjugate borylation/aldol,[11] and borylation/amination reactions.[12] To the best of our knowledge, no examples have been described in literature of asymmetric borylative cyclization of 1,6-enyne using a copper catalyst. Herein we communicated our finding in the Cu-catalyzed asymmetric tandem reaction between 1,6-enyne and B_2pin_2, which meanwhile provided an efficient approach to construct an enantioenriched *cis*-hydrobenzofuran framework with alkenylboronate and enone functionalities.

Scheme 1a shows several post-transformations of the borylated alkenyl-copper intermediates with different electrophiles: MeOH for the hydroboration,[13−16] CO_2 for the boracarboxylation,[17] and alkyl halides for the carboboration.[18] Encouraged by these elegant reports, we envisioned that the Cu-catalyzed tandem borylation/conjugate addition reaction of cyclohexadienone-containing 1,6-enynes would possibly take place (Scheme 1b). In order to obtain the cyclization product, we need to minimize the conjugate borylation[8] to the enone. For a linear substrate, (2*E*)-2-nonen-7-ynal, the conjugate borylation was found to be unfortunately preferred to the borylation of the C≡C bond.[8g] However, such conjugate

Scheme 1. Strategic Design for Cu-Catalyzed Asymmetric Borylative Cyclization of 1,6-Enynes



borylation was not observed for 4,4-dimethyl-2-cyclohexenone due to the steric hindrance from the quaternary carbon.[8c] In our case with prochiral cyclohexadienone-containing 1,6-enynes **1**[19] as the substrates for the Cu-catalyzed asymmetric borylative cyclization,[20] the conjugate borylation could be suppressed by the neighboring substituents. More importantly, the regioselective *β*-borylation of an alkyne could be achieved through the O-coordination of a propargyl ether unit (**T1**).[15] The resulting borylated alkenyl-copper **T2** could immediately undergo enantioselective conjugate addition to a cyclohexadienone moiety in a *syn* fashion to generate the chiral product **3**.

With this mind-set, we began to examine the borylation of the model substrate **1a** with Ph_3P as the ligand. To our delight, the desired racemic product **3a** was obtained, albeit in a modest yield of 49% (Table 1, entry 1). Chiral monophosphine ligand

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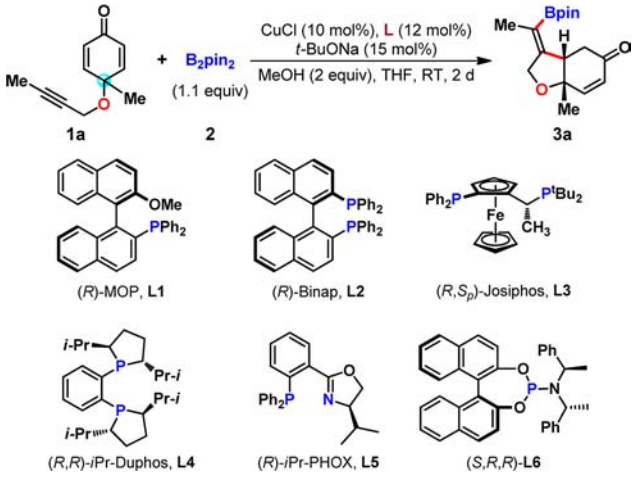
Table 1. Initial Evaluation of Various Ligands[a]



entry	L	conv. (%)[b]	yield (%)[c]	Ee (%)[d]
1	Ph_3P	75	49	–
2	**L1**	84	47	−2
3	**L2**	55	15	56
4	**L3**	40	12	−21
5	**L4**	43	7	−65
6	**L5**	65	33	−10
7	***L6***	*76*	*70*	*94*
8[e]	**L6**	73	58	90
9[f]	**L6**	*67*	51	87

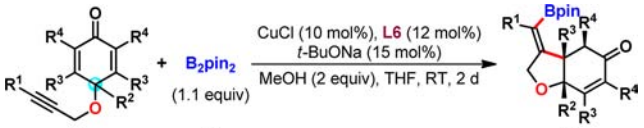
[a]Reactions were performed under a N_2 atmosphere. [b]Conversion was determined by the isolated recovered **1a**. [c]Yield of isolated product **3a**. [d]Determined by HPLC analysis using a chiral stationary phase. [e]B_2pin_2 (**2**, 1.2 equiv) was used. [f]B_2pin_2 (**2**, 1.3 equiv) was used.

(*R*)-MOP (**L1**) was subsequently subjected to this reaction. Unfortunately, almost no enantioselectivity was observed (Table 1, entry 2). Next, a set of representative chiral bisphosphine ligands (**L2**−**L4**) and phosphine-oxazoline ligand (**L5**) were investigated, still affording low yields and low to moderate enantioselectivities (Table 1, entries 3−6). Phosphoramidites proved to be versatile ligands for Cu-catalyzed conjugate addition reactions.[21] In our case, the application of ligand (*S*,*R*,*R*)-**L6** dramatically improved both the reaction yield (up to 70%) and the enantioselectivity (up to 94% *ee*, Table 1, entry 7). However, increasing B_2pin_2 (**2**) loading led to different levels of erosion in both yields and enantioselectivities (Table 1, entries 8−9), which might be caused by further conjugate borylation of the excessive B_2pin_2 to **3a** (Supporting Information).

With the optimal reaction conditions identified, various substrates were investigated and the results are summarized in Table 2. With the R^2 substituent as the alkyl, allyl, benzyl, vinyl, and phenyl group, the reactions proceeded smoothly with moderate to high yields (58%−70%) and excellent enantioselectivities (92−99% *ee*, Table 2, entries 1−8). With a heteroatom (O and Br) as part of R^2 in substrates **1**, the reaction yields and *ee* values remained high (Table 2, entries 9−13). It is worth mentioning that the alkyl bromide group in substrate **1l** was well tolerated in this reaction (Table 2, entry 12); i.e., the borylated alkenyl-copper intermediate selectively underwent conjugate addition rather than nucleophilic substitution.

Bigger R^1 substituents (Et and *n*-Bu) resulted in slightly lower enantioselectivities (Table 2, entries 14 and 15). As for

Table 2. Substrate Scope[a]



For **1b** to **1m**: R^1 = Me-, R^3 = R^4 = H
1b: R^2 = Et- **1c**: R^2 = *i*-Pr- **1d**: R^2 = CH_2=CH-CH_2-
1e: R^2 = $PhCH_2$- **1f**: R^2 = CH_2=CH- **1g**: R^2 = Ph-
1h: R^2 = 4-Br-Ph- **1i**: R^2 = MeOC(O)-CH_2- **1j**: R^2 = AcO-$(CH_2)_2$-
1k: R^2 = TBSO-$(CH_2)_2$- **1l**: R^2 = Br-$(CH_2)_3$- **1m**: R^2 = MeO-
For **1n** to **1p**: R^3 = R^4 = H
1n: R^1 = Et-, R^2 = Me- **1o**: R^1 = *n*-Bu-, R^2 = Me- **1p**: R^1 = H-, R^2 = $PhCH_2$-
For **1q** to **1r**: R^1 = R^2 = Me-
1q: R^3 = Me-, R^4 = H- **1r**: R^3 = H-, R^4 = Me-

entry	substrate	product	yield (%)[b]	Ee (%)[c]
1	**1a**	**3a**	70	94
2	**1b**	**3b**	70	99
3	**1c**	**3c**	65	95
4	**1d**	**3d**	60	99
5	**1e**	**3e**	58	99
6	**1f**	**3f**	63	99
7	**1g**	**3g**	65	92
8	**1h**	**3h**	64	97
9	**1i**	**3i**	51	92
10[d]	**1j**	**3j**	60	95
11	**1k**	**3k**	55	94
12[e]	**1l**	**3l**	72	99
13[e]	**1m**	**3m**	49	88
14	**1n**	**3n**	55	92
15[e]	**1o**	**3o**	47	87
16	**1p**	**3p**	63	70
17	**1q**	**3q**	65	90
18	**1r**	**3r**	61	82

[a]Reactions were performed under a N_2 atmosphere. [b]Yield of isolated product. [c]Determined by HPLC analysis using a chiral stationary phase. [d]B_2pin_2 (**2**, 1.2 equiv) was used. [e]B_2pin_2 (**2**, 1.3 equiv) was used.

the terminal alkyne substrate **1p** (R^1 = H), the reaction still worked well (Table 2, entry 16). With the substituent at the *β*- or *α*-position of the dienone, the reactions readily provided cyclization products possessing two quaternary stereocenters (**3q**) or three contiguous stereocenters (**3r**) in high yields and *ee* values, respectively (Table 2, entries 17 and 18).

To better understand the regioselectivity of Cu-catalyzed borylation which was proposed to be controlled through the coordination with the oxygen atom in the propargylic ether unit, substrates **1s** and **1t** with an additional O-coordinating center were prepared and applied to this reaction (Scheme 2). As for **1s**, due to the directing capacity $O^1 > O^2$ (less hindrance for −OBn), *α*-borylation of an alkyne took place, thus leading to noncyclized product **3s**, which was very unstable and directly oxidized to ketone **4s** in the air. In contrast, because of the directing capacity $O^2 > O^3$ (more hindrance for −OTrt) in **1t**, *β*-borylation of the alkyne occurred, resulting in the desired cyclization product **3t**. For the *N*-linked substrates (**1u**, **1v**, and **1w**), no desired cyclization products were observed under the standard reaction conditions, which may be attributed to the weak directing ability of N-functional groups.

To determine the absolute configurations of the *cis*-hydrobenzofuran products in Table 2, the boronate **3a** was converted, through Suzuki−Miyaura coupling with 4-bromo-

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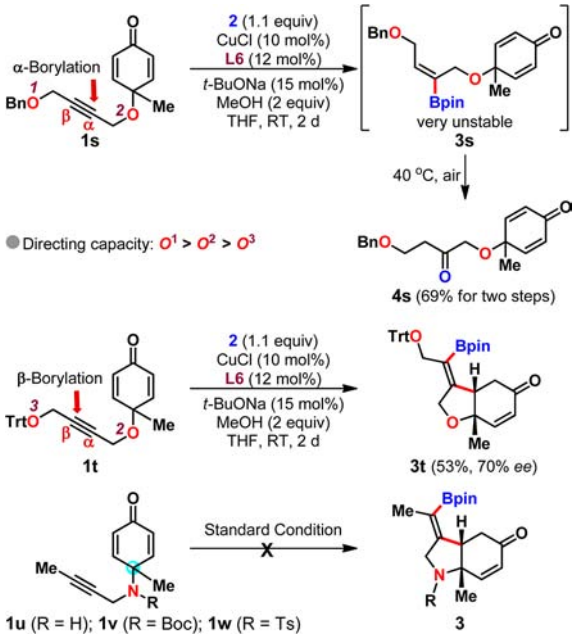
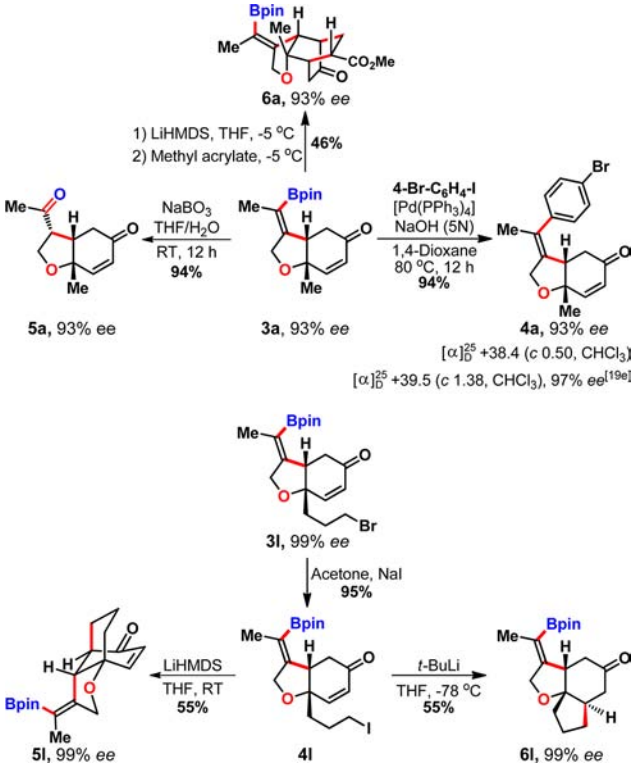
Scheme 2. Directing Capacity of Propargylic Oxygen Atom towards β-Borylation of Alkyne



phenyl iodide, to a known compound (*S*,*S*)-**4a** which was fully confirmed by X-ray crystallography (Scheme 3).[19e] The alkenylboronate and enone functionalities in the cyclization products could be further modified to other useful structures. A facile oxidation of alkenylboronate **3a** produced the methyl-ketone **5a** in 94% yield. The bridged cyclic product **6a** could be acquired from a formal [4 + 2] reaction between **3a** and methyl acrylate through double Michael additions. As for **3l**, the corresponding iodide product **4l** was easily obtained. Upon treatment of **4l** with LiHMDS, an intramolecular alkylation reaction occurred to deliver the bridged ring product **5l**. During treatment of **4l** with *t*-BuLi, the resulting alkyl lithium underwent an intramolecular Michael reaction to give the tricyclic product **6l**. All the above transformations proceeded smoothly with no loss of the enantiomeric excesses.

Scheme 3. Several Transformations of the Cyclization Products



In summary, the first Cu-catalyzed asymmetric borylative cyclization reaction between cyclohexadienone-containing 1,6-enynes and B_2pin_2 has been established through a tandem process: selective β-borylation of the propargylic ether and subsequent enantioselective conjugate addition to cyclohexadienone.[22] This reaction is conducted under mild and convenient conditions, affording enantioenriched *cis*-hydrobenzofuran with moderate yields and high to excellent enantioselectivities. The functional groups of alkenylboronate and enone in the cyclization products could be subjected to various transformations for elaborating the synthetic utility. The present results extend the realm of the Cu-catalyzed asymmetric tandem reaction using B_2pin_2. Further studies on the applications of cyclohexadienone-containing 1,6-enynes are in progress in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, structural proofs, and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) For the mechanistic studies see Supporting Information (Section 5).