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Copper-Catalyzed trans-Hydroboration of Terminal Aryl Alkynes: Stereodivergent Synthesis of Alkenylboron Compounds

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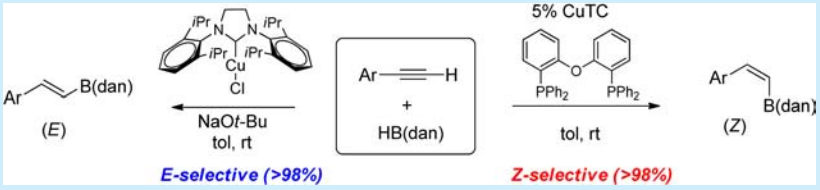
Supporting Information



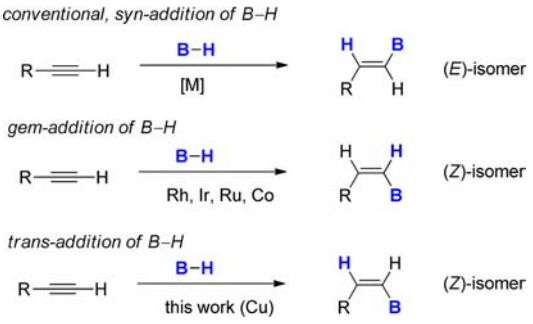
ABSTRACT: A Cu-catalyzed highly *Z*-stereoselective hydroboration of alkynes with 1,8-naphthalenediaminatoborane (HB(dan)) is developed. DPEphos (bis[(2-diphenylphosphino)phenyl]ether)-ligated Cu catalysts produced alkenylboron compounds from terminal alkynes with excellent *Z*-stereoselectivity. In contrast, using a SIPr−CuCl complex as the precatalyst exclusively produced *E*-hydroboration products at mild conditions. Both catalytic procedures form alkenylboron products stereocomplementary to each other, constituting stereodivergent hydroboration of alkynes through Cu catalysis. Deuterium labeling and isomerization studies support the *Z*-selective hydroboration via trans-addition of the boron reagent to terminal alkynes as opposed to precedent noble-metal-catalyzed trans-hydroborations.

Organoboron compounds are versatile synthetic intermediates in organic synthesis. The formation of stereodefined alkenylboron compounds is important due to their unique applicability in various cross-coupling reactions and low toxicity.[1]

Hydroboration of alkynes is a straightforward and practical method for the production of alkenylboron compounds.[2−4] The hydroboration of terminal alkynes mostly yields (*E*)-1-alkenylboron compounds as the major product via syn-addition of the borane (B−H) reagent.[4] In contrast, hydroboration reactions yielding (*Z*)-alkenylboranes from terminal alkynes have been scarcely reported,[5] with noble transition-metal-catalyzed hydroboration using Rh,[5a] Ir,[5a] and Ru[5b] catalysts. The reported trans-hydroboration reactions with *Z*-selectivity did not occur through genuine trans-addition of the borane reagent; the reactions formed metal−vinylidene intermediates by migration of an acetylenic hydrogen and subsequent gem-addition of the borane reagent to give the *Z*-product.[5,6] A recent Co-catalyzed hydroboration of terminal alkynes[7] also yielded *Z*-selective alkenylboron products with the terminal H migrated to the internal sp-carbon via a Co−H species but suffered from postcatalytic product isomerization.

The trans-hydroboration through the trans-addition of the borane reagent to alkynes is very rare, while a few trans-selective hydrosilylations of alkynes have been reported.[8] One exceptional case was recently reported for the hydroboration of internal alkynes using [Cp*Ru] catalysts by Sundararaju and Fürstner.[9] To the best of our knowledge, trans-hydroboration of terminal alkynes by the trans-addition of the B−H moiety has not been reported yet, and herein, we report the first Cu-catalyzed, highly stereoselective trans-hydroboration of terminal alkynes (Scheme 1). Moreover, we report combinations of ligand−Cu catalysts for the highly selective, stereodivergent hydroboration of alkynes to produce either (*Z*)- or (*E*)- alkenylboron compounds.

Scheme 1. Conventional syn-, gem-, and trans-Addition of B−H



Initial screening experiments were conducted with phenylacetylene using various catalyst−ligand combinations (Figure 1) and 1,8-naphthalenediaminatoborane (HB(dan)) as the borane reagent (Table 1). Preliminary results with pinacolborane (HB(pin)) resulted in a mixture of stereoisomers and dihydroborated products.[10] 1,8-Diaminonaphthalene is an

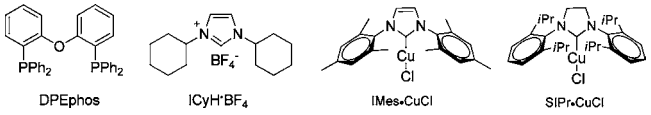


Figure 1. Structure of ligands and catalysts.

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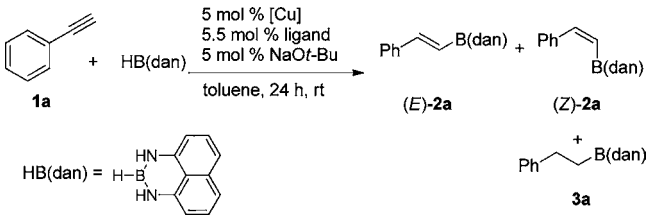
Table 1. Screening of the Hydroboration[a]



entry	[Cu]/ligand	conv (%)[b]	product ratio[c]	yield (%)[d]
1	CuTC/*rac*-binap	0		
2	CuTC/dppf	0		
3	CuTC/xantphos	73	12:56:32	58 (66:34)[e]
4	CuTC/DPEphos	>90	0:85:15	66 (85:15)[e]
5[f]	CuTC/DPEphos	74	0:86:14	ni[g]
6	Cu(OAc)/DPEphos	77	0:74:26	54 (85:15)[e]
7[h]	CuTC/DPEphos	>95	0:87:13	82 (90:10)[e]
8	CuCl/ICyH·BF_4	80	30:70:0	ni[g]
9	IMes·CuCl	81	67:33:0	ni[g]
10[i]	SIPr·CuCl	>95	>98:0:0	76

[a]Mixture of **1a** (0.5 mmol), HB(dan) (1 equiv), and catalyst (5 mol %) was stirred at rt in toluene (6 mL). [b]Determined by ^{1}H NMR analysis. [c]Product ratio ((*E*)-**2a**/(*Z*)-**2a**:**3a**) was determined by ^{1}H NMR analysis of a crude reaction mixture. [d]Combined yield of coeluted (*Z*)-**2a** with **3a** for entries 3−7 and isolated yield of (*E*)-**2a** (entry 10). [e]Ratio of (*Z*)-**2a** and **3a** in the isolated mixture. [f]THF was used instead of toluene. [g]Not isolated. [h]1.2 equiv of **1a** relative to HB(dan) was used in the absence NaO*t*-Bu and stirred for 6 h. [i]10 mol % of NaO*t*-Bu was used.

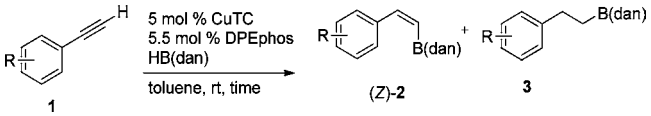
efficient protective group for the boronyl group in the iterative synthesis of Suzuki−Miyaura coupling of oligoarene derivatives, as reported by Suginome et al.[11] Thus, we changed the borane reagent to HB(dan), with the aim to establish a non-noble-metal-catalyzed, one-step preparation method of B(dan)-protected alkenylboron compounds.

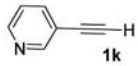
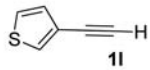
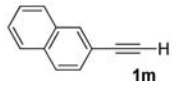
Interestingly, a significant influence of the ligand on the catalytic activity and selectivity was observed in the hydroboration. Copper(I)−thiophene-2-carboxylate (CuTC) with bidentate ligands, such as binap and dppf, led to no reaction; however, xantphos and DPEphos ligands showed a substantial conversion of the starting alkyne (entries 1−4). It was found that, surprisingly, the Cu−DPEphos catalyst furnished the corresponding (*Z*)-alkenylboron product ((*Z*)-**2a**) without the formation of the *E*-stereoisomer along with the reduced alkylboron product **3a**[12] (entry 4). Use of THF solvent instead of toluene and metal precursors[13] other than CuTC displayed lower catalytic activities (entries 5 and 6). However, the stereoisomeric ratio did not considerably change, affording the *Z*-product as the major stereoisomer. Finally, the catalyst gave a slightly better result, even in the absence of the NaO*t*-Bu base (entry 7).[14]

When strong σ-donating N-heterocyclic carbene ligands, particularly bulky NHC ligands, were applied to the hydroboration, (*E*)-alkenylboron product started to form as the major product over *Z*-products (entries 8−10). Finally, we found that the (*E*)-alkenylboron product was the only product that formed when the SIPr·CuCl complex was used (entry 10). It is noteworthy that stereodivergent hydroboration could be accomplished by choosing a proper ligand for the Cu catalyst in the hydroboration of alkynes with HB(dan).

Optimized reaction conditions for the production of (*Z*)-alkenylboron compounds were applied to other alkynes (Table 2). A variety of functional-group-substituted aryl alkynes were subjected to the hydroboration conditions, producing alkenyl-

Table 2. Hydroboration of Terminal Alkynes with CuTC−DPEphos and HB(dan)[a]



entry	R	(1)	time (h)	ratio[b] of (*Z*)-**2**:**3**	yield (%)[c]
1	4-CF_3	**1b**	6	85:15	87
2	3-F	**1c**	6	89:11	81
3	4-Cl	**1d**	18	86:14	88
4	4-Br	**1e**	18	85:15	77
5	4-Me	**1f**	24	89:11	68
6	4-OMe	**1g**	24	89:11	55
7	4-CO_2Me	**1h**	12	78:22	79
8	4-CN	**1i**	12	81:19	72
9	2-CF_3	**1j**	24	83:17	53
10	 **1k**		18	82:18	68[d]
11	 **1l**		12	78:22	61
12	 **1m**		12	85:15	76

[a]5 mol % of CuTC, 5.5 mol % of DPEphos, **1a** (1.2 equiv, 0.1 M), and HB(dan) (1 equiv) were used at rt in toluene. [b]Determined by NMR spectroscopy of crude reaction mixtures. No *E*-product was observed. [c]Isolated yield of coeluted (*Z*)-**2** with **3** based on the amount of HB(dan). Ratios of (*Z*)-**2** with **3** in the isolated products are almost the same as that in the crude reaction mixture or 2−4% higher, favoring (*Z*)-**2**. [d]Yield of pure (*Z*)-**2k**.

boron products in good yield and high *Z*-selectivity.[15] Arylacetylenes with an electron-withdrawing group reacted faster than those with an electron-donating substituent. It is noteworthy that sensitive functional groups such as Cl, Br, CO_2Me, and CN were tolerant under the reaction conditions, furnishing boron-masked functional modules[11] for Suzuki−Miyaura coupling or for further organic transformations. An ortho-substituted alkyne produced the corresponding *Z*-product, as well (entry 9). Heterocyclic aromatic compounds containing N and S atoms and naphthylacetylene were also suitable for the hydroboration, affording product with high selectivity (entries 10−12). Formation of alkylboron compound **3** (10−20%) was unavoidably observed in all terminal alkyne cases, which could be rationalized by further reaction of the alkenylboron compound **2** with the DPEphos−Cu catalyst.[16]

In contrast to the CuTC−DPEphos catalyst, the use of the SIPr−CuCl complex as the precatalyst afforded exclusively *E*-selective hydroboration products from terminal alkynes (Scheme 2). In the SIPr−Cu-catalyzed hydroboration, formation of alkylboron compound **3** was not detected and halogen groups (Cl, Br) were tolerated. Overall, the stereoselectivity of the hydroboration is greatly affected by the type of ligand applied.

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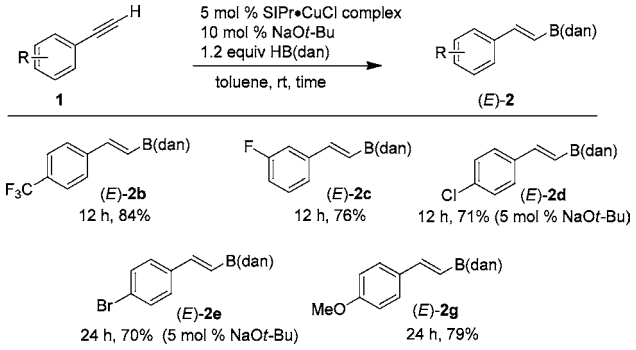
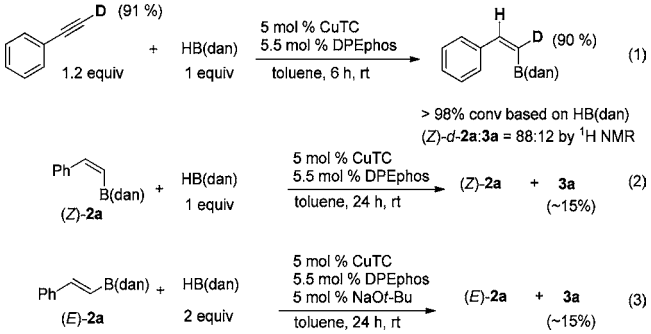
Scheme 2. SiPr−Cu-Catalyzed Hydroboration of Alkynes



Further, both of the catalytic procedures afford alkenylboron products stereocomplementary to each other, which constitute stereodivergent hydroboration of alkynes through Cu catalysis for the first time.

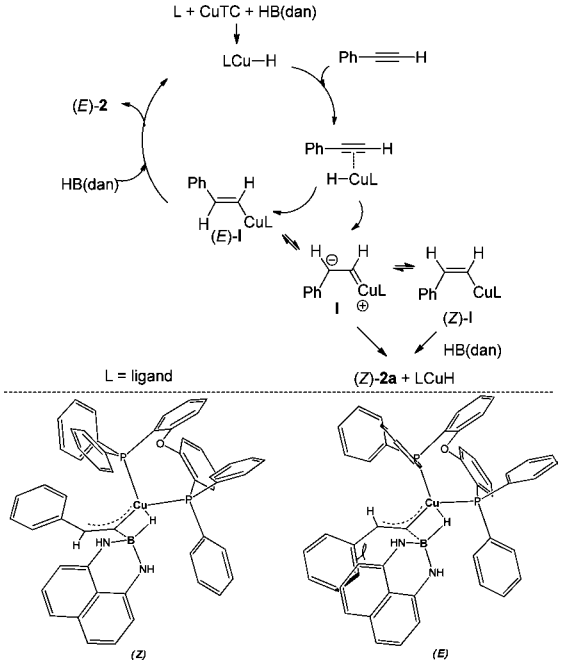
To gain insight into the reaction mechanism, a deuterium labeling experiment was conducted (Scheme 3). The hydroboration of deuterium-labeled phenylacetylene (91% *d* incorporation) with HB(dan) yielded a (*Z*)-alkenylboron product containing deuterium at the original terminal carbon (*β*-carbon from phenyl) with 99% deuterium retention (1). The result is the opposite result to the precedent noble metal (Rh, Ir, Ru)-catalyzed[5] or Co-catalyzed formal trans-hydroboration.[7] Hydroboration reactions of isolated (*Z*)-**2a** or (*E*)-**2a** were carried out, and no deterioration of the selectivity was observed (Scheme 3, (2,3)); the isomerization of (*Z*)-**2a** to (*E*)-**2a** or vice versa did not occur under the hydroboration conditions. Moreover, the reactivity and selectivity of the *Z*-selective hydroboration were not significantly affected by the inclusion of 1 equiv of TEMPO.[17] Therefore, radical-involved or a post-product isomerization mechanism could be ruled out in the hydroboration. The results indicated that a true trans-hydroboration of terminal alkynes via trans-addition of the boron reagent might be working in this catalytic system as in the hydrosilylation.

Scheme 3. Deuterium and Isomerization Studies



While a clear mechanistic picture cannot be drawn at this stage, two characteristic features seem to be involved in the catalytic cycle (Scheme 4): formation of a ligand-coordinated Cu−hydride and a stereodetermining transmetalation step. A ligand-coordinated Cu−H complex is considered as the active catalytic species in the cycle;[18,19] when CuTC was mixed with HB(dan) in the presence of PPh_3 or DPEphos as the ligand, a distinctive hydride peak at 3.52 ppm that corresponds to Stryker's reagent ($(PPh_3)CuH$) and a peak at 2.37 ppm appeared in ^{1}H NMR, respectively.[20] Moreover, the formation of Cu−B(dan) catalyst

Scheme 4. Possible Catalytic Cycle



in the cycle can be excluded since the SIPrCu−B(dan) catalyst was reported to display the opposite regioselectivity.[19a] The in situ generated Cu−H species reacts with alkyne to form organocopper intermediates. Since the stereoisomeric ratio of alkenylboron products is greatly varied by the kind of hydroborane even under the same Cu−DPEphos conditions (e.g., (*E*)-**2a**/(*Z*)-**2a** was 2.5:1 with pinacolborane[10] and 1:>99 with HB(dan) from Table 1), it could be concluded that the *σ*-bond metathesis step between organocopper intermediate and borane determines the overall stereoselectivity. Rapidly isomerizable vinylcopper intermediates or a common zwitterionic carbene−copper intermediate similar to η^2-vinyl complex in trans-hydrosilylation[21] is likely involved, but unfortunately, the intermediate complexes could not observed in our hands. The *Z*-selectivity could be rationalized by HB(dan) prefering the conformation of the intermediate with the phenyl group cis to the Cu to avoid steric interactions between the approaching dan group and the phenyl in the *σ*-bond metathesis step,[22] in contrast to the sterically bulky NHC−Cu, which disfavors such orientation of the intermediate.

In summary, we disclosed the highly selective, Cu-catalyzed stereodivergent hydroboration of terminal alkynes to produce either (*Z*)- or (*E*)-alkenylboron compounds, using HB(dan) as the hydroborating reagent. Depending on the ligand coordinated to the Cu, the ratio of (*Z*)- and (*E*)-alkenyl compounds largely varied from pure *Z* to *E*. While the use of a SIPr−CuCl complex as the precatalyst exclusively afforded *E*-selective hydroboration products from terminal alkynes, the combination of DPEphos−Cu resulted in the formation of (*Z*)-alkenylboron compounds with excellent stereoselectivity. The latter results are considered as true examples of trans-addition of the boron reagent to terminal alkynes. Further investigations are underway.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, characterization of products, and representative NMR spectra for **2** (PDF)

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Notes

The authors declare no competing financial interest.

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(10) With pinacolborane and DPEphos ligand, the *E* and *Z*-isomer ratio was 2.5:1. For the formation of dihydroborated product, see: Lee, S.; Li, D.; Yun, J. *Chem. - Asian J.* **2014**, *9*, 2440−2443.

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(13) Copper(II) precursors, such as $Cu(OAc)_2$ and copper(II) 2-ethylhexanoate, gave results similar to those for Cu(OAc) in terms of conversion and the ratio of (*Z*)-**2a** and **3a**. However, a cationic Cu complex ($[Cu(CH_3CN)_4]PF_6$) afforded a lower conversion and formation of both (*E*)-**2a** and (*Z*)-**2a** in approximately a 1:1.2 ratio.

(14) With 1.2 equiv of **1a** relative to HB(dan), NMR yields were 72% with NaO*t*-Bu and 77% without NaO*t*-Bu inclusion. Moreover, a stoichiometric amount of the base completely inhibits the hydroboration.

(15) Alkyl-substituted alkynes are not suitable substrates in the hydroboration, furnishing diborylated product with low conversion. This is possibly due to a reactivity of hydroborated alkenylboron compound higher than that of the starting alkyne. Feng, X.; Jeon, H.; Yun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3989−3992.

(16) It is presumed that alkenylboron compound **2** undergoes further addition of active Cu−H and subsequent protonation by a trace amount of water present in the reaction medium under the DPEphos−Cu-catalyzed conditions to yield the corresponding reduced alkylboron compound **3**. Separately prepared 1,1-diborylalkane **4** did not undergo any deborylation under the standard hydroboration conditions. See the Supporting Information for details.

(17) Only (*Z*)-**2a** was formed along with **3a** in a 4:1 ratio with 81% conversion under the same screening conditions of entry 4 (Table 1) in the presence of 1 equiv of TEMPO.

(18) In situ generation of Cu−H in the presence of hydroborane has been suggested in the following literature: (a) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440−14441. (b) Du, Y.; Xu, L.-W.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 16146−16147.

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(20) See the Supporting Information for details. In another experiment with dppbz (1,2-bis(diphenylphosphino)benzene) as the ligand in the presence of CuTC and HB(dan), a hydride peak at 1.41 ppm appeared, as well, which was assigned to (dppbz)Cu−H in the literature. (a) Baker, B. A.; Boškovic, Ž.; Lipshutz, B. H. *Org. Lett.* **2008**, *10*, 289−292. (b) Motokura, K.; Kashiwame, D.; Miyaji, A.; Baba, T. *Org. Lett.* **2012**, *14*, 2642−2645. For Stryker's reagent, see: (c) Lee, D.; Yun, J. *Tetrahedron Lett.* **2005**, *46*, 2037−2039.

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(22) Preliminary DFT calculations with defined (*E*)- and (*Z*)-vinylcopper showed a 3.3 kcal/mol activation barrier difference in the σ-bond metathesis step, favoring the formation of *Z*-isomer. See the Supporting Information for details.

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