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Efficient Boron−Copper Additions to Aryl-Substituted Alkenes Promoted by NHC−Based Catalysts. Enantioselective Cu-Catalyzed Hydroboration Reactions

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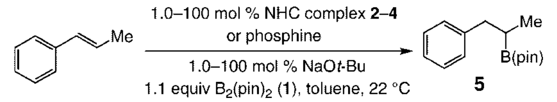
Development of efficient and stereoselective catalytic hydroboration reactions is a compelling objective in chemical synthesis;[1] a number of challenges, however, are yet to be addressed. For example, reactions of disubstituted olefins, furnishing regioisomers not accessible through the existing methods, have not been introduced. As part of studies regarding the development of N-heterocyclic carbenes (NHCs)[2] for facile site-selective and enantioselective synthesis,[3] we have begun to probe the ability of the derived metal complexes as catalysts for C−B bond formation. Herein, we disclose a protocol for catalytic boron−copper addition to acyclic and cyclic aryl olefins. Reactions are promoted by 0.5−5 mol % of a readily available NHC−Cu complex, proceed with >98:<2 site selectivity, and afford boronate isomers that complement those obtained through transformations with borohydride reagents or catalyzed by Rh- and Ir-based catalysts.[1,4] With chiral NHC complexes, Cu-catalyzed hydroborations proceed with high enantioselectivity [enantiomeric ratio (er) values up to 99:1].

Our studies were guided by previous disclosures on boron−copper addition to styrenes with stoichiometric amounts of an NHC−Cu complex and bis(pinacolato)diboron (**1**), affording secondary C−Cu and primary C−B bonds.[5] Development of a catalytic version, where protonation of the C−Cu bond constitutes net hydroboration, required us to identify an efficient procedure with the substantially less reactive disubstituted alkenes to obtain chiral alkylboranes.

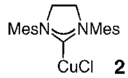
We first established that treatment of (*E*)-*β*-methylstyrene with Cu complex **2** (1 equiv), diborane **1**, and NaO*t*-Bu delivers a complex mixture, only 20% of which is boronate **5** (after aqueous quench; entry 1, Table 1). We then noted a report on reactions of α,*β*-unsaturated esters with **1**, promoted by phosphine−Cu complexes.[6] An alcohol additive was used to protonate the resulting C−Cu bond to generate a catalytically active Cu−alkoxide, enhancing reaction efficiency. Such considerations led us to determine that subjection of (*E*)-*β*-methylstyrene to 0.5 mol % **2** and NaO*t*-Bu and 1.1 equiv of **1** in the presence of 2.0 equiv of MeOH results in >98% conversion to **5** at 22 °C within 10 min (entry 2, Table 1); **5** is otained in >98% yield and >98% site selectivity. It should be noted that reaction of (*E*)-*β*-methylstyrene with $BH_3 \cdot THF$ or 9-BBN delivers the alternative boronate regioisomer preferably (benzylic C−B; 88:12 and 95:5, respectively, at 22 °C).

In the presence of MeOD, **5**-d_1 is obtained in >98% yield and as a single diastereomer (eq 1, >98:<2 dr, >98% D incorporation). The efficient and stereoselective C−D bond formation underlines an important advantage of the present approach (vs processes involving borohydrides):[7] diastereoselective capture of the intermediate C−Cu bond with other classes of (e.g., C-based) electrophiles might constitute the development of additional catalytic and versatile protocols.

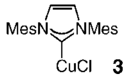
Table 1. Cu-Catalyzed Hydroboration of (*E*)-*β*-Methylstyrene with Various Lewis Bases[a]



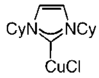
entry	NHC or phosphine, mol%	additive, equiv	mol % CuCl	time	conv (%)[b]
1	**2**; 100	none	−	10 min	20
2	**2**; ***0.5***	***MeOH*; *2.0***	−	***10 min***	***>98***
3	**3**; 1.0	MeOH; 2.0	−	10 min	65
4	**3**; 1.0	MeOH; 2.0	−	24 h	77
5	**4**; 1.0	MeOH; 2.0	−	10 min	13
6	**4**; 1.0	MeOH; 2.0	−	24 h	20
7	PPh_3; 1.0	MeOH; 2.0	1.0	24 h	<10
8	PCy_3; 1.0	MeOH; 2.0	1.0	24 h	50
9	$PPh_2(CH_2)_2PPh_2$; 1.0	MeOH; 2.0	1.0	24 h	75



2

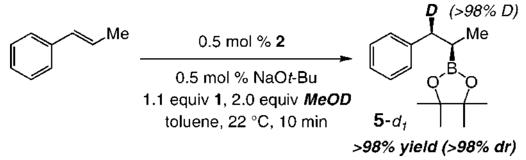


3



4

[a] Reactions under N_2 atm; >98:<2 site selectivity in all cases. [b] Conversion to the desired product by analysis of 400 MHz ^1H NMR spectra of unpurified reaction mixtures. Mes = (2,4,6)-trimethylphenyl; B(pin) = pinacolatoboron.



(1)

When unsaturated **3**, a complex related to the one employed in previously reported studies,[5] serves as the catalyst (entries 3−4, Table 1), additions are less efficient. Processes promoted by alkyl-substituted complex **4** (entries 5−6, Table 1) proceed even less readily (20% conv in 24 h). The above observations point to the structural requirements for an effective Cu-based chiral catalyst for enantioselective hydroboration (see below for details). It is further noteworthy that phosphine-based catalysts are substantially less effective than NHC complexes (see entries 7−9 of Table 1). The superior activity of the more strongly *σ*-donating[2] NHC−Cu systems (vs P-based variants) is consistent with theoretical studies indicating that the olefin substrate serves predominantly as a *π*-Lewis acid in this class of transformations.[8]

A range of aryl alkenes can be used (Table 2). Reaction with (*Z*)-*β*-methylstyrene is less efficient (entry 1; vs the *E* isomer); further conversion is not observed after 24 h. The observed low activity is presumably due to effective Cu−olefin coordination requiring aryl−alkene conjugation (lowering of alkene *π** and more effective back-bonding),[8] a conformation that suffers from allylic strain. When cyclic *Z*-alkenes indene (entry 2, Table 2) and dihydronaphthalene (entry 3) are used, however, complete conversion is achieved. The lower activity of *p*-methoxy-(*E*)-*β*-methylstyrene (entry 4) versus *p*-trifluoromethyl-(*E*)-*β*-methylstyrene and (*E*)-*β*-methylstyrene is consistent with the aforementioned electronic requirements.[8] Sterically hindered olefins (entries 6−7) undergo hydroboration with high efficiency and without detectable loss of site selectivity.

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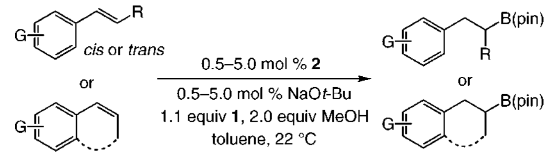
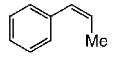
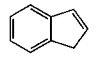
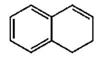
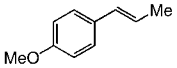
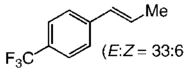
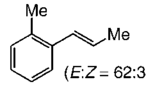
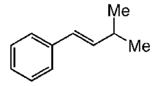
Table 2. Cu-Catalyzed Hydroboration of β-Substituted Aryl Olefins[a]



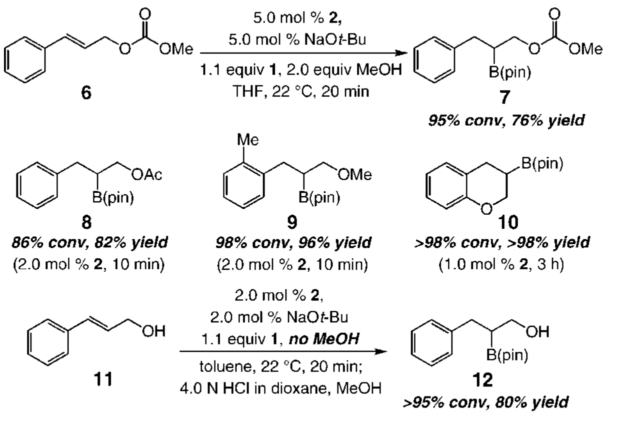
entry	substrate	mol % 2	time	conv (%)[b]	yield (%)[c]
1		5.0	10 min	49	41
2		1.0	24 h	>98	92
3		0.5	10 min	>98	97
4		3.0	10 min	>98[d]	95
5	 (*E*:*Z* = 33:67)	1.0	5 h	>98	91
6	 (*E*:*Z* = 62:38)	1.0	10 min	70[e]	66
7		5.0	3 h	93	88

[a] Reactions under N_2 atm; >98:<2 site selectivity in all cases. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. [c] Yield of pure products. [d] 1.5 equiv of **1** used. [e] 30% of *Z*-alkene recovered.

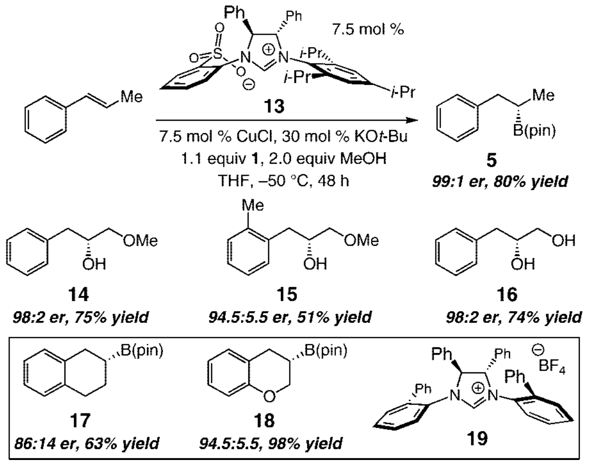
Cu-catalyzed hydroboration of allylic carbonate **6** delivers α-carbamylboronate **7** in 76% yield without complications arising from allylic substitution[9] (<2%; 400 MHz ^{1}H NMR analysis); oxidation with H_2O_2 affords the derived cyclic carbonate in 61% overall yield. Allylic acetate **8**, methyl ether **9**, and heterocyclic **10** are isolated in 82%, 96%, and >98% yield, respectively. With allylic alcohol **11**, use of MeOH is not needed: **12** is obtained in 80% yield (after mild acid workup and product purification).[10]

The efficiency of **2** in initiating additions to aryl-substituted alkenes bodes well for the development of Cu-catalyzed enantioselective hydroborations. We have thus established that reaction of (*E*)-β-methylstyrene with 7.5 mol % of bidentate imidazolinium salt **13** delivers boronate **5** in 99:1 er, >98:<2 site selectivity, and 80% yield. α-Hydroxymethyl ethers **14**−**15** and **16** are obtained in 98:2, 94.5:5.5, and 98:2 er, respectively, after oxidative workup. Thus far, reactions of cyclic olefins (**17**−**18**) proceed with slightly lower selectivity (86:14 and 94.5:5.5 er, respectively); optimal results are achieved through the use of monodentate NHC derived from **19**.[11] The methods furnishing enantiomerically enriched secondary alkylboronates can be used for stereoselective C−N[12a] and C−C[12b] bond formation, allowing access to an assortment of enantiomerically enriched compounds.

Scheme 1. Cu-Catalyzed Hydroboration of Allylic Esters, Ethers, and Alcohols



Scheme 2. Cu-Catalyzed Enantioselective Hydroboration Reactions[a]



[a] See SI for experimental details; oxidation conditions for **14**−**16**: H_2O_2, 2.0 N aqueous NaOH; MeOH not used for **16**. >98:<2 site selectivity in all cases.

Development of copper−boron additions to other classes of olefins and related processes are in progress.

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Supporting Information Available: Experimental procedures and spectral, analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) NHC−Cu-catalyzed hydroboration of styrene with catecholborane has been reported (2.3−7.3:1 site selectivity, favoring terminal C−B). See: Lillo, V.; Fructos, M. R.; Ramírez, J.; Braga, A. A. C.; Maseras, F.; Díaz-Requejo, M. M.; Pérez, P. J.; Fernández, E. *Chem.*−*Eur. J.* **2007**, *13*, 2614–2621.
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