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Enantioselective Catalysis

NHC-Cu-Catalyzed Enantioselective Hydroboration of Acyclic and Exocyclic 1,1-Disubstituted Aryl Alkenes**

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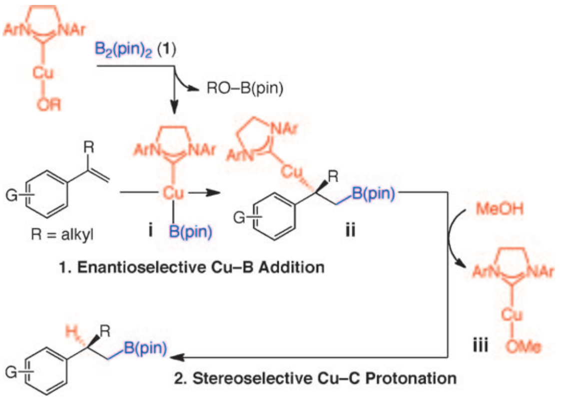
We recently discovered that hydroboration of 1,2-disubstituted aryl olefins can be catalyzed by chiral Cu-based bidentate N-heterocyclic carbene (NHC)[1] complexes.[2,3] Reactions proceed to deliver homobenzylic C–B bonds exclusively,[4] which is in contrast to transformations with alkylboranes or those catalyzed by the more costly Rh- or Ir-based complexes, where formation of benzylic C–B bonds is preferred.[3] We later showed that the NHC–Cu-catalyzed transformations proceed efficiently with β-vinylboronates to afford acyclic vicinal diboronates with complete site selectivity ($<2\%$ geminal).[5] The above protocols are enantioselective, delivering boron-substituted stereogenic centers at secondary carbon atoms in 86:14–99:1 enantiomeric ratio (e.r.). Despite such advances, as well as seminal findings reported by other research groups,[3] several shortcomings persist. One long-standing problem relates to catalytic enantioselective hydroborations of 1,1-disubstituted alkenes.[6] The use of stoichiometric quantities of chiral boranes in reactions of 1,1-disubstituted alkenes has been outlined;[7] however, high enantioselectivity (e.r. $> 90{:}10$) is only observed when there is a significant size difference between the olefin substituents. Rh- and Ir-catalyzed processes with catecholborane typically furnish low enantioselectivity with 1,1-disubstituted alkenes and, in some cases, control of site selectivity is problematic.[8] Recently, an Ir-catalyzed process with pinacolatoborane was found to afford complete site selectivity and e.r. $\geq 90{:}10$ in the case of two α-methylstyrene derivatives (overall range of e.r. $= 66{:}34$–$96{:}4$).[9] Herein, we present an NHC–Cu-catalyzed process for the site- and enantioselective catalytic hydroboration of 1,1-disubstituted aryl olefins (Scheme 1);[10] α-alkyl-β-pinacolatoboranes are formed with $> 98\%$ site selectivity, in up to $> 98\%$ yield and e.r. $= 96.5{:}3.5$. Reactions involving a range of acyclic 1,1-disubstituted aryl olefins, including those that contain alkyl substituents other than the typically utilized methyl unit, have been developed. Also included are transformations of exocyclic alkenes, which, to the best of our knowledge, have not been previously reported.



Scheme 1. The outcome of catalytic enantioselective NHC–Cu-catalyzed hydroborations of 1,1-disubstituted aryl olefins, in contrast to those involving 1,2-disubstituted olefins, depends on two stereochemistry-determining events: enantioselective Cu–B addition and the subsequent stereoselective Cu–C protonation. G = aryl substituent.

In considering the mechanism of catalytic 1,1-disubstituted alkene hydroborations (Scheme 1), we surmised that transformations would likely be initiated by [(NHC)Cu{B(pin)}][11] **i** [formed from reaction of bis(pinacolato)diboron (**1**) with an NHC-Cu-alkoxide]. Subsequent Cu–B addition would afford β-alkylborane **ii**, which contains a quaternary Cu-substituted stereogenic center. Protonation of the Cu–C bond,[12] likely occurring with retention of configuration,[4] can deliver the desired product and regenerate **iii**, which reacts with **1** to form **i**. An uncommon feature of the catalytic processes is that the eventual stereochemical outcome does not depend only on the enantioselectivity of the Cu–B addition: the stereochemistry of the intermolecular protonation of the enantiomerically enriched alkylcopper species with the alcohol additive (MeOH) is crucial as well.[13] Furthermore, the copper-containing intermediates might be utilized to access entities other than alkylboranes;[14] this is in contrast to the more traditional approach to metal-catalyzed hydroboration,[3] where the C–B bond is formed through an alkyl-metal–boron reductive elimination. Within this latter context, application of the catalytic method towards the synthesis of versatile 2-substituted allylboronates will be described.

We began by examining the ability of NHC–Cu complexes obtained from enantiomerically pure imidazolinium salts **2**–**8** (Table 1) to promote the enantioselective hydroboration of α-methylstyrene (**9a**; −15 °C, thf). The monodentate variants derived from C_1- or C_2-symmetric **2** and **3**, the latter of which is effective for reactions with cyclic

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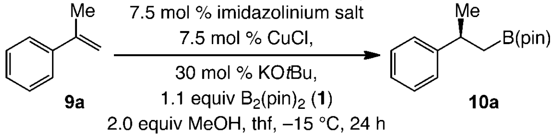
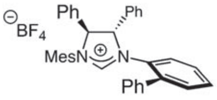
Table 1: Initial evaluation of chiral NHC complexes.[a]



Entry	Imidazolinium Salt	Conv. [%][b]	e.r.[c]
1	**2**	> 98	59:41
2	**3**	95	56:44
3	**4**	> 98	65:35
4	**5a**	98	75:25
5	**5b**	47	93:7
6	**6**	67	74:26
7	**7**	> 98	82:18
8	**8**	> 98	85.5:14.5

[a] Reactions were performed under N_2; > 98% site selectivity in all cases. [b] Determined through analysis of the 400 MHz ^{1}H NMR spectra of unpurified mixtures. [c] Determined by HPLC analysis; see the Supporting Information for details. $B_2(pin)_2$ = bis(pinacolato)diboron.



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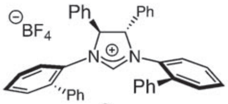

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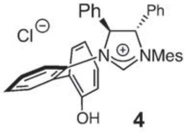

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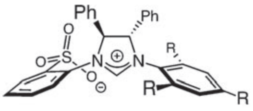
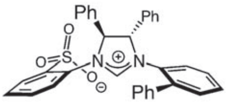


5a R = Me (Mes)
5b R = iPr



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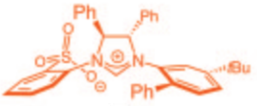

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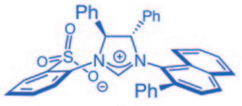

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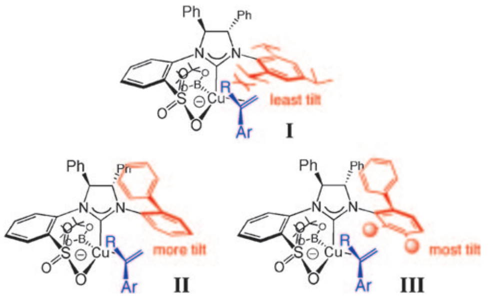
disubstituted aryl olefins,[4] led to minimal stereoselectivity (Table 1, entries 1 and 2).

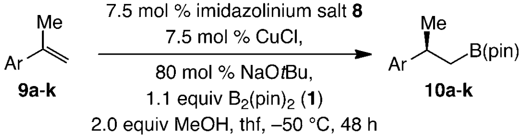
Enantioselectivity improves when bidentate complexes derived from **4** and **5a** are utilized (Table 1, entries 3 and 4). Alkylboronate **10a** is formed in a significantly higher enantiomeric ratio (93:7; Table 1, entry 5) when **5b** serves as the catalyst precursor; however, the reaction is less efficient (47% vs. ≥ 98% conversion with **4** and **5a**). We then turned to sulfonate-containing **6**, where both *N*-aryl units of the chiral imidazolinium salt are dissymmetric (vs. **4** and **5a,b**); here, moderate efficiency and enantioselectivity are observed (67% conversion, e.r. = 74:26).

The higher activity of the C_1-symmetric complex derived from **6**, despite its larger *ortho*-phenyl unit (vs. *i*Pr in **5b**), suggested that, as shown in **I** versus **II** (Scheme 2), the more severe tilting of the dissymmetric *N*-Ar group might be allowing better accommodation of the alkene. We argued that the enhanced flexibility of the *N*-Ar group in **II** towards adopting a more favorable conformation for substrate binding might be because the orthogonal conformation of the *ortho*-phenyl unit causes this substituent to engender less severe steric repulsion with the NHC backbone. We thus surmised that placement of substituents at the opposite side of the aryl group could increase its slant (**III**, Scheme 2), thereby permitting improved reactivity and/or selectivity. Accordingly, we prepared and examined several C_1-symmetric chiral bidentate imidazolinium salts, such as **7** and **8** (Table 1). These investigations led us to establish that positioning a *tert*-butyl group at the *meta* position of the nonchelating *N*-Ar moiety of the NHC (**7**; Table 1, entry 7) results in enhanced efficiency as well as an increase in enantioselectivity (> 98% vs. 67% conv., e.r. = 82:18 vs. 74:26). Further improvement in the enantiomeric purity of the product is achieved through the use of naphthyl-substituted salt **8** (> 98% conv., e.r. = 85.5:14.5; Table 1, entry 8). When the reaction is performed at –50 °C (vs. –15 °C), and with an NHC–Cu complex derived from **8** as the catalyst, **10a** is isolated in 95% yield and e.r. = 93.5:6.5 (Table 2, entry 1).



Scheme 2. Variations in the substitution pattern of the nonchelating *N*-aryl moiety of the NHC–Cu complex can have an impact on the course of a catalytic process.

Table 2: NHC–Cu-catalyzed hydroboration of α-methylstyrenes.[a]

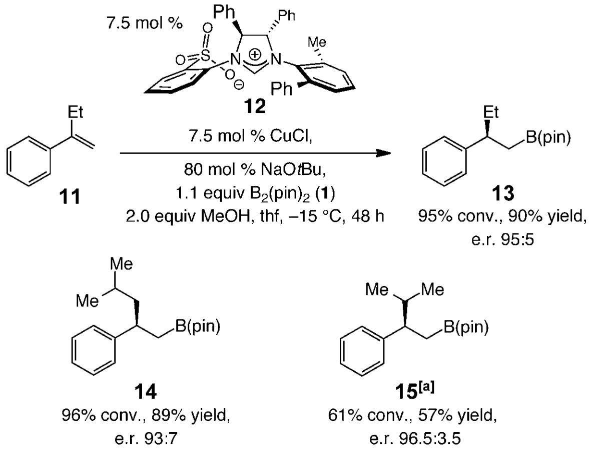


Entry	Substrate (aryl)		Conv. [%][b]	Yield [%][c]	e.r.[d]
1	C_6H_5	**9a**	96	95	93.5:6.5
2	2-naphthyl	**9b**	84	62	92:8
3	1-naphthyl	**9c**	50	37	96:4
4	mFC_6H_4	**9d**	73	60	87.5:12.5
5	mBrC_6H_4	**9e**	61	58	89.5:10.5
6	mCF$_3$C$_6$H$_4$	**9f**	63	52	80.5:19.5
7	mMeOC_6H_4	**9g**	> 98	> 98	91.5:8.5
8	mMeC_6H_4	**9h**	98	83	93.5:6.5
9	pCF$_3$C$_6$H$_4$	**9i**	93	79	82:18
10	pMeC_6H_4	**9j**	80	80	87:13
11	2-benzofuryl	**9k**	> 98	89	93.5:6.5

[a] Reactions were performed under N_2; > 98% site selectivity in all cases. [b] Conversion determined through analysis of the 400 MHz ^{1}H NMR spectra of unpurified mixtures. [c] Yields of isolated purified products (± 5%). [d] Enantiomeric ratio (e.r.) determined by HPLC analysis (± 2%); see the Supporting Information for details.

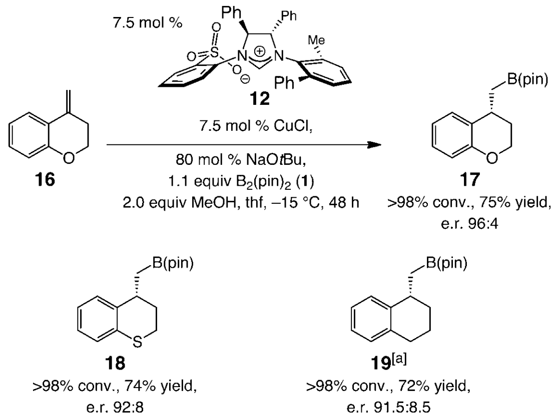
Various α-methyl aryl olefins can be used in Cu-catalyzed enantioselective hydroborations (Table 2); in all cases, > 98% site selectivity is observed.[15] A similarly high e.r. value (92:8) is obtained with 2-naphthyl-substituted **9b** (Table 2, entry 2); Cu–B addition to the more sterically demanding olefin **9c** (Table 2, entry 3), on the other hand, does not proceed beyond 50% conversion (37% yield) but the reaction is highly enantioselective (e.r. = 96:4). Although the electronic attributes of the alkene do not seem to have an impact on selectivity, reactions are less selective with substrates that carry a trifluoromethyl-substituted aryl group (compare Table 2, entries 6 and 7 as well as 9 and 10). The case of benzofuryl-substituted **10k** (Table 2, entry 11; 89% yield, e.r. = 93.5:6.5) illustrates that heterocyclic substrates can be used.[16]

NHC–Cu-catalyzed hydroborations of 1,1-disubstituted aryl olefins that bear larger alkyl groups (vs. Me, Table 2) proceed efficiently and with high enantioselectivity (Scheme 3). Catalytic hydroborations of such substrates have scarcely been examined previously and the few reported cases proceed with low selectivity (e.g., **13** in e.r. = 65.5:34.5 with a chiral phosphinooxazoline-derived Ir complex[9]). Several points regarding this set of reactions merit mention: 1) The use of imidazolinium salt **12**,[17] which contains an *o*-methyl-substituted *N*-aryl moiety (vs. *m*-*t*Bu and naphthyl in **7** and **8**, respectively), results in optimal efficiency and selectivity. Hydroborations with Cu complexes derived from **7** or **8** give rise to lower yield and/or selectivity,[18] thus leading us to identify **12** as a superior option by examination of the effect of the aforementioned structural modifications (cf. Scheme 2). 2) The higher efficiency of the NHC–Cu complex derived from **12** (vs. **7** or **8**) is consistent with the augmented tilt of the dissymmetric *N*-Ar moiety, which accommodates a larger alkyl substituent (R in **I**–**III**, Scheme 2). Enantioselectivities remain high (vs. α-methylstyrene (**9a**)), even though reactions are performed at −15 °C (vs. −50 °C in Table 2); although the presence of the sterically demanding isopropyl group reduces the rate of the catalytic process, alkylboronate **15** is formed in e.r. = 96.5:3.5.[19]



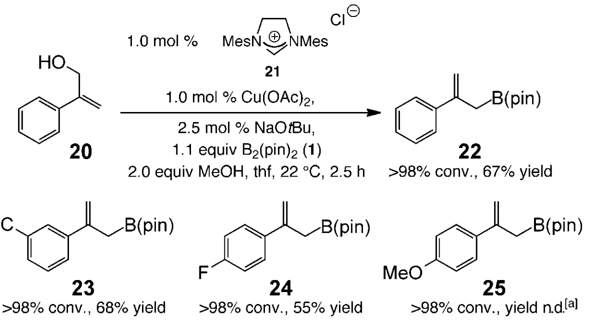
Scheme 3. NHC–Cu-catalyzed hydroborations of 1,1-disubstituted olefins can be performed with substrates bearing sterically demanding alkyl groups; such transformations, as well as certain heterocyclic alkenes, require a structurally modified chiral catalyst (derived from **12**) for optimal selectivity. [a] Reaction performed at 4 °C. See the Supporting Information for details.

Exocyclic 1,1-disubstituted alkenes are another class of substrates not previously utilized in highly enantioselective catalytic hydroborations. The NHC–Cu-catalyzed method provides an effective solution to this problem, as indicated by the examples in Scheme 4; the Cu complex derived from **12** is generally most effective.[20] Hetero- (**17** and **18**) and carbocyclic (**19**) alkenes are converted into alkylboronates in 72–75% yield and in up to e.r. = 96:4.[21]



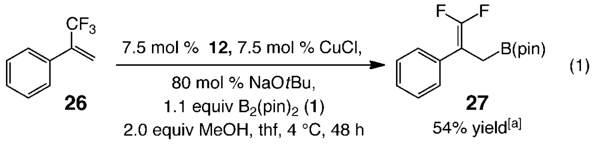
Scheme 4. Hydroborations of heterocyclic and carbocyclic 1,1-disubstituted olefins are most effectively promoted by the Cu complex derived from imidazolinium salt **12**. [a] Reaction performed at −30 °C. See the Supporting Information for details.

With allylic alcohols as substrates, 2-substituted allylboronates are generated (Scheme 5). Thus, Cu–B addition proceeds efficiently with the corresponding allylic alcohols (i.e., formation of **ii**, Scheme 1), but the Cu-alkoxide elimination is substantially faster than the rate of Cu–C protonation. The Cu-catalyzed approach to 2-aryl-substituted allylboronates offers an attractive alternative to the Pd-catalyzed process performed with allylic acetates and **1**.[22]



Scheme 5. NHC–Cu-catalyzed synthesis of 2-substituted allylboronates directly from readily accessible allylic alcohols. n.d. = not determined. [a] Yield was not measured due to instability, but treatment with benzaldehyde affords the corresponding allylic alcohol in 70% yield (over the two steps); see the Supporting Information for details.

Reactions can be easily promoted by the NHC–Cu complex derived from commercially available achiral **21** and air-stable $Cu(OAc)_2$. The derived allylboronates are formed cleanly; the moderate yields are due to the relative instability of such entities. A related Cu-catalyzed process, shown in Equation (1), involves the conversion of trifluoromethyl-substituted **26** into difluoroallylboronate **27**. The transforma-



[a] Reaction with achiral NHC–Cu complex derived from **21** affords **27** in 20% yield.

tion is significantly more efficient with the Cu complex derived from chiral imidazolinium salt **12** than that from achiral monodentate **21** (54% vs. 20% yield of **27** after purification).

The development of additional catalytic C–B bond-forming reactions and Cu complexes that furnish improved reactivity and selectivity are in progress.

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[16] Substrates that bear an *ortho*-aryl substituent are inert to the reaction conditions (e.g., Br- or Me-substituted). This is likely because formation of the Cu-substituted quaternary carbon atom at the benzylic site is prohibited on steric grounds. Moreover, adoption of the conformation for proper hyperconjugation with the alkene, leading to the required increase in the latter's π-Lewis acidity, is inhibited due to allylic strain; see: L. Dang, H. Zhao, Z. Lin, T. B. Marder, *Organometallics* **2007**, *26*, 2824–2832.

[17] The stereochemical identity of the rotamer of **12** was determined by nuclear Overhauser effect (NOE) experiments; see the Supporting Information for details.

[18] For example, with NHC–Cu complexes derived from **7** and **8**, conversion of **11** into **13** proceeds with $>98\%$ conv., 76% yield, and e.r. = 89:11 and 97% conv., 77% yield, and e.r. = 93:7, respectively.

[19] The use of the Cu complex derived from **12** (79% conv. and e.r. = 89:11 under the conditions of Table 1) in reactions of α-methylstyrenes (Table 1) leads to lower efficiencies and similar e.r. values as observed with **8**.

[20] For example, reaction of exocyclic alkene **16** with complex **8** under the conditions shown in Scheme 4 proceeds to 94% conversion, affording **17** in 65% yield and e.r. = 90:10.

[21] The enantioselectivity values for exocyclic alkenes can vary at different temperatures, but not in a uniform manner. As an example, whereas benzopyran **17** is formed in e.r. = 93.5:6.5 at $-30\,°C$ and e.r. = 96:4 at $-15\,°C$, carbocyclic **18** is obtained in e.r. = 91.5:8.5 and e.r. = 91:9, respectively ($>98\%$ conv. in all cases).

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