

Diverse Asymmetric Hydrofunctionalization of Aliphatic Internal Alkenes through Catalytic Regioselective Hydroboration

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S Supporting Information

ABSTRACT: We report a two-step strategy for diverse hydrofunctionalizations of aliphatic internal alkenes with high regioselectivity and enantioselectivity. This process comprises a copper-catalyzed asymmetric hydroboration and subsequent stereospecific derivatizations of the secondary boronates. By this strategy, a range of compounds, such as amides, alkyl fluorides and bromides, alcohols, aldehydes, arenes, and heteroarenes, were synthesized from an internal alkene with high regioselectivity and enantioselectivity. Computational studies provide insight into the origins of these selectivities.

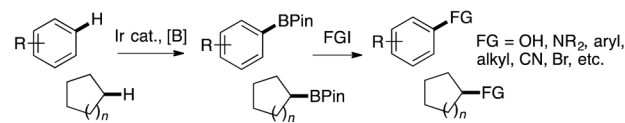
Alkenes are versatile starting materials that are available on a large scale from commercial sources or through chemical synthesis.¹ Many functionalizations of terminal alkenes have been reported, including functionalizations that occur enantioselectively.² However, functionalizations of internal alkenes are more limited, and enantioselective reactions of internal alkenes are particularly rare. Yet, asymmetric hydrofunctionalizations³ of internal alkenes, if they could be conducted with high regioselectivity and enantioselectivity, would generate functionalized alkyl groups efficiently with control of absolute and relative configuration by formation of C–C or C–X (X = O, N, S, or P, etc.) bonds.

Over the past two decades, we have developed first-row catalysts for the hydroboration of vinylarenes⁴ and catalysts for the borylation⁵ of aromatic and aliphatic C–H bonds that enable the preparation of a wide range of functionalized compounds after subsequent transformations of organoboronates.⁶ The synthetic versatility of a Bpin (pin = pinacolate) group makes organoboronates valuable intermediates for the formation of a range of products. We envisioned that an asymmetric hydroboration of internal alkenes, followed by stereospecific transformations⁷ of the resulting secondary boronates, would provide an array of enantioenriched compounds containing a diverse range of functional groups (Scheme 1).

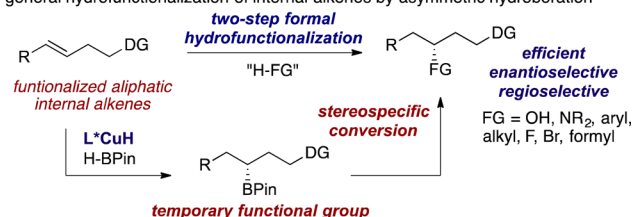
Transition-metal-catalyzed hydroborations^{7b,8} of alkenes have the potential to occur with chemo- and stereoselectivity that complements those of uncatalyzed hydroborations. However, catalytic enantioselective hydroboration of alkenes is mostly limited to styrene derivatives and strained alkenes.⁹ The few examples of hydroborations of internal alkenes include rhodium-catalyzed asymmetric hydroboration of disubstituted and trisubstituted alkenes reported by Takacs.¹⁰ In these cases, the

Scheme 1. Strategy for Regio- and Enantioselective Hydrofunctionalization of Internal Alkenes

Previous work: general functionalization of C–H bonds by C–H borylation



This work: general hydrofunctionalization of internal alkenes by asymmetric hydroboration



regioselectivity was dictated by coordination of an amide or an oxime group to the rhodium catalyst.

Recently, we reported that hydroaminations of internal alkenes containing polar groups at the homoallylic position occur with high regioselectivity that results from the inductive effects of electronegative groups proximal to the alkene.¹¹ This formal hydroamination was proposed to proceed via a chiral, non-racemic copper hydride¹² intermediate. Based on recent observations that the insertion of an internal alkene into a Cu–H bond is highly enantioselective and irreversible under the catalytic conditions,^{11,13} we envisioned that an asymmetric hydroboration of related alkenes would create a platform for diverse hydrofunctionalizations that form products containing new carbon–oxygen, carbon–halogen, and carbon–carbon bonds, if the intermediate alkylcopper complex would react with the borane to form a new B–C bond and regenerate the copper hydride.¹⁴

Herein, we report a two-step strategy for diverse hydrofunctionalizations of internal alkenes via regioselective and enantioselective copper-catalyzed hydroboration. This hydroboration occurs with a high regioselectivity that complements that of rhodium- and iridium-catalyzed hydroborations^{10a–d,15} and constitutes the first copper-catalyzed hydroboration of unconjugated internal alkenes.^{9d,16} We show that a wide range of functional groups can be incorporated in an acyclic aliphatic chain in a regio- and enantioselective manner by the combination

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of this hydroboration and a diverse set of reactions at the C–B bond.

To establish a system for regioselective hydroboration of internal alkenes, we investigated the reaction of pinacolborane and *trans*-3-hexenyl 2,4,6-trichlorobenzoate (**1a**), which we showed previously to undergo regioselective hydroamination,¹¹ in the presence of a copper catalyst, generated from CuCl and (*S*)-DTBM-SEGPHOS, and a base additive. Table S1 in the Supporting Information (SI) summarizes our studies on the identification of reaction conditions. These studies showed that reactions conducted with stronger bases, such as KO^tBu and KHMDS (entries 3, 5), occurred with much higher yields than did reactions with weaker bases, such as LiO^tBu and KOPh (entries 2, 4). Reactions conducted in cyclohexane were faster than those conducted in toluene (entry 6), whereas reactions in THF led to no products (entry 7).

In addition, we investigated the effect of substituents of the homoallylic benzoates on the regioselectivity and yield of the hydroboration (Table S2, SI). The studies showed that the regioselectivity was higher for substrates containing more electron-withdrawing groups on the phenyl ring of the benzoate than for substrates containing less electron-withdrawing groups on the phenyl ring of the benzoate (S1a–S1c). These data suggest that the regioselectivity is sensitive to electronic properties of the alkenes. However, the yield decreased with this change to the substrate because reduction of the ester moiety occurred by the copper hydride. The competing reduction was not observed for substrates containing substituents at both the 2- and 6-positions of the aryl ring.

After identifying suitable conditions for copper-catalyzed hydroboration, we evaluated the scope of the reactions with homoallylic esters, ethers, and sulfonamides (Table 1). Homoallylic trichlorobenzoates containing ethyl, isopropyl, *tert*-butyl, and cyclohexyl substituents (**1a–1d**) underwent hydroboration in good yields with high regioselectivity and excellent enantioselectivity. The reactions of alkenes with branching α to the alkene afforded a single constitutional isomer, suggesting that steric factors strongly influence the regioselectivity. The hydroboration of a non-conjugated diene (**1e**) occurred selectively at the alkene proximal to the trichlorobenzoyl group.

To assess further the effect of the electronic properties of the substituent on the regioselectivity, we conducted hydroboration with alkenes bearing phenoxy groups at the homoallylic position. Electron-poor, halogen-substituted homoallylic phenyl ethers underwent hydroboration to form boronates **2f** and **2g** in good yields. The regioselectivity of the hydroboration of the more electron-poor phenyl ether (**2f**, 7.9:1) was higher than that of the hydroboration of the less electron-poor phenyl ether (**2g**, 4.4:1).

To expand the potential synthetic applications of the hydroboration, we examined the hydroboration of aryl- and alkyl-substituted homoallylic tosylamides (**1h**, **1i**). The corresponding boronates **2h** and **2i** were formed in good yields and with high regioselectivity when the reaction was conducted with 5 mol% catalyst.

Reactions of chiral non-racemic alkenes occurred with diastereoselectivity controlled by the catalyst. Enantiopure trifluoromethylsulfonamide **1j** containing a remote stereocenter underwent hydroboration to form **2j** in high yield with high regioselectivity and excellent diastereoselectivity. Moreover, the reactions of enantioenriched alkenes in which the stereogenic center is proximal to the alkene occurred with diastereoselectivity controlled by the catalyst. The hydroboration of (*R*)-**1k**

Table 1. Scope of the Copper-Catalyzed Hydroboration of Internal Alkenes^{a,b}

Unsymmetrical internal alkenes

Et-CH ₂ -CH(BPin)-CH ₂ -OBzCl ₃ (2a) 80% yield, 97% ee regioselectivity 9.6:1 (A)	<i>i</i> Pr-CH ₂ -CH(BPin)-CH ₂ -OBzCl ₃ (2b) 80% yield, 99% ee regioselectivity 47:1 (A)	<i>t</i> Bu-CH ₂ -CH(BPin)-CH ₂ -OBzCl ₃ (2c) 79% yield, 99% ee regioselectivity >100:1 (B)
Cy-CH ₂ -CH(BPin)-CH ₂ -OBzCl ₃ (2d) 91% yield, 99% ee regioselectivity 29:1 (A)	Me-CH ₂ -CH(BPin)-CH ₂ -OBzCl ₃ (2e) 66% yield, 97% ee regioselectivity 6.0:1 (C)	Et-CH ₂ -CH(BPin)-CH ₂ -O-C ₆ H ₂ (F) ₃ (2f) 77% yield, 98% ee regioselectivity 7.9:1 (A)
Et-CH ₂ -CH(BPin)-CH ₂ -O-C ₆ H ₄ -Br (2g) 78% yield, 98% ee regioselectivity 4.4:1 (A)	Et-CH ₂ -CH(BPin)-CH ₂ -N(Ts)-Ph (2h) 84% yield, 96% ee regioselectivity 12:1 (B)	Et-CH ₂ -CH(BPin)-CH ₂ -N(Ts)-Bn (2i) 81% yield, 99% ee regioselectivity 9.5:1 (B)
Et-CH ₂ -CH(BPin)-CH ₂ -N(Tf)-Me (2j) 86% yield, d.r. >20:1 ^c regioselectivity 15:1 (C)	<i>n</i> Bu-CH ₂ -CH(BPin)-CH ₂ -OBzCl ₃ (2k) 77% yield, d.r. >20:1 ^c regioselectivity >20:1 ^c (C)	<i>n</i> Bu-CH ₂ -CH(BPin)-CH ₂ -OBzCl ₃ (2l^d) 76% yield, d.r. >20:1 ^c regioselectivity >20:1 ^c (C)
Symmetrical internal alkenes		
<i>n</i> Pr-CH ₂ -CH(BPin)-CH ₂ -OTBS (2m) 34% yield, 98% ee (D)	Cl ₃ BzO-CH ₂ -CH(BPin)-CH ₂ -OTBS (2n) 74% yield, >98% ee (C)	Cl ₃ BzO-CH ₂ -CH(BPin)-CH ₂ -OBzCl ₃ (2o) 82% yield, 97% ee (C)

Effect of olefin location and geometry on hydroboration

Me-CH ₂ -CH(BPin)-CH ₂ -OBzCl ₃ (1q) 17% GC yield (C) regioselectivity 1.2:1	Et-CH=CH-CH ₂ -OBzCl ₃ (1p) 9% GC yield (C) regioselectivity 8.7:1
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^aConditions: A, 2.5 mol% Cu loading; B, 5 mol% Cu loading; C, 10 mol% Cu loading; and D, 10 mol% Cu loading. See SI for details.

^bRegioselectivity determined by GC. ^cDetermined by ¹H NMR analysis. ^d(*R*)-DTBM-SEGPHOS used as the ligand. BzCl₃ = 2,4,6-trichlorobenzoyl group.

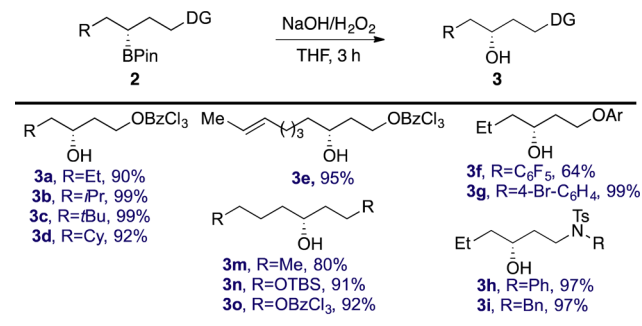
catalyzed by the (*S*)-DTBM-SEGPHOS-copper complex formed the addition product **2k** in 77% yield. The same reaction catalyzed by the (*R*)-DTBM-SEGPHOS-copper complex formed the corresponding diastereomer **2l** in a comparable yield (76%). Both reactions occurred with excellent diastereoselectivity (>20:1) and regioselectivity (>20:1).

In addition, symmetrical internal alkenes underwent hydroboration. Alkenes **1n** and **1o**, bearing siloxy and alkoxy carbonyl groups, reacted in good yields to form boronates **2n** and **2o**. However, the unfunctionalized internal alkene *trans*-4-octene reacted in less than 5% yield under conditions C. Reactions conducted with 3 equiv of alkene and limiting HBPIn (conditions D) did lead to the corresponding boronate **2m** in 34% yield, but the difference in reactivity of *trans*-4-octene and the symmetrical ethers suggests that polar groups proximal to the alkene enhance the reactivity of the alkene, even if the C=C bond lacks a dipole because it is symmetric.

To assess the potential of the asymmetric hydroboration of internal alkenes with pinacolborane to enable regio- and enantioselective hydrofunctionalizations to create a diverse set of products, we conducted transformations that convert C–B

bonds to various C–C and C–X bonds (X = F, Br, N, O) stereospecifically. Analogous to the classic combination of hydroboration and oxidation of terminal alkenes to afford linear alcohols, the combination of the asymmetric hydroboration and oxidation of the resulting secondary boronates afforded enantio-enriched secondary alcohols in excellent yields (Table 2). This sequence of hydroboration and oxidation constitutes a formal regio- and enantioselective hydration of internal alkenes.

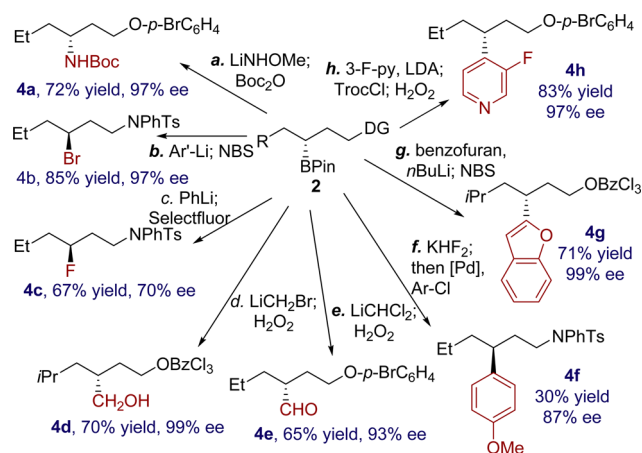
Table 2. Synthesis of Enantioenriched Secondary Alcohols



The chiral boronates also form a range of compounds containing new C–C and C–X bonds stereospecifically.^{7c} Compound **2g** underwent amination¹⁷ to form Boc-protected amine **4a**, and compound **2h** underwent stereo-invertive bromination¹⁸ and fluorination¹⁹ to afford the corresponding alkyl bromide **4b** and fluoride **4c**. In addition, **2b** and **2g** underwent homologation²⁰ with LiCH₂Br and LiCHCl₂ to yield primary alcohol **4d** and aldehyde **4e**, respectively. Finally, boronates **2b**, **2i**, and **2g** underwent stereospecific arylations and heteroarylations²¹ to produce products **4f–4h**. With the exception of the arylation with 4-chloroanisole to form the anisyl derivative, each of the reactions occurred in high yield and with complete or predominant conservation of the enantiomeric excess of the products from the hydroboration (Scheme 2).

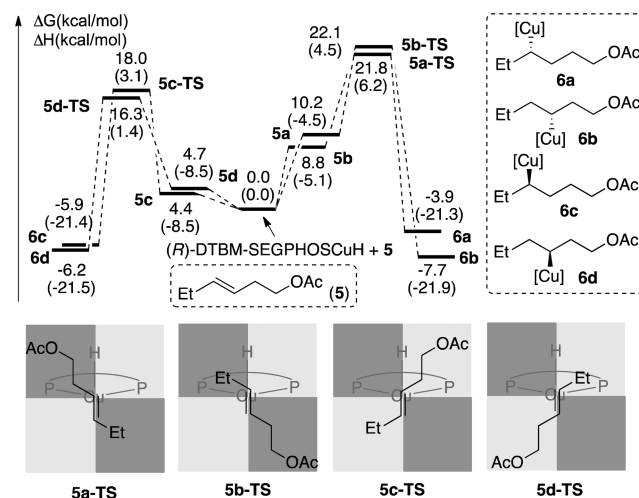
Previous data on the regioselectivity of the hydroamination of **1a**,¹¹ and the current data on the hydroboration of the same alkene, show that the regioselectivity is higher for reaction of the alkene bearing the more electron-withdrawing substituents than for reactions of the alkene bearing the less electron-withdrawing

Scheme 2. Diverse Hydrofunctionalization by Stereospecific Conversion of Secondary Boronates^a



^aSee SI for detailed conditions.

Scheme 3. DFT Calculations of Alkene Insertions To Form the Four Isomeric Alkylcopper Intermediates with (*R*)-DTBM-SEGPHOS^a



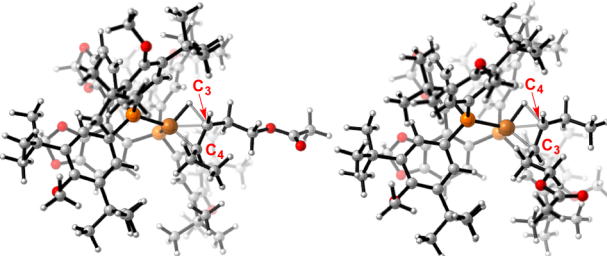
^aSee SI for details.

substituents at this position. To gain insight into the origin of this effect on regioselectivity, we calculated possible transition states for the insertion of the alkene **5** into the Cu–H bond of (*R*)-DTBM-SEGPHOSCuH.²² Scheme 3 (bottom) shows four isomeric transition states for alkene insertions (**5a-TS–5d-TS**) leading to either of the two constitutional isomers of the alkylboronate and the two enantiomers of each constitutional isomer.²³ These calculations were conducted on the smaller homoallylic acetate because reactions of the trichlorobenzoate, pivalate, and acetate all occur with similar regioselectivity.²⁴ The energy of transition state **5d-TS**, leading to the major constitutional isomer **6d**, is 1.7 kcal/mol lower than that of the second lowest-energy transition state, **5c-TS**, leading to the minor constitutional isomer **6c**. This difference in energy agrees well with the regioselectivity (5.4:1) observed for reaction of *trans*-3-hexenyl acetate **5**.

The results of these calculations also mirrored the observed enantioselectivity. The energies of transition states **5c-TS** and **5d-TS** forming the major enantiomers (**6c**, **6d**) were computed to be lower than those of transition states **5a-TS** and **5b-TS** leading to the minor enantiomers (**6a**, **6b**) by approximately 5 kcal/mol. This difference in energy appears to result from steric repulsion between substituents on the alkene and equatorial phosphorus-bound substituents of the ligand (dark gray areas in the quadrant diagrams).

To understand the factors that contribute to the observed regioselectivity, we performed an NBO analysis of the alkene reactant and the two transition states (**5c-TS** and **5d-TS**, see Scheme 3 and SI for structures) that form the two constitutional isomers. The regioselectivity appears to be determined by the differences between the charges on the olefinic carbons in the ground state and transition state. As shown in Table 3, a significant negative charge accumulates in the transition state at the carbon forming the Cu–C bond. This negative charge is stabilized by the positive charge on the nearby O-bound carbon due to the inductive effect of the acetoxy group.²⁵ This proposed inductive effect is consistent with the observation that the regioselectivity decreases when the alkene is located farther from the benzoyloxy group.

Table 3. NBO Analysis of Transition States That Determine the Regioselectivity of the Hydroboration



	5c-TS	5d-TS	S	LCuH ^a
NBO charge on C3	-0.264	-0.510	-0.194	-
NBO charge on C4	-0.498	-0.244	-0.166	-
NBO charge on Cu	-0.053	-0.051	-	0.087
NBO charge on H	-0.060	-0.072	-	-0.449

^aL = (R)-DTBM-SEGPPOS.

In summary, we report a strategy for diverse hydro-functionalization of aliphatic internal alkenes with high regioselectivity and enantioselectivity, comprising a copper-catalyzed asymmetric hydroboration and stereospecific derivatizations of the secondary boronate product of the hydroboration. By this strategy, we have generated, with high enantioselectivity, an array of products bearing distinct functional groups bound to one of the two carbon atoms of the alkene. DFT calculations strongly suggest that the regioselectivity is controlled by the stabilization of the accumulating negative charge on the copper-bound carbon atom by the proximal polar group during formation of the transition states. Efforts to expand the scope of the hydroboration are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02478.

X-ray crystallographic data for **2c** (CIF)

Experimental procedures, spectra, and DFT calculation data (PDF)

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Notes

The authors declare no competing financial interest.

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- (22) The alkene insertion step will be enantio- and regio-determining if it is irreversible, as suggested by the experimental observations that neither alkene isomerization nor chain-walking products were observed.
- (23) The formation of alkylboronate from alkylcopper intermediate and pinacolborane was proposed to proceed with retention of stereochemistry. See refs 14 and 16a.
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