Asymmetric Catalysis

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Synthesis of Chiral Tertiary Boronic Esters by Oxime-Directed Catalytic Asymmetric Hydroboration

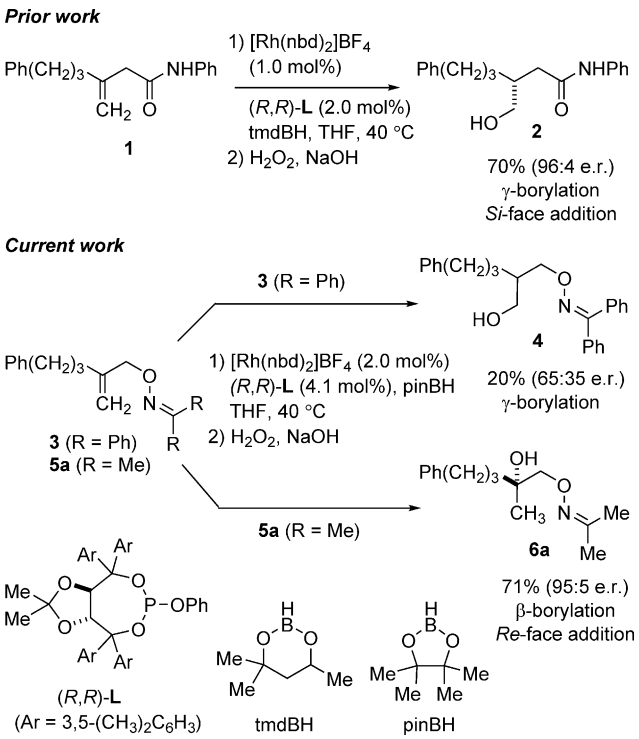
*Veronika M. Shoba, Nathan C. Thacker, Andrew J. Bochat, and James M. Takacs**

Abstract: *Chiral boronic esters are useful intermediates in asymmetric synthesis. We have previously shown that carbonyl-directed catalytic asymmetric hydroboration (CAHB) is an efficient approach to the synthesis of functionalized primary and secondary chiral boronic esters. We now report that the oxime-directed CAHB of alkyl-substituted methylidene and trisubstituted alkene substrates by pinacolborane (pinBH) affords oxime-containing chiral tertiary boronic esters with yields up to 87% and enantiomeric ratios up to 96:4 e.r. The utility of the method is demonstrated by the formation of chiral diols and O-substituted hydroxylamines, the generation of quaternary carbon stereocenters through carbon–carbon coupling reactions, and the preparation of chiral 3,4,4-trisubstituted isoxazolines.*

Catalytic asymmetric hydroboration (CAHB) has attracted renewed interest for the synthesis of chiral organoboronates. Many of the successful applications exploit the reaction of vinyl arene substrates.[1,2] Our research has instead focused on the directed CAHB of β,γ-unsaturated amide and ester substrates. The carbonyl moiety controls the regioselectivity of the rhodium-catalyzed addition of simple achiral boranes, such as pinacolborane (pinBH), and chiral phosphite and phosphoramidite ligands control the π-facial selectivity. A variety of chiral primary and secondary boronic esters are readily synthesized.[3] For example, under the conditions specified in Scheme 1, methylidene derivative **1** undergoes regioselective CAHB on the alkene *Si* face to afford chiral hydroxyamide **2** with 96:4 e.r. after oxidation of the intermediate γ-borylated amide.

Encouraged by the success of carbonyl-directed CAHB, we are exploring the effectiveness of other potential directing groups. Oxime functionality has been used in conjunction with a variety of transition-metal catalyst systems to direct metalation reactions, most frequently to direct *ortho*-C–H activation of aromatic substrates but increasingly for C(sp3)–H activation as well.[4] Neufeldt and Sanford also recently reported the oxime-directed palladium-catalyzed dioxygenation of an adjacent alkene.[5]

For our initial attempts at oxime-directed CAHB, we employed benzophenone-derived allylic oxime ethers, such as **3**. Whereas rhodium-catalyzed hydroboration of **3** led to some γ-borylation, the yield of **4** (after oxidation) was low, and the enantioselectivity was poor. The major side reactions are *ortho*-borylation of the benzophenone-derived oxime with concomitant alkene reduction.[6] We now report that the corresponding acetone-derived oxime ethers are excellent substrates for oxime-directed CAHB; for example, **5a** underwent oxime-directed CAHB/oxidation to give **6a** in good yield (71%) and with high levels of asymmetric induction (95:5 e.r.). Furthermore, the borylated intermediate is a tertiary boronic ester arising from *Re*-face β-borylation; in contrast, carbonyl-directed CAHB of **1** proceeds by *Si*-face γ-borylation. It seems likely that the contrasting regio- and stereochemical outcomes observed with **1** versus **5a** are due to the presence of the oxime substituents in the substrate–catalyst complex; however, more work is needed to prove this hypothesis unambiguously.



Scheme 1. In contrast to carbonyl-directed CAHB, the reaction of a similar oxime ether substrate leads to the formation of a chiral tertiary boronic ester. nbd = norbornadiene.

Chiral boronic acid derivatives are valuable intermediates in organic synthesis.[7] In particular, recent reviews by Leonori, Scott, and Aggarwal highlight transformations of chiral tertiary boronic esters,[8] including their use for the

[*] V. M. Shoba, Dr. N. C. Thacker, A. J. Bochat, Prof. Dr. J. M. Takacs
Department of Chemistry, University of Nebraska-Lincoln
807 Hamilton Hall, Lincoln, NE 68588-0304 (USA)
E-mail: jtakacs1@unl.edu

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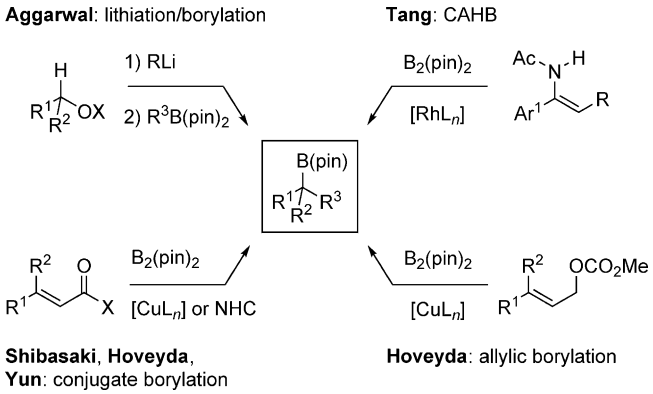
construction of multiple contiguous quaternary stereocenters.[9] However, the formation of tertiary organoboronates by metal-catalyzed or stoichiometric hydroboration is rare, since hydroboration generally proceeds in an *anti*-Markovnikov fashion to deliver boron to the less substituted site on the alkene.[1,10]

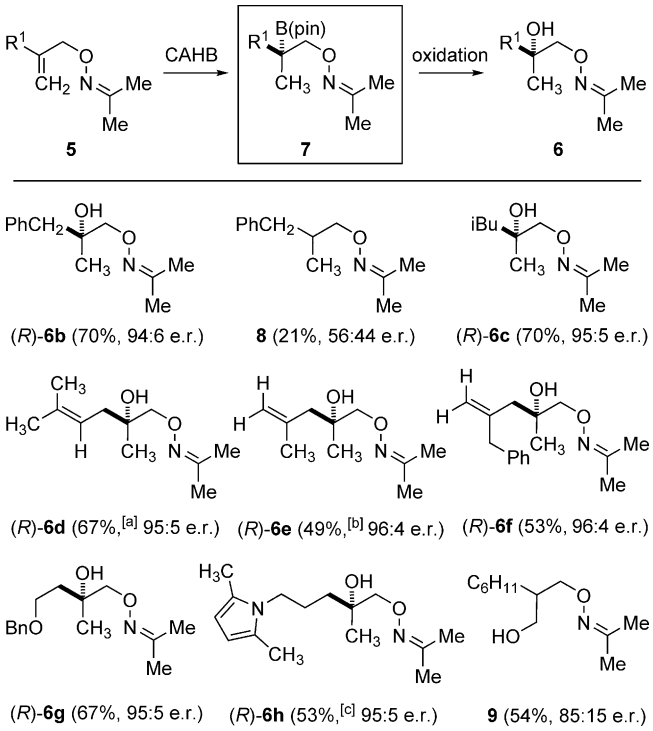
Several complementary methods for the preparation of chiral tertiary boronic esters have recently been reported (Scheme 2). Three of these methods use bis(pinacolato)diboron (B_2pin_2) for the net hydroboration of functionalized alkenes. For example, Tang and co-workers recently described



Scheme 2. Recently reported approaches to the synthesis of chiral tertiary boronic esters.

a remarkable rhodium-catalyzed reaction of α-aryl enamides with $B_2(pin)_2$ to provide the first enantioselective synthesis of chiral tertiary α-aminoboronic esters.[11] Shibasaki and co-workers,[12] Hoveyda and co-workers,[13] and Feng and Yun[14] independently developed asymmetric conjugate addition reactions of $B_2(pin)_2$ to unsaturated esters, ketones, and thioesters. Hoveyda and co-workers also developed an efficient copper-catalyzed S_N2' substitution of allylic carbonates by $B_2(pin)_2$.[15] Aggarwal and co-workers have very elegantly exploited enantioselective lithiation followed by the addition of a boronic ester and subsequent rearrangement to prepare chiral tertiary boronic esters bearing benzyl, allyl, propargyl, and most recently all-alkyl substituents.[16] Tertiary boronic esters can also be constructed by deborylative alkylation of geminal bis(boronates), as reported by Wommack and Kingsbury[17] and Morken and co-workers.[18]

A series of methylidene derivatives **5** in which the vinyl substituent R^1 varies were subjected to CAHB (Scheme 3). Oxime ether **5b** ($R^1 = CH_2Ph$) was converted into the intermediate chiral boronic ester **7b** ($R^1 = CH_2Ph$), and the tertiary alcohol **6b** (70%, 94:6 e.r.) was obtained after oxidation; alkene reduction, in this case leading to the formation of **8** (21%, 56:44 e.r.), was the major competing side reaction for all substrates. The isobutyl derivative **5c** ($R^1 = CH_2CH(CH_3)_2$) reacted similarly to give the tertiary derivative **6c** (70%, 95:5 e.r.). Several substrates with a second site of unsaturation in the R^1 substituent were also found to undergo CAHB. Notably, only the alkene closest to the oxime directing group underwent borylation in these diene substrates. For example, the reaction of 1,4-dienes **5d–f**

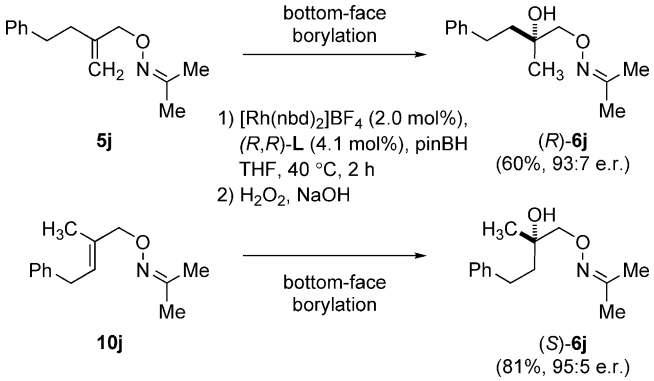


Scheme 3. CAHB of methylidene substrates **5** to form chiral tertiary boronic esters **7**. Typical reaction conditions: 1) $[Rh(nbd)_2]BF_4$ (2.0 mol%), (*R*,*R*)-**L** (4.1 mol%), pinBH (2.0 equiv), THF ($c = 0.04$ M), 40°C, 3–24 h; 2) H_2O_2, aqueous NaOH. [a] The boronic ester was formed in 84% yield. [b] The boronic ester was formed in 69% yield. [c] (*R*)-**6h** was formed in 70% yield according to the NMR spectrum of the crude product. Bn = benzyl.

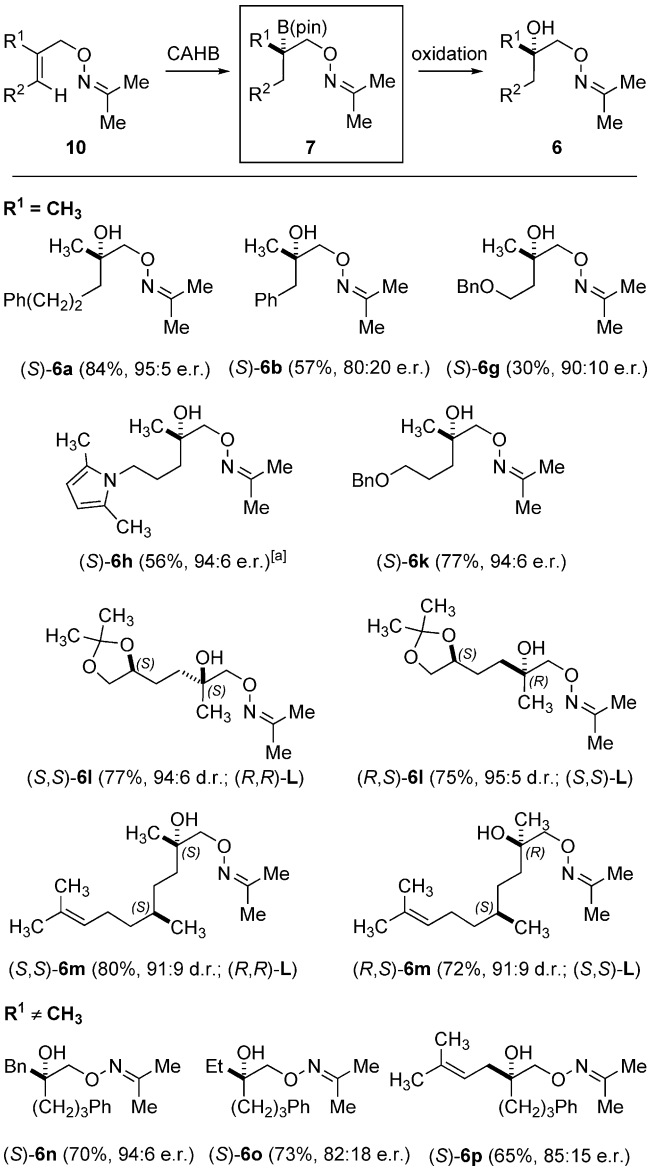
afforded monounsaturated alcohols **6d–f** after oxidation. Simple pendant oxygen and nitrogen substituents are tolerated, as illustrated by the formation of **6g** and **6h**. The level of regioselectivity in favor of β- over γ-borylation is high, except for substrates in which the vinyl substituent R^1 is more sterically demanding. For example, **5i** (R^1 = cyclohexyl) underwent predominantly γ-borylation to afford the regioisomeric primary alcohol **9** (54%, 85:15 e.r.) after oxidation.

Trisubstituted alkene substrates typically react sluggishly in catalyzed hydroboration but nevertheless readily underwent oxime-directed CAHB. The borane added to the same π-face as in the corresponding methylidene substrates and therefore yielded the enantiomeric tertiary boronic ester intermediate and the enantiomeric tertiary alcohol after oxidation. For example, CAHB/oxidation of methylidene **5j** afforded predominantly (*R*)-**6j** (60%, 93:7 e.r.); the isomeric trisubstituted substrate **10j** was transformed predominantly into (*S*)-**6j** (81%, 95:5 e.r.; Scheme 4).

Scheme 5 summarizes the results obtained for the oxime-directed CAHB/oxidation of a number of trisubstituted alkene derivatives **10**. Not only was the opposite enantiomer formed, but the yields observed with unhindered trisubstituted alkene substrates were often somewhat higher than those observed for the corresponding methylidene substrates owing to less competing alkene reduction. For example, (*S*)-**6a** (95:5 e.r.) was formed in 84% yield from trisubstituted alkene **10a** (R^1 = Me, $R^2 = PhCH_2CH_2$), whereas (*R*)-**6a** (95:5



Scheme 4. With the same catalyst system, isomeric methylidene and trisubstituted alkene substrates undergo CAHB with the same π-facial selectivity, thus giving the enantiomeric tertiary alcohols after oxidation.



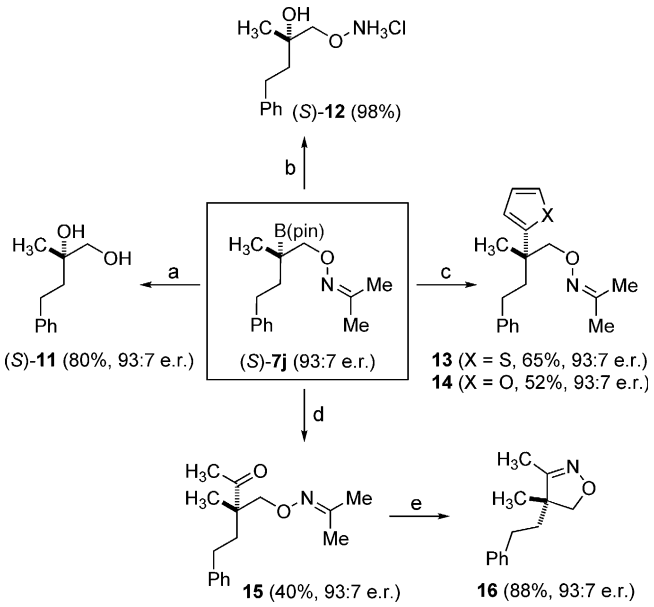
Scheme 5. CAHB of trisubstituted alkene substrates **10** to form of chiral tertiary boronic esters **7**. Typical reaction conditions: 1) [Rh(nbd)$_2$]BF$_4$ (2.0 mol%), **L** [(*R*,*R*)-isomer used unless noted otherwise; 4.1 mol%], pinBH (2.0 equiv), THF, 40°C, 3–16 h; 2) H_2O_2, aqueous NaOH. [a] (*S*)-**6h** formed in 78% yield according to the NMR spectrum of the crude product.

e.r.) was formed in 71% yield from methylidene **5a**.[19] However, in other cases, methylidene substrates reacted more efficiently. For example, **5b** and **5g** each underwent oxime-directed CAHB/oxidation to afford (*R*)-**6b** (70%, 94:6 e.r.) and (*R*)-**6g** (67%, 95:5 e.r.). The yields and levels of enantioselectivity are somewhat higher than those observed with the isomeric trisubstituted substrates **10b** [(*S*)-**6b** (57%, 80:20 e.r.)] and **10g** [(*S*)-**6g** (30%, 90:10 e.r.)]. In contrast to **10g**, substrate **10k**, in which the benzyl ether substituent resides further away from the site of reaction by one methylene group, underwent CAHB in good yield with high enantioselectivity to give (*S*)-**6k** (77%, 94:6 e.r.). A simple nitrogen-containing side chain can again be accommodated, as illustrated by the CAHB of **10h** to give (*S*)-**6h** (56%, 94:6 e.r.).

Trisubstituted alkene substrates with remote stereocenters underwent oxime-directed CAHB with good catalyst-controlled diastereoselectivity. For example, the chiral ketal-containing substrate (*S*)-**10l** afforded either (*S*,*S*)- or (*R*,*S*)-**6l**, depending on the configuration of the chiral ligand **L** used in the reaction. Similarly, catalyst-controlled CAHB afforded either diastereomer of **6m**; again only the proximal alkene in the diene substrate reacted. The examples described thus far all lead to chiral tertiary boronic esters in which one of the substituents is a methyl group. Substrate **10n** extends the scope of this approach with the formation of (*S*)-**6n** (70%, 94:6 e.r.). However, substrates in which the trisubstituted alkene is increasingly congested (e.g., **10o** and **10p**) tend to react slower and with lower levels of enantioselectivity under the conditions found to date.

Scheme 6 illustrates selected transformations of the chiral tertiary boronic ester **7j** (93:7 e.r.).[20] Oxidation of the C–B bond, followed by cleavage of the N–O bond, afforded the chiral diol **11** (80%, 93:7 e.r.). Alternatively, oxidation followed by hydrolysis afforded the chiral *O*-alkyl hydroxylamine **12** (98%, 93:7 e.r.). A method developed by Aggarwal and co-workers was used for carbon–carbon bond formation.[21] The addition of lithiated thiophene or furan, followed by electrophile-induced rearrangement of the intermediate borate with retention of configuration, afforded coupled products **13** and **14** in 65 and 53% yield, respectively. A similar sequence involving treatment with lithiated ethyl vinyl ether, followed by hydrolysis, afforded the keto-oxime **15** with high enantioselectivity, albeit in moderate yield (40%). Nonetheless, the exposure of **15** to an acid gave the chiral 3,4,4-trisubstituted isoxazoline **16** (88%, 93:7 e.r.). Chiral isoxazolines are found in many natural products and often exhibit diverse biological properties. Hence, isoxazolines are common pharmacophores of interest in medicinal chemistry.[22] The synthesis of **16** constitutes to our knowledge the first reported enantioselective preparation of a 3,4,4-trisubstituted isoxazoline.

In summary, asymmetric hydroboration would seem to be an unlikely approach for the preparation of chiral tertiary



Scheme 6. Selected transformations of the oxime-containing chiral, tertiary boronic ester **7j**. Reaction conditions: a) 1) aqueous H_2O_2, NaOH; 2) Ni-Raney, H_2 (1 atm), $B(OH)_3$; b) 1) aqueous H_2O_2, NaOH; 2) HCl/H_2O/MeOH (1:1:1), 40 °C; c) 1) *n*BuLi, furan or thiophene, −78 °C, THF; 2) *N*-bromosuccinimide; d) 1) LiC(OEt)=CH_2, −78 °C, THF; 2) I_2; 3) NaOMe, MeOH; e) HCl/H_2O/MeOH (1:1:1), 40 °C.

boronic esters, since hydroboration generally proceeds in an *anti*-Markovnikov fashion. Nonetheless, we have found that unsaturated substrates bearing acetone-derived oxime functionality are excellent substrates for directed CAHB and yield novel, functionalized tertiary organoboronates with good-to-excellent levels of enantioselectivity. Methylidene and trisubstituted alkene substrates, the latter traditionally considered poor substrates for catalyzed hydroboration, readily undergo oxime-directed CAHB. The borane adds with the same sense of π-facial selectivity in both classes of alkene substrates, and therefore, isomeric substrates yield enantiomeric tertiary boronic esters. A range of substituents are tolerated in the reaction. Of particular note are the findings that substrates bearing remote stereocenters undergo oxime-directed CAHB with good catalyst-controlled diastereoselectivity and that only the proximal alkene undergoes borylation in several diene substrates. The strategy complements other recently reported methods for the preparation of chiral tertiary boronic esters, particularly for the preparation of organoboronates possessing alkyl, rather than aryl, substituents at the carbon atom bearing the boron substituent. Chiral tertiary boronic esters are versatile synthetic intermediates, and the utility of the asymmetric hydroboration is illustrated by several subsequent transformations. In particular, chemistry introduced by Aggarwal and co-workers for stereoretentive C–C bond formation was applied to the enantioselective preparation of a 3,4,4-trisubstituted isoxazoline. Further studies are in progress.

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[19] The reaction of substrate (*Z*)-**10a** also afforded (*S*)-**6a**, but in somewhat lower yield and with lower enantioselectivity (55%, 90:10 e.r.).

[20] CAHB of **10j** was performed on a 1.3 mmol scale with a lower catalyst loading and higher concentration than described in Scheme 4 (reaction conditions: $[Rh(nbd)_2]BF_4$ (0.5 mol%), (*R*,*R*)-**L1** (1.03 mol%), pinBH (1.5 equiv), THF, $c = 0.13$ M, 40 °C, 7 h) to afford boronic ester **7j** in 78% yield, albeit with a slightly lower level of enantioselectivity (93:7 e.r.).

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