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

Veronika M. Shoba, **Dr. Nathan C. Thacker**, **Andrew J. Bochat**, and **Prof. Dr. James M. Takacs**[*]

Department of Chemistry University of Nebraska-Lincoln, 807 Hamilton Hall, Lincoln, NE, 68588-0304 USA

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 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 enantiomer ratios up to 96:4 er. The utility of the method is demonstrated by the formation of chiral diols and O-substituted hydroxylamines, the generation of quaternary carbon stereocenters via carbon-carbon coupling reactions, and the preparation of chiral 3,4,4-trisubstituted isoxazolines.

Abstract
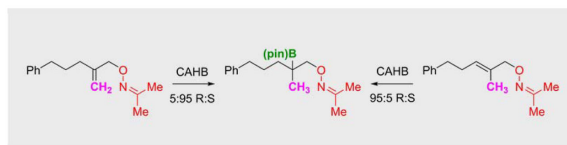
Keywords

hydroboration; asymmetric catalysis; rhodium-catalyzed; oxime-directed; homogeneous catalysis

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 regiochemistry in 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 Figure 1, methylidene derivative **1** undergoes regioselective

---

[*] jtakacs1@unl.edu.

Supporting information for this article is given via a link at the end of the document.

CAHB on the alkene *si* face to afford chiral hydroxyamide **2** in 96:4 er 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 metallation reactions, most frequently to direct *ortho*-C–H activation of aromatic substrates but increasingly applied to C_{sp3}–H activation as well.[4] In addition, Sanford and co-workers recently reported oxime-directed palladium-catalyzed dioxygenation of an adjacent alkene.[5]

Our initial attempts at oxime-directed CAHB employed benzophenone-derived allylic oxime ethers such as **3**. While rhodium-catalyzed hydroboration of **3** led to some γ-borylation, the yield of **4** (after oxidation) is low and the enantioselectivity is 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** undergoes oxime-directed CAHB/oxidation to give **6a** in good yield (71%) and with high levels of asymmetric induction (95:5 er). Furthermore, the borylated intermediate is a tertiary boronic ester arising from *re*-face β–borylation; in contrast, carbonyl-directed CAHB of **1** proceeds via *si*-face γ–borylation. It seems likely that the contrasting regio- and stereochemical outcomes obtained with **1** versus **5a** arise due to the presence of the oxime substituents in the substrate-catalyst complex, although more work is needed to prove this unambiguously.

Chiral boronic acid derivatives are valuable intermediates in organic synthesis.[7] In particular, recent reviews by Aggarwal highlight transformations of chiral tertiary boronic esters,[8] including their use for the construction of multiple contiguous quaternary stereocenters.[9] However, the formation of tertiary organoboronates via metal-catalyzed or stoichiometric hydroboration, is rare since hydroboration generally proceeds in an anti-Markovnikov fashion delivering 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 (Figure 2). Three of these methods use bis(pinacolato)diboron (B_2pin_2) to carry out the net hydroboration of functionalized alkenes. For example, Tang recently described a remarkable rhodium-catalyzed reaction of α-arylenamides with $B_2(pin)_2$ to provide the first enantioselective synthesis of chiral tertiary α-aminoboronic esters.[11] Shibasaki,[12] Hoveyda,[13] and Yun[14] independently developed asymmetric conjugate additions of $B_2(pin)_2$ to unsaturated esters, ketones, and thioesters. Hoveyda also developed an efficient copper-catalyzed S_N2' substitution of allylic carbonates by $B_2(pin)_2$.[15] Aggarwal has 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 Kingsbury[17] and Morken.[18]

A series of methylidene derivatives **5** in which the vinyl substituent R^1 varies were subjected to CAHB (Figure 3). Oxime ether **5b** ($R^1 = CH_2Ph$) affords the intermediate chiral boronic

ester **7b** (R^1 = CH$_2$Ph) leading to the tertiary alcohol **6b** (70%, 94:6 er) after oxidation; alkene reduction leading to **8** (21%, 56:44 er) is the major competing side reaction here and elsewhere. The isobutyl derivative **5c** (R^1 = CH$_2$CH(CH$_3$)$_2$) reacts similarly giving the tertiary derivative **6c** (70%, 95:5 er). Several substrates, in which the R^1 substituent contains a second site of unsaturation, were also found to undergo CAHB. It is particularly noteworthy that only the alkene closest to the oxime directing group undergoes borylation in these diene substrates. For example, the 1,4-dienes **5d-f** afford monounsaturated alcohols **6d-f** after oxidation. Simple pendant oxygen- and nitrogen-substituents are tolerated as illustrated in the formation of **6g** and **6h**. The level of regioselectivity favoring 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) undergoes predominantly γ-borylation to afford the regioisomeric primary alcohol **9** (54%, 85:15 er) after oxidation.

Trisubstituted alkene substrates typically react sluggishly in catalyzed hydroboration but nevertheless readily undergo oxime-directed CAHB. Borane adds to the same π-face as in the corresponding methylidene substrates and therefore yields the enantiomeric tertiary boronic ester intermediate and the enantiomeric tertiary alcohol after oxidation. For example, as shown in Figure 4, CAHB/oxidation of methylidene **5j** affords predominantly (*R*)-**6j** (60%, 93:7 er); the isomeric trisubstituted substrate **10j** affords predominantly (*S*)-**6j** (81%, 95:5 er).

Figure 5 summarizes the results obtained for the oxime-directed CAHB/oxidation of a number of trisubstituted alkene derivatives **10**. In addition to giving the opposite enantiomer, the yields obtained with unhindered trisubstituted alkene substrates are often somewhat higher than those obtained for the corresponding methylidene substrates due to less competing alkene reduction. For example, the formation of (*S*)-**6a** (84%, 95:5 er) from trisubstituted alkene **10a** (R^1 = Me, R^2 = PhCH$_2$CH$_2$) is a bit higher than the formation of (*R*)-**6a** (71%, 95:5 er) from methylidene **5a**.[19] However, in other cases, methylidene substrates react more efficiently. For example, **5b** and **5g** each undergo oxime-directed CAHB/oxidation to afford (*R*)-**6b** (70% 94:6 er) and (*R*)-**6g** (67% 95:5 er). The yields and levels of enantioselectivity are somewhat higher than those obtained with the isomeric trisubstituted substrates **10b** [(*S*)-**6b** (57%, 80:20 er)] and **10g** [(*S*)-**6g** (30%, 90:10 er)]. In contrast to **10g**, substrate **10k** in which the benzyl ether substituent resides one methylene group more remote to the site of reaction undergoes CAHB in good yield and high enantioselectivity to give (*S*)-**6k** (77%, 94:6 er). A simple nitrogen-containing side chain is again accommodated, as illustrated by CAHB of **10h** to (*S*)-**6h** (56%, 94:6 er).

Trisubstituted alkene substrates bearing remote stereocenters undergo oxime-directed CAHB with good catalyst-controlled diastereoselectivity. For example, the chiral ketal-containing substrate (*S*)-**10l** affords either (*S,S*)- or (*R,S*)-**6l** depending on the configuration of the chiral ligand **L** used in the reaction. Similarly, catalyst-controlled CAHB affords either diastereomer of **6m**, again noting that only the proximal alkene in the diene substrate reacts. 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 with the formation of (*S*)-**6n** (70%, 94:6 er). 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.

Figure 6 illustrates selected transformations of chiral tertiary boronic ester **7j** (93:7 er).[20] Oxidation of the C–B bond followed by cleavage of the N–O bond affords chiral diol **11** (80%, 93:7 er). Alternatively, oxidation followed by hydrolysis affords the chiral *O*-alkyl hydroxylamine **12** (98%, 93:7 er). Carbon-carbon bond formation is accomplished using the method developed by Aggarwal.[21] Addition of lithiated thiophene or furan followed by electrophile-induced rearrangement of the intermediate borate with retention of configuration affords coupled products **13** and **14** (65% and 53% yield, respectively). A similar sequence using lithiated ethyl vinyl ether followed by hydrolysis affords the keto-oxime **15** with high enantioselectivity, albeit in moderate yield (40%). Nonetheless, treatment with acid gives the chiral 3,4,4-trisubstituted isoxazoline **16** (88%, 93:7 er). 5,5-Disubstituted 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 is seemingly an unlikely candidate for the preparation of chiral tertiary boronic esters since hydroboration generally proceeds in an anti-Markovnikov fashion. Nonetheless, we find 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. 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 chemistry 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 bearing boron. Chiral tertiary boronic esters are versatile synthetic intermediates, and the utility of the chemistry is illustrated by several subsequent transformations. Of particular note is the application of chemistry introduced by Aggarwal for stereoretentive C–C bond formation which we have applied in the enantioselective preparation of a 3,4,4-trisubstituted isoxazoline. Further studies are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

[1] a). Carroll AM, O'Sullivan TP, Guiry P. J. Adv. Synth. Catal. 2005; 347:609–631.b) Crudden CM, Edwards D. Eur. J. Org. Chem. 2003; 24:4695–4712.

[2] a). Zhang L, Zuo Z-Q, Wan X-L, Huang Z. J. Am. Chem. Soc. 2014; 136:15501–15504. [PubMed: 25325782] b) Chen J, Xi T, Lu Z. Org. Lett. 2014; 16:6452–6455. [PubMed: 25438006] c) He Z, Zhao Y, Tian P, Wang C, Dong H, Lin G. Org. Lett. 2014; 16:1426–1429. [PubMed: 24528372] d) Feng X, Jeon H, Yun J. Angew. Chem., Int. Ed. 2013; 52:3989–3992.e) Moteki SA, Toyama K, Liu Z, Ma J, Holmes AE, Takacs JM. Chem. Commun. 2012:263–265.f) Noh D, Yoon SK, Won J, Lee JY, Yun J. Chem. Asian J. 2011; 6:1967–1969. [PubMed: 21523913] g) Noh D, Chea H, Ju J, Yun J. Angew. Chem., Int. Ed. 2009; 48:6062–6064.h) Moteki SA, Takacs JM. Angew. Chem., Int. Ed. 2008; 47:894–897.i) Moteki SA, Wu D, Chandra KL, Reddy DS, Takacs JM. Org. Lett. 2006; 8:3097–3100. [PubMed: 16805561] j) Kwong FY, Yang QT, Mak CW, Chan ASC, Chan KS. J. Org. Chem. 2002; 67:2769–2777. [PubMed: 11975527] k) Schnyder A, Hintermann L, Togni A. Angew. Chem., Int. Ed. 1995; 34:931–933.l) Togni A, Breutel C, Schnyder A, Spindler F, Landert H, Tijani A. J. Am. Chem. Soc. 1994; 116:4062–4066.m) Hayashi T, Matsumoto Y, Ito Y. J. Am. Chem. Soc. 1989; 111:3426–3428.

[3] a). Hoang GL, Yang ZD, Smith SM, Pal R, Miska JL, Perez DE, Pelter LSW, Zeng XC, Takacs JM. Org. Lett. 2015; 17:940–943. [PubMed: 25642639] b) Yang Z, Pal R, Hoang GL, Zeng XC, Takacs JM. ACS Catal. 2014; 4:763–773. [PubMed: 24804151] c) Smith SM, Hoang GL, Pal R, Khaled MOB, Pelter LSW, Zeng XC, Takacs JM. Chem. Commun. 2012:12180–12182.d) Smith SM, Thacker NC, Takacs JM. J. Am. Chem. Soc. 2008; 130:3734–3735. [PubMed: 18311977] e) Smith SM, Takacs JM. J. Am. Chem. Soc. 2010; 132:1740–1741. [PubMed: 20092272] f) Smith SM, Uteuliyev M, Takacs JM. Chem. Commun. 2011:7812–7814.

[4] a). Xu Y, Yan G, Ren Z, Dong G. Nature Chem. 2015; 7:829–834. [PubMed: 26391083] b) Wang H, Yu S, Qi Z, Li X. Org. Lett. 2015; 17:2812–2815. [PubMed: 25972069] c) Ebe Y, Nishimura T. J. Am. Chem. Soc. 2015; 137:5899–5902. [PubMed: 25928127] d) Guo K, Chen X, Guan M, Zhao Y. Org. Lett. 2015; 17:1802–1805. [PubMed: 25767937] e) Kang T, Kim H, Kim JG, Chang S. Chem. Commun. 2014; 50:12073–12075.f) Zhou B, Du J, Yang Y, Feng H, Li Y. Org. Lett. 2014; 16:592–595. [PubMed: 24369964] g) Xie F, Qi Z, Yu S, Li X. J. Am. Chem. Soc. 2014; 136:4780–4787. [PubMed: 24593822] h) Yeh C, Chen W, Gandeepan P, Hong Y, Shih C, Cheng C. Org. Biomol. Chem. 2014; 12:9105–9108. [PubMed: 25313516] i) Yu S, Wan B, Li X. Org. Lett. 2013; 15:3706–3709. [PubMed: 23822068] j) Chan W, Lo S, Zhou Z, Yu W. J. Am. Chem. Soc. 2012; 134:13565–13568. [PubMed: 22860697] k) Hyster TK, Rovis T. Chem. Commun. 2011; 47:11846–11848.l) Desai LV, Stowers KJ, Sanford MS. J. Am. Chem. Soc. 2008; 130:13285–13293. [PubMed: 18781752]

[5]. Neufeldt SR, Sanford MS. Org. Lett. 2013; 15:46–49. [PubMed: 23249401]

[6]. Thacker NC, Shoba VM, Geis AE, Takacs JM. Tetrahedron Lett. 2015; 56:3306–3310. [PubMed: 26120214]

[7] a). Matteson DS. J. Org. Chem. 2013; 78:10009–10023. [PubMed: 23875690] b) Li L, Zhao S, Joshi-Pangu A, Diane M, Biscoe MR. J. Am. Chem. Soc. 2014; 136:14027–14030. [PubMed: 25226092] c) Matthew SC, Glasspoole BW, Eisenberger P, Crudden CM. J. Am. Chem. Soc. 2014; 136:5828–5831. [PubMed: 24684649] d) Buesking AW, Ellman JA. Chem. Sci. 2014; 5:1983–1987.e) Zhang C, Yun J. Org. Lett. 2013; 15:3416–3419. [PubMed: 23773146] f) Mlynarski SN, Karns AS, Morken JP. J. Am. Chem.Soc. 2012; 134:16449–16451. [PubMed: 23002712] g) Imao D, Glasspoole BW, Laberge VS, Crudden CM. J. Am. Chem. Soc. 2009; 131:5024–2025. [PubMed: 19301820]

[8] a). Leonori D, Aggarwal VK. Angew. Chem. Int. Ed. 2014; 53:2–17.b) Leonori D, Aggarwal VK. Acc. Chem. Res. 2014; 47:3174–3183. [PubMed: 25262745] c) Scott HK, Aggarwal VK. Chem. Eur. J. 2011; 17:13124–13132. [PubMed: 22052475]

[9] a). Watson CG, Balanta A, Elford TG, Essafi S, Harvey JN, Aggarwal VK. J. Am. Chem. Soc. 2014; 136:17370–17373. [PubMed: 25469619] b) Marek I, Minko Y, Pasco M, Mejuch T, Gilboa N, Chechik H, Das JP. J. Am. Chem. Soc. 2014; 136:2682–2694. [PubMed: 24512113]

[10]. Burgess K, van der Donk WA. Inorg. Chim. Acta. 1994; 220:93.

[11]. Hu N, Zhao G, Zhang Y, Liu X, Li G, Tang W. J. Am. Chem. Soc. 2015; 137:6746–6749. [PubMed: 25938599]

[12] a). Chen IH, Yin L, Itano W, Kanai M, Shibasaki M. J. Am. Chem. Soc. 2009; 131:11664–11665. [PubMed: 19653692] b) Chen IH, Yin L, Kanai M, Shibasaki M. Org. Lett. 2010; 12:4098–4101. [PubMed: 20722382]

[13] a). O'Brien JM, Lee K, Hoveyda AH. J. Am. Chem. Soc. 2010; 132:10630–10633. [PubMed: 20681680] b) Radomkit S, Hoveyda AH. Angew. Chem. Int. Ed. 2014; 53:3387–3391.

[14]. Feng X, Yun J. Chem. Eur. J. 2010; 16:13609–13612. [PubMed: 21053219]

[15]. O'Brien M, Lee K, Hoveyda AH. J. Am. Chem. Soc. 2010; 132:10634–10637. [PubMed: 20681681]

[16] a). Stymiest JL, Bagutski V, French RM, Aggarwal VK. Nature. 2008; 456:778. [PubMed: 19079057] b) Bagutski V, French RM, Aggarwal VK. Angew. Chem., Int. Ed. 2010; 49:5142.c) Pulis AP, Aggarwal VK. J. Am. Chem. Soc. 2012; 134:7570. [PubMed: 22524150] d) Aggarwal VK, Binanzer M, Ceglie M. C. d. Gallanti M, Glasspoole BW, Kendrick SJF, Sonawane RP, Vázquez-Romero A, Webster MP. Org. Lett. 2011; 13:1490. [PubMed: 21332157] e) Partridge BM, Chausset-Boissarie L, Burns M, Pulis AP, Aggarwal VK. Angew. Chem., Int. Ed. 2012; 51:11795.f) Pulis AP, Blair DJ, Torres E, Aggarwal VK. J. Am. Chem. Soc. 2013; 135:16054–16057. [PubMed: 24138162] g) Watson CG, Aggarwal VK. Org. Lett. 2013; 15:1346–1349. [PubMed: 23461803]

[17]. Wommack AJ, Kingsbury JS. Tetrahedron Lett. 2014; 55:3163–3166.

[18]. Hong K, Liu X, Morken JP. J. Am. Chem. Soc. 2014; 136:10581–10584. [PubMed: 25019925]

[19]. (Z)-**10a** also affords (S)-**6a** but in somewhat lower yield and lower enantioselectivity (55%, 90:10 er).

[20]. CAHB of **10j** was performed on 1.3 mmol scale using lower catalyst loading and higher concentration than described in Figure 4 (0.5% Rh(nbd)$_2$BF$_4$, 1.03% (R,R)-**L1**, 1.5 pinBH, THF (c = 0.13 M, 40 °C, 7 h) to afford 78% of boronic ester **7j** albeit with a slightly lower level of enantioselecivity (93:7 er).

[21]. Bonet A, Odachowski M, Leonori D, Essafi S, Aggarwal VK. Nat. Chem. 2014; 6:584–589. [PubMed: 24950327]

[22]. Kaur K, Kumar V, Sharma AK, Gupta GK. Eur. J. Med. Chem. 2014; 77:121–133. [PubMed: 24631731]
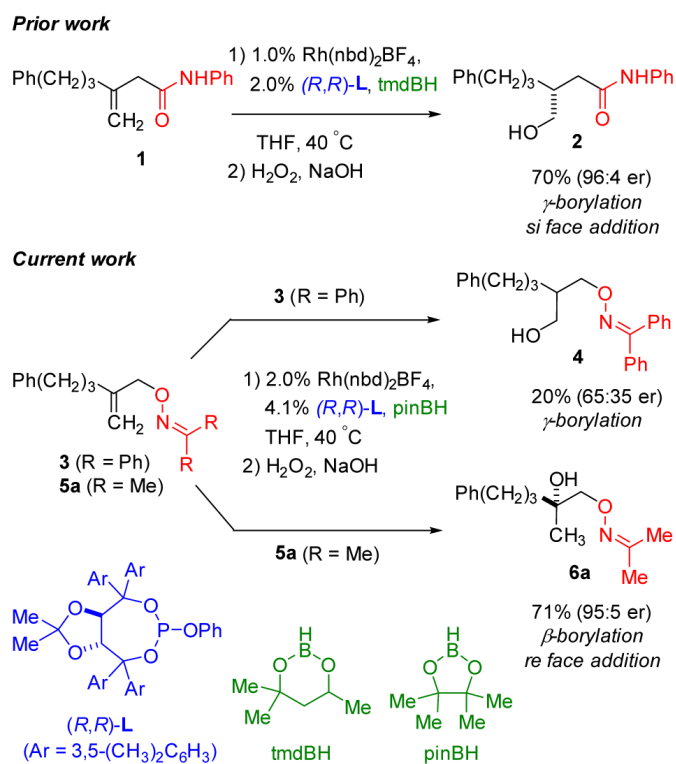
Figure 1.
In contrast to carbonyl-directed CAHB, the reaction of a similar oxime ether substrate leads to the formation of a chiral tertiary boronic ester.
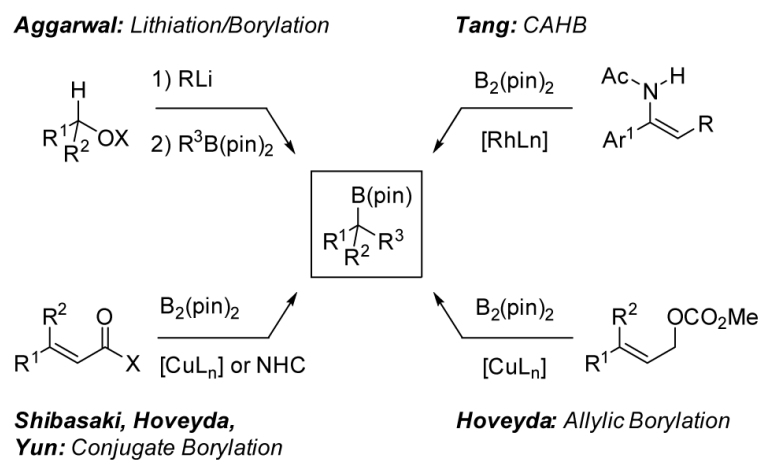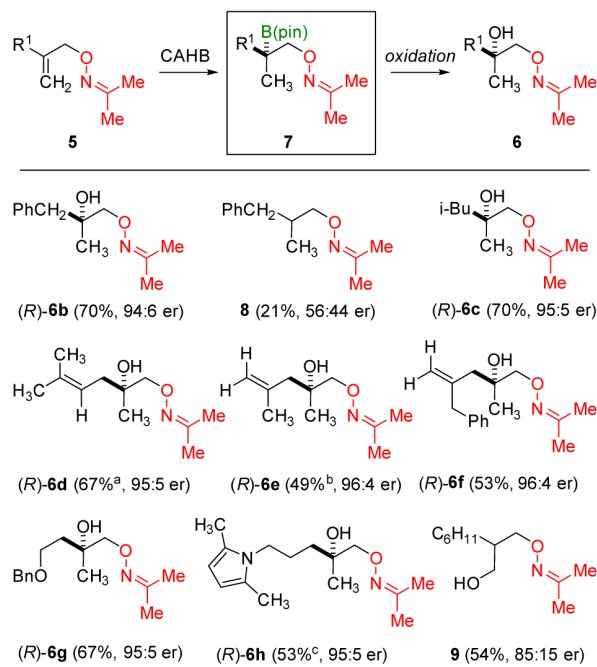
Figure 2.
Recently reported approaches to the synthesis of chiral tertiary boronic esters.

Figure 3.
CAHB of methylidene substrates **5** leading to the formation of chiral tertiary boronic esters
7.

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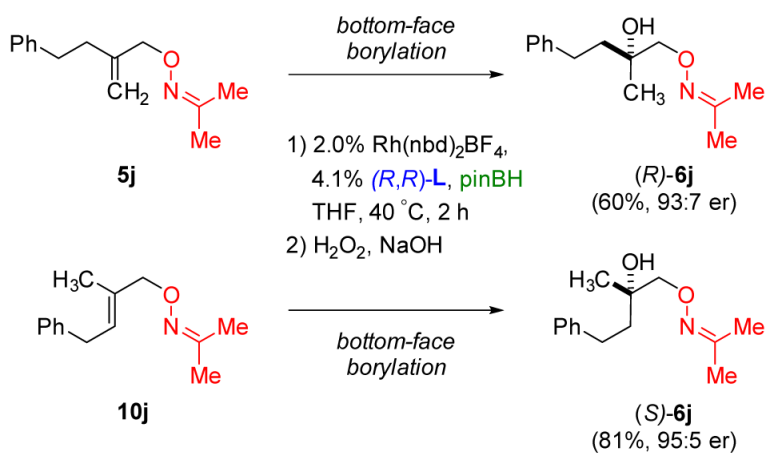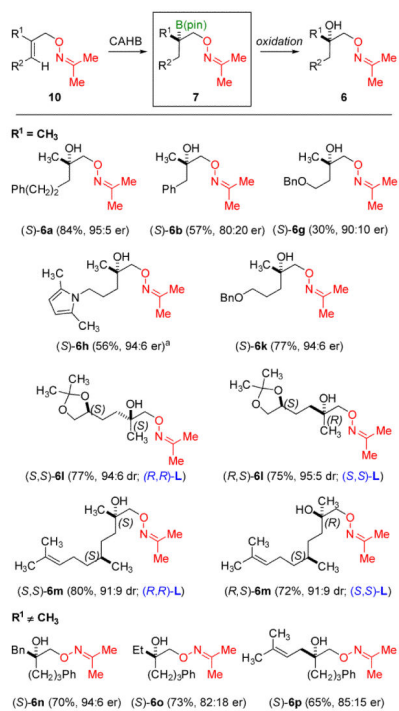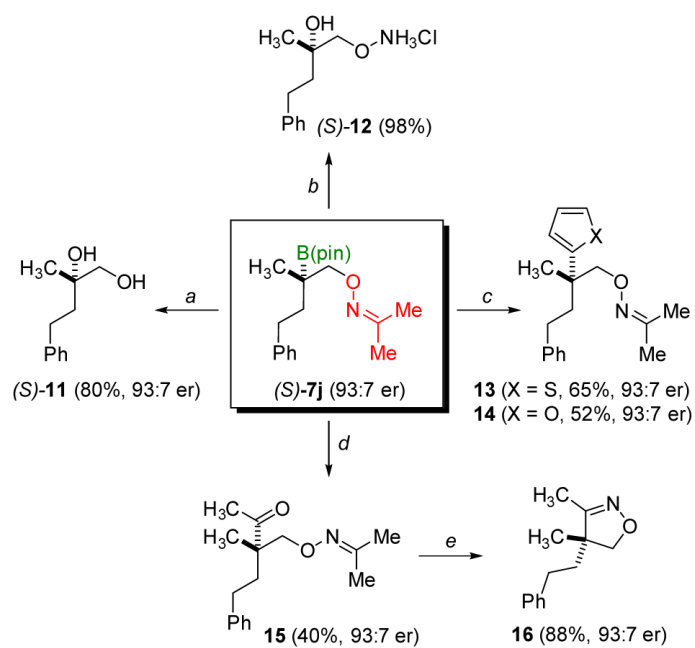Using the same catalyst system, isomeric methylidene and trisubstituted alkene substrates undergo CAHB with the same π-facial selectivity thus giving the enantiomeric tertiary alcohols after oxidation.

Figure 5.
CAHB of trisubstituted alkene substrates **10** leading to the formation of chiral tertiary boronic esters **7**.

Figure 6.
Selected transformations of oxime-containing chiral, tertiary boronic ester **7j**.