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Phosphonate-Directed Catalytic Asymmetric Hydroboration: Delivery of Boron to the More Substituted Carbon, Leading to Chiral Tertiary Benzylic Boronic Esters

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Abstract

Phosphonate-directed catalytic asymmetric hydroboration (CAHB) of β -aryl/heteroaryl methylenes and trisubstituted alkenes by pinacolborane enables facile access to functionalized, chiral tertiary benzylic boronic esters. Hydroboration is catalyzed by a chiral rhodium catalyst prepared *in situ* from a Rh(I)-precursor in combination with a simple TADDOL-derived chiral cyclic monophosphite in a 1:1 ratio. The regio- and stereochemistry arises from the combined effects of the relative disposition of the directing group to the alkene, the alkene substitution pattern, and the necessity of an aryl substituent attached to the alkene. A range of aryl and heteroaryl substituents can be accommodated, and for several chiral substrates, the reactions are efficiently catalyst-controlled enabling the choice of diastereomeric products as desired. Stereospecific transformations of the chiral boronic ester afford chiral phosphonates bearing a quaternary carbon stereocenter. The synthetic utility of the products is further demonstrated by α -oxidation of the phosphonate leading to hydroxy- and oxo-phosphonates; the latter readily undergo elimination/substitution reactions to unmask the phosphonate functionality with the formation of aldehydes, alcohols, esters, amides, acids and ketones.

Graphical Abstract

Keywords

chiral tertiary boronic esters; rhodium catalysis; asymmetric hydroboration; trisubstituted alkene hydroboration; oxophosphonates

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Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org> at DOI: 10.1021/acscatal.8b03591. Experimental procedures, characterization data (SI-1; PDF) and NMR Data (SI-2; PDF).

INTRODUCTION

Chiral boronic esters are useful synthons for diversity-oriented synthesis¹ due to the relative ease with which these compounds can be refunctionalized via stereospecific transformations of the C–B bond.² While an increasing variety of modern methods are available for the enantioselective preparation of primary and secondary organoboron derivatives,^{3,4} fewer methods efficiently access chiral tertiary boronic esters.⁵ The latter are important since they can serve as precursors to chiral tertiary alcohols and amines, and to the construction of all-carbon quaternary stereocenters via stereospecific C–B to C–C bond substitution.^{1,2} The latter structural motif is common in natural products and compounds of biological interest and often presents a challenge for their synthesis.⁶

We have been exploring rhodium-catalyzed, directed-catalytic asymmetric hydroborations (CAHB) of functionalized alkene substrates with the goal of obtaining multifunctional, chiral boronic ester synthons.^{4,5a–b} We find that several factors influence the regio- and stereochemical outcomes of these reactions; the nature of the directing group, the alkene substitution pattern, the nature of the alkene substituent and the nature of the chiral ligand each play pivotal roles. Using the TADDOL-derived phosphite **T1** in combination with a common Rh(I) catalyst-precursor, the amide- and oxime ether-directed CAHB of β -aryl substituted methylenes **1** and **3** result in boration at the less substituted terminus of the alkene affording γ -borylated products (*S*)-**2** (71%, 96.5:3.5 er) and (*R*)-**4** (70%, 95:5 er), respectively (Figure 1).^{4d} Others have found that methylene substrates bearing at least one aryl substituent undergo iridium-,^{3g} cobalt-,^{3h–i} or copper-catalyzed^{3j–k} CAHB by pinacolborane (pinBH) or pinacol diborane (B₂pin₂) with boration occurring at the less substituted carbon.

We now report that incorporating phosphonate functionality in otherwise similar β -aryl or β -heteroaryl substituted methylene (and trisubstituted alkene) substrates leads to delivery of boron predominantly to the more substituted β -position. For example, allyl phosphonate **5a** (R = H) undergoes efficient CAHB to afford the chiral tertiary benzylic boronic ester (*R*)-**6a** (81%, 97:3 er);⁷ less than 15% of the regioisomeric γ -borylated product is formed along with traces of the alkene reduction product.^{8,9} While the predominant regioisomer contrasts that obtained from the amide and oxime ether substrates, **6a** arises via the same sense of facial induction, that is, B–H adds to the *si*-face of the alkene.¹⁰ Similar results are obtained for related allylic phosphonates bearing trisubstituted alkenes (*vide infra*).

RESULTS AND DISCUSSIONS

Phosphonate-Directed CAHB of β -Aryl Methylene Substrates.

Figure 2 summarizes the isolated yield of chiral tertiary boronic ester obtained from a series of methylenes differing in the nature of the aromatic substituent appended to the alkene. In all cases, the major byproduct is the regioisomeric terminal boronic ester. The 3-methoxyphenyl (**5b**) and 4-methoxyphenyl (**5c**) substrates undergo efficient β -boration to yield the chiral tertiary benzylic boronic esters **6b** (76%, 97:3 er) and **6c** (70%, 94:6 er), respectively. Similarly, the 3,4-dimethoxyphenyl derivative **5d** and 3,5-dimethylphenyl analog **5e** undergo CAHB in good yield and with high enantioinduction to afford **6d** (77%,

94:6 er) and **6e** (76%, 96:4 er), respectively. Changing the electronic character of the aryl group does not significantly affect the outcome of CAHB. For example, substrates bearing 4-methylphenyl (**5f**) and 4-trifluoromethylphenyl (**5g**) groups undergo CAHB with similarly high efficiency yielding **6f** (81%, 96:4 er) and **6g** (77%, 96:4 er), respectively.

Halogenated aromatics can be versatile intermediates for subsequent cross-coupling chemistry, and substrates bearing 3- or 4-halogenated phenyl substituents react smoothly under standard conditions. β -Borylated products **6h–6k** are obtained with high enantioselectivity (94:6 to 97:3 er) and in moderate-to-very good yields (62–82%). Substrates bearing the thienyl ring system also undergo highly regioselective β -boration in good yield. However, the 2-thienyl derivative exhibits higher enantioselectivity than the corresponding 3-thienyl derivative; **6l** (85%, 97:3 er) and **6m** (80%, 88:12 er) are obtained.

Given the contrasting results obtained with phosphonate compared to amide or oxime ether directing groups, the question naturally arises as to whether the phosphonate directing group is solely responsible for the observed β -boration regiochemistry. In fact, this appears not to be the case (Figure 3). While aryl substrates bearing ring substituents in the *meta*- and *para*-positions undergo efficient β -boration, substrates having *ortho*-substituted phenyl groups (e.g., **5n** and **5o**) completely change the regiochemistry; γ -borylated products **6n** (82%, 78:22 er) and **6o** (80%, 74:26 er) are obtained with high regioselectivity but poor levels of asymmetric induction. Related phosphonates also exhibit differences in regioselectivity. Phosphonate **7** is similar to **5** except the methylenide bears a simple alkyl rather than an aryl substituent (i.e., benzyl vs. phenyl). CAHB of **7** under the standard conditions proceeds via predominant *si*-face-addition to afford γ -borylated product **8** (71%, 88:12 er) as the major product. The β -borylated isomer **9** is a minor product along with traces of alkene reduction product. To further probe the role the phosphonate group in directing the course of reaction, we prepared **10**, the one-carbon homologue of **5a**, and subjected it to CAHB conditions. Unlike **5a**, the γ,δ -unsaturated phosphonate **10** affords a 1:1 mixture of regioisomers with neither regioisomer exhibiting high levels of enantioselectivity. The results in Figure 3 indicate that the phosphonate group, as well as its disposition relative to the alkene, and the nature of the alkene substituent combine to control the regio- and enantioselectivity observed in the phosphonate-directed CAHB.

Phosphonate-Directed CAHB of β -Aryl Trisubstituted Alkene Substrates.

Few catalyst systems have been demonstrated to be effective for the CAHB of trisubstituted alkenes.^{3j,5a–b} We recently reported that a variety of prochiral and chiral β,γ -unsaturated phosphonates possessing a trisubstituted alkene, one that bears only alkyl substituents, are excellent substrates for CAHB (Figure 4).^{5a} For example, **13** undergoes efficient catalyst-controlled diastereoselective CAHB. The use of (*R,R*)-**T2** leads to the formation of (2*R*, 5*S*)-**14** (82%, 97:3 dr); (*S,S*)-**T2** affords (2*S*,5*S*)-**14** (81%, 98:2 dr). We now report that the corresponding β -aryl trisubstituted alkene substrate (*Z*)-**15a** also undergoes facile CAHB to afford highly hindered, chiral tertiary benzylic boronic esters. The use of (*R,R*)-**T2** leads to the formation of chiral tertiary benzylic boronic ester (2*S*,5*S*)-**16a** (82%, 95:5 dr), while (*S,S*)-**T2** affords the diastereomeric product (2*R*,5*S*)-**16a** (81%, 94:6 dr). The synthetically

more challenging (*E*)-**15a** substrate behaves similarly; (*R,R*)-**T2** affords (*2R,5S*)-**16a** (81%, 95:5 dr) and (*S,S*)-**T2** affords (*2S,5S*)-**16a** (79%, 95:5 dr).

Using the same configuration of ligand **T2**, **13** and **15a** both result in β -boration, however, the addition of pinBH occurs from opposite faces of the two π -systems. As illustrated in Figure 4, pinBH is added to **13** from the “bottom-face” in the perspective shown, while pinBH adds to **15a** from the “top-face”. This disparity in the π -facial selectivity may stem from π -stacking interactions between substrate and ligand or via involvement of the aromatic ring stabilizing a Rh–C intermediate. The latter argument has been long used to explain the regioselective hydroboration of simple vinylarenes.¹¹ The sense of π -facial selectivity observed for **15a** (and related substrates **15b–j**, *vide infra*) is consistent with the *si*-face addition of pinBH found for β -aryl methylenes substrates **5**. As a practical matter, the *re/si*-sense of π -facial selectivity is of no consequence; either configuration of ligand **T2** is equally accessible and hence both diastereomeric products can be prepared with comparable facility.

Substrates bearing a 2-thienyl moiety in the β -position as in **15a**, but with a simple alkyl substituent in the γ -position (e.g., **15b**), also undergo β -boration yielding the corresponding tertiary benzylic boronic ester product **16b** (85%, 93:7 er) (Figure 5). The chiral substrate derived from citronellal (i.e., **15c**) bears a pendant alkene as well as a remote stereocenter. It undergoes catalyst-controlled β -boration leaving the more distant alkene intact; (*R,R*)-**T2** affords (*2S*)-**16c** (55%, 92:8 dr) and (*S,S*)-**T2** affords (*2R*)-**16c** (57%, 92:8 dr).¹² The benzothiophene derivative **15d** gives (*2S*)-**16d** (68%, 92:8 dr) using (*R,R*)-**T2** and (*2R*)-**16d** (69%, 92:8 dr) with (*S,S*)-**T2**. The benzofuran derivative **15e** gives comparable results using (*R,R*)-**T2**, affording (*2R*)-**16e** (76%, 93:7 dr), but exhibits a mismatched effect with (*S,S*)-**T2** to give (*2S*)-**16e** (73%, 80:20 dr) with a reduced level of diastereoselectivity.

Chiral allylic phosphonates bearing β -phenyl substituents, for example (*E*)-**15f–i**, tend to undergo highly regioselective β -boration albeit with somewhat lower stereoselectivity. For example, CAHB of **15f** using (*R,R*)-**T2** affords (*2R*)-**16f** (80%, 91:9 dr) while the reaction with (*S,S*)-**T2** exhibits a modest mismatched effect in giving predominantly (*2S*)-**16f** (78%, 85:15 dr). Improved diastereoselection is observed for the isomeric substrate (*Z*)-**15f**; (*R,R*)-**T2** affords (*2R*)-**16f** (83%, 96:4 dr) and (*S,S*)-**T2** gives (*2S*)-**16f** (84%, 97:3 dr). A significant electronic effect is observed. The 4-methoxyphenyl substrate (*E*)-**15g** behaves like (*E*)-**15f**; (*2R*)- and (*2S*)-**16g** are formed with catalyst control in 75% yield (90:10 dr). However, the presence of an electron withdrawing substituent lowers the yield and diastereoselectivity. Substrates **15h** (4-chlorophenyl derivative) and **15i** (4-trifluoromethylphenyl derivative) afford 56–63% yields of **16h** (83:17 dr) and **16i** (ca. 85:15 dr).

Substrate (*E*)-**15j** bears phenyl groups in both β - and γ -positions presenting a potential competition for regiocontrol. Which of the two phenyl groups will determine the regiochemistry? In the event, CAHB with (*R,R*)-**T2** yields the β -borylated product (*R*)-**16j** (60%, 97:3 er) with good enantioinduction. However, unlike the improved enantioselectivity seen for the (*Z*)-isomer of **15f**, CAHB of the diastereomeric (*Z*)-**15j** affords (*R*)-**16j** (71%, 70:30 er) with a much lower degree of stereocontrol.

Synthetic Versatility of Chiral Borylated Phosphonate Products.

The CAHB of **5a** proceeds smoothly on gram scale using a reduced catalyst loading (0.5 mol% Rh) and one equivalent of pinBH to give **6a** (80% yield, 97:3 er). Several common transformations of boronic esters were carried out using **6a** to demonstrate the potential synthetic utility of phosphonate functionalized, chiral tertiary benzylic boronic esters (Figure 6). The chiral tertiary boronic ester is easily converted to the corresponding trifluoroborate salt **17** (87%),¹³ the latter are generally more stable than pinacol boronates and are of interest in metal-catalyzed cross-coupling chemistry.^{14,15} Oxidation of **6a** by NaBO₃·4H₂O affords the chiral tertiary alcohol **18a** (90%, 97:3 er). Protodeboronation¹⁶ of **6a** using TBAF/H₂O yields the known chiral phosphonate **19** (85%, 96:4 er).¹⁷ Cross-coupling of **6a** with 2-lithiofuran is very efficient under the conditions reported by Aggarwal^{1e} to produce the furan derivative **20** (91%, 97:3 er); the latter contains a quaternary stereocenter bearing two aryl groups, a structural motif attracting recent interest in medicinal chemistry.¹⁸ Cross-coupling with vinylmagnesium bromide under similar conditions affords the vinyl derivative **21** (70%, 97:3 er).¹⁹

Phosphonates and phosphonic acids are components of important biologically active compounds²⁰ principally due to their capacity to act as stable phosphate surrogates by resisting hydrolysis. In our prior work on phosphonate-directed CAHB, we demonstrated the versatility of the phosphonate functionality through its use in thiophosphonate olefination to complete the synthesis of all-carbon quaternary allylic stereocenter of bakuchiol.^{5a} Here, we further highlight the utility of the phosphonate moiety by focusing on the chemistry of α -oxophosphonates (i.e., acylphosphonates) (Figure 7). The preparation of acylphosphonates typically proceeds via the reaction of trialkylphosphite with an acid chloride,²¹ a modification of the Michaelis-Arbuzov reaction, or via addition of a dialkylphosphite anion to an aldehyde followed by oxidation.²² The direct α -oxidation of phosphonates is not common, however, Wiemer reported the oxidation of benzylic phosphonates to chiral α -hydroxyphosphonates by treatment of the phosphonate α -carbanion with camphorsulfonyl oxaziridine.²³ We used a similar strategy to oxidize our phosphonate intermediates using 2-(phenylsulfonyl)-3-phenyl-oxaziridine (Davis' oxaziridine).²⁴

Our initial attempts to α -oxidize the boronic ester functionalized phosphonate **6a** were unsuccessful. However, catalytic hydrogenation of **21** gives **22** which when treated with *n*BuLi and Davis' oxaziridine yields α -hydroxyphosphonate **23** (83%, 2:1 dr). α -Hydroxyphosphonates such as **23** are aldehyde equivalents and readily undergo elimination.²⁵ Thus, treating **23** with aqueous NaHCO₃ affords the chiral aldehyde (*S*)-**24** (88%, 95:5 er). Alternatively, oxidation of α -hydroxyphosphonate **23** with Dess-Martin periodinane affords acylphosphonate **25** (92%).²⁰ Reduction of **25** with LiAlH₄ affords the known chiral alcohol (*S*)-**26** (89%, 95:5 er)^{19,26}, confirming the absolute configuration assigned to **6a**. Acylphosphonates have recently attracted interest as surrogates for esters and amides in asymmetric organocatalysis by serving the role of an active ester.^{21,22} Thus, treatment of **25** with: (i) ethanol/DBU converts **25** to the chiral ester **27** (95%, 96:4 er), (ii) aqueous ammonia affords the chiral amide (*S*)-**28** (85%, 97:3 er),²⁷ or (iii) aqueous sodium hydroxide forms the known chiral carboxylic acid²⁸ (*S*)-**29** (91%, 96:4 er).²⁹ Treatment of **25** with phenylmagnesium bromide gives after aqueous workup the stable α -

hydroxyphosphonate as a mixture of diastereomers. Treatment of the latter with aqueous base liberates the known chiral phenyl ketone³⁰ (*S*)-**30** (78% overall yield).³¹

CONCLUSIONS

Phosphonate-directed CAHB of β -aryl methylenes and trisubstituted alkenes provides facile access to functionalized, chiral tertiary benzylic boronic esters for which few direct methods of synthesis are available. A simple and readily accessible TADDOL-derived chiral monophosphite ligand in 1:1 combination with a commercially available Rh(I)-precatalyst is used to generate an active catalyst in situ. Reactions can be carried out under conditions of ambience and are scalable without loss of yield or enantiopurity; catalyst loading as low as 0.5% has been demonstrated. A range of aryl and heteroaryl substituents can be accommodated, and in cases of chiral substrates, the reactions are often efficiently catalyst-controlled enabling the synthesis of diastereomeric products as desired. Stereospecific transformations of the chiral boronic ester afford chiral phosphonates bearing a quaternary carbon stereocenter. The synthetic utility of the products obtained via CAHB is further demonstrated via α -oxidation of the phosphonate leading to α -hydroxy- and α -oxophosphonates; the latter readily undergo elimination or substitution reactions to unmask the phosphonate functionality with the formation of aldehydes, alcohols, esters, amides, acids and ketones.

The regioselective CAHB of simple vinyl arenes is well preceded in the literature. Depending on the nature of chiral catalyst used benzylic selectivity is frequently observed, presumably due to formation of a π -benzyl complex.¹¹ Although the regiochemistry differs between phosphonate-directed CAHB of β -aryl trisubstituted allylic phosphonates and methylenes derivatives and the corresponding amide- and oxime-directed β -aryl methylenes substrates, the sense of π -facial discrimination remains the same. This contrasts with the π -facial selectivity observed from phosphonate-directed CAHB of all-alkyl trisubstituted alkenes. The change based on the alkyl/aryl-nature of an alkene is surprising given that our previous studies suggested changes in regioselectivity often coincide with changes in alkene substitution pattern or the directing group. The regio- and stereochemistry for the phosphonate-directed boration likely arises from the combined effects of the relative disposition of the directing group to the alkene, the alkene substitution pattern, and the necessity for a conjugated alkene. Further studies of CAHB are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Directed-CAHB of methylidene vinyl arenes: comparison of amide, oxime and phosphonate directing groups.

Figure 2.

Substrate scope of phosphonate-directed CAHB of β -aryl methylidenes.

CAHB conditions: 0.5 mol% $[\text{Rh}(\text{cod})\text{Cl}]_2$, 1.0 mol% AgBF_4 , 1.0 mol% (*R,R*)-**T2**, 1 eq. pinBH. rt. 3 h; yields are for the isolated major regioisomer.

Figure 5.

Substrate scope and catalyst control with trisubstituted alkenes. Note: Data highlighted in yellow are from reactions carried out using (*R,R*)-**T2**; non-highlighted data are from reactions carried out using (*S,S*)-**T2**.

Standard CAHB conditions: 0.5 mol% [Rh(cod)Cl]₂, 1.0 mol% AgBF₄, 1.0 mol% (*R,R*)/(*S,S*)-**T2**, 1 eq. pinBH. rt. 3 h.

Figure 6:

Synthetic utility of phosphonate functionalized, chiral tertiary benzylic boronic esters is illustrated by selected transformations of **6a**.

Reagents and conditions: (a) KHF_2 , MeOH ; (b) $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$; (c) $\text{TBAF} \cdot \text{H}_2\text{O}$; (d) (i) $n\text{BuLi}$, furan, -78°C , THF ; (ii) NBS ; (iii) aq. $\text{Na}_2\text{S}_2\text{O}_3$; (e) (i) $\text{CH}_2=\text{CHMgBr}$, (ii) I_2 (iii) MeONa , MeOH .

Figure 7:

Oxidations leading to α -hydroxy and oxophosphonates and their synthetic utility.

Reagents and conditions: (a) *n*BuLi, -78°C , THF; Davis' oxaziridine; (b) aq. NaHCO_3 reflux; (c) Dess-Martin Periodinane, CH_2Cl_2 ; (d) LiAlH_4 , THF; (e) EtOH, DBU; (f) aq. NH_3 , THF, cat. $(n\text{Bu})_4\text{NBr}$; (g) aq. NaOH; (h) (i) PhMgBr , -78°C , THF; (ii) aq. NH_4Cl ; (iii) aq. NaOH.