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Facile Access to Functionalized Chiral Secondary Benzylic Boronic Esters via Catalytic Asymmetric Hydroboration

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Allylic and homoallylic phosphonates bearing an aryl or heteroaryl substituent at the γ - or δ -position undergo rhodium-catalyzed asymmetric hydroboration by pinacolborane to give functionalized chiral secondary benzylic boronic esters in yields up to 86% and enantiomer ratios up to 99:1. Compared to minimally-functionalized terminal and 1,1-disubstituted vinyl arenes, there are relatively few reports of efficient catalytic asymmetric hydroboration (CAHB) of more highly functionalized internal alkenes. Phosphonate substrates bearing a variety of common heterocyclic ring systems, including furan, indole, pyrrole and thiophene derivatives, as well as those bearing basic nitrogen substituents (e.g., morpholine and pyrazine) are tolerated, although donor substituents positioned in close proximity of the alkene can influence the course of the reaction. Stereoisomeric (*E*)- and (*Z*)-substrates afford the same major enantiomer of the borated product. Deuterium-labelling studies reveal that rapid (*Z*)- to (*E*)-alkene isomerization accounts for the observed (*E/Z*)-stereoconvergence during CAHB. The synthetic utility of the chiral boronic ester products is illustrated by stereospecific C-B bond transformations including stereoretentive electrophile promoted 1,2-B-to-C migrations, stereoinvertive S_N2 reactions of boron-ate complexes with electrophiles, and stereoretentive palladium- and rhodium-catalyzed cross-coupling protocols.

Introduction

Chiral alkyl boronic esters possess a unique blend of benchtop stability and the potential to undergo a variety of C-B bond transformations via stereospecific 1,2-migration from an *in-situ* generated boron “ate-complex” rendering them especially versatile intermediates for asymmetric synthesis.^{1,2} Metal-catalyzed asymmetric protoboration³ and hydroboration^{4,5} of alkenes are among the most common approaches for the preparation of chiral alkyl boronic esters. While catalytic asymmetric hydroboration (CAHB) of minimally-functionalized terminal and 1,1-disubstituted vinyl arenes (e.g. simple substituted styrene derivatives) have been extensively investigated,⁶ there are relatively few reports using more highly functionalized di- or trisubstituted internal alkenes.⁷ The latter have been a focus of our research into CAHB. Herein, we disclose that 1,2-disubstituted allyl phosphonates bearing an aryl substituent at the γ -position are efficient substrates and provide facile access to functionalized chiral, secondary benzylic and related α -aryl boronic esters.⁸

We previously reported that methylenide substrates bearing β -phenyl substitution undergo efficient rhodium-

Prior work: CAHB of β -aryl methylenides & β,γ -bisaryl trisubstituted alkenes

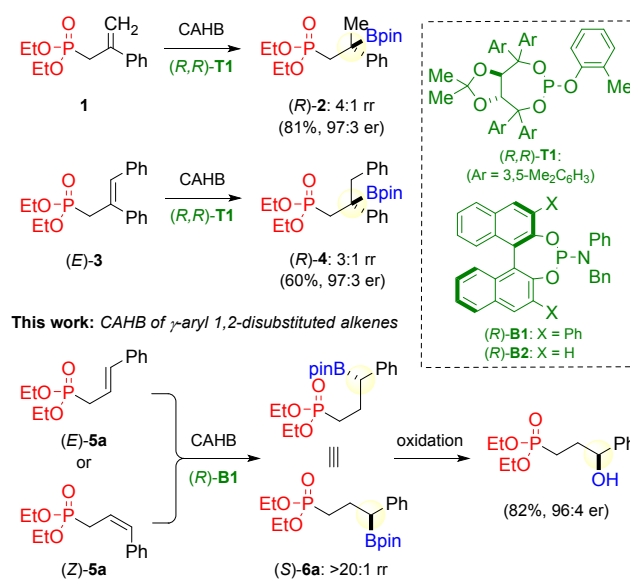


Figure 1: Directed-CAHB of allylic phosphonate-functionalized vinyl arenes varying in substitution pattern. Standard CAHB conditions: 1 mol% Rh(nbd)₂BF₄ or 0.5 mol% [Rh(cod)Cl]₂/1 mol% AgBF₄, 1 mol% (*R,R*)-**T1** or (*R*)-**B1**, 1.1 eq. pinacolborane (pinBH), 3 h, rt. Oxidation conditions: NaBO₃·4H₂O/H₂O.

catalyzed CAHB with pinacolborane (pinBH) to give chiral tertiary boronic esters via regioselective β -boration. For example, **1** affords (*R*)-**2** (81%) in a 97:3 enantiomer ratio (er); the β : γ regioisomer ratio (rr) is 4:1 or greater under the conditions described in Figure 1.^{5a} Similarly, the trisubstituted alkene (*E*)-**3**, bearing phenyl substituents at both the β - and γ -

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positions, undergoes preferential β -boration (3:1 rr) to afford the chiral, tertiary boronic ester product (*R*)-**4** (60%, 97:3 er).^{5a}

We now report that **5a** and related substrates bearing a phenyl, aryl or heteroaryl substituent at the γ -position undergo preferential γ -boration to afford new chiral, secondary benzylic boronic esters. The benzylic regiochemistry presumably arises from the favorable formation of a rhodium π -benzyl complex of the substrate in the course of reaction.⁹ We were surprised to find that the alkene stereochemistry does not impact the overall regio- or stereochemical course of the reaction. Both (*E*)- and (*Z*)-**5a** afford the same γ -borated product **6a** in greater than 20:1 rr using (*R*)-**B1**; C–B bond oxidation using $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ affords the known chiral alcohol¹⁰ shown (82%, 96:4 er).

Results and Discussions

Two alternative rhodium catalyst precursors are used in this study. A 1:1 combination of $[\text{Rh}(\text{nbd})_2\text{BF}_4]/(\text{R})\text{-B1}$ can be replaced by an in situ generated 1:1 $[\text{Rh}(\text{cod})\text{BF}_4]/(\text{R})\text{-B1}$ catalyst formed by treating $[\text{Rh}(\text{cod})\text{Cl}]_2$ with AgBF_4 and the chiral ligand. The catalysts afford near identical results, but the latter protocol is more economical. While pinBH is known to undergo relatively facile rhodium-catalyzed degradation,¹¹ thus

often necessitating its use in excess, a stoichiometric amount of pinBH is usually enough for complete CAHB of these allylic phosphonates.

The choice of chiral ligand is, of course, critical to the success of CAHB.¹² As indicated in Figure 1, rhodium catalyst systems incorporating the TADDOL-derived chiral cyclic monophosphite (*R,R*)-**T1** give efficient enantioinduction for β -aryl methylidene substrate **1** and the β,γ -bisaryl trisubstituted alkene (*E*)-**3**. Its use with **5a** gives (*S*)-**6a** in good yield (81%, after oxidation), but with only a low level of enantioinduction (64:36 er). In contrast, the BINOL-derived phosphoramidite (*R*)-**B1** affords high levels of regiocontrol and enantioselectivity.¹³

Scope of Aryl and Heteroaryl Substrates. Figure 2 summarizes results obtained for a series of substrates **5b–t** in which the nature of the aromatic ring appended at the γ -position varies. In addition to the major γ -boration product **6** and the minor regioisomeric β -boration product **7**, alkene reduction (i.e., **8**) typically comprises the remaining 5–15% of the product mixture. The latter reaction mode arises from a competing catalytic cycle and is the subject of ongoing studies;¹⁴ it will not be discussed further here. Herein, we focus on the regio- and enantioselectivity of the rhodium-catalyzed hydroboration mode.¹⁵

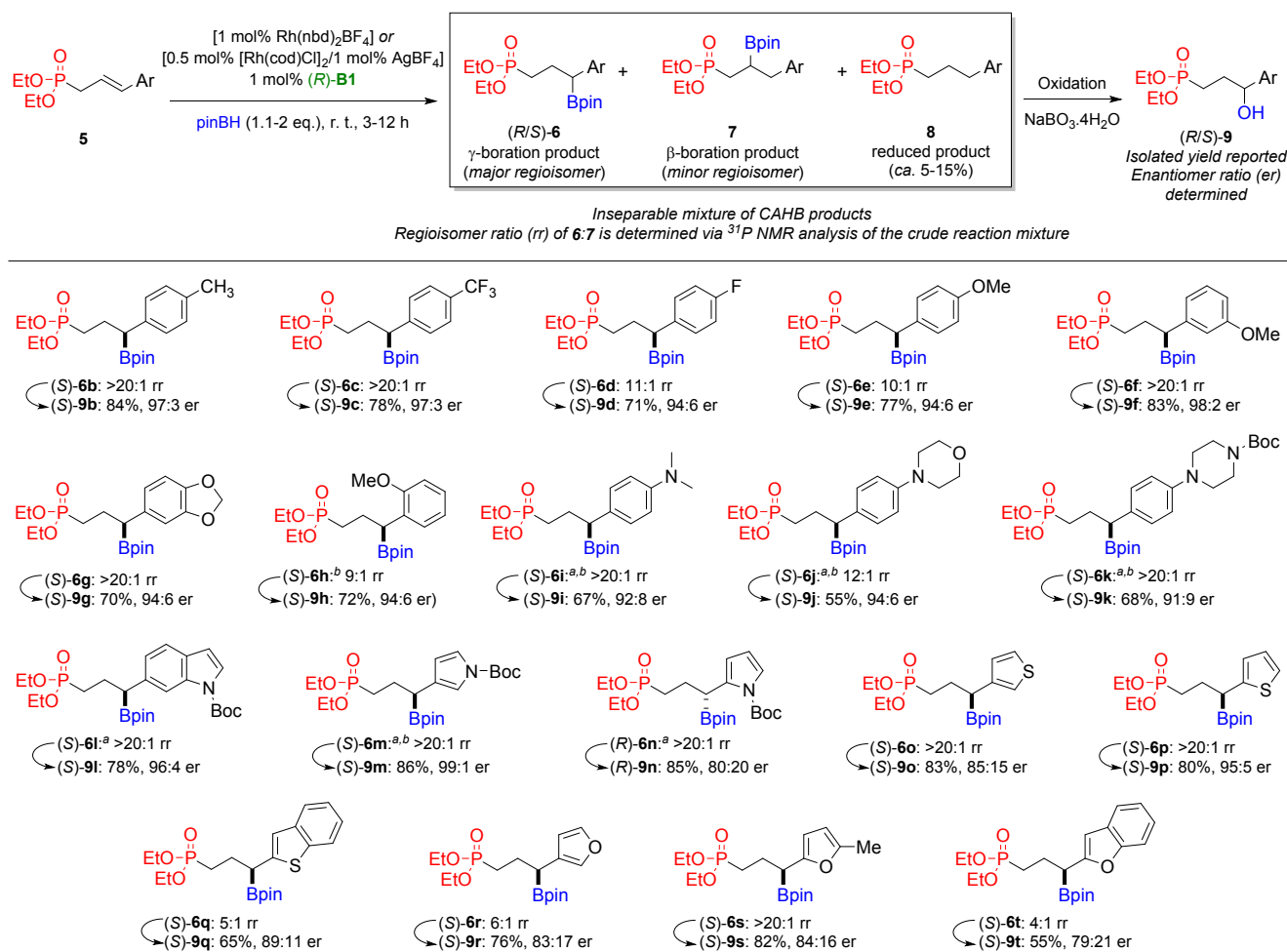


Figure 2: Substrate scope for CAHB of γ -aryl allylic phosphonates. Note: ^a Two equivalents of pinacolborane were used. ^b Reaction carried out for 12 hours.



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A range of donor and acceptor substituents are well-tolerated with relatively minor fluctuations in regio- and/or enantioselectivity. For example, the 4-methylphenyl derivative **5b** and the 4-trifluoromethylphenyl derivative **5c** undergo γ -boration with high regioselectivity (>20:1 rr) yielding **9b** (84%, 97:3 er) and **9c** (78%, 97:3 er) after oxidation of the corresponding secondary benzylic boronic esters (i.e., **6b** and **6c**). The 4-fluorophenyl (**5d**) and 4-methoxyphenyl (**5e**) derivatives exhibit somewhat lower levels of γ : β regioselectivity (**6d–e**, 10–11:1 rr) and enantioselectivity affording **9d** (71%, 94:6 er) and **9e** (77%, 94:6 er), respectively. In contrast, the 3-methoxyphenyl derivative **5f** and 3,4-methylenedioxyphenyl derivative **5g** again exhibit higher regioselectivity (**6f–g**: >20:1 rr) leading to **9f** (83%, 98:2 er) and **9g** (70%, 94:6 er), after oxidation. The 2-methoxyphenyl derivative **5h** exhibits reduced regioselectivity (**6h**: 9:1 rr), but otherwise good conversion to yield **9h** (72%, 94:6 er).¹⁶ The 4-dimethylamino, morpholine, and pyrazine derivatives **5i–k** demonstrate the viability of substrates bearing basic nitrogen functionality; **9i–k** are obtained in moderate to good yields (55–68%) and up to 94:6 er.

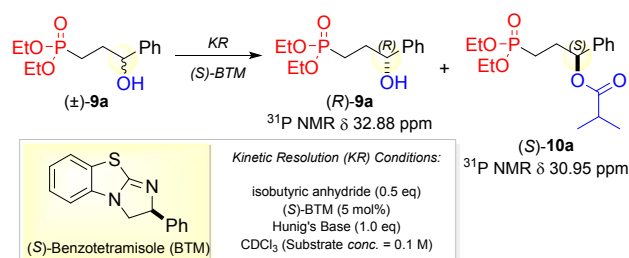
In addition to demonstrating tolerance for basic nitrogen in several of the substrates described in Figure 2, it is pleasing to see that substrates incorporating some heteroaromatic ring systems also undergo efficient CAHB, albeit with some unusual variation in regio- and/or enantioselectivity. For example, the Boc-protected indole derivative **5l** exhibits high γ -regioselectivity (**6l**, >20:1 rr) with good enantioinduction after oxidation to **9l** (78%, 96:4 er). Similarly, the 3-substituted *N*-Boc-protected pyrrole derivative **5m** is both highly regioselective (**6m**, >20:1 rr) and highly enantioselective; the er obtained for **9m** (86%, 99:1 er) is the highest obtained among the substrates tested. However, the results obtained for CAHB of the 2-substituted *N*-Boc-protected pyrrole derivative **5n** differ markedly. The regioselectivity of **6n** (>20:1 rr) is excellent. However, the level of enantioselectivity for **9n** (85%, 80:20 er) is not only much lower but results from hydroboration with the opposite sense of π -facial selectivity compared to most other substrates (*vide infra*); (*R*)-**9n** is the major product.

The 3- and 2-substituted thiophene substrates (i.e., **5o** and **5p**) exhibit high regioselectivity leading to **6o** and **6p** (>20:1 rr), respectively. However, the 3-substituted thiophene **5o** affords **9o** (83%, 85:15 er) with only modest levels of stereocontrol, while the 2-substituted thiophene **5p** gives **9p** (80%, 95:5 er) with good stereocontrol. The 2-substituted benzothiophene **5q** gives both lower levels of regiocontrol (**6q**, 5:1 rr) and enantioselectivity for **9q** (65%, 89:11 er). The corresponding furan derivatives **5r–t** give similar results.

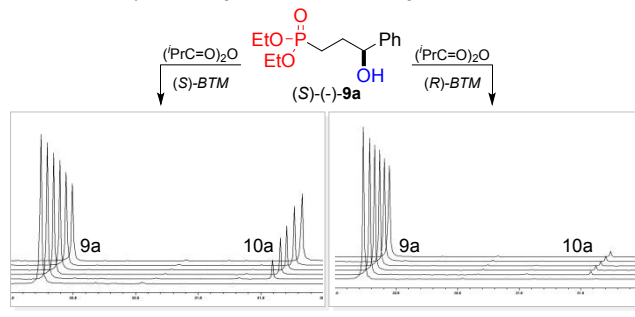
Stereochemical Assignments. The variable regio- and stereochemical results obtained with heteroaryl derivatives

illustrate a caveat for substrates bearing multiple donor groups in proximity to the alkene or bear relatively bulky aromatic ring systems. Using the Birman benzotetramisole (BTM)¹⁷ chiral acylation catalyst, a kinetic resolution (KR) strategy was employed to confirm the absolute configuration assignments for several of the previously unreported chiral secondary benzylic alcohols **9** prepared via CAHB. As shown in Figure 3A, the (*S*)-BTM-catalyzed acylation of a racemic sample of (\pm)-**9a** with 0.5 equivalents of isobutyric anhydride results in the rapid acylation of (*S*)-**9a** to (*S*)-**10a** and recovery of the known (*R*)-**9a** unreacted alcohol.

A. General Scheme for kinetic resolution via acylation using benzotetramisole (BTM)



B. ³¹P NMR analysis for assignment of absolute configuration via KR



C. Absolute configuration assignments of benzyl alcohol products containing heterocyclic ring systems via KR

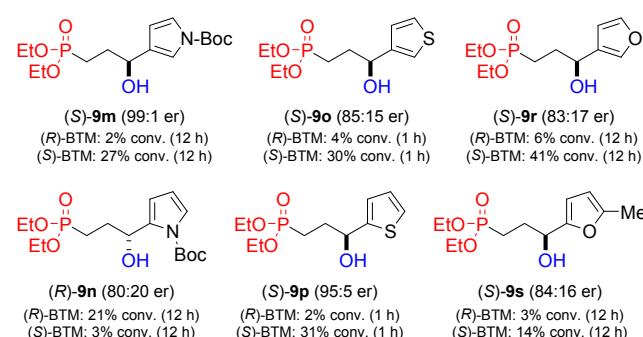


Figure 3: Stereochemical assignments based on kinetic resolution.

Alcohol **9** and ester **10** are readily differentiated by ³¹P NMR spectroscopy providing a convenient protocol for the rapid



determination of absolute configuration of these previously unreported chemical entities (Figure 3B). As demonstrated by the ^{31}P NMR stack-plot, (S)-**9a** (96:4 er) is more rapidly acylated using (S)-BTM than with (R)-BTM. Using this method, we assigned the absolute configurations for the α -hydroxy heteroaryl products obtained via CAHB/oxidation (Figure 3C). For example, the 3-substituted pyrrole derivative **9m** (99:1 er), synthesized via CAHB/oxidation using (R)-**B1**, undergoes more rapid (S)-BTM-catalyzed acylation to **10m** (27% conversion in 12 h) compared to (R)-BTM-catalyzed acylation (2% conversion in 12 h). The relative rates are consistent with predominant (S)-configuration of **9m**. In contrast, the 2-pyrrole derivative **9n** (80:20 er), also prepared via CAHB/oxidation, undergoes relatively sluggish (S)-BTM-catalyzed acylation to **10n** compared to (R)-BTM-catalyzed acylation. The results indicate that predominantly (R)-**9n** is formed from the 2-substituted pyrrole by CAHB with (R)-**B1**. We speculate that the *N*-Boc moiety in the latter acts as an alternative directing group in the rhodium-catalyzed hydroboration thereby switching the sense of alkene π -facial selectivity. Although one might reasonably expect that 2-substituted thiophene and furan derivatives behave similarly, the data summarized in Figure 3c indicate that (S)-**9o-p** and (S)-**9r-s** are the major stereoisomers produced via CAHB/oxidation.

In our prior studies of phosphonate-directed CAHB, we illustrated the synthetic utility of chiral bifunctional tertiary organoboron derivatives through thiophosphonate olefination^{5b} chemistry and α -oxophosphonate active ester^{5a} chemistry as well as through a number of stereospecific C-B bond transformations. Here, we focus on the use of (S)-**6a** (96:4 er) in stereoretentive and stereoinvertive C-B bond transformations via intermediate boron-ate complexes (Figure 4). Stereoretentive cross-coupling with carbanions derived from electron rich vinyl and aromatic derivatives via electrophile-promoted 1,2-B-to-C migration of a boron-ate complex is generally facile under conditions reported by Aggarwal.^{2b, 2e} For example, treatment of (S)-**6a** with excess vinyl magnesium bromide followed by I_2 and sodium methoxide affords the vinyl derivative (R)-**11** (79%, 95:5 er) in high levels of stereoretention.^{2e} Similarly, reaction of (S)-**6a** with 2-lithiobenzofuran followed by NBS affords the *gem*-bisaryl product (S)-**12** (68%, 96:4 er) with essentially complete enantiospecificity.^{2b}

The palladium-catalyzed cross-coupling of chiral boronic esters has attracted recent interest both due to its synthetic utility and the interesting mechanistic issue of stereoretention¹⁸ or stereoinversion;¹⁹ the outcome is often dependent upon participation or non-participation of polar substituents in the substrate.^{20, 21} Benzylic boronic esters are rather unique in the context of palladium-catalyzed cross-coupling. Only the protocol recently introduced by Crudden²² is reportedly effective. Its efficiency varies, but in favorable constructs, the latter proceeds with 84-94% stereoretention (sr). Thus, the outcome for the bifunctional substrate (S)-**6a** (96:4 er) was uncertain. In our hands, cross-coupling with 2-iodobenzofuran under the $[\text{Pd}_2(\text{dba})_3]/\text{PPh}_3/\text{Ag}_2\text{O}$ conditions reported by Crudden gives (S)-**12** (55%, 70:30 er, 73% sr); cross-coupling proceeds with predominant stereoretention, albeit with

significant erosion of enantiopurity. Using the same conditions, cross-coupling of (S)-**6a** with 4-iodoanisole yields (S)-**13** (60%, 77:23 er, 80% sr). The latter is useful, since we were unable to prepare **13** via the 1,2-B-to-C migration protocol. An alternative rhodium-catalyzed cross-coupling procedure reported by Aggarwal²³ effects the stereoretentive addition of (S)-**6a** to 4-nitrobenzaldehyde to afford aryl ketone (S)-**14** (74%, 94:6 er) after oxidation; the latter cross-coupling proceeds with only slight erosion of enantiopurity over two steps.

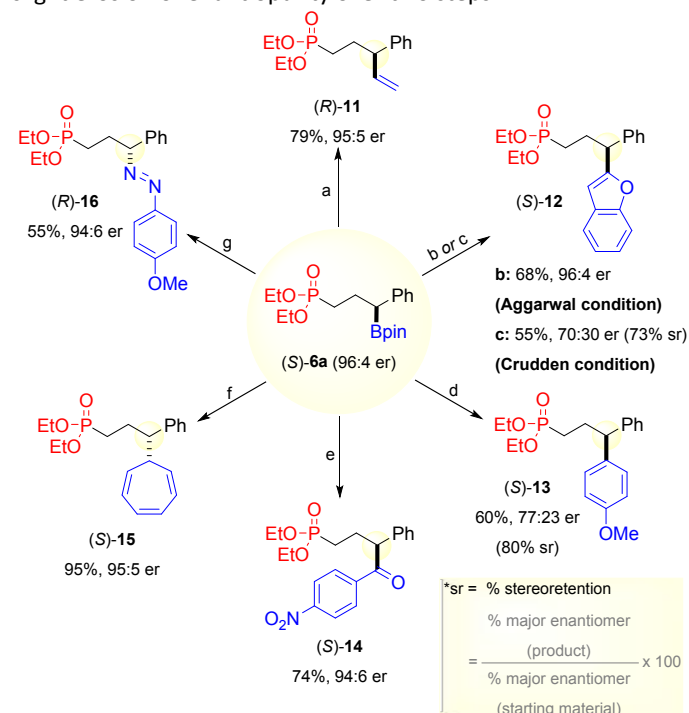


Figure 4: Product utility illustrated by stereoretentive and stereoinvertive C-B bond transformations.

Aggarwal reported that ate-complexes of secondary boronic esters react with strong electrophiles via a stereoinvertive $\text{S}_{\text{E}}2$ mechanism.^{2f} We find that the intermediate boron-ate complex formed by addition of (3,5-bis(trifluoromethyl)phenyl) lithium to (S)-**6a** (96:4 er) readily reacts with cycloheptatrienyl tetrafluoroborate to effect the net C-B to C-C bond substitution to give (S)-**15** (95%, 95:5 er) in excellent yield. Similarly, the net stereoinvertive C-B to C-N bond substitution is accomplished by treating the in situ generated boron ate-complex with 4-methoxybenzenediazonium tetrafluoroborate to give the diazo compound (R)-**16** (55%, 94:6 er).

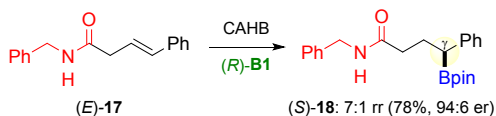
Additional Substrate Scope and Some Key Mechanistic Insights. The question naturally arises as to whether the phosphonate directing group is unique in promoting γ -boration



with these vinyl arene substrates. That appears not to be the case (Figure 5A); the corresponding benzamide substrate (*E*)-**17** undergoes regioselective (7:1 rr) amide-directed CAHB using (*R*)-**B1** to afford the analogous γ -borated benzylic ester (*S*)-**18** (78%, 94:6 er).²⁴

The one-carbon homolog of (*E*)-**5a**, that is, the γ,δ -unsaturated phosphonate substrate (*E*)-**19**, reacts under the standard conditions to afford predominantly (>20:1 rr) δ -borated benzylic boronic ester (*S*)-**20** (79%, 94:6 er) after oxidation (Figure 5B). Furthermore, as was noted for (*E*)- and (*Z*)-**5a**, the same major enantiomer of **20** is formed independent of the substrate alkene geometry; (*Z*)-**19** also affords (*S*)-**20** (81%, 94:6 er). The ability to start with pure (*E*)-, pure (*Z*)- or an (*E/Z*)-mixture and arrive at the same product is a practical advantage but raises mechanistic questions. We previously reported that the amide-directed CAHBs of (*E*)- and (*Z*)-trisubstituted alkenes proceed with the same sense of π -facial selectivity and therefore lead to diastereomers.^{5f} Those results would have suggested that (*E*)- and (*Z*)-**19** (and similarly (*E*)- and (*Z*)-**5a**) should lead to enantiomers not the same product.

A. Analogous amide substrate undergoes efficient CAHB using **B1**



B. One-carbon homologous substrates perform with similar efficiency: Same major enantiomer obtained from (*E*)- and (*Z*)-substrates

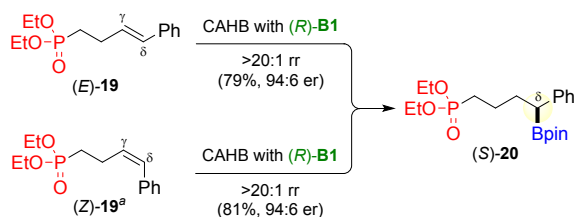


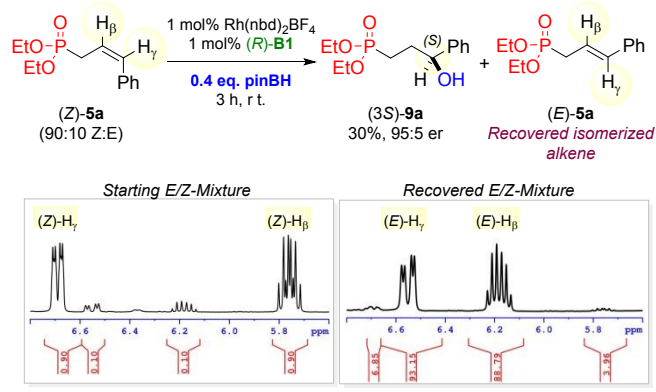
Figure 5: The influence of other structural variations on the directed CAHB of 1,2-disubstituted alkenes. Note: Yield and er were determined after oxidation to the corresponding alcohols. ^a Z:E ratio = 4:1.

The origin of (*E/Z*)-isomer stereoconvergence is resolved based on the results of CAHB of (*Z*)-**5a** using a limiting amount of pinBH (Figure 6A) and deuterium labelling via CAHB of (*E*)- and (*Z*)-**5a** with pinBD (Figure 6B). With respect to the first test, a sample enriched in (*Z*)-isomer of **5a** (90:10 Z:E) is subjected to the otherwise standard CAHB conditions, but using a limiting amount of pinBH (0.4 equiv.), leading to partial boration and recovered alkene. The ¹H NMR spectral windows for the starting and recovered *E/Z*-mixtures of **5a** shown in Figure 6A indicate that (*Z*)-**5a** is essentially completely converted to the (*E*)-isomer under the reaction conditions, thus providing a mechanism by which the two isomers lead to the same product.

Figure 6B shows the results of deuterium labelling. CAHB of (*E*)- and (*Z*)-**5a** using pinBD affords different distributions of non-, isomeric mono- and di-deuterated products. CAHB/oxidation of (*E*)-**5a** using pinBD yields essentially a single monodeuterated product 2-*d*-(2*S*,3*S*)-**9a** (83%) accompanied by the non-deuterated (3*S*)-**9a** (17%) with no apparent di-

deuteration as determined by mass spectral analysis. In contrast, CAHB/oxidation of (*Z*)-**5a** using pinBD affords 30% of non-deuterated (3*S*)-**9a**; 47% of a mixture of diastereomeric monodeuterated products 2-*d*-(2*S*,3*S*)-**9a**; and 2-*d*-(2*R*,3*S*)-**9a** and 21% of the dideuterated product 2,2-*d*₂-(3*S*)-**9a**. The dideuterated product presumably arises by the reaction of 2-*d*-(*E*)-**5a** with pinBD. The latter, when generated in situ via isomerization of (*Z*)-**5a** as described above, also generates an equivalent amount of pinBH that can react competitively to give the observed diastereomeric monodeuterated product and an increased amount of the non-deuterated product as is observed. See the SI for more detailed mechanistic schemes.

A. (*Z*)- to (*E*)-substrate isomerization is observed under standard CAHB conditions:



B. Different distributions of deuterated products are obtained when isomeric (*E*)- or (*Z*)-substrates react with PinBD under standard CAHB conditions:

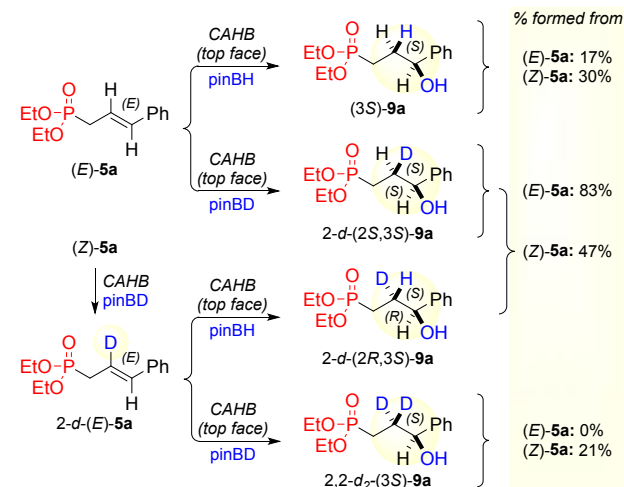


Figure 6: Mechanistic studies indicating the origin of (*E/Z*)-stereoconvergent CAHB arises via *Z* to *E* isomerization under the reaction conditions.

Some Current Limitations. The attempted CAHB of several related phosphonates reveal some current limitations of the [Rh(nbd)₂BF₄]/**B1** catalyst system (Figure 7). (i) The vinyl (i.e., α,β -unsaturated) phosphonate (*E*)-**21** is largely recovered unchanged when subjected to the standard CAHB conditions. (ii) The trisubstituted variants (*E*)-**22** and (*E*)-**23** react only sluggishly under the standard conditions. (iii) In contrast to the vinylarene substrate (*E*)-**5a**, similar internal alkenes bearing an alkyl rather than aryl/heteroaryl γ -substituent (e.g., (*E*)-**24**) undergo predominantly β -boration, albeit with modest regio- and enantioselectivity with the standard catalyst system. (iv)



The δ,ϵ -unsaturated vinyl arene (*E*)-**25** affords the corresponding benzylic boronic ester upon CAHB but again with only modest regioselectivity, yield, and enantiopurity. It should be noted, however, that these results can only be said to reflect limitations of the $[\text{Rh}(\text{nbd})_2\text{BF}_4/\text{B1}]$ catalyst system; systematic catalyst optimizations have not been carried out for these substrates.

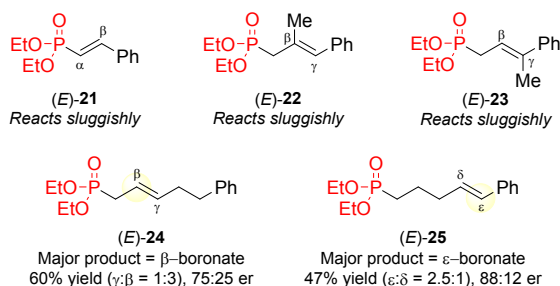


Figure 7: Current limitations of the methodology.

Conclusions

While the regioselective, CAHBs of minimally-functionalized terminal and 1,1-disubstituted vinyl arenes (e.g. simple substituted styrene derivatives) have been investigated rather extensively and quite successfully, there are relatively few reports using more highly functionalized di- or trisubstituted internal alkenes. We find that the rhodium-catalyzed CAHBs of allylic and homoallylic phosphonates derived from internal vinyl arenes give facile access to functionalized chiral secondary benzylic boronic esters. A range of substrates including some bearing heteroaromatic ring systems of interest in medicinal chemistry, such as furan, indole, morpholine, pyrazine, pyrrole and thiophene derivatives, can be accommodated. The absolute configurations of selected chiral secondary benzylic boronic ester products were confirmed or assigned via kinetic acylation of the corresponding benzylic alcohols using the BTM acylation catalyst highlighting the potential for other donor substituents in proximity of the alkene to influence the stereochemical course of the reaction. Stereoretentive and stereoinvertive C-B bond transformation protocols highlight the versatility of this methodology. We find that palladium-catalyzed cross-coupling under the conditions reported by Crudden proceeds mostly with stereoretention. Diastereomeric substrates, for example, (*E*)- and (*Z*)-**5a** and (*E*)- and (*Z*)-**16**, give the same borated product stereochemistry. Mechanistic studies reveal that (*Z*)- to (*E*)-alkene isomerization occurs rapidly under the reaction conditions. This observation along with deuterium incorporation data provides a reasonable explanation for the origin of (*E/Z*)-stereoconvergence during CAHB.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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