Facile access to functionalized chiral secondary benzylic boronic esters via catalytic asymmetric hydroboration†

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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. Metal-catalyzed asymmetric protoboration and hydroboration of alkynes 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, there are relatively few reports using more highly functionalized di- or trisubstituted internal alkenes. 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.

We previously reported that methyldiene substrates bearing β-phenyl substitution undergo efficient rhodium-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 Fig. 1. Similarly, the trisubstituted alkene (E)-3, bearing phenyl substituents at both the β- and γ-positions, undergoes preferential β-boration (3 : 1 rr) to afford the chiral, tertiary boronic ester product (R)-4 (60%, 97 : 3 er).

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 γ-benzyl complex of the substrate in the course of reaction. 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 NaBO3·4H2O affords the known chiral alcohol shown [82%, 96 : 4 er].
Results and discussions

Two alternative rhodium catalyst precursors are used in this study. A 1 : 1 combination of [Rh(nbd)2BF4]/(R)-B1 can be replaced by an in situ generated 1 : 1 [Rh(cod)BF4]/(R)-B1 catalyst formed by treating [Rh(cod)Cl]2 with AgBF4 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, 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. As indicated in Fig. 1, rhodium catalyst systems incorporating the TADDOL-derived chiral cyclic monophosphite (R,R)-T1 as the β,γ-bisaryl trisubstituted alkene (E)-3 can be replaced by an in situ generated 1 : 1 [Rh(cod)BF4]/(R)-B1 catalyst formed by treating [Rh(cod)Cl]2 with AgBF4 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, thus often necessitating its use in excess, a stoichiometric amount of pinBH is usually enough for complete CAHB of these allylic phosphonates.

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Fig. 1 Directed-CAHB of allylic phosphate-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.

Scope of aryl and heteroaryl substrates

Fig. 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; it will not be discussed further here. Herein, we focus on the regio- and enantioselectivity of the rhodium-catalyzed hydroboration mode.

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-dimethylenedioxyphenyl 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 (53–68%) and up to 94 : 6 er.

In addition to demonstrating tolerance for basic nitrogen in several of the substrates described in Fig. 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.

Stereocchemical assignments

The variable regio- and stereocchemical 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) 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 Fig. 3A, the (S)-BTM-catalyzed acylation of a racemic sample of (R)-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. Alcohol 9 and ester 10 are readily differentiated by $^{31}$P NMR spectroscopy providing a convenient protocol for the rapid determination of absolute configuration of these previously unreported chemical entities (Fig. 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 configuration for the a-hydroxy heteroaryl products obtained via CAHB/oxidation (Fig. 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 Fig. 3c indicate that (S)-9o–p and (S)-9q–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 thionophosphonate olefination chemistry and α-oxophosphonate active ester 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 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. For example, treatment of (S)-6a with excess vinyl magnesium bromide followed by I₂ and sodium methoxide affords the vinyl derivative (R)-11 (79%, 95 : 5 er) in high levels of stereoretention. 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. 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 stereoretention or stereoinversion; the outcome is often dependent upon participation or non-participation of polar substituents in the substrate. Benzylic boronic esters are rather unique in the context of palladium-catalyzed cross-coupling. Only the protocol recently introduced by Crudden 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 (Pd₂(db₃)₃/PPh₃/Ag₂O) 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 Aggarwal 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. Aggarwal reported that ate-complexes of secondary boronic esters react with strong electrophiles via a stereoinvertive Sₐ₂ mechanism. 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 (Z)-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 (Fig. 5A); the corresponding benzamide substrate (E)-17 undergoes regioselective (7 : 1 rr) amide-directed CAHB using (R)-B1 to afford the analogous γ-borated benzyl 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 benzylboronic ester (S)-20 (79%, 94 : 6 er) after oxidation (Fig. 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-face selectivity and therefore lead to diastereomers.5 Those results would have suggested that (E)- and (Z)-19 (and similarly (E)- and (Z)-5a) should lead to enantiomers not the same product.

The origin of (E/Z)-isomer stereocorvergence is resolved based on the results of CAHB of (Z)-5a using a limiting amount of pinBH (Fig. 6A) and deuterium labelling via CAHB of (E)- and (Z)-5a with pinBD (Fig. 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 Fig. 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.

Fig. 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

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**Fig. 6** Mechanistic studies indicating the origin of (E/Z)-stereocorvergence CAHB arising via Z to E isomerization under the reaction conditions: (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.

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**Fig. 7** Current limitations of the methodology.
(E)-5a using pinBD yields essentially a single monodeuterated product 2-d-(2S,3S)-9a (83%) accompanied by the non-deuterated (3S)-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 (3S)-9a; 47% of a mixture of diastereomeric monodeuterated products 2-d-(2S,3S)-9a; and 2-d-(2R,3S)-9a and 21% of the dideuterated product 2,2-d₂(3S)-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 ESI† for more detailed mechanistic schemes.

Some current limitations

The attempted CAHB of several related phosphonates reveal some current limitations of the [Rh(nbd)_2BF_4/B1] catalyst system (Fig. 7). (i) The vinyl (i.e., α,β-unsaturated) phosphate (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,δ-unsaturated vinyl arene (E)-25 affords the corresponding benzylic boronic ester upon CAHB but again with only modest regioselectivity, yield, and enantipurity. It should be noted, however, that these results can only be said to reflect limitations of the [Rh(nbd)_2BF_4/B1] catalyst system; systematic catalyst optimizations have not been carried out for these substrates.

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 heteroaromaric 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)-stereocconvergence during CAHB.

Conflicts of interest

The authors declare no conflicts of interest.

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10. Our recent studies on rhodium-catalyzed CAHB of functionalized alkene substrates focus on using the simple and readily available TADDOL- and BINOL-derived chiral phosphites and phosphoramidites. Our studies consistently find that these two privileged ligand scaffolds tend to be complementary in their effectiveness; in part, the choice of TADDOL- or BINOL-derived ligands hinges on the alkene substitution pattern.

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16. It is worth noting that unlike our previous work on 1,1-disubstituted alkenes (ref. 5a) in which ortho-substitution of the arene leads to a change in regioselectivity, substrates bearing 2-substituted arenes in this series of 1,2-disubstituted internal vinylarenes do not significantly impact the regioselectivity. For example, in addition to 5h, the 2-methylphenyl derived substrate 5 (Ar = 2-methylphenyl) also undergoes regioselective γ-boration (13 : 1 rr) to afford 6 (Ar = 2-methylphenyl) but with a relatively modest level of enantioselectivity determined after oxidation (74%, 91 : 9 er); see the ESI†.

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