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Nonracemic Allylic Boronates through Enantiotopic-Group-Selective Cross-Coupling of Geminal Bis(boronates) and Vinyl Halides

Bowman Potter, Adam A. Szymaniak,[†] Emma K. Edelstein,[†] and James P. Morken*

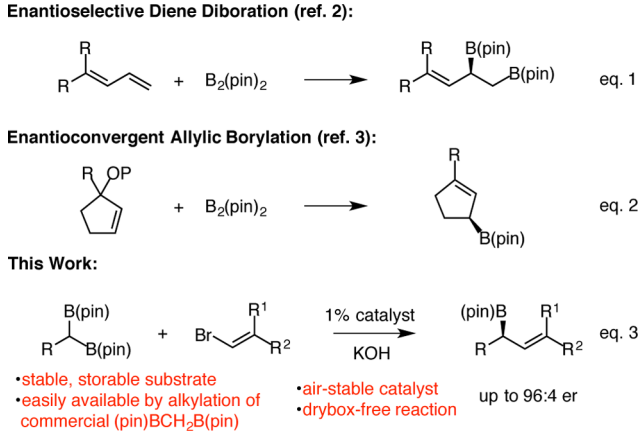
Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

Supporting Information

ABSTRACT: Under the influence of a chiral palladium catalyst, 1,1-bis(pinacolboronate) esters undergo asymmetric cross-coupling with bromoalkenes to generate nonracemic allyl boronates with high levels of enantioselectivity. The so-formed allyl boronates may be oxidized with hydrogen peroxide to provide secondary allylic alcohols or with nitrosobenzene to furnish nonracemic tertiary allylic alcohols. Mechanistic experiments suggest the operation of a pathway involving outer-sphere stereoinvertive transmetalation.

Nonracemic allyl boronates are valuable intermediates in organic synthesis. In particular, α-chiral γ,γ-disubstituted allylic boronates are attractive reagents: not only can they be directly converted to chiral γ,γ-disubstituted allylic alcohols and amines by oxidation and amination, but they can also engage in carbonyl allylations that establish chiral all-carbon quaternary centers.[1] However, in spite of their ability to address important synthesis problems, there remain few catalytic enantioselective methods for the construction of α-chiral allylic boronates that are doubly substituted at the γ position. Indeed, only two methods have been developed to construct this important motif, and they both result in specialized product functionality. In a strategy developed by our lab,[2] enantioselective 1,2-diboration of 4,4-disubstituted-1,3-dienes (Scheme 1, eq 1) results in a vicinal diboronate in which the allyl boronate unit bears two γ substituents. Allylic borylation is an alternate strategy that provides α-chiral allylic boronates, but this method can furnish γ,γ-disubstituted boronates with regio- and stereocontrol only when cyclic substrates are employed (eq 2).[3,4] Indeed, only the Aggarwal homologation reaction furnishes chiral γ,γ-disubstituted allylic boronates for a range of substrates in an asymmetric fashion.[5] To address this gap in catalytic synthesis technology, we considered cross-coupling of vinyl electrophiles and readily available achiral geminal bis(boronates) (eq 3).[6−8] We recently reported that this transformation can be accomplished with aryl electrophiles in the presence of a Pd catalyst and a chiral monodentate phosphoramidite ligand: upon enantiotopic-group-selective cross-coupling, chiral benzylic boronates are generated.[9] Herein we report a new catalyst system that enables the reaction between vinyl electrophiles and geminal boronates and allows rapid access to enantiomerically enriched allylic boronates. Additionally, we provide insight into the mechanistic features that govern this transformation and delineate strategically useful applications of the allylic boronates for the construction of structurally challenging chiral motifs.

Scheme 1. Catalytic Enantioselective Routes to γ,γ-Disubstituted Allyl Boronates



Our initial investigations focused on ligand selection for the enantiotopic-group-selective cross-coupling of geminal bis(boronate) **1** and 1-bromo-2-methylpropene. Unlike the cross-coupling of aryl electrophiles, the background reaction in the absence of ligand was sluggish (Table 1, entry 1), and the monodentate phosphoramidite ligand **L1** that was effective in aryl halide couplings failed to convert **1** to allylic boronate **3** (entry 2). Fortunately, JosiPhos ligand **L2** afforded the desired product, albeit in low yield, low enantioselection, and contaminated by significant amounts of 1,4-diene **4** that appeared to arise from coupling of boronate **3** and the vinyl halide. A survey of related Josiphos-type ligands revealed that alkyl substitution on the Cp-bound phosphine (R^2) minimized the yield of biscoupling product **4** and increased the enantioselectivity (entry 3 vs 4). Further enhancing the size of the alkyl groups from Cy to *tert*-Bu (**L4**) had a profound impact on the reaction (entry 5): not only were the biscoupling byproducts substantially minimized, but the enantioselectivity of the reaction was enhanced from 65:35 to 90:10 (cf. entries 4 and 5). The nature of the benzylic phosphine substituents (R^1) also influenced the outcome of the reaction: increasing the size from phenyl to *o*-tolyl resulted in lower yield and selectivity (entries 5 and 6), whereas *p*-trifluoromethylphenyl groups provided a higher-yielding transformation with a slight increase in selectivity (entry 7; for an exhaustive ligand optimization, see

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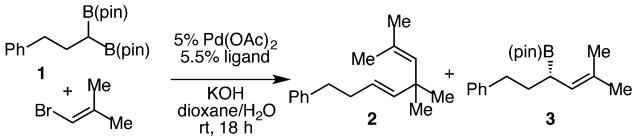
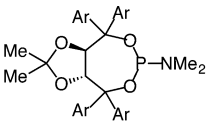
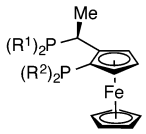
Table 1. Survey of Ligands in the Cross-Coupling of Bis(boronate) 1 and 1-Bromo-2-methylpropene[a]



entry	ligand	2 (% yield)[b]	3 (% yield)[b]	er 3[c]
1	none	<2	<2	–
2	**L1**	<2	<2	–
3	**L2**	27	21	57:43
4	**L3**	13	49	65:35
5	**L4**	<2	55	90:10
6	**L5**	<2	14	63:37
7	**L6**	<2	95	91:9
8[d]	**L6**	<2	95 (86)	93:7



L1: Ar = p-Tol



L2: R^1 = *m*-xylyl, R^2 = Ph
L3: R^1 = Ph, R^2 = Cy
L4: R^1 = Ph, R^2 = *t*-Bu
L5: R^1 = *o*-Tol, R^2 = *t*-Bu
L6: R^1 = *p*-CF_3-Ph, R^2 = *t*-Bu

[a]See the Supporting Information for the reaction conditions. [b]Yields were determined by NMR analysis in comparison to an internal standard and may include small amounts of the regioisomeric 1,4-dienes. [c]Enantiomer ratios (er) were determined by chiral SFC analysis of the corresponding secondary alcohols. [d]With 1 mol % **L6**·$PdCl_2$.

the Supporting Information). To simplify the experimental setup, the palladium dichloride complex with ligand **L6** was prepared, and a crystal structure is depicted in Figure 1.

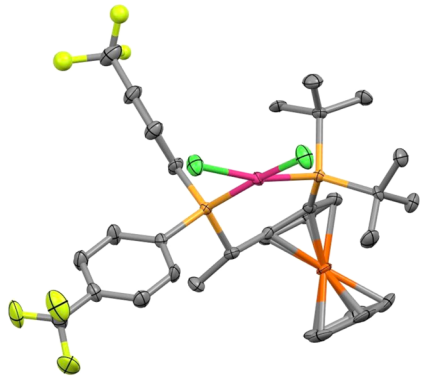
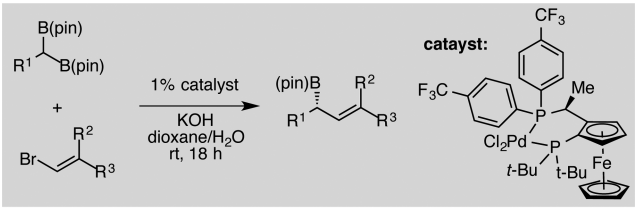


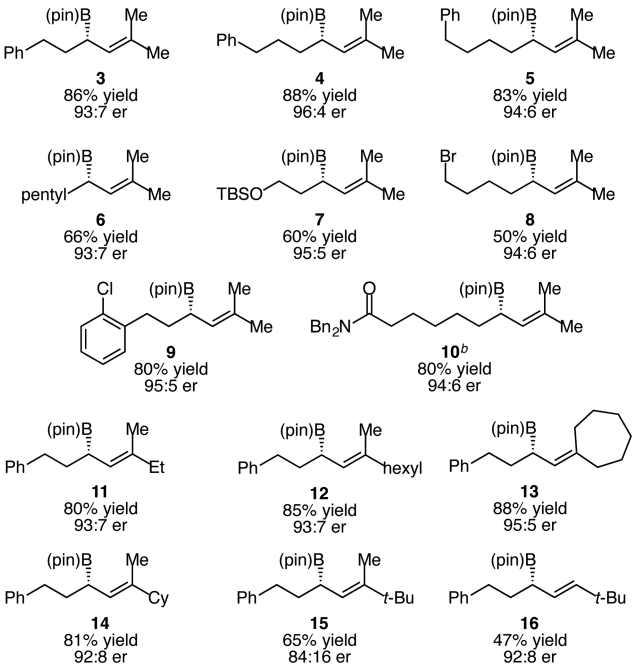
Figure 1. Crystal structure of **L6**·$PdCl_2$. The structure was obtained from a crystal of the racemic complex in the presence of CH_2Cl_2. Coordinates have been deposited at the Cambridge Crystallographic Data Centre under CCDC 1035172.

Importantly, when air-stable **L6**·$PdCl_2$ was used as the catalyst, lower catalyst loadings could be employed and the reaction exhibited a slight improvement in selectivity (entry 8). *Of paramount importance, with* **L6**·$PdCl_2$, *the reactions could be set up without the aid of a drybox and required only 1 mol % catalyst for effective reaction.*

The scope of the enantiotopic-group-selective cross-coupling in the presence of **L6**·$PdCl_2$ was examined with a variety of vinyl bromides and geminal bis(boronates) (Table 2). While phenyl-containing substrates were processed effectively and provided reaction products **3**, **4**, and **5**, aromatic substituents were not required, as demonstrated by the production of

Table 2. Substrate Scope in the Asymmetric Cross-Coupling of Vinylic Halides and Geminal Bis(boronates)[a]





[a]See the Supporting Information for the reaction conditions. Yields are isolated yields of purified materials and are averages of two experiments. er values were determined by chiral SFC analysis of the corresponding secondary allylic or homoallylic alcohols. [b]Yield determined by ^{1}H NMR analysis versus an internal standard.

compounds **6**–**8**. Of note, the reaction tolerated the presence of a silyl ether (**7**), aryl chloride (**9**), and amide (**10**). Moreover, even though Pd catalysis of alkyl bromide dehydrohalogenation can be efficient,[10] the cross-coupling process described here is quite tolerant of an alkyl bromide substituent (compound **8**). With regard to the electrophile, vinyl bromides with differentiated β substituents underwent smooth coupling (compounds **11**, **12**, and **14**–**16**), and a cyclic vinyl bromide could also be employed effectively (product **13**). In the case of 2-monosubstitued vinyl bromides, only a substrate with a bulky *tert*-butyl group afforded useful levels of monoaddition (product **16**); with the current catalyst system, smaller monosubstituted vinyl bromides afford significant amounts of biscoupling products (data not shown).

As mentioned above, chiral allyl boronates participate in a range of useful reactions. To probe whether these apply to unpurified products that arise from enantiotopic-group-selective cross-couplings, the transformations in Scheme 2 were conducted. In the first experiment, geminal bis(boronate) **1** and 1-bromo-2-methyloctene were linked by cross-coupling in the presence of 1 mol % **L6**·$PdCl_2$ complex. After filtration and a solvent swap, oxidation with $NaOH/H_2O_2$ furnished allylic alcohol **17** in excellent yield and enantiomeric purity. In a second experiment, addition to benzaldehyde was examined:

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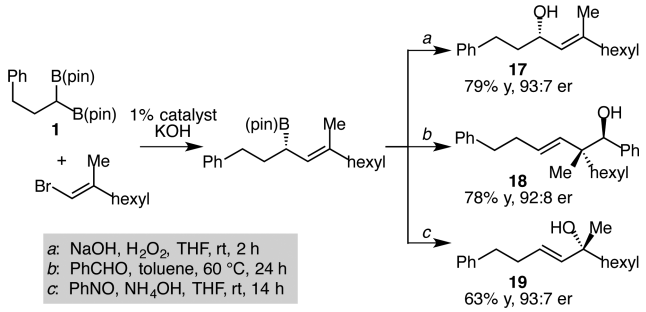
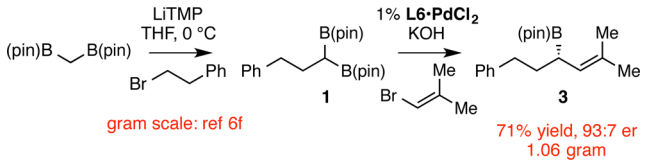
Scheme 2. Tandem Enantioselective Cross-Coupling/ Functionalization Cascades



following cross-coupling, filtration, and a solvent swap into toluene, benzaldehyde was added. As shown in Scheme 2, this procedure provided homoallylic alcohol **18** bearing an adjacent all-carbon quaternary center with complete enantiospecificity.[11] Lastly, it was found that oxidation with nitrosobenzene, a reaction that occurs with allyl migration,[12] directly furnished tertiary allylic alcohol **19** with excellent enantiomeric purity.

To study the ability of this catalytic cross-coupling to deliver synthetically useful quantities of material, the reaction in Scheme 3 was undertaken. In this experiment, the alkylation of

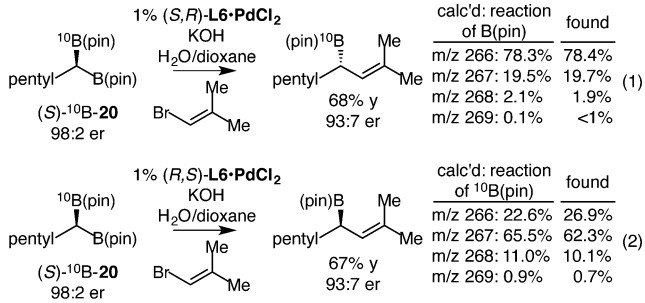
Scheme 3. Gram-Scale Enantioselective Cross-Coupling To Furnish Allyl Boronate 3



$(pin)BCH_2B(pin)$ was conducted on a 5 mmol scale by deprotonation with LiTMP and subsequent treatment with (2-bromoethyl)benzene. This delivered **1** in good yield and provided ample material to examine larger-scale cross-couplings. As depicted, the coupling with 1-bromo-2-methylpropene occurred effectively on a larger scale and furnished α-chiral allyl boronate **3** in 71% yield with 93:7 er. It should be noted that the product contained material derived from protodeboronation of **1**, and while this is difficult to remove on large scale, it does not interfere with subsequent allylation or oxidation reactions.

Our previous studies of enantiotopic-group-selective cross-coupling of aryl electrophiles employed a monodentate chiral phosphoramidite ligand, and it was determined that these reactions occurred with inversion of configuration at carbon during the cross-coupling process. Considering that **L6**·$PdCl_2$ contains a bidentate ligand, it was of interest to determine whether the reaction in the presence of this complex occurs with the same stereochemical outcome. To study this aspect, (*S*)-^{10}B-**20** was prepared[13] and subjected to cross-coupling with 1-bromo-2-methylpropene in the presence of both (*S*,*R*)-**L6**·$PdCl_2$ and (*R*,*S*)-**L6**·$PdCl_2$ (Scheme 4). Mass spectral analysis of the product from the reaction with the (*S*,*R*) complex was consistent with a process in which the ^{10}B-labeled B(pin) group remained in the product, whereas the natural-abundance B(pin) remained in the product when the (*R*,*S*) complex was employed. If it is assumed that the reductive elimination occurs with retention of configuration at carbon, the transmetalation reaction in the presence of **L6**·$PdCl_2$ appears to

Scheme 4. Analysis of the Stereochemistry of Transmetalation in Cross-Couplings with L6·$PdCl_2$



occur with inversion.[14] To learn more about boron species involved in this transmetalation, the pinacol ligands in **1** were replaced with neopentylglycol or 2,4-dimethylpentane-2,4-diol ligands. With these alternate boron ligands, lower reactivity and lower selectivity were observed in the cross-coupling with 1-bromo-2-methylpropene (18% ^{1}H NMR yield, 85:15 er for the former; 13% ^{1}H NMR yield, 89:11 er for the latter). These experiments suggest that the active participant in the cross-coupling is less likely to be the bis(boronic acid)-derived from **1** but is more likely to be the mono- or bis(boronic ester) derivative.

In summary, we have described a catalytic enantioselective cross-coupling that delivers chiral γ,γ-disubstituted allylic boronates from simple substrates under mild reaction conditions. The reaction products can be used to address important problems in asymmetric synthesis, and further studies in this regard are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Procedures, characterization, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

morken@bc.edu

Author Contributions

†A.A.S. and E.K.E. contributed equally.

Notes

The authors declare no competing financial interest.

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