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Enantiomerically-Enriched Tris(boronates): Readily Accessible Conjunctive Reagents for Asymmetric Synthesis

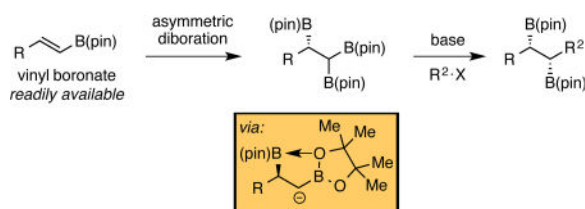
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Abstract

The catalytic enantioselective diboration of vinyl boronate esters furnishes chiral tris(boronates) in a selective fashion. Subsequent deborylative alkylation occurs in a diastereoselective fashion, both for intermolecular and intramolecular processes.

Graphical Abstract



Multiborylated compounds are emerging as useful conjunctive reagents for asymmetric synthesis.¹ They can either be crafted or manipulated in an enantioselective catalytic fashion and they provide opportunities for multiple sequential bond-forming transformations. Not surprisingly, the reactivity features that appear to govern multiborylated reagents are critically dependent upon the relative relationship between neighboring boronate units. Whereas internal chelation is proposed to enhance the Lewis acidity of vicinal bis(boronates) (**A**, Scheme 1a) and enable highly efficient cross-coupling reactions,² the ability of three-coordinate boron to stabilize adjacent carbanions appears to facilitate deborylation of geminal bis(boronates) providing reactive α -boryl carbanions (**B** to **C**, Scheme 1a).³ In this regard, we considered that 1,1,2-tris(boronates) might benefit from both features wherein internal chelation from a vicinal boronate would facilitate base-promoted deborylation of an adjacent geminal bis(boronate) thereby generating an internally chelated α -boryl carbanion (**D**, Scheme 1b). It was considered that the structural organization imparted by chelation of the anionic ensemble might facilitate a range of subsequent substrate-controlled stereoselective transformations. Herein, we demonstrate that

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ASSOCIATED CONTENT

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

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enantiomerically-enriched 1,1,2-tris(boronates) can be prepared by catalytic enantioselective diboration of readily available vinyl boronic esters. Further, the product tris(boronate) can engage in a range of stereoselective deborylative alkylation reactions, all of which preserve the stereochemical integrity of the chiral tris(boronate) intermediate.

A prerequisite for studies on the reactivity of 1,1,2-tris(boronates) is the development of a catalytic enantioselective route to these motifs. We considered that diboration⁴ of vinyl boronates, substrates that are readily prepared from alkynes,⁵ alkenes,⁶ or aldehydes,⁷ might provide a simple entry-point. Since Pt/phosphonite complexes are effective in the enantioselective diboration of terminal alkenes,⁸ dienes,⁹ and imines,¹⁰ they were considered as prospective catalysts for vinyl boronate diboration. As depicted in Table 1, compound **1** was employed as a probe substrate to examine the impact of the catalyst and reaction conditions. To gauge the extent of reaction from non-ligated Pt, vinylboronate **1** was first treated with B₂(pin)₂ in the presence of 2 mol% Pt(dba)₃ at 60 °C for 13 hours. This reaction delivered racemic 1,1,2-tris(boronate) **2** in good yield. While the reaction in the presence of chiral phosphonite ligand **L1** proceeded more sluggishly, it occurred with measureable enantioselectivity providing the product in 68:32 enantiomer ratio (entry 2). This observation clearly reveals the enhanced reactivity of vinylboronates versus simple alkenes in catalytic diboration reactions (*trans*-2-octene does not undergo diboration under these reaction conditions). To enhance reaction rates of vinyl boronates even further, B₂(cat)₂ was used in place of B₂(pin)₂ and, upon completion, the reaction mixture was subjected to transesterification with pinacol to furnish **2**; with the more reactive reagent,¹¹ the diboration occurred with slightly increased conversion (81%) and with a significant increase in enantioselectivity (88:12 er, entry 3). A focused ligand survey showed that smaller ligand **L2** (entry 4) offered no improvement in selectivity, while more bulky ligand **L3** (entry 5) provided an enhanced enantiomeric ratio of the product (95:5 er); a further increase in ligand size led to longer reaction times and did not greatly effect yield or selectivity (entry 6).

With phosphonite **L3** identified as an optimal ligand, the impact of catalyst loading, ligand:metal ratio, reagent stoichiometry, and temperature was investigated. From this study, optimized conditions were determined to be those which employed 3 mol% Pt(dba)₃, 6 mol % **L3**, and 2.0 equivalents of B₂(cat)₂ at 70 °C for 24 h. Following treatment with pinacol, the 1,1,2-tris(boronate) **2** could be isolated in 70% yield and 92:8 er (entry 7).

The scope of the catalytic enantioselective diboration of vinyl boronates was examined and results are shown in Table 2. In addition to **2**, phenyl-containing tris(boronates) **3** and **4** could be obtained in good yields and enantiomeric ratios. Substrates bearing a linear aliphatic hydrocarbon substituent also react with good yield and good control of enantiopurity (compounds **5–11**). Importantly, it was found that the reaction tolerates the presence of chloride, bromide, and silyl ether functional groups (compounds **6–10**). In addition, substrates bearing trisubstituted olefins in the chain could be transformed to the desired 1,1,2-tris(boronate) without any competing olefin diboration being observed (product **11**). Current limitations to the present catalyst system are that α -substituted substrates suffered from lower reactivity and diminished selectivity (products **12–14**). Lastly, it merits comment that all of the compounds in Table 2 were sufficiently stable that they could be isolated by silica gel chromatography with minimal degradation.

Deborylative alkylation reactions with chiral 1,1,2-tris(boronates) were examined and these are depicted in Table 3. After a survey of reaction conditions, it was found that reactions with NaO*t*Bu in toluene were most effective and provided 1,2-diols upon oxidative work-up. As depicted, the *syn* diastereomer was the predominant product in all cases and high yields could be obtained across an array of substrates. Not only was deborylative alkylation effective with primary aliphatic bromides, but secondary electrophiles could be engaged as well. With bromo(chloro)alkanes, reaction occurred exclusively with the bromide leaving the alkyl chloride group untouched (compound **22**). While more reactive electrophiles such as allyl chloride and benzyl chloride were met with slightly lower levels of diastereoselectivity (9:1 to 15:1 dr), their reactions proceeded in outstanding yields (products **20**, **21**, and **23**). Importantly, the reactions with alkenyl electrophiles furnish vicinal bis(boronates) that would be inaccessible by other borylation methodologies. For example, diboration of a diene precursor to **23** would occur preferentially at the terminal olefin site.^{8b}

The ability of the vinyl boronate diboration to accommodate alkyl halide substituents enables the construction of 1,1,2-tris(boronates) that may undergo intramolecular alkylation to form cyclic 1,2-bis(boronates). As depicted in Scheme 2a, this reaction is efficient for the construction of five-, six-, and seven-membered rings and in all cases the intramolecular alkylative coupling provided the *anti* 1,2-diol in excellent levels of diastereoselectivity after oxidation. Five-, six-, and seven-membered rings could be furnished efficiently with tethered alkyl chlorides or bromides (products **29**, **30**, and **31**). As shown in Scheme 2b, the deborylative alkylation occurs without racemization (see compound **32**). Moreover, the intermediate 1,2-bis(boronate) may engage in a homologation reaction with chloromethyl lithium to furnish *anti* 1,2-bis(hydroxymethyl)cyclohexane **33**. This sequence represents a synthetic route to cyclic *anti*-bis(boronates) that aren't accessible from alkene diboration.

The deborylative alkylation of tris(boronates) occurs under milder conditions than is required for reaction of geminal bis(boronates)¹² and this feature is consistent with activation of the substrate by internal chelation. However, the stereochemical outcome of the ensuing alkylation reaction merits comment. While it is plausible that the intermolecular reactions proceed by least-hindered approach of the electrophile to internally chelated structure **D** (Scheme 3) and furnish the observed vicinal boronate **F** selectively, the product configuration obtained from intramolecular reactions in Scheme 2 appears to be inconsistent with such a process: the tether between substrate and electrophile would be anticipated to deliver stereoisomer **G** from intramolecular alkylation of **D**. Alternatively, reaction through non-chelated intermediate **E** is consistent with the stereochemical outcome of both inter- and intramolecular reactions. In **E**, interaction of the electron-rich C-B σ bond with the adjacent C=B π -type bond would serve to enhance the nucleophilicity of the π bond (carbanion) and facilitate reaction.¹³ The configuration of the products observed from both intramolecular and intermolecular reactions are consistent with least hindered approach of electrophiles to **E**.

To examine the utility of 1,1,2-tris(boronates) for practical asymmetric synthesis, the construction of simple diol **36** was examined. Compound **36** has been converted to *exo*-brevicommin¹⁴ by an elegant single-pot Wacker oxidation/cyclization reaction.¹⁵ Because

oxidation of *trans* alkenes in the presence of terminal olefins isn't highly site selective, previous routes to **36** are multistep and require protecting group manipulations. As an alternate route we find that boron-Wittig reaction between bis(boryl)methane¹⁶ and propionaldehyde occurs with outstanding stereoselection and yield providing vinyl boronate **34** on multiple gram scale. Subsequent diboration furnishes **35**, and deborylative alkylation furnishes **36** in good yield and with high levels of enantio- and diastereoselectivity. Production of **36** represents a formal synthesis of exo-brevicommin and this sequence is amongst the shortest enantioselective routes to this target.

To conclude, synthesis of novel enantioenriched 1,1,2-tris(boronate) esters via a Pt-catalyzed asymmetric diboration has been described. This motif can be readily transformed to provide a variety of synthetically useful but challenging compounds via C-C bond-forming reactions, including internal vicinal bis(boronate) esters and cyclic *anti* 1,2-bis(boronate) esters. Furthermore, the described route provides a useful method for constructing 1,2-bis(boronates) with a broad substrate scope.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

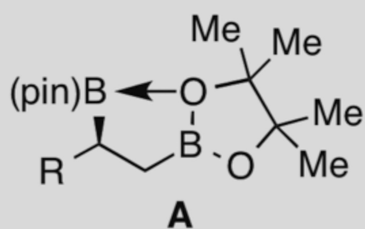
JRC is grateful for a LaMattina Graduate Fellowship. The NIH (GM-59471) is acknowledged for financial support. AllyChem is acknowledged for a donation of B₂(pin)₂.

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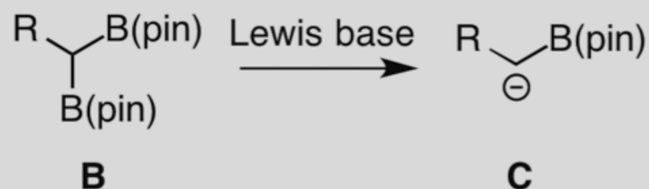
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12. For example, deborylative alkylation of simple geminal bis(boronates) is ineffective with NaO^tBu in toluene. See ref. 3a.
13. Analogous orbital interactions have been claimed to explain the stereoselectivity of reactions of allylsilanes, allylstannanes, and allyl boronates. See: Fleming I, Lawrence NJ. *Tetrahedron Lett.* 1988; 29:2073.Fleming I, Lawrence NJ. *Tetrahedron Lett.* 1988; 29:2077.Fleming I, Lawrence NJ. *J. Chem. Soc., Perkin Trans. I.* 1992:3309.Pelz NF, Morken JP. *Org. Lett.* 2006; 8:4557. [PubMed: 16986949] Kyne RE, Ryan MC, Kliman LT, Morken JP. *Org. Lett.* 2010; 12:3796. [PubMed: 20687578]
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16. The boron-Wittig reaction has not previously been disclosed with CH₂(Bpin)₂, perhaps because of reagent availability. For boron-Wittig reactions with other reagents, see reference 7. CH₂(Bpin)₂ is now commercially available from Sigma-Aldrich (cat. 794287). For a simple scalable preparative procedure, see the Supporting Information for ref. 3a.

a. Distinctive reactivity features of bis(boronate) esters

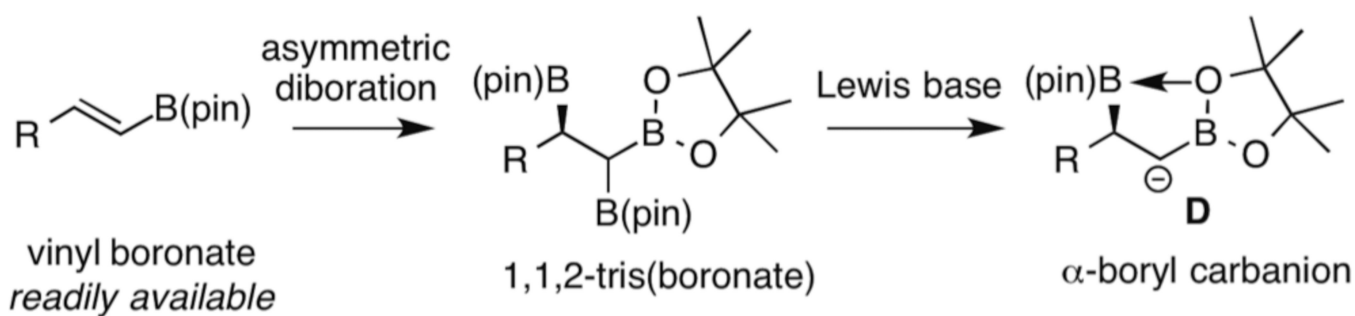


vicinal boronates:
internal chelation



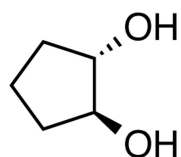
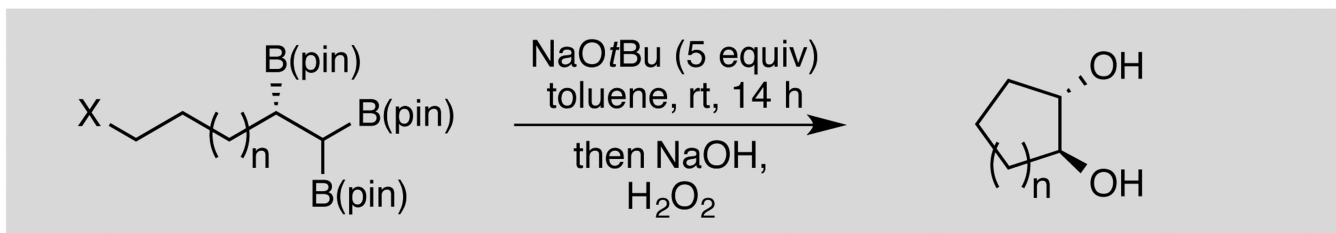
geminal boronates:
anion stabilization

b. Chiral tris(boronates): readily available chiral conjunctive reagents.

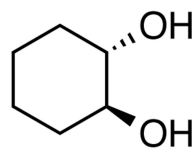


Scheme 1.

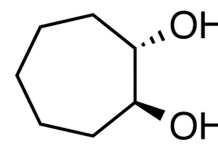
a. Stereoselective Intramolecular Deborylative Alkylation

**29**

X=Cl: 44%, >20:1 dr
X=Br: 36%, >20:1 dr

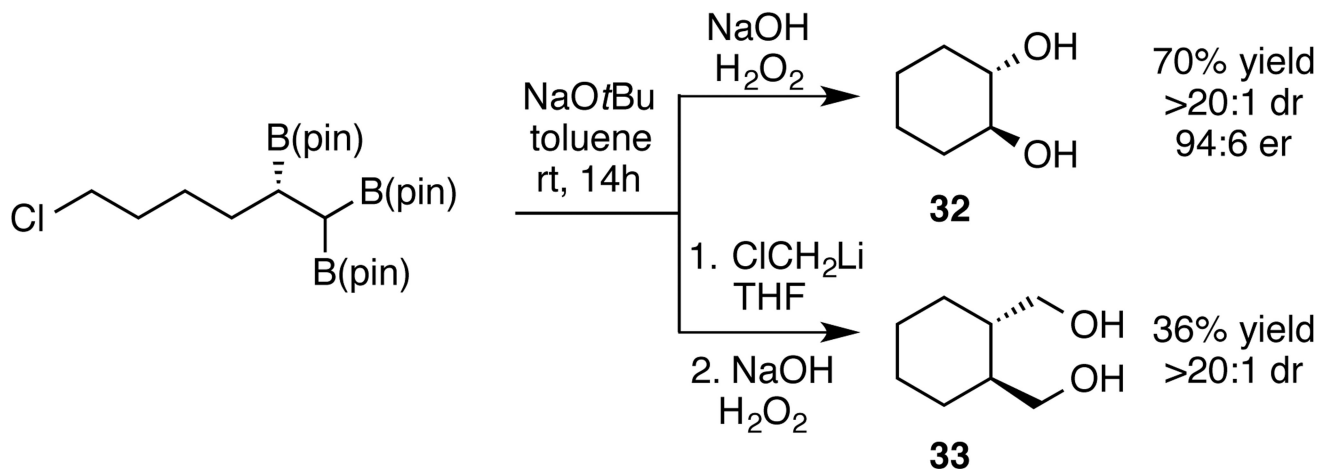
**30**

X=Cl: 67%, >20:1 dr
X=Br: 62%, >20:1 dr

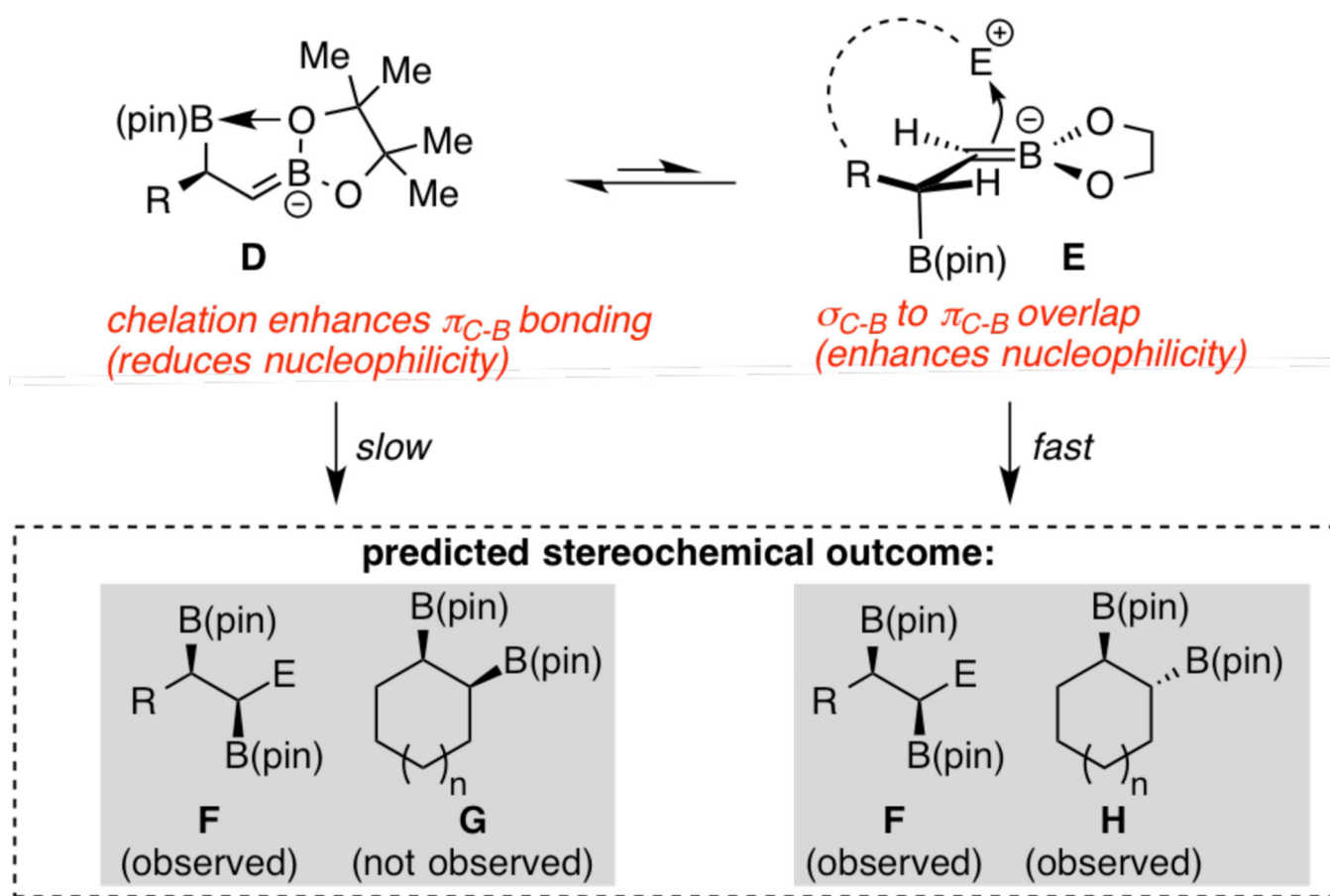
**31**

X=Br: 58%, >20:1 dr

b. Construction of Cyclic Diols from a 1,1,2-Tris(boronate).



Scheme 2.
Stereoselective Intramolecular Deborylative Alkylation Reactions.



Scheme 3.
Stereochemical Analysis of Deborylative Alkylation Reactions.

Table 1

Development of Catalytic Enantioselective Vinyl-boronate Diboration.^a

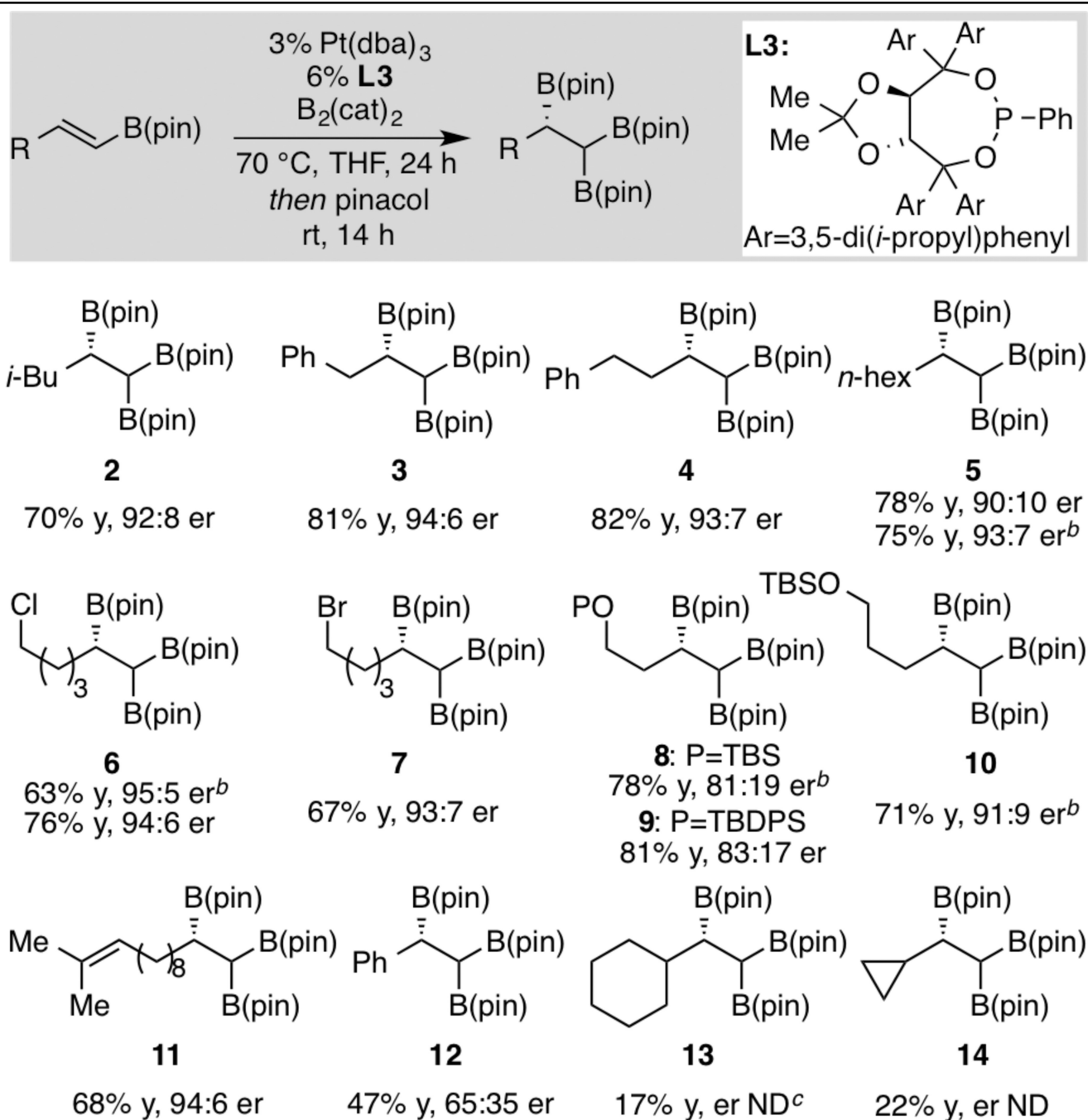
ligand:

L1: Ar=3,5-di(*t*-butyl)phenyl
 L2: Ar=3,5-diethylphenyl
 L3: Ar=3,5-di(*i*-propyl)phenyl
 L4: Ar=3,5-di(*t*-butyl)phenyl

entry	ligand	diboron	cat. (%) Pt/L	conv. (%)	yield (%) ^d	er ^c
1 ^b	-	B ₂ (pin) ₂	2/0	100	71	> <i>d</i>
2 ^b	L1	B ₂ (pin) ₂	5/10	72	49	68:32
3	L1	B ₂ (cat) ₂	5/10	81	50	88:12
4	L2	B ₂ (cat) ₂	5/10	78	43	89:11
5	L3	B ₂ (cat) ₂	5/10	80	51	95:5
6	L4	B ₂ (cat) ₂	5/10	90	48	94:6
7 ^c	L3	B ₂ (cat) ₂	3/6	>98	70	92:8

^a Conditions: Pt(dba)₃, ligand, and B₂(OR)₂ preheated to 80 °C for 30 minutes, prior to addition of substrate.^b The transesterification step was omitted from this experiment.^c Reaction at 70 °C for 24 h.^d Isolated yield of purified material and is an average of two experiments.

Table 2

Scope of the Catalytic Enantioselective Vinylboronate Diboration.^a

^aExcept where noted, reactions employed 2 equivalents of B₂(pin)₂. Each entry represents an average outcome of two experiments. % y refers to isolated yield.

^bReaction conducted with 1.0 mmol substrate.

^cReaction at 100 °C for 24 h.

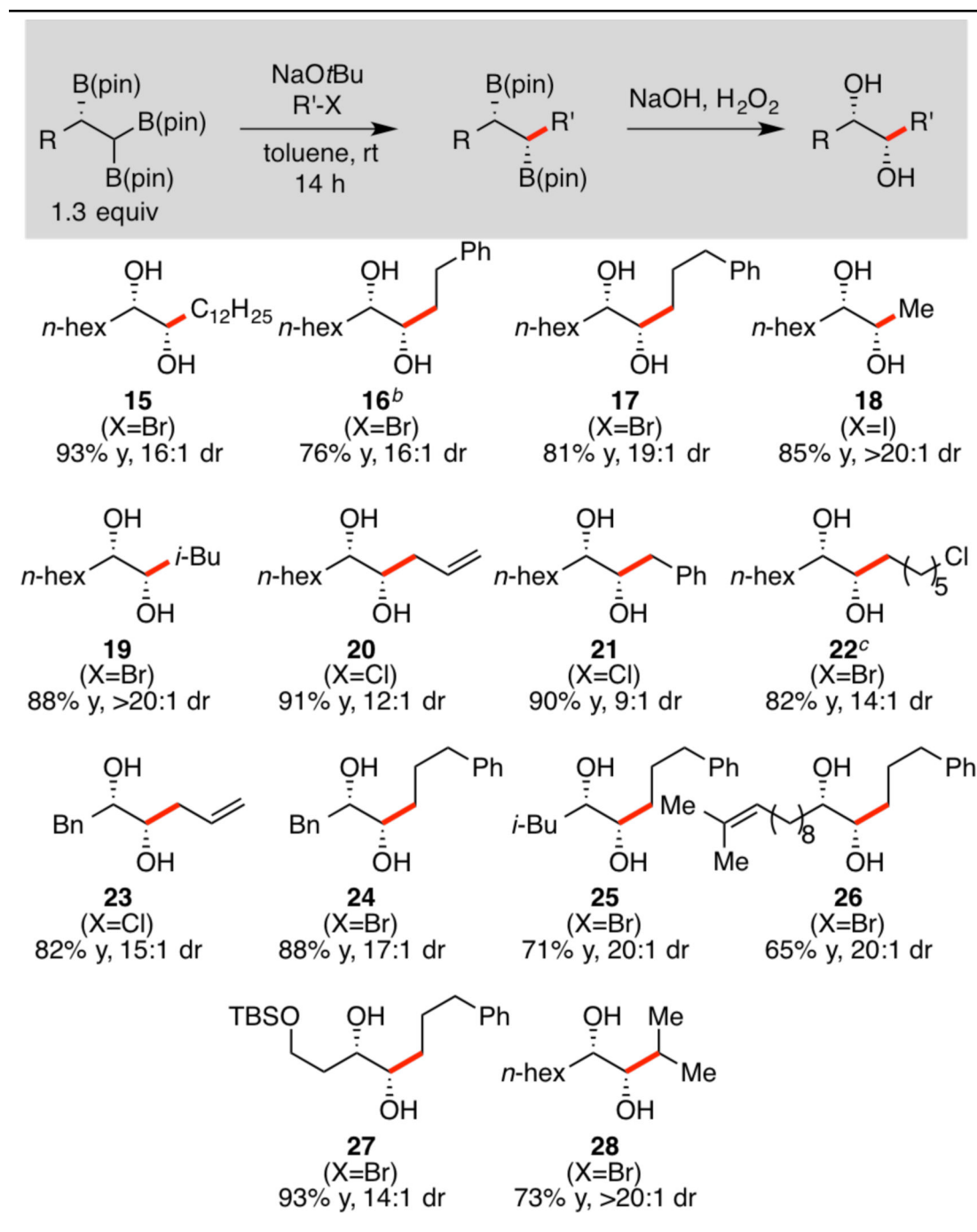
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Table 3

Deborlyative Alkylation of Chiral 1,1,2-Tris(boronates).^a

^aExcept where noted, reactions performed with 0.25 mmol substrate in toluene at rt. Each entry represents an average outcome of two experiments. % y refers to isolated yield.

^bStyrene is a minor side product.

^cReaction exclusively at the bromide; displacement of the chloride was not detected.

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