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Asymmetric synthesis from terminal alkenes by diboration/cross-coupling cascades

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Abstract

Amongst prospective starting materials for organic synthesis, terminal (monosubstituted) alkenes are ideal. In the form of α -olefins, they are manufactured on enormous scale and they are the core product features from many organic chemical reactions. While their latent reactivity can easily enable hydrocarbon chain extension, alkenes also have the attractive feature of being stable in the presence of many acids, bases, oxidants and reductants. In spite of these impressive attributes, relatively few catalytic enantioselective transformations have been developed that transform aliphatic α -olefins in >90% ee and, with the exception of site-controlled isotactic polymerization of α -olefins,¹ none of these processes result in chain-extending C-C bond formation to the terminal carbon.^{2, 3, 4, 5, 6} Herein, we describe a strategy that directly addresses this gap in synthetic methodology and present a single-flask catalytic enantioselective conversion of terminal alkenes into a range of chiral products. These reactions are enabled by an unusual neighboring group participation effect that accelerates Pd-catalyzed cross-coupling of 1,2-bis(boronates) relative to nonfunctionalized alkyl boronate analogs. In tandem with enantioselective diboration, this reactivity feature connects abundant alkene starting materials to a diverse array of chiral products. Importantly with respect to synthesis utility, the tandem diboration/cross-coupling reaction (DCC reaction) generally provides products in high yield and high selectivity (>95:5 enantiomer ratio), employs low loadings (1–2 mol %) of commercially available catalysts and reagents, it offers an expansive substrate scope, and can address a broad range of alcohol and amine synthesis targets, many of which cannot be easily addressed with current technology.

Development of catalytic enantioselective reactions that operate efficiently with low catalyst loadings and high levels of selectivity is a paramount challenge in organic chemistry. This challenge is even greater when one targets the transformation of α -olefins that have a small steric bias between prochiral π -faces. For this reason there are few catalytic asymmetric processes that operate effectively with aliphatic terminal alkenes. We sought to address this significant gap in synthesis methodology by developing a catalytic enantioselective reaction that converts terminal alkenes into chiral reactive intermediates; in this manner, one might

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

Author Contributions S.N.M. and C.H.S. developed the procedure for the DCC reaction and collected the data in Figure 2b and Figure 4. S.N.M. conducted the studies in Figures 5 and 6 and conducted the isotope labeling experiment in Figure 3. J.P.M. conceived and designed the studies, planned the research, and wrote the manuscript with assistance from C.H.S.

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introduce a number of useful catalytic asymmetric reactions simultaneously. A first step in the development of this strategy was achieved in engineering a Pt-catalyzed enantioselective alkene diboration (Figure 1a).⁷ In this manuscript, we present remarkably efficient cross-coupling reactions that apply to diboration products and collectively provide a strategy for enantioselective carbohydroxylation, carboamination, and bisalkylation of terminal alkenes. These strategies enable the construction of many biologically significant molecules and should allow practicing chemists to disconnect target structures in new ways. For example, the homoallylic alcohol embedded within the framework of the cytotoxic natural product epothilone C (Figure 1b) might be accessed by DCC reaction followed by oxidation. Alternatively, diboration followed by cross-coupling and amination could provide a new route to structural variants of the therapeutic agent tamsulosin from propene as a feedstock. Lastly, hydrocarbon stereocenters such as the one appearing in the antitumor macrolide kendomycin can be forged by DCC reaction followed by homologation of the remaining boronate.

The Pt-catalyzed enantioselective diboration of terminal alkenes with $B_2(\text{pin})_2$ offers a platform for the construction of new molecular ensembles. In tandem with diboration, oxidation transforms terminal alkenes to enantiomerically-enriched 1,2-diols. A far greater range of new molecular building blocks would arise from terminal alkenes if 1,2-bis(pinacol boronates) would directly participate in efficient cross-coupling. While related cross-couplings with bis(catechol boronates) are known,⁸ conversion of terminal alkenes to enantiomerically enriched 1,2-bis(catechol boronates) is generally not enantioselective. Therefore, a strategy for terminal alkene manipulation based on selective diboration reactions requires successfully engaging alkyl pinacol boronates as nucleophilic partners in Suzuki-Miyaura cross coupling.⁹ However, contrary to commonly employed alkyl boranes and boronic acids, alkyl pinacol boronates are generally recalcitrant substrates in such processes.¹⁰ Indeed, the only reported cross-coupling with a bis(pinacol boronate) involved two equivalents of a highly activated organic electrophile.¹¹ The contrasting reactivity between classes of boron reagents can be traced to a difference in transmetalation rates during the catalytic Suzuki cross-coupling reaction (Figure 2a). Meticulous mechanistic studies conducted by Hartwig¹² and Amatore and Jutand¹³ are in concert with prior assertions^{9,14} and suggest that one operative mechanism for transmetalation involves pre-association of a Pd(hydroxide) with a neutral trivalent boron center. Accordingly, it can be surmised that the diminished Lewis acidity of alkyl pinacol boronates relative to other boron derivatives lies at the root of the reactivity difference between these reagents. Thus, engaging pinacol alkyl boronates in cross-coupling has required the use of toxic bases¹⁵ or pre-formed “ate” complexes.¹⁶ Recent advances¹⁷ in the design of efficient ligands for metal-catalyzed cross-coupling reactions have begun to provide a solution to this problem and indeed one recent report¹⁸ suggests that pinacol boronates can participate in Suzuki reaction in the presence of the RuPhos,¹⁹ a monodentate phosphine ligand.

To determine whether 1,2-bis(pinacol boronates) can engage in efficient cross-couplings with unactivated organic electrophiles, the reaction between isolated and purified bis(boronate) **1** and bromobenzene was examined under a wide range of reaction conditions. Optimal conditions are depicted in Figure 2b and reveal that extraordinarily efficient cross-

couplings can be achieved. In the presence of 1 mol % Pd(OAc)₂, 1 mol % RuPhos, and employing aqueous KOH as the base for 1 hour, we obtained a 91% yield of alcohol **5** after oxidative work-up. Importantly, alcohol **5** was isolated as a single constitutional isomer; the product from coupling with the secondary boronate was not detected. The reaction of **5** is remarkable in comparison to cross-couplings of other pinacol boronates. For example, under the same conditions in which **1** reaches 91% conversion, *n*-octyl boronate **2** is not detectably transformed. Reactions of 1,3-bis(boronate) **3** and 1,4-bis(boronate) **4**, indicate that the rate acceleration experienced by **1** relies not just on the presence of a second boronate unit, but also on its position relative to the first.

To gain further insight into the special features of the 1,2-bis(pinacol boronate), we performed a direct competition experiment where both **1** and octylB(pin) **2** were subjected to cross-coupling in the same flask (Figure 2c). In this experiment, >95% conversion of the 1,2-bisboronate was achieved whereas only a trace amount of product was produced from the monoboronate. With the reasonable assumption that transmetallation in the presence of hydroxide is irreversible, the outcome of this experiment suggests that the enhanced reactivity of the bis(boronate) is likely due to an enhanced rate of transmetallation; if transmetallation occurred at similar rates with each substrate but the rate retardation with octylB(pin) was due to slow reductive elimination, then octylB(pin) should sequester the Pd catalyst and retard the reaction of both substrates. Thus the presence of the adjacent non-reacting boronate appears to have a profound effect on the rate of transmetallation leading to >50 fold enhancement in reactivity of the substrate.

While a number of plausible explanations may account for the reaction acceleration by the vicinal boronate in **1**, we consider two. Similar to the Lewis base induced activating effect that an adjacent carbonyl has on a reacting boronate,²⁰ it was considered that cooperative binding of hydroxide by the neighboring boron centers might furnish an "ate" complex such as **A** (Figure 3).²¹ Alternatively, we considered that the function of the adjacent boron atom might be to act as a Lewis acid, coordinating to the pinacolato oxygen (**B**) thereby enhancing the Lewis acidity and, in line with the discussion above, this might enhance the reactivity of the primary organoboronate. The stereochemical outcome of the cross-coupling reaction might provide a clue to the operative reaction mechanism: with four-coordinate boron in **A**, transmetallation would necessarily occur by an outer sphere path and result in inversion of configuration at the primary carbon.²⁰ Alternatively, reaction *via* **B** would most likely occur by an inner sphere path and occur with retention of configuration.^{14,22} To test these proposals, cross-coupling with isotopically labeled substrate **9** was examined and it was found to occur with retention of configuration at carbon providing **10** as the product. The outcome of this labeling experiment suggests an inner-sphere transmetallation may operate, perhaps involving association of a Pd(hydroxide) complex with **B**.

Conveniently, both alkene diboration and catalytic cross coupling can be accomplished in a one-pot protocol, transforming simple terminal olefins to secondary alcohols after oxidation. Utilizing bromobenzene as a model electrophile, 1-octene was found to successfully engage in the tandem sequence and provided homobenzylic alcohol **11** after oxidation of the cross-coupled product (Figure 4). Replacement of bromobenzene with chlorobenzene also resulted in effective conversion to **11** (88% yield); however, reactions with either iodobenzene (30%

yield) or phenyltriflate (48% yield) gave lower yields of the desired product. In addition to 1-octene, a number of other olefins were successfully engaged in the tandem sequence with bromobenzene as the electrophile, affording the products in high yield and with high enantioselectivity (products **12–18**). Both linear and branched aliphatic substrates as well as those containing pendant olefins and silyl ethers were well tolerated. Olefins derived from allylic or homoallylic alcohols underwent smooth reaction and importantly, when either hydrocarbon-based or oxygen-based β stereocenters are present (products **14 – 17**), effective catalyst control produces the products in excellent diastereomer ratios (17:1 to >20:1 dr). Examination of other aromatic electrophiles showed that electron poor and electron rich arenes as well as those that are sterically encumbered readily couple (**19 – 22**). Importantly, heteroaromatics can also be utilized and give highly enantioenriched adducts (**23 – 25**).

Homoallylic alcohols are strategically important compounds in synthetic organic chemistry and significant resources have been directed towards their asymmetric construction. Almost exclusively, these motifs are accessed by allylation of carbonyl electrophiles with nucleophilic reagents.²³ An alternate route to these structures from terminal alkenes becomes available when vinyl electrophiles are engaged in the tandem DCC reaction. In preliminary studies, we investigated the coupling of vinyl bromides, but these most often occurred with lackluster reaction efficiency (for example, 12% yield of **26** from the vinyl bromide). While vinyl iodides were also ineffective (<5 % yield), the reactions of vinyl chlorides were highly effective and furnished homoallylic alcohols in excellent yields upon oxidative work-up (Figure 5a). Because the olefin stereochemistry is retained during the course of Suzuki cross-coupling reactions, the DCC reaction provides ready access to homoallylic alcohols bearing configurationally defined trisubstituted (**27** and **28**), *cis* and *trans*-disubstituted (**26** and **29**), and cyclic alkenes (**30** and **31**) in a stereoselective fashion; construction of these substituted motifs with contemporary carbonyl allylation methods, when possible, requires specialized difficult-to-access reagents. Lastly, we considered that unsubstituted homoallylic alcohols might be accessed from vinyl chloride; however, handling this toxic and gaseous electrophile is cumbersome and requires specialized equipment. We found that a straightforward alternative arises from the use of dichloroethane: under the basic reaction conditions, this inexpensive liquid reagent is presumably converted to vinyl chloride and engages in cross-coupling (Figure 5b). After oxidative work-up, we isolated unsubstituted homoallylic alcohol **32** in outstanding yield and enantiomeric excess. Of note, homoallylic amines can also be accessed with the diboration/cross-coupling strategy by subjecting the purified DCC intermediate to amination rather than *in situ* oxygenation. This allowed construction of **33** from 1-octene also in outstanding levels of enantioselectivity and good yield.²⁴

The versatility of the catalytic DCC reaction provides a rapid route to important product motifs from simple alkene feedstocks. To demonstrate the power of this strategy, we targeted a diverse array of biologically important molecules. For example, chiral phenethylamine derivatives are broadly active pharmaceutical agents most often produced from ketone precursors.²⁵ Alternatively, as the sequence in Figure 6a indicates, the DCC reaction allows N-Boc-(*S*)-amphetamine to be prepared quickly from the commodity chemical propene as the starting material. Efficient diboration is followed by cross coupling

to give secondary boronate **34**. Subjection of **34** to stereospecific direct amination²⁶ and Boc protection furnished the target in excellent enantiomeric purity. Importantly, the modular nature of this new route to phenethylamine derivatives could dovetail with strategies for high-throughput synthesis and provide rapid access to new derivatives for biological studies. Utilizing the one-pot diboration/cross coupling in conjunction with boronate homologation²⁷ and oxidation converts propene to primary alcohol **35**. Chlorination followed by S_N2 reaction furnished the potent fungicide (*S*)-Fenpropimorph with high levels of enantioenrichment (Figure 6b).²⁸ Another application involves construction of lignan lactones, a broad class of natural products that exhibit a wide range of biological activity. Starting from commercially available safrole, we constructed key intermediate **36** in 3 steps: DCC reaction, boronate homologation, and oxidative olefin cleavage (Figure 6c). Simple alkylation of lactone **36** is known to furnish a variety of lignan natural products such as isodeoxypodophyllotoxin and isostegane.²⁹ Lastly, the DCC reaction applied to give **37**, followed by homologation, amination, and protection furnished **38**. Subsequent oxidative olefin cleavage and deprotection provides a new route to the pharmaceutical agent Lyrica® (pregabalin) from a unique set of organic chemical building blocks (Figure 6d).³⁰

In summary, the catalytic enantioselective diboration of terminal alkenes, combined with Pd-catalyzed cross-coupling, provides a flexible platform for the construction of a broad array of chiral compounds from non-functionalized terminal alkenes. While application of this methodology in target-oriented synthesis is easy to envision, when one considers the tremendous variety of α -olefins and aryl/vinyl electrophiles that are available, the DCC reaction sequence should provide new strategies for diversity-based synthesis as well. In addition to its direct impact on molecular synthesis, the studies presented herein define a unique reactivity characteristic of 1,2-bis(pinacol boronates). We anticipate that the proclivity of the 1,2-bis(boronate) towards transmetalation may enable a range of other important enantioselective terminal alkene transformations that will have an impact on the field of chemical synthesis.

Methods Summary

The general procedure for the one-pot DCC reaction as described in Figure 2 is as follows. Pt(dba)₃ (1.0 mol %), (*R,R*)-**L1** (1.2 mol %), B₂(pin)₂ (1.05 equiv.), and anhydrous THF ([substrate] = 1.0 M) are stirred together at 80 °C for 15 minutes. After cooling to ambient temperature, the alkene (1.0 equiv.) is added and the reaction mixture is stirred at 60 °C for 3 hours. Upon cooling to ambient temperature, Pd(OAc)₂ (1.0 mol %), followed by RuPhos (1.0 mol %), the electrophile (1.5 equiv.), KOH (3.0 equiv.), additional THF and deoxygenated water ([substrate] = 0.1 M; 10:1 v:v THF:H₂O) are added and the reaction mixture is heated to 70 °C for 12 hours. The reaction is then cooled to 0 °C and treated with 3M aqueous NaOH and 30% H₂O₂. After 4 hours at ambient temperature, excess H₂O₂ is carefully quenched with saturated aqueous Na₂S₂O₃, followed by extraction with ethyl acetate. The combined organics are dried over Na₂SO₄, filtered and concentrated. The resulting material is purified by flash chromatography on silica gel. For complete experimental details and characterization of all new compounds, see Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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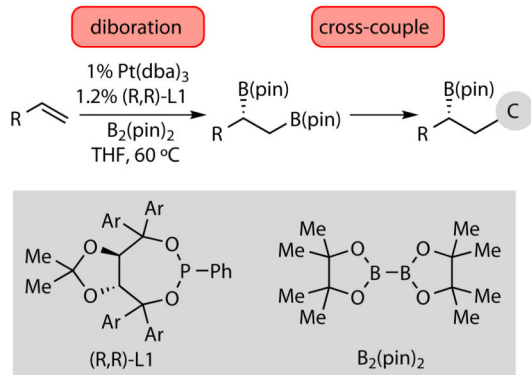
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Terminal, monosubstituted alkenes are ideal prospective starting materials for organic synthesis, as they are manufactured on very large scales and can be functionalized via a broad range of chemical transformations. Alkenes also have the attractive feature of being stable in the presence of many acids, bases, oxidants, and reductants. In spite of these impressive attributes, relatively few catalytic enantioselective transformations have been developed that transform aliphatic α -olefins in chiral products with >90% ee. With the exception of site-controlled isotactic polymerization of α -olefins,¹ none of these processes result in chain-extending C–C bond formation to the terminal carbon.^{2–6} Herein, we describe a strategy that directly addresses this gap in synthetic methodology and present a single-flask, catalytic enantioselective conversion of terminal alkenes into a number of chiral products. These reactions are facilitated by a neighboring functional group that accelerates Pd-catalyzed cross-coupling of 1,2-bis(boronates) relative to nonfunctionalized alkyl boronate analogs. In tandem with enantioselective diboration, this reactivity feature transforms alkene starting materials into a diverse array of chiral products. Importantly, the tandem diboration/cross-coupling reaction (DCC reaction) generally provides products in high yield and high selectivity (>95:5 enantiomer ratio), employs low loadings (1–2 mol %) of commercially available catalysts and reagents, it offers an expansive substrate scope, and can address a broad range of alcohol and amine synthesis targets, many of which cannot be easily addressed with current technology.

a Diboration cross-coupling cascade



b Prospective targets

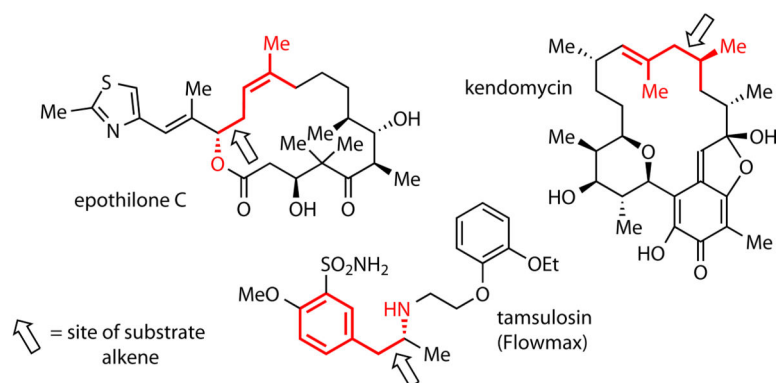


Figure 1. The diboration/cross coupling (DCC) strategy and potential applications

a, An efficient cross-coupling reaction that applies to alkyl pinacol boronates would enable conversion of terminal alkenes to a broad array of useful building blocks. **b**, The DCC reaction followed by oxidation provides an alternative to carbonyl allylation for the construction of homoallylic alcohols as in epothilone C. Amination or homologation of the DCC product can provide access to chiral amines and simple chiral hydrocarbon building blocks. Ar=3,5-diisopropylphenyl.

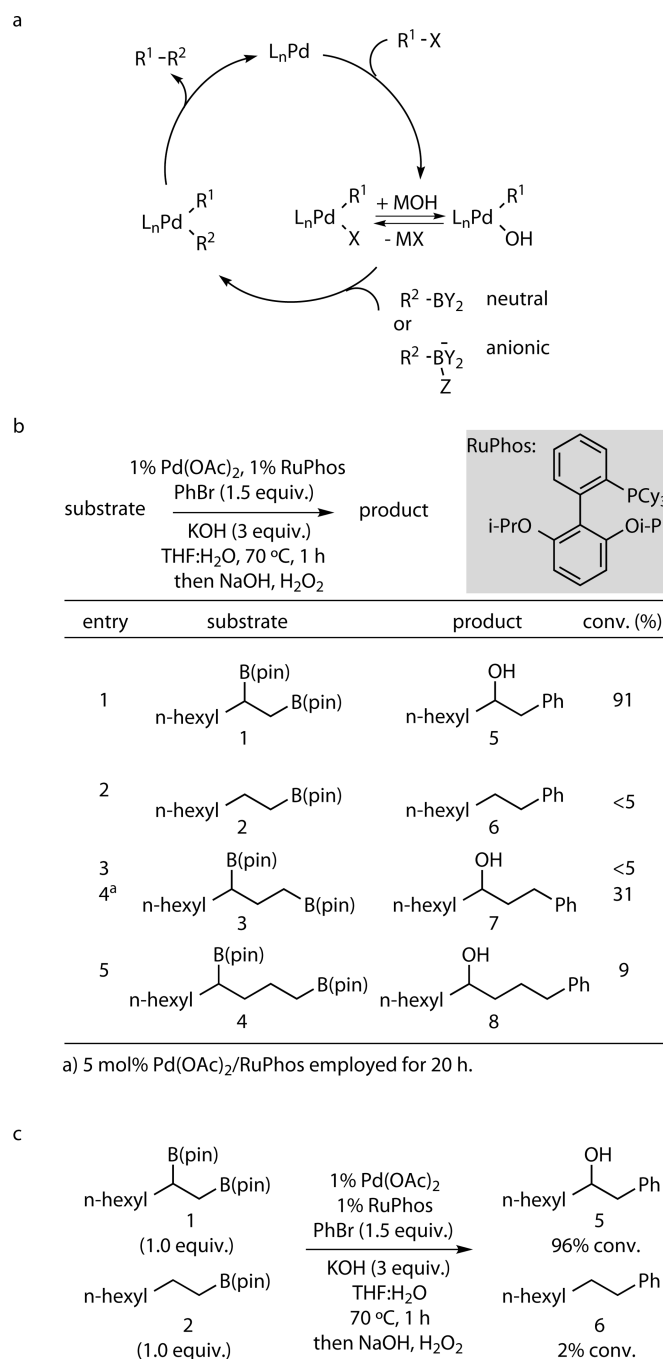
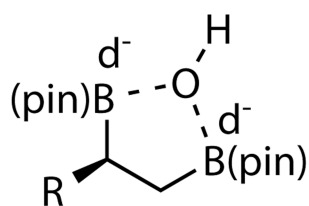


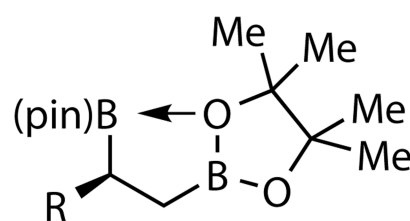
Figure 2. Observations on the Pd-catalyzed cross-coupling of 1,2-bis(boronates) with bromobenzene

a, Generalized mechanism for the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction. **b**, Cross-coupling of bromobenzene with alkyl pinacol boronates shows a pronounced rate enhancement due to the presence of a vicinal boronate. **c**, A direct competition experiment suggests that the rate enhancement occurs at the first irreversible step or any step that precedes it.

a



A



B

b

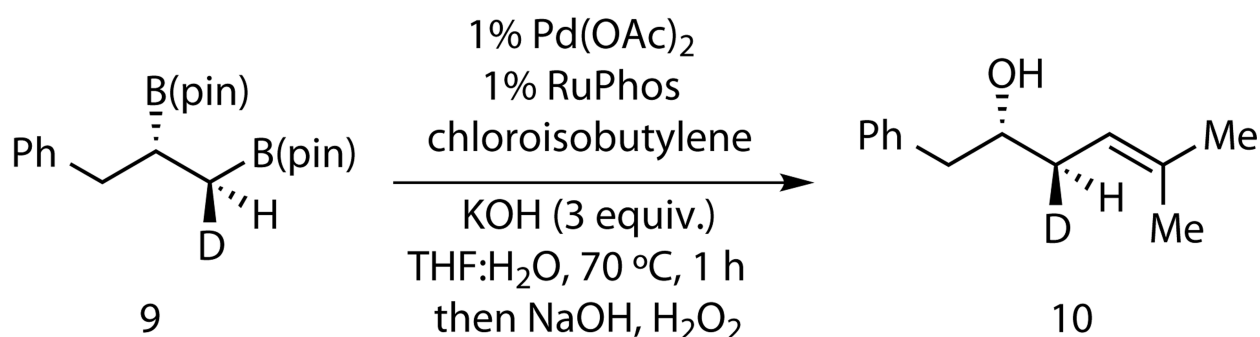


Figure 3. Mechanistic considerations for the cross-coupling rate enhancement observed with 1,2-bis(boronates)

a, While rate enhancements in Suzuki-Miyaura couplings might result from internal Lewis base donation to the reacting boronate (as in **A**) internal Lewis acid activation as in **B** may allow the boronate to better bind a reactive Pd(OH) species. **b**, the stereochemical outcome of cross-coupling (retention of configuration at carbon) is consistent with an inner-sphere transmetallation suggesting internal Lewis acid activation is the more likely pathway.

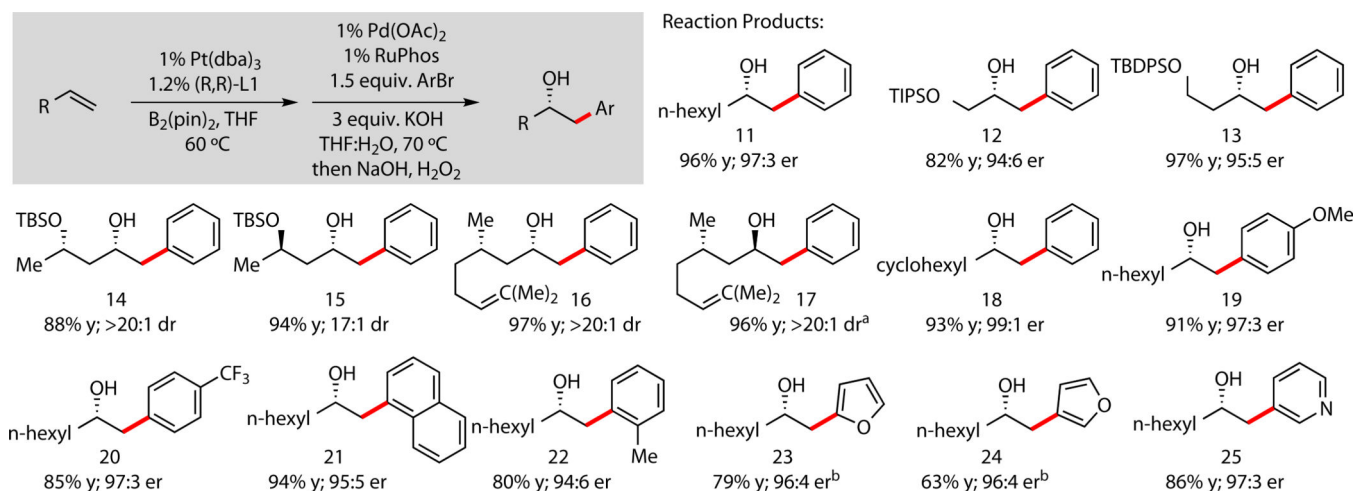
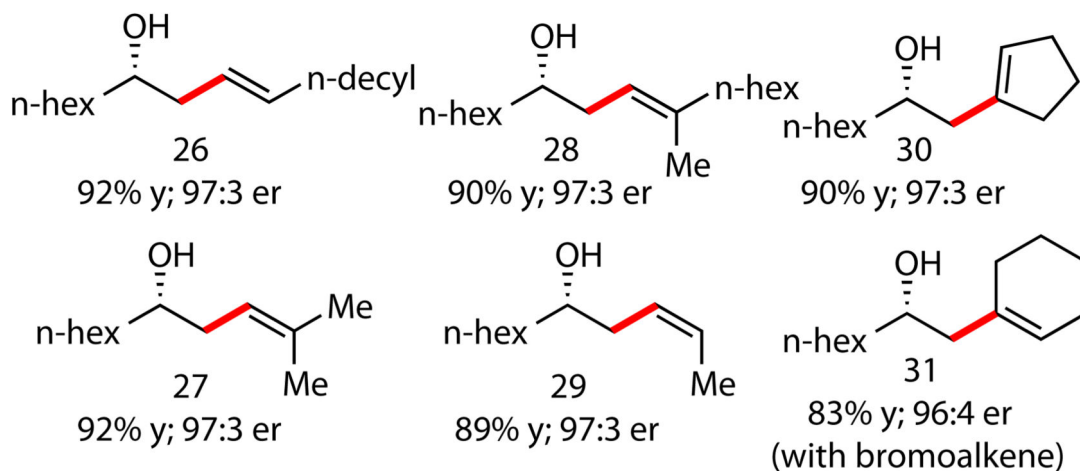
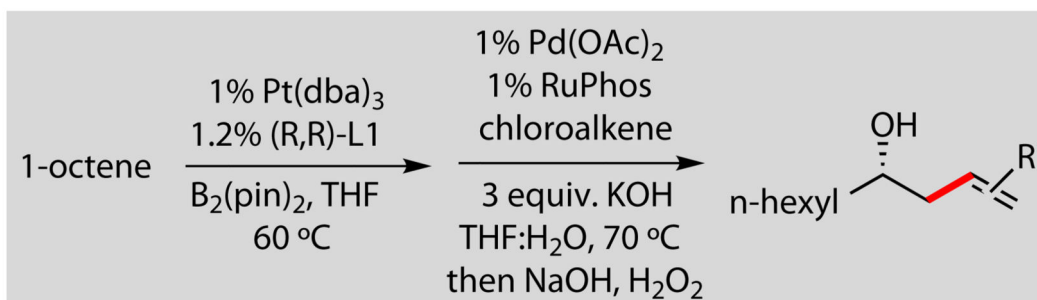


Figure 4. Tandem single-pot diboration/cross coupling provides a new route to enantiomerically-enriched benzylic alcohols from terminal alkenes

Yield refers to isolated yield of purified product and is an average of two experiments (individual experimental values are within 10%). Enantiomeric ratio (er) was determined by chiral chromatography with an error $< \pm 2\%$. Note ligand (*S,S*)-**L1** employed for compound **17** and cross-coupling for **23** and **24** employed 1 equiv. LiCl. (*R,R*)-3,5-diethylphenyl-derived ligand used in place of **L1** for **12**. NaBO₃ used for oxidation of **12**, **14**, and **15**.

a



b

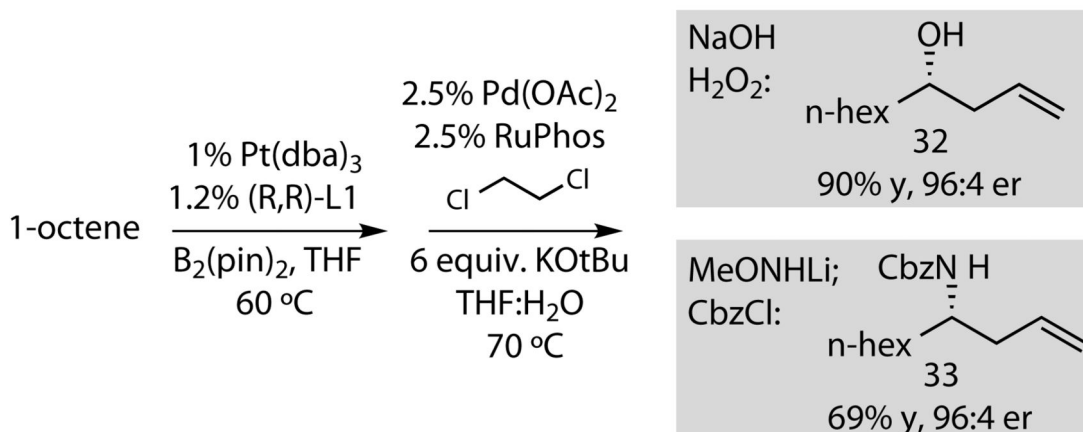


Figure 5. The diboration/cross-coupling tandem sequence provide access to synthetically useful chiral homoallylic alcohols that aren't readily prepared by carbonyl allylation reactions

a. Construction of substituted homoallylic alcohols by DCC reaction/oxidation. **b.** Use of dichloroethane allows for *in situ* formation of vinyl chloride and provides an effective route to unsubstituted homoallylic alcohols and amines. Note: Yield refers to isolated yield of purified product and is an average of two experiments (individual experimental values are within 10%). Enantiomeric ratio (er) was determined by chiral chromatography with an error $< \pm 2\%$.

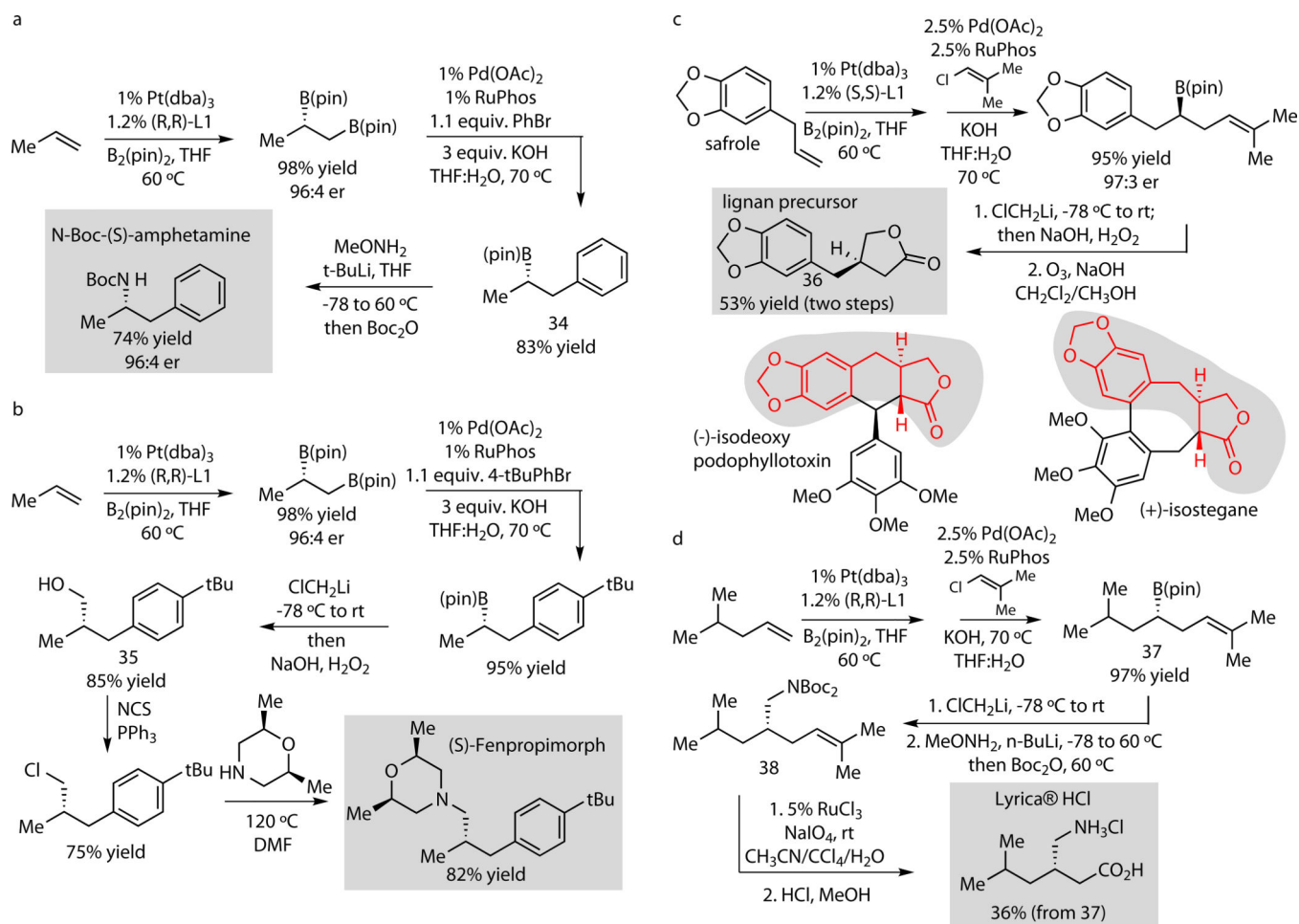


Figure 6. Diboration/cross-coupling tandem reactions provide short new synthesis routes to important medicinal agents. That these routes employ new feedstocks relative to existing routes and can facilitate new SAR studies

a, Preparation of Boc protected (*S*)-amphetamine. **b**, Preparation of (*S*)-fenpropimorph. **c**, Construction of a key lignan building block. **d**, Synthesis of non-racemic Lyrica.