Asymmetric synthesis from terminal alkenes by cascades of diboration and cross-coupling

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Terminal, monosubstituted alkenes are ideal prospective starting materials for organic synthesis because 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 attributes, relatively few catalytic enantioselective transformations have been developed that transform aliphatic α-olefins into chiral products with an enantiomeric excess greater than 90 per cent. With the exception of site-controlled isotactic polymerization of α-olefins, none of these catalytic enantioselective processes results in chain-extending carbon–carbon bond formation to the terminal carbon. Here 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 neighbouring functional group that accelerates palladium-catalysed cross-coupling of 1,2-bis(boronates) relative to non-functionalized alkyl boronate analogues. In tandem with enantioselective diboration, this reactivity feature transforms alkene starting materials into a diverse array of chiral products. We note that the tandem diboration/cross-coupling reaction generally provides products in high yield and high selectivity (>95.5 enantiomer ratio), uses low loadings (1–2 mol per cent) of commercially available catalysts and reagents, 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 the prochiral faces of the alkene. 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 introduce a number of useful catalytic asymmetric reactions simultaneously. A first step in the development of this strategy was achieved in engineering a Pt-catalysed enantioselective alkene diboration (Fig. 1a). In this Letter we present remarkably efficient cross-coupling reactions that apply to diboration products and collectively provide a strategy for enantioselective carboxyhydroxylation, carbamoylation and bisalkylation of terminal alkenes. These strategies enable the construction of many biologically significant molecules and should allow practicing chemists to assemble target structures in new ways. For example, the homoallylic alcohol embedded within the framework of the cytotoxic natural product epothilone C (Fig. 1b) might be accessed by a diboration/cross-coupling (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. Last, hydrocarbon stereocentres such as the one appearing in the antitumour macrolide kendomycin can be forged by DCC reaction followed by homologation of the remaining boronate.

The Pt-catalysed enantioselective diboration of terminal alkenes with B₂(pin)₂ (here pin indicates pinacolato) 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. Although related cross-couplings with bis(catechol boronates) are known, 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. However, contrary to commonly employed

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**Figure 1 | The diboration/cross-coupling (DCC) strategy and potential applications.** a, The DCC cascade. 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, Prospective targets. The DCC reaction followed by oxidation provides an alternative to carbonyl alkylation 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. Open arrow indicates site of substrate alkene. Ar = 3,5-di-isopropylphenyl, dba = dibenzylideneacetone.
alkyl boranes and boronic acids, alkyl pinacol boronates are generally recalcitrant substrates in such processes\(^1\). Indeed, the only reported cross-coupling with a bis(pinacol boronate) involved two equivalents of a highly activated organic electrophile\(^1\). The contrasting reactivity between classes of boron reagents can be traced to a difference in transmetallation rates during the catalytic Suzuki cross-coupling reaction (Fig. 2a). Meticulous mechanistic studies\(^2,3\) are in concert with prior assertions\(^4,5\) and suggest that one operative mechanism for transmetallation involves pre-association of a Pd(hydroxide) with a neutral trivalent boron centre. 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 bases\(^15\) or pre-formed anionic four-coordinate “ate” complexes\(^16\). Recent advances\(^17\) in the design of efficient ligands for metal-catalysed cross-coupling reactions have begun to provide a solution to this problem and indeed one recent report\(^18\) suggests that pinacol boronates can participate in the Suzuki reaction in the presence of RuPhos\(^19\), a monodentate phosphine ligand.

To determine whether 1,2-bis(pinacol boronates) can engage in efficient cross-couplings with unactivated organic electrophiles, we examined the reaction between isolated and purified bis(boronate) 1 (Fig. 2b) and bromobenzene under a wide range of reaction conditions. Optimal conditions are depicted in Fig. 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 h, we obtained a 91% yield of alcohol 5 (Fig. 2b) 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 (Fig. 2b). 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 (Fig. 2c). In this experiment, >95% conversion of the 1,2-bisboronate was achieved whereas only a trace amount of product was produced from the monoborinate. 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 probably 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.

A number of plausible explanations may account for the reaction acceleration by the vicinal boronate in 1, but here we consider two. Similarly to the Lewis-base-induced activating effect that an adjacent carbonyl has on a reacting boronate\(^20\), we considered that cooperative binding of hydroxide by the neighbouring boron centres might furnish an “ate” complex such as A (Fig. 3); for related observations in cross-coupling of geminal boronates, see ref. 21. Alternatively, we considered

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**Figure 2** | Observations on the Pd-catalysed cross-coupling of 1,2-bis(boronates) with bromobenzene. **a.** Generalized mechanism for the palladium-catalysed Suzuki-Miyaura cross-coupling reaction. **b**. Cross-coupling of bromobenzene with alkyl pinacol boronates in the presence of RuPhos (structure shaded) shows a pronounced rate enhancement due to the presence of a vicinal boronate. Note that for entry 4, 5 mol% Pd(OAc)\(_2\)/RuPhos was employed for 20 h. **c.** A direct competition experiment suggests that the rate enhancement occurs at the first irreversible step or any step that precedes it.

**Table 2** | Cross-coupling of bromobenzene with 1,2-bis(pinacol boronates) in the presence of Pd catalysts and RuPhos ligands.

| Entry | Substrate | Product | Conv. (%) |
|-------|-----------|---------|-----------|
| 1     | n-hexylB(pin) | B(pin) | OH | 91 |
| 2     | n-hexylB(pin) | B(pin) | OH | <5 |
| 3     | n-octylB(pin) | B(pin) | OH | <5 |
| 4     | n-octylB(pin) | B(pin) | OH | 31 |
| 5     | n-octylB(pin) | B(pin) | OH | 96% conv. |

**Figure 3** | Mechanistic considerations for the cross-coupling rate enhancement observed with 1,2-bis(boronates). **a.** Whereas rate enhancements in Suzuki-Miyaura couplings might result from internal Lewis base donation to the reacting boronate (as in compound A), internal Lewis acid activation (as in compound 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 that internal Lewis acid activation is the more likely pathway.
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 of the neighbouring boron centre; in line with the discussion above, this might enhance the reactivity of the primary organoborane. The stereochemical outcome of the cross-coupling reaction might provide a clue to the operative reaction mechanism: with four-coordinate boron in A, transmetalation would necessarily occur by an outer-sphere path and result in inversion of configuration at the primary carbon \(^\text{2\text{0}.}\) Alternatively, reaction via B would most probably occur by an inner-sphere path and occur with retention of configuration \(^\text{14,2\text{2}.}\) To test these proposals, the cross-coupling of isotopically labelled substrate \(9\) and chloroisobutylene was examined and it was found to occur with retention of configuration \(^\text{14,2\text{2}.}\)

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. Using bromobenzene as a model electrophile, 1-octene was found to successfully engage in the tandem sequence and provide homobenzyl alcohol \(11\) after oxidation of the cross-coupled product (Fig. 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 \(12\text{-}18\)). 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 \(\beta\) stereocentres are present (products \(14\text{-}17\)), effective catalysis control produces the products in excellent diastereomeric ratios (17:1 to >20:1 d.r.). Examination of other aromatic electrophiles showed that electron-poor and electron-rich arenes 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 \(\beta\) stereocentres are present (products \(14\text{-}17\)).

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. \(^\text{2\text{3}.}\) An alternative 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 lacklustre reaction efficiency (for example, 12% yield of \(26\) from the vinyl bromide). Whereas vinyl iodides were also ineffective (<5% yield), the reactions of vinyl chlorides were highly effective and furnished homoallylic alcohols in excellent yields on oxidative work-up (Fig. 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 \(27\text{ and }28\), cis- and trans-}

**Figure 4** | Tandem single-pot DCC provides a new route to enantioenriched benzyl alcohols from terminal alkenes. Shaded area shows the reaction: varying ‘R’ in the reactant gives reaction products shown. Under each product are given yield in per cent, and either enantiomeric ratio (e.r.) or diastereomer ratio (d.r.). Yield refers to isolated yield of purified product and is an average of two experiments (individual experimental values are within 10%). The e.r. was determined by chiral chromatography with an error <±2%. Note ligand (S,S)-1 was employed for compound 17, and cross-coupling for 23 and 24 employed 1 equiv. LiCl. (R,R)-3,5-diethylphenyl-derived ligand was used in place of L1 for 12. NaBO\(_3\) was used for oxidation of 12, 14 and 15. TIPS = triisopropylsilylethyl, TBDPS = tert-butyldiphenylsilylethyl.

**Figure 5** | The DCC tandem sequence provides access to synthetically useful chiral homoallylic alcohols that are not readily prepared by carbonyl allylation reactions. a. Construction of substituted homoallylic alcohols by DCC reaction/oxidation. Shaded area shows reaction: products are shown under. Variation of the chloroalkene employed in the cross-coupling gives differently substituted alkenes in the product. b. Use of dichloethane allows for \(\text{in situ}\) formation of vinyl chloride and provides an effective route to unsubstituted homoallylic alcohols and amines (shaded). Yield and e.r. are as defined in Fig. 4 legend. Cbz = carboxybenzyl.
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. Last, 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 (Fig. 5b). After oxidative work-up, we isolated unsubstituted homoallylic alcohol 32 in outstanding yield and enantioemic excess. Of note, homoallylic amines can also be accessed with the DCC strategy by subjecting the purified DCC intermediate to amination rather than oxygenation. This allowed construction of 33 from 1-ocitene (Fig. 5b) also in outstanding levels of enantioselectivity and good yield; for recent efficient catalytic enantioselective imine allylation to give allyl amines see ref. 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 contemporary carbonyl allylation methods, when possible, requires specialized difficult-to-access reagents. Last, 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 (Fig. 5b). After oxidative work-up, we isolated unsubstituted homoallylic alcohol 32 in outstanding yield and enantioemic excess. Of note, homoallylic amines can also be accessed with the DCC strategy by subjecting the purified DCC intermediate to amination rather than in situ oxygenation. This allowed construction of 33 from 1-ocitene (Fig. 5b) also in outstanding levels of enantioselectivity and good yield; for recent efficient catalytic enantioselective imine allylation to give allyl amines see ref. 24.

Figure 6 | DCC tandem reactions provide short new synthesis routes to important medicinal agents. These routes employ new feedstocks relative to existing routes and can facilitate new structure–activity relationship studies. a, Preparation of Boc protected (S)-amphetamine (shaded). b, Preparation of (S)-fenpropimorph. RT, room temperature. c, Construction of a key lignan building block 36, which is a known precursor to isodoxyophyllotoxin and isostegane (red portion of the natural products shows the carbon framework of precursor 36). d, Synthesis of non-racemic Lyrica.

In summary, the catalytic enantioselective diboration of terminal alkenes, combined with Pd-catalysed cross-coupling, provides a flexible platform for the construction of a broad array of chiral compounds from non-functionalized terminal alkenes. Although application of this methodology in target-oriented synthesis is easy to foresee, when one considers the tremendous variety of α-olefins and aryl/vinyl electrophiles that are available, the DCC reaction sequence should also provide new strategies for diversity-based synthesis. In addition to its direct impact on molecular synthesis, the studies presented here define a unique reactivity characteristic of 1,2-bis(pinacol boronates). We anticipate that the enhanced reactivity of the 1,2-bis(boronate) in trans-stereochemistry will have an impact on molecular synthesis, the studies presented here define a unique reactivity characteristic of 1,2-bis(pinacol boronates). We anticipate that the enhanced reactivity of the 1,2-bis(boronate) in trans-stereochemistry. The general procedure for the one-pot DCC reaction as described in Fig. 4 is as follows: P(t-Bu)_3 (1.0 mol%), (R,R)-L1 (1.2 mol%), B(pin)_2 (1.05 equiv.) and anhydrous THF ([substrate] = 1.0 M) are stirred together at 80 °C for 15 min. After cooling to ambient temperature, the alkene (1.0 equiv.) is added and the reaction mixture is stirred at 60 °C for 3 h. On 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 h. The reaction is then cooled to 0°C and treated with 3 M aqueous NaOH and 30% H2O2. After 4 h 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.

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

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Author Contributions S.N.M. and C.H.S. developed the procedure for the DCC reaction and collected the data in Figs 2b and 4. S.N.M. conducted the studies in Figs 5 and 6 and conducted the isotope labelling experiment in Fig. 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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ERRATUM

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Erratum: Asymmetric synthesis from terminal alkenes by cascades of diboration and cross-coupling
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In Fig. 2b of this Letter, the structure of RuPhos should be depicted with a PCy₂ (not PCy₃) substituent. The correct structure for RuPhos is 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (CAS number 787618-22-8). Also, the first step of Fig. 6d should read 1% Pt(dba)₃, 1.2% (R,R)-L1. These errors have been corrected in the online versions of the paper.