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Regioselective *trans*-Carboboration of Propargyl Alcohols

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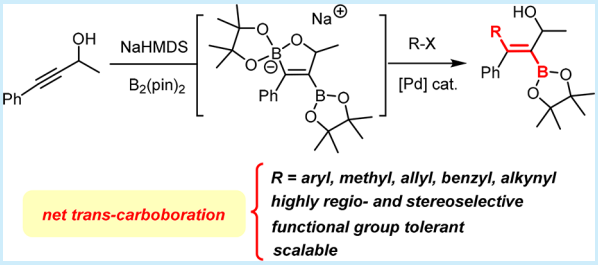
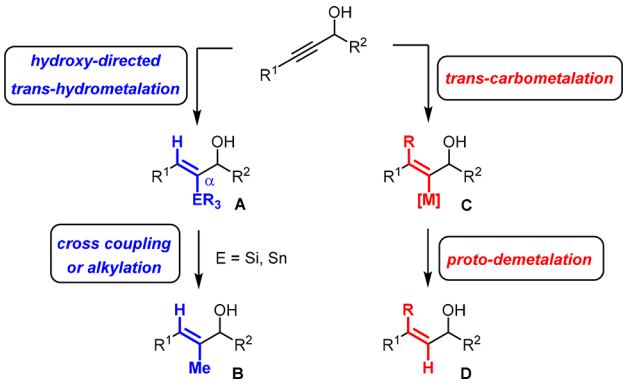
Supporting Information

ABSTRACT: Proper choice of the base allowed *trans*-diboration of propargyl alcohols with $B_2(pin)_2$ to evolve into an exquisitely regioselective procedure for net *trans*-carboboration. The method is modular as to the newly introduced carbon substituent (aryl, methyl, allyl, benzyl, alkynyl), which is invariably placed distal to the −OH group.



As a substructure of polyketide origin, allylic alcohols of type **B** are prominently featured in innumerous natural products. Our group has recently devised a new entry into this important motif based on a sequence commencing with a stereochemically unorthodox *trans*-hydrometalation of a propargyl alcohol followed by C-methylation of the resulting product **A** by formal cross-coupling (Scheme 1).[1,2] This methodology is

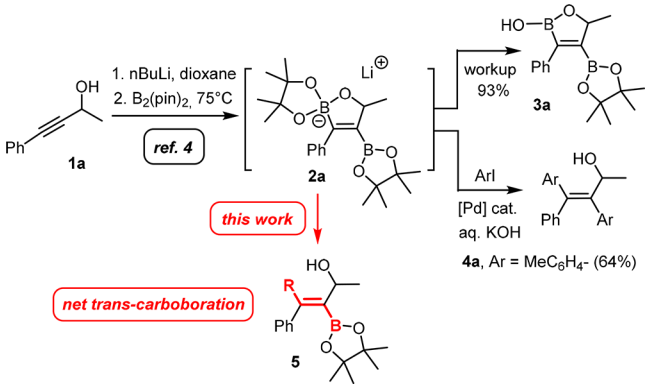
Scheme 1. Regio-complementary Functionalization of Propargyl Alcohols: Access to Polyketide Motifs B and D



very functional group tolerant and has already stood the test of total synthesis.[3] For its exquisite regioselectivity, however, the procedure does not broker formation of the isomeric motif **D** (R = Me), which is equally prominent in the polyketide estate.

Inspired by a literature report,[4] we saw an opportunity to attain compounds of type **D** via formal *trans*-carboboration, although broadly applicable manifestations of this type of reactivity are exceedingly rare.[5−10] Specifically, it is known that propargyl alcohols such as **1a**, on deprotonation with *n*BuLi, followed by reaction with $B_2(pin)_2$ in THF at increased temperature, undergo *trans*-selective diboration to give 4-borylated 1,2-oxaborolol derivatives **3a** after hydrolytic workup (Scheme 2).[4,11] The reaction likely passes through the mixed ate-complex **2a**; in one case, this putative intermediate has been

Scheme 2



subjected to subsequent Suzuki coupling[12] with 4-tolyl iodide in the presence of catalytic palladium and aqueous KOH as a promoter. In the present context, it is important to note that *both* boron sites of **2a** reacted under these conditions to give the tetrasubstituted alkene **4a** in 64% yield.[4] Because ate-complexes per se are competent intermediates for cross-coupling,[12] we surmised that addition of excess base might actually be unnecessary. Rather, advantage could be taken of the distinct chemical character to the two boron centers in a compound of type **2**: cross-coupling should occur selectively at the endocyclic borate site, whereas the tricoordinate boron moiety is expected to persist in the absence of external base; if so, many opportunities for downstream functionalization can be envisaged. As the borate site does not survive workup (see the formation of product **3a**), any such selective derivatization is contingent on the ability to generate and manipulate an ate-complex of type **2** in "one pot".

However, our initial efforts to intercept the putative intermediate **2** derived from the model substrate **1b** by simply

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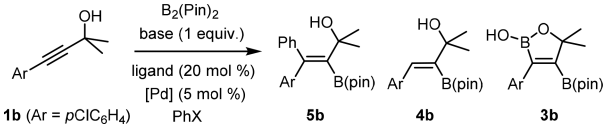
complementing the original recipe for *trans*-diboration[4] with an appropriate electrophilic partner (PhI, PhOTf, $[Ph_2I]OTf$, MeI, allyl bromide), a catalytic amount of a palladium source ($Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$), and an adequate phosphine ligand (PPh_3, PCy_3, P(*o*-tol)$_3$, P(2-furyl)$_3$, X-Phos, dppf, Xantphos, etc.) basically met with failure (Table 1, entries 1–4).

Table 1. Optimization of the *trans*-Arylboration[a]



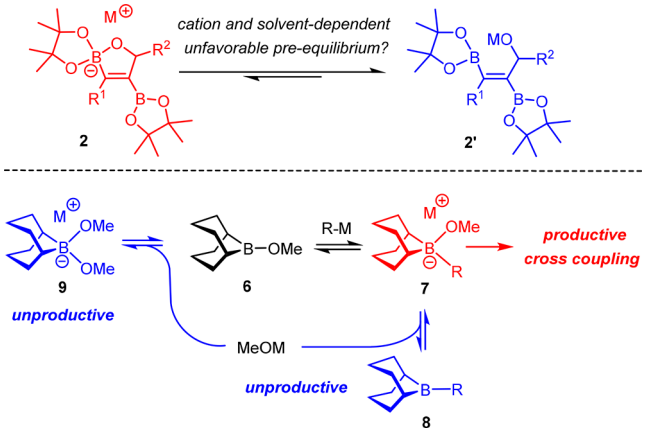
entry	base	PhX	[Pd]	ligand	**5b** (%)
1	BuLi	PhOTf	$Pd(OAc)_2$	dppf	0[b]
2	LiHMDS	PhOTf	$Pd(OAc)_2$	dppf	<10[c]
3	LiHMDS	PhI	$Pd(PPh_3)_4$		0
4	LiHMDS	Ph_2IOTf	$Pd_2(dba)_3$	P(*o*-tol)$_3$	31
5	NaHMDS	Ph_2IOTf	$Pd_2(dba)_3$	P(*o*-tol)$_3$	62[d]
6	NaHMDS	Ph_2IOTf	$Pd_2(dba)_3$	P(2-furyl)$_3$	81[d]
7	NaHMDS	Ph_2IOTf	$Pd_2(dba)_3$	P(2-furyl)$_3$	82[e]

[a]Unless stated otherwise, the reactions were performed in THF at 70 °C (bath temperature). [b]73% of **3b** was obtained after workup. [c]62% of **3b** and 9% of **4b** were formed. [d]In 1,4-dioxane. [e]In 1,2-dichloroethane + THF (10 equiv).

In most cases, the boracycle **3b** was formed as the major product; it was accompanied by varying amounts of the protodeborylated compound **4b** but only traces—if any—of the desired product **5b**.

In an attempt to rationalize this renitence, we wondered whether the borate subunit in **2** actually subsists under the chosen conditions. Earlier work from this laboratory on the "9-MeO-9-BBN variant" of the Suzuki reaction showed that the stability of ate-complexes of type **7** derived from the highly Lewis acidic **6** and polar organometallic reagents R–M is strongly cation-dependent (Scheme 3).[13,14] The ease of scrambling complex **7** as the competent nucleophile for cross-coupling into unproductive **8** and **9** roughly follows the order: $Na^+ \approx K^+ < Li^+ \ll MgX^+, ZnX^+$. The analogous equilibration of the borate unit in **2** is arguably more facile because it derives

Scheme 3. Presumed Equilibration of the 1,2-Oxaborolol Intermediate[a]



[a]The cation- and solvent-dependent scrambling of ate-complexes in the 9-BBN series provides relevant precedent.

from an inherently much less Lewis acidic $RB(OR)_2$ entity.[15] Under this premise, a lithium counterion is unlikely to be the ideal escort as the neutral boron species **2'** might be favored, which will not engage in cross-coupling in the absence of an external base. Therefore, we rescreened different counterions with the hope of stabilizing the critical borate intermediate **2**, even though the original report on *trans*-diboration had identified *n*BuLi as the optimal promoter.[4]

In accord with the empirical order observed in our previous study,[13,14] replacement of *n*BuLi by NaHMDS[16] opened the doorway to the desired net *trans*-carboboration chemistry (Table 1; for further details, see the Supporting Information). In a first foray, *trans*-diboration was merged with classical Suzuki-type sp^2–sp^2 coupling: to this end, the use of diaryliodonium salts in combination with $Pd_2(dba)_3$/P(2-furyl)$_3$ proved optimal. Although the reaction proceeded well in 1,4-dioxane in many cases, the use of 1,2-dichloroethane/THF (10 equiv) was found to be more general (Figure 1). The

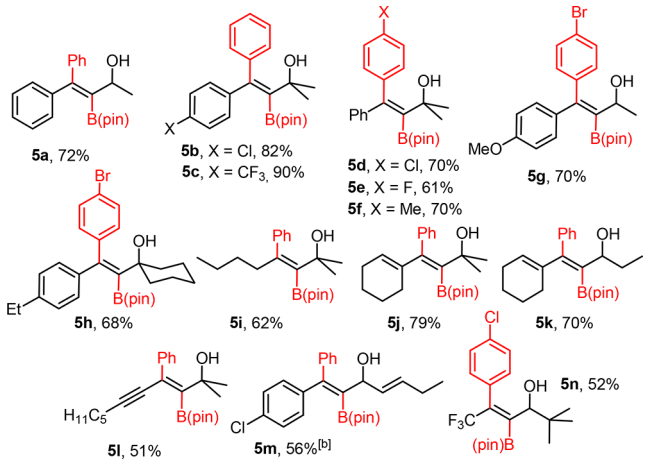


Figure 1. Products **5** formed by *trans*-arylboration of propargyl alcohols. [a]Reagents and conditions: NaHMDS (1 equiv), $B_2(pin)_2$ (1.1 equiv), $Pd_2(dba)_3$ (5 mol %), P(2-furyl)$_3$ (20 mol %), $[Ar_2I]OTf$ (2 equiv), 1,2-dichloroethane/THF, 60 °C. [b]In 1,4-dioxane.

crude products are usually very clean, but partial loss of material upon flash chromatography on silica diminishes the isolated yields. In the case of *tert*-propargyl alcohols as the substrates, the basic conditions can entail retro-alkynylation, leading to the formation of the corresponding ketones as minor impurities.

The functional group compatibility is remarkable in that preexisting aryl bromides or chlorides remained intact, regardless whether they originate from the propargyl alcohol substrate or from the transferred aryl substituent; conceivable oligomerization of the resulting products carrying a C–X as well as a C–B unit was not observed. This favorable outcome shows that the residual tricoordinate boron substituent in the product formed is "silent" in the absence of an external base, whereas the ate site of transient **2** (M = Na) readily engages in cross-coupling.[17] The excellent regioselectivity harnessed in reactions of 1,3-enyne or even 1,3-diyne substrates is an additional asset: only the propargylic triple bond undergoes carbometalation, whereas an additional site of unsaturation does not interfere.

The new procedure also lends itself to the introduction of a methyl substituent at the distal propargylic C atom; a slightly modified catalyst system ($Pd_2(dba)_3$/P(1-nap)$_3$ in 1,4-dioxane) in combination with MeI gave the best results (Figure 2 and Supporting Information). In all cases investigated, C–C bond

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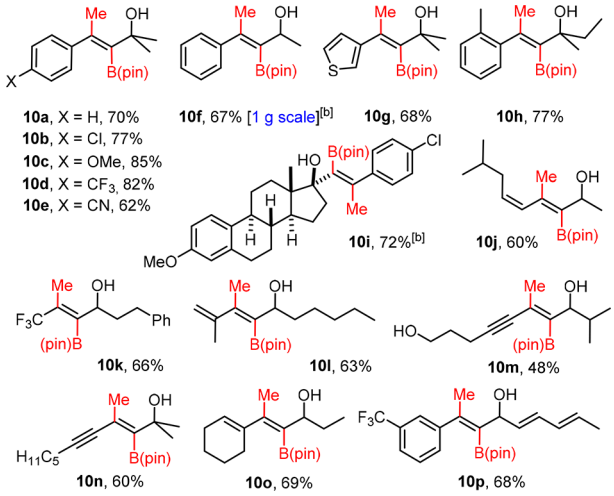


Figure 2. Products **10** formed by *trans*-methylboration of propargyl alcohols. [a]Reagents and conditions: NaHMDS (1 equiv), $B_2(pin)_2$ (1.1 equiv), $Pd_2(dba)_3$ (5 mol %), P(1-naphthyl)$_3$ (20 mol %), MeI (3 equiv), 1,4-dioxane, 60 °C. [b]With KHMDS.

formation occurred exclusively distal to the alcohol substituent. Extensive NMR investigations and crystallographic data confirmed connectivity and double bond geometry of the products (for the structures of compounds **3b**, **5b**,**n**, and **10i** in the solid state, see the Supporting Information). Once again, the observed regio- and stereoselectivities were excellent as were the functional group tolerance; moreover, the method scales well. It is important to note that O-methylation of the propargylic alcohol substrate did not interfere with productive *trans*-methylboration to any noticeable extent, which indicates a perfect orchestration of events along the reaction coordinate.

For this very reason, other reactive electrophiles are equally competent partners (Figure 3). Specifically, allyl and benzyl

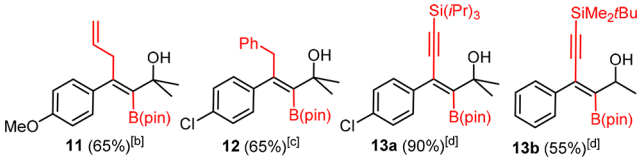
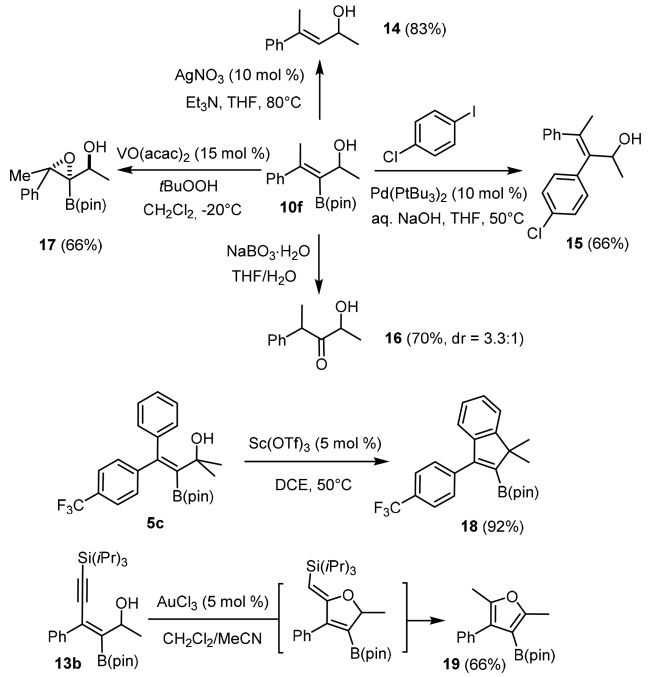


Figure 3. Additional *trans*-carboboration reactions. [a]Reagents and conditions: NaHMDS (1 equiv), $B_2(pin)_2$ (1.1 equiv), $Pd_2(dba)_3$ (5 mol %), supplemented by [b]Pd(P*t*Bu$_3$)$_2$ (10 mol %), allyl bromide (3 equiv), 1,4-dioxane, 75 °C; [c]P(1-naphthyl)$_3$ (20 mol %), BnBr (3 equiv), 1,4-dioxane, 60 °C; [d]P(2-furyl)$_3$ (20 mol %), $(R_3Si)C{\equiv}CBr$ (3 equiv), toluene/THF, 75 °C.

bromide could be used without O-alkylation intervening. Likewise, the incorporation of an alkynyl substituent was successful; the resulting enynes **13** are regioisomeric to the products formed by the transition-metal-free *trans*-alkynylboration using $RC{\equiv}C{-}B(pin)$ as the reagent recently described in the literature.[5] Overall, these data show that the concept underlying this new *trans*-carboboration manifold is pleasingly general, although its different incarnations require some catalyst optimization. Further extensions are subject to ongoing investigations in our laboratory.

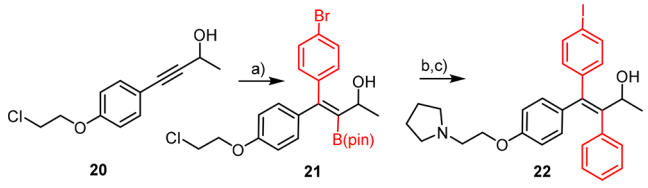
The alkenyl boronate products thus formed lend themselves to numerous downstream transformations;[18] only a few possibilities are shown in Scheme 4: (i) Although protodeborylation of **10** "wastes" the valuable C−B bond, it leads to

Scheme 4



the important polyketide motif **D** cited in the introduction; as shown for product **14**, the reaction can be readily achieved using catalytic $AgNO_3$.[19] (ii) Addition of aq NaOH "arms" the remaining boron atom in **10** for cross-coupling with a second electrophilic partner. In this manner, *two different hydrocarbyl residues* can be stitched *trans* to each other across the triple bond;[20] the resulting tetrasubstituted alkenes such as **15** are difficult to make in rigorously stereodefined format by other means.[21] This aspect is highlighted by the concise approach to compound **22**, which is a key metabolite of the nonsteroidal estrogen receptor modulator idoxifen (Scheme 5);[22] this

Scheme 5[a]



[a]Reagents and conditions: (a) $Pd_2(dba)_3$ (5 mol %), Pd(2-furyl)$_3$ (20 mol %), NaHMDS, $B_2(pin)_2$, $(4\text{-}BrC_6H_4)_2IOTf$, THF/1,2-dichloroethane, 60 °C, 62%; (b) PhI, aq KOH, (dppf)$PdCl_2$ (5 mol %), THF, 97%; (c) (i) pyrrolidine, EtOH, reflux; (ii) CuI, NaI, *N*,*N*′-dimethylethane,1,2-diamine, 1,4-dioxane, 110 °C, 75%

example further substantiates the compatibility of the method with alkyl as well as aryl halides. (iii) Oxidation of the C−B bond[23] in **10** unmasks the corresponding acyloin **16**, whereas directed epoxidation affords the building block **17** with high diastereoselectivity.[24] (iv) Addition of catalytic amounts of $Sc(OTf)_3$ as an oxophilic Lewis acid activates the allylic −OH group of **5c** without damaging the C−B bond as evident from the intramolecular Friedel−Crafts alkylation, furnishing the borylated indene **18**.[25] (v) Finally, we note that the triple bond of compounds **13** constitutes yet another valuable handle for functionalization; the formation of the tetrasubstituted bory-

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lated furan **19** with the aid of $AuCl_3$ as a carbophilic catalyst illustrates this aspect.[26,27]

In summary, a robust yet modular procedure for net carboboration of propargyl alcohols is reported. The transformation is distinguished by the unorthodox *trans*-addition mode and benefits from exquisite regio- and chemoselectivity. For these virtues and for the multifaceted character of the resulting products, we expect that the new method qualifies for many applications. Studies along these lines are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01225.

Experimental section including characterization data, NMR spectra of new compounds, and supporting crystallographic data (PDF)

Accession Codes

CCDC 1895345−1895348 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(17) ^{11}B NMR confirms the presence of a tricoordinate ($\delta_B \sim 31$ ppm, br) and a tetracoordinate boron center ($\delta_B = 11$ ppm) in the putative intermediate **2b** formed from **1b** on treatment with NaHMDS and $B_2(pin)_2$; for details, see the Supporting Information.

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