Enantioselective Catalysis Hot Paper

International Edition: DOI: 10.1002/anie.201600309
German Edition: DOI: 10.1002/ange.201600309

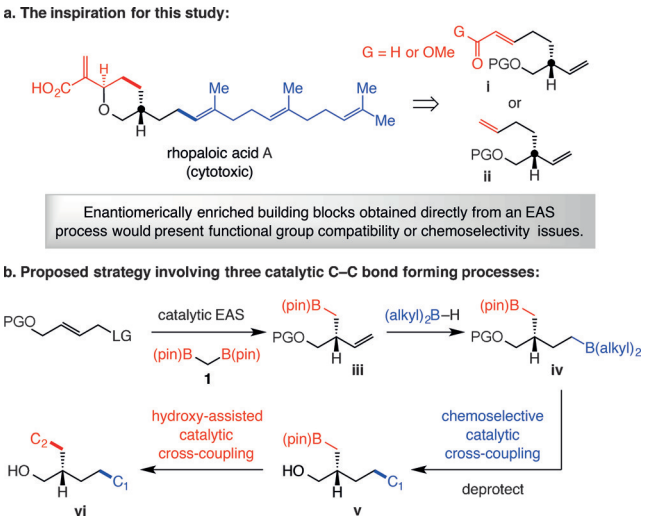
Catalytic S_N2'- and Enantioselective Allylic Substitution with a Diborylmethane Reagent and Application in Synthesis

*Ying Shi and Amir H. Hoveyda**

Abstract: *A catalytic method for the site- and enantioselective addition of commercially available di-B(pin)-methane to allylic phosphates is introduced (pin = pinacolato). Transformations may be facilitated by an NHC–Cu complex (NHC = N-heterocyclic carbene) and products obtained in 63–95 % yield, 88:12 to > 98:2 S_N2'/S_N2 selectivity, and 85:15–99:1 enantiomeric ratio. The utility of the approach, entailing the involvement of different catalytic cross-coupling processes, is highlighted by its application to the formal synthesis of the cytotoxic natural product rhopaloic acid A.*

Catalytic enantioselective allylic substitution (EAS) generates valuable products that contain a stereogenic center adjacent to a transposed alkene.[1] These processes may involve various organometallic reagents (e.g., Zn-, Mg-, or Al-based) and can be promoted by Cu complexes derived from chiral O-, N-, or P-based ligands or N-heterocyclic carbenes (NHCs).[1] Several applications in total synthesis have demonstrated their utility.[2] Lately, organoboron species have been adopted in this area because of their robustness and tolerance towards some of the more common organic functional groups (e.g., carboxylic esters or ketones). The groundbreaking advance was achieved by Sawamura and co-workers, who illustrated that trialkylboron molecules, formed in situ by hydroboration of α-olefins, can be made to participate in efficient S_N2'- and enantioselective phosphine–Cu-catalyzed EAS.[3] Allenyl–,[4] alkenyl–,[5] and propargyl–B(pin)[6] species (pin = pinacolato) have since been used in related NHC–Cu-catalyzed transformations. Another current development entails processes involving in situ generated allylcopper species that furnish modifiable boron-containing products.[7]

Nonetheless, key shortcomings remain, one of which revealed itself while we evaluated a possible route to the cytotoxic natural product rhopaloic acid A[8,9] (Scheme 1 a). Preparation of enantiomerically enriched **i** called for an organoboron reagent that requires site-selective hydroboration of a somewhat sensitive dienyl aldehyde (or ester derivative). The alternative pathway via diene **ii**, accessible by previously reported EAS methods,[10] would demand the differentiation of two terminal olefins, likely to generate difficult-to-separate isomeric mixtures. We thus envisioned



Scheme 1. Problems associated with the application of catalytic enantioselective allylic substitution (EAS) to the synthesis of rhopaloic acid A and a possible solution. LG = leaving group, PG = protecting group, pin = pinacolato.

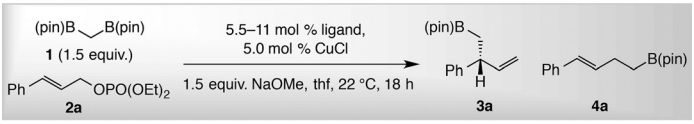
the possibility of a catalytic EAS with commercially available di-B(pin)-methane (**1**),[11] a member of a class of compounds conceived by Matteson[12] and co-workers that has been the focus of several studies following the pioneering work of Endo and Shibata.[13] Such processes would not only involve an organoboron reagent, they would deliver products containing a versatile C–B(pin) bond as well. We imagined a subsequent sequence entailing hydroboration of the EAS product (**iii**), furnishing **iv** with differentiable C–B bonds that could then be converted chemoselectively into **vi** by a pair of catalytic cross-coupling reactions (via **v**); the first would chemoselectively involve the dialkylboron site, and the second would benefit from the presence of the neighboring hydroxy group[14] that would then be deployed to form the pyran ring. Herein, we describe the realization of these plans.

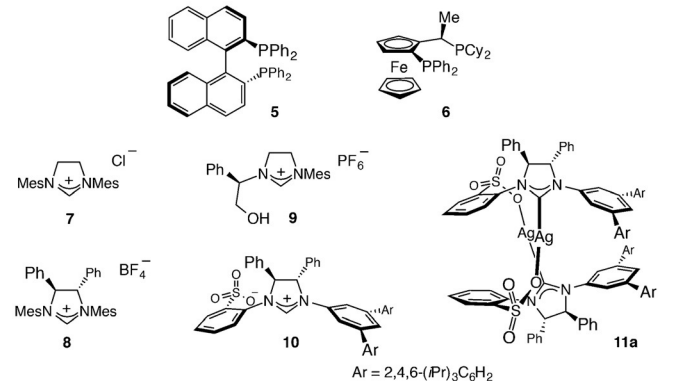
We favor allylic phosphates as substrates because the Lewis basic phosphate may bind to a chiral Cu complex, an association that is often pivotal to achieving high S_N2' and/or enantioselectivity.[4–6,7] We first found that EAS with only CuCl (no ligand) proceeds to 45 % conversion, affording the linear isomer (**4a**) exclusively (Table 1, entry 1). A chiral ligand would have to bind efficiently to the transition metal and/or the derived Cu complex to promote C–C bond formation considerably faster than a free Cu complex. We then determined that catalysts containing bisphosphines **5** and **6** generate the linear isomer (**4a**) selectively (entries 2 and 3). With imidazolinium salts **7**–**9**[15] (entries 4–6), **4a** was again favored. Matters improved with the NHC–Cu species derived

[*] Y. Shi, Prof. A. H. Hoveyda
Department of Chemistry, Merkert Chemistry Center
Boston College
Chestnut Hill, MA 02467 (USA)
E-mail: amir.hoveyda@bc.edu

Supporting information for this article can be found under http://dx.doi.org/10.1002/anie.201600309.

Table 1: Examination of different types of Cu complexes.[a]





Entry	Ligand (mol%)	Conv.[b] [%]	Yield[c] [%]	S_N2'/S_N2[b] (**3a**/**4a**)	e.r.[d]
1	–	45	21	<2:>98	NA
2	**5** (11)	80	76	2:98	NA
3	**6** (11)	65	41	7:93	ND
4	**7** (11)	>98	73	5:95	ND
5	**8** (11)	>98	54	20:80	ND
6	**9** (11)	>98	69	<2:>98	NA
7	**10** (11)	>98	77	76:24	97:3
8	**11** (5.5)	>98	83	95:5	97:3

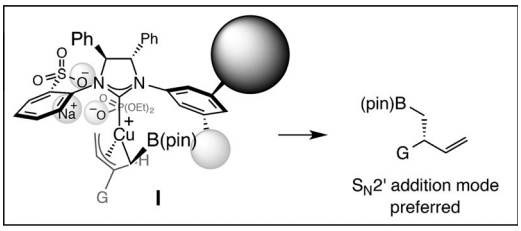
[a] Performed under N_2 atmosphere; ≤5% of the linear methoxy addition products observed in all cases. [b] Conversions and S_N2'/S_N2 ratios determined by analysis of ^{1}H NMR spectra of the unpurified mixtures; conv. (±2%) refers to the disappearance of **2a**. [c] Yields of isolated and purified products but as a mixture of **3a** and **4a** (±5%). [d] e.r. values determined by HPLC (±1%). See the Supporting Information for details. Mes = 2,4,6-$(Me)_3C_6H_2$, NA = not applicable, ND = not determined.

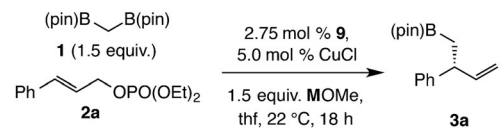
from sulfonate-containing **10** (entry 7), which afforded **3a** with 76% S_N2' selectivity and 97:3 enantiomeric ratio (e.r.). Based on the finding that **4a** is produced by a ligand-free Cu catalyst (entry 1), we used the crystalline and air-stable dimeric Ag complex **11a**,[6] one of a set of complexes found to exchange ligands with exceptional efficiency;[16] the branched isomer **3a** was thus formed in 95:5 S_N2'/S_N2 selectivity and 97:3 e.r. (entry 8).

The method has considerable range (Scheme 2). Various aryl-substituted substrates, including those with an electron-donating or -withdrawing substituent, whether it is at the *ortho*, *meta*, or *para* position (**12a**–**12j**), were converted into the corresponding primary alcohols in 61–95% yield (after oxidation), 88:12 to >98:2 S_N2'/S_N2 selectivity, and 85:15–99:1 e.r. There were no complications due to the aryl ketone substituent in **12i**, a functional unit not typically tolerated by the more nucleophilic organometallic species and, notably, in NHC–Cu-catalyzed transformations with a propargyl–B(pin) reagent.[6] The Cu catalyst remained operative in the presence of Lewis basic and potentially catalyst-deactivating N- and S-containing heterocyclic moieties: Pyridyl- and thienyl-substituted **12k** and **12l** were obtained with similar efficiency and selectivity. Alkyl-substituted allylic phosphates (e.g., **12m**) were suitable. The reaction with a 1,3-dienyl substrate was somewhat less site- and enantioselective but none of the side products from the formation of a benzylic C–C bond could be detected (**12n**). Allylsilane **12o** may be utilized in stereoselective synthesis.[17]

A distinct feature of the sulfonate-containing chiral NHC ligands (compare **8** and **9**) is that the Cu complexes promote highly S_N2'-selective reactions (see Table 1 and Scheme 2). This is congruent with the most recent mechanistic and computational studies,[6] revealing that the active species is likely a monodentate system wherein the sulfonate group, without the geometric constraints of chelation with the Cu center,[18] is oriented *anti* to the nearby phenyl substituent (**I**, Figure 1). Formation of an alkali metal bridge between the anionic tether of the chiral catalyst and the Lewis basic phosphate unit can engender a well-defined transition structure with the Cu–C bond disposed for S_N2' addition. There is indeed measurable dependence of branch selectivity on the identity of the base used (Figure 1). With the more Lewis acidic lithium salt, there was >98% S_N2' selectivity, albeit at lower yield owing to solubility issues. More of the achiral isomer was generated with the less Lewis acidic and larger potassium methoxide.

We then probed the feasibility of the application of this process to the synthesis of rhopaloic acid A[8,9] (Scheme 3). Organoboron compound **12p** was purified by column chromatography on silica gel and isolated in 89% yield, >98:2 S_N2'/S_N2 selectivity, and 96:4 e.r.; in this case, the Cu complex derived from **11b** gave higher enantioselectivity (84:16 e.r. with **11a**).[19] Hydroboration afforded diboron product **13**, which was coupled in situ with *E*-alkenyl iodide **14**[20] by a phosphine–Pd-catalyzed process,[21] affording **15** (>98% chemoselectivity, 87% yield). Removal of the silyl ether and NHC–Cu-catalyzed cross-coupling involving the alkyl–B(pin) moiety and commercially available allyl



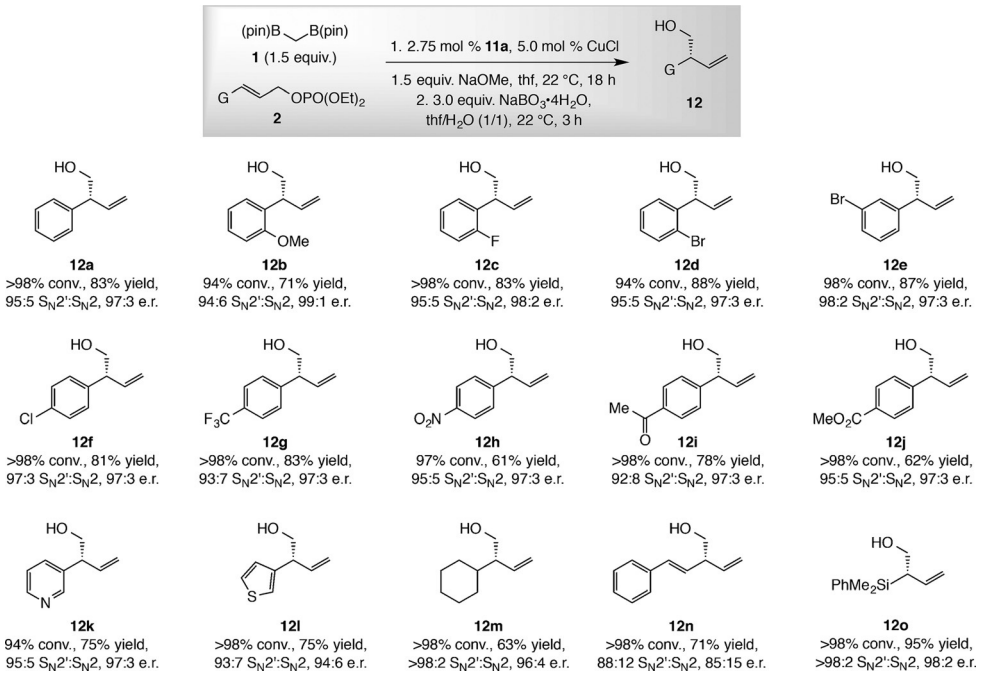


M = Li 29% conv., 29% yield, **>98:2 S_N2':S_N2**, 94:6 e.r.

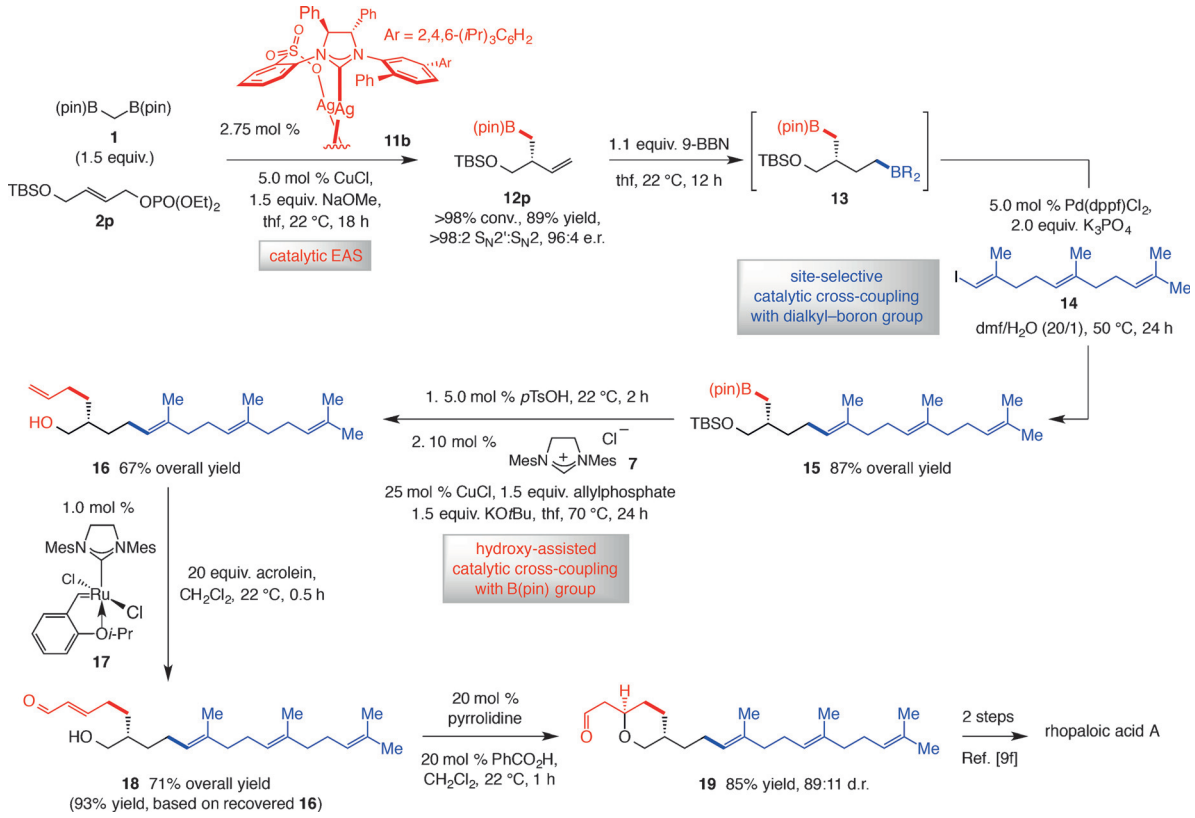
M = Na >98% conv., 83% yield, **95:5 S_N2':S_N2**, 97:3 e.r.

M = K >98% conv., 45% yield, **90:10 S_N2':S_N2**, 96:4 e.r.

Figure 1. Mechanistic model to account for the origin of stereoselectivity and evidence pointing to the significance of the counterion of the basic reagent used. See the Supporting Information for details.



Scheme 2. Scope of the method. Conversions refer to the consumption of allylic phosphate and were determined by analysis of the ^{1}H NMR spectra of the unpurified reaction mixtures (the same for the S_N2'/S_N2 ratios); ≤5% of the linear methoxy addition products observed in all cases. For **12h–12k**, the mixture was treated with $NaIO_4$/NH_4OAc at 22 °C for 1 h (acetone/H_2O, 1:1). Yields refer to the isolated and pure S_N2' isomers, except for **12k** (5% linear product isomer), **12l** (3% boryl addition side product), and **12n** (3% product from the *Z* isomer of the substrate). Enantioselectivities were determined by HPLC analysis. See the Supporting Information for details.



Scheme 3. Application to the enantioselective synthesis of rhopaloic acid A. d.r. = diastereomeric ratio. See the Supporting Information for details. 9-BBN = 9-borabicyclo[3.3.1]nonane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, *p*TsOH = *para*-toluenesulfonic acid, TBS = *tert*-butyldimethylsilyl.

phosphate delivered tetraene **16** in 67% overall yield. As noted earlier, this latter process strongly benefits from the proximal hydroxy group:[14] there was <2% C–C bond formation with silyl ether **15**.[22] Cross-metathesis with Ru complex **17** and acrolein led to enal **18** (71% overall yield). Intramolecular conjugate addition[23] delivered pyran **19**, which has previously been converted into rhopaloic acid A in 85% yield and 89:11 diastereomeric ratio (d.r.).[9f]

To conclude, we have introduced an EAS method involving commercially available and functional-group-tolerant di-B(pin)-meth-

ane as the reagent, furnishing products efficiently and with exceptional S_N2' and enantioselectivity. We have demonstrated that in combination with chemoselective and hydroxy-assisted catalytic cross-coupling transformations, the EAS method can efficiently provide access to an assortment of useful organic molecules in high enantiomeric purity.

Acknowledgements

Financial support was provided by the NIH (GM-47480) and the NSF (CHE-1362763).

Keywords: allylic substitution · boron · copper · enantioselective synthesis · N-heterocyclic carbenes

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 3455–3458
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Received: January 12, 2016
Published online: February 4, 2016

