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Practical, efficient, and broadly applicable synthesis of readily differentiable vicinal diboronate compounds by catalytic three-component reactions

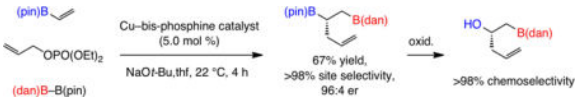
Suttipol Radomkit, **Zhenxing Liu**, **Anna Closs**, **Malte S. Mikus**, and **Amir H. Hoveyda**[1]

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, USA

Abstract

A practical, efficient and broadly applicable catalytic method for synthesis of easily differentiable vicinal diboronate compounds is presented. Reactions are promoted by a combination of PCy_3 or PPh_3, CuCl and LiO*t*-Bu and may be performed with readily accessible alkenyl boronate substrates. Through the use of an alkenyl–B(pin) (pin = pinacolato) or alkenyl– B(dan) (dan = naphthalene-1,8-diaminato) starting material and commercially available (pin)B– B(dan) or $B_2(pin)_2$ as the reagent, a range of vicinal diboronates, including those that contain a B-substituted quaternary carbon center, may be prepared in up to 91% yield and with >98% site selectivity. High enantioselectivities can be obtained (up to 96:4 er) through the use of commercially available chiral bis-phosphine ligands for reactions that afford mixed diboronate products.

Graphical Abstract



Keywords

Allylic substitution; Boron; Catalysis; Copper; Enantioselective synthesis; Vicinal diboron compounds

1. Introduction

Organoboron compounds that contain vicinal C–B(pin) (pin = pinacolato) bonds are of considerable value in chemical synthesis and may be accessed through diboron additions to alkenes catalyzed by Pd- or Pt-based complexes,[1] metal alkoxides[2] or carbohydrate-based diboron species.[3] A primary C–B bond may be induced to undergo cross-coupling reactions site selectively because of activation provided by the neighboring, more substituted C–B(pin) unit.[4] In 2009 we showed that vicinal diboronate compounds may be synthesized through exceptionally site-selective (<2% *geminal* diboronate) and stereoselective (*syn*) Cu–B(pin) addition to alkenyl–B(pin) moiety; the resulting Cu–C bond was then reacted with

[1]Corresponding author: Tel.: +1 617 552 3618, amir.hoveyda@bc.edu (A. H. Hoveyda).

deuterio-methanol *in situ*, affording **ii** with complete diastereoselectivity (>98% retention of stereochemistry; Scheme 1a).[5] More recently, we envisioned that three-component fusion of an alkenyl–B(pin) with (dan)B–B(pin) (dan = naphthalene-1,8-diaminato)[6] and an allyl electrophile (in place of MeOH) might deliver, through site-selective Cu–B(dan) addition/ allylic substitution,[7] valuable easy-to-differentiate vicinal diboronate products (e.g., **viii**, Scheme 1b). Specifically, we surmised that the intermediate copper-alkoxide (**iii**, Scheme 1b) should favor interaction with the more Lewis acidic B(pin) unit (**iv**), which would afford a Cu-B(dan) complex (**v**) along with products containing a terminal B(dan) and an internal B(pin) group (**vi**). Differentiation of a B(pin) and a B(dan) moiety would be easier [vs two B(pin) groups]; as a result, the method would offer a distinct advantage, especially when selective functionalization at the typically less reactive secondary C–B bond is desired [e.g., internal B(pin) and a terminal B(dan) group]. Alternatively, a sequence involving an alkenyl–B(dan) substrate and $B_2(pin)_2$ would furnish the complementary diboron isomer [i.e., primary C–B(pin) and secondary C–B(dan)]. Herein, we disclose the realization of these objectives.

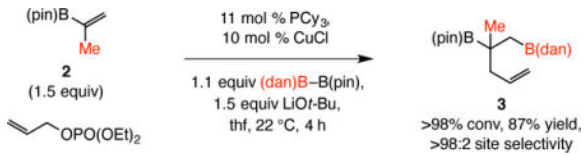
2. Results and discussion

We first probed the possibility of a three-component process with vinyl–B(pin), allylphosphate and (dan)B–B(pin) (Table 1).[8] With NaO*t*-Bu as the base but without a ligand there was near complete (~95%) disappearance of the limiting reagent [(vinyl– B(pin)] but **1a** was obtained in 39% yield (entry 1). Efficiency improved substantially with the addition of 11.0 mol % PPh_3, as vicinal diboronate **1a** was isolated in 78% yield (entry 2). Evaluation of other alkali metal alkoxides (entries 3–4) and several mono- and bidentate phosphines with distinct steric and electronic attributes (entries 5–9) indicated that the combination of PCy_3 and LiO*t*-Bu is optimal (>98% conv, 84% yield; entry 6, Table 1). Reactions with N-heterocyclic carbene (NHC) complexes of copper were less efficient (e.g., entry 10), probably arising from competitivereaction of the Cu–B(dan) with allylphosphate to afford allyl–B(dan)[9] (i.e., lower chemoselectivity).

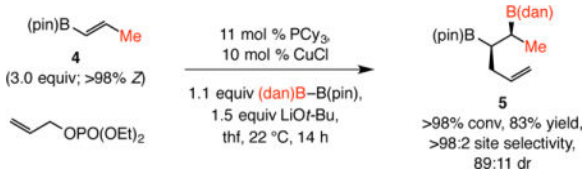
A variety of 2-substituted allylic phosphates, including those that contain a versatile allyl silyl ether (**1c**), an alkenyl silyl group (**1e**), a furyl moiety (**1f**), or a chloride or bromide that might be used in catalytic cross-coupling (**1g**, **1h**), may be used (Scheme 2). Products containing a primary C–B(dan) bond and a secondary C– B(pin) moiety were generated with complete selectivity: <2% of the alternative isomer could be detected based on ^{1}H NMR spectra of the unpurified mixtures. The identity of the products was ascertained by determination of X-ray structures of **1d** and **1f** (Scheme 2).

As the transformation in Eq. 1 illustrated, the method is applicable to the formation of a boron-substituted quaternary carbon center.[10] Thus, diboronate **3** was obtained in 87% yield after four hours at room temperature. Conversion of the commercially available 1,2-disubstituted alkenylboronate **4** to 5, isolated in 83% yield, further highlights the utility of the method (Eq. 2). This latter transformation is especially notable; although longer reaction time was needed (14 vs 1–4 h), site- and diastereoselectivity levels were high [>98:2 vicinal:geminal, 89:11 diastereomeric ratio (dr)]. Similarly noteworthy is the transformation with vinyl–B(dan) (Eq. 3), accessible in a single step from vinyl–B(pin), leading to the

formation (>98% conv, 1 h) of the transposed diboronate product **6** in 88% yield, the identity of which was confirmed by X-ray crystallography.

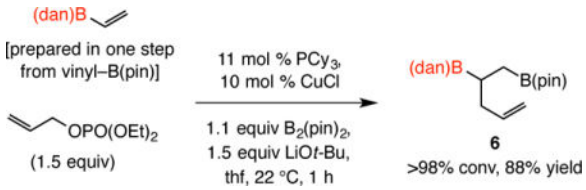


(1)

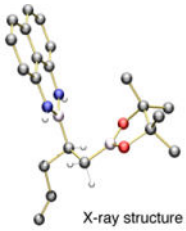


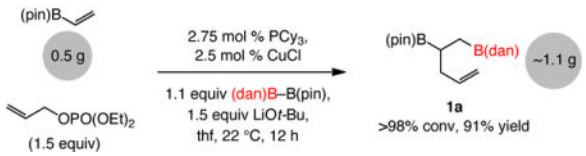
(2)

Reactions are scalable, as illustrated by the example in Eq. 4. The transformations were performed with 2.5 mol % of the phosphine–copper complex (vs 10 mol % used above), although this required a longer reaction time (12 vs 2 h).



(3)





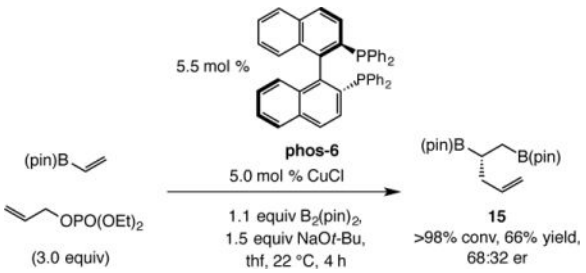
(4)

The C–B(pin) bond of the bis-boronate products can be site selectively oxidized to afford the corresponding alcohol products (e.g., **7** and **8**, Scheme 3). The remaining C–B(dan) bond can then be converted to a C–C bond,[11] as the examples in Scheme 3, leading to the formation of silyl ethers **10** and **12** illustrate. In these latter transformations, C–B(pin) oxidation/B(dan)-to-B(pin) exchange/silyl ether formation afforded products **9** and **11** in 71% and 65% yield, respectively, after a single purification. The state-of-the-art regarding direct conversion of a C–B(dan) to a C–C bond by catalytic cross-coupling is less advanced [vs those containing a C–B(pin)];[6,12] future developments in this key area will likely elevate the utility of the approach.

Another example of product modification takes advantage of recently developed catalyst-controlled stereoselective cross-metathesis approaches for accessing alkenyl halide compounds (Scheme 4).[13] *Z*-Alkenyl chloride **13**, offers three distinct sites for highly site-selective catalytic cross-coupling reactions, and alkenyl fluoride **14** should allow access to various other desirable organofluorine compounds.[14]

Initial studies indicate that high enantioselectivity may be achieved with this class of transformations through the use of commercially available chiral bis-phosphine ligands (Scheme 5).[15] Thus, diboronates **1a** and **6** were obtained in 96:4 and 86:14 er, respectively. The examples involving **1b**, silyl allyl ether **1c** (47% yield and 94:6 er) as well as styrene **1d**, and **3**, which contains a B-substituted quaternary carbon stereogenic center (57% yield, 87:13 er) represent additional promising results in regards to accessing readily differentiable vicinal diboronate products enantioselectively. The identity of diboronate product **3** was ascertained through X-ray crystallography.[15]

It merits note that transformations affording mixed bis–B(pin) products[16] do not proceed with similarly high levels of enantomeric purity. For example, as presented in Eq. 5, the highest enantioselectivity that we were able to obtain in the formation of diboronate **15** was 68:32 (vs 96:4 and 86:14 er for **1a** and **6**).



(5)

3. Conclusions

In summary, the catalytic multicomponent processes described here offer a practical, direct and strategically distinct entry to a variety of easily differentiable vicinal diboronate compounds. The ability for facile access to either regioisomeric product with a C– B(pin) and an adjacent C–B(dan) bond that can be site selectively modified is a noteworthy feature

of the new approach. Future studies will be aimed at expanding the scope of the enantioselective variants and applications towards development of other catalytic protocols that deliver versatile and valuable organoboron compounds are in progress.

4. Experimental section

4.1. General

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.xxxxx.

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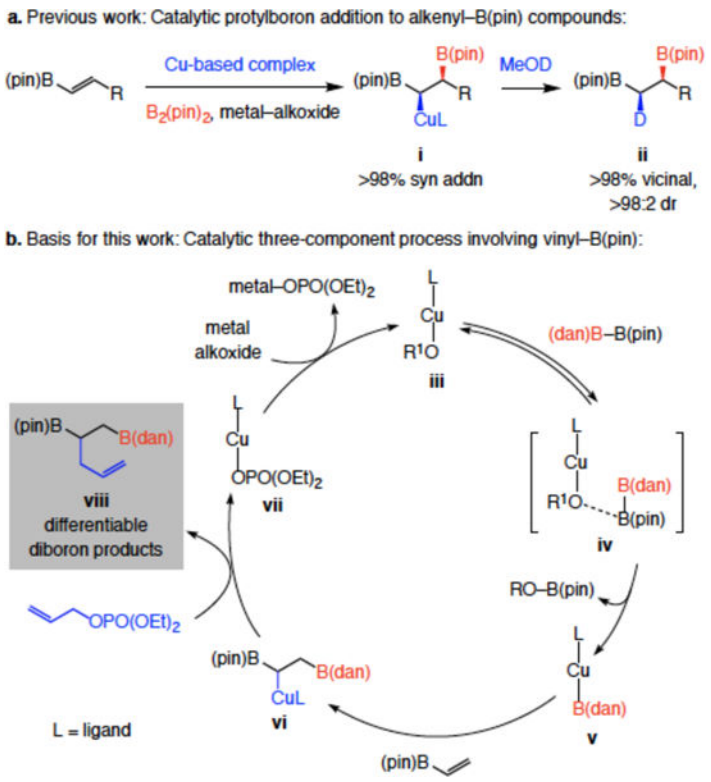
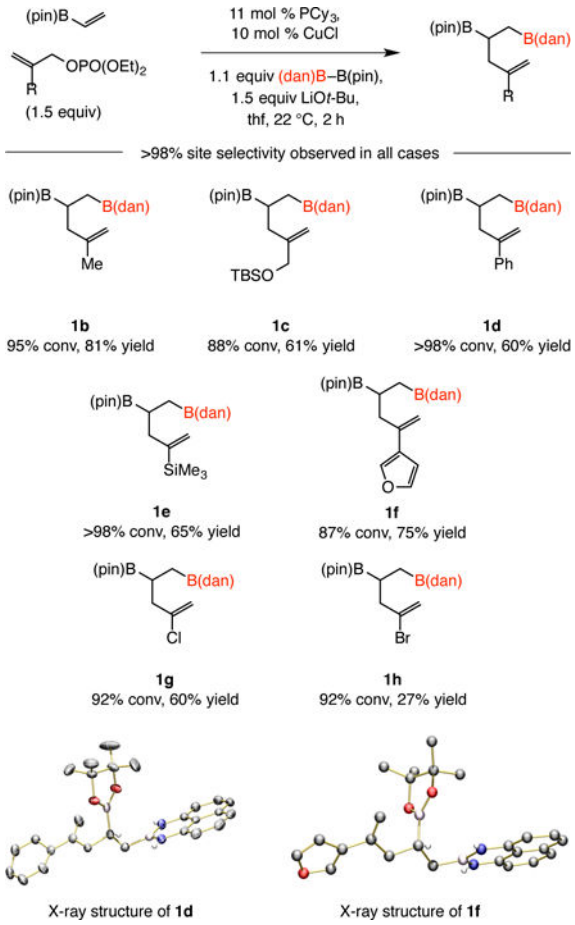
15. See the Supporting Information for results of screening studies

16. See the Supporting Information for the full range of reactions affording vicinal di–B(pin) compounds



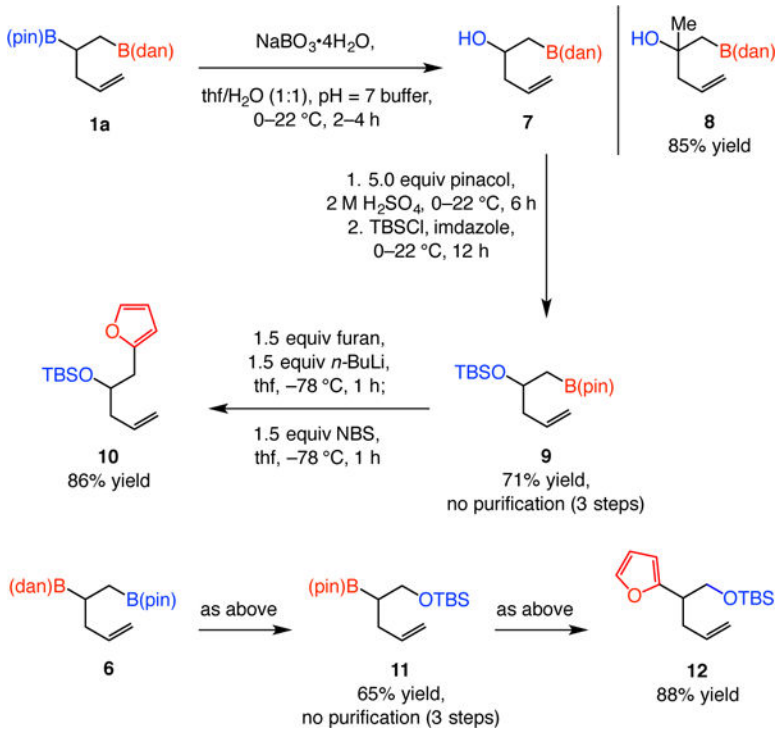
Scheme 1.

Related previous work and the basis for the present studies.



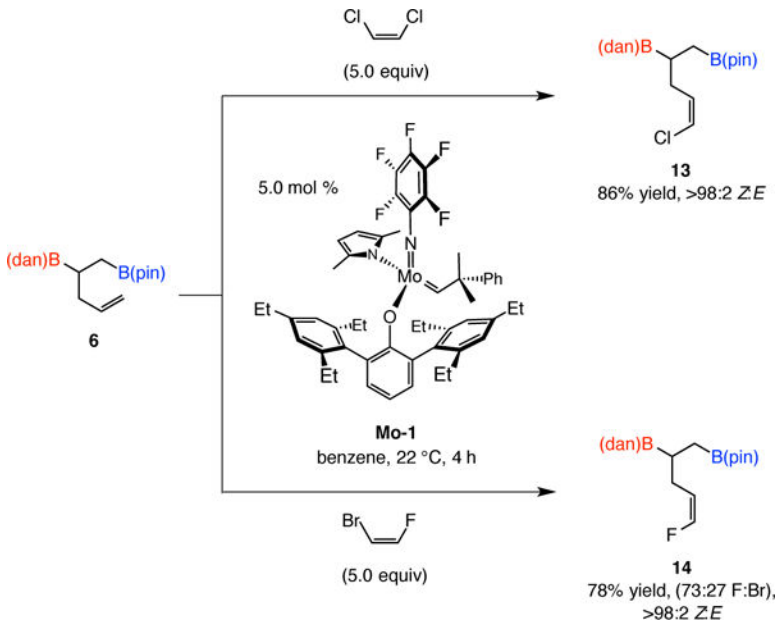
Scheme 2.

Reactions with 2-substituted allylic phosphates. See the Supporting Information for experimental and analytical details.



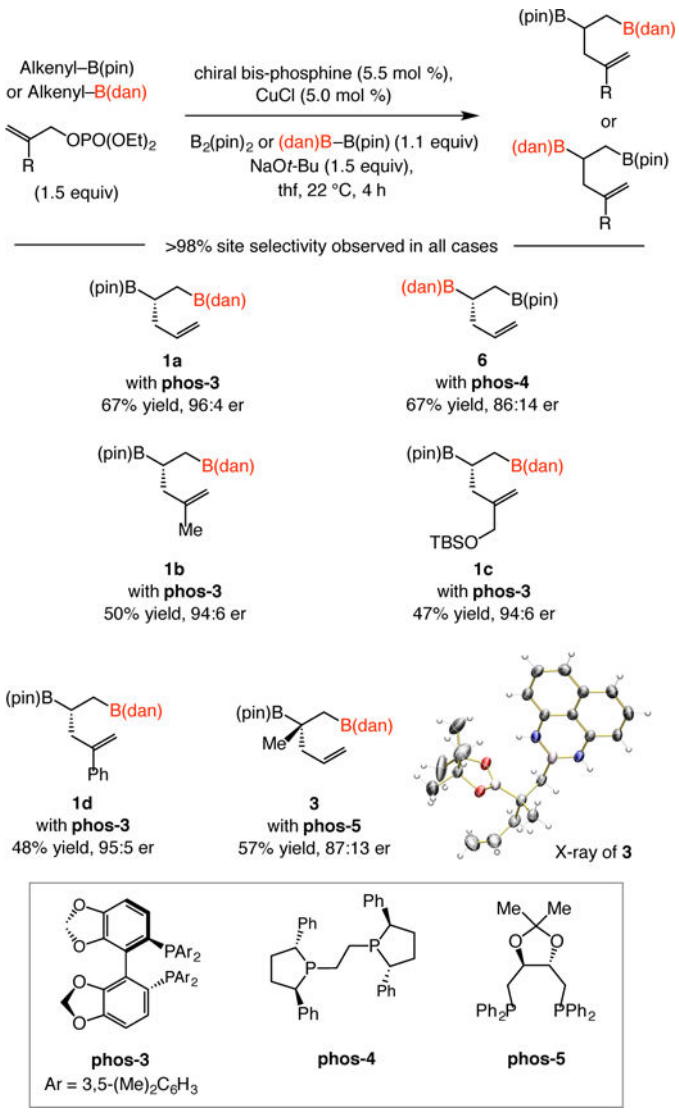
Scheme 3.

Functionalization through chemoselective oxidation and cross-coupling. See the Supporting Information for experimental and analytical details.



Scheme 4.

Functionalization through catalytic *Z*-selective cross-metathesis reactions. See the Supporting Information for experimental and analytical details.

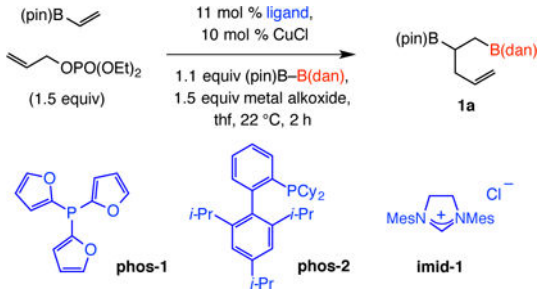


Scheme 5.

Catalytic enantioselective variants. For **3**, 1.5:1 ratio of vinyl– B(pin): allylphosphate was used; see the Supporting Information for experimental and analytical details.

Table 1

Examination of different Cu complexes.[a]



entry	ligand	alkoxide	conv (%)[b]	yield (%)[c]
1	none	NaO*t*-Bu	93	39
2	PPh_3	NaO*t*-Bu	>98	78
3	PPh_3	LiO*t*-Bu	>98	81
4	PPh_3	KO*t*-Bu	91	58
5	$P(nBu)_3$	LiO*t*-Bu	96	77
6	PCy_3	LiO*t*-Bu	>98	84
7	**phos-1**	LiO*t*-Bu	50	19
8	**phos-2**	LiO*t*-Bu	43	21
9	*rac*-binap	LiO*t*-Bu	74	61
10	**imid-1**	LiO*t*-Bu	86	18

[a] Performed under N2 atm.

[b] Determined by analysis of 1H NMR spectra of unpurified mixtures; conv. (±2%) refers to disappearance of vinyl–B(pin).

[c] Yields of isolated and purified products (±5%). See the Supporting Information for details. Abbreviations: pin, pinacolato; Mes, 2,4,6-$(Me)_3C_6H_2$, dan = naphthalene-1,8-diaminato.