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Regioselective Allene Synthesis and Propargylations with Propargyl Diethanolamine Boronates

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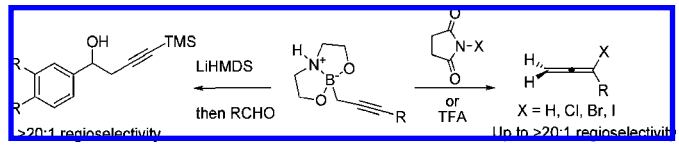
ABSTRACT



The utility of propargyl diethanolamine boronates as reagents for the preparation of allenes and homopropargylic alcohols is presented. Protonolysis with TFA and electrophilic substitution with *N*-halosuccinimides proceeded with inversion to provide the corresponding allene in high yield and regioselectivity. Alternatively, the propargylation of aldehydes was achieved with use of the in situ generated lithiated complex.

Organoboronic acids and their derivatives are valuable synthetic building blocks.[1] Typically, the utility of these reagents is achieved through a Lewis base interaction with a Lewis acidic boron atom. Such reactivity is exemplified through boron-based transmetalations,[2] Petasis reactions,[3] Matteson homologation,[4] and the closed six-membered transition states proposed for allenylations, allylations, and propargylations.[5] However, organoboronic acids pose difficulties in characterization due mainly to the ease with which they dehydrate and oligomerize.[2b] While boronic esters are more stable toward oligomerization, they are still susceptible to hydrolysis and oxidation upon prolonged exposure to air. Derivatization of organo-boronic acids or esters to the crystalline trifluoroborate salts,[2b,6] diethanolamine based[7,8] or *N*-methyl-iminodiacetic acid (MIDA)[8] complexes dramatically facilitates the isolation of the organoboron compounds

(1) Hall, D. G. *Boronic Acids*; Wiley-VCH: Weinheim, Germany, 2005.

(2) For examples see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286. (c) Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F.; Pericas, M. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1098–1101. (d) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603. (e) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468–14470. (f) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345–347.

(3) (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583–586. (b) Lou, S.; Schaus, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 6922–6923.

(4) For examples see: (a) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588–7590. (b) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591. (c) Brown, H. C.; Jayaraman, S. *J. Org. Chem.* **1993**, *58*, 6791–6794. (d) Brown, H. C.; Roy, C. D.; Soundararajan, R. *Tetrahedron Lett.* **1997**, *38*, 765–768. (e) Fang, G. Y.; Wallner, O. A.; Blasio, N. D.; Ginesta, X.; Harvey, J. N.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2007**, *129*, 14632–14639. (f) Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 165–168. (g) Berree, F.; Gernigon, N.; Hercouet, A.; Lin, C. H.; Carboni, B. *Eur. J. Org. Chem.* **2009**, 329–333.

(5) For examples see: (a) Wang, K. K.; Liu, C. *J. Org. Chem.* **1985**, *50*, 2578–2580. (b) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483–486. (c) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236–1240. (d) Hernandez, E.; Burgos, C. H.; Alicea, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 4089–4091. (e) Paton, R. S.; Goodman, J. M.; Pellegrinet, S. C. *Org. Lett.* **2009**, *11*, 37–40.

(6) For a review see: Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288–325.

(7) Brown, H. C.; Prasad, J. V. N. V. *J. Org. Chem.* **1986**, *51*, 4526–4530, and references cited therein.

(8) (a) Mancilla, T.; Carrillo, L.; Reducindo, M. de la P. *Polyhedron* **1996**, *15*, 3777–3785, and references cited therein. (b) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717. (c) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466–468. (d) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085. (e) Contreras, R.; Garcia, C.; Mancilla, T. *J. Organomet. Chem.* **1983**, *246*, 213–217.

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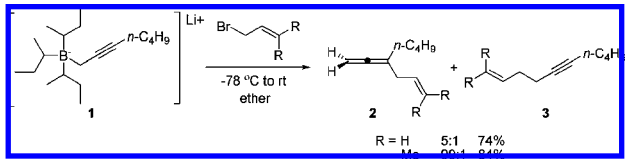
Scheme 1. Precedent Regioselective Alkylation with Propargyl Boronates (ref 10)

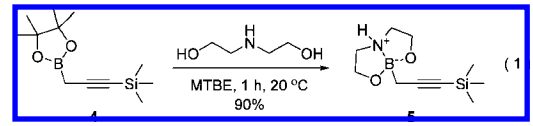


and increases the stability of these reagents to air, moisture, and numerous reaction conditions. X-ray analysis of the *N*-methyldiethanolamine and MIDA organo-boronates demonstrated bonding between the boron and nitrogen atoms.[8] According to Gutmann's rules,[9] the boron "ate" character of the diethanolamine derivatives should enhance the nucleophilicity of the organic component. For example, propargyl boron "ate" complexes are reasonably nucleophilic, and the regioselective alkylation with allyl bromides and addition to carbonyl species for the generation of allenes have been demonstrated (Scheme 1).[10] Although the diethanolamine-type derivatives have shown utility for Suzuki−Miyaura couplings,[11] hydrolysis, and transesterifications,[12] limited extension to directly reacting the activated organic functionality with electrophiles has been reported.[13] Herein we report the regioselective electrophilic substitution of propargyl diethanolamine (DEA) boronates for the preparation of allenes and propargylation of aldehydes with use of the lithiated reagent.

Reaction of propargyl borolane **4**[14] with diethanolamine in MTBE afforded the DEA boronate **5**, which directly crystallized from the reaction mixture (Scheme 2). The DEA propargyl boronate **5** can be stored at ambient temperature for months without detectable degradation. Our initial interest in the DEA derivative was as an intermediate to facilitate transesterification.[12] However, under numerous acidic conditions, the major product identified was trimethylsilylallene in surprisingly high regioselectivity.

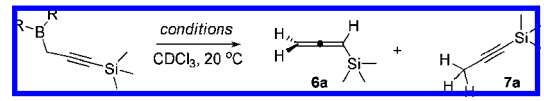
Conditions to effect protonolysis of both the pinacolyl and DEA propargyl boronates were further investigated (Table 1). Treatment of propargyl borolane **4** with ethanol or TFA

Scheme 2. Preparation of DEA Boronate **4**



in chloroform afforded only partial conversion to the trimethylsilyl allene and propyne in low yield (entries 1−3). Alternatively, protonolysis of DEA propargyl boronate **5** with a strong anhydrous acid such as TFA afforded the allenyl product **15** in 90% yield and >40:1 regioselectivity (entry 9). The protonolysis with a strong aqueous acid afforded a lower yield and poor regioselectivity (entry 6). This contrast can be rationalized by a competitive hydrolysis under aqueous conditions and subsequent nonselective protonolysis of the resulting boronic acid.

Table 1. Conditions Examined for the Protodeborolation of Propargyl Boronates



entry	substrate	conditions[a]	regioselectivity **6**:**7**[b]	yield,[c] %
1	**4**	EtOH (1 equiv) 18 h	1.0:1.1	6[d]
2[e]		EtOH (3 equiv) 18 h	1:1.3	30
3		TFA (1 equiv) 18 h	<1:40	23[f]
4	**5**	EtOH (1 equiv) 18 h	1.0:1.0	5
5		H_2O[g] 18 h	1:7.9	83
6		HCl[h] (1 equiv) 18 h	1:1.5	69
7		AcOH (1 equiv) 6 h	1:3.5	69
8		TFA (1 equiv) 1 h	>40:1	73
9		TFA (2 equiv) 0.25 h	>40:1	90
10		MsOH (1 equiv) 1 h	>40:1	65

[a] Time until complete conversion or until 18 h. [b] Ratio determined by GC and ^{1}H NMR analysis. [c] Assay yield determined by GC or ^{1}H NMR with dimethyl fumarate as an internal standard. [d] ~80 mol % starting material remaining. [e] Reaction conducted at 60 °C. [f] <10 mol % starting borolane remaining. [g] 30 vol % H_2O to $CDCl_3$. [h] 3 M HCl (aq). TFA = trifluoroacetic acid. MsOH = methanesulfonic acid.

After optimizing the protonolysis, examination of other DEA propargyl boronates was initiated (Table 2). The silylated DEA propargyl boronates underwent rapid protonolysis in good to high regioselectivity with excellent yields (entries 1−5). In general, the regioselectivity for the protodeborolation was sensitive to steric effects wherein the highest selectivities were observed with the smaller alkynyltrialkylsilyl substituent (TMS, TES, $PhMe_2Si$ > TBS > TIPS). The alkyl-substituted DEA propargyl boronate **12** also reacted with TFA but required 18 h and proceeded with no selectivity.

The propargyl DEA boronates are also reactive for halodeborolation. Typically, electrophilic substitution of aryl boronic acids[15] or DEA boronates[13a,b] with halides provides the corresponding *ipso*-substituted product. Treatment of propargyl borolane **4** with NBS at 55 °C for 15 h afforded

(9) Jenson, W. B. *The Lewis Acid-Base Concepts*; John Wiley & Sons: New York, 1980; Chapter 4.

(10) Pearson, N. R.; Hahn, G.; Zweifel, G. *J. Org. Chem.* **1982**, *47*, 3364–3366.

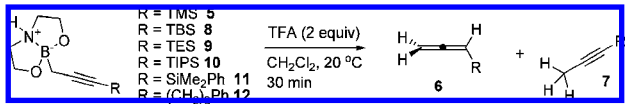
(11) For examples see: (a) Bouillon, A.; Lancelot, J.-C.; Sopkova-de Oliveira Santos, J.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043–10049. (b) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685–687. (c) Gros, P.; Doudouh, A.; Fort, Y. *Tetrahedron Lett.* **2004**, *45*, 6239–6241. (d) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695–4698.

(12) For examples see: (a) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348. (b) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943–11952. (c) Jung, M. E.; Lazarova, T. I. *J. Org. Chem.* **1999**, *64*, 2976–2977.

(13) For examples of flourinations see: (a) Diorazio, L. J.; Widdowson, D. A.; Clough, J. M. *Tetrahedron* **1992**, *48*, 8073–8088. (b) Clough, J. M.; Diorazio, L. J.; Widdowson, D. A. *Synlett* **1990**, 761–762. For an example of a cycloaddition see: (c) Davies, C. D.; Marsden, S. P.; Stokes, E. S. E. *Tetrahedron Lett.* **2000**, *41*, 4229–4233.

(14) Hoffmann, R. W.; Brinkmann, H.; Frenking, G. *Chem. Ber.* **1990**, *123*, 2387–2394.

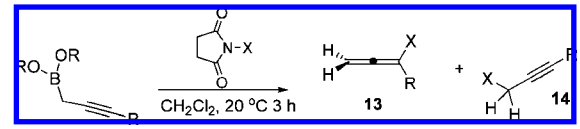
Table 2. Regioselective Protonolysis of Propargyl DEA Boronates



entry	boronate	major product[a]	regioselectivity **6:7**[b]	yield[c]
1	**5**	**6a** TMS	>20:1	89%[d]
2	**8**	**6b** TBS	19:1	78%
3	**9**	**6c** TES	>20:1	90%
4	**10**	**6d** TIPS	8:1	83%
5	**11**	**6e** $SiMe_2Ph$	>20:1	97%
6[e]	**12**	**6f**	1:1	84%

[a] Major regioisomer product. [b] Regioselectivity determined by ^1H NMR. [c] Isolated yields. [d] The volatile oil was isolated as a solution in $CDCl_3$ and yield was determined by ^1H NMR assay with internal standard. [e] Reaction conducted for 18 h. TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl.

Table 3. Regioselective Halogenation of Propargyl DEA Boronates



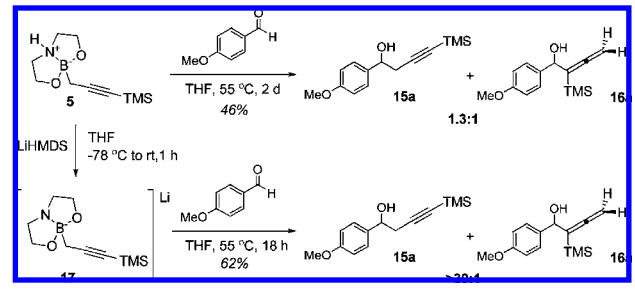
boronate	reagent	major product[a]	regioselectivity **13:14**	yield[c]
4	NBS[d]	**13a** Br, TMS	7:1	20%
5	NBS	**13a**	>20:1	90%
	NCS[d]	**13b** Cl, TMS	>20:1	79%
	NIS	**13c** I, TMS	8.4:1	89%
11	NBS	**13d** Br, $SiMe_2Ph$	>20:1	96%
	NIS	**13e** I, $SiMe_2Ph$	1:1	92%
12	NIS	**13f**	>20:1	80%

[a] Major regioisomer product. [b] Regioselectivity determined by ^1H NMR. [c] Isolated yields. [d] Reaction preformed at 55 °C for 15 h in $CHCl_3$. NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide. NIS = *N*-iodosuccinimide.

the allenyl bromide in moderate selectivity and poor conversion (Table 3). DEA boronates **5** and **11** were more reactive toward NBS than the borolane species and furnished the allene product in good yield. Electrophilic substitution of DEA boronate **5** with NCS is also effective but requires 15 h at 55 °C for complete conversion. The halo-deborolation with NCS and NBS afforded high regioselectivities (>20:1) with the examined DEA boronates. Interestingly, iodo-deborolation of the alkyl DEA boronate **12** also proceeded in high yield and regioselectivity under the standard conditions contrary to the corresponding proto-deborolation. The regioselectivity for the reactions with NIS proved sensitive to steric effects with a similar trend for higher selectivities with the smaller alkynyl substituent (RCH_2 > TMS > $PhMe_2Si$).

Reactions of propargyl boron species with carbonyl compounds, in general, provide the allene product due to an inversion mechanism through either an addition with a boron "ate" complex[10] or a Zimmerman−Traxler-type transition state with trivalent boron reagents.[5] The nucleophilic addition of propargyl DEA boronate **5** to *p*-anisaldehyde proceeded with essentially no regioselectivity (Scheme 3). The reactivity of the DEA boronate toward aldehydes should be perturbed by deprotonation of the heteroatom proton. *N*-Deprotonation and *N*-alkylation of iminodiacetic acid boronates has been demonstrated.[8a] After treatment of the DEA boronate **5** with LiHMDS, the nucleophilic addition to *p*-anisaldehyde proceeded with nearly complete selectivity for the homopropargylic product. The use of NaHMDS as a base afforded an 8:1 regioselectivity and only 20% yield. The propargylation is general for a variety of substituted aryl aldehydes and proceeded with moderate yields (Table 4).

Scheme 3. Regioselective Propargylation with DEA Boronates[a]

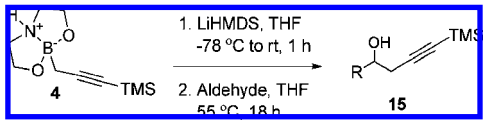


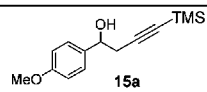
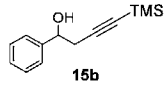
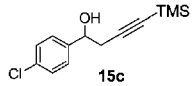
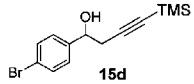
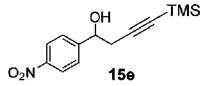
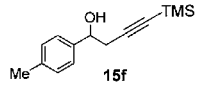
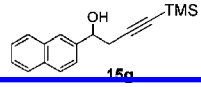
[a] Regioselectivity was determined by HPLC.

A reasonable rationalization for the regioselectivity observed for the reaction of propargyl DEA boronates toward electrophiles relates to the reactions proceeding through either an open or closed transition state (Scheme 4). The selectivity observed for electrophilic substitution of DEA boronates indicates an open transition state with preference for reaction at the alkyne functionality. Silicon substituents are known

(15) (a) Petasis, N. A.; Zavialov, I. A. *Tetrahedron Lett.* **1996**, *37*, 567–570. (b) Thiebes, C.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **1998**, 141–142.

Table 4. Propargylations with DEA Boronate **5**



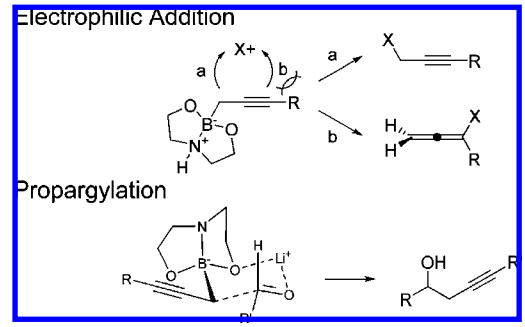
entry	product	yield[a]
1	 **15a**	62%
2	 **15b**	56%
3	 **15c**	61%
4	 **15d**	55%
5	 **15e**	54%
6	 **15f**	57%
7	 **15g**	53%

[a] Isolated yields. LiHMDS = lithium bis(trimethylsilyl)amide.

to facilitate electrophilic substitution of alkenes and favor reaction at the α-position.[16] This effect appears to operate for protonolysis of propargyl DEA boronates wherein reactions with alkynyl-silyl substituents are both more reactive and regioselective than that with alkyl substituents. The effect is minimized for reactions with *N*-halo-succinimides, and no difference between these substituents was observed. The steric effect of the alkynyl substituent can hinder the electrophilic attack at the alkynyl position and enable the reaction at the sp^3 position to compete. Therefore, higher

(16) (a) Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496–1500. (b) Lambert, J. B.; Wang, G. T.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838–7845. (c) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React. (N.Y.)* **1989**, *37*, 57–575. (d) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599–7662.

Scheme 4. Regioselectivity Rationalization



regioselectivity for both proto- and halo-deborolation was observed with the smaller alkynyl substituent. Interestingly, reaction of propargyl DEA boronates toward aldehydes was not regioselective. After deprotonation with LiHMDS, the reaction strongly favored the homopropargylic product. A six-membered closed transition state with a chelated lithium cation can explain this reversal in regioselectivity. Accordingly, a lower reactivity and regioselectivity was observed with the sodium cation. The deprotonation can also lead to a stronger B−N bond thereby perturbing the conformational dynamics of the DEA complex[8] and influencing the regioselectivity by making the boron p-orbital relatively inaccessible. Precedented alkylations of lithiated iminodiacetic acid boronates demonstrated preference for nucleophilic addition at the nitrogen atom.[8a] However, this addition with aldehydes is reversible, and the reaction ultimately proceeded with C−C bond formation.

In conclusion, we demonstrated the utility of propargyl DEA boronates as reagents for the preparation of allenes and homopropargylic alcohols. In addition to improving the reactivity of the propargyl functionality toward electrophiles, the DEA boronates afforded higher regioselectivities than the corresponding borolane species. Furthermore, the crystalline nature of the DEA boronates provides ease of handling and ability for purification by recrystallization.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR for boronates **5**, **8**−**12** and all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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