Boron Trihalide Mediated Substitution of Hydroxyl Groups with Alkenyl, Alkynyl, and Allyl Moieties

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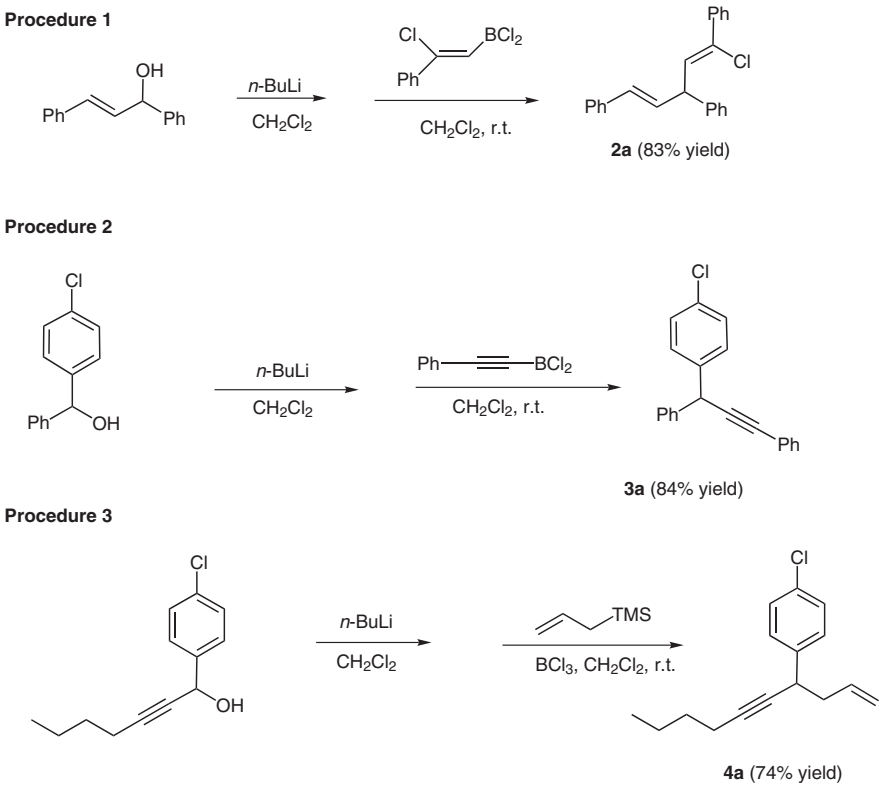
Received 1 June 2007; revised 26 June 2007

Abstract: The coupling of alcohols with alkenyl- and alkynylboron dihalides with high olefin stereoselectivity is described. The reaction provides a facile route to internal acetylenes. Notably, the allylation of propargylic alcohols mediated by boron trichloride proceeds smoothly at room temperature and gives excellent regioselectivity.

Key words: coupling, boron halide, substitution, Lewis acid



Scheme 1

Introduction

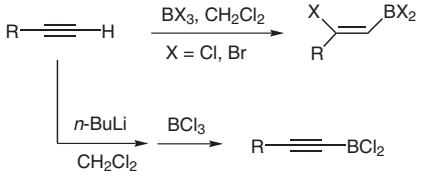
Allylic, benzylic and propargylic alcohols constitute ideal starting materials in synthesis due to their structural diversity and ready availability. Classic methods for substitution of the hydroxyl group in these types of alcohols are centered on transformation of the hydroxyl moiety into a more reactive leaving group (Br, I, OTf, etc.). Strategies for direct carbon–carbon bond coupling using these alcohols generally require transition-metal catalysts that include palladium,[1] ruthenium,[2] rhenium,[3] copper,[4] gold,[5] and rhodium.[6] These reactions typically require stringent reaction conditions (high reaction temperatures and sealed tubes) and prolonged periods of time. Recently, our research group demonstrated the direct cross-coupling of allylic alcohols with aryl- and vinylboronic acids in ionic liquids.[6] Main group Lewis acids such as bismuth[7] and indium[8] halides have also been successfully employed for nucleophilic allylation in benzylic and propargylic alcohols.

SYNTHESIS 2008, No. 2, pp 0325–0329
Advanced online publication: 25.09.2007
DOI: 10.1055/s-2007-990816; Art ID: Z14007SS

Our research group has focused on developing boron trihalide (BCl_3 and BBr_3) mediated carbon–carbon bond-forming reactions. We have described the coupling of allylic and benzylic alcohols with alkenylboron dihalides[9–11] and with alkynylboron dihalides[12] (Procedures 1 and 2, Scheme 1). Based on the observation that the oxyboron halide moiety can function as a leaving group to generate an intermediate carbocation (Procedures 1 and 2, Scheme 1), we turned our attention to an allylation reaction.[13] The representative reaction is shown in Procedure 3 (Scheme 1). This method complements classic methods for generating carbocations from alcohols since it provides a Brønsted acid free route to carbocations from alcohol **l**.

Scope and Limitations

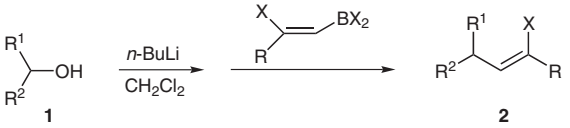
The exploration of the substitution of hydroxyl groups with alkenyl and alkynyl moieties using organoboron dihalides is a consequence of our previous discovery of a boron trihalide mediated alkyne–aldehyde coupling reaction.[14] Preliminary mechanistic studies of this coupling reaction indicated that it involved a halovinyl group migration from boron to carbon. To validate the vinyl group migration, we designed the reaction shown in Procedure 1 (Scheme 1) and finally extended the reaction to alkynylboron dichlorides. The highly regio- and stereoselective vinylboron dihalides and alkynylboron dichlorides were generated from terminal alkynes under mild reaction conditions (Scheme 2).



Scheme 2 Synthesis of organoboron dihalides

Allylic alcohols can couple readily with stereodefined alkenylboron dichlorides and alkenylboron dibromides derived from aryl alkynes; it has been observed that alkenylboron dibromides (but not alkenylboron dichlorides) derived from aliphatic alkynes undergo the coupling reactions (Table 1, entry 4). NMR analysis also revealed that unsymmetrical allylic alcohols produce regiochemically pure products; this circumvents a drawback of transition-metal-catalyzed reactions in which isomeric products are often formed via π-allyl intermediates.[15] We also applied this methodology to benzylic alcohols (Table 1, entries 6–10) and propargylic alcohols (Table 1, entries 11–13). In all cases the reactions produce the *Z*-stereoisomers as the major product, thus the configuration of the halovinyl group is retained. The *Z*-stereochemistry is supported by the X-ray crystal structure analysis of **2h**.

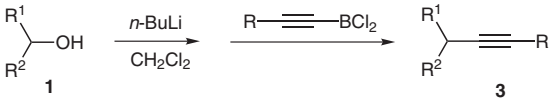
Table 1 Representative Examples of Alkenylation of Alcohols **1**[a]



Entry	R^1	R^2	R	X	Product	Yield (%)[b]
1	(*E*)-PhCH=CH	Ph	Ph	Cl	**2a**	83
2	(*E*)-PhCH=CH	Ph	3-FC_6H_4	Cl	**2b**	78
3	(*E*,*E*)-Ph(CH=CH)$_2$	Ph	Ph	Cl	**2c**	66
4	(*E*)-PhCH=CH	Ph	*n*-Bu	Br	**2d**	62
5	(*E*)-PhCH=CH	Ph	4-MeC_6H_4	Br	**2e**	68
6	Ph	Ph	Ph	Cl	**2f**	79
7	4-ClC_6H_4	Ph	Ph	Cl	**2g**	69
8	Ph	Ph	4-MeC_6H_4	Cl	**2h**	58
9	Ph	Me	Ph	Br	**2i**	64
10	4-$NO_2C_6H_4$	Ph	4-MeC_6H_4	Br	**2j**	44
11	PhC≡C	4-ClC_6H_4	Ph	Cl	**2k**	90
12	*n*-BuC≡C	Ph	Ph	Cl	**2l**	60
13	PhC≡C	4-FC_6H_4	Ph	Br	**2m**	85

[a] Stereodefined vinylboron dihalides were prepared in situ at 0 °C and used directly for the coupling reaction (see experimental section for details).
[b] Isolated yields based on the precursor alkynes.

Table 2 Representative Examples of Alkynylation of Alcohols **1**[a]



Entry	R^1	R^2	R	Product	Yield (%)[b]
1	Ph	4-ClC_6H_4	Ph	**3a**	84
2	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-MeC_6H_4	**3b**	77
3	Ph	Ph	Ph	**3c**	68
4	4-FC_6H_4	4-FC_6H_4	4-$MeOC_6H_4$	**3d**	57
5	(*E*)-PhCH=CH	Ph	2-FC_6H_4	**3e**	86
6	(*E*,*E*)-$Ph(CH=CH)_2$	Ph	Ph	**3f**	71
7	PhC≡C	4-MeC_6H_4	4-MeC_6H_4	**3g**	83
8	PhC≡C	4-ClC_6H_4	Ph	**3h**	69

[a] Alkynylboron dichlorides were prepared in situ at 0 °C and used directly for the coupling reaction (see experimental section for details).
[b] Isolated yields based on the precursor alkynes.

Although transition-metal-catalyzed and acid-mediated methods can be used to replace hydroxyl groups with aryl, allyl and alkenyl moieties,[16] the replacement of hydroxyl groups with stereodefined halovinyl moieties had not been reported. The direct substitution of the hydroxyl group in alcohol **1** with an alkenyl moiety using alkenylboron dihalides can be viewed as a formal transition-metal-free Suzuki reaction.[17] In addition, the reaction products provide a potential route to trisubstituted olefins.

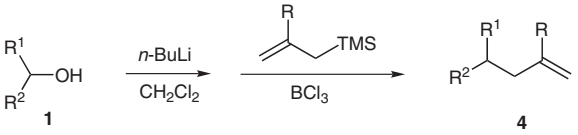
Encouraged by the successful replacement of hydroxyl groups with halovinyl moieties using halovinylboron dihalides, we postulated that the replacement of hydroxyl groups with alkynyl moieties using alkynylboron dihalides might also occur (Procedure 2, Scheme 1). This would provide a novel route to internal acetylene derivatives, specifically, secondary alkylacetylenes.

Traditional preparations of secondary alkylacetylene derivatives rely on methods such as substitution of secondary halides or elimination reactions involving 1,2-dihalides. Since these reactions often require the use of strong bases or high temperatures, the desired products are often contaminated with allene by-products that are difficult to remove. Although there have been advances in Sonogashira chemistry,[18] the preparation of secondary acetylenes is still a synthetic challenge due to their tendency to isomerize to allenes.

We examined the feasibility of coupling alcohols with alkynylboron dichlorides. The versatility of the reaction is clearly illustrated by its applicability to allylic, benzylic and propargylic, alcohols (Table 2). Similar to the coupling reactions with alkenylboron dihalides, the reactions of alkynylboron dichlorides with primary alcohols do not work. Most likely, the reaction proceeds via a cationic mechanism.

The generation of cations from alkoxides using alkenyl/alkynylboron dihalides, through the intermediacy of alkoxyboron monohalides, led us to investigate the use of boron trihalides as reagents in the new coupling reactions. We discovered that the allylation of alcohols using allylsilane proceeded smoothly in the presence of boron trichloride at room temperature (Table 3). No reaction occurred between allyltrimethylsilane and boron trichloride, which precludes the formation of an intermediate allylboron dichloride. The generation of a cation intermediate from an alkoxide by boron trihalide was further supported by the coupling of lithium alkoxide with alkynes.[13]

Table 3 Representative Examples of Allylation of Alcohols[a]



Entry	R^1	R^2	R	Product	Yield (%)[b]
1	*n*-BuC≡C	4-ClC_6H_4	H	**4a**	74
2	3-FC_6H_4C≡C	3,4,5-$(MeO)_3C_6H_2$	H	**4b**	53
3	PhC≡C	4-ClC_6H_4	Me	**4c**	65
4	4-MeC_6H_4C≡C	4-ClC_6H_4	Me	**4d**	72
5	Ph	4-ClC_6H_4	H	**4e**	96
6	Ph	Ph	H	**4f**	90
7	(*E*)-PhCH=CH	Ph	H	**4g**	78

[a] See experimental section for details.
[b] Isolated yields based on the starting alcohols.

In summary, we have discovered that hydroxyl groups, via their alkoxides (RO^-), can be readily replaced by stereodefined halovinyl, alkynyl and allyl moieties at room temperature. These new reactions obviate many difficulties associated with transition-metal-catalyzed syntheses, especially those involving Csp^2–Csp^3, Csp–Csp^3 carbon–carbon bond formation. We believe that there are two factors leading to weakening of the C–O bond and the subsequent generation of a carbocation: steric hindrance in the unstable complexes lengthens the C–O bond, and the electronegativity of chlorine strengthens the B–O bond.

All chemicals were used as received. The glassware was oven-dried for a period of 24 h prior to use. CH_2Cl_2 was distilled from an appropriate drying agent (CaH_2) prior to use. BCl_3 (1.0 M CH_2Cl_2 solution) and BBr_3 were used as received. Reactions were magnetically stirred and monitored by TLC using 254 nm UV light or staining with a 50% solution of phosphomolybdic acid in EtOH. Products were purified by flash chromatography using silica gel (230–400 mesh, 60 Å). ^1H NMR and ^{13}C NMR spectra were recorded at 250.13 and 62.89 MHz, respectively. Chemical shifts for ^1H NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents. Microanalysis was performed by Atlantic Microlab, Inc. Norcross, Georgia.

Alkenylboron Dihalides; General Procedure

Boron trihalide (1.5 mmol, 1.5 mL of a 1.0 M solution in CH_2Cl_2), alkyne (1.5 mmol), and anhyd CH_2Cl_2 (8 mL) were combined in a 50 mL flask at 0 °C and stirred for 1 h under N_2.

Alkynylboron Dichlorides; General Procedure

A solution of alkyne (1.5 mmol) in anhyd hexane (8 mL) was treated with *n*-BuLi (1.0 mL of a 1.6 M solution in hexanes) at 0 °C under N_2. After stirring at r.t. for 30 min, BCl_3 (1.5 mmol, 1.5 mL of a 1.0 M solution in CH_2Cl_2) was added to the mixture at 0 °C.

Coupling of Alcohols 1 with Alkenylboron Dihalides (Procedure 1)

Under N_2, 1,3-diphenylprop-2-en-1-ol (336 mg, 1.6 mmol) in anhyd CH_2Cl_2 (8 mL) was treated with *n*-BuLi (1.0 mL of a 1.6 M solution in hexanes) at 0 °C and stirred at r.t. for 1 h. The solution was then transferred to the (*Z*)-2-chloro-2-phenylvinylboron dihalide solution and allowed to stir at r.t. overnight. H_2O (20 mL) was added, the mixture was extracted with EtOAc (3 × 12 mL), and the combined organic layers were dried ($MgSO_4$). The solvents were removed under reduced pressure and the crude product was purified by silica gel column chromatography using hexane as eluent to give **2a** (410 mg, 83%). Typical analytic data are provided for **2a**, **2f**, and **2k**.

2a

^1H NMR ($CDCl_3$): δ = 7.57–7.60 (m, 2 H), 7.15–7.37 (m, 13 H), 6.34–6.58 (m, 3 H), 4.94 (dd, *J* = 9.0, 8.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 142.1, 137.9, 137.1, 133.4, 130.9, 130.3, 128.7, 128.5, 128.3, 127.8, 127.4, 126.9, 126.6, 126.3, 48.5.

Anal. Calcd for $C_{23}H_{19}Cl$: C, 83.50; H, 5.79. Found: C, 83.57; H, 5.65.

2f

^1H NMR ($CDCl_3$): δ = 7.56–7.59 (m, 2 H), 7.17–7.30 (m, 13 H), 6.59 (d, *J* = 9.5 Hz, 1 H), 5.42 (d, *J* = 9.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 142.9, 137.8, 133.4, 129.5, 128.6, 128.3, 126.6, 50.8.

Anal. Calcd for $C_{21}H_{17}Cl$: C, 82.75; H, 5.62. Found: C, 82.57; H, 5.65.

2k

^1H NMR ($CDCl_3$): δ = 7.29–7.62 (m, 14 H), 6.27 (d, *J* = 9.3 Hz, 1 H), 5.30 (d, *J* = 9.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 137.9, 137.2, 133.6, 133.1, 131.7, 129.0, 128.8, 128.7, 128.6, 128.4, 128.3, 126.7, 126.6, 123.0, 87.6, 84.2, 37.4.

Anal. Calcd for $C_{23}H_{16}Cl_2$: C, 76.04; H, 4.44. Found: C, 75.88; H, 4.22.

Coupling of Alcohols 1 with Alkynylboron Dihalides (Procedure 2)

Under N_2, 1-phenyl-1-(4-chlorophenyl)methanol (349 mg, 1.6 mmol) in anhyd CH_2Cl_2 (8 mL) was treated with *n*-BuLi (1.0 mL of a 1.6 M solution in hexanes) at 0 °C and then warmed to r.t. After stirring at r.t. for 30 min, the solution was transferred to the 2-phenylaceteyleneboron dichloride solution and the mixture allowed to stir overnight. H_2O (20 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3 × 12 mL), the combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The product was purified by silica gel column chromatography using hexane as eluent to give **3a** (380 mg, 84%). Typical analytic data are provided for **3a**, **3e**, and **3g**.

3a

^1H NMR ($CDCl_3$): δ = 7.21–7.47 (m, 14 H), 5.14 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 141.2, 140.3, 132.7, 131.6, 129.2, 128.7, 128.2, 128.1, 127.8, 127.1, 123.2, 89.6, 85.2, 43.1.

Anal. Calcd for $C_{21}H_{15}Cl$: C, 83.30; H, 4.99. Found: C, 83.77; H, 5.04.

3e

^1H NMR ($CDCl_3$): δ = 7.19–7.47 (m, 13 H), 6.89–6.97 (m, 1 H), 6.71 (d, *J* = 15.5 Hz, 1 H), 6.30 (dd, *J* = 15.4, 6.19 Hz, 1 H), 4.71 (d, *J* = 6.19 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 164.3, 160.4, 141.8, 139.9, 136.7, 130.6, 129.8, 129.2, 128.5, 127.6, 126.5, 125.3, 125.2, 118.7, 118.3, 115.5, 115.0, 89.9, 84.2, 41.1.

Anal. Calcd for $C_{23}H_{17}F$: C, 88.43; H, 5.49. Found: C, 88.65; H, 5.81.

3g

^1H NMR ($CDCl_3$): δ = 7.16–7.56 (m, 14 H), 5.15 (s, 1 H), 2.33 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 137.1, 135.0, 131.7, 129.4, 128.1, 127.2, 123.0, 86.8, 82.6, 29.7, 21.1.

Anal. Calcd for $C_{24}H_{18}$: C, 94.08; H, 5.92. Found: C, 94.47; H, 5.84.

Boron Trichloride Mediated Coupling of Alcohols 1 with Allylsilanes (Procedure 3)

Under N_2, a solution of 1-(4-chlorophenyl)-3-butylpropargylic alcohol (333 mg, 1.5 mmol) in anhyd CH_2Cl_2 (10 mL) was treated with *n*-BuLi (1.0 mL of a 1.6 M solution in hexanes) at 0 °C and the mixture warmed to r.t. After stirring at r.t. for 30 min, allyltrimethylsilane (1.8 mmol) and BCl_3 (1.5 mL of a 1.0 M solution in CH_2Cl_2) were added sequentially. The mixture was allowed to stir for 10 h at r.t. H_2O (20 mL) was added to quench the reaction. The crude product was extracted into EtOAc (3 × 12 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was removed in vacuo and the product purified by silica gel column chromatography using hexane as eluent to give **4a** (270 mg, 74%). Typical analytic data are provided for **4a**, **4e**, and **4g**.

4a

^{1}H NMR ($CDCl_3$): δ = 7.11–7.34 (m, 4 H), 5.73–5.84 (m, 1 H), 4.91–5.06 (m, 2 H), 3.52–3.64 (m, 1 H), 2.23–2.45 (m, 2 H), 2.15–2.21 (m, 2 H), 1.37–1.55 (m, 4 H), 0.91 (t, *J* = 6.53 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 140.6, 135.3, 132.3, 128.9, 128.4, 116.9, 84.1, 80.6, 42.9, 37.4, 31.1, 21.9, 18.4, 13.6.

Anal. Calcd for $C_{16}H_{19}Cl$: C, 77.87; H, 7.76. Found: C, 77.35; H, 7.64.

4e[8]

^{1}H NMR ($CDCl_3$): δ = 7.03–7.26 (m, 9 H), 5.65–5.76 (m, 1 H), 4.91–5.04 (m, 2 H), 3.92–3.98 (m, 1 H), 2.75–2.81 (m, 2 H), 2.25 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 144.7, 141.5, 136.7, 135.5, 129.1, 128.3, 127.8, 127.7, 126.0, 116.1, 50.8, 40.0, 20.9.

4g[19]

^{1}H NMR ($CDCl_3$): δ = 7.12–7.34 (m, 10 H), 6.34–6.36 (m, 2 H), 5.70–5.80 (m, 1 H), 4.95–5.07 (m, 2 H), 3.49–3.51 (m, 1 H), 2.54–2.60 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 137.4, 136.5, 133.4, 129.7, 128.5, 127.7, 127.1, 126.3, 126.2, 116.3, 48.9, 40.2.

Acknowledgment

We wish to thank the Donor of the American Chemical Society Petroleum Research Foundation (ACS-PRF #41768-AC1) and the Robert H. Cole Foundation for support of this research.

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