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Substitution of Benzylic Hydroxyl Groups with Vinyl Moieties Using Vinylboron Dihalides

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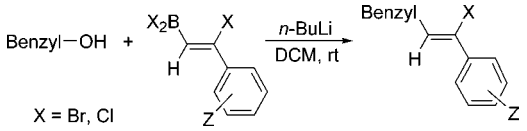
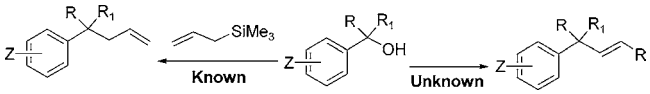
ABSTRACT



Substitution of benzylic hydroxyl groups with vinyl moieties using vinylboron dihalides has been achieved. The reaction provides a novel method for preparing stereodefined alkenyl halides.

Benzylic alcohols are generally transformed into the corresponding halides or esters prior to reactions with nucleophiles due to the fact that the hydroxide group is such a poor leaving group. The direct utilization of benzylic alcohols as electrophiles would be quite useful since it would be both atom efficient and more environmentally sound.[1] To date, very few direct substitutions have been achieved.[2−5] Among those reported, the straightforward substitution of the benzylic hydroxide moiety with an allyl group using allyltrimethylsilane[5] represents the most attractive transformation (Scheme 1). However, to the best of our knowledge, the direct substitution of a benzylic hydroxyl group by a vinyl moiety has not been achieved using a Lewis acid or transition metal catalyst.

Scheme 1. Direct Substitution of Benzylic Hydroxyl Group



We have investigated the chemistry of boron halide derivatives for many years, and several novel reactions have been developed.[6,7] The alkylation[7b−e] and dialkenylation[7a,8] of aryl aldehydes using alkylboron dihalides and dialkenylboron halides were reported previously. Encouraged by these initial results, we turned our attention to the chemistry of

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(1) Trost, B. M. *Science* **1991**, *254*, 1471.

(2) Dehydroxylation: (a) Singh, S.; Chhina, S.; Sharma, V. K.; Sachdev, S. S. *J. Chem. Soc., Chem. Commun.* **1982**, 453. (b) Ono, A.; Suzuki, N.; Kamimura, J. *Synthesis* **1987**, 736. (c) Olah, G. A.; Wu, A. H.; Farooq, O. *J. Org. Chem.* **1991**, *56*, 2759. (d) Stoner, E. J.; Cothron, D. A.; Balmer, M. K.; Roden, B. A. *Tetrahedron* **1995**, *51*, 11043. (e) Miyai, T.; Ueba, M.; Baba, A. *Synlett* **1999**, 182. (f) Gevorgyan, V.; Rubin, M.; Benson, S.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 6179. (g) Gordon, P. E.; Fry, A. J. *Tetrahedron Lett.* **2001**, *42*, 831. (h) Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741.

(3) Reaction with KCN: (a) Fleming, I.; Loreto, M. A.; Wallace, I. H. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 349. (b) Wilk, B. K. *Synth. Commun.* **1993**, *23*, 2481. (c) Aesa, M. C.; Baán, G.; Novák, L.; Szántay, C. *Synth. Commun.* **1995**, *25*, 1545.

(4) Reaction with organic reactants: with carbon−carbon multi-bond: (a) Cravotto, G.; Giovenzana, G. B.; Sisti, M.; Palmisano, G. *Tetrahedron* **1996**, *52*, 13007. (b) Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823. (c) Marquet, J.; Moreno-Manas, M. *Chem. Lett.* **1981**, 173. with malonate derivatives: (d) Bott, K. *Angew. Chem.* **1965**, *77*, 967. (e) Kell, D. R.; McQuillin, F. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2100. (f) Takacs, J. M.; Xu, Z.; Jiang, X.-T.; Leonov, A. P.; Theriot, G. C. *Org. Lett.* **2002**, *4*, 3843.

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(6) For BX_3-mediated reactions: (a) Kabalka, G. W.; Wu, Z. *Tetrahedron Lett.* **2000**, *41*, 579. (b) Kabalka, G. W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* **2001**, *42*, 5793. (c) Kabalka, G. W.; Wu, Z.; Ju, Y. *Synthesis* **2004**, 2927.

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alkenylboron dihalides.[9] (*Z*)-2-Halo-1-alkenylboron dihalide derivatives can be readily prepared by the haloboration of terminal alkynes using 1 equiv of boron trihalide. The reaction occurs in a stereo- and regioselective fashion via the syn addition of the B−X moiety to the carbon−carbon triple bond.[10]

We wish to report the substitution of benzylic hydroxyl groups by alkenylboron dihalides. In this new reaction, alkenylboron dihalides act as both Lewis acids and reactants. This transformation, in the absence of transition metals, is particularly appealing from an industrial perspective. Pharmaceutical syntheses often involve the challenging step of removing transition metals from intermediates.

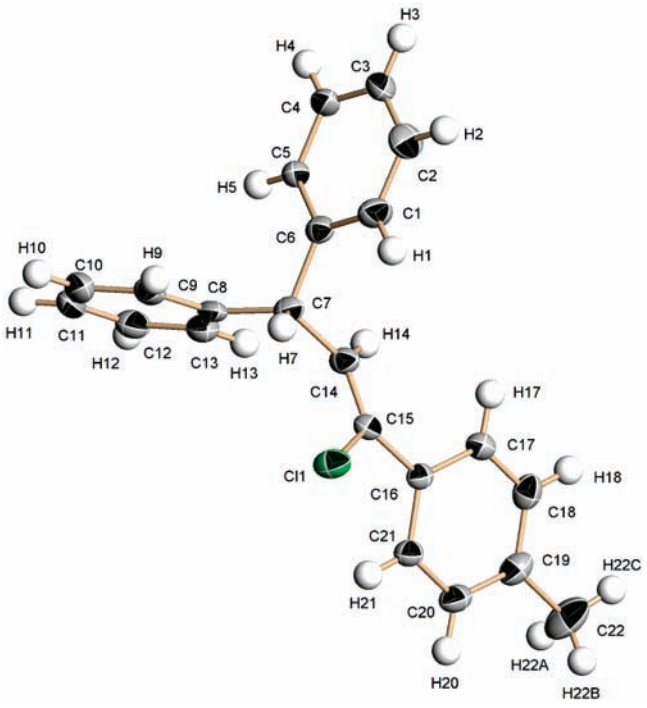
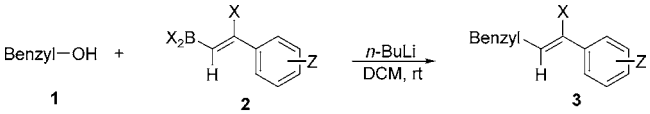


Figure 1. ORTEP plot of compound **3b**.

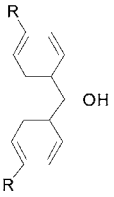
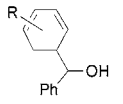
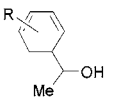
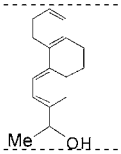
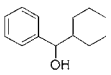
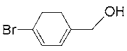
The reaction of diphenylmethanol (**1a**) and (*Z*)-2-chloro-2-phenylethenylboron dichloride was chosen as the model system. After surveying potential solvents and bases, we found that the new reaction proceeds most effectively in the presence of 1 equiv of *n*-BuLi in dry dichloromethane.[11] Analysis of the ^{1}H and ^{13}C NMR spectroscopic data for **3a** revealed that the *Z* isomer formed exclusively. Thus, the configuration of the vinyl group is retained in the reaction. The *Z* stereochemistry is unambiguously supported by X-ray analysis of **3b** (Figure 1).[12]

To examine the scope of the reaction, different types of benzylic alcohols were prepared and subjected to the reaction conditions (Table 1). Both alkenylboron dichlorides and alkenylboron dibromides derived from aryl alkynes produced the desired products in moderate to good yields. Alkenylboron dihalides derived from aliphatic alkynes were unreactive. Due to the ready decomposition of alkenyl bromides on silica gel, the isolated yields are somewhat lower for the alkenylboron dibromides. The NMR spectra of all products reveal that only the *Z* isomers formed. Under the reaction conditions, most functional groups are tolerated. It is quite

Table 1. Coupling of Benzylic Alcohols with Vinylboron Dihalides



1 2 3

	alcohols	Z	X	product	yield (%)[b]
	1a: R = H	H	Cl	**3a**	79
	1a: R = H	*p*-Me	Cl	**3b**	58
	**1a:** R = H	H	Br	**3c**	74
	1a: R = H	*p*-Me	Br	**3d**	53
	1b: R = OMe	H	Cl	**3e**	73
	1b: R = OMe	*m*-F	Cl	**3f**	75
	1b: R = OMe	*p*-Me	Br	**3g**	59
	1c: R = F	*p*-Me	Cl	**3h**	76
	**1d:** R = *p*-Cl	H	Cl	**3i**	69
	1e: R = *o*-Me	*p*-Me	Cl	**3j**	77
	1f: R = *p*-NO_2	*p*-Me	Br	**3k**	44
	**1g:** R = H	H	Br	**3l**	64
	1h: R = *p*-SMe	H	Cl	**3m**	65
	1i: R = *o*-OMe	H	Cl	**3n**	32
	**1j**	H	Cl	**3o**	70
	1j	*p*-Me	Cl	**3p**	62
	**1k**	H	Cl	--	0
	**1l**	H	Br	--	0[c]

[a] Reaction carried out at room temperature on a 1.5 mmol scale in DCM using *n*-BuLi as the base (for the detailed procedure, see ref 11). [b] Yield of isolated product based on the precursor of halovinylboron dihalide (alkyne). [c] 4-Bromobenzyl bromide was isolated.

(7) For RBX_2- and R_2BX-mediated reactions: (a) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2002**, *4*, 1491. (b) Kabalka, G. W.; Wu, Z.; Trotman, S. E.; Gao, X. *Org. Lett.* **2000**, *2*, 255. (c) Kabalka, G. W.; Wu, Z.; Ju, Y. *Tetrahedron* **2001**, *57*, 1663. (d) Kabalka, G. W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* **2000**, *41*, 5161. (e) Kabalka, G. W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* **2001**, *42*, 6239.

(8) Dialkenylation of aldehydes using other Lewis acids, see: (a) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2002**, *4*, 1491. (b) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **2005**, *70*, 57. (c) Yadav, J. S.; Reddy, B. V. S.; Eeshwaraiah, B.; Gupta, M. K.; Biswas, S. K. *Tetrahedron Lett.* **2005**, *46*, 1161.

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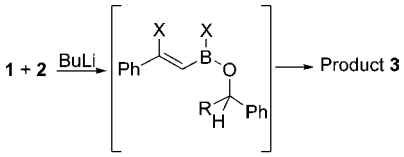
(10) (a) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: New York, 1988. (b) Lappert, M. F.; Prokai, B. *J. Organomet. Chem.* **1964**, *1*, 384. (c) Suzuki, A. *Pure Appl. Chem.* **1986**, *58*, 829. (d) Suzuki, A. *Rev. Heteroatom Chem.* **1997**, *17*, 271.

remarkable that the methoxy group is tolerated, since it is well-known that Lewis acids such as BBr_3 are quite effective in cleaving ether linkages.[13]

Though a detailed mechanistic study has not been undertaken, the reaction of lithium benzyloxide with alkenylboron dihalide presumably generates (halovinyl)benzyloxyboron halide intermediate **4**, which undergoes a rearrangement to **3** (Scheme 2).

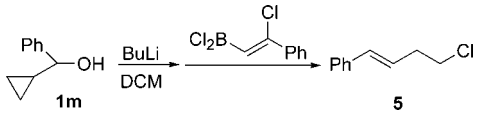
Scheme 2 Proposed Intermediate **4** for Alkenyl Migration



4

To gain mechanistic insight, a reaction was carried out using (*S*)-**1g**.[14] Racemization occurred, which precludes a concerted rearrangement and supports formation of a benzylic cation intermediate. Further evidence supporting a cationic mechanism was provided by the observation that the reaction of cyclopropyl derivative **1m** produced the ring-opened product, **5** (Scheme 3). A cationic mechanism could also explain the failure of **1k** to generate **3k** since loss of a β-hydrogen in the benzylic cation generated from **1k** would be expected to be quite rapid.

Scheme 3. Reaction of a Cyclopropyl Derivative



1m **5**

A new, straightforward substitution of benzylic hydroxide moieties with stereodefined vinyl groups has been developed. The reaction provides a novel route to trisubstituted alkenyl halides from readily available benzylic alcohols and terminal alkynes (the precursor of (*Z*)-alkenylboron dihalides).

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Supporting Information Available: Typical experimental procedure and analytical data for all products, including CIF data for **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **Typical Experimental Procedure.** Boron trihalide (1.5 mmol), alkyne (1.5 mmol), and dry dichloromethane (8 mL) were combined in a 50 mL flask and stirred for 1 h at room temperature. In a separate flask, the benzylic alcohol (1.6 mmol) in dry dichloromethane (8 mL) was treated with *n*-butyllithium (1.0 mL of a 1.6 M solution in hexanes) at 0 °C and warmed to room temperature. After stirring at room temperature for 30 min, the solution was transferred to the first flask and the mixture was allowed to stir overnight. Water (20 mL) was added to quench the reaction. The reaction mixture was extracted with ethyl acetate and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the product purified by silica gel column chromatography using hexane as an eluent to provide **3a**. ^{1}H NMR (250.13 MHz, $CDCl_3$ with TMS as the internal standard): δ 7.56−7.59 (m, 2H), 7.17−7.30 (m, 13H), 6.59 (d, J = 9.47 Hz, 1H), 5.42 (d, J = 9.47 Hz, 1H). ^{13}C NMR (62.89 MHz, $CDCl_3$): 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.

(12) For details of the crystallographic data of compound **3b**, see Supporting Information.

(13) Meyers, A. I.; Nolen, R. L.; Collington, E. W.; Narwid, T. A.; Strickland, R. C. *J. Org. Chem.* **1973**, *38*, 1974.

(14) Determined by chiral GC-MS. Column: Varian CP-chirasil-DEX CB 25 m × 0.25 mm × 0.25 mm; initial temperature/initial time = 50 °C/3 min; final temperature/final time = 200 °C/10 min; rate = 2 °C/min.