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A One-Pot Three-Component Route to *anti*-Homoallylic Alcohols Based on the Hydroboration of Propargyl Bromide

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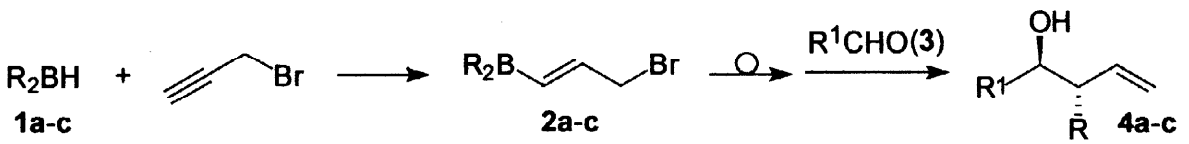
Abstract: (3-Bromoalken-1-yl)dialkylboranes, generated by hydroboration of propargyl bromide with dialkylboranes, smoothly rearranges to (*E*)-allylic boranes which can be trapped with aldehydes. The resulting one-pot three-component sequence represents a route to *anti*-homoallylic alcohols in fairly good yields. © 1998 Published by Elsevier Science Ltd. All rights reserved.

A new protocol to *anti*-homoallylic alcohols **4** based on a one-pot three-component consecutive coupling of a dialkylborane **1**, propargyl bromide and an aldehyde **3**, is reported (Scheme 1).



a: R = cyclohexyl **b**: R = cyclopentyl **c**: R = siamyl

Scheme 1

In early 70's Zweifel prepared (3-chloroalken-1-yl)dialkylboranes by hydroboration of propargyl chloride with dialkylboranes; addition of 2 equivalents of methyllithium resulted in a migration of an alkyl group from boron to the adjacent carbon with concomitant shift of the double bond and elimination of chloride to give an allylic borane.[1] The same chemistry was applied by Arase to the hydroboration product of 1,4-dichloro-but-2-yne in a synthesis of 2-substituted 1,3-dienes.[2] Pelter also reported that (3-bromoalken-1-yl)dialkylboranes and (3-iodoalken-1-yl)dialkylboranes, deriving from the reaction of trialkylalkynyl borates with CH_2X_2, gave an allylic borane *via* an almost identical mechanistic pathway.[3] Finally, chiral γ-acetoxyvinylboranes were reported to undergo enantioselective base-induced migration of an alkyl group from boron to carbon affording optically active allylic boranes.[4]

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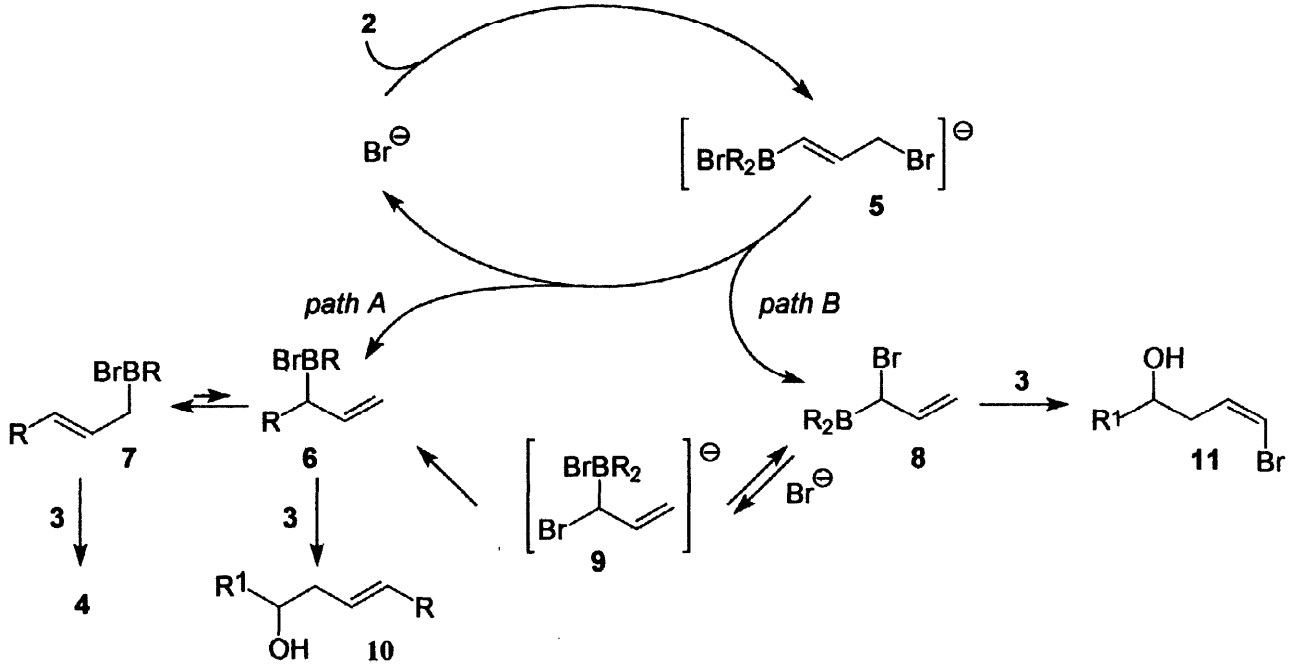
We found that hydroboration of propargyl bromide with **1a-c** (THF, 0°C, 1 h) gives an intermediate (3-bromoalken-1-yl)dialkylborane **2** which, upon standing at 20°C, equilibrates to allylic boranes **6,7** and **8**, identified on the basis of their addition products (**4, 10** and **11**) to aldehydes. Table 1 reports data of reactions carried out with **1a**, **1c** and propargyl bromide using different equilibration times before the addition of benzaldehyde, chosen as model aldehyde. A mechanistic rationale is proposed in Scheme 2.



Scheme 2

We believe that the key intermediate borate ion **5** derives from quaternisation of **2** by bromide ion, which is conceivable to be present in catalytic amounts in the reaction mixture. Competitive migration from boron to carbon of an alkyl ligand (path A) or bromine (path B) accounts for formation of **6** and **8**, respectively. Attention has to be paid to the following aspects: i) the migratory aptitude of Br with respect to R leading to different amounts of **6** and **8**, and ii) the borotropic stability of the intermediate allylic boranes **6** and **8**. We observed that, at short equilibration times, bromine displays a migratory aptitude higher than cyclohexyl (run 1) but much lower than siamyl (run 5), as expressed by the **4+10/11** ratio. As refers to the second point, rearrangement of **6** into **7** is fast when R = cyclohexyl (runs 1-3), while it takes place slowly when R = siamyl (runs 5,6). Allylic borane **8**, on the other hand, is stable to 1,3-borotropic shift, as demonstrated by the structure of **11a**[5] (run 1).

Bromide ion, freed in solution by the transformation of **5** into **6** or **8**, may also generate borate ion **9** which slowly, but irreversibly, collapses to **6** upon migration of the alkyl ligand. This is confirmed by **4+10/11** ratios observed after longer equilibration times (runs 2 and 3). On the basis of this mechanism, addition of supplementary bromide should have the beneficial effect of displacing equilibrium towards **7** *via* **9**. We

confirmed this assumption by adding a catalytic amount of triethyl benzyl ammonium bromide (TEBABr); the effect of bromide is unambiguously shown by runs 4 and 7. A final synthetic protocol ensued[6] which allowed us to synthesise diastereoselectively pure homoallylic alcohols **4** in a one-pot three-component process involving *in situ* preparation of dialkylborane[7] followed by consecutive additions of propargyl bromide, TEBABr (0.1 eq.) and the aldehyde. Experiments carried out according to this modified procedure are reported in Table 2.

By a synthetic point of view it is important to notice that allylic boranes **7** always display a pure (*E*)-geometry, as demonstrated by alkaline hydrogen peroxide quenching to give pure (*E*)-allylic alcohols (J_{trans} ~ 16-17 Hz) in 70-80 % yield. The direct consequence of the (*E*)-configuration of **7** is that addition to aldehydes leads to diastereomerically pure homoallylic alcohols **4a-c** to which we assign the *anti* configuration on the basis of the known behaviour of (*E*)-crotyl boranes and boronates.[8] Yields of **4** are good to excellent, considering that they are the result of a one-pot four-step sequence.

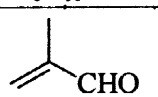
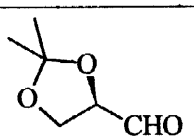
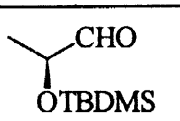
Facial selectivity was tested using (*R*)-glyceraldehyde (run 4) and (*S*)-lactaldehyde (run 5) with **1a**. No facial preference was displayed by *O*-silylated

Table 1. One-pot coupling of 1a or 1c, propargyl bromide and benzaldehyde.[a]

Run	R_2BH	TEBABr (eq.)	t_1 [b] (h)	t_2 [c] (h)	**4/10/11** Yield (%)[d]	**4+10/11**
1	**1a**	-	0.5	2	22/-/57	28/72
2	**1a**	-	2	2	63/-/12	84/16
3	**1a**	-	12	2	73/-/-	100/0
4	**1a**	0.1	1	2	85/-/-	100/0
5	**1c**	-	1	3	1/65/-	100/0
6	**1c**	-	12	3	26/25/-	100/0
7	**1c**	0.1	12	3	46/18/-	100/0

[a]The reaction were conducted on a 2 mmol scale. [b]Equilibration time before the addition of benzaldehyde. [c]Reaction time after the addition of benzaldehyde. [d]Isolated yields after flash-chromatography on silica gel. Diastereomeric purity of **4** was always > 98:2, as determined by GC on two different columns. Alcohol **10c** had pure (*E*)-geometry (J_{trans} = 15.5 Hz), while **11a** was a 9/1 mixture of *Z/E* isomers (see Note 4).

Table 2. Synthesis of *anti*-homoallylic alcohols 4 in the presence of TEBABr.[a]

Run	R_2BH	R^1CHO (**3**)	**4** Yield (%)[b]	d.r.[c]
1	**1a**	*i*PrCHO	72	-
2	**1a**	$nC_6H_{11}CHO$	82	-
3	**1a**		84	-
4	**1a**		40	85/15
5	**1a**		83	50/50
6	**1b**	PhCHO	45	-
7	**1b**	*i*PrCHO	60	-

[a]For a typical procedure see Note 5. [b]Isolated yields after flash-chromatography on silica gel. Diastereomeric purity of **4** was always > 98:2, as determined by GC. [c]Diastereomeric ratios (d.r.) were determined by GC.

lactaldehyde while an appreciable selectivity was observed using glyceraldehyde acetonide. We assigned the *anti-anti* stereorelationship to the more abundant isomer on the basis of the well known intrinsic diastereofacial bias of glyceraldehyde acetonide observed in a number of literature reports related, *inter alia*, to the addition of allylic organometallic species,[9] allylic boronates[10] and borolanes.[11]

In conclusion, a short one pot three-component route to *anti*-homoallylic alcohols **4** carrying an alkyl group, deriving from **1**, at the allylic position, is reported. This protocol is based on four consecutive steps consisting in i) preparation of a dialkylborane, ii) formation of a (3-bromopropen-1-yl)dialkylborane, iii) bromide-promoted formation of an allylic borane, and iv) addition of an aldehyde. The scope of this reaction sequence is under investigation.

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5. *Z/E* **11a** were detected in the 9/1 ratio by GC-MS. (*Z*)-**11a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (br s, 1H, OH), 2.70 (m, 2H), 4.85 (dd, 1H, *J* = 5.7/7.5 Hz, C*H*OH), 6.19 (q, 1H, *J* = 6.9 Hz), 6.30 (dt, 1H, *J* = 1.2/6.9 Hz, CHBr), 7.20-7.42 (m, 5H, ArH).
6. Three component coupling of dicyclopentylborane, propargyl bromide and 2-methylpropanal in the presence of TEBABr (Table 2, run 7), typical procedure: to a stirred THF solution (5 mL) of cyclopentene (273 mg, 4 mmol) was added at -78°C $BH_3{\cdot}SMe_2$ (152 mg, 2 mmol). After 3 min at -78°C a 80% solution of propargyl bromide in toluene (240 μL, 2 mmol) was added and the solution was stirred for 1 h while temperature was brought to 0°C. TEBABr (55 mg, 0.2 mmol) was added and the heterogeneous mixture was equilibrated at 20°C for 1 additional h. 2-Methylpropanal (144 mg, 2 mmol) was added and the reaction mixture was stirred at 20°C for 2 h. Oxidative work-up (H_2O_2/NaOH) and extraction with ether were followed by column chromatography (cyclohexane/ethyl acetate 95:5) which gave 4-cyclopentyl-2-methyl-hex-5-en-3-ol (220 mg, 60%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, 3H, *J* = 6.8 Hz, CH_3), 0.98 (d, 3H, *J* = 6.8 Hz, CH_3), 1.03-1.28 (m, 3H), 1.45-1.72 (m, 5H), 1.75-1.88 (m, 1H), 1.92-2.08 (m, 2H), 3.26 (dd, 1H, *J* = 3.1//8.0 Hz, H-3), 5.06 (dd, 1H, *J* = 2.3/17.2 Hz, H-6), 5.15 (dd, 1H, *J* = 2.3/10.4 Hz, H-6), 5.77 (ddd, 1H, *J* = 9.3/10.4/17.2 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 19.2, 25.0 (2C), 30.7, 30.8, 31.3, 40.3, 52.3, 78.0, 117.1, 137.2. C, H analysis calcd. for $C_{12}H_{22}O$: C 79.06, H 12.16; found: C 79.11, H 12.27.
7. Boranes **1a,c** are obtained by equilibrating $BH_3{\cdot}SMe_2$ and the corresponding alkene at 0°C in THF; see H. C. Brown, *Organic Syntheses via Boranes*, Wiley, New York, 1975. Dicyclopentyl borane **1b**, rather unstable to disproportionation, was prepared according to the procedure reported in Note 5.
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