The Hydroboration of Propargyl Chloride: A Flexible One-pot Three-component Process Easily Directed Towards the Synthesis of (*E*)-Homoallylic Alcohols or *anti*-Homoallylic Alcohols

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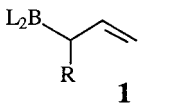
Abstract: The hydroboration of propargyl chloride by means of a dialkylborane affords 3-chloro-prop-1-en-1-yl boranes **6** which, in the presence of a quaternary ammonium chloride, rearrange into allylic boranes **9** and **10**, precursors of (*E*)-homoallylic alcohols **7** or *anti*-homoallylic alcohols **5**, respectively. Synthetic protocols for the selective generation of **5** and **7** were developed.

Key words: propargyl chloride, hydroboration, one-pot synthesis, (*E*)-homoallylic alcohols, *anti*-homoallylic alcohols

The construction of the propionate fragment of macrolide antibiotics has attracted lot of attention in the scientific community for the last two decades. A main synthetic route to polyketide-derived products involves the addition of suitable crotyl organometallic reagents to aldehydes. Crotyl boranes and boronates,[1] a class of intensely studied reagents for mechanistic and stereochemical purposes, revealed to be extremely useful tools for assembling sets of three consecutive stereogenic centers in a highly diastereoselective and predictable way.[2]

Much more restricted is the number of examples of preparations and applications in the addition to aldehydes of α or γ-alkyl substituted allyl boranes and boronates **1** and **2** (Figure 1).[3-5]



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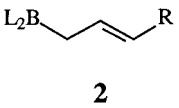

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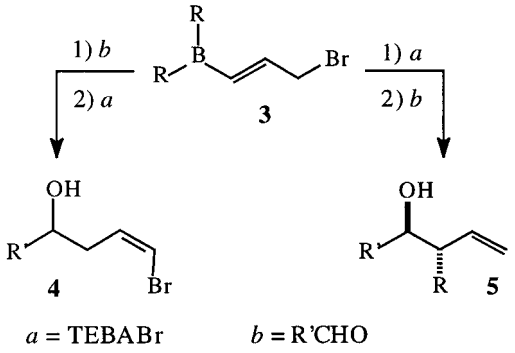
R = alkyl
a) L = alkyl
b) L = alkoxy

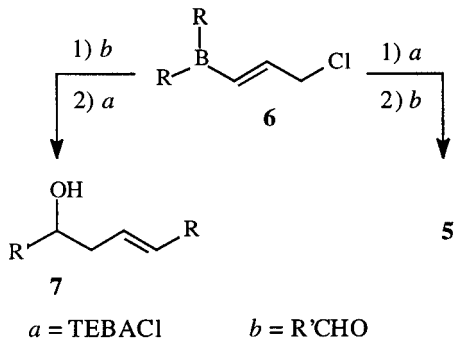
Figure 1

Recently we developed a one-pot three component synthesis of homoallylic alcohols based on the regioselective hydroboration of propargyl bromide with dialkyl boranes. When the intermediate 3-bromo-prop-1-en-1-yl borane **3** is exposed to the action of a quaternary ammonium bromide (TEBABr) and of an aldehyde, (*Z*)-1-bromo-alk-1-en-4-ols **4** or *anti*-homoallylic alcohols **5** are obtained, depending on the order of addition of the two reagents (Scheme 1).[6,7]



Scheme 1

Here we report the synthesis of **5** and of (*E*)-homoallylic alcohols **7** by exploiting similar protocols based on propargyl chloride (Scheme 2), where the R group in **5** and **7** derives from the starting dialkylborane.



Scheme 2

The hydroboration of propargyl chloride with dialkylboranes occurs regioselectively to give **6**, as reported by Zweifel in the early 70s.[8] Exposure of **6** to a source of chloride ions, namely triethyl benzyl ammonium chloride (TEBACl), promotes a catalytic cycle (Scheme 3) based on the formation of the quaternary ate species **8**. Anionotropic migration of an alkyl substituent from boron to carbon follows, regenerating a free chloride ion and leading to the allylic species **9**. The main difference between the use of propargyl bromide and chloride lies on the fact that, while bromide displays a migratory aptitude higher than cyclohexyl,[6] chloride does not compete with the simple

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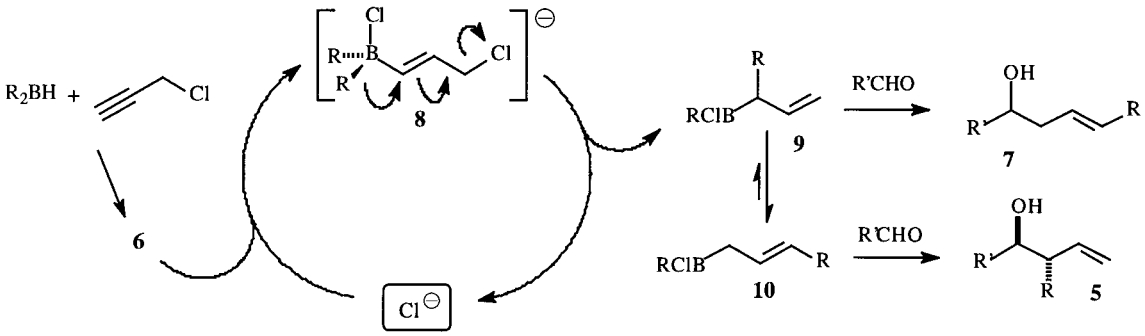

	R	R'		R	R'		R	R'		R	R'
a	cC_6H_{11}	Ph	**c**	cC_6H_{11}	Me_2CH	**e**	cC_6H_{11}	cC_6H_{11}	**g**	nC_8H_{17}	cC_6H_{11}
b	cC_6H_{11}	nC_6H_{13}	**d**	cC_6H_{11}	PhCH=CH	**f**	nC_8H_{17}	Ph	**h**	siamyl	Ph

Scheme 3

Table Synthesis of *anti*-homoallylic alcohols **5** and (*E*)-homoallylic alcohols **7** in THF

Entry	R in R_2BH	R'CHO	Protocol	t_{eq} (h)	T_{eq}	**5** Yield[a] (*anti*/*syn*)[b]	**7** Yield[a] (*E*/*Z*)[c]
1	cyclohexyl	PhCHO	**A**	-	-	**5a** nd[d]	**7a** 82% (65/35)
2	cyclohexyl	$CH_3(CH_2)_5CHO$	**A**	-	-	**5b** 9%	**7b** 52% (90/10)
3	cyclohexyl	$(CH_3)_2CHCHO$	**A**	-	-	**5c** 6%	**7c** 44% (80/20)
4	cyclohexyl	PhCH=CHCHO	**A**	-	-	**5d** nd[d]	**7d** 80% (55/45)
5	cyclohexyl	$cC_6H_{11}CHO$	**A**	-	-	**5e** 4%	**7e** 80% (72/28)
6	*n*-octyl[e]	PhCHO	**A**	-	-	**5f** nd[d]	**7f** 44% (98/2)
7	*n*-octyl[e]	$cC_6H_{11}CHO$	**A**	-	-	**5g** nd[d]	**7g** 41% (88/12)
8	siamyl	PhCHO	**A**	-	-	**5h** nd[d]	**7h** 42% (>98/2)
9	cyclohexyl	PhCHO	**B**	1	25°C	**5a** 68% (>98:2)	**7a** nd[d]
10	cyclohexyl	$CH_3(CH_2)_5CHO$	**B**	1	25°C	**5b** 65% (>98:2)	**7b** nd[d]
11	cyclohexyl	$(CH_3)_2CHCHO$	**B**	1	25°C	**5c** 22% (>98:2)	**7c** nd[d]
12	cyclohexyl	PhCH=CHCHO	**B**	1	25°C	**5d** 86% (>98:2)	**7d** nd[d]
13	cyclohexyl	$cC_6H_{11}CHO$	**B**	1	25°C	**5e** 87% (>98:2)	**7e** nd[d]
14	*n*-octyl[e]	PhCHO	**B**	1	25°C	**5f** 24% (>98:2)	**7f** 24% (98/2)
15	*n*-octyl[e]	PhCHO	**B**	12	25°C	**5f** 43% (>98:2)	**7f** nd[d]
16	*n*-octyl[e]	$cC_6H_{11}CHO$	**B**	12	25°C	**5g** 38% (96/4)	**7g** nd[d]
17	siamyl	PhCHO	**B**	1	25°C	**5h** 6%[g]	**7h** 47%[f]
18	siamyl	PhCHO	**B**	12	25°C	**5h** 35%[g]	**7h** 15%[f]
19	siamyl	PhCHO	**B**	36	25°C	**5h** 46%[g]	**7h** traces

[a] Isolated yields after column chromatography. [b] Determined by GC-MS and ^1H NMR of the crude reaction mixture. [c] Determined by GC-MS of the crude reaction mixture. [d] Not detected. [e] Thexyl octylborane was produced in situ in the presence of propargyl chloride; see experimental. [f] A single peak was detected in GC-MS analysis. [g] Two diastereomeric products among four possible enantiomeric pairs were detected by CG-MS in 85:15 ratio.

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alkyl groups (1-octyl, cyclohexyl, 3-methyl-but-2-yl) examined as migrating groups. Thus, a single reaction pathway is accessible for **8** leading to **9**, in fluxional equilibrium with **10**. The addition of **9** and **10** to an aldehyde selectively produces alcohols **7** and **5**, respectively. Exerting a control on the haptotropic rearrangement will allow to selectively produce **5** or **7**, and, to this purpose, we identified two procedures, henceforth referred to as protocol **A** and **B**. In protocol **A** the aldehyde is added to the hydroboration mixture before the addition of TEBACl. Under these conditions, as soon as the catalytic cycle starts producing **9**, addition of **9** to the aldehyde occurs with a rate higher than the haptotropic rearrangement, and **7** is selectively produced. E/Z Ratios range in the 55/45 – 98/2 interval, depending on the nature of R and R' groups (entries 1-8).

On the other hand, in protocol **B** an equilibration time (t_{eq}) between the addition of TEBACl and the aldehyde is adopted in order to allow the conversion of **9** into the thermodynamically more stable **10** to occur. The extension of t_{eq} depends on the rearrangement rate which, in turn, mainly depends on the nature of the alkyl substituent R. When R = cyclohexyl conversion of **9** into **10** is complete in 1 h at 25 °C, while 12 h and 36 h are required when R = octyl or siamyl, respectively.

We wish to emphasize that chemical yields reported in the Table refer to isolated and cumulative yields of a sequence of two hydroboration steps, a quaternization process, migration, haptotropic rearrangement, addition to an aldehyde and final oxidative quenching.

The main difference between the one-pot protocol here reported and the previously reported synthetic procedure based on the use of propargyl bromide[6] lies on the high stability of 3-chloro-prop-1-en-1-yl borane **6** compared to 3-bromo-prop-1-en-1-yl borane **3**. This allows to develop procedures which are both simpler and more chemoselective since: i) propargyl chloride has not to be distilled immediately prior to use, ii) products deriving from chloride migration have been never detected, iii) formation of (*E*)-homoallylic alcohols **7** occurs in higher yield (e.g. compare 82% in entry 1 and 55% obtained starting from propargyl bromide), and iv) a change of solvent is not required, while THF must be replaced by a pentane-dichloromethane solution when **7** is prepared from propargyl bromide.

In conclusion, the preparation of costitutionally and stereochemically defined homoallylic alcohols **5** and **7** is reported, based on two very simple synthetic procedures differing in the reagent addition order. The one-pot three components syntheses developed involve a sequence of four reactions: i) formation of a dialkylborane, ii) hydroboration of propargyl chloride, iii) quaternization with TEBACl, iv) reaction of the resulting allylic boranes with an aldehyde. Depending on the order of addition of TEBACl and the aldehyde the overall process may be addressed toward the formation of **5** or **7**.

General procedure for the synthesis of (*E*)-homoallylic alcohols (7).[9] Protocol A.

Entry 1: (*E*)-1-Phenyl-4-cyclohexyl-but-3-en-1-ol (7a). $BH_3{\cdot}SMe_2$ (0.5 mL, 2 M solution in THF, 1 mmol) was added at 0 °C to a solution of cyclohexene (0.2 mL, 2 mmol) in THF (2 mL) and the reaction mixture was vigorously stirred at 0 °C for 1h. Propargyl chloride (0.075 mL, 1 mmol) was added and the mixture was stirred for an additional hour, until the white precipitate of dicyclohexyl borane dissolved. Benzaldehyde (0.1 mL, 1 mmol) was added followed by TEBACl (0.012 g) and the mixture was was stirred at 25 °C for 3 h. The reaction mixture was quenched at 0 °C by consecutive addition of 3 N NaOH and 30% H_2O_2 and finally stirred for 30 min. The aqueous layer was extracted with ether (3 × 5 mL), the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash-chromatography (SiO_2, cyclohexane:ether 95:5) afforded 0.19 g (0.82 mmol, 82%) of **7a**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.98-1.40 (m, 5H), 1.57-1.82 (m, 5H), 1.90-2.05 (m, 1H), 2.34-2.62 (m, 2H), 4.68 (dd, *J* = 5.1/8.1 Hz, 1H), 5.36 (dt, *J* = 7.8 /15.6 Hz, 1H), 5.54 (dd, *J* = 6.6/15.6 Hz, 1H), 7.22-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 26.0, 26.1, 33.0, 40.6, 42.7, 73.4, 122.7, 125.7, 127.1, 128.1, 140.7, 143.9; MS (EI): m/z (%) = 124 (26), 107 (100), 82 (18), 79 (63), 77 (37), 67 (13), 55 (7). $C_{16}H_{22}O$ (230.35): calcd C 83.43, H 9.63; found C 83.49, H 9.70.

General procedure for the synthesis of *anti*-homoallylic alcohols 5.[9] Protocol B.

Entry 12: (1*E*)-1-Phenyl-4-cyclohexyl-esa-1,5-dien-3-ol (5d). $BH_3{\cdot}SMe_2$ (0.5 mL, 2 M solution in THF, 1 mmol) was added at 0 °C to a solution of cyclohexene (0.2 mL, 2 mmol) in THF (2 mL) and the reaction mixture was vigorously stirred at 0 °C for 1 h. Propargyl chloride (0.065 mL, 1 mmol) was added and the mixture was stirred for an additional hour, until the white precipitate of dicyclohexyl borane dissolved. TEBACl (0.015 g) was added and the reaction mixture was equilibrated with stirring for 1 h while temperature was allowed to raise to 20 °C, then cinnamaldehyde (0.25 mL, 2 mmol) was added and the mixture was allowed to react at r.t. for 3 h. The reaction mixture was quenched at 0 °C by the consecutive addition of 3 N NaOH and 30% H_2O_2 followed by stirring for 30 min. The aqueous layer was extracted with ether (3 × 5 mL), the combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash-chromatography (SiO_2, cyclohexane:ether 95:5) afforded 0.44 g (1.7 mmol, 86%) of **5d**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.92-1.34 (m, 5H), 1.46-1.81 (m, 6H), 1.94-2.01 (m, 1H), 4.31-4.37 (m, 1H), 5.13 (dd, *J* = 2.1/17.0 Hz, 1H), 5.26 (dd, *J* = 2.1/10.5 Hz, 1H), 5.80 (dt, *J* = 10.5/17.0 Hz, 1H), 6.24 (dd, *J* = 7.5/16.0 Hz, 1H), 6.60 (d, *J* = 16.0 Hz, 1H), 7.20-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 26.38, 26.43, 26.5, 31.8, 37.8, 56.9, 72.3, 118.8, 126.3, 127.4, 128.4, 131.1, 136.5, 136.7; MS (EI): m/z (%) = 133 (100), 115 (14), 103 (11), 91 (8), 81 (8), 77 (16), 67 (8), 55 (34). $C_{18}H_{24}O$ (256.39): calcd C 84.32, H 9.44; found C 84.27, H 9.47.

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References and Notes

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