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Regio- and Stereoselective Deuteration of Allylic Chlorides Controlled by Neighboring Alcohol or Ether Groups

Pher G. Andersson

Department of Organic Chemistry, Uppsala University,
Box 531, S-751 21, Uppsala, Sweden

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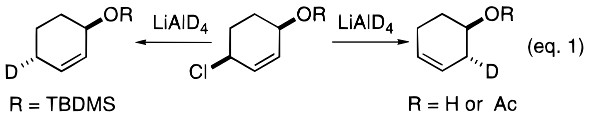
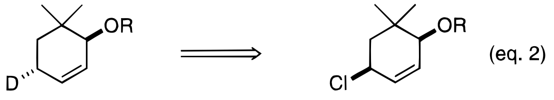
The regio- and stereoselective functionalization of allylic substrates constitutes an important synthetic method in organic chemistry.[1] Taken together with the fact that many mechanistic studies rely upon the availability of selectively deuterated compounds, it is highly desirable to develop new methods for the selective incorporation of deuterium in an allylic position. We now report on a novel reduction of allylic halides in which the regio- and stereochemical outcome of the reaction can be easily controlled by an adjacent oxygen functionality (eq 1).



In the course of our mechanistic studies on the palladium-catalyzed elimination of allylic acetates[2] there was a need for specifically deuterium labeled allylic alcohols which were anticipated to be readily available via reduction of allylic chlorides **1** with either lithium triethylborodeuteride (Super-Deuteride, $LiBEt_3D$) or lithium aluminum deuteride ($LiAlD_4$) (eq 2).

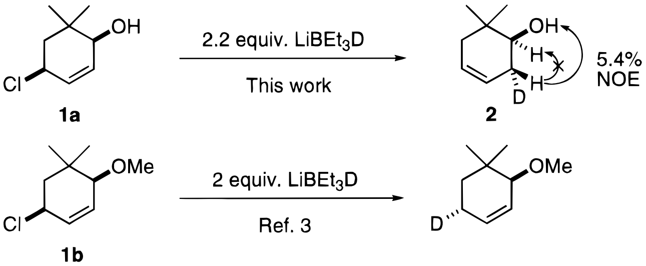


1

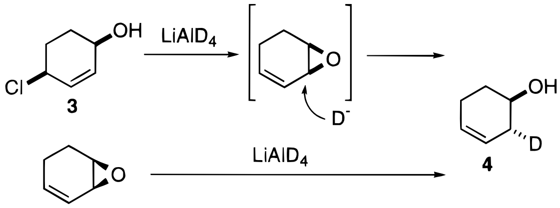
However, when chloro alcohol **1a** was treated with Super-Deuteride at 0 °C homoallylic alcohol **2** was obtained as the sole product. It was clear that it was the unprotected alcohol which determined the stereochemical outcome of the reaction since the corresponding methyl ether **1b** has been previously reported[3] to yield the expected deuterated allylic alcohol under the same reaction conditions (Scheme 1). The stereochemical relationship between the deuterium and the alcohol was established by NOE studies and was found to be *trans*, thus excluding an S_N2' *syn* substitution of the chloride.

The formation of homoallylic alcohol **2** is best explained by a rapid formation of an intermediate vinyl epoxide (Scheme 2). This is presumably formed by a fast deprotonation of the unprotected alcohol by the deuteride and a subsequent intramolecular S_N' *syn* displacement of the chloride.[4] The addition of deuteride to the resulting vinyl epoxide is likely to take place on the allylic carbon due to both steric and electronic effects,[5] which is in agreement with the observed product.[6] In order to strengthen this hypothesis, a control experiment was carried out in which 3,4-epoxycyclohexene[7] was shown to give the same product as **3** when reduced with $LiAlD_4$ (Scheme 2). The intermediacy of a vinyl epoxide is also suggested by the fact that both *cis* and *trans* chloro alcohols **3** and **5** gave rise to the same diastereomer of homoallylic alcohol **4** (see Table 1).

Scheme 1



Scheme 2



Furthermore, reduction of acetylated chloro alcohol **7** furnished the same regioisomer as the unprotected alcohol, presumably via a fast reduction of the ester which results in the same vinyl epoxide intermediate as for **3**. The readily available stereodefined chloroacetates from the chloroacetoxylation protocol developed by Bäckvall[8] should make this transformation of broad scope in organic synthesis.

A complete change of the regioselectivity could easily be obtained by simply protecting the alcohol as its silyl ether prior to reduction. When the protected alcohols (entries 8−10, Table 1) were subjected to the reduction, allylic alcohols **15-17** were produced in good yield and with excellent regioselectivity. A number of substrates were tried, and the results are summarized in Table 1.

It should also be noted that this stereoselective process is not limited to cyclic allylic chlorides. The reduction of the acyclic chloroacetate **13** (entry 7, Table 1) resulted in the highly regio- and stereoselective formation of homoallylic alcohol **14**.

In conclusion, we have shown that regio- and stereocontrol can be achieved by use of an adjacent alcohol or the corresponding silyl ether in the reduction of allylic chlorides. This methodology should prove to be of importance for the regio- and stereoselective synthesis of deuterated compounds.

Experimental Section

^1H NMR (200, 300, or 400 MHz) and ^{13}C NMR (50, 75, or 100 MHz) spectra were determined for chloroform-*d* solutions unless otherwise stated, and tetramethylsilane (for ^1H) or the choroform

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[1] For a review, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.

[2] Andersson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1.

[3] Rabasco, J. J.; Kass, S. R. *J. Org. Chem.* **1993**, *58*, 2633.

[4] Evidence for intramolecular S_N2' *syn* displacements of allylic acetates in the analogous formation of vinylcyclopropanes has previously been reported: Bäckvall, J. E.; Vågberg, J. O.; Genét, J. P. *J. Chem. Soc., Chem. Commun.* **1987**, 159.

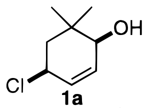
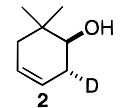
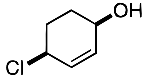
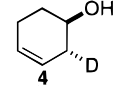
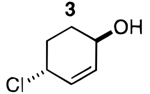
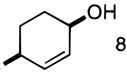
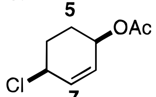
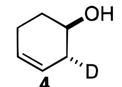
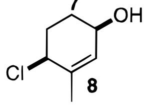
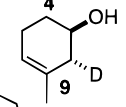
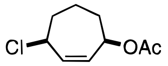
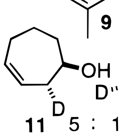
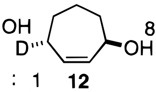
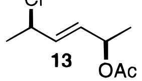
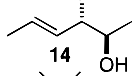
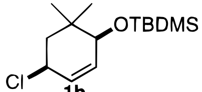
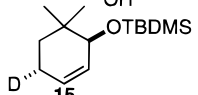
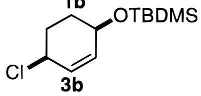
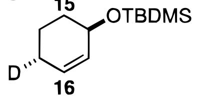
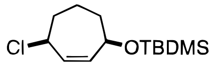
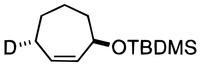
[5] Gorzynski Smith, J. *Synthesis* **1984**, 629.

[6] (a) A similar example has been reported by Uebel *et al.*[6b] In this case nearly identical reactivities were observed for both *cis*- and *trans*-4-(phenylthio)-2-cyclohexen-1-yl 3,5-dinitrobenzoate, and this was explained by a common intermediate episulfonium ion. (b) Uebel, J. J.; Milaszewski, R. F.; Arlt, R. E. *J. Org. Chem.* **1977**, *42*, 585.

[7] The 3,4-epoxycyclohexene was prepared from 1,3-cyclohexadiene according to the method reported by Korach, M.; Nielsen, D. R.; Rideout, W. H. *J. Am. Chem. Soc.* **1960**, *82*, 4328.

S0022-3263(96)00188-0 CCC: $12.00

Table 1. Reduction of Allylic Chlorides with $LiAlD_4$

entry		temp		yield
1	 **1a**	rt	 **2**	81 %
2	 **3**	rt	 **4**	83 %
3	 **5**	-20°	 **4** 7 : 2  **6**	84 %
4	 **7**	rt	 **4**	86 %
5	 **8**	rt	 **9**	87 %
6	 **10a**	-10°	 **11** 5 : 1  **12**	85 %
7	 **13**	-5°	 **14**	87 %^{a,b}
8	 **1b**	rt	 **15**	85 %
9	 **3b**	rt	 **16**	78 %
10	 **10b**	rt	 **17**	80 %

[a] Structure tentatively assigned. [b] Contains <10% of allylic alcohol.

signal at 77.0 ppm (for ^{13}C) was used as reference. IR spectra were obtained for thin films or CH_2Cl_2 solutions, and only the strongest/structurally most important peaks are listed. Diethyl ether was distilled under nitrogen from purple solutions of Na/benzophenone. Merck silica gel 60 (240−400 mesh) was used for flash chromatography. Commercial $LiAlD_4$ (Dr. Glaser AG, Basel) and $LiBEt_3D$ (Aldrich) were handled and stored under argon. Chloroacetates were prepared via chloroacetoxylation of the correspnonding 1,3-dienes.[8] Chloro alcohols were prepared by DIBALH reduction of the corresponding chloro acetates.[9]

Reduction of 1a with $LiBEt_3D$. $LiBEt_3D$ (1.1 mL 1M in THF, 1.1 mmol) was added dropwise to a solution of **1a** (0.5 mmol, 80 mg) in THF (3 mL) under Ar at rt. The resulting mixture was allowed to stir at rt until the reaction was complete according to TLC. Water (one drop) was added to quench the excess deuteride, and then 2 M NaOH (1 mL) and 30% H_2O_2 (1 mL) were added to oxidize the boranes. The aqueous layer was extracted with ether (3 × 3 mL), and the combined organic phases were washed with brine (3 mL) and dried ($MgSO_4$). The solvent was removed by distillation at atmospheric pressure to yield **2** (49 mg, 76%).

Method A (Reduction of Chloro Alcohol with $LiAlD_4$). A solution of **3** (68 mg, 0.5 mmol) in ether (0.5 mL) was added dropwise to a stirred solution of $LiAlD_4$ (42 mg, 1.0 mmol) in anhydrous ether (3 mL) under Ar at rt. The reaction was monitored by TLC, and when complete the solution was cautiously treated with water (0.042 mL), NaOH (2 M, 0.084 mL), and water (0.042 mL), respectively. After an additional 20 min the resulting slurry was dried over $MgS0_4$ and filtered. The solvent was removed by distillation at atmospheric pressure to yield **4** (40 mg, 83%) as an oil.

Method B (Reduction of Chloroacetate with $LiAlD_4$). A solution of **7** (87.3 mg, 0.5 mmol) in ether (0.5 mL) was added dropwise to a stirred solution of $LiAlD_4$ (63 mg, 1.5 mmol) in anhydrous ether (3 mL) under Ar at rt. The reaction was monitored by TLC, and when complete the solution was cautiously treated with water (0.063 mL), NaOH (2 M, 0.126 mL), and water (0.063 mL), respectively. After an additional 20 min, the resulting slurry was dried over $MgS0_4$ and filtered. The solvent was removed by distillation at atmospheric pressure to yield **4** (42 mg, 86%) as an oil: ^1H NMR (400 MHz) δ 5.66 (dm, J = 10.8 Hz, 1 H), 5.55 (dm, J = 10.8 Hz, 1 H), 3.94 (m, 1 H), 2.33 (m, 1 H), 2.24−2.05 (m, 2 H), 1.86 (m, 1 H), 1.77−1.56 (m, 2 H); ^{13}C NMR (50 MHz) δ 126.8, 123.9, 66.8, 33.8 (t, J = 19.4 Hz), 30.7, 23.5; IR 3356, 3026, 2923, 1072, 1051 cm^{-1}; high-resolution EI MS m/z calcd for C_6H_9DO (M^+) 99.0793, found 99.0794. Anal. Calcd for C_6H_9DO: C, 72.7; H, 11.2. Found: C, 73.0; H, 11.2.

Method C (Reduction of Silylated Chloro Alcohol with $LiAlD_4$). A solution of **3b** (123 mg, 0.5 mmol) in ether (0.5 mL) was added dropwise to a stirred solution of $LiAlD_4$ (25 mg, 0.6 mmol) in anhydrous ether (3 mL) under Ar at rt. The reaction was monitored by TLC, and when complete the solution was cautiously treated with water (0.025 mL), NaOH (2 M, 0.050 mL), and water (0.025 mL), respectively. After an additional 20 min, the resulting slurry was dried over $MgSO_4$ and filtered. The solvent was removed by distillation at atmospheric pressure to yield **16** (83 mg, 78%) as an oil: ^1H NMR (300 MHz) δ 5.75 (dm, J = 10.4 Hz, 1 H), 5.62 (dm, J = 10.4 Hz, 1 H), 4.22 (m, 1 H), 2.03−1.81 (m, 3 H), 1.52−1.48 (m, 2 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz) δ 131.2, 129.0, 66.7, 32.0 (t, J = 19.2 Hz), 26.0, 24.9, 19.7, 18.3, −4.5, −4.6; IR 3027, 2930, 2858, 1253, 1086, 1022 cm^{-1}; high-resolution EI MS m/z calcd for $C_{12}H_{23}DOSi$ (M^+) 213.1658, found 213.1659. Anal. Calcd for $C_{12}H_{23}DOSi$: C, 67.5; H, 11.8. Found: C, 67.3; H, 11.6.

Reduction of 3,4-epoxycyclohexene (1.0 mmol, 96mg) was done according to method C at rt and yielded **4** (72 mg, 73%).

Reduction of **1a** (0.5 mmol, 80 mg) using method A at rt yielded **2** (52 mg, 81%): ^1H NMR (300 MHz) δ 5.59 (dm, J = 10.3 Hz, 1 H), 5.52, (dm, J = 10.3 Hz, 1 H), 3.49 (m, 1 H), 2.31 (m, 1 H), 1.95 (dm, J = 16.8 Hz, 1 H), 1.82 (dm, J = 16.8 Hz, 1 H), 1.55 (br s, 1 H), 0.93 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz) δ 126.1 123.1, 73.8, 37.3, 31.3 (t, J = 19.1 Hz), 29.7, 26.2, 22.0; IR 3385, 3025, 2953, 2220, 1470, 1364, 1080, 1058, 1023 cm^{-1}; high-resolution EI MS m/z calcd for $C_8H_{13}DO$ (M^+) 127.1106, found 127.1107. Anal. Calcd for $C_8H_{13}DO$: C, 75.5; H, 11.9. Found: C, 75.6; H, 12.0.

Reduction of **5** using Method A at −20 °C resulted in a 7:2 mixture of **4** and **6** (41 mg, 84%): ^1H NMR for **6** (as a mixture with **4**, 300 MHz) δ 5.84 (dm, J = 10.3 Hz, 1 H), 5.75 (dm, J = 10.3 Hz, 1 H), 4.19 (m, 1 H), 2.08−1.53 (m, 6 H); ^{13}C NMR (75 MHz) δ 130.4, 129.8, 65.4, 31.4 (t, J = 19.5 Hz) 25.0, 18.9.

Reduction of **8** (0.5 mmol, 73 mg) using method A at rt yielded **9** (49 mg, 87%): ^1H NMR (200 MHz) δ 5.38 (m, 1 H), 3.97 (m, 1 H), 2.22 (m, 1 H), 2.17−2.02 (m, 2 H), 1.88−1.50 (m, 4 H), 1.67 (br s, 3 H); ^{13}C NMR (50 MHz) δ 133.2, 122.5, 69.3, 40.7 (t, J = 19.4 Hz), 32.4, 25.5, 25.1; IR 3355, 2926, 2132, 1439, 1376, 1080, 1037 cm^{-1}; high-resolution EI MS m/z calcd for $C_7H_{11}DO$ (M^+) 113.0950, found 113.0952. Anal. Calcd for $C_7H_{11}DO$: C, 74.3; H, 11.6. Found: C, 74.4; H, 11.8.

Reduction of **10a** (0.5 mmol, 94 mg) using method B at rt yielded **11** and **12** (66 mg, 85%) in a 4:1 ratio: ^1H NMR for **11** (as a mixture with **12**, 300 MHz) δ 5.93 (app dt, J = 6.9, 10.4 Hz, 1 H), 5.62 (dd, J = 7.8, 10.4 Hz, 1 H), 3.71 (m, 1 H), 2.34 (m, 1 H), 2.17−1.98 (m, 3 H), 1.80−1.51 (m, 3 H), 1.40 (m, 1 H); ^{13}C NMR for **11** (as a mixture with **12**, 300 MHz) δ 134.8, 125.9, 69.0, 40.8, 36.8 (t, J = 19.5 Hz), 28.3, 23.1; IR 3337, 3022, 2923, 2854, 2127, 1445, 1285, 1107, 1073, 1042 cm^{-1}; high-resolution EI MS m/z calcd for $C_7H_{11}DO$ (M^+) 113.0950, found 113.0951. Anal. Calcd for $C_7H_{11}DO$: C, 74.3; H, 11.6. Found: C, 74.5; H, 11.7.

Reduction of **13** (0.5 mmol, 88 mg) using method B at −5 °C yielded **14** (44 mg, 87%): ^1H NMR (200 MHz) δ 5.57 (dd, J = 5.3, 15.8 Hz, 1 H), 5.42 (dd, J = 5.9, 15.8 Hz, 1 H), 3.78 (app p, J = 5.7 Hz, 1 H), 2.17 (m, 1 H), 1.69 (d, J = 5.9 Hz, 3 H), 1.25 (d, J = 6.3 Hz); ^{13}C NMR (50 MHz) δ 132.4, 123.5, 66.7, 40.6 (t,

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(8) (a) Bäckvall, J. E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676. (b) Bäckvall, J. E.; Granberg, K. L.; Hopkins, R. B. *Acta Chem. Scand.* **1990**, *44*, 492.

(9) Schink, H. E.; Petterson, H.; Bäckvall, J. E. *J. Org. Chem.* **1991**, *56*, 2769.

J = 19.3Hz), 25.7, 22.7; IR 3353, 2945, 2876, 1474, 1375, 1030 cm^{-1}; high-resolution EI MS m/z calcd for $C_6H_{11}DO$ (M$^+$) 101.0950, found 101.0952. Anal. Calcd for $C_6H_{11}DO$: C, 71.2; H, 13.0. Found: C, 71.3; H, 13.2.

Reduction of **1b** (0.5 mmol, 137 mg) using method C at rt yielded **15** (103 mg, 85%): ^{1}H NMR (200 MHz) δ 5.63 (dm, J = 10.2 Hz, 1 H), 5.47 (app dt J = 2.3, 10.2 Hz, 1 H), 3.80 (m, 1 H), 2.00 (m, 1 H), 1.49 (dd, J = 6.1, 13.0 Hz, 1 H), 1.39−1.23 (m, 2 H), 0.91 (s, 12 H), 0.85 (s, 3 H), 0.06 (s, 6 H); ^{13}C NMR (50 MHz) δ 130.8, 127.3, 74.5, 34.0 (t, J = 19.5 Hz), 27.4, 25.9, 22.3, 20.7, 18.1, 14.1, −4.0, −4.9; IR 2930, 2886, 1473, 1254, 1093, 1071, 1007 cm^{-1}; high-resolution EI MS m/z calcd for $C_{14}H_{27}DOSi$ (M$^+$) 241.1971, found 241.1972. Anal. Calcd for $C_{14}H_{27}DOSi$: C, 69.6; H, 12.1. Found: C, 69.4; H, 11.8.

Reduction of **10b** (0.5 mmol, 130 mg) using method C at rt yielded **17** (91 mg, 80%): ^{1}H NMR (200 MHz) δ 5.71 (m, 2 H), 4.35 (dm, J = 8.3 Hz), 2.10−1.47 (m, 6 H), 1.30 (m, 1 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz) δ 139.8, 128.8, 72.8, 37.0, 28.2 (t, J = 19.2 Hz), 27.2, 26.6, 25.9, 18.2, −4.7, −4.8; IR 3024, 2929, 2126, 1472, 1254, 1071, 1006 cm^{-1}; high-resolution EI MS m/z calcd for $C_{13}H_{25}DOSi$ (M$^+$) 227.1815, found 227.1816. Anal. Calcd for $C_{13}H_{25}DOSi$: C, 68.7; H, 12.0. Found: C, 68.5; H, 11.6.

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