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# ALTERNATING HIGH REGIOSELECTION IN METHYL GROUP TRANSFER TO ALICYCLIC OXIRANES. SIGNIFICANCE OF THE PRESENCE OF A REMOTE POLAR GROUP

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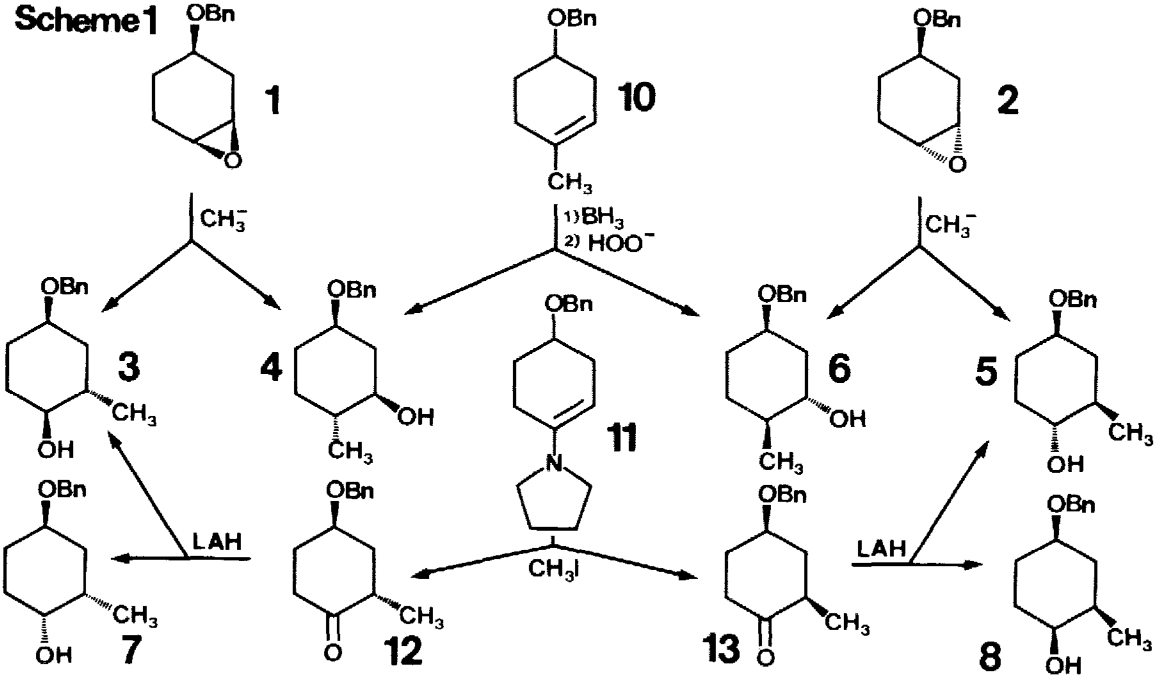
**Summary**: *An alternating high regiocontrol of the methylating ring opening of oxiranes* **1** *and* **2** *by means of metal-assisted chelating or non-chelating processes is reported.*

Oxiranes constitute an important class of organic compounds, particularly useful for the contemporary construction of two adjacent chiral centers in molecules. The oxirane ring opening process under stereo- and regiochemical control can be successful in the synthesis of complex molecules such as natural organic substances.[1]

With anti stereochemistry of nucleophilic ring opening of aliphatic and cycloaliphatic oxiranes providing the basis for stereocontrol, the most important challenge in the utilization of these epoxides in syntheses is the regiocontrol of the ring opening reactions of unsymmetrical systems.[2] Thus, in principle, in unsymmetrical cases, two classes of regioisomeric compounds can be obtained by switching the attacking nucleophile from one oxirane carbon to the other. The realization of methods for the regioselective ring opening of epoxides and the identification of factors able to influence the regiochemistry are therefore of importance in synthesis, particularly where C-nucleophiles are concerned.

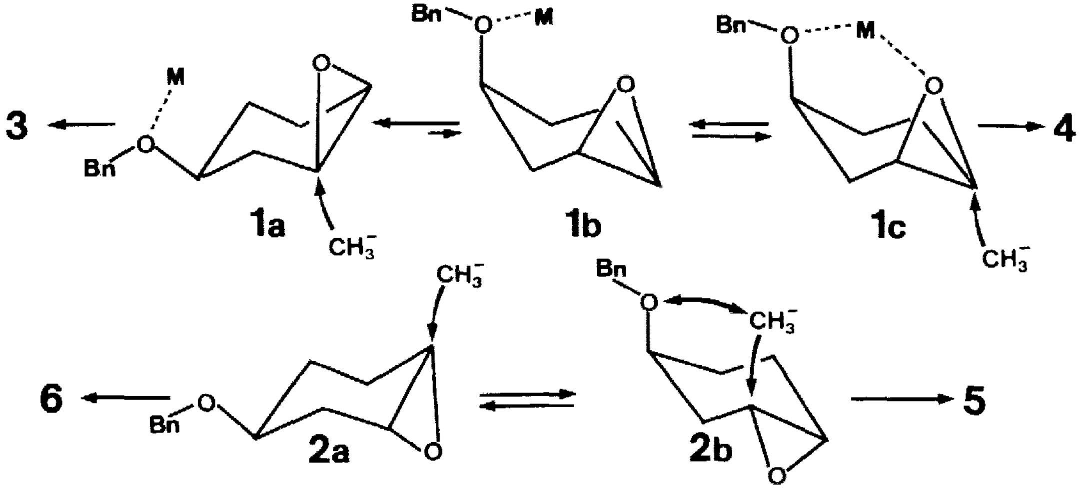
In a program aimed at controlling the regioselection of the ring opening of oxiranes through the presence of a remote polar hetero-functionality, we intended to verify this effect in conformationally semirigid models such as the diastereoisomeric 4-benzyloxycycloexene oxides *cis* **1** and *trans* **2**.[3] We report here the findings of a particular alkylative ring opening methodology by methyl group donating reagents. When the methodology was applied to the *cis* epoxide **1**, it turned out to be highly regioselective, yielding alternately the two regioisomeric methyl alcohols **3** and **4** by simple modification of the procedure protocol. Treatment of the epoxide **1** under several ring opening conditions [$Al(CH_3)_3$, $Al(CH_3)_3$-BuLi,[4] $(CH_3)_2CuLi$, $CH_3Li$] yielded largely (90-97%) and sometimes almost exclusively (98-99%) the methyl alcohol **4** (Table 1). In dramatic contrast, however, using very similar reaction conditions [$Al(CH_3)_3$ and $Al(CH_3)_3$-BuLi mixture in pentane] but in the presence of a crown ether (12-crown-4), the reaction of **1** afforded almost exclusively (98%) the regioisomer **3**. On the other hand, the behaviour of the *trans* epoxide **2** was practically indifferent to the experimental conditions : in this case mixtures of **5** and **6** were obtained in which the latter always largely predominated (>85%)(Scheme 1 and Table 1). For confirmation of their structure and regiochemistry, the methyl opened products **3**-**6**[5] were prepared by alternative independent synthetic routes as shown in scheme 1.[6]

**Scheme 1**



In epoxides **1** and **2** the polar benzyloxy group is far enough from the two oxirane carbons to make sure that it should not influence to any large extent the reactivity of the two oxirane carbons from either an electronic or a steric point of view. Therefore it could be expected that the methylative opening of epoxides **1** and **2** should largely take place through the attack of the C-nucleophile in trans diaxial fashion, in accordance with the Fürst-Plattner rule,[10] in their most stable conformations (**1a** for the *cis* epoxide and a conformational equilibrium between **2a** and **2b** for the *trans* epoxide).[3] Contrary to expectations, the reaction of **1** under the usual conditions yielded almost regiospecifically the alcohol **4** which could be assumed to arise from an unlikely almost complete diequatorial attack of the nucleophile in the most stable conformation **1a** or from a diaxial ring opening in the less stable conformation **1b** having the benzyloxy group axial. These results can be explained through a scheme which implicates the remote O-functionality and the assistance of a metal. The initial complexation of the metal (M) with the oxygen of the benzyloxy group of the epoxide **1**, either in the conformation **1a** or **1b**, can lead, through an entropically favoured intramolecular attack, to the chelated system **1c** in which the epoxide is forced to adopt the less stable conformation (**1b**) having the benzyloxy group axial. Attack of the methyl carbanion on **1c**, largely in a trans diaxial fashion according to the Fürst-Plattner rule[10], will lead to the methyl alcohol **4**, as is actually found. However, the use of a crown ether in a non-polar solvent (pentane), makes the metal-assisted process impossible; thus epoxide **1** reacts with the methyl nucleophile in the most stable conformation **1a** through the usual diaxial opening, affording mainly the regioisomeric alcohol **3**.

As regards the *trans* epoxide **2**, no possibility exists for chelating processes as found for **1**. In this case, the reaction with methyl anion could occur in either of the two almost equivalent conformations[3] **2a** and **2b** along the trans diaxial pathway, affording almost equimolar amounts of the two regioisomeric alcohols **5** and **6**. The largely preferred formation of alcohol **6** actually found can be rationalized on the basis of the unfavourable interactions of the nucleophile ($Me^-$) with the benzyloxy oxygen in the diaxial ring opening through conformation **2b**, effects not present in the reaction through conformation **2a**. According to this rationale, no particular variation in the regiochemistry is observed with epoxide **2**, as the reaction conditions are modified.



In conclusion, it appears that the remote polar functionality can exercise a large degree of control on the regiochemistry of the methylating ring opening of oxiranes through metal-assisted chelating processes. However, the addition of a crown ether can essentially reverse the regiochemical outcome of the reaction, thus leading to regioalternating processes.[11]

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**Table 1. Regioselectivity of epoxides 1 and 2 with several methyl group donating reagents.**

| epoxide | reagents | solvent | conditions[a] | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| **1** | $(CH_3)_2CuLi$ | $Et_2O$ | A[b] | 2 | 98 | | |
| **2** | | | A[b] | | | 7 | 93 |
| **1** | $CH_3Li$ | $Et_2O$ | B[b] | 3 | 97 | | |
| **1** | $Al(CH_3)_3$ | pentane | C[b] | 9 | 91 | | |
| **2** | | | C[b] | | | 15 | 85 |
| **1** | $Al(CH_3)_3$ | $CH_2Cl_2$ | C[b] | 1 | 99 | | |
| **1** | $Al(CH_3)_3$-BuLi[4] | pentane | D[b] | 1 | 99 | | |
| **2** | | | D[b] | | | 13 | 87 |
| **1** | $CH_3Li$-$Al(CH_3)$-Crown | $Et_2O$ | E[b] | 6 | 94 | | |
| **1** | $Al(CH_3)_3$-BuLi-Crown | pentane | E[b] | 98 | 2 | | |
| **2** | | | E[c] | | | 15 | 85 |
| **1** | $CH_3Li$-Crown | pentane | F[d] | 5 | 95 | | |
| **1** | $Al(CH_3)_3$-Crown | pentane | G[b] | 98 | 2 | | |

[a] A, epoxide : cuprate=1:3, -15°C/1h - 0°/4h; B, epoxide : $CH_3Li$=1:2.4, 0°/1h - r.t./2h; C, epoxide : $Al(CH_3)_3$=1:3, 0°C/1h - r.t./20h; D, epoxide : $Al(CH_3)_3$: BuLi=1:2.4:0.24, -50°C/10 min - 0°C/5h; E, **Typical procedure**: $Al(CH_3)_3$ (3 mmol) in the solvent (5 ml) is treated at -50°C under $N_2$ with BuLi (or $CH_3Li$)(0.32 mmol). After 10 min at -50°C, the reaction mixture is warmed to 0°C and treated with 12-crown-4 (3.1 mmol) and the resuting mixture vigorously stirred 15 h at r.t. The epoxide (1 mmol) is then added. After 5 h at r.t. the reaction mixture is worked-up as usually; F, as in B, with $CH_3Li$ and crown ether stirred 12 at r.t. before epoxide is added; G, as in E without adding BuLi; [b] the isolated yield of methylalcohols was 75-85%; [c] the reaction was only 50% complete; [d] the reaction was only 20% complete.

## References and notes

1) See for example Pfenninger,A. *Synthesis*, **1986**, 89 and references cited therein.

2) Chong,J.M.; Cyr,D.R.; Mar,E.K. *Tetrahedron Lett.*, **1987**, *28*, 5009 ; b) Hanamoto,T.; Katsuky,T.; Yamaguchi,M. *ibidem*, **1987**, *28*, 6195.

3) The diastereoisomeric epoxides **1** and **2** were well characterized from the stereochemical point of view. A conformational study ($^1H$ NMR) showed that **1** exists almost exclusively in the conformation **1a**, whereas **2** exhibits an almost equimolar equilibrium between conformers **2a** and **2b**. Their preparation, together with the ring opening reactions with O-nucleophiles, $Cl^-$ and hydride will be reported in a forthcoming paper.

4) Pfaltz,A.; Mattenberger,A. *Angew.Chem.Suppl.* **1982**, 161.

5) The alcohols **3-6** exhibit satisfactory analytical and spectral data ($^1H$ NMR, 200 MHz): **3** (liquid),$\delta$ 4.49(s,2H,$OCH_2$),3.62(m,1H,$H_4$),3.15(m,1H,$H_1$),1.00(d,3H,$CH_3$) **4** (mp 40-40.5 C°), $\delta$ 4.55 (s,2H,$OCH_2$),3.38 (m,1H,$H_5$),3.09 (m,1H,$H_1$),1.00 (d,3H,$CH_3$); **5** (liquid), $\delta$ 4.54 (s, 2H,$OCH_2$),3.36(m,1H,$H_4$),3.16(m,1H,$H_1$),1.03(d,3H,$CH_3$); **6** (mp 67-68 C°),$\delta$ 4.49 (s,2H,$OCH_2$), 3.81(m,1H,$H_5$),3.56(m,1H,$H_1$),1.03(d,3H,$CH_3$).

6) Reaction of 4-benzyloxycyclohexanone (**9**)[7] with $CH_3MgI$ yielded a mixture of the tertiary alcohols which were dehydrated to the olefin **10**. Hydroboration-oxidation of **10** afforded the two *trans*-2-methylcyclohexanols **4** and **6** (almost 1:1 ratio). The pyrrolidine enamine of **9** (**11**) was methylated to give a mixture of the two 2-methylcyclohexanones **12** and **13**[8] (55:45) which were separated and LAH reduced to give mixtures of the corresponding couples of the diastereoisomeric alcohols **3** and **7** (from **12**) and **5** and **8** (from **13**) in which the former ones [**3** (92%) and **5** (75%)] largely predominate.[9]

7) Prins,D.A. *Helv.Chim.Acta.*, **1957**, *15*, 1621.

8) The relative configuration of **12** and **13** can be inferred on the basis of the much larger halfband width of the signal of the proton ($H_4$) $\alpha$ to the benzyloxy group in **13** than in **12** in their $^1H$ NMR spectra:**12**, $\delta$ 4.61(s,2H,$OCH_2$),3.84 (m,1H,$W\frac{1}{2}$=7.7 Hz,$H_4$),1.02 (d,3H,$CH_3$); **13**, $\delta$ 4.6 (s,2H,$OCH_2$),3.85(m,1H,$W\frac{1}{2}$=20.1 Hz,$H_4$),1.05(d,3H,$CH_3$).

9) The stereochemistry of the LAH reduction of **11** and **12** can be easily accounted for on the basis of the usual reactivity of these systems in their most stable conformation (see for example House,H.O. "Modern Synthetic Reactions",W.A.Benjamin,Inc.,2nd ed.,p 63.

10) Fürst,A.; Plattner,P.A. Abstracts of Papers,12th International Congress of Pure and Applied Chemistry, New York, 1951, p 409.

11) We propose to call *regioalternating processes*, those procedures or strategies which afford alternately either of the two possible regioisomeric products.

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