COMMUNICATION

Effect of $BF_3{\cdot}Et_2O$ reagent on the base-promoted rearrangements of epoxides attached to eight-membered rings

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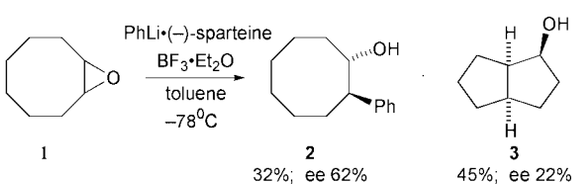
Received (in Cambridge, UK) 7th July 2000, Accepted 18th September 2000
First published as an Advance Article on the web 2nd October 2000

Cyclooctene oxide 1, cycloocta-1,3-diene oxide 4, and cycloocta-1,5-diene oxide 7 react with organolithium reagents by nucleophilic opening or α- or β-deprotonation. The addition of $BF_3{\cdot}Et_2O$ affects the course of the reaction, and also strongly accelerates it. If (−)-sparteine is present, a moderate to high asymmetric induction is obtained.

During the course of our study on the enantioselective nucleophilic opening of *meso*-epoxides promoted by aryllithium–(−)-sparteine–BF_3 reagent, we were very intrigued to notice that under these conditions cyclooctene oxide **1** provided a mixture of the expected arylcyclooctanol **2** and the (−)-*endo cis*-fused bicyclic alcohol **3** as a single diastereoisomer (Scheme 1).[1] Compound **3** was previously obtained by Cope,[2] starting



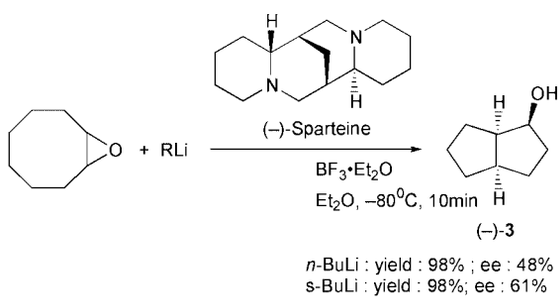
Scheme 1

from the same epoxide and using strong basic conditions ($LiNEt_2$, boiling Et_2O, 48 h). Its formation was rationalised as a result of an α-deprotonation followed by a transannular C–H insertion of the resulting carbenoid species.[3] We were very surprised by the complete stereoselectivity (and a slight enantioselectivity) of our reaction even in the presence of a strong Lewis acid such as $BF_3{\cdot}Et_2O$.

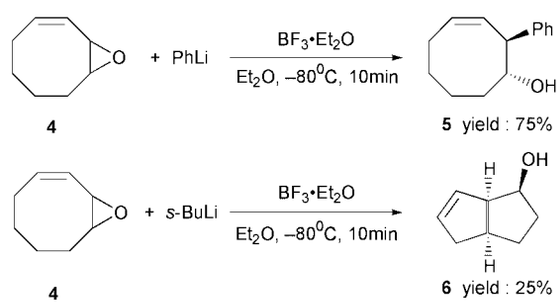
Hodgson recently reported an enantioselective version of the Cope reaction using alkyllithium bases in the presence of (−)-sparteine.[4] Under the optimum conditions (i-PrLi, Et_2O, −98 °C 6 h to room temperature 12 h) the alcohol **3** was obtained in good yield and enantiomeric excess up to 84%. Therefore, we decided to investigate the possible effects of the nature of the base on the chemo- and enantioselectivity of the reaction, in the presence of $BF_3{\cdot}Et_2O$. Our results are summarized in Scheme 2.

Using stronger bases than PhLi, the reaction was chemoselective, yielding exclusively the rearranged alcohol **3** in quantitative yield at −80 °C. Moreover, we observed a strong accelerating effect of the Lewis acid which allowed a complete conversion after the addition of the last drop of one full equivalent of $BF_3{\cdot}Et_2O$. Compared with Hodgson's results,[4] the ees are slightly different: an increase with n-BuLi (48% *versus* 31%), and a decrease with s-BuLi (61% *versus* 77%).

The effect of the nature of the base was also studied (without (−)-sparteine) on a racemic sample of the more reactive, cycloocta-1,3-diene oxide **4** (Scheme 3).



Scheme 2



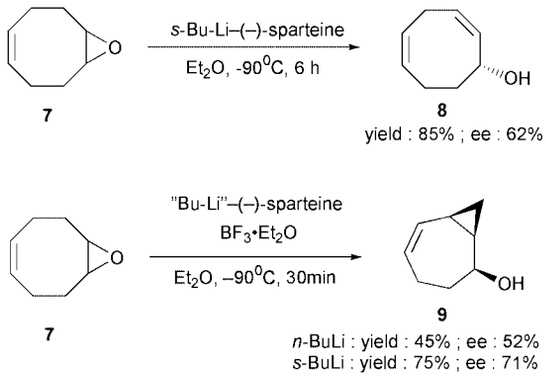
Scheme 3

The product obtained using PhLi did not result from an α-deprotonation but from a nucleophilic opening reaction yielding exclusively the homoallylic alcohol **5**. In contrast, the only product **6** obtained using s-BuLi, under the same conditions, was the result of an α-deprotonation as previously reported by Crandall, from an experiment carried out without $BF_3{\cdot}Et_2O$.[5]

We next turned our attention to *meso*-cycloocta-1,5-diene oxide **7** whose reactivity with RLi reagents has not been reported. As shown in Scheme 4, the addition of epoxide **7** to a 1:1 s-BuLi–(−)-sparteine mixture at −90 °C gave, in 85% yield, the allylic alcohol **8** resulting from a β-deprotonation with an ee up to 62%. Such enantioselective β-deprotonation of the *meso*-epoxide, without using a chiral amide type base, has been observed by Hodgson in the case of cyclohexene oxide (24%, ee 20%) and cyclododecene oxide (38%, ee 58%).[4b] Under the same conditions, but in the presence of $BF_3{\cdot}Et_2O$, the course of the reaction was dramatically changed: the major compound, obtained in 75% yield, was the cyclopropylcycloheptane alcohol **9** as a single diastereoisomer.[6] This procedure gives the first access to this alcohol enantioselectively, with an ee up to 71%! The absolute configuration could be assessed by derivatisation with (+)- and (−)-methoxymandelic acid,[7] and was found to be 1*S*,2*R*,3*S*.

In conclusion, we have demonstrated that the influence of $BF_3{\cdot}Et_2O$ in the reactions of RLi reagents on eight-membered

 DOI: 10.1039/b005474g



Scheme 4

ring epoxides is multiple.[8] It strongly accelerates carbenoidic, nucleophilic opening and β-eliminative ring-opening of the epoxide. It may also change the chemoselectivity of the reaction. Despite the presence of a strong Lewis acid, highly enantioselective rearrangements are possible. Detailed mechanistic consideration will be reported in due course.

Notes and references

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8 Typical procedure for reactions in Scheme 4.
Cycloocta-2,5-dien-1-ol: To a cooled (−90 °C) solution of (−)-sparteine (0.92 mL, 4 mmol) in ether (10 mL), under an argon atmosphere, was added dropwise a solution of s-BuLi (3 mL, 4 mmol) in hexane. After stirring for 30 minutes at this temperature, a solution of cycloocta-1,5-diene oxide (248 mg, 2 mmol) in ether (2 mL) was slowly added dropwise (over 5 minutes). After stirring for 6 hours at −90 °C, the reaction was quenched with MeOH (2 mL) and an aqueous solution of 5% H_2SO_4 (10 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), the combined organic phases were washed with brine, dried over $MgSO_4$ and filtered off. The solvents were removed under reduced pressure and the product was purified by column chromatography on silica gel with pentane–ether: 75 : 25 as eluent to afford cycloocta-2,5-dien-1-ol (186 mg, 75%) as a colourless oil. $C_8H_{12}O = 124$. Anal. Calcd. for $C_8H_{12}O$: C, 77.38, H, 9.74. Found: C, 77.30, H, 9.90%. $[\alpha]_D^{20} = -45.95$ ($c = 1.48$, $CHCl_3$) for 62% ee as measured by ^{31}P NMR according to ref. 9. ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (m, 1H), 1.86 (m, 2H), 2.09 (m, 1H), 2.84 (m, 1H), 2.84 (br s, 2H), 4.91 (m, 1H), 5.37 (m, 1H), 5.51 (m, 1H), 5.65 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 29.3, 31.8, 69.3, 127.4, 128.9, 129.3, 134.0. ^{31}P NMR (162 MHz, (1*R*,2*R*)-(+)-*N,N′*-dimethyl-1,2-diphenylethane-1,2-diamine, in the presence of S_8, $CDCl_3$) δ 83.03 (s, 19%), 83.20 (s, 81%), ee = 62%; *(1S)-bicyclo[5.1.0]oct-5-en-2-ol*: To a cooled (−90°C) solution of (−)-sparteine (0.92 mL, 4 mmol) in ether (10 mL), under an argon atmosphere, was added dropwise a solution of s-BuLi (3 mL, 4 mmol) in hexane. After stirring for 30 minutes at this temperature, a solution of $BF_3{\cdot}Et_2O$ (0.38 mL, 3 mmol) in ether (2 mL) was slowly added (over 20 minutes) in order to maintain the temperature at −90 °C. A solution of cycloocta-1,5-diene oxide (248 mg, 2 mmol) in ether (2 mL) was then slowly added dropwise (over 20 minutes) at this temperature. After stirring for 10 minutes, the reaction was quenched with MeOH (2 mL) and an aqueous solution of 5% H_2SO_4 (10 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), the combined organic phases were washed with brine, dried over $MgSO_4$ and filtered off. The solvents were removed under reduced pressure and the product was purified by column chromatography on silica gel with pentane–ether: 75 : 25 as eluent. First to elute was a colourless oil, *trans*-2-*sec*-butylcyclooct-5-en-1-ol (25 mg, 7%, $R_f = 0.42$). $C_{12}H_{22}O = 182$. IR: 3380, 2903, 1450, 1030, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, $J = 6.7$ Hz, 3H), 0.89 (t, $J = 7.2$ Hz, 3H), 1.24–2.27 (m, 14H), 3.75 (m, 1H), 4.28 (m, 1H), 5.52 (m, 1H), 5.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 12.9, 14.2, 18.2, 24.1, 24.3, 25.0, 25.4, 25.6, 28.2, 34.3, 35.1, 36.6, 44.2, 47.2, 73.6, 128.2, 128.8, 130.5, 131.1. Second to elute was a colourless oil, (1*S*)-bicyclo[5.1.0]oct-5-en-2-ol (179 mg, 72%, $R_f = 0.25$). $C_8H_{12}O = 124$. $[\alpha]_D^{20} = -83.4$ ($c = 1.03$, $CHCl_3$) for 71% ee as measured by ^{31}P NMR according to ref. 9. ^1H NMR (400 MHz, $CDCl_3$) δ 0.51 (dt, $J = 4$, 6.1 Hz, 1H), 0.87 (dt, $J = 4$, 8.9 Hz, 1H), 1.39–2.03 (m, 7H), 4.28 (m, 1H), 5.45 (ddd, $J = 2.7$, 7.6, 11 Hz, 1H), 5.78 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 15.9, 24.3, 26.9, 34.2, 72.4, 127.9, 129.6. ^{31}P NMR (162 MHz, (1*R*,2*R*)-(+)-*N,N′*-dimethyl-1,2-diphenylethane-1,2-diamine, in the presence of S_8, $CDCl_3$) δ 82.11 (s, 14.5%), 82.52 (s, 85.5%), ee = 71%. Derivatisation of this alcohol with (*R*)-(−)-2-methoxy-2-phenylacetic acid:[7] ^1H NMR (400 MHz, $CDCl_3$) δ 0.43 (dt, 13%, H_{cya}), 0.57 (dt, 87%, H_{cya}), 0.73 (dt, 14%, H_{cyb}), 0.95 (dt, 86%, H_{cyb}), 3.44 (s, 86%, OMe), 3.45 (s, 14%, OMe) (H_{cya} and H_{cyb} refer to the H_a and H_b of cyclopropane). Derivatisation of this alcohol with (*S*)-(+)-2-methoxy-2-phenylacetic acid:[7] ^1H NMR (400 MHz, $CDCl_3$) δ 0.43 (dt, 85%, H_{cya}), 0.57 (dt, 15%, H_{cya}), 0.73 (dt, 87%, H_{cyb}), 0.95 (dt, 13%, H_{cyb}), 3.43 (s, 16%, OMe), 3.45 (s, 84%, OMe).

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