Metalated Epoxides as Carbenoids. Solvent Effect on Competing Intramolecular C−H and Intermolecular C−Li Insertions in α-Alkoxy Epoxide Systems

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Received June 2, 1999

Introduction

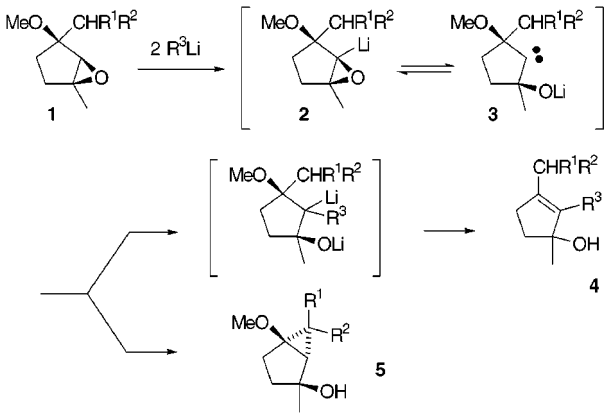
Metalated oxiranes are versatile reagents of wide scope and applicability.[1] We recently surveyed the diverse behavior of these epoxide-derived carbenoids in a review article.[2] We also reported that, upon treatment with an excess of an organolithium reagent, cyclic α-alkoxy epoxides afford allylic alcohols in a regioselective fashion (Scheme 1). This reaction was first observed in our laboratories in 1996.[3]

The reaction proceeds across the carbenoid intermediate **2**, which is derived from epoxide **1** through metalation. The insertion of the organolithium reagent, followed by instantaneous elimination of lithium methoxide (which preponderates Li_2O elimination), yields the corresponding allylic alcohol **4**. In few cases, we observed the formation of trace amount of a product (**5**) that arises from the insertion of the carbenoid species into the adjacent C−H bond. We therefore decided to probe the conditions that would favor a chemoselective intramolecular C−H over a classical intermolecular C−Li insertion into the epoxide-derived carbenoid.

Results and Discussion

Perusal of the literature indicated that the chemoselectivity of carbene-type species is solvent dependent.[4] Furthermore, we recently demonstrated that, in systems analogous to **2**, the carbene character of the key intermediate was either more or less pronounced depending on the solvent.[5] We thus examined the influence of various solvents on the selectivity observed in cyclic α-alkoxy epoxides. For this purpose, different cyclic α-methoxy epoxides were synthesized[6] starting from 3-methyl-2-cyclopenten-1-one oxide **6**[7] (Scheme 2). We obtained the expected syn α-alkoxy epoxide[8] **1** in overall yields ranging from 77 to 85%.

Scheme 1



Scheme 2

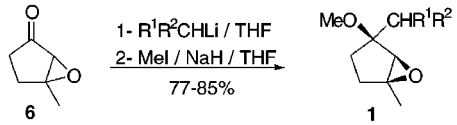
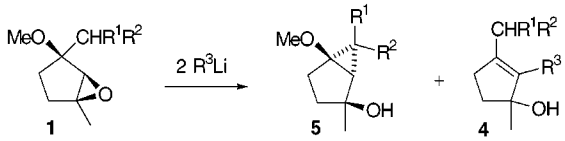


Table 1. Solvent Influence on the Chemoselectivity of the Epoxide-Derived Carbenoid



entry	R^1	R^2	R^3Li	solvent	ratio[a] 5/4
1	Me	Et	*n*-BuLi	THF	25/75[b]
2	Me	Et	*n*-BuLi	THF	29/71
3	Me	Et	*n*-BuLi	hexane	44/56
4	Me	Et	PhLi	hexane	70/30
5	*n*-Pr	H	PhLi	hexane	42/58[c]
6	H	H	PhLi	hexane	10/90

[a] Ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Reaction performed at −78 °C and allowed to warm to room temperature. [c] The utilization of *t*-BuLi as base led to the exclusive formation of **4**.

Upon treatment of the α-alkoxy epoxide **1** with 2 equiv of R^3Li, compound **1** underwent metalation and further reaction to furnish two products, **4** and **5**, in different ratios. The results are collated in Table 1.

To increase the intramolecular C−H insertion, slow addition of the organolithium reagent to a dilute solution of the epoxide (5×10^{-2} M) was found to provide the best results. In all cases the reaction afforded a combined nearly quantitative yield of products (**4** + **5**). Running

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(1) For reviews on metalated oxiranes, see: Crandall, J. K.; Apparu, M. *Org. React.* **1983**, 345−443. Satoh, T. *Chem. Rev.* **1996**, *96*, 3303−3325. For recent developments, see: Satoh, T.; Kobayashi, S.; Nakanishi, S.; Horiguchi, K.; Irisa, S. *Tetrahedron* **1999**, *55*, 2515−2528. See also: Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 7943−7946. Agami, C.; Dechoux, L.; Doris, E.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 4071−4074.

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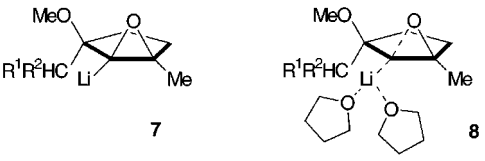
(8) The preferential formation of syn hydroxy epoxide is due to the steric hindrance of the oxirane, which directs nucleophilic addition to the side opposite to the epoxide. See: Sepùlveda, J.; Soto, S.; Mestres, R. *Bull. Soc. Chim. Fr.* **1983**, *II*, 233−236 and following papers.

10.1021/jo990887l CCC: $18.00 © 1999 American Chemical Society
Published on Web 11/20/1999

Chart 1



the reaction either at −78 °C (entry 1) or at room temperature (entry 2) in THF using *n*-BuLi as base did not influence noticeably the observed ratios; **4** was obtained as the major product in a ratio of approximately 3:1. When hexane was used as solvent, a higher C−H chemoselectivity was observed (entry 3). To minimize the intermolecular C−Li insertion, phenyllithium emerged as the reagent of choice (entry 4) since a very good selectivity in favor of compound **5** was observed. This may be rationalized by the fact that, in the absence of solvation of the carbenoid lithium in hexane, the key intermediate **2** does not decompose to the corresponding carbene **3** (Chart 1, structure **7**). The intermediacy of such an anionic species enhances the electronic repulsions with the incoming R^3Li. Insertion of C−Li into the carbenoid is thus retarded. Indeed, for intermolecular reactions that involve two anionic species, the rate of the reaction decreases with the dielectric constant of the solvent.[9]

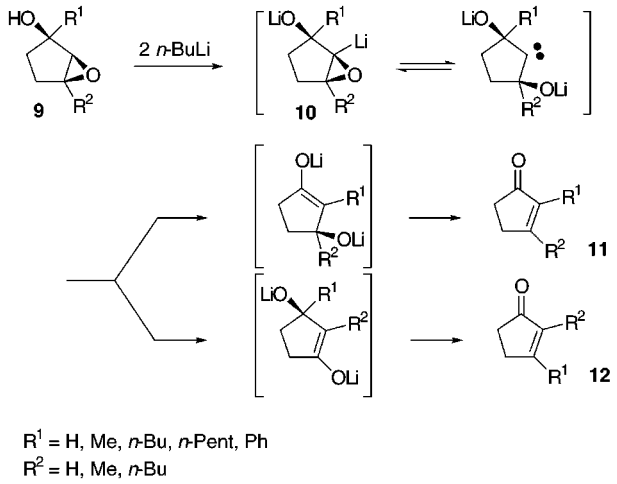
This electronic effect is minimized in THF since the solvent coordinates the lithium atom of the carbenoid species **2**. This complexation polarizes the C−Li bonds and, hence, promotes the carbene character of the key intermediate (Chart 1, structure **8**). The electrostatic repulsions at the reactive carbon center are thus minimized, thereby facilitating the approach of the organolithium reagent. The intermediacy of a species that ressembles the carbene **3** in dipolar solvents is responsible for the increased ratios of C−Li intermolecular insertion.

The substitution of the carbon bearing the labile hydrogen was also studied. We surmised that the carbenoid C−H insertion rate decreases concurrently with the substitution at the vicinal carbon atom (entries 4−6). This result is in accord with the literature.[10]

Interestingly, when the α-oxygen atom on the starting epoxide **1** was not protected as a methyl ether, the resulting α-hydroxy epoxide **9** displayed anomalous behavior (Scheme 3). We did not observe any C−H insertion when the epoxide was treated with *n*-BuLi in THF; rather, two products (**11** and **12**) that result from an alkyl 1,2-shift were obtained.[6] However, the C−Li insertion is, for the most part, insignificant. This difference in reactivity between the α-methoxy carbenoid **2** and the α-alkoxide carbenoid **10** can be attributed to an increased electrostatic repulsion (OLi) in the latter case. This favors the 1,2-rearrangement over the intermolecular insertion.

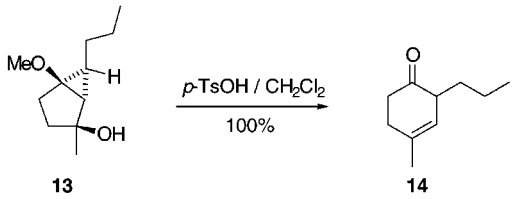
The final objective of this study was to design a new route to deconjugated cyclohexenones. Upon treatment with a catalytic amount of hydrated *p*-toluenesulfonic acid in dichloromethane, compound **13** (Table 1, entry 5) smoothly afforded substituted cyclohex-3-enone **14** in quantitative yield (Scheme 4). The reaction involves the

Scheme 3



R^1 = H, Me, *n*-Bu, *n*-Pent, Ph
R^2 = H, Me, *n*-Bu

Scheme 4



regioselective cleavage of the cyclopropane ring with elimination of the hydroxyl group.[11] The overall reaction sequence allows the transformation of cyclopentanones into β,γ-unsaturated cyclohexenones in only a few steps.

Conclusion

In summary, this paper decribes the conditions that favor an intramolecular C−H insertion above an intermolecular C−Li insertion into carbenoids derived from α-methoxy epoxides. Solvation of the carbenoid lithium atoms is decisive as regards the chemoselectivity of the process.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz using residual $CHCl_3$ (7.25 ppm) and $CDCl_3$ (77 ppm) as internal standard, respectively. Anhydrous THF and hexane were obtained by distillation over sodium. Flash column chromatography was performed on Merck silica gel (60 Å, 230−400 mesh). Reagents were purchased from Aldrich Chemical Co.

A typical experimental procedure is given for products obtained in Table 1, entry 5. Under Ar and at room temperature, PhLi (0.4 mL of a 1.8 M solution in cyclohexane/Et_2O, 2 equiv) was added dropwise, over a period of 20 min, to a stirred solution of 4-butyl-4-methoxy-1-methyl-6-oxabicyclo[3.1.0]hexane (0.066 g, 0.36 mmol, 1 equiv) in 7 mL of anhydrous hexane. The mixture was stirred at room temperature for 1 h. The reaction was then quenched with H_2O, extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude was chromatographed on NEt_3 pretreated silica (EtOAc/hexane, 2/8) to yield two products.

3-Butyl-1-methyl-2-phenylcyclopent-2-enol (C−Li insertion product, 0.044 g, 53%). ^1H NMR: δ 0.82 (t, J = 7.2 Hz, 3 H), 1.18−1.45 (m, 4 H), 1.28 (s, 3 H), 1.74 (brs, 1 H), 2.00−2.09 (m, 4 H), 2.30−2.35 (m, 1 H), 2.47−2.54 (m, 1 H), 7.20−7.36 (m,

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5 H). ^{13}C NMR: δ 13.9, 22.5, 26.7, 29.1, 30.1, 31.6, 39.7, 85.3, 126.6, 127.9, 129.5, 135.1, 136.4, 142.2. HRMS: calcd for $C_{16}H_{21}O$ $(M - H)^+$ 229.1592, found 229.1587.

5-Methoxy-2-methyl-6-propylbicyclo[3.1.0]hexan-2-ol (13) (C−H insertion product, 0.026 g, 39%). This product was obtained as a single (> 95:5) diastereomer. ^{1}H NMR: δ 0.62−0.71 (m, 1 H), 0.91 (t, J = 7.1 Hz, 3 H), 1.06−1.25 (m, 3 H), 1.19 (s, 3 H), 1.28−1.59 (m, 4 H), 1.89 (dd, J = 7.9, 12.1 Hz, 1 H), 2.04 (brs, 1 H), 2.22 (m, 1 H), 3.33 (s, 3 H). ^{13}C NMR: δ 13.9, 22.8, 24.9, 27.4, 27.5, 28.4, 36.9, 39.9, 55.6, 73.1, 79.0. HRMS: calcd for $C_{11}H_{19}O_2$ $(M - H)^+$ 183.1385, found 183.1382.

Entry 3. 2-Butyl-3-*sec*-butyl-1-methylcyclopent-2-enol, C−Li insertion product as a 1/1 mixture of diastereomers a and b (53%). ^{1}H NMR: δ 0.74 (t, J = 7.3 Hz, 3 Ha), 0.80 (t, J = 7.3 Hz, 3 Hb), 0.89−0.97 (m, 6 Ha + b), 1.29 (s, 3 Ha + b), 1.26−1.37 (m, 6 Ha + b), 1.72−2.41 (m, 7 Ha + b).^{13}C NMR: δ 12.3, 12.4, 13.9, 19.1, 19.4, 23.3, 24.4, 25.8, 26.0, 26.2, 27.8, 28.2, 33.0, 33.1, 34.3, 40.0, 40.1, 85.3, 140.3, 142.7, 143.1. HRMS: calcd for $C_{14}H_{24}$ $(M - H_2O)^+$ 192.1878, found 192.1871.

Entry 4. 3-*sec*-Butyl-1-methyl-2-phenylcyclopent-2-enol, C−Li insertion product as a 3/2 mixture of diastereomers a and b (28%). ^{1}H NMR: δ 0.74 (t, J = 7.4 Hz, 3 Ha), 0.78 (t, J = 7.3 Hz, 3 Hb), 0.94 (d, J = 6.8 Hz, 3 Hb), 0.99 (d, J = 6.9 Hz, 3 Ha), 1.26 (s, 3 Ha), 1.31 (s, 3 Hb), 1.27−1.37 (m, 3 Ha + b), 1.68 (brs, 1 Ha + b), 2.08 (m, 2 Ha + b), 2.20−2.46 (m, 2 Ha + b), 7.16−7.37 (m, 5 Ha + b). ^{13}C NMR: δ 12.2, 12.3, 19.2, 19.6, 26.5, 26.9, 27.8, 28.1, 34.7, 39.5, 85.1, 85.3, 126.8, 128.4, 129.6, 129.7, 136.4, 136.5, 142.0, 142.1, 145.9. HRMS: calcd for $C_{16}H_{21}O$ $(M - H)^+$ 229.1592, found 229.1590.

6-Ethyl-5-methoxy-2,6-dimethylbicyclo[3.1.0]hexan-2-ol, C−H insertion product as a 3/1 mixture of diastereomers a and b (65%). ^{1}H NMR: δ 0.91−1.03 (m, 3 Ha + b), 1.09 (s, 3 Ha + b), 1.18 (m, 1 Ha + b), 1.21 (s, 3 Ha), 1.22 (s, 3 Hb), 1.34−1.57 (m, 3 Ha + b), 1.85−2.06 (m, 2 Ha + b), 2.22−2.30 (m, 1 Ha + b), 2.49 (brs, 1 Ha + b), 3.28 (s, 3 Ha), 3.29 (s, 3 Hb).^{13}C NMR: δ 10.8, 11.9, 12.8, 14.1, 19.2, 22.7, 26.1, 26.6, 27.1, 28.9, 31.1, 31.8, 39.8, 40.7, 44.4, 47.6, 55.5, 55.8, 78.1, 78.2, 79.7, 79.9. HRMS: calcd for $C_{11}H_{19}O$ $(M - H)^+$ 183.1385, found 183.1379.

Entry 6. 1,3-Dimethyl-2-phenyl-cyclopent-2-enol, C−Li insertion product (81%). ^{1}H NMR: δ 1.29 (s, 3H), 1.68 (s, 3 H), 2.07 (m, 2 H), 2.42 (m, 1 H), 2.51 (m, 1 H), 7.25−7.36 (m, 5 H). ^{13}C NMR: δ 15.3, 26.7, 34.5, 39.9, 85.4, 125.3, 126.5, 127.8, 129.3, 136.2, 138.2. HRMS: calcd for $C_{13}H_{14}$ $(M - H_2O)^+$ 170.1095, found 170.1097.

5-Methoxy-2-methyl-bicyclo[3.1.0]hexan-2-ol, C−H insertion product (9%). ^{1}H NMR: δ 0.45 (dd, J = 3.9, 5.7 Hz, 1 H), 0.92 (m, 1 H), 1.19 (m, 1 H), 1.22 (s, 3 H), 1.42−1.66 (m, 2 H), 1,97 (dd, J = 7.8, 12 Hz, 1 H), 2.21 (m, 1 H), 3.33 (s, 3 H). ^{13}C NMR: δ 15.1, 24.8, 26.9, 34.7, 36.5, 55.4, 69.8, 78.9. HRMS: calcd for $C_8H_{13}O_2$ $(M - H)^+$ 141.0916, found 141.0912.

4-Methyl-2-propyl-cyclohex-3-enone (14). At rt, monohydrated *p*-toluenesulfonic acid (1 mg, cat.) was added to a solution of 5-methoxy-2-methyl-6-propylbicyclo[3.1.0]hexan-2-ol **13** (0.02 g, 0.11 mmol, 1 equiv) in 1 mL of CH_2Cl_2. The mixture was stirred at room temperature for 15 min. The reaction was then quenched with 10% Na_2CO_3. The organic layer was collected, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases are dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude only contained the desired product (0.016 g, quantitative). ^{1}H NMR: δ 0.88 (t, J = 7.2 Hz, 3 H), 1.24−1.35 (m, 2 H), 1.48−1.60 (m, 2 H), 1.75 (s, 3 H), 2.33−2.38 (m, 2 H), 2.43−2.49 (m, 2 H), 2.71 (brs, 1 H), 5.37 (m, 1 H). ^{13}C NMR: δ 14.0, 19.8, 23.0, 30.8, 34.7, 37.4, 48.1, 123.7, 134.2, 213.2. HRMS: calcd for $C_{10}H_{15}O$ $(M - H)^+$ 151.1122, found 151.1119.

Acknowledgment. Dr. J. Albert Ferreira is gratefully acknowledged for reviewing this manuscript.

JO990887L