PERKIN 1 COMMUNICATION

Regioselective S_N2 opening of α,β-ethylenic epoxides by RLi–BF_3 combination

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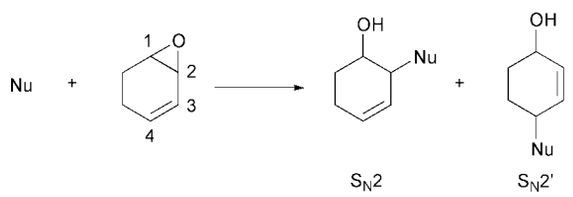
Organolithium reagents effect a regioselective S_N2 nucleophilic cleavage of α,β-ethylenic epoxides only when $BF_3{\cdot}Et_2O$ is added. The reaction works with a variety of RLi reagents and with cyclic as well as acyclic epoxides.

α,β-Ethylenic epoxides, particularly the cyclic ones, are versatile synthons in organic synthesis. The problem with these compounds concerns the regioselectivity of the nucleophilic ring opening, *via* an S_N2 or an S_N2' process (Scheme 1).

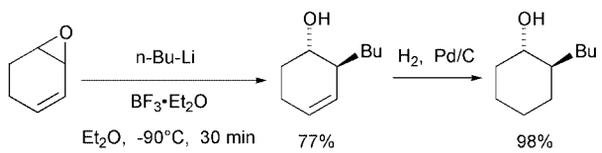


Scheme 1

Among carbon nucleophiles, organocopper reagents are known for their smooth and stereoselective reaction, where both the S_N2 and the S_N2' are *anti* processes. The regioselectivity using acyclic α,β-ethylenic epoxides has been extensively studied by several authors, and depends strongly on steric factors.[1] However, in cyclic compounds, such as cyclohexa-1,3-diene oxide, the difference in steric bias toward attack at C2 and C4 is minimised. Although lithium organocuprate reagents give excellent stereoselectivity and yield, the regioselectivity on this epoxide is poor.[1,2] A breakthrough in this area was the discovery by Marino that cyanocopper derivatives RCuCNLi afford regioselectively the S_N2' product.[3] Several synthetic applications have taken advantage of this excellent regiocontrol.[4,5]

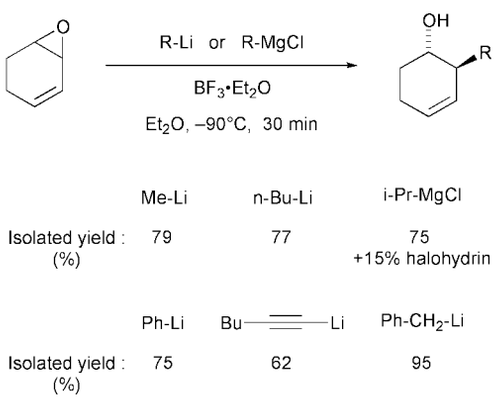
On the other hand, there are only scarce reports of a selective S_N2 ring opening.[2,6,7] It might be predicted that a harder nucleophile should have a preference for the S_N2 process, whereas a soft nucleophile (such as a copper reagent) would prefer a softer center, such as C4. Indeed, we have shown that a strong Lewis acid, $BF_3{\cdot}Et_2O$,[8] promotes the reaction of RLi and Grignard reagents at the propargylic position of an α,β-acetylenic epoxide (S_N2).[9] In a similar manner, we demonstrate in this communication that the use of $BF_3{\cdot}Et_2O$ allows regioselective attack at the C2 position by RLi and RMgCl reagents on cyclic and acyclic α,β-ethylenic epoxides.

As representative epoxides we chose cyclohexa-1,3-diene oxide and cycloocta-1,3-diene oxide. When cyclohexadiene oxide is reacted with n-BuLi, only degradation products are observed, slowly at −78 °C, but quickly at 0 °C. However, the nucleophilic opening occurs when $BF_3{\cdot}Et_2O$ is added to the reaction mixture at −78 °C.[10] Running the reaction at −90 °C improves the yield of 2-butylcyclohex-3-en-1-ol **1**. The isolated yield is good in toluene or Et_2O as solvents (75% and 77% respectively), but much lower in THF (<25%). That a clean *anti*-process is involved, was checked by hydrogenation of the double bond and comparison with authentic samples of *trans*-2-butylcyclohexanol **2**. It should be pointed out that no product arising from an S_N2' process is detected by ^1H NMR analysis of the crude product (Scheme 2).



Scheme 2

The results obtained with other organolithium reagents are shown in Scheme 3. The reaction appears to be quite



Scheme 3

general with a variety of structural types of R groups. The reaction with Grignard reagents suffers from the competitive formation of the 1,2-halohydrin.[10] This process is minimised when R–MgCl is used instead of R–MgBr or R–MgI. This 1,2-halohydrin is easily removed from the crude reaction mixture by an aqueous NaOH washing, during the workup.

The reactivity of cycloocta-1,3-diene oxide follows the same trend (Scheme 4), although the reaction has to be performed at a slightly higher temperature (−75 °C) in order to achieve goods yields. The reaction works well with moderately basic RLi, but not with strongly basic ones, such as n-BuLi or s-BuLi. Again, when Grignards reagents are used, the formation of a small amount of halohydrin is observed.

The case of cyclopentadiene oxide was extensively studied. However, in reactions with alkyllithium reagents, mixtures of several unidentified products are observed, even at low temperature. This epoxide seems too sensitive to strongly basic or Lewis acidic conditions. Only alkenyl- or alkynyl-lithium

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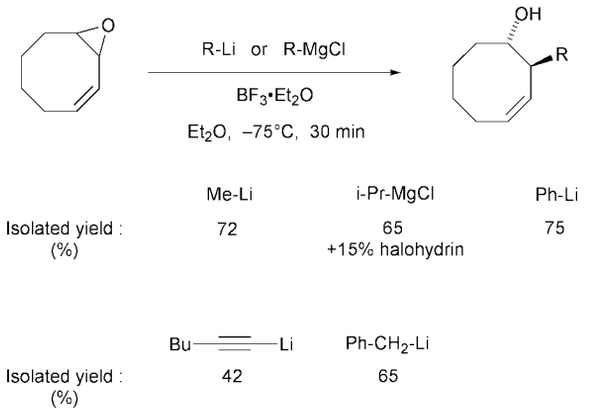
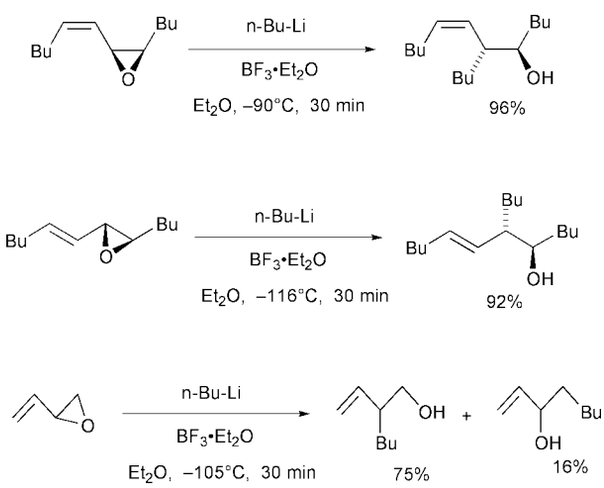


Scheme 4

reagents are known to undergo nucleophilic ring opening at the C2 position.[6]

Finally, we extended the reaction to acyclic cases having the same substitution pattern at C2 and C4, in order to have an unbiased system. (*Z,Z*)- and (*E,E*)-dodeca-5,7-diene oxides were chosen as representative substrates. Both react by a clean S_N2 process in excellent yield, under the same experimental conditions as above, although the (*E,E*) isomer has to be reacted at lower temperature. It is noteworthy that the *Z* double bond retains its configuration. In addition, butadiene oxide, despite being unsubstituted at the terminal ethylenic carbon, gives no trace of S_N2' product. However, some product from S_N2 attack at the least substituted epoxide carbon is isolated in 16% yield (Scheme 5).



Scheme 5

In conclusion, these results demonstrate that a regioselective S_N2 opening of α,β-ethylenic epoxides is indeed possible under strictly controlled experimental conditions.[11] The scope and limitations of this methodology are presently under investigation.

Notes and references

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11 Typical procedure. *trans-2-Butylcyclohex-3-en-1-ol*: cyclohexa-1,3-diene oxide (192 mg, 2 mmol) in dry Et_2O (1 ml) was added dropwise to a stirred solution of *n*-butyllithium (1.6 M in hexane, 2.5 ml, 4 mmol) in 12 ml of dry Et_2O at −95 °C, under a nitrogen atmosphere. Then $BF_3{\cdot}Et_2O$ (0.38 ml, 1.5 mmol) in dry Et_2O (2 ml) was slowly added (30 min) *via* a syringe pump in order to maintain the temperature of the reaction mixture below −95 °C. After stirring for 5 min, the reaction was quenched with MeOH (2.5 ml) and Et_3N (1.5 ml). The mixture was allowed to warm up to room temperature and was poured into 5% aqueous H_2SO_4 (10 ml). After standard work-up, the crude product was purified by column chromatography on silica gel (eluent pentane–Et_2O = 85:15) to afford 238 mg (77% yield) of *trans*-2-butylcyclohex-3-en-1-ol as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H), 1.21–2.1 (m, 12H), 3.59 (m, 1H), 5.55 (m, 1H), 5.64 (m, 1H). ^{13}C NMR 14.46, 23.42, 23.97, 29.17, 30.10, 33.07, 44.13, 71.48, 126.57, 129.30.

trans-2-Methylcyclooct-3-en-1-ol: cycloocta-1,3-diene oxide (250 mg, 2 mmol) in dry Et_2O (1 ml) was added dropwise to a stirred solution of methyllithium (2 M in ether, 3 ml, 6 mmol) in 12 ml of dry Et_2O at −75 °C, under a nitrogen atmosphere. Then $BF_3{\cdot}Et_2O$ (0.38 ml, 1.5 mmol) in dry Et_2O (2 ml) was slowly added (30 min) *via* a syringe pump in order to maintain the temperature of the reaction mixture below −75 °C. After stirring for 5 min, the reaction was quenched with MeOH (2.5 ml) and Et_3N (1.5 ml). The mixture was allowed to warm up to room temperature and poured into 5% aqueous H_2SO_4 (10 ml). After standard work-up, the crude product was purified by column chromatography on silica gel (eluent pentane–Et_2O = 80:20) to afford 202 mg (72% yield) of *trans*-2-methylcyclooct-3-en-1-ol as a colorless oil. Anal. calcd. for $C_9H_{16}O$: C, 77.09, H, 11.50. Found: C, 77.05, H, 11.56%. IR (film): 3369, 3009, 2928, 1760, 1459, 1009 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, J = 6.4 Hz, 3H, H9), 1.25–2.60 (m, 10H, H2, H5–H8, and OH), 3.39 (m, 1H, H1), 5.25 (ddd, J = 1.5, 8.9, 10.5 Hz, 1H, H3), 5.64 (m, 1H, H4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 21.7, 27.1, 28.7, 29.6, 34.8, 36.9, 77.1, 130.0, 134.6.

(*Z*)-*trans-6-Butyloct-5-en-7-ol*: (*Z,Z*)-dodeca-5,7-diene oxide (364 mg, 2 mmol) in dry Et_2O (1 ml) was added dropwise to a stirred solution of *n*-butyllithium (1.6 M in hexane, 2.5 ml, 4 mmol) in 12 ml of dry Et_2O at −90 °C, under nitrogen atmosphere. Then $BF_3{\cdot}Et_2O$ (0.38 ml, 1.5 mmol) in dry Et_2O (2 ml) was slowly added (30 min) *via* a syringe pump in order to maintain the temperature of the reaction mixture below −90 °C. After stirring for 5 min, the reaction was quenched with MeOH (2.5 ml) and Et_3N (1.5 ml). The mixture was allowed to warm up to room temperature and poured into 5% aqueous H_2SO_4(10 ml). After standard work-up, the crude product was purified by column chromatography on silica gel (eluent pentane–Et_2O = 95:5) to afford 432 mg (92% yield) of (*Z*)-*trans*-6-butyloct-5-en-7-ol as a colorless oil. Anal. calcd. for $C_{10}H_{18}O$: C, 79.93, H, 13.42. Found: C, 79.91, H, 13.30%. IR (film): 3400, 2985, 1400, 1050, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (m, 12H, H1, H12 and H16), 1.15–1.45 (m, 15H, H2–H4, H10, H11, H13-H15 and OH), 2.06 (m, 2H, H9), 2.51 (m, 1H, H6), 3.32 (m, 1H, H5), 5.10 (dd, J = 10.7, 10.7 Hz, 1H, H7), 5.53 (dt, J = 7.4, 10.7 Hz, 1H, H8). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.4, 22.8, 23.1, 23.2, 27.9, 28.6, 29.9, 31.0, 32.3, 34.1, 44.1, 75.5, 130.7, 133.0.