Regiospecific access to cyclic allylic alcohols by reductive alkylation of α-alkyloxy-epoxides

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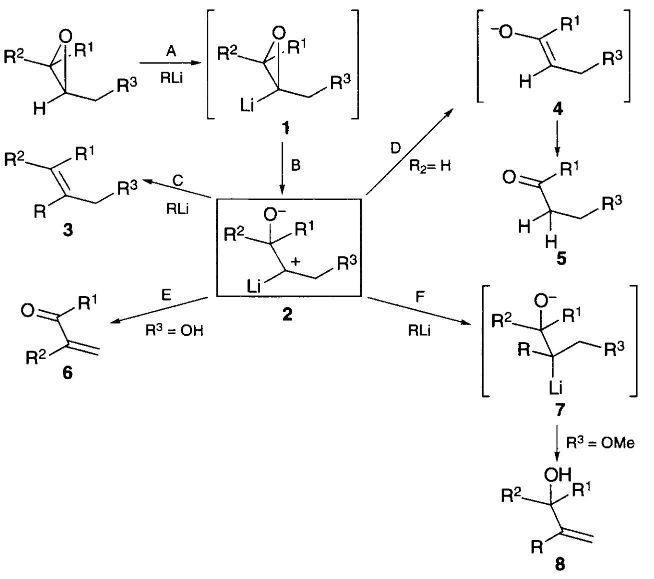
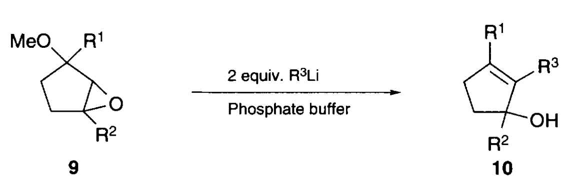
Allylic alcohols are synthesized by treatment of α-alkyloxy-epoxides with organolithium reagents; The reaction proceeds *via* a carbenoid pathway.

In the presence of a strong base epoxides exhibit many different reactivities,[1] including metallation of the oxirane ring (Scheme 1, path A). The highly reactive species **1** easily undergoes α-elimination (Scheme 1, path B) leading to the carbenoid **2**.[2] An alkyl-lithium insertion followed by Li_2O elimination allows the stereospecific synthesis of alkenes **3** (Scheme 1, path C).[3] While hydride migration furnishes isomerized ketone **5** (Scheme 1, path D),[4] a 1,2-alkyl shift leads to α,β-unsaturated ketone **6** (R^3 = OH) (Scheme 1, path E).[5] Classically, epoxides can be converted to allylic alcohols by treatment with several basic reagents through β-elimination,[6] but in most cases without any regioselectivity. Here we report a new regiocontrolled access to allylic alcohols **8** by treatment of an oxirane ring bearing a neighbouring β-alkyloxy group (R^3 = OMe) (Scheme 1, path F) with an organolithium reagent.[7]



Scheme 1

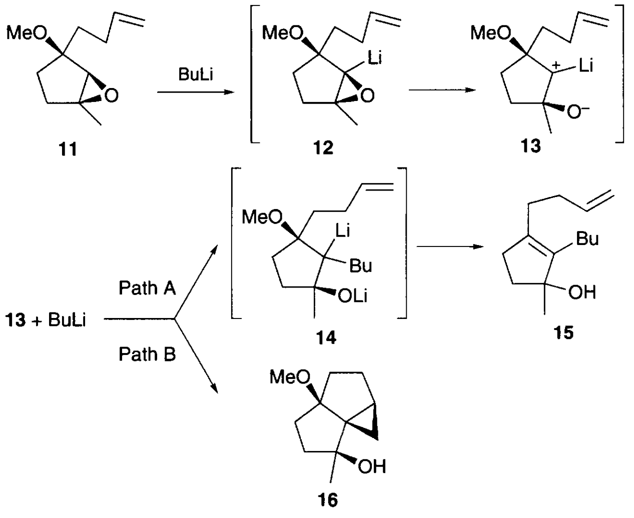


Scheme 2

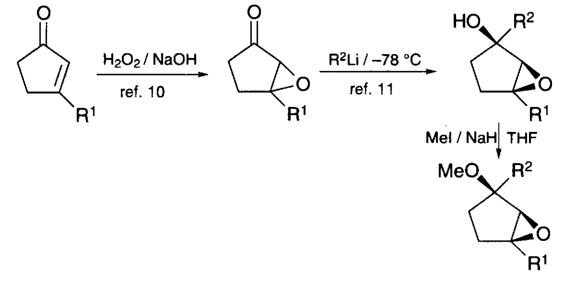
We recently found that substituted cyclic allylic alcohols can be synthesized from α-epoxy-ethers (Scheme 2) by treatment with 2 equiv. of an organolithium reagent.

The reaction mechanism is illustrated for the synthesis of the allylic alcohol **15** (Scheme 3). A proposed model involves proton abstraction leading to an α-lithiated epoxide intermediate **12** that can readily undergo ring opening by α-elimination to form an α-alkoxy-α′-alkyloxy-carbenoid **13**.[8] The insertion of an alkyl group followed by instantaneous MeOLi elimination (which dominates over Li_2O elimination) leads to the corresponding alkylated α,β-unsaturated alcohol **15** with total regiocontrol (Scheme 3, path A).

In this particular case we were able also to isolate as a byproduct (yield 14%) the tricyclomethoxy alcohol **16** as a result of an intramolecular trapping [2 + 1] cycloaddition, arguing the case for the occurence of a carbenoid intermediate **13** (Scheme 3, path B). Several alkyloxy epoxides were prepared from the corresponding α,β-unsaturated ketones, Scheme 4, and reacted with various organolithium reagents.† The results are summarized in Table 1.

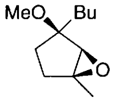
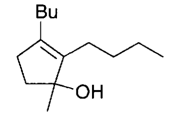
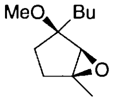
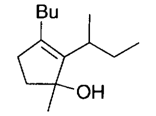
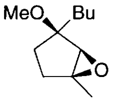
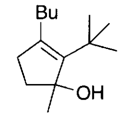
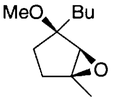
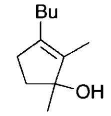
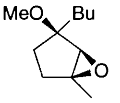
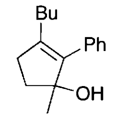
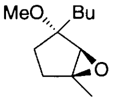
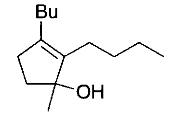
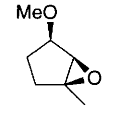
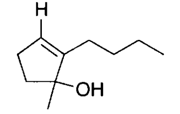
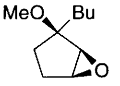
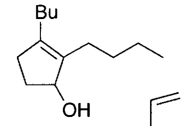
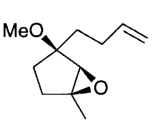
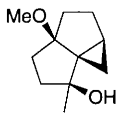
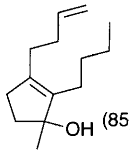
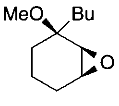
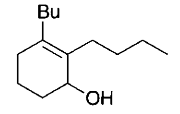
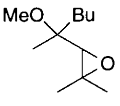
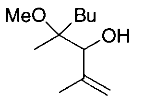


Scheme 3



Scheme 4

Table 1 Examples of allylic alcohol synthesis

Entry	Substrate	RLi	Products[a] (ratio %)	Yield[b] (%)
1		BuLi		> 95
2		*sec*-BuLi		> 95
3		*tert*-BuLi		> 95
4		MeLi		83
5		PhLi		79
6		BuLi		> 95
7		BuLi		88
8		BuLi		85
9		BuLi	 + (15)  (85)	91
10		BuLi		76
11		BuLi		89

[a] If necessary, the products were chromatographed over silica gel pretreated with triethylamine. [b] Combined isolated yields.

The overall yields are excellent and range from 76 to >95%. Many organolithium reagents were utilized (Table 1, entries 1–5), leading always to the expected compounds. All the experiments were carried out with the *syn* α-alkyloxy epoxide isomers,[9,10] but we also noticed that the corresponding *anti*-substrates (Table 1, entry 6) undergo the same reaction,‡ indicating that no stereochemical requirements are needed. The methodology was applied to five and six membered rings (Table 1, entries 1–10), while non-cyclic substrates failed to react *via* a carbenoid path but afforded a classical β-eliminated product (Table 1, entry 11).

Treatment of substrate **9** with a butyl Grignard reagent led to oxirane ring opening. However, BuLi treatment of the resulting β-alkyloxy alcohol failed to give the corresponding allylic alcohol **10**. This experiment precludes an addition–elimination mechanism, arguing the case for the insertion–elimination pathway.

This publication describes a new regiospecific access to cyclic allylic alcohols. The reaction proceeds *via* a carbenoid stemmed from a metallated oxirane followed by RLi insertion and subsequent MeOLi elimination. This reaction should be of further interest to organic chemists, for example, in the synthesis of dienes.[11]

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Footnotes

† *Typical experimental procedure*: BuLi (0.85 ml, 1.6 mol dm^{-3} in hexanes, 2.5 equiv.) was added dropwise to a stirred solution of 4-butyl-4-methoxy-1-methyl-6-oxa-bicyclo[3,1,0]hexane (100 mg, 0.54 mmol, 1 equiv.) in 5 ml anhydrous THF at −78 °C under argon. The mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was then quenched with a pH 7 phosphate buffer (the products are acid-sensitive and easily undergo dehydration into dienes) and extracted twice with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated. 2,3-Dibutyl-1-methyl-cyclopent-2-enol was obtained as a colourless oil (Table 1, entry 1) and did not need further purification. All products were fully characterised by ^1H, ^{13}C NMR and by mass spectroscopy. *Selected Spectral data* for 2,3-dibutyl-1-methyl-cyclopent-2-enol (Table 1, entry 1). ^1H NMR($CDCl_3$, 200 MHz) δ 0.90 (t, J = 5.6 Hz, 3 H), 0.92 (t, J = 5.6 Hz, 3 H), 1.20–240 (m, 16 H), 1.31 (s, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 14.0, 22.7, 23.3, 24.4, 26.0, 28.7, 30.1, 31.2, 32.9, 40.0, 85.4, 139.2 and 140.2. *IR* (neat) cm−^{1} 3423 (OH). *MS* (CI-NH_3): *m*/*z* 193 (M^+ − OH, 100%).

‡ The *trans* alkyloxy-epoxide was obtained as major product by MCPBA epoxidation of the corresponding allylic methyl ether.

References

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10 The epoxy-alcohol was obtained regiospecifically with excellent diastereofacial selectivity (>20:1). The stereochemistry of the epoxy-alcohol moiety was confirmed by MCPBA epoxidation of the corresponding substituted allylic alcohol. See: T. Itoh, K. Jitsukawa, K. Kaneda, S. Teranishi, *J. Am Chem. Soc.*, 1979, **101**, 159.
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