Alkenes from Terminal Epoxides Using Lithium 2,2,6,6-Tetramethylpiperidide and Organolithiums or Grignard Reagents

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As originally reported by Crandall and Lin,[1] and subsequently studied in more detail by Mioskowski and co-workers,[2] terminal epoxides **1** can function as vinyl cation equivalents with organolithiums. This is potentially a very powerful process for the synthesis of alkenes **3**, because of its convergent nature, the regiospecificity in the double bond installation, and the ready availability of the starting materials. However, the reaction currently suffers from three significant limitations: (1) only simple alkyllithiums are effective partners in the chemistry (for example, aryllithiums, vinyllithiums, and α-silyl-substituted alkyllithiums all give secondary alcohols **4** by direct epoxide ring-opening);[3] (2) high *E*-selectivity is observed only with secondary and tertiary alkyllithiums (*E*:*Z*, 3:1 and 2:1 are obtained using 1,2-epoxydodecane in THF with BuLi and MeLi, respectively);[2] and (3) at least 2 equiv of the organolithium are required (the first equivalent functions as a base to form an α-lithiated epoxide **2**, and the second as nucleophile on this transient carbenoid).[4]
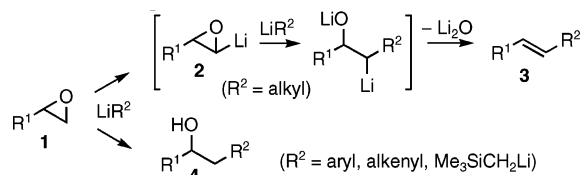
We recently reported the reaction of terminal epoxides with lithium 2,2,6,6-tetramethylpiperidide (LTMP), which proceeds through trapping of a *trans*-α-lithiated epoxide **2**[5] with LTMP to give an enamine **3** (R² = tetramethylpiperidin-1-yl).[6] During this study we considered whether the presence of an organolithium might divert the chemistry to alkene synthesis. This could provide a solution to the limitations mentioned above, provided (i) α-lithiation of the epoxide by LTMP is faster than direct ring-opening (and/or α-lithiation) of the epoxide by the organolithium, (ii) the resulting *trans*-α-lithiated epoxide **2** is preferentially trapped by the organolithium rather than by LTMP, and (iii) the organolithium is not consumed in deprotonating tetramethylpiperidine[7] generated by the desired epoxide lithiation pathway. Although these are demanding criteria, in the present Communication we report that the combination of LTMP and organolithiums (or Grignard reagents) provides promising new and straightforward methodology for alkene synthesis from terminal epoxides.

Initial studies on the addition of 1,2-epoxydodecane to a mixture of LTMP (2 equiv) and PhLi (1.3 equiv) indicated that the desired alkene **6a** was isolated in excellent yield (93%) when the reaction was carried out in hexane (Table 1, entry 1). In ethereal solvents, secondary alcohol and enamine (isolated as the aldehyde after

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Table 1. Alkenes **6** from Epoxide **5** Using LTMP and Aryl- or Alkenyllithiums

Entry	LiR	Alkene 6	Yield (%)ᵃ	Ratioᵇ
1	LiPh	**6a**	93	98:2
2	LiC₆H₄*p*-OMe	**6b**	70	98:2
3ᶜ		**6c**	73	98:2
4		**6d**	85	*E*-only
5		**6e**	82	98:2
6		**6f**	84	99:1
7		**6g**	72	98:2
8		**6h**	70	90:10
9		**6i**	80	91:9
10		**6j**	85	91:9

ᵃ Isolated yield. ᵇ Determined by GCMS. Ratios refer to *E*:*Z* (entries 1–3), *E,E*:*Z,E* (entries 5–7, 10), *Z,E*:*E,E* (entry 8), and *Z,E*:other isomers (entry 9). ᶜ 1.5 equiv of RLi used.

column chromatography) byproducts became more noticeable. The chemistry was also applicable to *p*-MeOC₆H₄Li (entry 2), and to a range of alkenyllithiums which gave the corresponding dienes (entries 3–10). The reaction was highly *E*-selective for the newly formed double bond. *E*-Alkenyllithiums gave *E,E*-dienes with ≥98:2 selectivity (entries 5–7). Using *Z*-vinyllithiums (entries 8 and 9) gave the corresponding *Z,E*-dienes as the major isomers (≥90% selectivity). Using an unsymmetrical 2,2-disubstituted 1-alkenyllithium gave the diene **6j** in 85% yield and 91% isomeric purity (entry 10). In each case, addition of the alkenyllithium (3 equiv) to the terminal epoxide under the same reaction conditions, but without LTMP present, gave the corresponding homoallylic secondary alcohol from direct ring-opening of the epoxide as the major product (72–99%).[3,8]

Regio- and stereo-defined allylsilanes are valuable intermediates in synthesis.[9] *E*-Allylsilanes **7** were found be conveniently accessed (Table 2) by addition of a variety of terminal epoxides to a mixture of LTMP and commercially available Me₃SiCH₂Li, or 1-(trimethylsilyl)hexyllithium (generated by the addition of BuLi to vinyltrimethylsilane).[10] For Me₃SiCH₂Li, *E*-selectivity is higher in ethereal solvents compared to that obtained in reactions carried out in hexane. Entries 4–7 illustrate a straightforward way to access α-alkylated *E*-allylsilanes in a completely regioselective manner.

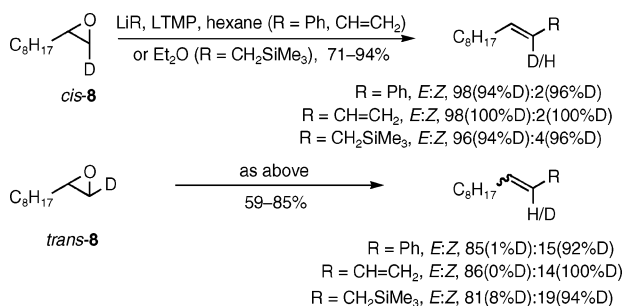**Table 2.** Allylsilanes **7** from Terminal Epoxides[a]

Entry	Epoxide	Allylsilane 7		Yield (%)[b]	E:Z[c]
1[d]	$C_{10}H_{21}$ epoxide	$C_{10}H_{21}$—SiMe₃	7a	65	97:3
2[e]	i-Pr epoxide	i-Pr—SiMe₃	7b	71	98:2
3[e]	t-Bu epoxide	t-Bu—SiMe₃	7c	63	E-only
4	$C_{10}H_{21}$ epoxide	$C_{10}H_{21}$ SiMe₃ C_5H_{11}	7d	74	E-only
5	alkenyl epoxide	SiMe₃ C_5H_{11}	7e	75	E-only
6	Ph epoxide	Ph SiMe₃ C_5H_{11}	7f	78	98:2
7	TBSO epoxide	TBSO SiMe₃ C_5H_{11}	7g	71	E-only

[a] Hexane as solvent unless otherwise indicated. [b] Isolated yield. [c] Determined by GCMS. [d] Et₂O as solvent (in hexane, 84% yield, E:Z, 65:35). [e] THF as solvent (in hexane (entry 2), 88% yield, E:Z, 80:20; (entry 3) 83% yield, E:Z, 83:17).

It was considered important to probe whether the stereochemistry of the α-lithiated epoxide influences product alkene geometry. This was studied using an α-deuterated epoxide **8** and LTMP with PhLi, vinyllithium, and Me₃SiCH₂Li. Reaction of *cis*-**8** gave the corresponding *E*-alkenes with high deuterium retention (≥94%). With *trans*-**8** the major product in each case is still the *E*-alkene, but with low deuterium content (≤8%). These results suggest that, for these organolithiums, a *trans*-lithiated epoxide leads mainly to *E*-alkene formation. With *trans*-**8** a kinetic isotope effect leads to increased levels of *Z*-alkene; the high deuterium content (≥92%) in the *Z*-alkene indicates that it is mainly formed from *cis*-lithiated epoxide.

R = Ph, E:Z, 98(94%D):2(96%D)
R = CH=CH₂, E:Z, 98(100%D):2(100%D)
R = CH₂SiMe₃, E:Z, 96(94%D):4(96%D)

R = Ph, E:Z, 85(1%D):15(92%D)
R = CH=CH₂, E:Z, 86(0%D):14(100%D)
R = CH₂SiMe₃, E:Z, 81(8%D):19(94%D)

Use of the LTMP-modified alkene synthesis with 1,2-epoxy-dodecane and a representative primary alkyllithium (BuLi, 1.4 equiv) in Et₂O[11] gave alkene **6k** (73%) with only a modest improvement in stereoselectivity (*E*:*Z*, 90:10) compared to the LTMP-free reaction (3 equiv of BuLi, 76%, *E*:*Z*, 81:19). The likely origin of the *Z*-alkene in these reactions is removal of the *cis*-terminal hydrogen by BuLi, since reaction of *cis*-**8** with BuLi in Et₂O gave the corresponding alkene exclusively as the *E*-isomer (100%D). MeLi (1.5 equiv), LTMP (2 equiv), and 1,2-epoxydode-cane in Et₂O[11] also gave modest stereoselectivity (alkene **6l**, 61%, *E*:*Z*, 72:28).[12] In seeking to improve stereocontrol in the synthesis

Table 3. Alkenes **6** from Epoxide **5** Using LTMP and Grignard Reagents[a]

Entry	ClMgR	Alkene 6		Yield (%)[b]	Ratio[c]
1	ClMgBu	$C_{10}H_{21}$ Bu	6k	69	96:4
2[d]	ClMgMe	$C_{10}H_{21}$	6l	71	98:2
3	ClMg C_6H_{13}	$C_{10}H_{21}$ C_6H_{13}	6i	67	91:9
4	ClMg C_4H_9	$C_{10}H_{21}$ C_4H_9	6j	70	94:6

[a] Et₂O as solvent unless otherwise indicated. [b] Isolated yield. [c] Determined by ¹H NMR, 500 MHz (entry 1) or GCMS (entries 1−3). Ratios refer to *E*:*Z* (entries 1, 2), *Z*,*E*:other isomers (entry 3), and *E*,*E*:*Z*,*E* (entry 4). [d] Hexane as solvent, 1.8 equiv of ClMgMe, and 1.5 equiv of LTMP used.

of such alkenes from epoxides, we have found that Grignard reagents offer an attractive solution (Table 3, entries 1 and 2).[13] Dienes are also accessible using alkenyl Grignard reagents (entries 3 and 4). To our knowledge, these are the first examples of Grignard reagents inserting into α-metalated epoxides to produce alkenes.

In summary, we report chemistry that significantly broadens the use of epoxides as regio- and stereo-defined vinyl cation equivalents. The ability of lithium amides and organolithiums (or Grignard reagents), present in the same flask, to operate apparently independently of each other[14] but in defined sequence on a terminal epoxide substrate, resulting in transformations that neither can achieve by themselves, may have broader utility.

Supporting Information Available: Experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4527−4528.
(2) Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 7943−7946.
(3) See Supporting Information.
(4) For a recent review, see: Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625−1642.
(5) Yanagisawa, A.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* **1994**, 2103−2104.
(6) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *J. Am. Chem. Soc.* **2004**, *126*, 6870−6871. See also: Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 8664−8665.
(7) Podraza, K. F.; Bassfield, R. L. *J. Org. Chem.* **1988**, *53*, 2643−2644.
(8) The geometry of the homoallylic alcohols confirmed the geometrical integrity of the alkenyllithiums used.
(9) Sarkar, T. K. In *Science of Synthesis*; Fleming, I., Ed.; Thieme: Stuttgart, 2001; Vol. 4, pp 837−925.
(10) Ager, D. J. *Org. React.* **1990**, *38*, 1−227.
(11) Use of hexane led to lower stereoselectivities.
(12) In the absence of LTMP, MeLi in Et₂O gave only the corresponding secondary alcohol from direct ring-opening.
(13) In the absence of LTMP, only secondary alcohols and chlorohydrins are observed.
(14) (a) Pratt, L. M.; Newman, A.; St. Cyr, J.; Johnson, H.; Miles, B.; Lattier, A.; Austin, E.; Henderson, S.; Hershey, B.; Lin, M.; Balamraju, Y.; Sammonds, L.; Cheramie, J.; Karnes, J.; Hymel, E.; Woodford, B.; Carter, C. *J. Org. Chem.* **2003**, *68*, 6387−6391. (b) Pratt, L. M. *Mini-Rev. Org. Chem.* **2004**, *1*, 209−217. (c) Shimizu, M.; Fujimoto, T.; Liu, X.; Hiyama, T. *Chem. Lett.* **2004**, *33*, 438−439.

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