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The Reactivity of Epoxides with Lithium 2,2,6,6-Tetramethylpiperidide in Combination with Organolithiums or Grignard Reagents

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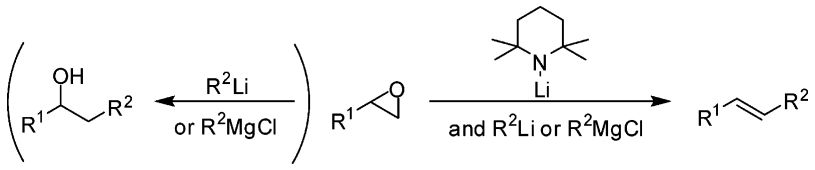

The scope and limitations of lithium 2,2,6,6-tetramethylpiperidide (LTMP)-modified reductive alkylation of epoxides is detailed. A variety of organolithiums are added to terminal and 2,2-disubstituted epoxides in the presence of LTMP to generate alkenes in a completely regio- and highly stereoselective manner. Arylated alkenes, dienes, allylsilanes, and enynes are accessed using this procedure. The methodology is applied in the synthesis of the roller leaf moth pheromone, (3*E*,5*Z*)-dodecadienyl acetate. The corresponding reaction without LTMP has also been examined, and a study using deuterated epoxides provides insight into the mechanism. In the presence of LTMP, Grignard reagents are also shown to produce *E*-alkenes directly from epoxides.

Introduction

The nucleophilic addition of an organolithium to an epoxide **1** to form an alcohol **2** via an S_N2 pathway is a well-established synthetic protocol (Scheme 1, path *A*).[1] It has been demonstrated, initially by Crandall and Lin[2] and then subsequently in more detail by Mioskowski and co-workers,[3a] that another reactivity mode is possible whereby the organolithium first functions as a base and α-deprotonates the epoxide. The resulting α-lithiated epoxide **3** can react in a variety of ways depending on the reaction conditions and substrate structure.[4] The ring strain of the α-lithiated epoxide, combined with the weakening of the α C−O bond because of its greater polarization, makes α-lithiated epoxides highly electrophilic species.[5] Under certain reaction conditions (typically ≥2 equiv of organolithium in THF), another equivalent of organolithium can add to the α-lithiated epoxide to form lithiated species **4**, which β-eliminates Li_2O to form alkene **5** (Scheme 1, path *B*). This process has been termed reductive alkylation.[6]

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(1) (a) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693−3694. (b) Chemla, F.; Vrancken, E. In *The Chemistry of Organolithium Reagents*; Rappoport, Z., Marek, I., Eds.; Wiley and Sons: New York, 2004; pp 1165−1242. (c) For a recent example, see: Mena, M.; Valls, N.; Borregán, M.; Bonjoch, J. *Tetrahedron* **2006**, *62*, 9166−9173. (d) For the use of HMPA as an additive, see: Reich, H. J.; Sanders, A. W.; Fiedler, A. T.; Bevan, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 13386−13387.

(2) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4526−4727.

(3) (a) Mioskowski, C.; Dechoux, L.; Doris, E. *Tetrahedron Lett.* **1994**, *35*, 7943−7946. (b) See also: Mordini, A.; Peruzzi, D.; Russo, F.; Valacchi, M.; Reginato, G.; Brandi, A. *Tetrahedron* **2005**, *61*, 3349−3360.

(4) (a) Crandall. J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345−443. (b) Satoh, T. *Chem. Rev.* **1996**, *96*, 3030−3325. (c) Doris, E.; Dechoux, L.; Mioskowski, C. *Synlett* **1998**, 337−343. (d) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625−1642. (e) Hodgson, D. M.; Bray, C. D. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley: Weinheim, Germany, 2006; pp 145−184. (f) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, 1−22. (g) Hodgson, D. M.; Humphreys, P. G.; Hughes, S. P. *Pure Appl. Chem.* **2007**, *79*, 269−279.

(5) (a) Boche, G.; Lohrenz, C. W. *Chem. Rev.* **2001**, *101*, 697−756. (b) Braun, M. In *The Chemistry of Organolithium Reagents*; Rappoport, Z., Marek, I., Eds.; Wiley and Sons: New York, 2004; pp 829−900.

(6) For similar reactions, see: (a) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1976**, *41*, 2615−2621. (b) Ukaji, Y.; Fujisawa, T. *Tetrahedron Lett.* **1988**, *29*, 5165−5168. (c) Ukaji, Y.; Yoshida, A.; Fujisawa, T. *Chem. Lett.* **1990**, 157−160. (d) Santiago, B.; Lopez, C.; Soderquist, J. A. *Tetrahedron Lett.* **1991**, *32*, 3457−3460. (e) Taniguchi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1991**, *32*, 2783−2786. (f) Lopez, C.; Soderquist, J. A. *Tetrahedron Lett.* **1991**, *32*, 6305−6306. (g) O'Brien, P.; Rosser, C. M.; Caine, D. *Tetrahedron* **2003**, *59*, 9779−9791.

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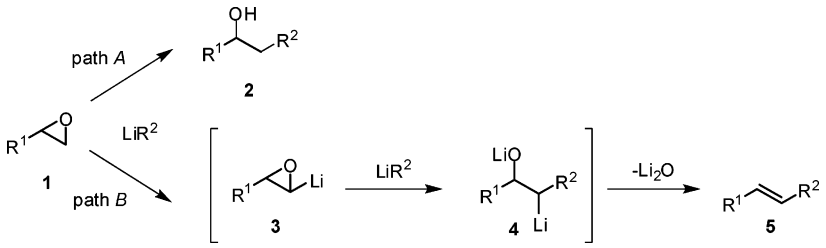
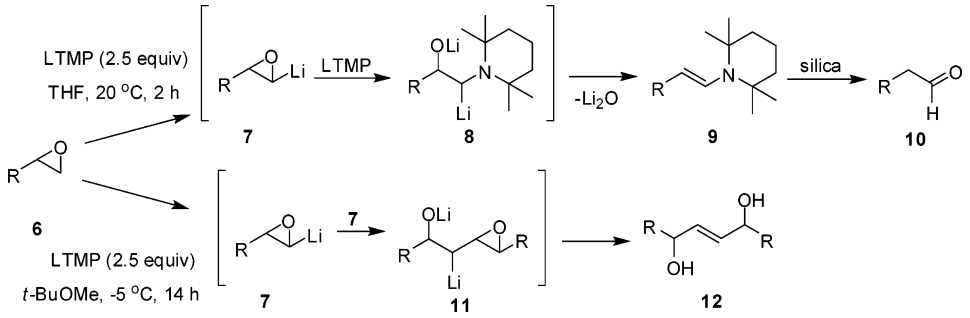
SCHEME 1. Epoxide Reactivity Modes with Organolithiums



SCHEME 2. Enamines and Ene-Diols from Epoxides and Lithium Amides[10,11]



If nucleophilic addition is the desired reaction pathway, a Lewis acid (e.g., $BF_3{\cdot}Et_2O$) can be added to increase the electrophilic character of the epoxide and maximize the yield of alcohol **2**.[1] However, prior to the studies reported herein, there was no general way to maximize alkene formation. We considered reductive alkylation of epoxides to be a potentially very powerful process for the synthesis of alkenes because of its convergent nature, the regiospecificity in the double bond installation, and the ready availability of the starting materials. However, at the outset of our studies the reaction (as discussed above) suffered from three significant limitations: (1) only simple alkyllithiums had been shown to be effective partners in the chemistry,[3] (2) high *E*-selectivity was observed only with secondary and tertiary alkyllithiums,[3,7] and (3) at least 2 equiv of the organolithium were required (the first equiv functioning as a base forming α-lithiated epoxide **3** and the second as nucleophile on this transient carbenoid). The latter is undesirable if the precursor to the organolithium (normally an organohalide or stannane) is prepared by a multistep procedure. We considered a potential solution to this problem by α-deprotonating epoxide **1** with one type of base and then trapping the resulting oxiranyl anion **3** with an organometallic,[8] which after elimination of metal oxide from intermediate **4** would afford the desired alkene **5**. This would reduce the number of equiv of organometallic needed and expand the range of products available. This article details our studies toward this goal.[9]

Results and Discussion

In 1994, Yamamoto and co-workers reported the selective and high-yielding isomerization of a variety of terminal epoxides **6** to aldehydes **10** using a bulky lithium amide, namely lithium 2,2,6,6-tetramethylpiperidide (LTMP, Scheme 2); the latter being straightforwardly generated from commercially available 2,2,6,6-tetramethylpiperidine (TMP) using *n*-BuLi in THF at 0 °C.[10] With evidence from experiments using deuterium-labeled epoxides, Yamamoto and co-workers suggested a reaction pathway proceeding via epoxide α-deprotonation (*trans* to the alkyl substituent on the oxirane ring) to form α-lithiated epoxide **7**. More recently, we reported that aldehyde **10** is formed via hydrolysis of enamine **9**, the latter being generated by a mechanism analogous to that of reductive alkylation (Scheme 2).[11] Thus, after α-deprotonation of the epoxide, the resulting α-lithiated epoxide **7** is likely attacked by excess LTMP to give intermediate **8**, from which elimination of Li_2O generates enamine **9**. We have also observed that, if the reaction is carried out under more concentrated conditions and at a lower temperature, the α-lithiated epoxide preferentially dimerizes to give a 2-ene-1,4-diol **12** (possibly via **11**) as the major product.[12] The latter is an encouraging observation in the current context, as it suggests that (sterically demanding) LTMP does not rapidly attack the transient α-lithiated epoxide intermediate **7**.

Since LTMP had been shown to efficiently α-deprotonate terminal epoxides in a highly regio- and stereoselective manner, it was evaluated as a potential base in the proposed modified reductive alkylation process. 1-Hexynyllithium was chosen as the organolithium, as it had been demonstrated to be a poor nucleophile with an epoxide in the absence of a Lewis acid and therefore formation of secondary alcohol **2** should be avoided.[13] Using this organolithium with 1,2-epoxydodecane (**13**) should give enyne **14a**. Initially, LTMP (1 equiv) in Et_2O

(7) It has recently been reported that both PhLi and MeLi undergo reductive alkylation with (1-aminoalkyl)epoxides in THF to give the corresponding *E*-alkenes. See: (a) Concellon, J. M.; Suarez, J. R.; Del Solar, V. *Org. Lett.* **2006**, *8*, 349−351. (b) Concellon, J. M.; Bernad, P. L.; Del Solar, V.; Suarez, J. R.; Garcia-Granda, S.; Diaz, M. *J. Org. Chem.* **2006**, *71*, 6420−6426.

(8) Shimizu, M.; Fujimoto, T.; Liu, X.; Hiyama, T. *Chem. Lett.* **2004**, *33*, 438−439.

(9) (a) Hodgson, D. M.; Fleming, M. J.; Stanway, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 12250−12251. (b) The chemistry has subsequently been used. See: Wang, Z.; Fang, H.; Xi, Z. *Tetrahedron* **2006**, *62*, 6967−6972.

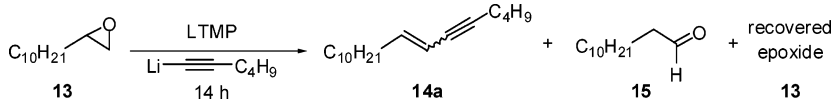
(10) (a) Yanagisawa, H.; Katsutaka, Y.; Yamamoto, H. *J. Chem. Soc., Chem. Commun*. **1994**, 2103−2104. (b) See also: Wiedemann, S. H.; Ramírez, A.; Collum, D. B. *J. Am. Chem. Soc*. **2003**, *125*, 15893−15901.

(11) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *J. Am. Chem. Soc.* **2004**, *126*, 6870−6871.

(12) (a) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *Org. Lett*. **2005**, *7*, 6870−6871. See also: (b) Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 8664−8665. (c) Hodgson, D. M.; Chung, Y. K.; Nuzzo, I.; Freixas, G.; Kulikiewicz, K. K.; Cleator, E.; Paris, J.-M. *J. Am. Chem. Soc.* **2007**, *129*, 4456−4462.

(13) See Supporting Information for initial studies investigating product distribution when various organolithiums are added to terminal epoxides.

TABLE 1. Reactions of Epoxide 13 with LTMP/1-Hexynyllithium[a]



13 14a 15 13

entry	equiv of LTMP	solvent	temp, °C	**14a** yield, %	**14a** *E*/*Z* ratio	**15** yield, %	**13** recovered, %
1	1	Et_2O	0	29	58:42	7	40
2[b]	1	Et_2O	0	21	55:45	15	41
3	1	THF	0	19	70:30	11	48
4	1	hexane	0	37	55:45	18	28
5	2	Et_2O	0	36	61:39	11	17
6	2	hexane	0	48	56:44	9	15
7	2	hexane	−20	45	53:47	8	20
8[c]	2	hexane	−20	61	57:43	0	15
9[c]	2	hexane	0	72	58:62	0	0
10[c]	2	hexane	25	68	52:58	0	0
11[c]	2	THF	25	37	62:38	30	0
12[c,d]	**2**	**hexane**	**0**	**80**	**57:43**	**0**	**0**
13[c,e]	2	hexane	0	60	55:45	0	0
14[c,f]	1.5	hexane	0	51	51:49	0	15
15[c,d,g]	**2**	**hexane**	**0**	**80**	**57:43**	**0**	**0**

[a] 4 equiv of alkynyllithium were used, and LTMP was added over 1 h unless otherwise stated. [b] LTMP added over 10 min. [c] Epoxide added to a solution of LTMP/alkynyllithium. [d] 3 equiv of alkynyllithium were used. [e] 2 equiv of alkynyllithium were used. [f] A quantity of 1.5 equiv of alkynyllithium was used. [g] Reaction left for 2 h.

was added slowly (over 1 h) to a mixture of epoxide **13** and 1-hexynyllithium (4 equiv) in Et_2O at 0 °C. After 14 h, the reaction was quenched, and this led to the formation of the desired enyne **14a** in 29% yield (48% based on recovered epoxide, Table 1, entry 1). However, GC−MS and NMR analyses indicated the reaction was not stereoselective, and enyne **14a** was produced as a 58:42 mixture of *E*/*Z* isomers. Traces of aldehyde **15** (derived from enamine hydrolysis following column chromatography) were also isolated, and a significant quantity of epoxide **13** was also recovered. The solvent, temperature, and number of equiv of LTMP and alkynyllithium were then varied in an attempt to improve the yield of enyne **14a**. We also investigated if changing the order of addition of reagents had any beneficial effect.

Higher yields of enyne **14a** were obtained if the epoxide **13** was added to a solution of LTMP and lithium acetylide (Table 1, entries 8−15), as opposed to LTMP being added to a solution of epoxide **13** and alkynyllithium (entries 1−7). Hexane proved to be more suitable than ethereal solvents (comparing entry 4 with entries 1 and 3). Lowering the temperature had no effect on the yield or the *E*/*Z* selectivity (comparing entries 6 and 7). Two equiv of LTMP and 3 equiv of alkynyllithium were found to give the best yield of enyne **14a** (comparing entry 12 with entries 9 and 13). Lowering the amount of LTMP and alkynyllithium to 1.5 equiv had a detrimental effect on the product yield (entry 14). The reaction was repeated again under the best conditions (entry 12) but quenched after 2 h rather than 14 h (entry 15); the yield and stereoisomeric ratio remained the same, giving enyne **14a** in 80% yield and *E*/*Z* = 57:43.[14]

After finding conditions that successfully converted a terminal epoxide and an alkynyllithium to an enyne (albeit with poor stereocontrol), we next investigated whether this methodology could be extended to aryllithiums. The best conditions that had been developed for enyne formation (Table 1, entry 15) were therefore applied to 1,2-epoxydodecane (**13**) and PhLi (using 2 equiv of commercially available 2.0 M PhLi in *n*-Bu_2O). Pleasingly, this resulted in the formation of alkene **14b** in high yield (85%) and excellent stereoselectivity (*E*/*Z* = 98:2, Table 2, entry 1). Repeating the reactions in ethereal solvents led to a reduced yield of alkene **14b** (71% in Et_2O and 65% in THF), and enamine-derived and secondary alcohol byproducts were also isolated (entries 2 and 3). The reaction was repeated using fewer equiv of PhLi to ascertain whether a large excess of reagent was actually necessary. Gratifyingly, the yield of alkene **14b** remained high (93%) when only 1.3 equiv of PhLi were used (entry 4). This latter result implies that the organolithium is not consumed in deprotonating TMP generated by the desired epoxide lithiation pathway.[15] To demonstrate that this methodology was also compatible with aryllithiums generated in situ by halogen−lithium exchange, *p*-$MeOC_6H_4Li$ was prepared by addition of *t*-BuLi (2 equiv) to 4-bromoanisole in THF at −78 °C. Addition of 1,2-epoxydodecane (**13**) to a mixture of *p*-$MeOC_6H_4Li$ and LTMP gave alkene **14c** in good yield (70%) and excellent stereoselectivity (*E*/*Z* = 99:1). Secondary alcohol **16c** was also isolated in 15% yield.

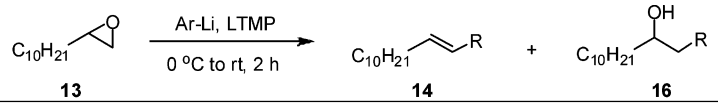
Attempts to synthesize heteroarylated alkenes using lithiated heterocycles proved less successful. When epoxide **13** was added to a mixture of LTMP (1.3 equiv) and 2-furanyllithium (2 equiv) in hexane, the major product isolated was secondary alcohol **16d** in 60% yield (entry 6); some of the desired alkene **14d** was also formed, in 32% yield (*E*/*Z* = 98:2). Similarly, 2-thienyllithium gave alkene **14e** in only 39% yield (*E*/*Z* = 99:1), along with, predominantly, alcohol **16e** in 59% yield (entry 7).

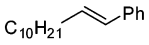
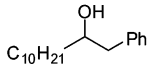
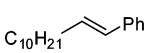
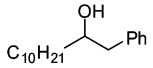
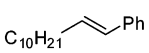
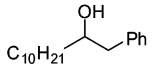
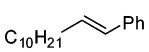
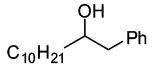
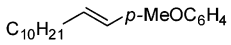
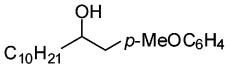
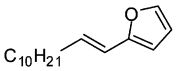
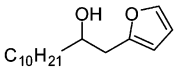
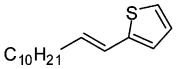
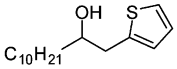
The conditions developed above were then applied to a range of alkenyllithiums. Epoxide **13** was added to a mixture of the alkenyllithium (1.3 equiv) and LTMP (2 equiv) in hexane to form the corresponding 1,3-dienes in 70−85% yield and with good stereoselectivity (Table 3). Using vinyllithium gave terminal diene **14f** in 73% yield (entry 1). A trialkyl-substituted alkenyllithium gave diene **14g**, which demonstrates that one of the alkene units incorporated in the diene can be fully substituted

(14) The addition of diamine ligands (TMEDA or (−)-sparteine) was also investigated, but these had no effect on the diastereoselectivity.

(15) Podraza, K. F.; Bassfield, R. L. *J. Org. Chem.* **1988**, *53*, 2643−2644.

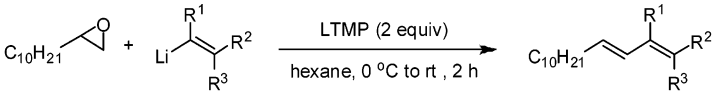
TABLE 2. Reaction of Epoxide 13 with LTMP/Aryllithiums[a]

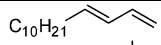
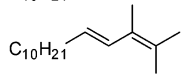
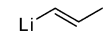
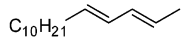
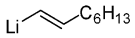
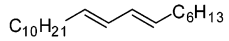
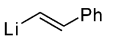
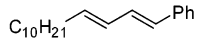
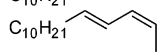
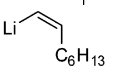
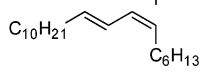
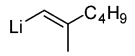
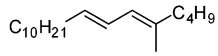


entry	Ar-Li	alkene **14**		yield, %[b,c]	alcohol **16**		yield, %[b]
1[d]	PhLi		**14b**	85		**16b**	–
2[e,f]	PhLi		**14b**	71		**16b**	10
3[e,g]	PhLi		**14b**	65		**16b**	10
4	PhLi		**14b**	93		**16b**	–
5	*p*-MeOC$_6$H$_4$Li		**14c**	70		**16c**	15
6			**14d**	32		**16d**	60
7			**14e**	39		**16e**	59

[a] RLi (1.3 equiv) and LTMP (2 equiv) in hexane unless indicated otherwise. [b] Isolated yield. [c] *E*/*Z* ≥ 98:2 determined by GC−MS. [d] 2 equiv of RLi and 3 equiv of LTMP were used. [e] Aldehyde **15** was also isolated. [f] Et_2O as solvent. [g] THF as solvent.

TABLE 3. Addition of Epoxide 13 to Various Alkenyllithiums and LTMP



entry	alkenyllithium	diene		yield, %[a]	ratios[b]
1			**14f**	73	98:2
2			**14g**	85	*E*-only
3			(*E*,*E*)-**14h**	82	98:2
4			(*E*,*E*)-**14i**	84	99:1
5			**14j**	72	98:2
6			(*Z*,*E*)-**14h**	70	90:10
7			(*Z*,*E*)-**14i**	80	91:9
8			**14k**	85	91:9

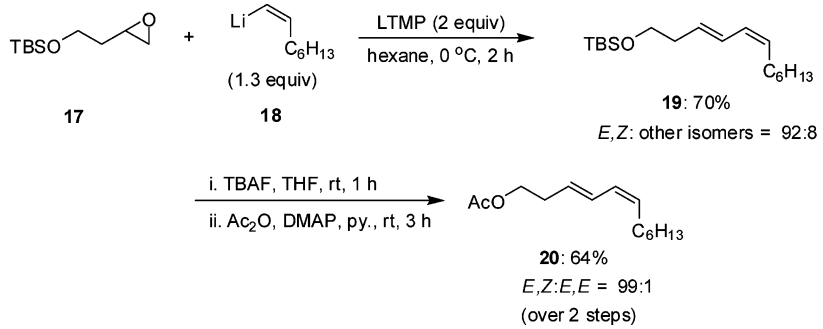
[a] Yield of isolated material. [b] Determined by GC−MS analysis. Ratios refer to *E*/*Z* (entry 1); *E*,*E*/*Z*,*E* (entries 3, 4, 5, 8); *Z*,*E*/*E*,*E* (entry 6); *Z*,*E*/other isomers (entry 7);

(entry 2). *E*-Alkenyllithiums gave the corresponding *E*,*E*-dienes **14h**−**j** in high isomeric purity (*E*,*E*/*Z*,*E* ≥ 98:2), which demonstrates that the geometry of these alkenyllithiums is maintained in the resulting diene (entries 3−5). *Z*-Alkenyllithiums gave *Z*,*E*-dienes **14h** and **14i** in good yield (≥70%); however, there was a slight loss in isomeric purity (*Z*,*E*/*E*,*E* ≥ 90:10) (entries 6 and 7). A 2,2-disubstituted *E*-alkenyllithium gave the corresponding *E*,*E*-diene **14k**, again with a slight loss of isomeric purity (*E*,*E*/*Z*,*E* = 91:9) (entry 8). Repeating these latter reactions in ethereal solvents did not improve the stereocontrol in the resulting dienes.

To demonstrate the potential of the above methodology for diene formation, we applied the method to the total synthesis of the pheromone of the roller leaf moth, (*3E*,5*Z*)-dodecadienyl acetate **20** (Scheme 3); the moth is the most economically important insect pest on apples in southern Brazil.[16] The key step in our synthesis was the coupling between *Z*-alkenyllithium **18** and epoxide **17**; this occurred to give diene **19** in 70% yield and with a selectivity of 92:8 (*E*,*Z*/other isomers). After removal of the TBS protecting group and acetylation of the resulting alcohol, the natural product (*E*,*Z*)-**20** could be isolated essentially isomerically pure after column chromatography on silver nitrate-impregnated silica gel.[17]

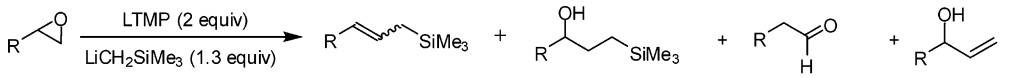
(16) (a) Chong, J. M.; Heaft, M. A. *Tetrahedron* **1999**, *55*, 14243−14250. (b) Ragoussis, V.; Panopoulou, M.; Ragoussis, N. *J. Agric. Food Chem.* **2004**, *52*, 5047−5051.

SCHEME 3. Application of Diene Synthesis to the Total Synthesis of (3*E*,5*Z*)-Dodecadienyl Acetate (20)



17 18

TABLE 4. Allylsilanes from Terminal Epoxides Using $LiCH_2SiMe_3$/LTMP



14l (R = $C_{10}H_{21}$) **16l** (R = $C_{10}H_{21}$) **15** (R = $C_{10}H_{21}$) **27** (R = $C_{10}H_{21}$)
21 (R = *i*-Pr) **23** (R = *i*-Pr) **25** (R = *i*-Pr) **28** (R = *i*-Pr)
22 (R = *t*-Bu) **24** (R = *t*-Bu) **26** (R = *t*-Bu) **29** (R = *t*-Bu)

entry	R	solvent	allylsilane yield, %[a]	*E*/*Z*[b]	alcohol yield, %[a]	aldehyde yield, %[a]	allylic alcohol yield, %[a]
1	$C_{10}H_{21}$	hexane	84	65:35	0	0	0
2	$C_{10}H_{21}$	THF	71	92:8	7	5	10
3[c]	$C_{10}H_{21}$	THF	67	93:7	13	4	10
4	$C_{10}H_{21}$	Et_2O	65	97:3	10	18	5
5	*i*-Pr	hexane	88	80:20	0	0	0
6	*i*-Pr	THF	71	98:2	10	0	0
7	*i*-Pr	Et_2O	63	98:2	9	13	5
8	*t*-Bu	hexane	83	83:17	0	0	0
9	*t*-Bu	THF	63	100:0	10	0	5

[a] Isolated yields. [b] Determined by GC−MS. [c] Reaction carried out at −40 °C and left for 14 h.

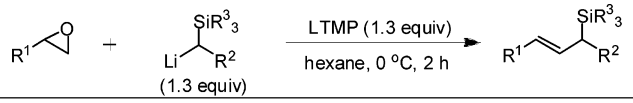
We next turned our attention to terminal allylsilane formation. Pleasingly, allylsilane **14l** was isolated in high yield (84%) when 1,2-epoxydodecane was added to a mixture of LTMP and commercially available $LiCH_2SiMe_3$ in hexane (Table 4, entry 1). However, the stereoselectivity (*E*/*Z* = 65:35) was not as good as that observed with the aryl- and vinyllithiums. Given the value of regio- and stereo-defined allylsilanes in synthesis,[18] we decided at this stage to modify the reaction conditions (and the structure of the epoxide) with the aim of improving the stereoselectivity of the reaction. Other byproducts observed along with the allylsilane when carrying out these reactions were secondary alcohols (**16l**, **23**, or **24**) formed by direct ring opening of the epoxide by the organolithium, aldehydes (**15** or **25**) formed from enamine hydrolysis (cf. Scheme 2), and allylic alcohols **27**−**29**; the later could be produced by some minor elimination of $LiSiMe_3$ instead of Li_2O occurring from the putative organolithium intermediate **4** ($R^2 = CH_2SiMe_3$, Scheme 1). Using THF as solvent gave allylsilane **14l** in 71% yield with improved stereoselectivity (*E*/*Z* = 92:8) (entry 2); however, byproduct alcohols **16l** and **27** and aldehyde **15** became more prominent in this solvent. Reducing the temperature to −40 °C while carrying out the reaction in THF did not benefit the reaction (entry 3), but changing the solvent to Et_2O improved the *E*/*Z* ratio further to 97:3 (entry 4). We next investigated if the structure of the epoxide influenced the reaction. Addition of isopropyloxirane to a mixture of $LiCH_2SiMe_3$ and LTMP in hexane gave the desired allylsilane **21** in 88% yield (entry 5). The *E*-isomer predominated (*E*/*Z* = 80:20). Changing to an ethereal solvent reduced the yield of allylsilane **21** (71 and 63% in THF and Et_2O, respectively); however, the *E*/*Z* ratio improved to 98:2 (entries 6 and 7). Addition of *tert*-butyloxirane to a mixture of $LiCH_2SiMe_3$ and LTMP in hexane gave the desired allylsilane **22** in 83% yield (entry 8). Predominantly, the *E*-isomer was formed (*E*/*Z* = 83:17). A solvent change to THF reduced the yield of allylsilane **22** to 63% (alcohols **24** and **29** became noticeable); however, pleasingly, only the *E*-isomer was isolated (entry 9).

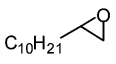
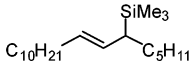
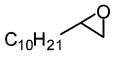
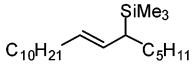
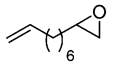
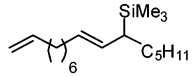
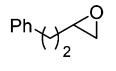
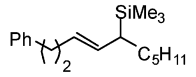
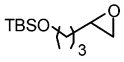
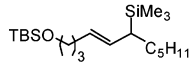
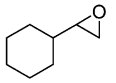
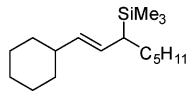
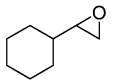
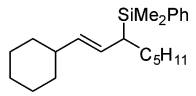
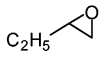
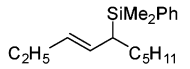
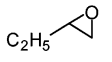
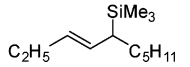
After successfully developing methodology to prepare terminal *E*-allylsilanes from epoxides, we investigated whether α-alkyl-substituted α-silyllithiums could be used in this chemistry to prepare *E*-allylsilanes with a higher degree of substitution. The addition of 1,2-epoxydodecane to a mixture of 1-(trimethylsilyl)hexyllithium (prepared by addition of *n*-BuLi to trimethylvinylsilane)[19] and LTMP in either THF or hexane gave allylsilane **14m** in 62 and 74% yields, respectively (Table 5, entries 1 and 2). In both cases, allylsilane **14m** was isolated exclusively as a single stereoisomer.

The stereoselectivity is evidently not solvent dependent for such a substituted α-silyllithium, and the methodology was then applied to a variety of terminal epoxides to demonstrate functional group compatibility and ease of preparation of branched allylsilanes. Terminal alkene (entry 3), aryl (entry 4),

(17) Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425−447.
(18) (a) Sarkar, T. K. In *Science of Synthesis*; Fleming, I., Ed.; Thieme: Stuttgart, 2001; Vol. 4, pp 837−925. (b) For a recent synthesis of allylsilanes, see: Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068−8077.
(19) Ager, D. *Org. React.* **1990**, *38*, 1−227.

TABLE 5. Allylsilanes from Terminal Epoxides and α-Silyllithium Reagents



entry	epoxide	allylsilane		yield, %[a]	ratio, *E*:*Z*[b]
1[c]			**14m**	62	*E*-only
2			**14m**	74	*E*-only
3			**30**	75	*E*-only
4			**31**	70	98:2
5			**32**	65	*E*-only
6			**33**	80	*E*-only
7			**34**	72	*E*-only
8			**35**	72	95:5
9			**36**	77	94:6

[a] Isolated yield. [b] Determined by GC−MS. [c] THF as solvent.

and silyl ether (entry 5) functionality were all tolerated. It was also possible to vary the substitution on silicon by using a different vinylsilane when generating the α-silyllithium (entries 7 and 8). With 1,2-epoxybutane, *E*/*Z* selectivity was slightly lower (entries 8 and 9).

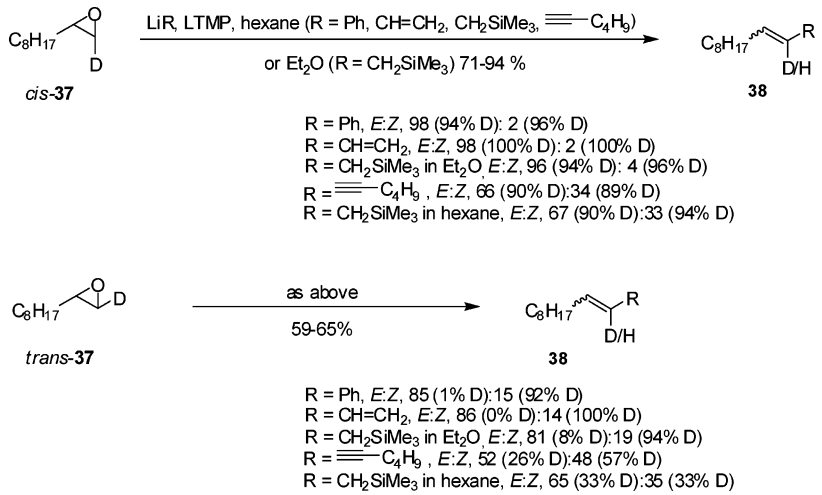
The majority of organolithiums investigated during this modified reductive alkylation procedure reacted highly stereoselectively, generating only *E*-alkene isomers. However, in some instances (enyne formation and terminal allylsilane formation in hydrocarbon solvent) the process did not display good stereoselectivity. In an attempt to gain a greater insight into why this was the case, *cis*- and *trans*-deuterated epoxides **37** were synthesized and subjected to the developed reaction conditions. α-Deuterated epoxides **37** were first reacted with organolithiums that had generated alkenes with high stereocontrol [PhLi and vinyllithium (both in hexane) and $LiCH_2SiMe_3$ (in Et_2O)] in combination with LTMP. The resulting alkenes were then analyzed by GC−MS to determine the *E*/*Z* ratio and the relative deuterium levels in each isomer. Reaction of *cis*-**37** gave the corresponding *E*-alkenes **38** with high deuterium retention (≥94%). With *trans*-**37**, the major product in each case was still the *E*-alkene **38**, but with low deuterium content (≤8%). These results suggest that, for these organolithiums under the conditions indicated, a *trans*-lithiated epoxide leads mainly to *E*-alkene formation. With *trans*-**37**, a kinetic isotope effect leads to raised levels of *Z*-alkene; the high deuterium content (≥92%) in the *Z*-alkene indicates that it is mainly formed from *cis*-lithiated epoxide (Scheme 4).

The α-deuterated epoxides **37** were then reacted with organolithiums that had not been found to be so stereoselective [1-hexynyllithium and $LiCH_2SiMe_3$ (in hexane), Scheme 4]. For both these organolithiums, the reaction of *cis*-**37** gave the corresponding alkene **38** as an *E*/*Z* mixture in a ratio similar to that when using the undeuterated epoxide. Both isomers possessed high levels of deuterium retention (≥89%), which demonstrates that the *cis*-isomer is produced by initial *trans* deprotonation of the epoxide. The loss of stereochemistry in enyne and allylsilane formation (in hexane) is therefore not due to lack of stereoselectivity in the initial deprotonation of the epoxide. With these organolithiums, the reaction with *trans*-**37** gave the corresponding alkenes **38** as *E*/*Z* mixtures and with varying levels of deuterium incorporation. These results further indicate that the site of deprotonation does not influence the stereoselectivity of the alkene under these reaction conditions.

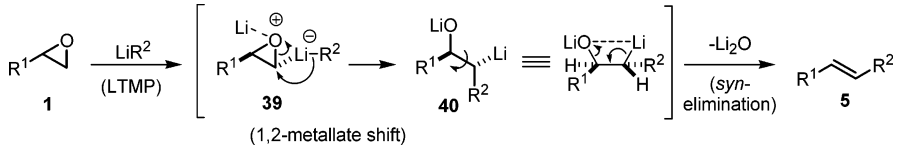
A 1,2-metallate rearrangement[20] can be invoked to explain the high degree of stereoselectivity observed for the majority of organolithiums examined (Scheme 5): following initial deprotonation of the terminal epoxide (*trans* to the alkyl group using the sterically demanding LTMP as base),[10] a stereospecific 1,2-metallate shift (with inversion of stereochemistry) on lithiated epoxide **39** gives stereodefined organolithium intermediate **40**. To explain the observed *trans*-alkene geometry, a *syn*-

(20) (a) Kocieński, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933−1940. (b) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 5275−5280. (c) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 6201−6205.

SCHEME 4. Mechanistic Studies Using Deuterated Epoxides



SCHEME 5. Possible Origin of Alkene Stereochemistry



elimination of Li_2O must then occur,[6c,e] with the elimination rate being faster than any loss of configurational integrity in organolithium **40**. For enyne formation, the absence of significant stereocontrol could be due to configurational instability of the putative propargyl-allenyllithium[21] **40** (R^2 = alkyn-1-yl group) prior to elimination of Li_2O (Scheme 5). The enhanced stereoselectivity of allylsilane formation when carried out in ethereal solvent compared to a hydrocarbon solvent could be due to a faster rate of elimination of Li_2O in Et_2O, hence giving the organolithium intermediate less time in which to lose its relative configuration.

Our above efforts focused solely on converting terminal (monosubstituted) epoxides to 1,2-disubstituted alkenes. This was because of the presumed lack of reactivity of LTMP with 2,2-disubstituted epoxides. Yamamoto and co-workers had reported in 1974 the attempted isomerization of a 2,2-disubstituted epoxide with LTMP (in benzene, 0 °C, 1 h), but they obtained <5% yield of allylic alcohol, along with >70% recovery of starting epoxide.[22] Notwithstanding this report, epoxide **41** was added to a mixture of PhLi and LTMP in hexane. Surprisingly, this resulted in complete consumption of the epoxide within 2 h and alkene **42** was isolated in 42% yield, along with (*Z*)-cyclodecene-1-methanol in 47% yield (Table 6, entry 1). The geometry of the latter allylic alcohol was determined by NOE studies. Under these conditions, LTMP can evidently α-deprotonate a 2,2-disubstituted epoxide to some extent, but *β*-elimination[4] is a competing process. The formation of lithium amide and organolithium mixed aggregates[23] could explain the enhanced reactivity of LTMP during this reaction. Carrying out the same reaction using $LiCH_2SiMe_3$ gave allylsilane **43** in 40% yield, along with *β*-elimination-derived allylic alcohol in 48% yield (entry 2).

We also examined whether the reaction could be stereoselective if an unsymmetrical 2,2-disubstituted epoxide was used. Subjecting such epoxides **44** and **46** to a mixture of LTMP and PhLi gave arylated alkenes **45** and **47** in 41 and 62% yields, respectively (Table 6, entries 3 and 4). In both cases, the reaction was stereoselective, forming predominantly the *E*-isomer. Subjecting the same epoxides to a mixture of LTMP and $LiCH_2SiMe_3$ generated allylsilanes **48** and **49** in 42 and 44% yields, respectively (entries 5 and 6). These latter reactions were less stereoselective, although the *E*-isomer (determined by NOE experiments) was still prominent.

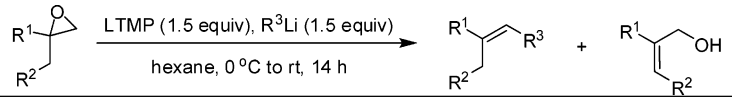
As previously stated, at the outset of our studies the reductive alkylation of terminal epoxides to form simple *E*-alkenes with *alkyl* substituents (i.e., using alkyllithiums) suffered from two limitations: (1) at least 2 equiv (and typically a large excess) of alkyllithium reagent are required, because it acts as both the base and the nucleophile (this is undesirable if the precursor to the alkyllithium is generated from a multistep synthesis), and (2) only secondary or tertiary alkyllithiums give exclusively *E*-alkenes, while primary alkyllithiums give a mixture of *E*- and *Z*-isomers.[3a,7] The addition of excess *n*-BuLi to deuterated epoxides *cis*/*trans*-**37** indicated that the lack of stereoselectivity in alkene formation was due to reduced stereoselectivity during the initial deprotonation of the epoxide (Table 7). Reaction of *cis*-**37** in Et_2O gave the corresponding *E*-alkene **50** with complete deuterium retention. The kinetic isotope effect forces deprotonation exclusively *trans* to the alkyl group, and the resulting trans-lithiated epoxide generates only *E*-alkene **50** (entries 1 and 2).

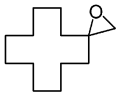
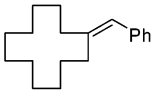
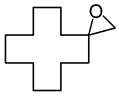
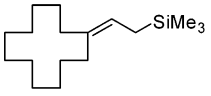
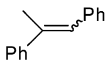
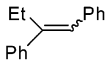
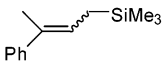
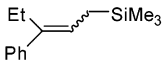
(21) Reich, H. J.; Holladay, J. E.; Walker, T. G.; Thompson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 9769−9780.

(22) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513−6514.

(23) (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) Pratt, L. M.; Ramachandran, B. A. *J. Org. Chem.* **2005**, *70*, 7238−7242. (d) Pratt, L. M.; Le, L. T.; Truong, T. N. *J. Org. Chem.* **2005**, *70*, 8298−8302.

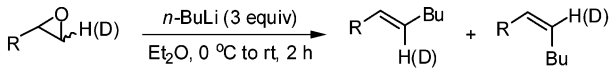
TABLE 6. Expanding the Reaction to 2,2-Disubstituted Epoxides

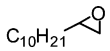
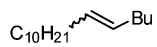
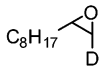
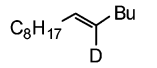
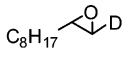
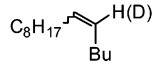


entry	epoxide		R^3Li	alkene		yield, %[a]	*E*:*Z* ratio[b]	alcohol yield, %[a,c]
1		**41**	PhLi		**42**	42	–	47
2		**41**	$LiCH_2SiMe_3$		**43**	40	–	48
3		**44**	PhLi		**45**	41	84:16	–
4		**46**	PhLi		**47**	62	82:18	–
5		**44**	$LiCH_2SiMe_3$		**48**	42	76:24	–
6		**46**	$LiCH_2SiMe_3$		**49**	44	53:47	–

[a] Isolated yield. [b] Determined by GC−MS analysis. [c] *Z*-Isomer isolated only.

TABLE 7. Studies Using Deuterated Epoxides with *n*-BuLi

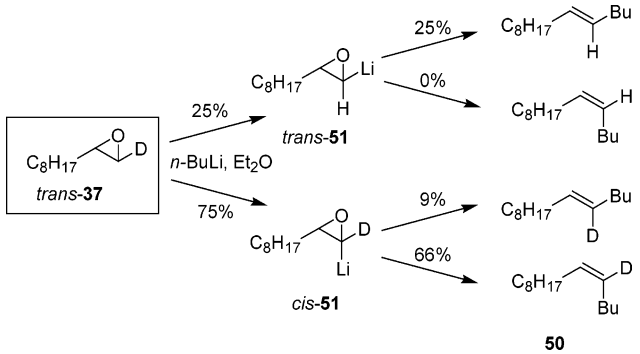


entry	epoxide		alkene		yield, %[a]	alkene ratio *E*-isomer[b] (D, %)[b]	alkene ratio *Z*-isomer[b] (D, %)[b]
1		**13**		**14n**	76	81	19
2		*cis*-**37**		**50**	65	100 (100)	0 (0)
3		*trans*-**37**		**50**	34	34 (29)	66 (94)

[a] Yield of isolated material. [b] Determined by GC−MS analysis.

The addition of excess *n*-BuLi to *trans*-**37** in Et_2O resulted in predominantly *Z*-alkene **50** with high deuterium content (94%, entry 3). *E*-Alkene **50** retained 29% deuterium, which implies that this isomer comes from both *cis*- and *trans*-lithiated epoxide intermediates. From this result, it can be calculated that initial α-deprotonation of *trans*-**37** gives trans-lithiated epoxide **51** and deuterated *cis*-lithiated epoxide **51** in a ratio of 25:75 (Scheme 6). The *trans*-lithiated epoxide **51** generates exclusively *E*-**50** (no deuterium retained). Once formed, *cis*-lithiated deuterated epoxide **51** gives predominantly *Z*-alkene **50** (88%) and some of *E*-alkene **50** (12%).[24] We can therefore conclude that, when *n*-BuLi is used as the base in Et_2O, the initial stereoselectivity of epoxide α-deprotonation principally determines the geometry of the resulting alkene.

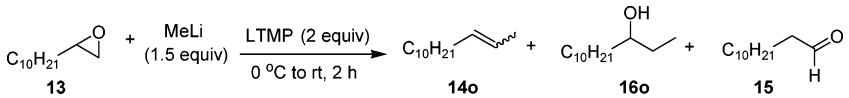
SCHEME 6. Reaction of Deuterated Epoxide *trans*-37 with *n*-BuLi



Mioskowski et al. reported that addition of excess MeLi to 1,2-epoxydodecane (**13**) in THF resulted in alkene **14o** in 48% yield (*E*/*Z* = 66:34).[3a] Repeating this reaction in THF and in Et_2O indicated that another significant product was secondary alcohol **16o**, formed via direct ring opening of the epoxide (Table 8, entries 1 and 2). Also, a significant quantity of the

(24) The formation of the minor *trans*-alkene isomer ((*E*)-**50**) from the cis-lithiated epoxide (*cis*-**51**) probably occurs because, following the 1,2-metallate shift to the organolithium intermediate, syn-elimination of Li_2O is slowed due to developing eclipsing interactions between alkyl groups (cf. Scheme 5), which allows time for partial loss of configurational integrity in the organolithium intermediate prior to elimination of Li_2O.

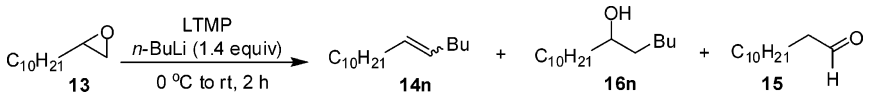
TABLE 8. Attempted Alkene Formation from Epoxide 13 and MeLi



entry	RLi	solvent	**14o** yield, %[a]	ratio, *E*/*Z*[b]	**16o** yield, %[a]	**15** yield, %[a]
1[c]	MeLi	THF	40	74:26	29	0
2[c]	MeLi	Et_2O	trace	–	63	0
3	MeLi	Et_2O	61	72:28	trace	10
4	MeLi·LiBr	Et_2O	30	87:13	45	trace
5[d]	MeLi·LiBr	Et_2O	71	72:28	trace	10
6	MeLi·LiBr	hexane	90	50:50	trace	0

[a] Isolated yield. [b] Determined by GC−MS analysis. [c] 3 equiv of MeLi without LTMP. [d] Using MeLi·LiBr to deprotonate TMP.

TABLE 9. Attempted *E*-Alkene Formation from Epoxide 13 and *n*-BuLi



entry	solvent	LTMP equiv	**14n** yield, %[a]	ratio, *E*/*Z*[b]	**16n** yield, %[a]	**15** yield, %[a]
1[c]	Et_2O	0	76	81:19	15	–
2	Et_2O	2	73	90:10	trace	8
3	Et_2O	5	75	90:10	trace	trace
4	hexane	2	91	45:55	0	trace
5[d]	Et_2O	2	53	90:10	trace	17

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis. [c] 3 equiv of *n*-BuLi used. [d] LiBr (1 equiv) present.

starting epoxide was recovered (24−30%). As the rate of nucleophilic ring opening and α-deprotonation of the epoxide by MeLi was found to be relatively slow (24−30% of epoxide **13** left after 16 h), it was considered a good candidate for LTMP-modified reductive alkylation to form alk-2-enes. 1,2-Epoxydodecane was therefore added to a mixture of MeLi and LTMP, with the aim of generating alkene **14o** in high yield and with good stereoselectivity. Factors varied included the solvent and whether MeLi or MeLi/LiBr complex was used (Table 8). The yield of alkene **14o** could be improved to 61% when the reaction was carried out in Et_2O (entry 3), although there was no change in stereoselectivity (*E*/*Z* = 72:28). A solvent change to hexane improved the yield further (to 90%); however, the stereoselectivity fell to *E*/*Z* = 50:50 (entry 6).

We then considered whether simple *E*-alkenes could be formed with high selectivity when an epoxide was added to a mixture of LTMP and a primary alkyllithium. For this reaction to be successful, LTMP would have to out-compete the alkyllithium in deprotonating the epoxide to exclusively form the *trans*-lithiated epoxide and hence only the *E*-alkene (cf. Scheme 6). In the event, using *n*-BuLi in Et_2O, alkene **14n** could be isolated in 73% yield and the *E*/*Z* ratio had improved to 90:10 (from 81:19 without LTMP present, Table 9, entries 1 and 2). The amount of LTMP present was raised in an attempt to increase the proportion of α-deprotonation by the lithium amide base relative to the alkyllithium; however, this did not improve the stereoselectivity (entry 3). Changing the solvent to hexane (entry 4) or adding LiBr (entry 5) did not have a beneficial effect on the reaction.

Because the likely origin of the *cis*-isomer (when the reaction is carried out in Et_2O) is deprotonation of the epoxide *cis* to the alkyl group by the alkyllithium, then one solution to this problem might be to use another alkyl metal that is not sufficiently basic enough to deprotonate the epoxide and hence would not compete with LTMP. A variety of organometallic reagents were screened (including organozinc, zirconium, aluminum, and cerium species), but none proved to be successful, as judged by ^{1}H NMR and TLC analyses of the crude reaction mixtures. However, addition of 1,2-epoxydodecane (**13**) to a mixture of LTMP (2 equiv) and a Grignard reagent,[25] *n*-BuMgCl (2 equiv), gave the desired alkene **14n** in modest yield but with excellent stereoselectivity when the reaction was carried out in Et_2O or hexane (Table 10, entries 1 and 2). Secondary alcohol **16n** and allylic alcohol **52** were the major coproducts. Reducing the amount of Grignard reagent used while maintaining the same amount of LTMP increased the yield of alkene **14n** to a respectable 69% (entry 3). In the absence of LTMP, only secondary alcohols and chlorohydrins were observed.

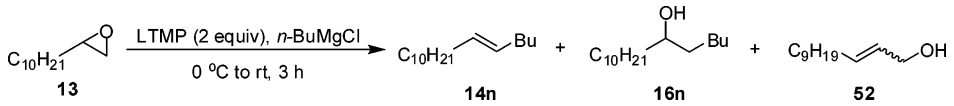
Following the success of using *n*-BuMgCl to form the corresponding *E*-alkene **14n**, we carried out the same protocol with MeMgCl[26] (Table 11). Alkene **14o** could be formed in good yield (71%) and pleasingly with high *E*-selectivity (*E*/*Z* = 98:2) when carrying out the reaction in hexane using 1.8 equiv of MeMgCl and 1.5 equiv of LTMP (entry 4).

Other Grignard reagents were examined to see if this chemistry could be applied to them and thereby solve some of the limitations of using organolithium reagents (Table 12). However, 2-thienylmagnesium chloride gave a poor yield of the corresponding arylated alkene **14e** (entry 1). There was also

(25) (a) Wakefield, B. J., Ed. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995. (b) Silverman, G. S., Rakita, P. E., Eds. *Handbook of Grignard Reagents*; Marcel Dekker: New York, 1996. (c) Richey, H. G., Ed. *Grignard Reagents: New Developments*; Wiley and Sons: New York, 1999.

(26) Use of MeMgBr in hexane only led to traces of alkene **14o**, and direct epoxide ring opening by LTMP (ref 11) and by bromide ion was observed.

TABLE 10. Reactions of Epoxide 13 with *n*-BuMgCl and LTMP

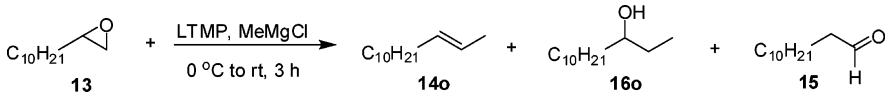


13 14n 16n 52

entry	solvent	*n*-BuMgCl (equiv)	**14n** yield, %[a]	ratio, *E*/*Z*[b]	**16n** yield, %[a]	**52** yield, %[a,c]
1	Et_2O	2	45	98:2	27	21
2	hexane	2	33	98:2	10	50
3	Et_2O	1.4	69	96:4	10	8

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis. [c] *E*/*Z* = 85:15, determined by ^{1}H NMR analysis.

TABLE 11. Reaction of Epoxide 13 with Methyl Grignard Reagents and LTMP

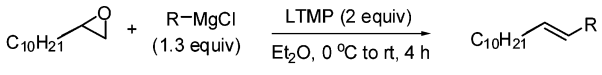


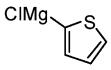
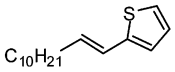
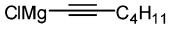
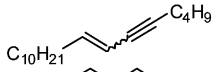
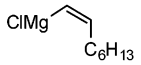
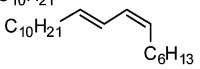
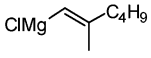
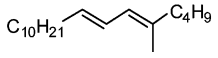
13 14o 16o 15

entry	solvent	MeMgCl (equiv)	LTMP (equiv)	**14o** yield, %[a]	ratio, *E*/*Z*[b]	**16o** yield, %[a]	**15** yield, %[a]
1	Et_2O	2	2	trace	*c*	40	15
2	hexane	2	2	45	99:1	10	40
3	hexane	2	1.5	65	98:2	20	trace
4	hexane	1.8	1.5	71	98:2	12	trace

[a] Isolated yield. [b] Determined by GC−MS analysis. [c] Not determined.

TABLE 12. Reductive Alkylation of Epoxide 13 with Grignard Reagents



entry	ClMg−R	product		yield, %[a]	ratios[b, c]
1			**14e**	10	99:1[e]
2[d]			**14a**	28	50:50[e]
3			(*Z*,*E*)-**14i**	67	91:9[f]
4			**14k**	70	94:6[g]

[a] Isolated yield. [b] Determined by GC−MS analysis. [c] Isomeric purity of major component. [d] 2 equiv of RMgCl and 1.5 equiv of LTMP were used. [e] Ratio *E*/*Z*. [f] Ratio *Z*,*E*/other isomers. [g] Ratio *E*,*E*/*Z*,*E*.

no improvement in stereoselectivity in enyne formation when an alkynyl Grignard reagent was employed (entry 2) or in the stereoselectivity of diene formation when stereodefined Grignard reagents were used (entries 3 and 4).

In conclusion, we have reported a detailed investigation on the reaction of terminal and 2,2-disubstituted epoxides with LTMP and organolithium/Grignard reagents to form alkenes in a regiospecific manner. In general, good yields and stereoselectivity have been obtained for the syntheses of arylated alkenes, dienes, allylsilanes, and enynes. In seeking to improve stereocontrol in the synthesis of *trans*-1,2-dialkyl-substituted alkenes from terminal epoxides, we have found that Grignard reagents offer an attractive solution. To the best of our knowledge, these are the first examples of Grignard reagents inserting into α-metalated epoxides to produce alkenes. This chemistry significantly broadens the use of epoxides as regio- and stereodefined vinyl cation equivalents and highlights the ability of lithium amides and organolithiums (or Grignard reagents), present in the same flask, to operate apparently independently of each other but in a defined sequence on a terminal epoxide substrate, resulting in transformations that neither of these reagents can achieve by themselves.

Experimental Section

General Experimental Details Described in Supporting Information. General Procedure A: Optimized Conditions for Alkene Formation via LTMP-Modified Reductive Alkylation Using Preformed or Commercially Available Organolithiums, or Grignard Reagents, Described for (*E*)-1-Phenyl-1-dodecene 14b. To a solution of 2,2,6,6-tetramethylpiperidine (153 mg, 1.08 mmol) in hexane (8 mL) at 0 °C (ice bath) was added *n*-BuLi (1.6 M in hexanes; 0.68 mL, 1.08 mmol) dropwise. The reaction mixture was stirred at this temperature for 10 min, and then a solution of PhLi (2.0 M in *n*-Bu_2O; 0.35 mL, 0.70 mmol) was added dropwise. The reaction was stirred for a further 5 min, and then 1,2-epoxydodecane 13 (100 mg, 0.54 mmol) was added. The ice bath was removed, and the reaction mixture was stirred for 2 h. After being quenched with saturated brine solution (10 mL), the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL), the combined organic layers were dried ($MgSO_4$), and solvent was removed in vacuo. The residue was purified by column

chromatography (SiO_2, 100% petrol) to give *alkene* **14b** (123 mg, 93%, *E*/*Z* = 98:2, by GC−MS analysis, t_R *Z*-**14b** 13.02 min, t_R *E*-**14b** 14.22 min, initial temp 80 °C, max temp 280 °C, rate 10 °C/min) as a colorless oil; R_f 0.48 (100% petrol); IR (neat)/cm^{-1} 3025m, 2956s, 2925s, 2853s, 1625w, 1599w, 1494w, 1466m, 927s; ^{1}H NMR (400 MHz) δ 7.38−7.29 (m, 4H), 7.21 (tt, J = 7.5, 1.5, 1H), 6.41 (d, J = 16, 1H), 6.26 (dt, J = 16, 7, 1H), 2.22 (dt, J = 7, 7, 2H), 1.53−1.45 (m, 2H), 1.40−1.25 (m, 14H), 0.92 (t, J = 6.5, 3H); ^{13}C NMR (100 MHz) δ 138.0, 131.3, 129.7, 128.5, 126.7, 125.9, 33.1, 32.0, 29.7, 29.6, 29.4, 29.4, 29.3, 22.7, 14.1; MS *m*/*z* (CI) 245 (M + H^+, 18), 244 (57), 117 (47), 104 (100), 91 (14); HRMS calcd for $C_{18}H_{29}$ (M + H^+) 245.2269, found 245.2267.

General Procedure B: Optimized Conditions for Alkene Formation via LTMP-Modified Reductive Alkylation Using Organolithiums Generated in Situ via Halogen−Lithium Exchange, Described for (*E*)-1-Dodec-1-enyl-4-methoxybenzene 14c. To a solution of 4-bromoanisole (131 mg, 0.70 mmol) in THF (1 mL) at −78 °C was added *t*-BuLi (1.5 M in pentane; 0.94 mL, 1.40 mmol) dropwise. The reaction mixture was stirred at this temperature for 30 min and then warmed to 0 °C (ice bath). After 5 min, a solution of LTMP (prepared by the addition of *n*-BuLi (1.6 M in hexanes; 0.68 mL, 1.08 mmol) to 2,2,6,6-tetramethylpiperidine (153 mg, 1.08 mmol) in hexane (8 mL) at 0 °C) was added dropwise. The reaction was left for a further 5 min at 0 °C, and then 1,2-epoxydodecane **13** (100 mg, 0.54 mmol) was added. The ice bath was removed, and the reaction mixture was stirred for a further 2 h. After being quenched with saturated brine solution (10 mL), the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL), the combined organic layers were dried ($MgSO_4$), and solvent was evaporated in vacuo. The residue was purified by column chromatography (SiO_2, 2% Et_2O in petrol) to give *alkene* **14c** (104 mg, 70%, *E*/*Z* = 98:2 by GC−MS analysis, t_R *Z*-**14c** 14.35 min, t_R *E*-**14c** 16.78 min, initial temp 100 °C, max temp 280 °C, rate 10 °C/min) as a white solid; R_f 0.48 (10% Et_2O in petrol); mp 36−39 °C; IR ($CHCl_3$)/cm^{-1} 2954m, 2920s, 2850m, 1608w, 1513w, 1465w, 1251w, 1176w, 1023w, 962w; ^{1}H NMR (400 MHz) δ 7.31 (d, J = 9, 2H), 6.87 (d, J = 9, 2H), 6.35 (d, J = 16, 1H), 6.12 (dt, J = 16, 7, 1H), 3.82 (s, 3H), 2.21 (q, J = 7, 2H), 1.52−1.44 (m, 2H), 1.41−1.25 (m, 14H), 0.92 (t, J = 7, 3H); ^{13}C NMR (400 MHz) δ 158.6, 130.8, 129.1, 129.0, 127.0, 113.9, 55.2, 33.1, 31.9, 29.7, 29.6, 29.6, 29.4, 29.3, 22.7, 14.1; MS *m*/*z* (CI) 275 (M + H^+, 100), 274 (69), 147 (63), 134 (18), 121 (25); HRMS calcd for $C_{19}H_{31}O$ (M + H^+) 275.2375, found 275.2373.

General Procedure C: Optimized Conditions for Allylsilane Formation via LTMP-Modified Reductive Alkylation Using α-Silyllithiums Generated in Situ, Described for (*E*)-(1-Pentyltridec-2-en-1-yl)trimethylsilane 14m. To a solution of vinyltrimethylsilane (84 mg, 84 mmol) in THF (1 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes; 0.44 mL, 0.70 mmol) dropwise. The reaction mixture was stirred at this temperature for 2 h and then at −30 °C for 2 h. The reaction mixture was warmed to 0 °C (ice bath), and a solution of LTMP (prepared from the addition of *n*-BuLi (1.6 M in hexanes; 0.44 mL, 0.70 mmol) to 2,2,6,6-tetramethylpiperidine (99 mg, 0.70 mmol) in hexane (7 mL) at 0 °C) was added dropwise. After 5 min, 1,2-epoxydodecane **13** (100 mg, 0.54 mmol) was added, and the reaction mixture was stirred for 2 h at 0 °C. After being quenched with saturated brine solution (10 mL), the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL), the combined organic layers were dried ($MgSO_4$), and solvent was evaporated in vacuo. The residue was purified by reverse-phase column chromatography[27] (C_{18} silica, 15% Et_2O in MeCN) to give *allylsilane* **14m** (130 mg, 74%, *E*-only by GC−MS analysis, *E*-**14m** 10.18 min, initial temp 80 °C, max temp 280 °C, rate 20 °C/min) as a colorless oil; R_f 0.13 (C_{18} silica, 15% Et_2O in MeCN); IR (neat)/cm^{-1} 2924s, 2854s, 1467m, 1378w, 1258m, 969m, 861m; ^{1}H NMR (400 MHz) δ 5.24−5.12 (m, 2H), 1.99 (dt, J = 6.5, 6.5, 2H), 1.42−1.16 (m, 25 H), 0.91−0.86 (m, 6H), −0.01 (s, 9H); ^{13}C NMR (100 MHz) δ 131.5, 128.2, 32.9, 32.9, 31.9, 31.8, 30.1, 29.7, 29.6, 29.5, 29.4, 29.1, 29.0, 28.9, 22.7, 22.6, 14.2, 14.1, −3.1; MS *m*/*z* (CI) 325 (M + H^+, 34), 251 (13), (8), 250 (48), 90 (100), 73 (25); HRMS calcd for $C_{21}H_{45}Si$ (M + H^+) 325.3291, found 325.3287.

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Note Added after ASAP Publication. There were errors in Table 10 in the version published May 26, 2007; the corrected version was published May 29, 2007.

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

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