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Substituted Epoxides by Lithiation of Terminal Epoxides

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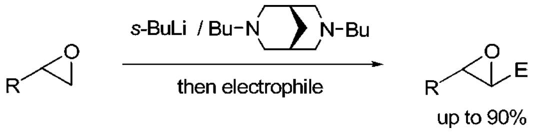
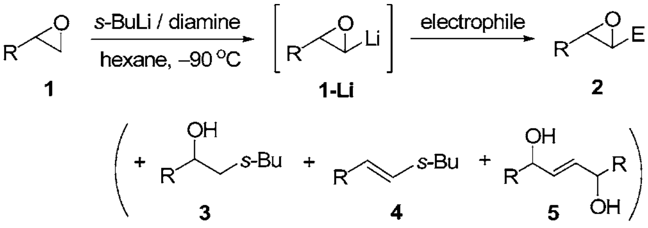
ABSTRACT



Diamine-ligand-assisted direct hydrogen–lithium exchange allows the generation of nonstabilized (H-substituted) oxiranyllithium species and their subsequent trapping by Bu_3SnCl and carbonyl-based electrophiles. This reaction provides a new concise route to α,β-epoxystannanes and substituted epoxides.

In contrast to chemistry exploiting the electrophilicity of epoxides, the utility of lithiated epoxides as nucleophiles (oxiranyl anions, e.g., **1-Li**), first studied by Eisch and Galle,[1] is far less developed, even though such reactions can provide a very direct way to assemble substituted epoxides.[2] Until recently, this latter strategy required epoxides possessing an activating substituent (electron-withdrawing, trialkylsilyl, trialkylstannyl, or sulfinyl group). Although such reactions illustrate the value of oxiranyllithiums in the elaboration of epoxides, they also indicate the potential limitation of requiring a prefunctionalized epoxide precursor in order to perform the chemistry. Recently, we demonstrated a new approach to substituted epoxides by enantioselective lithiation−electrophile trapping, at epoxide functionality fused to eight- and seven-membered rings.[3] This followed a report in which we showed that direct lithiation of simple terminal epoxides **1**, followed by electrophile trapping of the nonstabilized (H-substituted) oxiranyl anion intermediates, was possible in the presence of a diamine ligand.[4] However, the latter reaction was restricted to silylation (Me_3SiCl present during generation of the oxiranyl anion)[5] and deuteration (CD_3OD as external electrophile). Here we communicate a significant advance in the area of direct epoxide functionalization: direct deprotonation of unactivated terminal epoxides and subsequent trapping with a range of (external) electrophiles, including C−C bond formation.

Scheme 1. Terminal Epoxide Lithiation



Compared to lithiation−electrophile trapping using epoxides of medium-sized cycloalkenes, terminal epoxides

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[1] (a) Eisch, J. J.; Galle, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 4646−4648. (b) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1976**, *121*, C10−14. (c) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1988**, *341*, 293−313. (d) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835−4840.

[2] (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303−3325. (b) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625−1642. (c) Chemla, F.; Vrancken, E. In *The Chemistry of Organolithium Reagents*; Rappoport, Z., Marek, I., Eds.; Wiley & Sons: New York, 2004; pp 1165−1242.

[3] (a) Hodgson, D. M.; Gras, E. *Angew. Chem.* **2002**, *114*, 2482−2484; *Angew. Chem., Int. Ed.* **2002**, *41*, 2376−2378. (b) Hodgson, D. M.; Buxton, T. J.; Cameron, I. D.; Gras, E.; Kirton, E. H. M. *Org. Biomol. Chem.* **2003**, *1*, 4293−4301.

[4] Hodgson, D. M.; Norsikian, S. L. M. *Org. Lett.* **2001**, *3*, 461−463.

[5] For an alternative in situ epoxide silylation method, see: Hodgson, D. M.; Reynolds, N. J.; Coote, S. J. *Tetrahedron Lett.* **2002**, *43*, 7895−7897.

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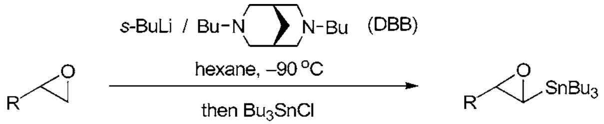
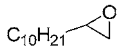
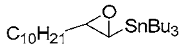
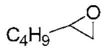
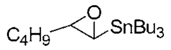
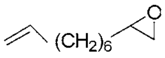
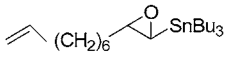
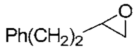
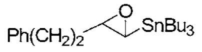
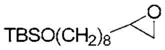
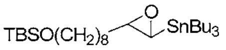
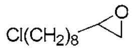
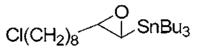
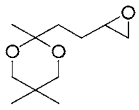
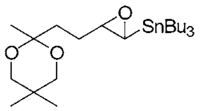
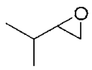
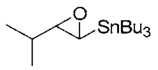
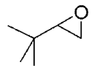
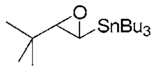
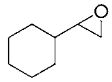
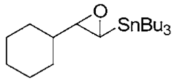
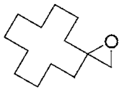
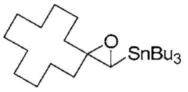
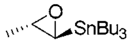
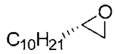
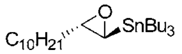
represent a greater challenge due to comparatively reduced epoxide C−H acidity,[6] combined with a higher propensity of both the starting and α-lithiated epoxides to undergo ring-opening reactions leading to alcohols **3**, alkenes **4**,[7] and alkenediols **5**[8] as byproducts. In our original screen of diamine ligands,[4] the use of 3,7-dibutyl-3,7-diazabicyclo-[3.3.1]nonane (dibutylbispidine, DBB)[9]/*s*-BuLi (2.5 equiv) in the lithiation−deuteration of **1** ($R = C_{10}H_{21}$) in hexane at −90 °C for 15 min had afforded 82% recovered epoxide with only 45% D incorporation; as other bispidine-type ligands were more efficient,[4] DBB was not studied in more detail at the time. However, subsequent extensive investigations with DBB have revealed that, by applying the above conditions but using a reduced reactant concentration (0.025 M rather than 0.050 M) together with a longer lithiation period (1−1.5 h), DBB becomes the preferred ligand for minimizing byproduct formation and achieving electrophile incorporation into terminal epoxides. For example, if Bu_3SnCl (2.5 equiv) was added neat, after 1.5 h, to epoxide **1** ($R = C_{10}H_{21}$) under the above conditions,[10] *trans*-α,*β*-epoxystannane **6** ($R = C_{10}H_{21}$, Table 1) was obtained in good yield (78%, after column chromatography on Florisil).[11] α,*β*-Epoxystannanes are useful for indirect oxiranyl anion generation via transmetalation[8] and may also allow subsequent introduction of other electrophiles using cross-coupling techniques;[12] therefore, the scope of stannylation was assessed with a range of epoxides (Table 1).

As shown in Table 1, stannylation of 1,2-epoxyhexane (entry 2), as well as a range of epoxides bearing additional functionality (entries 3−7), was successful (67−83% yields).[13,14] Isopropyl and *tert*-butyl oxiranes gave the best yields of epoxystannanes (90% and 87%, respectively, entries 8 and 9). Lithiation of a 2,2-disubstituted epoxide (entry 11) was significantly slower than for the other monosubstituted epoxides, requiring a 4-h lithiation period to afford the corresponding epoxystannane in good yield (64%). Commercially available (*S*)-propylene oxide was successfully stannylated (54%, entry 12), and (*S*)-1,2-epoxydodecane

Table 1. Direct Stannylation of Terminal Epoxides



1 6

entry[a]	epoxide **1**	α,β-epoxystannane **6**	yield (%)[b]
1			78
2			70
3			67
4			72
5			83
6			78
7			72
8			90
9			87
10			73
11			64
12[c]			54
13			65

[a] Solution of epoxide **1** in hexane was added to *s*-BuLi/DBB (2.5 equiv) in hexane at −90 °C, and then stirred at −90 °C for 1 h (1.5 h, entry 1; 4 h, entry 11) before addition of Bu_3SnCl. [b] Isolated yield after column chromatography on Florisil (neutral alumina, entry 11). [c] Epoxide added neat to *s*-BuLi/DBB (2.5 equiv) at −100 °C, and then reaction continued at −90 °C.

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(6) Morgan, K. M.; Gronert, S. *J. Org. Chem.* **2000**, *65*, 1461−1466.

(7) Doris, E.; Dechoux, L.; Mioskowski, C. *Synlett* **1998**, 337−343.

(8) Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615−618.

(9) Bertini Gross, K. M.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679−7689. For an improved synthesis of DBB, see ref 3b.

(10) Other solvents (Et_2O, cumene, *t*-BuOMe, or THF) and different equivalents of *s*-BuLi/DBB gave inferior results.

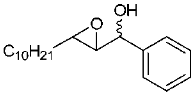
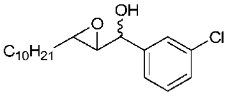
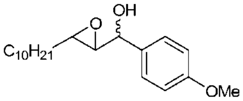
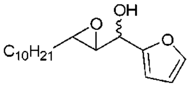
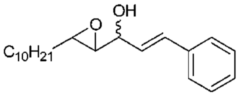
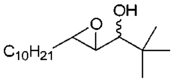
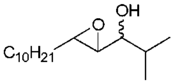
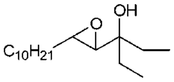
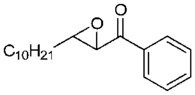
(11) Use of SiO_2 for column chromatography resulted in partial decomposition of the epoxystannane.

(12) Falck, J. R.; Bhatt, R. K.; Reddy, K. M.; Ye, J. *Synlett* **1997**, 481−482.

(13) **General Procedure for Lithiation-Electrophile Trapping of 1,2-Epoxydodecane.** To a solution of DBB (162 mg, 0.68 mmol) in hexane (8.5 mL) at −90 °C under an argon atmosphere was added dropwise *s*-BuLi (1.4 M in cyclohexane, 0.48 mL, 0.67 mmol), and the mixture was allowed to warm to 0 °C over 5 min. On recooling to −90 °C, a solution of epoxide **1** ($R = C_{10}H_{21}$, 50 mg, 0.27 mmol) in hexane (1 mL + 1 mL wash) was added dropwise over a period of 15 min, and the mixture was stirred at −90 °C for 1.5 h. The electrophile (0.68 mmol) was then added neat in one portion, and the mixture was manually agitated at −90 °C for 10 min before warming slowly to 0 °C (over 14 h). After quenching with 0.5 M H_3PO_4 (2.5 mL), the aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by column chromatography (Florisil or SiO_2, petrol/Et_2O) gave the substituted epoxide.

(14) Epoxides in Table 1 were commercially available or prepared according to: (a) Elings, J. A.; Downing, R. S.; Sheldon, R. A. *Eur. J. Org. Chem.* **1999**, 837−846 (entry 4). (b) Yang, L.; Weber, A. E.; Greenlee, W. J.; Patchett, A. A. *Tetrahedron Lett.* **1993**, *34*, 7035−7038 (entry 5). (c) Rothberg, I.; Schneider, L.; Kirsch, S.; OFee, R. *J. Org. Chem.* **1982**, *47*, 2675−2676 (entry 6). (d) 2,5,5-Trimethyl-2-(2-oxiranylethyl)-1,3-dioxane was prepared in two steps from 5-hexen-2-one (entry 7). (e) Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631−632 (entries 10 and 11). (f) Savle, P. S.; Lamoreaux, M. J.; Berry, J. F.; Gandour, R. D. *Tetrahedron: Asymmetry* **1998**, *9*, 1843−1846 (entry 13).

Table 2. Direct C−C Bond Formation Using 1,2-Epoxydodecane

entry[a]	electrophile	product **2**[b]	yield (%)[c]
1	PhCHO		75
2	3-ClC_6H_4CHO		72
3	4-$MeOC_6H_4CHO$		57
4	furfural		67
5	cinnamaldehyde		73
6	*t*-BuCHO		70
7	*i*-PrCHO		56
8	Et_2CO		63
9	$PhCONMe_2$		50

[a] Solution of epoxide **1** (R = $C_{10}H_{21}$) in hexane was added to *s*-BuLi/DBB (2.5 equiv) in hexane at −90 °C and then stirred at −90 °C for 1.5 h before addition of electrophile. [b] Secondary alcohols obtained with dr 1:1. [c] Isolated yields after column chromatography (combined yields for diastereomeric epoxy alcohols that, with the exception of entry 4, were largely chromatographically separable).

(readily available by hydrolytic kinetic resolution)[14f,15] gave a similar yield (65%, entry 13) to that of the racemate.

An examination of lithiation−electrophile trapping to achieve C−C bond formation was then carried out. Lithiation of 1,2-epoxydodecane for 1.5 h, followed by addition of benzaldehyde, gave a mixture of chromatographically separable diastereoisomeric epoxy alcohols (75% combined yield, dr 1:1, Table 2, entry 1). The lack of diastereoselectivity is consistent with that observed for other oxiranyl anions.[16] The methodology was successfully extended to the trapping of a range of aromatic aldehydes (Table 2, entries 2−4). Similarly, nonenolizable aldehydes (cinnamaldehyde and pivaldehyde) were trapped in good yields (73% and 70%, respectively, entries 5 and 6). Potentially enolizable carbonyl electrophiles (isobutyraldehyde and 3-pentanone) were also incorporated, albeit in slightly lower yields (56 and 63%, respectively, entries 7 and 8). Acylation using a comparatively unreactive amide (*N*,*N*-dimethylbenzamide) also proceeded (50%, entry 9).[17]

In conclusion, we have demonstrated a new, concise, and stereocontrolled conversion of terminal epoxides to α,*β*-epoxystannanes. Furthermore, we have shown that terminal epoxides can be deprotonated and trapped with a variety of carbonyl-based electrophiles. Compared to epoxides of medium-sized cycloalkenes, the pool of potential terminal epoxide substrates is considerably larger and the resulting substituted epoxides products are of significantly greater utility. Further studies in the area of direct epoxide functionalization and the synthetic utility of the substituted epoxide products are currently underway.

Acknowledgment. We thank the EPSRC for a research grant (GR/N26302) and the EPSRC and GlaxoSmithKline for a CASE award (to N.J.R.). We also thank the EPSRC National Mass Spectrometry Service Center (Swansea) for mass spectra.

Supporting Information Available: Characterization data for epoxystannanes **6** and substituted epoxides **2** including ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

(16) Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042−4050.

(17) Attempted trapping with other electrophiles, such as allyl bromide, EtOTf, and MeI, has so far been unsuccessful.