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First Direct Deprotonation–Electrophile Trapping of Simple Epoxides: Synthesis of α,β-Epoxysilanes from Terminal Epoxides

David M. Hodgson* and Stephanie L. M. Norsikian

Dyson Perrins Laboratory, Department of Chemistry, University of Oxford, South Parks Road, Oxford OX1 3QY, U.K.

david.hodgson@chem.ox.ac.uk

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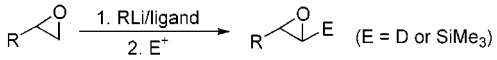
ABSTRACT



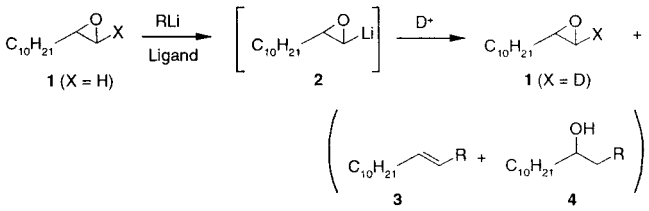
The presence of a suitable diamine ligand is the key to achieving ring lithiation–substitution of epoxides without the need for activating substituents on the epoxide and constitutes a new synthetic entry to *trans*-α,β-epoxysilanes.

Epoxides are widely utilized as versatile synthetic intermediates.[1] Their reactions are dominated by the electrophilic nature of the epoxide, generally involve cleavage of the strained three-membered ring, and include a wide range of nucleophilic ring openings and acid- and base-induced isomerization reactions. In contrast, the utility of epoxides as nucleophiles (via oxiranyl anions, e.g., **2**), first studied by Eisch and Galle,[2] is less developed, although such reactions can provide a very direct way to assemble substituted epoxides.[3] A current requirement with this strategy is the apparent necessity of using epoxides possessing electron-withdrawing or trialkylsilyl or trialkylstannyl groups attached to the epoxide ring. Electron-withdrawing and trialkylsilyl substituents facilitate formation of oxiranyl anions by promoting deprotonation (usually lithiation) and prolonging the solution lifetime of these otherwise very labile intermediates. Trialkylstannyl- and sulfinyl-substituted epoxides react with organolithiums (by transmetalation and desulfinylation, respectively) rapidly enough at low temperatures such that the resultant unstabilized oxiranyl anions can exhibit synthetically useful nucleophilic (rather than carbene-type) reactivity with a range of electrophiles.[4]

Arising out of our studies concerning the lithiation−rearrangement of epoxides,[5] we considered that the presence of appropriate ligands might be able to serve the dual role of accelerating deprotonation and reducing the rate of oxiranyl anion decomposition. In this paper we report our preliminary results concerning the development of this concept for the direct deprotonation−electrophile trapping of unfunctionalized terminal epoxides.

We first set out to find conditions for lithiation−deuteration of a simple terminal epoxide (Scheme 1). In the absence

Scheme 1



of a ligand, or in the presence of TMEDA, no deuterium (D) incorporation could be obtained. For example, addition

(1) Erden, I. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 1A, pp 97−171.

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(4) (a) Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615−618. (b) Satoh, T.; Kobayashi, S.; Nakanishi, S.; Horigushi, K.; Irisa, S. *Tetrahedron* **1999**, *55*, 2515−2528.

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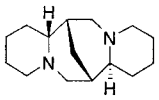
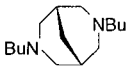
over 10 min of a solution of 1,2-epoxydodecane (**1**) (1 equiv) in diethyl ether to *i*-PrLi (2.5 equiv) in diethyl ether at −78 °C followed by D_2O after 1.5 min led after chromatography to recovered **1** (35% yield, 0% D incorporation), *trans*-alkene **3** (34%) arising from reductive alkylation,[6] and alcohol **4** (R = *i*-Pr, 22%). Reaction under the same conditions but in the presence of TMEDA (2.5 equiv) gave a mixture of **1** and **3** (**1**:**3**, 20:80, no **4** (R = *i*-Pr) detected); at −90 °C the ratio was **1**(0% D):**3**, 50:50. No reaction of **1** was observed at −90 °C with *i*-PrLi in diethyl ether or in THF/TMEDA.

Ligands **5**-**8**



(−)-**5**



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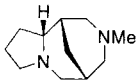
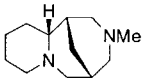


(+/−)-**7**



(+/−)-**8**

The first indications that D incorporation is possible were found using (−)-sparteine[5,7] (**5**) as the ligand. Fifteen minutes after addition of **1** to a mixture of **5** and *n*-BuLi, *t*-BuLi, or *i*-PrLi in diethyl ether at −90 °C, D incorporation in **1** showed 0% D, 10% D, and 22% D incorporation, respectively. After 1 h at −90 °C with *i*-PrLi/**5** in diethyl ether, **1** was recovered (50% yield) with 45% D incorporation, along with **3** (18%) and **4** (R = *i*-Pr, 11%). D was incorporated exclusively *trans* to the alkyl substituent on the oxirane ring, as anticipated from the reductive alkylation studies of Mioskowski et al.[6] Switching to hexane as solvent gave, after 1 h at −90 °C with *i*-PrLi/**5** (Table 1, entry 1), a similar level of D incorporation in **1** to that observed using diethyl ether, but significantly less **3** was formed (6%), no **4** was observed, and more epoxide was recovered (60%).

Table 1. Effect of Experimental Conditions on the Lithiation−Deuteration of 1,2-Epoxydodecane (**1**) in Hexane at −90 °C

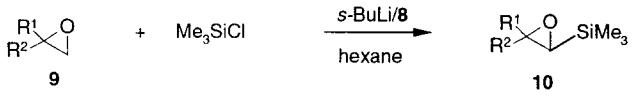
entry[a]	RLi	ligand	time (min)	% D[b] in **1**	yield of **1** (%)[c]
1	*i*-PrLi	**5**	60	46	60
2	*i*-PrLi	**5**	180	50	50
3	*s*-BuLi	**5**	15	75	70
4[d]	*s*-BuLi	**5**	60	90	40
5	*s*-BuLi	**6**	15	45	82
6	*s*-BuLi	**7**	15	50	85
7	*s*-BuLi	**7**	60	52	80
8	*s*-BuLi	**8**	15	63	91
9	*s*-BuLi	**8**	60	70	75

[a] Reactions were carried out by addition over 10 min of a solution of **1** (1 equiv) in hexane to a mixture of RLi/ligand (2.5 equiv each) in hexane at −90 °C, followed by addition of MeOD after the time indicated. [b] Determined by ^{1}H NMR. [c] Isolated yields after chromatography. [d] **4** (R = *s*-Bu) was only observed (5%) in entry 4.

The most encouraging results with **5** were obtained with *s*-BuLi in hexane at −90 °C, which after 15 min gave **1** in 70% yield with 75% D incorporation (Table 1, entry 3). In this case, only 9% of **3** was isolated. Longer reaction times resulted in diminished recovery of **1** (Table 1, entries 2 and 4). The success with **5** (compared with TMEDA) prompted us to examine **6**−**8**,[8] which all possess the 3,7-diazabicyclo-[3.3.1]nonane structural feature of **5** (Table 1, entries 5−8). For **6**−**8** the deprotonation step was slower than with **5**. The best results were obtained with *s*-BuLi/**8** in hexane at −90 °C (Table 1, entries 8 and 9); using *s*-BuLi/**8** in diethyl ether was less effective, giving after 1 h a mixture of **1** and **3** (**1**:**3**, 96:4), with only 48% D incorporation in **1**.

While trapping with other external electrophiles (Me_3SiCl, $ClCO_2Me$, PhCHO, EtCHO) has so far been unsuccessful, we have been able to prepare α,β-epoxysilanes **10** when Me_3-SiCl is present during the generation of the oxiranyl anion (Scheme 2, Table 2).[9,10] α,β-Epoxysilanes **10** are especially valuable in organic synthesis since, for example, they can be hydrolyzed to give carbonyl compounds, undergo regioselective and stereospecific ring-opening with a range of nucleophiles to give substituted β-hydroxysilanes, and are used as vinyl cation equivalents.[11]

Scheme 2



9 **10**

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

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(9) **Typical procedure for α,β-epoxysilane preparation:** A solution of **8** (116 mg, 0.60 mmol) in hexane (1 mL) was added to a stirred solution of *s*-BuLi (1.3 M in cyclohexane, 0.45 mL, 0.59 mmol) in hexane (4 mL) at −90 °C, and the reaction mixture was then allowed to warm to 0 °C over 15 min. After a few seconds at 0 °C, the mixture was recooled to −90 °C and a solution of 1,2-epoxydodecane (44.1 mg, 0.24 mmol) and Me_3-SiCl (36 μL, 0.28 mmol) in hexane (1 mL) was added dropwise over 10 min. After the reaction mixture had been stirred for 2 h at −90 °C, it was allowed to warm slowly to −50 °C over 30 min and then MeOH (1 mL) was added, followed by 1 N HCl (2 mL) at 0 °C. The two phases were separated, and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic extracts were washed with brine (1 × 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane/diethyl ether 99.5/0.5) to give 45.1 mg of **10** ($R^1 = C_{10}H_{21}$, R^2 = H, 73% yield): R_f = 0.3 (pentane); IR (neat) 2957, 2925, 2854, 1467, 1249, 848 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76−2.74 (m, 1H), 1.97 (d, 1H, J = 3.5 Hz), 1.62−1.26 (m, 18H), 0.88 (t, 3H, J = 7 Hz), 0.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 51.7, 34.1, 31.9, 29.6, 29.5, 29.3, 26.4, 22.7, 14.1, −3.7; CIMS *m*/*z* (relative intensity) 257 ($M + H^+$, 15), 129 (15), 90 (100), 73 (15); HRMS calcd for $C_{15}H_{32}OSi$ 257.2300, found 257.2300.

(10) The structure of the diamine used is important (TMEDA also failed in this transformation, whereas the use of (−)-**5** effected partial kinetic resolution (Norsikian, S. L. M. unpublished results)). Other electrophiles (BuOTf, Bu_3SnCl, MeI) tried in situ were unsuccessful.

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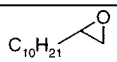
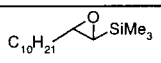
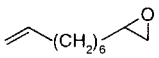
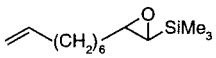
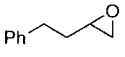
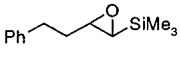
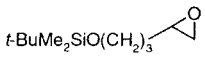
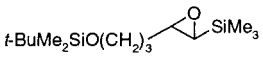
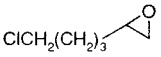
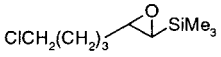
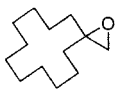
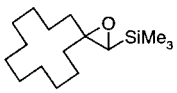
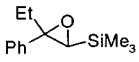
Table 2. Direct Synthesis of α,β-Epoxysilanes **10** from Epoxides **9**

Entry[a]	**9**	Time (h)	**10** (Yield, %)[b]
1		2	 (73)
2		2.5	 (71)
3		4.5	 (61)
4		2	 (74)
5		3	 (65)
6		4.5	 (67)
7		3	 (71)

[a] Reactions were carried out at −90 °C (−83 °C for entry 3) for the time indicated, followed by warming to −80 °C over 5 min (to −50 °C over 30 min for entries 1 and 7). [b] Isolated yield of **10** after chromatography.

The results in Table 2 indicate that the process is compatible with a range of functionalized epoxides[12] leading to *trans*-α,β-epoxysilanes (entries 2−5).[13] The reaction is also applicable to the preparation of trisubstituted epoxides (entries 6 and 7).[14] For the unsymmetrical epoxide in entry 7, silylation occurred with a high degree of regioselectivity (97/3) *trans* to the phenyl substituent.[14b]

In conclusion, we have demonstrated for the first time that simple unfunctionalized epoxides can, via direct lithiation in the presence of a suitable diamine ligand, be ring-substituted with an external electrophile (although at the moment this is restricted to deuteration) and with a silylating agent present in situ. The latter chemistry provides a new, concise stereocontrolled access from terminal epoxides (also readily available as either enantiomer)[15] to α,β-epoxysilanes. We are currently studying other ligands in order to improve this reaction and to extend the process to other epoxides and electrophiles.

Acknowledgment. This work was supported by the Engineering and Physical Sciences Research Council (EPSRC) in the U.K. and by a Marie Curie Fellowship of the European Community (program TMR under contract number HPMF-CT-1999-00264). We also thank the EPSRC Mass Spectrometry Service Centre for mass spectra and Dr. P. O'Brien (York) for initial test samples of ligands **7** and **8**.

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(12) 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 3). (b) Yang, L.; Weber, A. E.; Greenlee, W. J.; Patchett, A. A. *Tetrahedron Lett.* **1993**, *34*, 7035−7038 (entry 4). (c) Rothberg, I.; Schneider, L.; Kirsch, S.; OFee, R. *J. Org. Chem.* **1982**, *47*, 2675−2676 (entry 5). (d) Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631−632 (entries 6−7).

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