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Straightforward synthesis of α,β-epoxysilanes from terminal epoxides by lithium 2,2,6,6-tetramethylpiperidide-mediated deprotonation-in situ silylation

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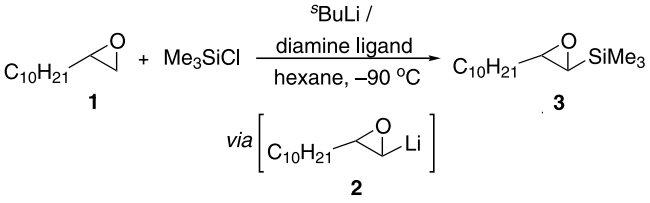
Abstract—Lithiation-in situ silylation of simple terminal epoxides using lithium 2,2,6,6-tetramethylpiperidide in combination with trimethylsilyl chloride provides a direct and experimentally convenient process for the synthesis of *trans*-α,β-epoxysilanes.

α,β-Epoxysilanes are synthetically valuable substrates since, for example, they can be hydrolysed to produce carbonyl compounds, undergo regioselective and stereospecific ring-opening with a range of nucleophiles to afford β-hydroxysilanes and serve as vinyl cation equivalents for the preparation of olefins.[1] Recently, we reported the first direct deprotonation-electrophile trapping of simple terminal epoxides with a silylating agent present in situ to afford α,β-epoxysilanes, e.g. **3** from **1**, via a transient oxiranyllithium **2** (Scheme 1).[2] The key to achieving this transformation was the presence of a suitable diamine ligand [(−)-sparteine, or ligands structurally related to sparteine] at low temperature (−90°C).

In connection with our studies of the above transformation, we became interested in a report by Yamamoto and co-workers on the selective isomerisation of terminal epoxides to aldehydes using lithium 2,2,6,6-tetramethylpiperidide (LTMP).[3] Yamamoto suggested that



Scheme 1.

aldehyde formation proceeds by rearrangement of an oxiranyllithium (e.g. **2**). Also, the low nucleophilicity of LTMP is known to give it compatibility with certain electrophiles, e.g. Me_3SiCl,[4] thus providing a way to trap reactive lithiated intermediates in situ. We therefore considered that the use of LTMP as base could provide an alternative and more experimentally convenient approach to the in situ deprotonation-electrophile trapping of terminal epoxides. Advantages of using LTMP over an organolithium·(−)-sparteine (or sparteine-like ligand) protocol, include ease of preparation from inexpensive, commercially available reagents and greater functional group compatibility due to lithium amide nature. Also, in contrast to (−)-sparteine, the achiral nature of LTMP avoids issues concerning partial kinetic resolution of racemic epoxides[2] and the different reactivity of separate epoxide enantiomers (e.g. attempted silylation of (*R*)-**1** with ^{s}BuLi·(−)-sparteine failed, whereas (*S*)-**1** gave **3** in 72% yield).[5]

A study of the LTMP-mediated in situ silylation of 1,2-epoxydodecane **1**, with Me_3SiCl as electrophile to give *trans*-α,β-epoxysilane **3**, has been made with an investigation of the effect of varying the experimental parameters (Scheme 2).

By addition of a solution of epoxide **1** and Me_3SiCl to LTMP (1:1.2:2.5 equiv., respectively) in THF it was found that some silylation could be achieved at reaction temperatures between −80°C and 20°C. Only a trace amount of silylation was achieved at −80°C, while at −45°C **3** was obtained in 20% isolated yield. Surprisingly, given the supposed thermal instability of such an

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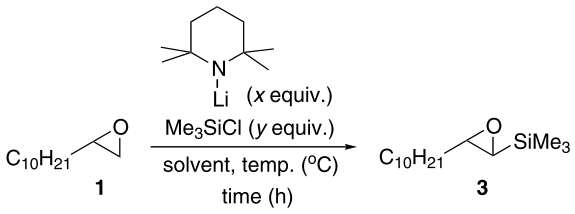
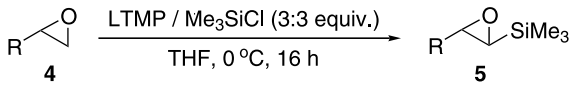


Scheme 2.

unstabilised oxiranyl anion intermediate **2**,[2,6] reaction at 20°C for 3 h gave **3** in 45% yield.[7] Starting the reaction at −78°C and allowing it to warm slowly to 20°C (over 16 h) with 2.5:1.5 equiv. LTMP/Me_3SiCl in THF afforded only a poor yield of **3** (16%). However, an improvement was ultimately achieved by altering the order of reagent addition, so that epoxide **1** was added to LTMP pre-mixed with Me_3SiCl. Although **3** was obtained in low yield (24%) with 2.5 equiv. each of LTMP and Me_3SiCl in Et_2O at 20°C for 6 h, this was improved using 2.5:2 equiv. in THF at 0°C for 16 h (50%). The best results were achieved using equimolar quantities of LTMP and Me_3SiCl, namely 3:3 and 5:5 equiv. at 0°C for 16 h in THF, producing 60% and 61% isolated yields of **3**, respectively. Further experimentation showed that excess Me_3SiCl relative to LTMP diminished the production of silylated epoxide **3**, probably due to silylation of the lithium amide base, while with LTMP in relative excess more epoxide was consumed, but at the expense of increased levels of impurities. Also, addition of additives (TMEDA or DMPU) did not lead to improved levels of silylation,[8] but it was found that silylation was also possible with the more bulky Et_3SiCl. With this electrophile the rate of oxiranyl anion trapping was reduced, so excess Et_3SiCl was required to prevent otherwise predominant aldehyde formation (optimised result: 1.3:5 equiv. LTMP/Et_3SiCl provided 64% and 28% isolated yields of silylated epoxide and dodecanal, respectively).[3]

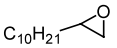
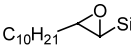
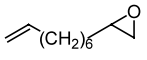
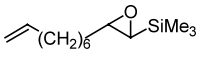
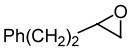
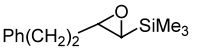
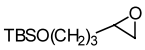
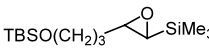
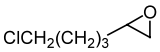
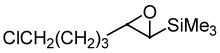
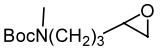
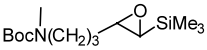
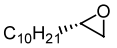
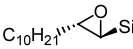
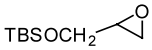
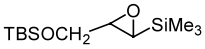
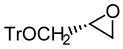
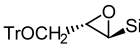
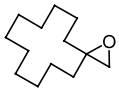
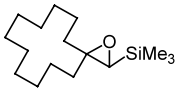
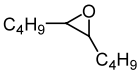
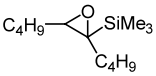
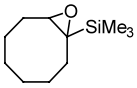
The protocol involving epoxide addition to LTMP/Me_3SiCl (3:3 equiv.) in THF at 0°C was subsequently applied to a number of more functionalised epoxides **4**[9,10] to produce *trans*-α,β-epoxysilanes **5** (Scheme 3, Table 1, entries 2–9).

Moderate to good yields of α,β-epoxysilanes **5** were obtained (56–75%, Table 1, entries 1–9), similar to those previously reported using the organolithium·diamine ligand procedure.[2] It was later found that reaction times shorter than 16 h at 0°C also gave similar levels of silylation, even at an increased reaction scale [e.g. using epoxide **1** (2.72 mmol) afforded, after 2 h at 0°C, **3** in 56% yield]. The present method using LTMP as base is advantageous because it involves much more experimentally straightforward conditions



Scheme 3.

Table 1. Direct synthesis of α,β-epoxysilanes from epoxides

Entry[a]	Epoxide	α,β-Epoxysilane	Yield (%)[b]
1			61
2			63
3			60
4			58
5			63
6			75
7			63
8			56
9			66
10			0[c]
11			0[c]
12			0[c]

[a] Reactions carried out using 0.272 mmol of epoxide for 16 h, except for entry 6 which showed complete consumption of starting epoxide within 6 h.
[b] Isolated yield of α,β-epoxysilane after column chromatography.
[c] >80% recovery of starting epoxide.

(e.g. an internal reaction temperature of 0°C compared to the strict −90°C required with the earlier diamine ligand procedure).[2] Interestingly, 5-(*N*-Boc-*N*-methylamino)-1,2-epoxypentane gave the highest yield of silylated product (75%, entry 6) possibly due to rate enhancement provided by coordination of LTMP to the Boc functionality. Enantiopure (*S*)-1,2-epoxydodecane gave a similar yield to that for the racemic epoxide (entry 7). Glycidyl ethers were also successfully subjected to the reaction conditions (entries 8 and 9). Application of the silylation conditions to the 2,2-disubstituted epoxide (entry 10) and the 1,2-disubstituted epoxides (entries 11 and 12) afforded none of the desired trisubstituted epoxides, with the starting epoxides being recovered in >80% yield. Presumably, LTMP is too bulky to effect the deprotonation of these latter epoxides,[11] but this could allow the chemoselective silylation of a monosubstituted epoxide in the presence of a disubstituted epoxide.

In conclusion, we have demonstrated that terminal epoxides can be silylated under experimentally straightforward conditions with a simple lithium amide base and silylating agent in situ. This chemistry provides an alternative, concise and stereocontrolled conversion of terminal epoxides to α,β-epoxysilanes without the need for strictly controlled low temperature reaction conditions, or the use of diamine ligands only available from multistep synthesis. It has special merit for the synthesis of enantiopure α,β-epoxysilanes,[12] since enantiopure terminal epoxides are now easily available by Jacobsen hydrolytic kinetic resolution.[13]

General procedure for α,β-epoxysilane preparation:

To a solution of 2,2,6,6-tetramethylpiperidine (141 μL, 0.835 mmol) in dry THF (2 mL) at 0°C under an argon atmosphere was added dropwise ^{n}BuLi (1.6 M in hexanes, 0.51 mL, 0.82 mmol). The mixture was allowed to warm to 20°C over 30 min and then re-cooled to 0°C. To this LTMP solution, Me_3SiCl (104 μL, 0.816 mmol) was added followed immediately by the appropriate epoxide (0.272 mmol) in THF (1 mL). After stirring for 16 h at 0°C, satd aq. NH_4Cl (2 mL) and Et_2O (5 mL) were added. The phases were separated and the aqueous layer was extracted with Et_2O (2×5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, pentane/ether) gave the α,β-epoxysilane.

Acknowledgements

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10. Data for 5-(*N*-Boc-*N*-methylamino)-1,2-epoxypentane: ν_{max}(neat)/cm^{-1} 3053w, 2976m, 2932m, 2871w, 1694s, 1483m, 1396m, 1366m, 1160m, 881w, 772w; δ_H (400 MHz; $CDCl_3$) 3.25 (2H, t, J=6.3 Hz, NCH_2), 2.93 (1H, m, CH), 2.84 (3H, s, NMe), 2.76 (1H, t, J=4.8 Hz, CH_2), 2.48 (1H, dd, J=2.7 and 4.8 Hz, CH_2), 1.75–1.54 (4H, m, 2×CH_2), 1.46 (9H, s, ^{t}Bu); δ_C (100 MHz; $CDCl_3$) 155.7 (C=O), 79.2 (CMe_3), 51.9 (CH), 48.0 (NCH_2), 47.0 (CH_2), 34.0 (NMe), 29.6 (CH_2), 28.4 (CMe_3), 24.5 (CH_2); m/z (CI) 233 (10%, M+NH_4^+), 216 (90, M+H^+), 177 (100), 160 (50), 116 (35); HRMS: found 216.1599 (M+H^+), $C_{11}H_{21}NO_3$ requires 216.1599.
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