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Application of chiral lithium amide bases to the thia-Sommelet dearomatization reaction

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Abstract—Thia-Sommelet dearomatization reactions of benzylsulfonium ylides can create highly congested quaternary centers. Chiral bis-lithium amide bases were shown to effect enantiotopic deprotonation of benzylsulfonium ions, leading to thia-Sommelet rearrangement. The chiral trienes were generated in up to 50% ee.
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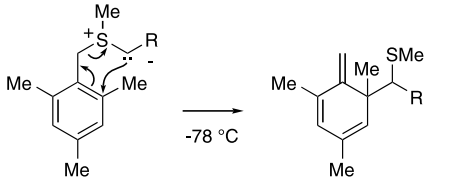
The [2,3] sigmatropic rearrangement of benzylsulfonium ylides (thia-Sommelet rearrangement) is a powerful method for punching quaternary centers into aromatic rings,[1] yet there have been no examples of enantiocontrolled thia-Sommelet rearrangements. Enantiocontrolled ylide formation is the key to enantioselective [2,3] sigmatropic rearrangement of both benzylsulfonium ylides and allylsulfonium ylides. The metal-catalyzed addition of diazoalkanes to allyl thioethers is one of the most promising methods for generating chiral sulfonium ylides that subsequently rearrange. Typical enantiomeric excesses are between 50% and 60%,[2] but Zhang and co-workers have recently obtained rearrangement products in up to 80% ee using α-aryl-α-diazoesters[3] Further enhancement in stereocontrol has been achieved through the combined use of chiral auxiliaries and chiral catalysts.[4] In spite of the continuing improvements in enantioselection, the α-diazo esters commonly used in transition metal-catalyzed reactions generate sulfonium ylides that are too stabilized to undergo thia-Sommelet dearomatization reactions. For example, while ylide **1a** rearranges rapidly at −78°C, the corresponding stabilized ylide **1b** is unreactive at or below room temperature (Scheme 1). When heated, ylide **1b** undergoes the expected homolytic [1,2] Stevens rearrangement.[5]



1a R = H
1b R = CO_2Et

2a R = H 90%
2b R = CO_2Et no [2,3]

Scheme 1.

The first example of an enantioselective [2,3] sulfonium ylide rearrangement was not effected by a transition metal. Instead, a combination of a chiral lithium alkoxide and chiral diamine was used to deprotonate a symmetrical sulfonium salt; the enantiomeric excess of the rearrangement product was modest (12% ee)[6] and no further attempts to use chiral bases have been reported. However, since this initial work, dramatic improvements have been made in the design of chiral bases and their application to enantiotopic deprotonation of epoxides, ketones, and η^6-arene chromium tricarbonyl complexes.[7] Chiral bis-lithium amides have proven to be particularly effective in enantiotopic deprotonation of chromium η^6-benzyl allyl ether complexes leading to [2,3]-Wittig rearrangements.[8] High levels of enantioselection are generally assumed to require lithium–oxygen coordination,[9,10] yet chiral bis-lithium amide bases have even been shown to deprotonate η^6-chromium complexes of benzylthioethers with remarkable levels of enantioselection. Thus, enantioselective deprotonation appeared to offer a more expedient approach to enantioselective thia-Sommelet reactions than transition metal-catalysis.

Keywords: dearomatization; sigmatropic; rearrangement; enantioselectivity; sulfonium.
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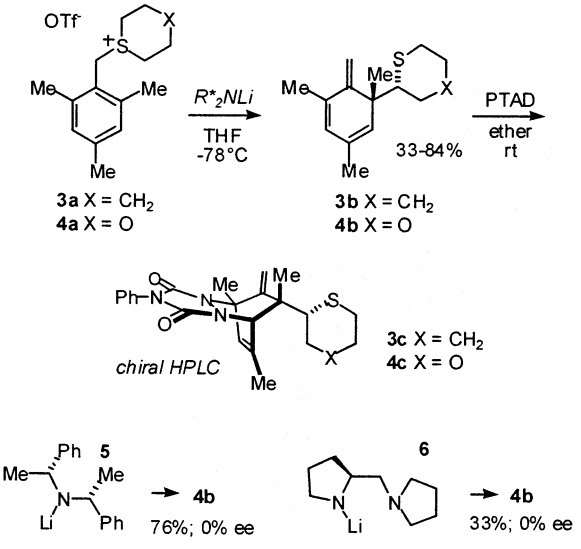
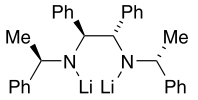
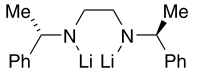
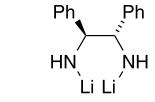
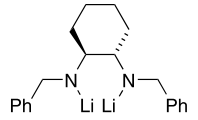
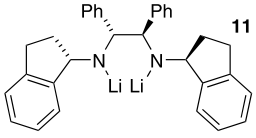
Since all good substrates for chiral lithium amide bases seem to have at least one Lewis basic site, we first synthesized the benzylsulfonium salts **3a** (without oxygen) and **4a** (with oxygen) by alkylation of the corresponding thioethers with 2,4,6-trimethylbenzyl bromide. Silver triflate was used to drive the equilibrium toward the sulfonium ion. The sulfonium salt **3a** was added to a solution of 105 mol% of the lithium amide at −78°C to effect deprotonation.[11] The rearrangement was essentially complete as soon as all of the base was added. The yield and diastereoselection (≥20:1) were generally good (Scheme 2). In order to assess the enantioselectivity, the triene was converted to the Diels–Alder adduct with 4-phenyl-[1,2,4]triazole-3,5-dione (PTAD) and subjected to chiral HPLC.[12] Unfortunately, the first reactions carried out with Whitesell's methylbenzylamine derived base **5**, with or without additional lithium bromide, gave no enantioselection. Similar reactions using Koga's pyrrolidinylproline base **6** was equally ineffective. No enantioselection was observed when these reactions were repeated with the oxa-substrate **4a**. However, when Simpkins' newer bis-lithium amide base **7** was appplied to dearomatization of sulfonium ion **4a** the enantiomeric trienes (**3b**) were generated in a 3.0:1.0 ratio. The carbon analog **4a** gave no enantioselection under identical conditions, suggesting that the ether oxygen is chelating to the base.

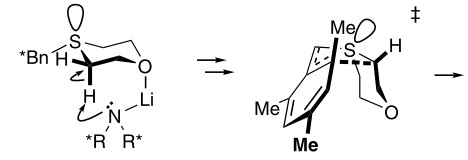
Gibson, O'Brien and co-workers have applied a number of analogs of bis-lithium amide base **7** in order to probe which features are necessary for chiral discrimination in the metalation of chromium η^6-benzyl ether complexes.[13] We studied a related series of bases (a) to better understand why the bis-amide base is effective, and (b) in the hope that more effective asymmetric induction might result. The ethylenediamine derivative **8** gave much lower enantioselection (12% ee) than the fully functionalized bis-amide **7**. However, the phenethyl substituents proved to be critical for chiral recognition since bases **9** and **10** gave no enantioselection. Thus, the trends in enantioselection revealed in



Scheme 2.

Table 1. Enantioselective thia-Sommelet reaction of **4a** with bis-lithium amide bases

Base (R^*_2NLi)		[2,3] Yield (**4b**)	ee (**4b**)
	**7**	84%	50% ee
	**8**	41%	12% ee
	**9**	84%	6% ee
	**10**	79%	0% ee
	**11**	78%	16% ee



Scheme 3.

Table 1, for deprotonation beta to a critical oxygen functionality, are related to the trends for deprotonation of benzylic ethers, alpha to a critical oxygen functionality. To further probe the importance of the phenethyl substituents, a conformationally restricted bis-indanyl analog, **11**, was prepared using the original Simpkins route.[14] The bis-indanyl base **11** is a conformationally restricted analog bis-phenethyl base **7**. However, in this case, removing degrees of freedom seems to diminish, rather than improve, the enantioselection.

The importance of the oxygen substituent supports the idea that lithium–oxygen chelation plays a key role in the competing enantiotopic transition states.[15] Not surprisingly, when the dearomatization of **4a** was carried out with the bis-amide base **7** in a mixture of 4:1 THF/DMPU, no asymmetric induction was observed. Therefore, we hypothesize that deprotonation involves a six-membered transition state reminiscent of the Ireland transition state for enolate formation (Scheme 3).

In conclusion, we have demonstrated the first example of an enantioselective thia-Sommelet rearrangement. The method is based on enantiotopic deprotonation of a symmetrical sulfonium ion to produce a chiral sulfonium ylide. Only bis-lithium amide bases were effective,

giving products with high diastereoselectivity (>20:1 de) and with low to moderate enantioselectivity (up to 50% ee). An oxygen substituent was essential for asymmetric induction.

Acknowledgements

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11. (a) A representative procedure used for lithium amide bases: To a round bottom flask charged with a solution of diisopropylamine (0.80 mL, 0.57 mmol) in THF (5 mL) at −78°C was added *n*-BuLi (2.1 M/hexane, 0.27 mL, 0.57 mmol) and the cooling bath was removed and the mixture was stirred for 10 min and then cooled to −78°C. A solution of **4a** (0.20 g, 0.52 mmol) in THF (5 mL) at −78°C was added via cannula to the LDA solution. After complete addition the reaction mixture was warmed to rt, quenched with H_2O, and diluted with ether. The mixture was washed with H_2O, brine and dried over $MgSO_4$. Filtration and concentration of the solvent in vacuo provided the crude product as a yellow oil. Purification by silica gel chromatography (20% CH_2Cl_2/hexanes) afforded **4b** (0.086 g, 70%) as a clear oil. (b) Characterization data: **4a**: mp 112–114°C; IR (KBr) 2929, 1608, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 2H); 4.96 (s, 2H); 4.35 (dt, $J=10.9$, 2.7, 2H); 4.38 (ddd, $J=10.1$, 6.6, 3.4, 2H); 3.51 (m, 4H); 2.42 (s, 6H); 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 138.8, 130.3, 119.9, 63.9, 41.9, 34.8, 20.9, 20.4. Anal. Calcd for $C_{15}H_{21}F_3O_4S_2$: C, 46.62; H, 5.48. Found C, 46.72; H, 5.32; **4b**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.62 (s, 1H); 5.35 (s, 1H); 5.25 (d, $J=1.8$, 1H); 5.23 (s, 1H); 4.10 (dd, $J=11.7$, 2.6, 1H); 4.03 (dt, $J=11.6$, 3.0, 1H); 3.52 (td, $J=11.6$, 2.2, 1H); 3.48 (dd, $J=11.6$, 10.0, 1H); 2.86 (m, 2H); 2.44 (dt, $J=13.6$, 2.2, 1H); 1.91 (s, 3H); 1.77 (d, $J=1.4$, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 133.0, 130.1, 128.4, 125.9, 112.1, 70.5, 68.3, 52.7, 43.0, 28.3, 27.4, 21.3, 19.4; LRMS (EI) m/z (relative intensity): 236 (70) $[M]^+$, 133 (100), 102 (80); **4c**: mp 214–216 °C; IR (KBr) 1775, 1712, 1402 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.45 (m, 4H), 7.33 (m, 1H), 5.89 (t, $J=1.7$, 1H); 5.52 (s, 1H); 5.03 (s, 1H); 4.85 (d, $J=1.3$, 1H); 4.28 (d, $J=2.6$, 1H); 4.26 (d, $J=2.6$, 1H); 4.10 (t, $J=3.1$, 1H); 4.08 (t, $J=3.1$, 1H); 3.74 (dd, $J=11.2$, 9.6, 1H); 3.62 (dt, $J=11.5$, 2.1, 1H); 2.85 (m, 1H); 2.71 (dd, $J=9.5$, 2.6, 1H); 2.53 (d, $J=13.7$, 1H); 2.09 (d, $J=1.7$, 3H); 2.00 (s, 3H); 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 153.5, 148.6, 140.5, 131.5, 129.0, 128.1, 126.3, 125.6, 112.5, 70.9, 68.2, 62.9, 62.6, 46.3, 46.2, 28.2, 21.5, 20.6, 18.4; LRMS (CI+) m/z (relative intensity): 411 (20) $[M]^+$, 309 (20), 177 (25), 133 (100); HRMS (CI+): Calcd for $C_{22}H_{25}N_3O_3S$, 411.1617 $[M]^+$, found 411.1600.
12. Analytical chiral HPLC was carried out on an Astec® Cyclobond I 2000 SN column using *i*-PrOH/hexane as the mobile phase.
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15. We were unable to determine the absolute stereochemistry of the rearrangement products. Therefore, the transition states represented in Scheme 3 may be mirror images of the actual transition states.