Stereospecificity of the 1,2-Wittig Rearrangement: How Chelation Effects Influence Stereochemical Outcome

Robert E. Maleczka, Jr.,* and Feng Geng

Department of Chemistry
Michigan State University
East Lansing, Michigan 48824

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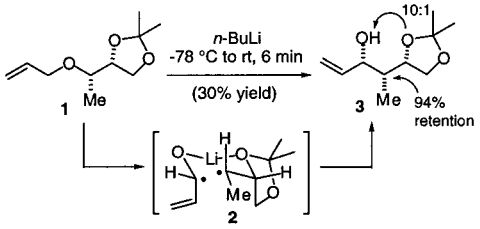
Since its discovery the rearrangement of α-metalated ethers, particularly the [2,3]-Wittig rearrangement, has been the subject of intensive mechanistic and synthetic investigations.[1] Relative to the [2,3]-shift, the [1,2]-Wittig rearrangement has received relatively little publicity. Most studies of the [1,2]-Wittig have been mechanistic in origin, resulting in the widely accepted theory that the reaction proceeds via a radical pair dissociation−recombination mechanism.[2]

Several years ago, Schreiber[3] reported an important observation on the stereospecific nature of this rearrangement (Scheme 1). Deprotonation of **1** resulted in "synthetically useful levels" of the [1,2]-rearrangement product that was heavily biased toward the syn isomer **3**. Schreiber postulated that the product arose from bond reorganization via a diradical transition state in which a lithium tether **2** sets up the syn stereochemistry. Another surprising feature of this rearrangement was the high level of retention (94%) at the migrating center.

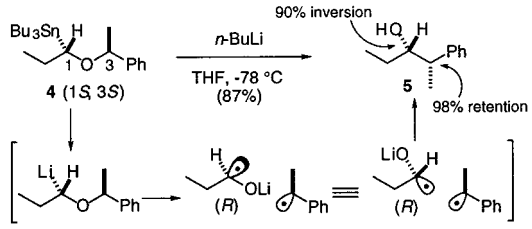
This observation became more interesting upon Cohen's[4] and Brückner's[5] recent evidence that [1,2]-Wittig rearrangements proceeded with inversion of the lithium-bearing terminus. Nakai[6] addressed this question and showed clearly that the [1,2]-Wittig rearrangement of enantiodefined α-alkoxylithium species proceeds with retention of the migrating center and with inversion of the lithium-bearing terminus (Scheme 2). In these examples, the stereochemistry of the product alcohols is not the result of chelation control, but rather decided by the configuration of the stannane precursor.

While there is little argument with either mechanistic explanation for the observed stereochemistries, it is important to note that the enantiodefined stannanes studied by Nakai did not hold the possibility of rearrangement under chelation control.[7] We found it intriguing to consider substrates with an ether oxygen capable of coordinating with the lithium of the stereodefined lithium terminus. In such substrates the appropriate stereochemical combination could put Schreiber's mechanism in stereochemical conflict with the results of Nakai, Cohen, and Brückner (Scheme 3). We therefore sought to prepare and study such substrates to provide a deeper understanding of the [1,2]-Wittig rearrangement. We believed that knowledge of the stereochemical

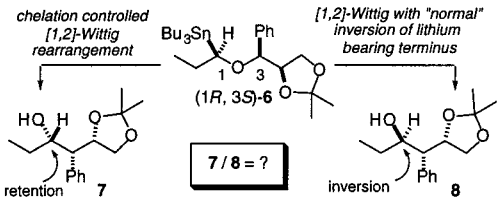
Scheme 1. [1,2]-Wittig Rearrangement Where Chelation Sets the Stereochemistry of the Newly Formed Alcohol[3]



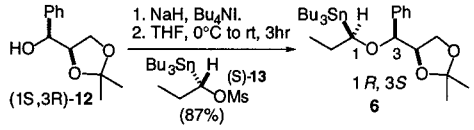
Scheme 2. [1,2]-Wittig Rearrangement with "Normal" Inversion of Configuration at the Metal Terminus[6]



Scheme 3



Scheme 4



influences imparted by these two mechanistic pathways would allow the discovery of new reaction conditions which should enable the practitioner to predict and control the stereochemical course of the [1,2]-Wittig rearrangement. Such reaction control would be of considerable value as it would represent a means for the selective construction of either *syn*- or *anti*-1,3 polyols, via a common reaction manifold.

Our preliminary experiments began with the preparation of the enantiodefined stannanes **6**, **9**, **10**, and **11**. The syntheses of these compounds paralleled established procedures[8] and involved the displacement of the known enantiodefined stannyl mesylates[9] (*R*)-**13** and (*S*)-**13** by the alkoxides of erythro and threo forms of 1-*C*-phenyl-2,3-*O*-isopropylidene-D-glycerol[10] (Scheme 4). This method provided the desired stannanes in 87% yield and in greater than 95% de as judged by the ^{1}H NMR.

Once model compounds **6**, **9**, **10**, and **11** were in hand, the [1,2]-Wittig rearrangement reaction was investigated. Compound **6** was first exposed to *n*-BuLi in 30% THF/hexanes, the same solvent system employed by Schreiber. The reaction gave a 64%

(1) (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885−902. (b) Marshal, J. A. In *Comprehensive Organic Synthesis*; Pattenden, G., Ed.; Pergamon: London, 1991; Vol. 3, pp 975−1014.

(2) (a) Schäfer, H.; Schöllkopf, U.; Walter, D. *Tetrahedron Lett.* **1968**, 2809−2814, and references therein. (b) Evans, D. A.; Baillargeon, D. J. *Tetrahedron Lett.* **1978**, 3315, 3315−3322. (c) Azzena, U.; Denurra, T.; Melloni, G.; Piroddi, A. M. *J. Org. Chem.* **1990**, *55*, 5532−5535. (d) Tomooka, K.; Yamamoto, H.; Nakai, T. *J. Am. Chem. Soc.* **1996**, *118*, 3317−3318. (e) Tomooka, K.; Yamamoto, H.; Nakai, T. *Liebigs Ann. Chem.* **1997**, 1275−1281.

(3) (a) Schreiber. S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 1043−1046. (b) Goulet, M. T. Ph.D. Thesis, Yale University, 1988.

(4) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375−377.

(5) Hoffmann, R.; Brückner, R. *Chem Ber.* **1992**, *125*, 1957−1963.

(6) (a) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron Lett.* **1993**, *34*, 8139−8142. (b) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron* **1994**, *50*, 5927−5932.

(7) Nakai has reported chelation-controlled rearrangements of racemic lithio species (see ref 2e).

(8) Tomooka, K.; Igarashi, T.; Watanabe, M.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 5795−5798.

(9) Matteson, D. S.; Tripathy, P. B.; Sarkar, A.; Sadhu, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 4399−4402 and references therein.

(10) (a) Ohgo, Y.; Yoshimura, J.; Kono, M.; Sato, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2957−2961. (b) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843−2846.

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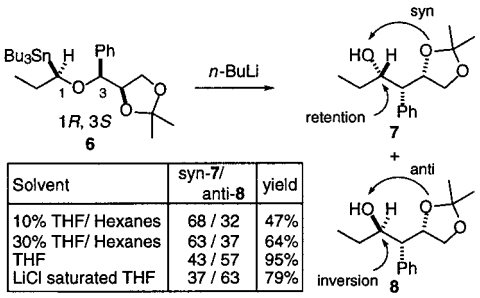
Scheme 5



Solvent	syn-**7**/ anti-**8**	yield
10% THF/ Hexanes	68 / 32	47%
30% THF/ Hexanes	63 / 37	64%
THF	43 / 57	95%
LiCl saturated THF	37 / 63	79%

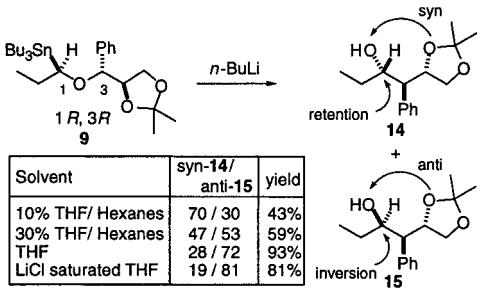
yield of a mixture of both the syn and anti alcohols,[11] with the syn alcohol **7** in slight excess.[12] While the selectivity was not great, it did represent evidence that the chelation-controlled reaction pathway was operative (Scheme 5). We reasoned that a less polar solvent would further favor the chelation-controlled product. This proved to be the case, as an experiment using 10% THF/hexanes as the solvent slightly increased the ratio of **7** to **8** to 68:32. The same line of thinking would suggest that a more polar solvent would disfavor the production of the chelation-controlled product. Indeed, running the reaction in pure THF reversed the stereochemical outcome. Compound **8**, that which results from an inversion of the configuration at the C1 center, became the major product albeit in only slight excess (**7**:**8**; 43: 57). Finally, THF saturated with LiCl was examined in the expectation that the lithium counterion would break up the intramolecular chelation even further. In fact, this experiment resulted in a complete stereochemical turnaround from the 10% THF/hexanes solvent system. The inversion product **8** was now favored by a ratio of 2:1.

Consistent with previous studies, it was found that there was a high level of retention of configuration at the migrating carbon center. In this case, the observed level of retention was always higher than 90%.

We observed the same pattern upon [1,2]-Wittig rearrangement of **9** (Scheme 6). With this substrate, however, changing the solvent polarity had an even more dramatic effect. Here, we were able to reverse the ratio of **14**:**15** from 2:1 under conditions for retention of configuration or chelation control (10% THF/hexanes) to 1:4 in favor of the inversion of configuration or nonchelation-controlled anti product.[11,12]

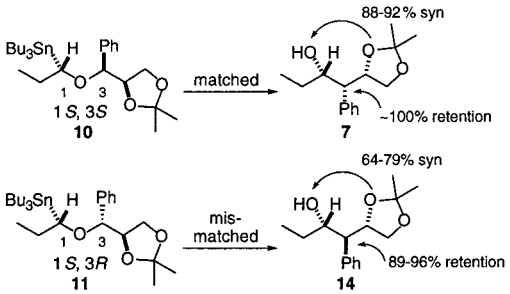
For **10** and **11**, the chelation-controlled reaction pathway leads to the inversion of C1 configuration. So even if a change in the solvent system were to affect the extent of chelation during the reaction, it should not greatly affect the stereochemistry of the products. Indeed, the [1,2]-Wittig rearrangement of **10** and **11** always gave the syn alcohol as the main product, regardless of variations in the solvent system (Scheme 7).[11,12]

Scheme 6



Solvent	syn-**14**/ anti-**15**	yield
10% THF/ Hexanes	70 / 30	43%
30% THF/ Hexanes	47 / 53	59%
THF	28 / 72	93%
LiCl saturated THF	19 / 81	81%

Scheme 7



It should be noted that regardless of solvent the rearrangement of **10** was always more stereoselective than for that of **11**. This suggests that there is a mutual recognition on the enantiomers during the recombination of the two radical species.[6] Apparently the *R,S* radical pair is the matched pair and recombines faster than the *R,R* or mismatched pair (Scheme 7).

Our results clearly show that the "normal" tendency for the α-oxylithium species to undergo an inversion of configuration can be suppressed, and even overturned, by the chelation effect. In systems such as **6** and **9**, the stereochemical course can be controlled to give *either* syn or anti 1,3-diol compounds as the main products. Further studies aimed at increasing our understanding of these rearrangements and improving the associated stereoselectiveties are currently underway and will be reported in due course.

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Supporting Information Available: Spectroscopic and analytical data for all new compounds pictured as well as selected experimental procedures (41 pages, print/PDF). See any masthead page for ordering information and Web access instructions.

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(11) The relative stereochemistries of diastereomers **7** and **14** were determined by the ^{1}H NMR method employed by Brückner et al. on similar molecules. See: (a) Hoffmann, R.; Brückner, R. *Chem Ber.* **1992**, *125*, 1471−1484. (b) Priepke, H.; Brückner, R. *Chem Ber.* **1990**, *123*, 153−168. Sterochemistries of **8** and **15** were secured by a combination of ^{1}H NMR and single-crystal X-ray analysis of the tris-3,5-dinitrobenzoate derivative of **8**.

(12) Diastereomeric ratios were measured by esterification of the crude product mixture with 3,5-dinitrobenzoyl chloride and subsequent HPLC analysis.