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Enantioselective [2,3]-Wittig Rearrangement Induced by Asymmetric Lithiation with a *t*-Butyllithium / Chiral Bis(oxazoline) System

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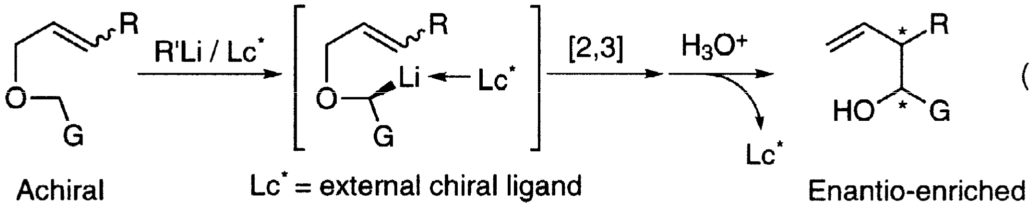
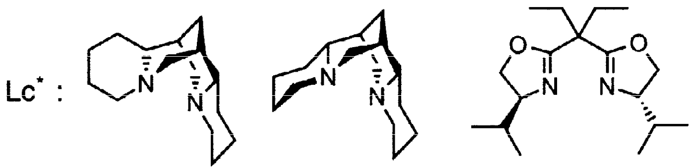
Abstract: *The [2,3]-Wittig rearrangement of (E)-crotyl propargylic ethers, when induced with a t-BuLi / chiral bis(oxazoline) complex, is shown to provide high enantioselectivity (up to 89% ee) along with high diastereoselectivity.*

The [2,3]-Wittig rearrangement, particularly its asymmetric version using enantio-enriched substrates, enjoys widespread application in many facets of organic synthesis.[1] However, only a few examples have been reported of the *enantioselective* version that permits direct access to an enantio-enriched product from an achiral substrate.[2] In view of the recent progress in the asymmetric lithiation protocol, mostly using (-)-sparteine (**1**) as an external chiral ligand (ECL),[3] we directed our attention to the exploration of enantioselective [2,3]-Wittig variants induced by the ECL-based asymmetric lithiation protocol (eq. 1). Of course, a key to success is the proper choice of ECL effective for each of the [2,3]-Wittig variants with different G groups. During the course of our studies, Kang *et al.* reported that the [2,3]-Wittig variants of crotyl propargyl ethers, when induced with *s*-BuLi / (-)-α-isosparteine (**2**), show modest levels of enantioselectivity (up to 42% ee).[4] We now wish to disclose that the use of the chiral bisoxazoline (*S,S*)-**3** as ECL provides significantly high levels of enantioselectivity in the [2,3]-Wittig rearrangement.[5,6] This is the first example of the utilization of a chiral bis(oxazoline) as ECL for the enantioselective [2,3]-Wittig rearrangement.[7]



(1)



(-)-**1** (-)-**2** (*S*, *S*)-**3**

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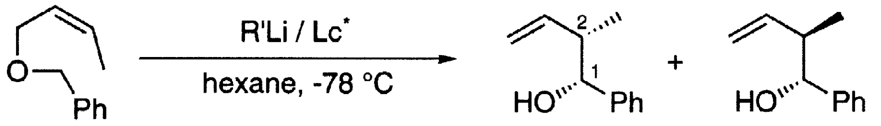
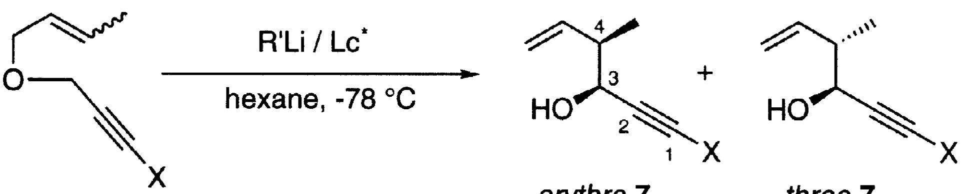
At the outset, we examined the enantioselectivity in the highly *erythro*-selective [2,3]-Wittig rearrangement of (*Z*)-crotyl benzyl ether (**4**)[8] by the combined use of *s*- or *t*-BuLi with (-)-sparteine (**1**) or (*S,S*)-bis(oxazoline) **3**[9] (eq. 2). Interestingly, the use of *s*-BuLi / (*S,S*)-**3** was found to provide a slightly higher % ee than that achieved with *s*-BuLi / **1** and the *t*-BuLi / (*S,S*)-**3** system to afford (1*R*, 2*S*)-**5** in 40% ee with 89% *erythro*-selectivity.[10,11]



(*Z*)-**4** (92% *Z*) → *erythro*-**5** + *threo*-**5** (2)

s-BuLi / (*S,S*)-**3**	92% *erythro*	29% ee (1*R*, 2*S*)
t-BuLi / (*S,S*)-**3**	89% *erythro*	40% ee (1*R*, 2*S*)
s-BuLi / (–)-**1**	88% *erythro*	24% ee (1*S*, 2*R*)

Encouraged by these findings, we next examined similar enantioselective rearrangements of (*E*)- and (*Z*)-crotyl propargylic ethers **6**[12] (eq. 3). Table 1 summarizes the diastereo- and enantioselectivities thus observed.[13]



(*E*)- or (*Z*)-**6**
a: X=SiMe$_3$, **b**: X=CH$_3$

erythro-**7** *threo*-**7** (3)

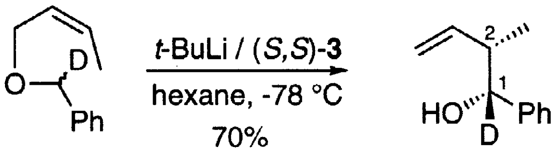
Table 1. Enantioselective [2,3]-Wittig Rearrangement of **6**[a]

Entry	Substrate	RLi / Lc*	Diastereo-selectivities[f]	Enantio-selectivities of major diastereomer[g]
1	(*E*)-**6 a**[c]	*t*-BuLi / (*S,S*)-**3**	80% *erythro*	32% ee (3*S*, 4*R*)
2[b]	(*E*)-**6 a**[c]	*s*-BuLi / **1**	82% *erythro*	16% ee (3*R*, 4*S*)
3	(*Z*)-**6 a**[d]	*t*-BuLi / (*S,S*)-**3**	95% *erythro*	45% ee (3*S*, 4*S*)
4	(*Z*)-**6 a**	*s*-BuLi / **1** or **2**[b]	92%, 100%[b] *erythro*	24% ee, 42% ee[b] (3*R*, 4*S*)
5	(*E*)-**6 b**[c]	*t*-BuLi / (*S,S*)-**3**	93% *threo*	75% ee (3*S*, 4*S*)
6	(*E*)-**6 b**[c]	*s*-BuLi / **1**	68% *threo*	2% ee (3*R*, 4*R*)
7	(*Z*)-**6 b**[d]	*t*-BuLi / (*S,S*)-**3**	94% *erythro*	39% ee (3*S*, 4*R*)
8	(*E*)-**6 b**[c,e]	*t*-BuLi / (*S,S*)-**3**	>95% *threo*	89% ee (3*S*, 4*S*)

[a] Unless otherwise noted, the reactions were run in hexane at -78 °C using a 1.5 eq. of R'Li / Lc*. >90% yield in all of cases. [b] Cited from J. Kang's results (ref. 4). [c] >99% *E*. [d] 92% *Z*. [e] Carried out in pentane at -95 °C. 47% yield. [f] Determined by ^{1}H NMR analysis. [g] Determined as described in refs. 14 and 15.

As seen in entries 1~4, the rearrangement of **6a** (X=SiMe$_3$), when induced with *t*-BuLi / (*S,S*)-**3**, provided a higher % ee than those reported using the *s*-BuLi / **1** or **2** systems.[4] Unfortunately, the % ee of the major diastereomer was still moderate for both (*E*)- and (*Z*)-**6a**, while the latter showed a slightly higher % ee. More significantly, the rearrangement of (*E*)-**6b** (X=CH$_3$) with *t*-BuLi / (*S,S*)-**3** provided (*S,S*)-**7b** in a respectably high % ee (75% ee), while the use of *s*-BuLi / **1** led to a considerably decreased % ee and % de. Rather surprisingly, a similar rearrangement of (*Z*)-**6b** resulted in a much lower % ee, while the *erythro*-selectivity was high. As expected, the rearrangement of (*E*)-**6b**, when carried out at a lower temperature (-95 °C), provided a much improved % ee (89% ee) (entry 8).

The question immediately arises whether the enantioselectivity is determined at the lithiation step or post-lithiation step. In order to answer this question, we carried out a similar rearrangement of the racemic α-deuterated benzyl ether (*Z*)-**4**-*d* with *t*-BuLi / (*S,S*)-**3** (eq. 4).[16] As shown in eq. 4, the deuterated product **5**-*d* with 98% *d*-content was formed in an enantio-enriched form, although the % ee was considerably decreased (14% ee), suggesting that the enantioselectivity might be determined predominantly at the lithiation step in this case. Nonetheless, in the cases of propargylic ethers **6**, the asymmetric induction would occur predominantly at the post-lithiation step because the chiral (*S,S*)-**3**-bound lithium terminus is configurationally very labile and hence easily epimerizable. Obviously, more detailed mechanistic studies are needed to determine the origin of the enantioselection.



(4)

(*Z*)-**4**-*d*
>99% *d*

erythro-**5**-*d*
98% *d*
(86% *erythro*, 14% ee)

In summary, we have demonstrated that the use of the chiral bis(oxazoline) (*S,S*)-**3** is effective as an external chiral ligand for the enantioselective [2,3]-Wittig rearrangement of a propargyl ether system. Further work to develop enantioselective carbanion reactions using the chiral bisoxazoline / alkyllithium system is in progress.

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10. The diastereoselectivity was determined by ^{1}H NMR analysis. The enantiomeric purity was determined by ^{1}H NMR analysis of the MTPA esters. The absolute configuration was assigned by the specific rotation: $[\alpha]_D^{23}$ -7.1 (*c* 0.85, CHCl$_3$) (24% ee, entry 4). The literature value for the (1*S*, 2*R*)-isomer (55% ee): $[\alpha]_D^{25}$ -15.0 (*c* 0.93, CHCl$_3$): Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348.
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13. Furthermore, we found that the rearrangement of (*Z*)-cinnamyl γ-(trimethylsilyl)propargyl ether with *t*-BuLi / (*S,S*)-**3** afforded the *threo*-product with 73% ee and 10% de.
14. The diastereoselectivities were determined by ^{1}H NMR analysis. The enantiomeric purity of *erythro*-**7** was determined by chiral GC analysis (column: CP-chiral-DEX CB capillary column, column temp.: 100 °C, detection: FID): t_R=20.6 min for (3*S*, 4*S*), 22.5 min for (3*R*, 4*R*)-isomer. The enantiomeric purity of *threo*-**7** was determined by ^{1}H NMR analysis of the MTPA esters.
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