

Tetrahedron Letters 39 (1998) 5513-5516

TETRAHEDRON LETTERS

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

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Received 22 April 1998; revised 21 May 1998; accepted 22 May 1998

**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. © 1998 Elsevier Science Ltd. All rights reserved.

The [2,3]-Wittig rearrangement, particularly its asymmetric version using enantio-enriched substrates, enjoys widespread application in many facets of organic synthesis.<sup>1</sup> 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.<sup>2</sup> In view of the recent progress in the asymmetric lithiation protocol, mostly using (-)sparteine (1) as an external chiral ligand (ECL),<sup>3</sup> 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 / (-)- $\alpha$ -isosparteine (2), show modest levels of enantioselectivity (up to 42% ee).<sup>4</sup> 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.<sup>5,6</sup> This is the first example of the utilization of a chiral bis(oxazoline) as ECL for the enantioselective [2,3]-Wittig rearrangement.<sup>7</sup>



0040-4039/98/\$19.00 © 1998 Elsevier Science Ltd. All rights reserved. *PII:* S0040-4039(98)01086-7 At the outset, we examined the enantioselectivity in the highly *erythro*-selective [2,3]-Wittig rearrangement of (Z)-crotyl benzyl ether (4)<sup>8</sup> 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 (1R, 2S)-5 in 40% ee with 89% *erythro*-selectivity.<sup>10,11</sup>



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.<sup>13</sup>



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

"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. <sup>b</sup> Cited from J. Kang's results (ref. 4). <sup>c</sup> >99% E. <sup>d</sup> 92% Z. <sup>c</sup> Carried out in pentane at -95 °C. 47% yield. <sup>f</sup> Determined by <sup>l</sup>H NMR analysis. <sup>s</sup> Determined as described in refs. 14 and 15.

As seen in entries 1~4, the rearrangement of **6a** (X=SiMe<sub>3</sub>), when induced with t-BuLi / (S,S)-3, provided a higher % ee than those reported using the s-BuLi / 1 or 2 systems.<sup>4</sup> 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<sub>3</sub>) 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 *erythroselectivity* 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 postlithiation step. In order to answer this question, we carried out a similar rearrangement of the racemic  $\alpha$ deuterated benzyl ether (Z)-4-d with t-BuLi / (S,S)-3 (eq. 4).<sup>16</sup> 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.



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.

Acknowledgment: This work was supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan and the Research for the Future Program administered by the Japan Society for the Promotion of Science.

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- 14. The diastereoselectivities were determined by <sup>1</sup>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<sub>R</sub>=20.6 min for (3S, 4S), 22.5 min for (3R, 4R)-isomer. The enantiomeric purity of threo-7 was determined by <sup>1</sup>H NMR analysis of the MTPA esters.
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