



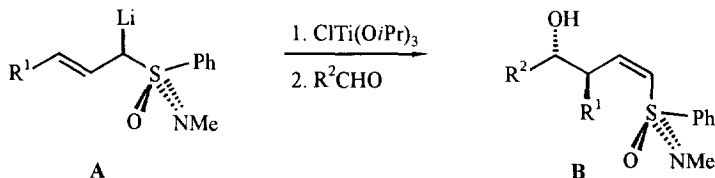
## Stereoselective Hydroxyalkylation of Titanated Allyl Sulfoximines at the $\alpha$ - as well as the $\gamma$ -Position Through Variation of the Titanation Reagent

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**Abstract:** Titanation of the lithioallyl sulfoximines *E*-2 and *Z*-2 with  $\text{ClTi}(\text{NEt}_2)_3$  gives allyltitanium species which react with aldehydes highly regio- and diastereoselectively at the  $\alpha$ -position to form the *syn*- $\alpha$ -hydroxyalkyl allyl sulfoximines *E*-3 and *Z*-3, respectively. With  $\text{ClTi}(\text{OiPr})_3$  as the titanation reagent *anti*- $\gamma$ -hydroxyalkyl vinyl sulfoximines are obtained instead with equally high selectivities. NMR spectroscopic evidence points to the formation of the monoallyltitanium sulfoximine *E*-4 upon reaction of *E*-2 with  $\text{ClTi}(\text{NEt}_2)_3$ . Copyright © 1996 Elsevier Science Ltd

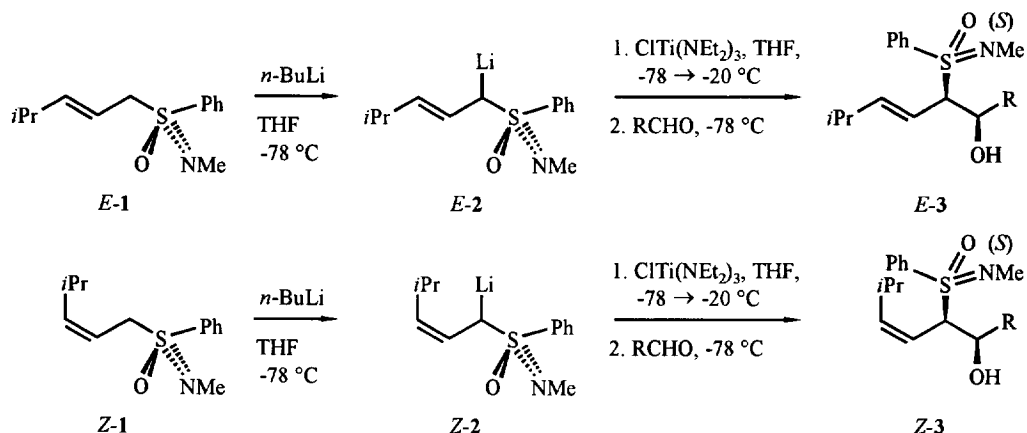
Lithioallyl sulfoximines of type **A** react after transmetalation with chlorotris(isopropoxy)titanium with aldehydes with high regio- and diastereoselectivity at the  $\gamma$ -position.<sup>2,3</sup> The thus obtained *anti*-*Z*- $\gamma$ -hydroxyalkyl vinyl sulfoximines of type **B** (Scheme 1), whose absolute configuration has been determined by X-ray analysis,<sup>4</sup> are synthetically promising compounds. The sulfoximine group can be replaced by aryl and alkyl groups through a Ni-catalyzed cross-coupling reaction with organometallics.<sup>2,5-7</sup> In this way enantiomerically pure mono- and disubstituted homoallyl alcohols are accessible. The chiral auxiliary is recovered as *N*-methyl phenylsulfonamide under complete retention of configuration at the S atom.



Scheme 1

We now report that by a mere switch from chlorotris(isopropoxy)titanium to chlorotris(diethylamino)-titanium<sup>8</sup> as the titanation reagent a highly regio- and diastereoselective hydroxyalkylation at the  $\alpha$ -position can also be achieved (Scheme 2).

Transmetalation of the lithioallyl sulfoximine *E*-2, prepared by treatment of the allyl sulfoximine *E*-1<sup>2</sup> with *n*-butyllithium, with chlorotris(diethylamino)titanium gave a titanated allyl sulfoximine which reacted with aldehydes under formation of the *syn*- $\alpha$ -hydroxyalkyl allyl sulfoximines *E*-3 with high regioselectivity ( $\geq 95\%$ ) and diastereoselectivity in good yield (Scheme 2, Table 1).



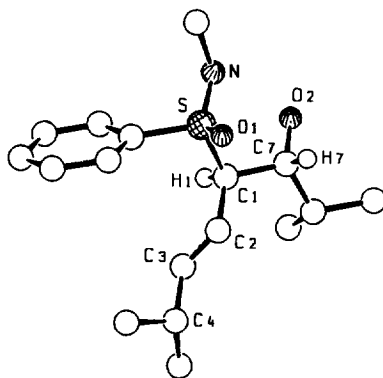
Scheme 2

Table 1. Synthesis of  $\alpha$ -Hydroxyalkyl Allyl Sulfoximines *E-3* and *Z-3*.

compd	R	$\alpha:\gamma^b$	de (%) <sup>b</sup>	yield (%) <sup>a</sup>	$[\alpha]_D$ (MeOH)	mp (°C)
<i>E-3a</i>	<i>iPr</i>	95:5	$\geq 95$	76	+127.7 <sup>c</sup>	82
<i>E-3b</i>	Ph	$\geq 98:2$	$\geq 95$	70	+44.3 <sup>d</sup>	60
<i>Z-3a</i>	<i>iPr</i>	$\geq 98:2$	91	73	+205.0 <sup>e</sup>	102
<i>Z-3b</i>	Ph	$\geq 98:2$	94	73	+70.4 <sup>f</sup>	131

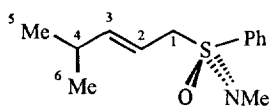
<sup>a</sup> After chromatography. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup> *c* 1.64. <sup>d</sup> *c* 1.53. <sup>e</sup> *c* 1.20. <sup>f</sup> *c* 1.07.

The configuration of the allyl sulfoximine *E-3a* was determined by X-ray analysis (Figure 1).<sup>9</sup> In the case of the *S*-configuration of the sulfoximine group both C atoms have the *R*-configuration. The relevant interatomic angles and distances point to a hydrogen bond between the N atom and the hydrogen atom of the hydroxy group. NOE experiments and the value of the vicinal coupling constant ( $J_{1,2} = 9.6$  Hz) indicate that the preferred conformation of *E-3a* in solution is similar to the one found in the crystal.

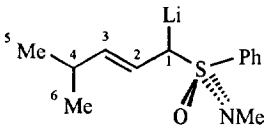
Figure 1. Structure of the  $\alpha$ -hydroxyalkyl allyl sulfoximine *E-3a* in the crystal.

Upon a similar treatment of the *Z*-configured lithioallyl sulfoximine *Z*-2, prepared by deprotonation of the allyl sulfoximine *Z*-1<sup>2</sup> with *n*-butyllithium, with chlorotris(diethylamino)titanium and aldehydes the corresponding *syn*- $\alpha$ -hydroxyalkyl allyl sulfoximines *Z*-3 were obtained with high regioselectivity ( $\geq 95\%$ ) and a slightly lower diastereoselectivity in good yield.<sup>10</sup> This contrasts the behavior of the titanated species formed from *Z*-2 and chlorotris(isopropoxy)titanium which has a much lower reactivity than its *E*-isomer.<sup>2</sup> In reactions of the allyltitanium species formed from lithioallyl sulfoximines of type **A** and chlorotris(isopropoxy)-titanium with aldehydes the yields are usually only about 50%. Approximately half of the starting allyl sulfoximine is recovered which upon deuterative work-up contains one D atom in the  $\alpha$ -position. NMR spectroscopic evidence suggests that lithioallyl sulfoximines of type **A** react with 1 equiv of chlorotris(isopropoxy)-titanium, as observed for lithioalkyl sulfones,<sup>11,12</sup> under formation of bis(allyl)titanium compounds, which at low temperatures transfer only one allylic unit with high selectivity to an aldehyde.<sup>2</sup> An NMR spectroscopic investigation of the titanation of the lithioallyl sulfoximine *E*-2 with 1 equiv chlorotris(diethylamino)titanium revealed one set of new signals corresponding to the formation of a monoallyltitanium compound (Table 2). On the basis of these data and of those reported for a crotyltitanium compound<sup>13</sup> we assign to the species formed for the present the structure of an  $\alpha$ -titanated allyl sulfoximine, *E*-4, of yet unknown configuration at the  $C_{\alpha}$ -atom.

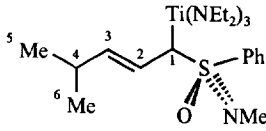
Table 2. <sup>1</sup>H NMR Chemical Shifts ( $\delta$  in ppm) and Coupling Constants (*J* in Hz) for *E*-1, *E*-2, and *E*-4 at Room Temperature (at 300 MHz in [D<sub>8</sub>]-THF Relative to [D<sub>7</sub>H]-THF).



*E*-1



*E*-2



*E*-4

comp	H-1	H-2	H-3	CH(CH <sub>3</sub> ) <sub>2</sub>	NCH <sub>3</sub>	NCH <sub>2</sub> CH <sub>3</sub>
	<i>J</i> <sub>1,1</sub> , <i>J</i> <sub>1,2</sub>	<i>J</i> <sub>1,2</sub> , <i>J</i> <sub>2,3</sub>	<i>J</i> <sub>2,3</sub> , <i>J</i> <sub>3,4</sub>	<i>J</i> <sub>4,5(6)</sub>		<i>J</i> <sub>1,2</sub>
<i>E</i> -1	3.73 dd 13.4, 6.7 3.83 dd 13.4, 7.1	5.35 dt 6.7, 15.5	5.26 dd 15.5, 5.7	2.18 oct, 0.86 d, 0.83 d 6.7, 6.7, 6.7	2.60	
<i>E</i> -2	3.10 d 10.5	5.96 dd 11.1, 14.9	4.38 dd 14.9, 6.9	2.12 oct, 0.86 d 6.7, 6.7	2.43	
<i>E</i> -4	3.24 d 10.6	5.78 dd 10.6, 15.3	5.01 dd 15.3, 6.7	2.22 oct, 0.94 d, 0.91 d 6.7, 6.7, 6.7	2.69	3.40-3.80 m, 1.07 t 7.1

The data available thus far do not allow distinction between the formation of only one diastereomer of the allyltitanium species *E*-4, being either configurationally stable or labile, and the formation of both diastereomers of *E*-4 which rapidly interconvert on the NMR time scale at room temperature.<sup>2,3</sup> Furthermore, nothing can be said at present about a possible equilibrium between *E*-4 and its  $\gamma$ -isomer.<sup>13</sup> We are currently studying these questions which are of considerable importance for the understanding of the origin of the high selectivities observed. For other functionalized allyltitanium compounds no such difference in the regioselectivity of their hydroxyalkylation was observed whether chlorotris(isopropoxy)titanium or chlorotris(diethylamino)titanium was used for their synthesis.<sup>14,15</sup>

Without prior titanation the lithioallyl sulfoximine *E*-2 likewise reacts with aldehydes with  $\geq 98\%$  regioselectivity at the  $\alpha$ -position. The diastereoselectivity, however, is only modest.<sup>16,17</sup> In the case of isobutyraldehyde a 60:19:12:4 mixture of the four possible  $\alpha$ -hydroxyalkyl allyl sulfoximines was obtained. The major diastereomer has the same configuration as the one obtained from the reaction of the titanium species *E*-4.<sup>18</sup>

Allyl sulfoximines of type **3** ought to have a considerable synthetic potential. The synthesis of enantiomerically pure homoallyl alcohols with three stereogenic centers can be envisaged through a regio- and stereoselective  $\gamma$ -substitution of the allylic sulfoximine group with organocopper reagents.<sup>19-21</sup> Furthermore, enantiomerically pure alkenes endowed with an allylic amino as well as hydroxy group should be attainable by a Pd-catalyzed<sup>22</sup> or thermal rearrangement.<sup>23</sup>

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