

ASYMMETRIC [2,3]WITTIG REARRANGEMENT OF 2'-ALKENYLOXYACETAMIDE BEARING  
TRANS-2,5-BIS(METHOXYMETHOXYMETHYL)PYRROLIDINE MOIETY AS A CHIRAL AUXILIARY

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Summary: [2,3]Wittig rearrangement of (2S,5S)-N-(alkenyloxyacetyl)-2,5-bis-(methoxymethoxymethyl)pyrrolidine enolate was studied and zirconium enolates of the corresponding (E)-alkenyloxyacetyl compounds were found to rearrange with high syn-diastereo and diastereoface selection.

In contrast to the stereochemically well-understood [3,3]sigmatropic rearrangement, its [2,3]counterpart had not found its proper position in synthetic control until recently when extensive studies by Nakai et al.<sup>1)</sup> disclosed that this type of reaction was also very useful for acyclic stereocontrol in the synthesis of alcohols. In studies directed to the asymmetric synthesis of hydroxy acids<sup>2)</sup> as potent building blocks for the construction of natural products, we examined the rearrangement of alkenyloxyacetamides (1) bearing trans-2,5-bis-(methoxymethoxymethyl)pyrrolidine<sup>3)</sup> as a chiral auxiliary. It has already been reported by Nakai et al. that though dianions of alkenyloxyacetic acids rearranged in poor stereoselectivity,<sup>4)</sup> their oxazoline or oxazine derivatives gave high diastereoselectivity (98% ds).<sup>5)</sup> Asymmetric induction (up to 78% de) in the reaction of optically active oxazoline derivatives has also been examined.<sup>6)</sup>

Here are described several features of the [2,3]Wittig rearrangement of 1, and the finding that zirconium enolates<sup>7)</sup> of the (E)-alkenyloxyacetyl compounds rearrange with high diastereo and diastereoface selection.

Examples of [2,3]Wittig rearrangement of the enolates derived from (2S,5S)-N-(alkenyloxyacetyl)-2,5-bis(methoxymethoxymethyl)pyrrolidines are given in Table 1. The reaction of lithium enolates proceeded with high diastereoface selectivity at C2' (entries 1, 2, and 6) except for particular cases (entries 8 and 9) which will be discussed later. The (2S,5S)-auxiliary gave preferentially (2'S)-products and therefore the sense of asymmetric induction was the same as observed in alkylation and acylation.<sup>3)</sup> The diastereoselectivity in the reaction of lithium enolates was, however, unsatisfactory though there was an obvious trend that the (E)- or (Z)-configuration in the alkenyloxy moiety favored syn- or anti-product (C2' and C3'), respectively.

On the other hand, when the reaction was conducted (-70 °C) after the addition (-100 °C) of dicyclopentadienylzirconium dichloride (Cp<sub>2</sub>ZrCl<sub>2</sub>) to the solution of lithium enolates derived from (E)-alkenyloxy substrates, a remarkable enhancement of syn-diastereoselectivity was observed also with the improvement of the asymmetric induction at C2' (entries 3 and 4). However, the addition of

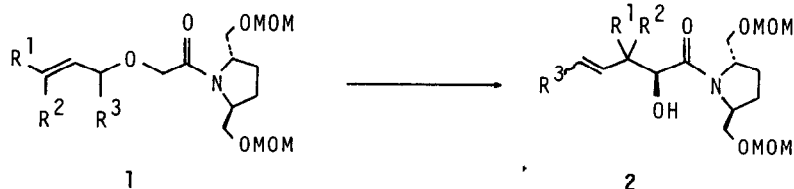


Table 1. [2,3]Wittig Rearrangement of (2*S*,5*S*)-*N*-2-Alkenyloxyacetyl-2,5-bis(methoxymethoxymethyl)pyrrolidines (1)

Entry	Substituents in 1			Metal	Yield(%)	Product (2)		Asymm. Induction at C2' (%de)
	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>			Diastereom. Ratio <sup>a)</sup>	2' <sub>S</sub> ( <u>syn</u> : <u>anti</u> ) : 2' <sub>R</sub> <sup>b)</sup>	
1	H	H	H	Li	61	98 <sup>c)</sup>	: 2	96
2	Et	H	H	Li	75	96 <sup>c)</sup> (2 <sup>d)</sup> : 1)	: 4	92
3	Me	H	H	Zr	43	98 (28 <sup>e)</sup> : 1)	: 2	96
4	Et	H	H	Zr	65	98 <sup>c)</sup> (30 <sup>d)</sup> : 1)	: 2	96
5	Et	H	H	Mg	13	91 <sup>c)</sup> (4 <sup>d)</sup> : 1)	: 9	82
6	H	Et	H	Li	33	95 <sup>c)</sup> (1 <sup>d)</sup> : 3.5)	: 5	90
7	H	Et	H	Zr	7	96 <sup>c)</sup> (1 <sup>d)</sup> : 1)	: 4	92
8	H	H	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	Li	82			67 <sup>c, f)</sup>
9	H	H	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	Li	83			33 <sup>g, h)</sup>
10	H	H	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	Zr	25			87 <sup>g, i)</sup>
11	H	H	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	Zr	70			41 <sup>g, j, k)</sup>

a) Diastereomeric ratio was determined by <sup>1</sup>H NMR (90 MHz). b) Configuration at C3' was not determined. c) Configuration at C2' was assigned to be S by comparison after acetylation and subsequent hydrogenation, with an authentic sample which was obtained by alkylation of (2*S*,5*S*)-*N*-benzyloxyacetyl-2,5-bis(methoxymethoxymethyl)pyrrolidine (reference 2) followed by debenylation and acetylation. d) Configuration was established to be syn by its transformation including i) hydrolysis of amide linkage and ii) iodolactonization of the resulting hydroxy acid, to 3-ethyl-2-hydroxy-5-iodo-4-pentanolide, the stereochemistry of which was determined to be 2,3- and 3,4-trans by <sup>1</sup>H NMR decoupling and NOE experiments. e) Configuration was determined after appropriate conversion (see experimental procedure) by comparison with an authentic specimen (references 11 and 12). f) Configuration of newly formed double bond was not determined. g) Predominant 2'<sub>S</sub> configuration was inferred from <sup>1</sup>H NMR spectra of the corresponding acetate. <sup>1</sup>H NMR spectra (C<sub>6</sub>D<sub>6</sub>) showed the characteristic peak at δ1.74-1.80 for acetoxy protons in 2'<sub>S</sub> isomer and at δ1.60-1.66 in 2'<sub>R</sub> isomer. h) A mixture of E and Z isomers: 2'<sub>S</sub> isomer, E/Z= 4/1; 2'<sub>R</sub> isomer, E/Z= 1.3/1. i) A mixture of E and Z isomers: 2'<sub>S</sub> isomer, E/Z= 1/3. j) The reaction was conducted at -20 °C after the addition of Cp<sub>2</sub>ZrCl<sub>2</sub> at -100 °C. k) A mixture of E and Z isomers: 2'<sub>S</sub> isomer, E/Z= 1/3; 2'<sub>R</sub> isomer, E/Z= 1/1.8.

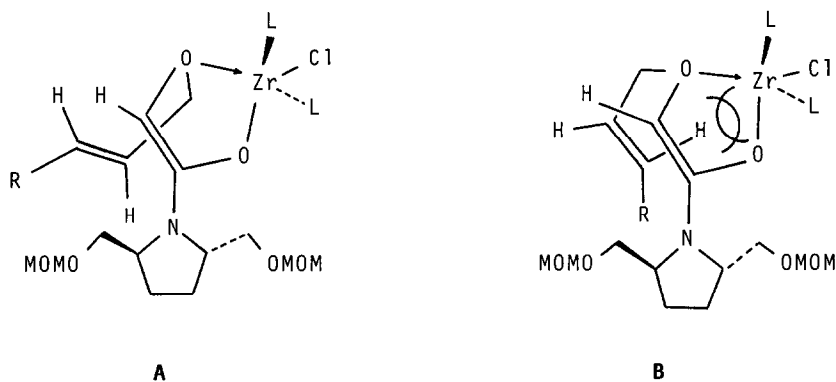


Fig. 1

the same complex to the corresponding (Z)-substrate did not give any favorable result (entry 7). The influence of zirconium ion on (E)-substrates may be explained by transition state models shown in Fig. 1.<sup>8)</sup> The conformation **A** leading to syn-selection is less sterically constrained than **B** which suffers the repulsion between the metal ion and a hydrogen atom of the double bond. Displacement of the lithium ion by a zirconium ion bearing bulky ligands increases the repulsion.

The addition of magnesium bromide as a similar Q-chelating metal salt did not find particular merits and that of dicyclopentadienyltitanium dichloride gave a complex reaction mixture.

In substrates bearing secondary alkenyloxy groups, two stereocontrolling factors, transfer of chirality from the asymmetric center present in the alkenyloxy moiety and asymmetric induction by the chiral auxiliary, must be considered. Inferring from the results obtained with lithium enolates by using substrates having d1-alkenyloxy moieties (entries 8 and 9), both the effects seem to be comparable in the mismatched pair in terms of double diastereoselection and cancel out to each other. In the case of the zirconium enolate, the matched pair underwent the preferential rearrangement reaction at -78 °C to give the product of 87% de at 25% conversion (entry 10). However, the fact that the diastereomeric purity of 41% de obtained at 70% conversion indicated that the chirality transfer strongly overrode the asymmetric induction in the mismatched pair (entry 11).<sup>9)</sup>

A typical example of experimental procedure is given below.

$n\text{-BuLi}$  ( $1.6 \text{ mol dm}^{-3}$ ,  $258 \mu\text{l}$ , 1.2 eq) was added slowly to a THF ( $330 \mu\text{l}$ ) solution of (2S,5S,2'E)-N-2'-butenyloxyacetyl-2,5-bis(methoxymethoxymethyl)-pyrrolidine<sup>10)</sup> (114.0 mg) at -100 °C under nitrogen. After stirring at -100 °C for 2 h, a solution of  $\text{Cp}_2\text{ZrCl}_2$  (120 mg, 1.2 eq) in THF (1.5 ml) was added slowly to the solution and the mixture was stirred at the same temperature for 3 h and then at -70 °C for 3 h. Saturated aqueous KF ( $150 \mu\text{l}$ ) was added and the mixture was allowed to warm to room temperature and then, passed through

a short column of silica gel. Concentration and chromatography on silica gel gave the rearranged product (2;  $R^1=Me$ ;  $R^2, R^3=H$ ; 47.4 mg) in 42% yield.

The product (32 mg) was hydrogenated ( $H_2/Pd$  on C, EtOH) and hydrolyzed<sup>5)</sup> ( $1\text{ mol dm}^{-3}$  HCl,  $100\text{ }^\circ\text{C}$ ) to give (2S,3R)-2-hydroxy-3-methylpentanoic acid [11 mg;  $[\alpha]_D^{25} +11.2^\circ$  ( $c=0.36, H_2O$ ), lit.<sup>11)</sup>  $[\alpha]_D +9.5^\circ$  ( $c=1.0, H_2O$ )] in quantitative yield.

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