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ASYMMETRIC [2,3]WITTIG SIGMATROPIC REARRANGEMENTS INVOLVING CHIRAL AMIDE ENOLATES AS THE MIGRATING TERMINI

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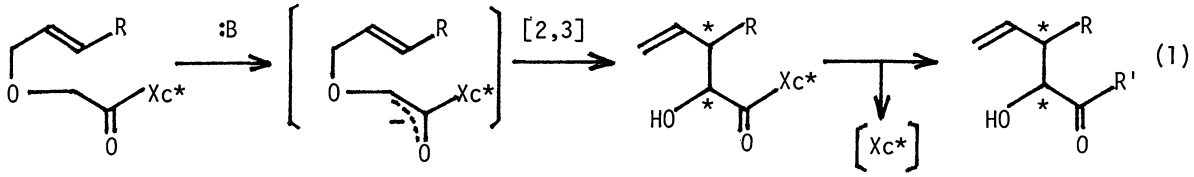
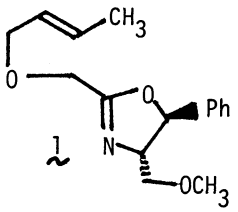
The title rearrangement of the chiral (E-crotyloxy)acetamides derived from (S)-prolinol has been shown to provide a modest level of asymmetric induction (52-60%) along with a high erythro-selectivity (95-98%). The influence of the metal centers (Li, K, and Zr) and the ligating substituents on the prolinol part has been discussed.

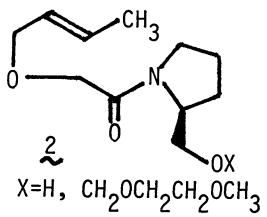
In view of the tremendous advance in the development of chiral enolates and their utilities in asymmetric alkylation and aldol reactions,[1] the asymmetric enolate [2,3]Wittig rearrangement, generalized by Eq. 1, should constitute a new strategy for asymmetric synthesis of diastereomerically defined α-hydroxy β-alkyl carbonyl compounds, a key class of intermediates for natural product synthesis. Recently we have reported that the [2,3]Wittig process of the chiral oxazoline (1) involving Meyers' lithium azaenolate provides a relatively high optical yield (78%) along with a high erythro-selectivity (90%).[2] Its use in synthesis, however, is discouraged by the rather low yields in conversions of the rearrangement product to the carboxylic acid derivatives. To overcome this drawback and also to obtain a higher optical yield, we have now investigated the feasibility of the asymmetric [2,3]Wittig process of the chiral amides (2) on the basis of Evans' observations that the (S)-prolinol-derived amide system is readily hydrolysable and, more significantly, its metal enolates provide extremely high optical yields in the asymmetric alkylation and aldol reactions.[3] Disclosed herein are our preliminary observations in the asymmetric rearrangement of 2 and a related system (3).



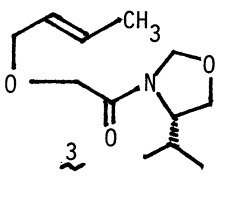
(1)



1

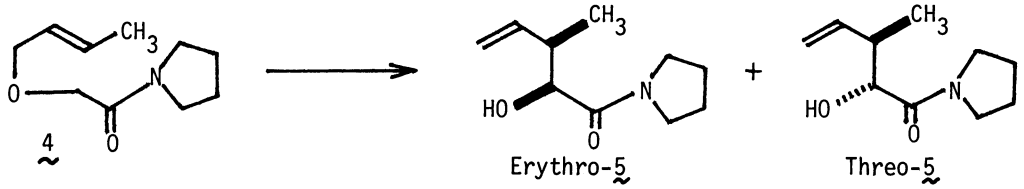


2
X=H, $CH_2OCH_2CH_2OCH_3$



3

First of all, we studied the diastereoselection in the present [2,3]Wittig variant using the achiral amide 4 (Eq. 2). We found that 4 was treated with LDA or LHDS in THF at -85 °C for several hours to afford the [2,3]-rearranged product (5) in an excellent yield and, very fortunately, in an extremely high erythro-selectivity[4] (Table 1). The erythro/threo ratio was determined by GLC analysis[2] of the corresponding methyl ester which was readily obtained via hydrolysis of 5 followed by treatment with diazomethane. A notable trend of the amide enolate rearrangement is that the diastereoselectivity is little influenced by changing the nature of the base or the solvent used and the reaction temperature (entries 3-5); this suggests that the (Z)-enolate kinetically generated[5] is maintained in geometry under the varied conditions. On the basis of our transition state model for the [2,3]Wittig shift,[6] the observed erythro selection can be depicted by Eq. 3, where the gauche repulsion of $G \leftrightarrow CH_3$ in T_1 prevails over the 1,3-repulsion of $G \leftrightarrow H\beta$ in T_2, thus leading preferentially to the erythro isomer.

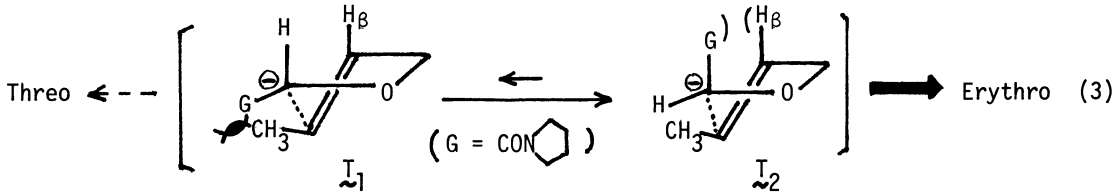


(2)

Table 1. Rearrangements of 4 (93% E)

Entry	Base[a]	Solvent[b]	Temp / °C	Erythro : Threo	Yield / %
1	LDA	THF	-85	96 : 4	98
2	LHDS	THF	-85	96 : 4	96
3	LDA	23% HMPA-THF	-85	96 : 4	98
4	KHDS	THF	-85	96 : 4	88
5	LHDS	THF	0-5	92 : 8	86

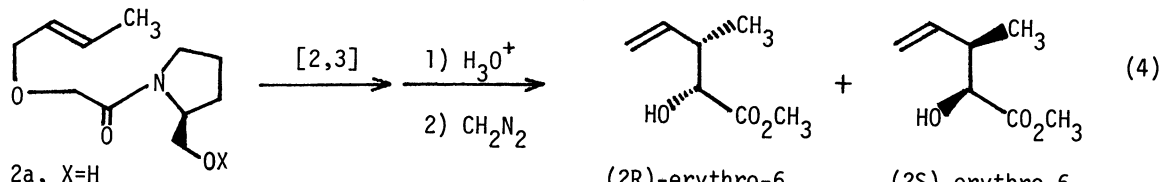
a) LDA = $LiN(i\text{-}Pr)_2$, LHDS = $LiN(SiMe_3)_2$, KHDS = $KN(SiMe_3)_2$.
b) THF = Tetrahydrofuran, HMPA = Hexamethylphosphoramide.



(3)

With the high erythro-selectivity obtained above, we next carried out the asymmetric rearrangement of the chiral amides (2a, 2b, and 3)[7] which afforded, after hydrolysis under the reported conditions[3] (e.g. 1 M HCl 3 h), the optically-active α-hydroxy ester (6)[8] in 70-80% yields (Eq. 4). Table 2 summarizes the representative results. The enantiomeric excess (% ee) was determined by NMR analysis of 6 using (+)-Eu(DPPM)$_3$[2,9] as a chiral shift reagent. The absolute configuration of erythro-6 was assigned as described in our previous paper.[2]

Inspection of the data in Table 2 reveals several significant trends. (1) Unexpectedly, this type of intramolecular reaction provides a much lower level of asymmetric induction in general, as compared with the intermolecular versions



(4)

2a, X=H
2b, X=MEM ($CH_2OCH_2CH_2OCH_3$)

(2R)-erythro-6 (2S)-erythro-6

Table 2. Rearrangements of 2 and 3[a]

Entry	Substrate[b]	Base[c]/Additive	Erythro : Threo[d]	% ee[e]	Config.[e]
1	2a (X=H)	LDA	95 : 5	52	2R
2		LDA / $MgBr_2$	96 : 4	36	2R
3		KH-LDA	93 : 7	20	2R
4		LHDS	95 : 5	20	2R
5	2b (X=MEM)	LDA	97 : 3	20	2S
6		LDA / Cp_2ZrCl_2[f]	98 : 2	60	2S
7	3	LDA	95 : 5	12	2R

a) Run at -85—-80 °C. b) The geometric purity was of 93% E. c) The amount of the base(s) used was 2.1 equiv. for 2a and 1.1 equiv. for 2b and 3. d) Determined by GLC. e) Refers to that of the major erythro isomer. f) Di(cyclopentadienyl)-zirconium dichloride.

previously reported.[3] (2) The rearrangement of the (S)-prolinol-derived system (2) afforded a higher enantioselectivity than that of the (S)-valinol-derived counterpart (3) containing no chelating pendant, indicating that the state of chelation in the enolates concerned plays an important role in dictating the diastereoface selection. (3) The sense of asymmetric induction is strongly influenced by the nature of the pendent oxygen substituent (X) in 2, just as previously reported for the asymmetric alkylations.[3b] Thus, the changeover in π-facial selection can tentatively be visualized in Fig. 1;[10] the rearrangement of 2a takes place favorably from the Re-face of the enolate as depicted by A, whereas the rearrangement of 2b occurs preferentially from the Si-face as drawn by B. (4) Another striking trend is the enhanced diastereoface selection observed with the zirconium enolate (entry 6). Superficially, this finding is consistent with a similar but greater enhancement previously observed for the asymmetric aldol reactions with the same zirconium enolate system.[11]

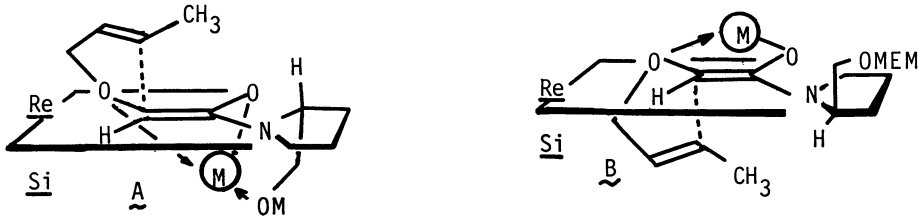


Fig. 1.

In summary, we have uncovered the stereochemical features of the asymmetric [2,3]Wittig rearrangement involving various chiral amide enolates derived from (S)-prolinol and (S)-valinol. The results of this work, though not outstanding from

the standpoint of synthetic utility, provide important considerations which must be addressed in the design of chiral auxiliaries, particularly for the asymmetric [2,3]Wittig rearrangement.[12] Further effort is now in progress to develop highly enantioselective variants of the enolate [2,3]Wittig rearrangement using different chiral auxiliaries.[13]

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References

1) Recent reviews:a) "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, New York (1984), Vol. 3, Chap. 1-4; b) D. A. Evans, J. V. Nelson, and T. R. Taber, *Top. Stereochem.*, 13, 1 (1982).

2) K. Mikami, K. Fujimoto, T. Kasuga, and T. Nakai, *Tetrahedron Lett.*, 25, 6011 (1984).

3) a) Review on this specific topics: D. A. Evans, J. M. Takacs, L. R. McGee, M. D. Ennis, D. J. Mathre, and J. Bartroli, *Pure Appl. Chem.*, 53, 1109 (1981); b) alkylations: D. A. Evans and J. M. Takacs, *Tetrahedron Lett.*, 21, 4233 (1981);cf. P. E. Sonnet and R. R. Heath, *J. Org. Chem.*, 45, 3137 (1980); c) aldol reactions: D. A. Evans and L. R. McGee, *J. Am. Chem. Soc.*, 103, 2876 (1981).

4) In contrast, we found that a similar rearrangement of the Z-crotyl counterpart with LDA was totally non-diastereoselective (erythro/threo = 45 : 55).

5) Enolization of the pyrrolidine-derived propionamide with LDA has been shown to give exclusively the (Z)-enolate (Ref. 3b). In addition, it is well documented that β-alkoxy enolates tend to occupy the (Z)-geometry by the chelating effect of the alkoxy group (Ref. 1).

6) K. Mikami, Y. Kimura, N. Kishi, and T. Nakai, *J. Org. Chem.*, 48, 2303 (1983).

7) The amides 2a and 3 were readily prepared via reactions of (E-crotyloxy)acetyl chloride with the chiral amines, whereas 2b was derived from 2a and methoxyethoxymethyl chloride: 2a, $[\alpha]_D^{19}$ -46.6° (c 2.54, $CHCl_3$); 2b, $[\alpha]_D^{22}$ -29.6° (c 1.01, acetone); 3, $[\alpha]_D^{14}$ -30.3° (c 0.97, $CHCl_3$).

8) For the conversion of (2R, 3S)-6 to (+)-verrucarinolactone: Ref. 2.

9) Eu(DPPM)$_3$ = Tris[di(perfluoro-2-propoxypropionyl)methanato]europium (III): cf. H. Kawa, F. Yamaguchi, and N. Ishikawa, *Chem. Lett.*, 1982, 153.

10) These drawings are based on Evans' drawings made for the prolinol-derived amide lithium enolates: Chap. 1 in Ref. 1a.

11) The origin of the enhanced aldol stereoselection has been discussed in terms of the sterically demanded bent-sandwich zirconium enolate complex (Ref. 3c).

12) Quite recently Yamaguchi and Katsuki have developed a highly enantioselective [2,3]Wittig variant that involves a chiral amide enolate with the C_2-symmetry: T. Katsuki, the 19th Tennenbutsu Danwakai, July 1984, Abstract, p. 72; cf. M. Yamaguchi, et al., *Tetrahedron Lett.*, 25, 857 (1984).

13) Quite recently we have found that the [2,3]Wittig variant involving a chiral oxazolidone imide system developed by Evans (Ref. 3a) does not proceed at all under similar conditions to those described herein.

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