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ASYMMETRIC ALDOL REACTION OF AMIDE ENOLATES BEARING trans-2,5-DISUBSTITUTED PYRROLIDINES AS CHIRAL AUXILIARIES

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Summary: Condensation of aldehydes with Zr enolate of chiral N-propionyl-trans-2,5-disubstituted pyrrolidine proceeded with high diastereo- and diastereoface-selection. Stereoselectivity in the reaction of the corresponding N-acetyl compounds was also examined.

The frequent occurrence of β-hydroxy carbonyl moiety in a variety of natural products, such as macrolide or ionophore antibiotics and other acetogenins, has prompted methodological development of its stereocontrolled synthesis, and the most successful establishments have been realized in aldol reaction.[1] Here, we wish to describe another highly diastereo- and diastereoface-selective aldol reaction of the amide enolates bearing the trans-2,5-disubstituted pyrrolidine (**1**) moiety as the amine component, which has been proved to be the excellent chiral auxiliary in the asymmetric alkylation[2] and acylation[3] of the same type of amide enolates.

Examples of the aldol reaction of dl- or (2S,5S)-N-propionyl-2,5-bis-(methoxymethoxymethyl)pyrrolidine enolate (**3**) are given in Table 1. In contrast to the alkylation or acylation referred above, the use of the Li enolate did not give good stereoselection either at the C2' or the C3' chiral center in the present reaction, as exemplified by the condensation with benzaldehyde (entry 1, Table 1). On the other hand, the Zr enolate[4] prepared from the Li enolate and bis(cyclopentadienyl)zirconium dichloride (Cp_2ZrCl_2) exhibited the remarkably high selectivity (erythro-diastereoselection >100:1 and diastereoface-selection 60:1 ~ 100:1). The stereochemical assignment of the condensation products revealed that the sense of asymmetric induction in this reaction is opposite to that experienced in the previous alkylation[2]

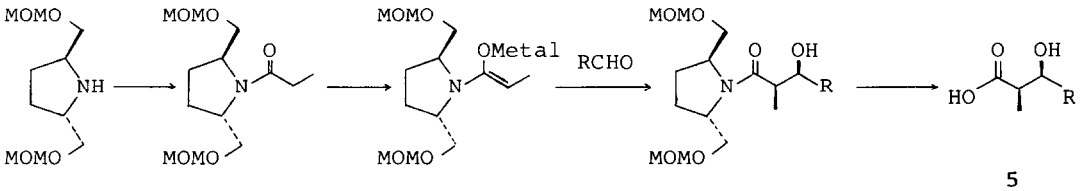


Table 1. Aldol Reaction of Propionamide Enolate (**3**) with Aldehydes[a)]

Entry	R in RCHO	Metal	Ratio of Diastereomers[b)] in Product (**4**)				Yield[c)] %
			erythro	erythro	threo	threo	
1	C_6H_5[d)]	Li	30[e)] (2S*,5S*,2'R*,3'R*)	: 50[e)] (2S*,5S*,2'S*,3'S*)	: < 1[f)]	: 20[e)] (2S*,5S*,2'S*,3'R*)	82
2	C_6H_5[d)]	Zr	60[e)] (2S*,5S*,2'R*,3'R*)	: 1[e)] (2S*,5S*,2'S*,3'S*)	: < 1 (other two isomers)[f)]		88
3	$(CH_3)_2CH$[g)]	Zr	100[h)] (2S,5S,2'R,3'S)	: < 1 (other three isomers)[f)]			85
4	CH_3CH_2[g)]	Zr	100[h)] (2S,5S,2'R,3'S)	: < 1 (other three isomers)[f)]			92
5	$CH_3CH{=}CH$[d)]	Zr	100[i)] (2S*,5S*,2'R*,3'S*)	: 1[i)] (2S*,5S*,2'S*.3'R*)	: < 1 (other two isomers)[f)]		98

a) Reaction conditions: See experimental procedure. b) Determined after TLC separation (entry 1) or by ^{1}H NMR (90 Hz instrument, S/N ~ 100) (entries 2 ~ 5). c) Isolated yield including all the isomers. d) dl-**3** was used as the amide enolate. e) Configurational relationship between C2' and C3' stereocenters of each isomer was determined by comparison (^{1}H NMR) of the respective hydroxy acid obtained after hydrolysis, with the authentic specimen. For the determination of configuration at C2', the product was hydrogenolized to dl-N-(2'-methyl-3'-phenylpropionyl)-**1** and the latter was compared (^{1}H NMR) with (2S,5S,2'S)-isomer prepared by asymmetric benzylation of (2S,5S)-N-propionyl-**1**.[2)] f) Not detectable by ^{1}H NMR. g) (2S,5S)-**3** was used. h) Configuration was determined after hydrolysis, by comparison (^{1}H NMR and the sign of optical rotation) with the authentic specimen. i) Tentative assignment by analogy.

and acylation.[3)] This indicates that the Zr atom bearing bulky ligands is exclusively located in the bottom hemisphere respective to the plane of the (Z)-enolate, as illustrated with a (2S,5S)-model in Fig. 1, and that aldehyde molecules approach from the same side (re-si face) coordinating to the Zr atom and taking a chair-like transition state leading to the formation of erythro-aldols. On the other hand, the attack of alkyl or acyl halides in the alkylation or acylation, occurs directly upon the top face (si-re face) of the Li (Z)-enolates.[5)] In the aldol reaction of the Li enolate (entry 1), the predominant formation of erythro-diastereomer (> 30 : 1) in the minor (2'S)-product may well be explained by a six-membered chair-like transition state. However, as to the reason of major si-re face attack and the product distribution therein, no clear mechanistic view is provided at present. A non-cyclic transition state may be involved.

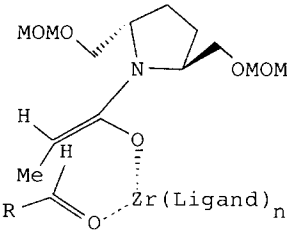
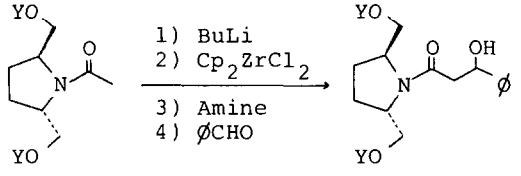


Fig. 1. Approach of aldehydes to (2S,5S)-amide enolate

The hydrolysis of the aldol adducts (**4**) by boiling with aqueous 1 mol dm^{-3}

HCl gave the corresponding β-hydroxy carboxylic acids (**5**) without appreciable epimerization at either stereocenter.[4a,6] One exception was the adduct with crotonaldehyde (entry 5) where allylic rearrangement and/or dehydration seemed to be much faster than N→O acyl transfer in the hydrolysis conditions, giving rise to the formation of a complicated mixture.

It has been recognized that enolates derived from chiral acetates or acetamides do not usually give high diastereoselectivity in the aldol reaction,[7] in contrast to those derived from the corresponding propionates or propionamides. In experiments using the present chiral auxiliary, the observed asymmetric induction was also very small even with the Zr enolate (entries 1 and 2, Table 2). A CPK Model examination indicated that on account of the absence of C2'-standing methyl group, it was possible for the reactants to take a boat-like transition state[8] as well as the chair-like one. We therefore considered that if the coordination site of zirconium for the aldehyde was blocked by an appropriate ligand added to the reaction mixture, the approach of the aldehyde would occur only at the opposite face with improved stereoselectivity. After some trials, several amines were found to be fairly



6 **7**

Table 2. Aldol Reaction of Acetamide (**6**)[a] with Benzaldehyde

Entry	Y in **6** and **7**	Amine	Product (**7**) Diastereomeric Ratio (3'R)[c] : (3'S)[c]	Yield[b] %
1	MOM	non[d]	0.9 : 1[e]	78
2	MOM	non	1.2 : 1[e]	59
3	MOM	$(Me_2CH)_2NH$	1.3 : 1[e]	84
4	MOM	$BuNH_2$	1.8 : 1[e]	40
5	$SiMe_2Bu^t$	$(Me_2CH)_2NH$	3.7 : 1[f]	97
6	$SiMe_2Bu^t$	DMAP[g]	4.4 : 1[f]	94
7	$SiMe_2Bu^t$	Et_2NH	5.3 : 1[f]	62
8	$SiMe_2Bu^t$	$BuNH_2$	8.5 : 1[f]	20

a) (2S,5S)-**6** was used. b) Total yield of both isomers. c) The configuration was determined after TLC separation and hydrolysis, by comparison (sign of optical rotation) with the authentic specimen. d) Without the addition of Cp_2ZrCl_2. e) The ratio was determined by ^1H NMR. f) The ratio was determined by HPLC. g) 4-Dimethylaminopyridine.

effective as additives, as we expected (Table 2). A combination of bis(t-butyldimethylsiloxy) derivative (6, Y = t-$BuMe_2Si$) and butylamine (entry 8) gave the highest selectivity, but, unfortunately, the chemical yield decreased as the selectivity increased. Further study is under progress.

An example of experimental procedure is given below.

A solution of the (2S,5S)-amide (**2**, 154 mg)[2] in THF (0.5 ml) was added slowly to a solution of lithium diisopropylamide in THF (0.69 mol dm^{-3}, 980 µl, 1.1 eq) at -78°C. The mixture was stirred for 1 h at -20°C and then cooled to -78°C. Cp_2ZrCl_2 (180 mg, 1.1 eq) and, after 5 min, propionaldehyde (45 µl, 1.1 eq) were added. The mixture was stirred for 4 h at the same temperature. Aqueous phosphoric acid (5%, 200 µl) was added and the mixture was allowed to warm to room temperature and then extracted with dichloromethane. Drying over anhydrous sodium sulfate, concentration, and chromatography on silica gel gave the aldol adduct [**4**, R^2 = Et, 170 mg, $[\alpha]^{23}$-62.4° (c = 1.25, EtOH)] in 92% yield. The adduct (**4**, 157 mg) was refluxed in 1 mol dm^{-3} HCl (4 ml) for 3 h. The mixture was neutralized with saturated aqueous sodium hydrogencarbonate and then brought to pH 1 with conc. HCl. The usual work-up gave (2R,3S)-3-hydroxy-2-methylpentanoic acid [60 mg; $[\alpha]^{23}$-4.1° (c = 1.72, $CHCl_3$), lit.[9] $[\alpha]^{26}$-4.10° (c = 1.72, $CHCl_3$)] in quantitative yield.

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References and Notes

1) For recent reviews, see; a) D.A.Evans, J.V.Nelson, and T.R.Taber, in "Topics in Stereochemistry," ed by N.L.Allinger, E.L.Eliel, and S.H.Silen, John Wiley & Sons, New York 1982, Vol. 13, pp 1-115. b) T.Mukaiyama, Org.React., **28**, 203 (1982).2) Y.Kawanami, Y.Ito, T.Kitagawa, Y.Taniguchi, T.Katsuki, and M. Yamaguchi, Tetrahedron Lett., **25**, 857 (1984). 3) Y.Ito, T.Katsuki, and M. Yamaguchi, Tetrahedron Lett., **25**, 6015 (1984). 4) a) D.A.Evans and L.R.McGee, J.Am.Chem.Soc., **103**, 2876 (1981). b) Y.Yamamoto and K.Maruyama, Tetrahedron Lett., **21**, 4607 (1980). 5) See references 2 and 3. This seems to indicate that the coordination of these halides to Li ion assuming a cyclic transition state is not likely in the alkylation and acylation. 6) The hydrolysis of the aldol adduct of benzaldehyde under the conditions, caused some epimerization (ca. 10%), but it could be achieved without detectable epimerization (^1H NMR) by treating the adduct with a mixture (1:1) of aqueous perchloric acid (1 mol dm^{-3}) and dioxane, at 70°C for 13 h. 7) Excellent chiral aldolizations of acetic acid derivatives have recently been developed: a) C.Mioskowski and G.Solladie, Tetrahedron, **36**, 227 (1980); b) N.Iwasawa and T.Mukaiyama, Chem. Lett., **1983**, 297; c) M.Braun and R.Devant, Tetrahedron Lett., **25**, 5031 (1984). 8) a) D. Seebach and J.Golinski, Helv.Chim.Acta, **64**, 1413 (1981). b) E.Nakamura and I. Kuwajima, Tetrahedron Lett., **24**, 3343 (1983). 9) S.Masamune, W.Choy, F.A.J. Kerdesky, and B.Imperiali, J.Am.Chem.Soc., **103**, 1566 (1981).

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