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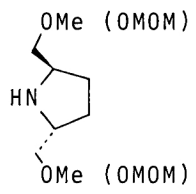
Diastereoselective Reduction of α-Keto Amides Having trans-2,5-Disubstituted Pyrrolidines as Chiral Auxiliaries

Yasuhiro KAWANAMI,* Izumi FUJITA, Yoshiyuki TANIGUCHI,†
Tsutomu KATSUKI,† and Masaru YAMAGUCHI†

Department of Chemistry, Faculty of Education, Kagawa University,
Takamatsu, Kagawa 760
†Department of Chemistry, Kyushu University 33, Higashi-ku, Fukuoka 812

The reduction of α-keto amides derived from (2R,5R)-trans-2,5-bis(methoxymethoxymethyl)pyrrolidine with $LiBEt_3H$ or $KBEt_3H$ proceeded with high diastereoselectivity (up to 99% ds) to afford the corresponding α-hydroxy amides in good yield. The effect of added crown ethers or LiBr was also examined.

Chiral α-hydroxy acid derivatives are versatile building blocks in organic synthesis and many useful methods have so far been reported for their preparation.[1,2] Although the reduction of α-keto acid derivatives which bear an appropriate chiral auxiliary is one of the conventional approaches to optically active α-hydroxy acids,[3] the utility of the methods has been restricted by its insufficient optical yield. The major obstacles presented by this process are obviously twofold: (i) The substrate should be fixed to one of the possible conformers at the transition state, and (ii) a particularly effective chiral auxiliary is required in order to provide a strong bias for the diastereoface selection at the prochiral center which is three bonds away from the chiral source. For the first requirement, it is obvious that amines are preferable to alcohols as chiral sources because of the well established planarity of the amide structure. For example, Soai et al. have recently used proline esters as chiral amine components in the complex metal hydride reduction of α-keto amides and obtained α-hydroxy acids with high ee's up to 87%.[4] Aiming at the further promotion of the diastereoselectivity in the process, we examined the introduction of 2,5-disubstituted pyrrolidines (**1**) as chiral sources. The auxiliaries have proved to be very effective to a variety of asymmetric reactions



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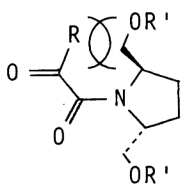


Fig. 1.

when utilized as the corresponding N-acylated compounds,[5] and they are also considered to be quite advantageous for the conformational singularity of the transition state in the present reaction. The confomational divergence due to the rotation of the bond between the amide carbonyl carbon atom and nitrogen atom need not be considered here because of the C_2-symmetry in the auxiliary and the planarity of the amide structure. Furthermore, the complexity due to the rotation of the single bond between the two carbonyl groups may also be simplified because of the bulkiness of the auxiliaries, which makes the s-cis conformation (Fig. 1) energetically less favored than s-trans one, on account of the strong interference between the α-alkyl group and the pyrrolidine moiety.

The α-keto amides (**2a**, **2b**, **3a**, and **3b**) were prepared from (2R,5R)-bis(methoxymethyl)- and (2R,5R)-bis(methoxymethoxymethyl)pyrrolidine, respectively, by N-acylation with mixed pivalic benzoylformic or pivalic pyruvic anhydride in the presence of 4-dimethylaminopyridine in dichloromethane in 77-97% yield, and reduced by treatment with various metal borohydrides or by hydrogenation (H_2/Pd-C). The results are summarized in Table 1. The reduction of **2a** and **3a** with ordinary borohydrides proceeded with moderate stereoselectivity in a range of 65-80% ds (entries 1-3 and 7-10). The reduction with zinc borohydride exhibited no diastereoselectivity (entry 4). In this case, s-cis transition state fixed by the chelation of two carbonyl groups to the oxygenophilic zinc ion may compete with the otherwise preferred s-trans one. The catalytic hydrogenation also exhibited a moderate level of selectivity (entry 6). In an attempt to improve the stereoselectivity, we next examined the reaction with the bulky trialkylborohydrides which is expected to discern the diastereomerically different environment more effectively than the less bulky borohydrides, and found that $LiBEt_3H$ markedly enhanced the preference of 2R-isomer to 96-99% ds (entries 11 and 12). On the other hand, the diastereoselectivity in the reduction of pyruvic acid amides (**2b** and **3b**) was not so good as that of **2a** and **3a**, reflecting the small steric requirement of methyl group compared to phenyl group. The reduction of **3b** with $KBEt_3H$ and with $KB(OPr^i)_3H$ gave diastereoselectivity of 88% and 84% ds, respectively (entries 21 and 24). The addition of lithium bromide[4] or crown ether further improved the selectivity up to 95 and 90% ds, respectively (entries 23 and 25). The hydroxy amide **5b** thus obtained was hydrolyzed (1 mol dm^{-3} HCl, reflux) to the corresponding α-hydroxy acid without racemization. In the case of **5a** obtained in 99% ds, however, the partial epimerization was observed during the hydrolysis, giving (R)-mandelic acid of 92% ee.[6]

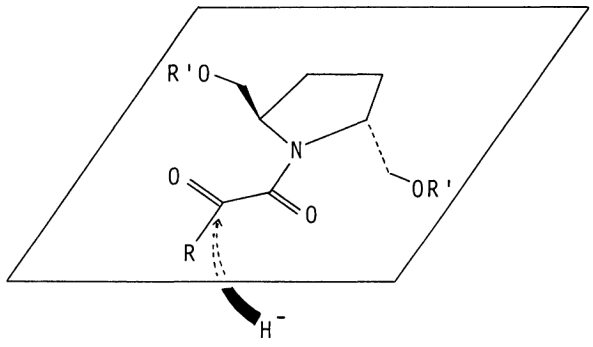
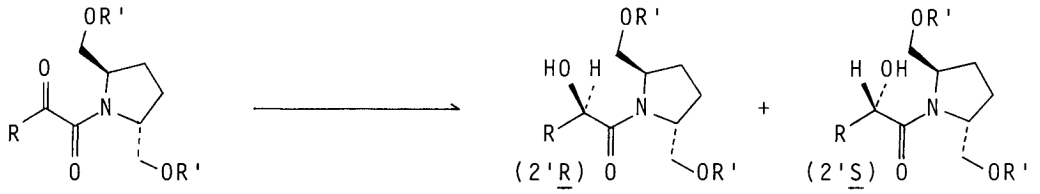


Fig. 2.

Although the exact steric course is not clear at present, the observed stereochemical outcome that except for zinc borohydride, the (R,R) auxiliary invariably gave the (2'R) products in excess, indicates that the attack of the hydride anion occurs on the less hindered side (si-face) of α-carbonyl carbon of the predominating



2a, R=Ph, R'=Me
2b, R=Me, R'=Me
3a, R=Ph, R'=MOM
3b, R=Me, R'=MOM

4a, R=Ph, R'=Me
4b, R=Me, R'=Me
5a, R=Ph, R'=MOM
5b, R=Me, R'=MOM

Table 1. Asymmetric Reduction of Chiral α-Keto Amides

Entry	Amide	Reducing agent[a] /Additive	Solvent	Temp/°C	Yield/%[b]	Ratio[c,d] 2'R : 2'S
1	**2a**	$NaBH_4$	i-PrOH	0	84	68 : 32[e]
2	**2a**	KBH_4	i-PrOH[f]	0	87	79 : 21[e]
3	**2a**	$n\text{-}Bu_4NBH_4$	CH_2Cl_2	rt	72	83 : 17[e]
4	**2a**	$Zn(BH_4)_2$	Et_2O	0	80	50 : 50[e]
5	**2a**	$LiBEt_3H$	THF	-78	61	97 : 3[e]
6	**3a**	H_2 (Pd-C)	i-PrOH	rt	71	78 : 22
7	**3a**	$LiBH_4$	THF	0-rt	64	73 : 27
8	**3a**	$NaBH_4$	i-PrOH	0	87	65 : 35
9	**3a**	KBH_4	i-PrOH[f]	0-rt	78	77 : 23
10	**3a**	$n\text{-}Bu_4NBH_4$	CH_2Cl_2	rt	77	78 : 22
11	**3a**	$LiBEt_3H$	Et_2O	-78	93[c]	96 : 4
12	**3a**	$LiBEt_3H$	THF	-78	92	99 : 1
13	**3a**	$KBEt_3H$	THF	-78	67[c]	92 : 8
14	**3a**	$KB(OPr^i)_3H$	Et_2O	-78	81[c]	64 : 36
15	**2b**	$LiBEt_3H$	THF	-78	94	80 : 20[e]
16	**2b**	$KB(OPr^i)_3H$	Et_2O	-78	55	91 : 9[e]
17	**3b**	$LiBH_4$	THF	-55	67	53 : 47
18	**3b**	$LiBH_4$/12-crown-6	THF	-23	73	68 : 32
19	**3b**	$LiBEt_3H$	THF	-78	94	82 : 18
20	**3b**	$LiBEt_3H$/12-crown-6	THF	-78	82	87 : 13
21	**3b**	$KBEt_3H$	THF	-78	83	88 : 12
22	**3b**	$KBEt_3H$/18-crown-6	THF	-78	68	88 : 12
23	**3b**	$KBEt_3H$/LiBr	THF	-78	89	95 : 5
24	**3b**	$KB(OPr^i)_3H$	Et_2O	-78	67	84 : 16
25	**3b**	$KB(OPr^i)_3H$/18-crown-6	Et_2O	-78	78	90 : 10

a) The molar ratio, amide : reducing agent= 1 : 1, or amide : reducing agent : additive= 1 : 1 : 1 except for entry 25, where a ratio, amide : $KB(OPr^i)_3H$: 18-crown-6= 1 : 3 : 3 was used. b) Isolated yield. c) Determined by GLC analysis (1.5% Silicone OV-17). d) Configurations of predominant enantiomers of α-hydroxy amides (**5a** and **5b**) were determined to be 2'R by the optical rotations of the respective hydrolysis products, (R)-(-)-mandelic and (R)-(-)-lactic acid. That of **4a** was assigned to be 2'R by the comparison of the NMR spectra with authentic sample derived from (S)-mandelic acid. That of **4b** was tentatively assigned to be 2'R by mechanistic analogy. e) Determined by ^1H NMR analysis. f) Contained 10% H_2O.

s-trans conformer, as shown in Fig. 2.[7] This seems to hold even for the Pd-catalyzed reduction (entry 6) though the s-cis conformation has been suggested to catalytic hydrogenation of α-keto amides bearing amine components which are less bulky than the present pyrrolidine auxiliary.[8]

In a typical experiment, a THF solution of $LiBEt_3H$ (1 mol dm^{-3}, 0.23 ml, 1 equiv.) was added to a solution of **3a** (80 mg) in THF (4.5 ml) at -78 °C. After stirring for 1 h, the mixture was quenched with 5% H_3PO_4 solution, diluted with ethyl acetate (10 ml), washed with saturated $NaHCO_3$ solution and brine successively, and dried over $MgSO_4$. An alliquot of the solution was analyzed by glc giving a diastereomeric ratio of 99:1. The solution was concentrated and submitted to preparative tlc (hexane-ethyl acetate= 4:1) to give **5a** in 92% yield. **5a**, $[\alpha]_D^{26}$ -14.6° (c 0.55, H_2O).

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2) M. Enomoto, Y. Ito, T. Katsuki, and M. Yamaguchi, Tetrahedron Lett., 26, 1343 (1985) and references cited therein.

3) a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Englewood Cliffs, New Jersy (1971), Chap. 2; b) K. Harada, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Orland (1985), Vol. 5, pp. 345-383.

4) K. Soai, T. Isoda, H. Hasegawa, and M. Ishizaki, Chem. Lett., 1986, 1897, and references cited therein. Soai et al. suggested that the high diastereo selectivity observed in the reduction of α-ketoamide with $LiBH_4$-LiBr system, may be due to the coordination of the metallic salt with oxygen atom(s) of α-keto amides reducing the number of possible conformations.

5) Y. Kawanami, Y. Ito, T. Kitagawa, Y. Taniguchi, T. Katsuki, and M. Yamaguchi, Tetrahedron Lett., 25, 857 (1984); Y. Ito, T. Katsuki, and M. Yamaguchi, ibid., 26, 4643, 6015 (1985); T. Katsuki, and M. Yamaguchi, ibid., 26, 5807 (1985); T. Hanamoto, T. Katsuki, and M. Yamaguchi, ibid., 27, 2463 (1986); M. Uchikawa, T. Hanamoto, T. Katsuki, and M. Yamaguchi, ibid., 27, 4577 (1986).

6) The hydrolysis of aliphatic α-hydroxy amides derived from 2,5-bis(methoxy-methoxymethyl)pyrrolidine (1 mol dm^{-3} HCl, reflux) generally proceeds without any detectable epimerization (Ref. 2).

7) Soai et al. reported that an opposite sense of asymmetric induction was observed in the reduction of chiral α-keto amides with $LiBH_4$ on the one hand and that with DIBAL on the other (Ref. 4). However, reduction of **2a** and **3a** with these two reducing agents exhibited the same sense of asymmetric induction, though reduction with DIBAL (ether, -78 °C) gave poor to moderate diastereoselectivities (**4a**, 80% ds; **5a**, 54% ds).

8) Harada et al. have discussed the steric course in the catalytic hydrogenation of α-keto amides bearing chiral primary amines, on the basis of a cis conformer of α-dicarbonyl moiety locked by chelation to palladium metal. See Ref. 3b.

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