Diastereoselective Reduction of α-Keto Amides Having *trans*-2,5-Disubstituted Pyrrolidine as a Chiral Auxiliary

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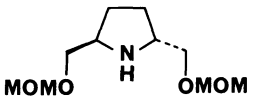
The reduction of α-keto amides derived from (2*R*,5*R*)-*trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine [(*R*)-BMOMP, **1**] with $LiBEt_3H$ or $KBEt_3H$ proceeded with high diastereoselectivity (up to 99% ds) to afford the corresponding α-hydroxy amides in good yields. The additive effect of crown ethers or metallic salts on the stereoselectivity was also examined.

Optically active α-hydroxy acid derivatives are versatile building blocks for the synthesis of natural products[1] and many methods have so far been reported for their preparation.[2] Among them, the diastereoselective reduction of chiral α-keto acid derivatives which bear an appropriate chiral auxiliary, is a conventional approach.[3] However the utility of the reaction has been restricted mainly by its insufficient optical yield. In the course of our investigation on asymmetric reactions using *trans*-2,5-disubstituted pyrrolidine possessed of C_2-axis of symmetry as a chiral auxiliary,[4] we have communicated highly diastereoselective reduction of α-keto amides derived



1 (R)-BMOMP

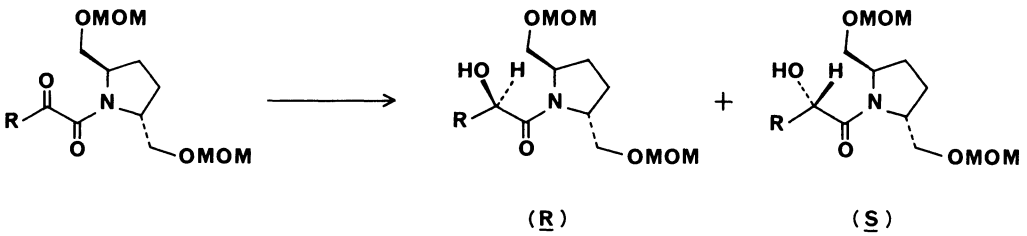
from **1** as illustrated in Scheme 1.[5] The full details of the study is described here.

Results and Discussion

α-Keto amides (**2a** and **2b**) were prepared from (*R*)-BMOMP by *N*-acylation with mixed pivalic benzoylformic or pyruvic anhydride in the presence of 4-dimethylaminopyridine in good yields. Then, the compounds (**2a** and **2b**) were submitted to reduction by metal borohydrides or DIBAL, or to hydrogenation (H_2/Pd–C), where the preferential formation of (*R*)-hydroxy amides (**3a** and **3b**) was observed except for one case. The diastereoselectivity of the reactions was determined by ^1H NMR and/or GLC analysis. The results obtained are summarized in Table 1. Reduction of **2a** (R=Ph) with ordinary metal borohydrides proceeded with moderate diastereoselectivity in a range of 62—77% diastereoselectivity (ds) (Entries 1—3). Reduction with zinc borohydride or DIBAL exhibited very poor diastereoselectivity (Entries 4 and 7), although the former reagent is known to exhibit high erythro-selectivity on the reduction of β-keto esters[6] and amides.[7] The slightly better selectivity was observed in the reduction with tetrabutylammonium borohydride having low ability of chelation (Entry 5). The catalytic hydrogenation also showed a moderate level of selectivity (Entry 6).

We next examined the reduction of **2a** with the bulky trialkylhydroborates which were expected to discern the diastereomerically different environment more effectively and, as expected, it was found that the diastereoselectivity was markedly enhanced up to 96—99% ds, when $LiBEt_3H$ was used in THF or ether at −78 °C (Entries 8 and 9).

On the other hand, the diastereoselectivity in the reduction of pyruvamide (**2b**, R=Me) with borohydrides was generally not so good as that of **2a** (Entries 13—15 and 17),[8] and zinc borohydride reduction of the same substrate showed the opposite sense of diastereoselection (Entry 16). These results suggested that, although α-keto amides (**2a** and **2b**) existed in the form of *s*-trans conformer (**A**) rather than *s*-cis conformer as discussed later (Scheme 2), the relative proportion of **A**



2a R=Ph
2b R=Me

3a R=Ph
3b R=Me

Scheme 1.

Table 1. Asymmetric Reduction of Chiral α-Keto Amides

Entry	Amide	Reducing agent	Solvent	Temp °C	Yield[a] %	Ratio[b,c] R : S
1	**2a**	$LiBH_4$	THF	0—rt	64	73 : 27
2	**2a**	$NaBH_4$	*i*-PrOH	0	87	65 : 35
3	**2a**	KBH_4	*i*-PrOH[d]	0—r	78	77 : 23
4	**2a**	$Zn(BH_4)_2$	Et_2O	0	83	52 : 48
5	**2a**	*n*-Bu_4NBH_4	CH_2Cl_2	rt	77	78 : 22
6	**2a**	H_2(Pd-C)	*i*-PrOH	rt	71	78 : 22
7	**2a**	DIBAL	Et_2O	−78	65	54 : 46
8	**2a**	$LiBEt_3H$	Et_2O	−78	93[b]	96 : 4
9	**2a**	$LiBEt_3H$	THF	−78	92	99 : 1
10	**2a**	$KBEt_3H$	Et_2O	−78	81[b]	86 : 14
11	**2a**	$KBEt_3H$	THF	−78	83	88 : 12
12	**2a**	$KB(OPr^i)_3H$	Et_2O	−78	81[b]	64 : 36
13	**2b**	$LiBH_4$	THF	−78	67	62 : 38
14	**2b**	$NaBH_4$	*i*-PrOH	0	30	71 : 29
15	**2b**	KBH_4	*i*-PrOH[d]	0	77	70 : 30
16	**2b**	$Zn(BH_4)_2$	Et_2O	−78	56	46 : 54
17	**2b**	$LiBEt_3H$	THF	−78	94	82 : 18
18	**2b**	$KBEt_3H$	Et_2O	−78	80	83 : 17
19	**2b**	$KBEt_3H$	THF	−78	83	88 : 12
20	**2b**	$KB(OPr^i)_3H$	Et_2O	−78	67	87 : 13
21	**2b**	$KB(OPr^i)_3H$	THF	−78	76[b]	84 : 16

a) Isolated yield. b) Determined by GLC analysis. c) Configurations of predominant diastereomers of α-hydroxy amides were determined to be 2*R* by the optical rotations of the corresponding hydrolysis products, (*R*)-(−)-mandelic acid and (*R*)-(−)-lactic acid.[9] d) Contained 10% H_2O.

Table 2. The Effect of Crown Ether on the Stereoselectivity[a]

Entry	Reducing agent	Crown ether	Solvent	Yield %	Ratio R : S
1	$LiBEt_3H$	—	THF	94	82 : 18
2	$LiBEt_3H$	12-Crown-4	THF	82	87 : 13
3	$LiBEt_3H$	15-Crown-5	THF	53	85 : 15
4	$LiBEt_3H$	18-Crown-6	THF	80	80 : 20
5	$LiBEt_3H$	Kryptofix-211	THF	81	85 : 15
6	$LiBEt_3H$	Kryptofix-221	THF	89	87 : 13
7	$KBEt_3H$	—	THF	83	88 : 12
8	$KBEt_3H$	18-Crown-6	THF	68	88 : 12
9	$KB(OPr^i)_3H$	—	Et_2O	67	84 : 16
10	$KB(OPr^i)_3H$	15-Crown-5	Et_2O	83	90 : 10
11	$KB(OPr^i)_3H$	18-Crown-6	Et_2O	78	90 : 10
12	$KB(OPr^i)_3H$	18-Crown-6	THF	79	83 : 17
13	$KB(OPr^i)_3H$	Dibenzo-18-crown-6	Et_2O	69	83 : 17

a) All reactions were carried out at −78 °C using α-keto amide (**2b**) as a substrate.

and **B** was affected by steric bulkiness of α-alkyl group (R) and strongly by the oxygenophilicity of metal ions, and that, especially in the latter case, the equilibrium leaned to **B** due to the chelation of two carbonyl groups to the oxygenophilic zinc ion. Therefore, use of $KBEt_3H$ or $KB(OPr^i)_3H$ bearing less oxygenophilic potassium ion was considered to improve the selectivity and actually higher selectivities (88% and 87% ds) were observed with these reagents (Entries 19 and 20).

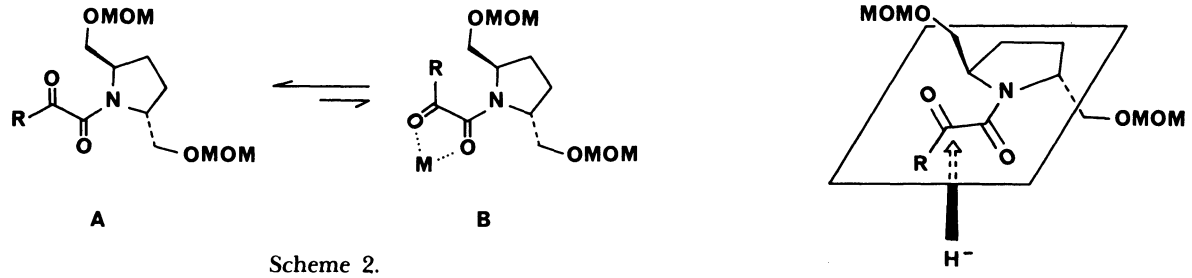
In the further attempt to improve the stereoselectivity in the reduction of **2b**, we next examined the additive effect of crown ethers which is expected to capture metal ions and to disturb chelate formation. The results are summarized in Table 2. In the reduction with $LiBEt_3H$, addition of a proper size of 12-crown-4 or kryptofix-221 enhanced the selectivity from 82% ds to 87% ds (Entries 2 and 6). Although the combination of 18-crown-6 and $KBEt_3H$ gave no effect on selectivity, that with $KB(OPr^i)_3H$ further improved the selectivity from 84% ds to 90% ds (Entry 11).

Recently Soai et al. reported that diastereoselectivity in the reduction of benzylformamide derived from (*S*)-proline methyl ester, with $LiBH_4$ was improved up to 93.5% ds by addition of LiBr in the reaction mixture, while reduction of the corresponding isobutylformamide proceeded with diminished stereoselectivity of 79% ds even in the presence of LiBr.[3d] Aiming at the further promotion of the stereoselectivity in the re-

Table 3. The Effect of Metallic Salt on the Stereoselectivity[a]

Entry	Reducing Agent	Additive[b]	Yield	Ratio
			%	*R* : *S*
1	$LiBH_4$	—	67	53:47
2	$LiBH_4$	LiBr	76	63:37
3	$LiBEt_3H$	—	94	82:18
4	$LiBEt_3H$	LiBr	89	84:16
5	$LiBEt_3H$	LiCl	97	88:12
6	$KBEt_3H$	—	83	88:12
7	$KBEt_3H$	LiBr	83	95:5
8	$KBEt_3H$	LiBr[c]	68	93:7
9	$KBEt_3H$	LiCl	65	94:6
10	$KBEt_3H$	$ZnBr_2$	78	76:24
11	$KBEt_3H$	$ZnBr_2$[d]	61	58:42
12	$KBEt_3H$	$MgBr_2$[d]	47	58:42

a) All reactions were carried out in THF at −78 °C using α-keto amide (**2b**). b) Molar ratio; amide: reducing agent: metallic salt=1:1:2. c) Molar ratio; 1:1:1. d) In ether.



Scheme 2.

duction of **2b**, we also examined the additive effect of the salt. As shown in Table 3, addition of lithium salts increased the selectivity (Entries 2, 4, 5, and 7—9), whereas that of the metal salt such as Mg^{2+} or Zn^{2+}, decrease substantially (Entries 10—12). The optimal result (95% ds) was obtained in the reduction with $KBEt_3H$ in the presence of 2 equiv LiBr (Entry 7).

The hydroxy amide (**3b**) thus obtained was hydrolyzed by refluxing in 1 mol dm^{-3} HCl to give (*R*)-lactic acid without racemization. In the case of **3a** obtained in 99% ds, however, the partial epimerization was observed during hydrolysis, giving (*R*)-mandelic acid of 92% ee.[9]

The exact steric course of the reduction is not clear at present, but preferential formation of (*R*)-α-hydroxy amides and a CPK-model examination suggest as follows. α-Keto amide exists in the equilibrium of two plane conformers (**A** and **B**)[3b] as shown in Scheme 2. The *s*-cis conformer (**B**) is considered to be destabilized by the dipole repulsion of two carbonyl groups and the steric repulsion between α-alkyl group (R) and the amine moiety, and the α-keto amide having a bulky amine component like BMOMP takes *s*-trans conformer preferentially. Another advantage of the use of BMOMP is that the conformational divergence due to the rotation of the bond between the amide carbonyl carbon and nitrogen atoms need not be considered here because of its C_2-symmetry and the planarity of the amide structure. Thus the attack of a hydride anion would occur preferentially from the less hindered side (*si*-face) of α-carbonyl carbon of the predominating *s*-trans conformer to afford the (*R*)-hydroxy amide, as shown in Fig. 1. This seems to hold even for the Pd-catalyzed reduction (Table 1, Entry 6) though *s*-cis conformation has been suggested to catalytic hydrogenation of α-keto amides bearing amine components which are not bulkier than the present pyrrolidine auxiliary.[10]

In summary, we found that highly diastereoselective reduction of α-keto amide could be achieved by using sterically bulky BMOMP as a chiral auxiliary, which weighted the conformational equilibrium of α-keto amide in favor of the *s*-trans conformer, and that addition of crown ethers or lithium salts in the reaction mixture was effective for the further enhancement of the stereoselectivity to a certain extent.

Experimental

Melting points are uncorrected. IR spectra were determined on a Shimadzu IR-435 spectrophotometer and UV spectra on a Shimadzu UV-260 spectrophotometer. ^1H NMR spectra were recorded at 90 MHz with a Hitachi R-90H spectrometer. All NMR spectra were taken in $CDCl_3$ solution with TMS as an internal standard. Optical rotations were determined on a Yanagimoto OR-50 polarimeter. GLC analysis was carried out with a Shimadzu GC-7A chromatograph.

Reactions were carried out under an atmosphere of

nitrogen unless otherwise stated. Tetrahydrofuran (THF) and ether were freshly distilled from sodium benzophenone ketyl before use. Dichloromethane was distilled from calcium hydride. Thin-layer chromatography (TLC) was carried out on Merck glass plates precoated with silica gel 60F-254 (0.25 mm) and column chromatography was performed by using Merck 230—400 mesh silica gel.

(2*R*,5*R*)-*N*-Benzoylcarbonyl-*trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine (2a). Pivaloyl chloride (0.34 ml, 2.78 mmol) was added to a solution of benzoylformic acid (430 mg, 2.78 mmol) and triethylamine (0.39 ml, 2.78 mmol) in dichloromethane (2 ml) at 0 °C and the mixture was stirred for 2 h. (*R*)-BMOMP (152 mg, 0.694 mmol) in dichloromethane (0.5 ml) and 4-dimethylaminopyridine (85.2 mg, 0.694 mmol) were added to the mixture and stirred over night. The reaction mixture was diluted with ether and filtered through Celite. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution and brine successively, and dried over $MgSO_4$. The residue was chromatographed on silica gel (hexane–acetone, 5:1) to give the colorless viscous oil (**2a**, 238 mg, 98%): $[\alpha]_D^{25}$ +165° (*c* 1.07, MeOH); UV (EtOH) 254 nm (ε 54640); IR (neat) 2950, 1678, 1630, 1600, 1428, 1240, 1150, 1110, and 1040 cm^{-1}; ^1H NMR δ=1.53—2.49 (4H, m), 3.04 (3H, s), 3.21—3.32 (2H, m), 3.39 (3H, s), 3.72—3.87 (2H, m), 4.00, 4.15 (2H, ABq, *J*=6.3 Hz), 4.21—4.53 (2H, m), 4.67 (2H, s), 7.30—7.60 (3H, m), 7.95—8.12 (2H, dd, *J*=8.6, 2.0 Hz); Found: C, 61.25; H, 7.40; N, 3.80%. Calcd for $C_{18}H_{25}NO_6$: C, 61.53; H, 7.17; N, 3.99%.

(2*R*,5*R*)-*N*-Acetylcarbonyl-*trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine (2b). Compound **2b** was prepared in a similar manner to that described for **2a**. Yield 77%; $[\alpha]_D^{25}$ +79.7° (*c* 3.314, MeOH); UV (EtOH) 238 nm (ε 2846); IR (neat) 2900, 1710, 1628, 1430, 1210, 1150, 1110, and 1040 cm^{-1}; ^1H NMR δ=1.80—2.24 (4H, m), 2.36 (3H, s), 3.06—3.52 (2H, m), 3.28 (3H, s), 3.33 (3H, s), 3.53—3.81 (2H, m), 4.30 (1H, m), 4.45—4.89 (1H, m), 4.51 (2H, s), 4.58 (2H, s); Found: C, 53.70; H, 8.29; N, 4.54%. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84%.

General Procedure for Reduction of α-Keto Amide. (2*R*,5*R*)-*N*-[(2*R*)-2-Hydroxy-2-phenylacetyl]-*trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine (**3a**). A THF solution of $LiBEt_3H$ (1 mol dm^{-3}, 0.23 ml, 0.23 mmol) was added to a solution of the α-keto amide (**2a**, 80 mg, 0.228 mmol) in THF (4.5 ml) at −78 °C. After stirring for 1 h at the same temperature, the reaction mixture was quenched with 5% aqueous H_3PO_4 solution and diluted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine successively, and dried over $MgSO_4$. An aliquot of the solution was analyzed by GLC (1.5% silicone OV-17 on Chromosorb G, 3 mm×5 m, 210 °C) to give the diastereomeric tatio of 99:1 (34 and 36 min). The solution was concentrated and submitted to preparative TLC on silica gel with hexane–ethyl acetate (1:4) to give the α-hydroxy amide (**3a**) as a colorless oil (74.3 mg, 92%); $[\alpha]_D^{26}$ +5.4° (*c* 1.49, MeOH); IR (neat) 3400, 2900, 1635, 1440, 1370, 1145, 1105, 1030 cm^{-1}; ^1H NMR δ=1.30 (1H, s), 1.56—2.30 (4H, m), 3.28 (3H, s), 3.39 (3H, s), 3.42—3.94 (4H, m), 4.05—4.65 (2H, m), 4.47 (2H, s), 4.63 (2H, s), 5.16 (1H, s), 7.32 (5H, s). 2*S* epimer had the similar spectrum except for δ 5.38 instead of 5.16. Found: C, 60.93; H, 7.92; N, 3.88%. Calcd for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96%.

(2*R*,5*R*)-*N*-[(2*R*)-2-Hydroxypropanoyl]-*trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine (3b). A THF solution of $KBEt_3H$ (1 mol dm^{-3}, 0.31 ml, 0.31 mmol) was added to a solution of (**2b**, 90 mg, 0.31 mmol) and lithium bromide (54 mg, 0.62 mmol) in THF (3 ml) at −78 °C and stirred for 1 h. The mixture was quenched with 5% H_3PO_4 solution, diluted with $CHCl_3$–EtOH (3:1), washed with saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. Concentration of the solvent and preparative TLC (hexane–ethyl acetate) afforded **3b** (75 mg, 83%) as a colorless oil. GLC analysis showed that the diastereomeric ratio was 95:5 (17 and 19 min, 180 °C). $[\alpha]_D^{25}$ +25.5° (*c* 1.88, MeOH); IR (neat) 3400, 2900, 1635, 1480, 1150, 1110, and 1040 cm^{-1}; ^1H NMR δ=1.31 (3H, d, *J*=6.6 Hz), 1.57 (1H, s), 1.70—2.28 (4H, m), 3.33 (6H, s), 3.38—3.70 (4H, m), 3.95 (1H, m), 4.25 (1H, m), 4.40—4.70 (1H, m), 4.57 (4H, s); Found: C, 53.35; H, 8.93; N, 4.72%. Calcd for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81%.

Hydrolysis of (+)-3a to (*R*)-(−)-Mandelic Acid. The amide (**3a**, 37.2 mg, 0.105 mmol) was refluxed in 1 mol dm^{-3} HCl (0.422 ml) for 2 h. The mixture was neutralized with saturated aqueous $NaHCO_3$, washed with dichloromethane, and then adjusted to pH 1 with 2 mol dm^{-3} HCl. The aqueous solution was saturated with sodium chloride, extracted with ethyl acetate, and dried over $MgSO_4$. Evaporation of the solvent gave (−)-mandelic acid (12.8 mg, 80%); $[\alpha]_D^{26}$ −146° (*c* 0.555, H_2O); [lit,[11] $[\alpha]_D$ +158° (H_2O)]. Esterification with diazomethane afforded (−)-methyl mandelate, $[\alpha]_D^{26}$ −167° (*c* 0.48, benzene) [lit,[2d] $[\alpha]_D$ −181.9° (*c* 0.69, benzene)].

Hydrolysis of (+)-3b to (*R*)-(−)-Lactic Acid. A similar treatment of (+)-**3b** (90% de) as described above afforded (*R*)-(−)-lactic acid; $[\alpha]_D^{26}$ −2.0° (*c* 0.76, water). [lit,[12] $[\alpha]_D$ −2.3±0.5° (*c* 3, water)]; lithium salt; $[\alpha]_D^{26}$ +12.7° (*c* 0.315, water). [lit,[13] $[\alpha]_D^{22}$ −14.0° (*c* 3, water)].

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8) The similar results were reported in the reduction of α-keto acid derivatives; from 89% ee (R=Ph) to 48% ee (R=Me), see Ref. 2b; from 72% ee (R=Ph) to 46% ee (R=Me), see Ref. 3c.

9) The hydrolysis of aliphatic α-hydroxy amides derived from BMOMP (1 mol dm^{-3} HCl, reflux) generally proceeds without any detectable epimerization. See Ref. 2c.

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

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