Efficient Stereoselective Synthesis of α-Hydroxy Aldehydes with (*R*)-Piperidin-3-ol as a New Chiral Auxiliary

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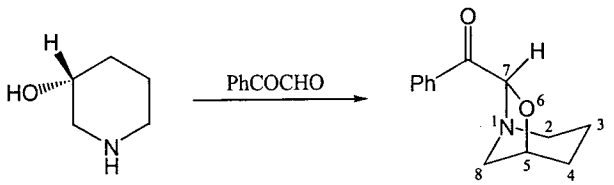
Chiral α-hydroxy carbonyl compounds have been used as chiral synthons in the preparation of many natural products.[1] They can be prepared efficiently by stereoselective addition of organometallics to a chiral ketone possessing two heteroatoms in the neighborhood of the carbonyl group.[2−5] For example, the reaction of 2-benzoyl-1,3-oxathianes or perhydro-2-benzoyl-1,3-oxazines with organometallics results in a high degree of asymmetric induction that was attributed to the chelation control.[2,3]

Here, the ring oxygen atom chelates much more effectively than the ring sulfur or nitrogen atom with the metals of Grignard reagents as well as other organometallics. However, there have been some reports that the sulfur or the nitrogen atom can be involved in the chelation.[4,5] In this paper, we describe the excellent diastereoselectivity observed in the reaction of Grignard reagents with the chiral 2-acyl-1,3-oxazolidine which can be prepared from commercially available (*R*)-piperidin-3-ol,[6] and propose a chelation model with the nitrogen atom instead of the oxygen atom.

The condensation of phenylglyoxal monohydrate and (*R*)-piperidin-3-ol (**1**) in the presence of molecular sieves (4 Å) gave (5*R*,7*R*)-7-benzoyl-6-oxa-1-azabicyclo[3.2.1]-octane (**2**) in 85% yield. Only a trace amount of the C-7 epimer of compound **2** was detected by ^{1}H NMR, probably because of severe steric hindrance between the benzoyl group and H-3a (Scheme **1**).[7]

Without further purification, the reactions of keto oxazolidine **2** with organometallic reagents were carried out at −78 °C in THF to give carbinols **3** and **4**. The reaction yields and diastereomeric excesses were determined by the integration of the H-7 peak on their ^{1}H NMR spectra, and the configuration of the major product was assigned by comparing optical rotation values of the mixture of α-hydroxy aldehydes **5** and **6** prepared by the hydrolysis of a mixture of carbinols **3** and **4** with the known values.[2,5] The reactions proceeded to near completion, and chiral auxiliary **1** was recovered in over 80% yield (Scheme **2**).

Scheme 1



1 **2**

Table 1. Reactions of 2 with Organometallic Reagents

entry[a]	RM	**3**	**4**	yield, %[c]
1	MeMgBr	93	7	84
2	EtMgBr	98	2	85
3	VinylMgBr	98	2	84
4	*i*PrMgBr	98	2	82
5	*n*BuMgCl	77	23	NA[d]
6	MeLi	40	60	83
7[b]	MeLi	28	72	82
8	MeLi+$CeCl_3$	69	31	62
9	*n*BuLi	39	61	NA[d]

[a] The molar ratio of RM to the ketone was 3. The reaction was run in THF at −78 °C, and the ratio was determined by the integration of H-7 peak. [b] The reaction was run in THF−HMPA. [c] Isolated yield of a mixture of **5** and **6**. [d] A mixture of **5e** and **6e** was partially decomposed during isolation.

As shown in Table **1**, the addition of the Grignard reagents to benzoyl oxazolidine **2** generally proceeded with high diastereoselectivity giving *S*-carbinol **3**, while organolithium reagents gave *R*-carbinol **4** as a major product with lower stereoselection. The selectivity with MeLi was enhanced slightly by addition of HMPA to the reaction solvent (entry 7), whereas reversed diastereoselectivity was observed with the addition of $CeCl_3$ (entry 8).

The stereoselectivity observed with the Grignard reagents can be rationalized on the basis of a chelation model.[2,3,8] Magnesium cation preferentially chelates between the carbonyl oxygen and the nitrogen atom to the ether oxygen atom in 1,3-oxazolidine ring. These results are comparable with those of 2-benzoyl-1,3-oxazolidine, derived from (2-pyrrolidinyl)methanol,[5] but are different from those of perhydro-2-benzoyl-1,3-oxazine.[2e,3]

In the reaction of perhydro-2-benzoyl-1,3-oxazine with organometallics, the facial selectivity was explained by the chelation of the metal between the carbonyl oxygen and the ether oxygen.[2,3] The preference of the oxygen to the nitrogen was proposed by the effective alignment, based on the orbital geometry.[3] The lone pair electrons of the nitrogen are not aligned with those of the carbonyl oxygen. However, the electrons of the nitrogen at the bridgehead in compound **2** are aligned with the carbonyl oxygen such that chelation with the nitrogen becomes

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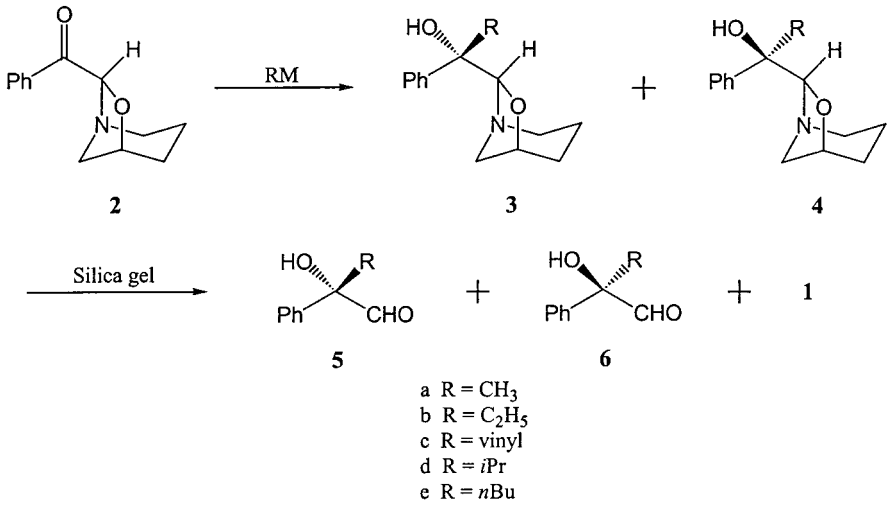
Scheme 2



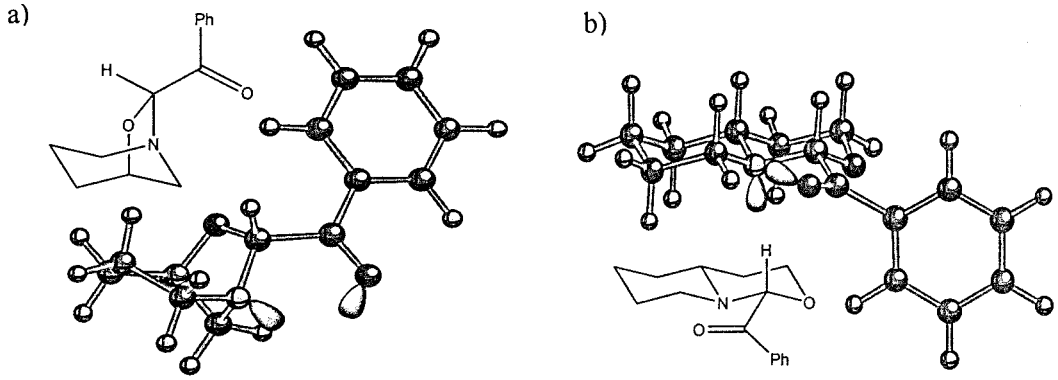


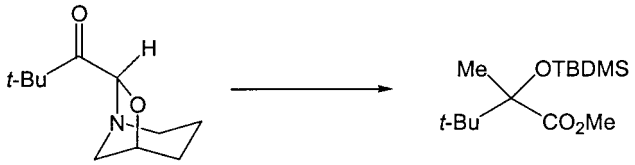
Figure 1. Directionality of the lone pair electrons of nitrogen and carbonyl oxygen atoms in (a) perhydro-2-benzoyl-1,3-oxazine and (b) 2-benzoyl-1,3-oxazolidine.

more effective (Figure **1**). As a result, *re* face attack is predominant in case of compound **2**.

When organolithium reagents were employed, the opposite *si* face attack was observed. The chelation with the nitrogen may not be stronger, because lithium is smaller than magnesium. So steric hindrance becomes the larger factor in the control of diastereoselectivity. In the presence of HMPA, the chelation becomes less effective, while the steric bulkiness has more effect (entry 7). When cerium is added with the lithium reagent, chelation with nitrogen becomes more effective, because cerium is larger than lithium (entry 8). While compounds **5a**−**d** and **6a**−**d** were quite stable to isolate, **5e** and **6e** cannot be isolated (entries 5 and 9). In the reaction with DIBAL or $NaBH_4$, the corresponding carbinols were too labile to be isolated, unlike the reaction of perhydro-1,3-oxazines.

In addition to phenylglyoxal, *tert*-butylglyoxal was employed.[9] The condensation of *tert*-butylglyoxal with (*R*)-piperidin-3-ol gave ketooxazolidine **7** which was used in the addition reaction with MeMgBr or MeLi. Since the resulting carbinol was unstable, it was hydrolyzed to 2-hydroxy-2,3,3-trimethylbutanal which was identified by ^{1}H NMR. The hydroxy aldehyde was also slightly unstable and converted to methyl 2-*tert*-butyldimethylsilyloxy-2,3,3-trimethylbutanoate (**8**) by the sequence: oxidation,[4c] methyl ester formation,[10] and protection of the hydroxy moiety[11] (Scheme 3). The diastereoselectivity in the addition reaction could be determined by measuring the enantiomeric ratio of silyl ester **8** using a chiral GC. Like phenylglyoxal, the selectivity with MeMgBr was opposite to that with MeLi.

Scheme 3[a]



[a] Conditions: (i) MeMgBr or MeLi, (ii) silica gel, (iii) $NaClO_2$, 2-methyl-2-butene, (iv) $Me_3SiCH_2N_2$, (v) TBDMSCl, imidazole.

In conclusion, the addition reaction of bridged 2-acyl-1,3-oxazolidine, prepared from (*R*)-piperidin-3-ol, with Grignard reagents proceeded with high diastereoselectivity to give nearly optically pure α-hydroxy aldehydes. The selectivity can be attributed to a chelation model involving the nitrogen and carbonyl oxygen atoms. Thus, chiral piperidin-3-ol has been demonstrated to be an efficient chiral auxiliary for the preparation of α-hydroxy carbonyl compounds in the present study.[12]

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Experimental Section

All chemicals were reagent grade (Aldrich Chemical Co.) and were used as purchased without further purification. ^{1}H NMR spectra were recorded at 250 and 300 MHz (75 MHz for ^{13}C NMR).

(5*R*,7*R*)-7-Benzoyl-6-oxa-1-azabicyclo[3.2.1]octane (2). A mixture of (*R*)-piperidin-3-ol (0.140 g, 1.38 mmol), phenylglyoxal monohydrate (0.185 g, 1.38 mmol), and molecular seives (4 Å) in dry CH_2Cl_2 (30 mL) was refluxed overnight. After cooling, the reaction mixture was washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by recrystallization with CH_2Cl_2 and *n*-hexane to give ketooxazolidine **2 (**0.256 g, 85%) as a yellow solid: mp 128−129 °C; ^{1}H NMR δ 1.53−1.69 (m, 2H), 1.89−2.24 (m, 2H), 2.97−3.18 (m, 3H), 3.18−3.31(m, 1H), 4.44−4.50 (m, 1H), 5.85 (s, 1H), 7.44−7.68 (m,3H), 8.00−8.13 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8, 30.5, 54.3, 57.8, 73.6, 94.6, 128.9, 129.4, 133.6, 135.4, 194.3. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.83; H, 7.08; N, 6.38.

General Procedure for the Grignard Reaction using MeMgBr. To a solution of ketone **2** (0.020 g, 0.092 mmol) in dry THF (1 mL) at −78 °C under N_2 was added dropwise 3.0 M methylmagnesium bromide in ether (0.01 mL, 0.27 mmol). After stirring for 1 h, the reaction was quenched with saturated NH_4-Cl solution at −78 °C and allowed to warm to room temperature, and ethyl acetate (5 mL) and brine (5 mL) were added. The organic layer was separated, and the aqueous layer was further extracted with ethyl acetate (5 mL) twice. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a mixture of oily carbinols **3a** and **4a** (0.018 g, 84%). A mixture of **3a** and **4a**; ^{1}H NMR δ 1.39−1.53 (m, 2H), 1.61 (s, 3H), 1.78−2.11(m, 2H), 2.29−2.36 (m, 1H), 2.80−3.00 (m, 3H), 3.63−3.79 (m. 1H), 4.08−4.11 (m, 1H), 4.81 and 4.77 (s, 1H), 7.19−7.58 (m, 5H). In the case of other compounds, the chemical shift of H-7 is described.

A mixture of **3b** and **4b**: 4.79 and 4.76 (s, 1H). A mixture of **3c** and **4c**: 4.86 and 4.84 (s, 1H). A mixture of **3d** and **4d**: 5.05 and 5.03 (s, 1H). A mixture of **3e** and **4e**: 4.78 and 4.77 (s, 1H).

Hydrolysis of the Mixture of 3a and 4a.[2,5] A mixture of carbinols **3a** and **4a** (54 mg, 0.23 mmol), silica gel (5 g), and CH_2Cl_2 (20 mL) was stirred for 2 h at room temperature. The reaction mixture was subjected to column chromatography on silica gel (elution with 20% ethyl acetate in *n*-hexane). After most of hydroxy aldehydes **5a** and **6a** (30 mg, 87%) were eluted, the chiral auxiliary, (*R*)-piperidin-3-ol (19 mg, 82%), was eluted with MeOH. A mixture of **5a** and **6a**: $[\alpha]^{20}_D$ +190° (*c* 0.18, benzene, lit.[2a] **5a**; $[\alpha]^{23}_D$ +244°).

A mixture of **5b** and **6b**; $[\alpha]^{20}_D$+215° (*c* 0.18, benzene, lit.[2a] **5b**; $[\alpha]^{23}_D$ +239°).

A mixture of **5c** and **6c**; $[\alpha]^{20}_D$ +100° (*c* 0.022, benzene, lit.[2a] **5c**; $[\alpha]^{23}_D$ +179°).

A mixture of **5d** and **6d**; $[\alpha]^{20}_D$ +272° (*c* 0.50, benzene, lit.[2a] **5d**; $[\alpha]^{23}_D$ +310°).

Determination of Chirality at the Benzylic Position, Diastereomeric Excess, and the Reaction Yield. By comparing the [α] value of the mixture of **5** and **6** with the known [α] value, the major component between **3** and **4** was determined. Since [α] value of the mixture of **5a** and **6a** was +190°, and that of (*S*)-2-hydroxy-2-phenylpropanal was +244°,[2a] carbinol **3a** having *S* chirality at the benzylic position was predominant, resulting from *re* face attack. The ratio of the peak intensities at 4.81 and 4.77 ppm (H-7) was 93:7. Therefore, the diastereoselectivity was 93:7 in favor of **3a**. The diastereoselectivity was also confirmed by a chiral GC with methyl 2-hydroxy-2-phenylpropanoate (methyl atrolactate),[2a] derived from a mixture of **5a** and **6a**. The same calculations were done for other reactions.

7-(2,2-Dimethyl-1-oxo)propyl-6-oxa-1-azabicyclo[3.2.1]-octane (7). The condensation adduct was subjected to a short columm on alumina to give a yellow oil (58.3%); ^{1}H NMR δ 1.17 (s, 9H), 1.41−1.55 (m, 2H), 1.77−1.97 (m, 2H), 2.73−2.98 (m, 4H), 4.33−4.37 (m, 1H), 5.30 (s, 1H); ^{13}C NMR δ 17.7, 24.3, 27.7, 40.6, 51.3, 54.3, 70.5, 89.9, 207.7. HRMS-EI (*m*/*z*): M^+ calcd for $C_{11}H_{19}NO_2$, 197.1416; found, 197.1415.

Methyl 2-*tert*-Butyldimethylsilyloxy-2,3,3-trimethyl-butanoate (8). 2-Hydroxy-2,3,3-trimethylbutanal (93.8 mg, 0.72 mmol, 79%) was prepared from **7** (180 mg. 0.91 mmol) by organometallic reaction and hydrolysis; ^{1}H NMR δ 0.94 (s, 9H), 1.20 (s, 3H), 9.71 (s, 1H). To a solution of the aldehyde and 2-methyl-2-butene (2.5 mL) in acetone (8 mL) was added a freshly prepared solution (8 mL) of KH_2PO_4 (910 mg) and $NaClO_2$ (810 mg) in H_2O (15 mL) dropwise. The mixture was stirred at room temperature for 45 min and then concentrated to remove acetone. To this residue was added 5% aqueous Na_2-CO_3. The basic water layer was extracted with ethyl ether (15 mL × 3) and then acidified with 5% HCl until pH 1. The water layer was saturated with brine and extracted with ethyl ether (15 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give an oil (90 mg, 0.62 mmol, 86%) which was identified by ^{1}H NMR as 2-hydroxy-2,3,3-trimethylbutanoic acid; ^{1}H NMR δ 1.00 (s, 9H), 1.40 (s, 3H).

To a solution of the α-hydroxy acid in THF (5 mL) and methanol (2 mL) was added dropwise 2.0 M trimethylsilyldiazomethane (1.54 mL, 3.08 mmol) in hexane at room temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo. The residue oil was dissolved in DMF (2 mL), and imidazole (147 mg, 2.15 mmol) and TBDMSCl (139 mg, 0.92 mmol) were added at room temperature. The mixture was stirred overnight and then poured into water (20 mL). The aqueous solution was extracted with ethyl ether (20 mL × 2). The combined organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (methylene chloride) to give an oil (136 mg, 80.5%): ^{1}H NMR δ 0.00 (s, 6H), 0.82 (s, 9H), 0.87 (s, 9H), 1.27 (s, 3H); ^{13}C NMR δ −6.97, 15.5, 18.1, 22.9, 23.2, 35.0, 49.8, 76.9, 175.0. HRMS-CI (*m*/*z*): MH^+ calcd for $C_{14}H_{30}O_3Si$, 275.2043; found, 275.2046.

Determination of Diastereomeric Excess Using *tert*-Butylglyoxal. The de could be determined by measuring ee of **8** using a chiral GC. The enantiomeric ratio was 94:6 with MeMgBr, while the ratio was 19:81 with MeLi.

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Supporting Information Available: ^{1}H NMR spectra for compound **2**, **7**, **8**, mixtures of **3a**−**e** and **4a**−**e**, and ^{13}C NMR spectra for compound **2**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Addition of Grignard reagents to the oxazolidine having the methoxycarbonylmethyl moiety in the equatorial position at C-2 proceeded in much lower diastereoselection (Reddy, P. N.; Han. S.-S.; Chung, K.-H. *Bull. Korean Chem. Soc.* **1998**, *19*, 617−618), presumably because the side chain is involved in the chelation to some extent (Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484−489).