An Asymmetric Synthesis of Alcohols Using Chiral 2-Piperidineethanols

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Optically active tertiary alcohols bearing a carbonyl function at the α-position were synthesized enantioselectively by using chiral 1,3-oxathianes, 1,3-oxazines or 1,3-oxazolidines.[1,2,3] The tertiary alcohols were generally prepared by the reaction of 2-acyl derivatives with organometallics. Among the heterocycles, 2-acyl-1,3-oxathianes have been extensively studied to examine the diastereoselection.[1,2]

In the reaction of 2-acyl-1,3-oxathianes or perhydro-2-acyl-1,3-oxazines with organometallics, the stereoselectivities support the assumption that chelation of an organometallic reagent between the carbonyl oxygen and the ether oxygen of the ring is necessary for a high degree of asymmetric induction. However, some results were different among 1,3-oxathianes, 1,3-oxazines, and 1,3-oxazolidines depending on the nature of organometallics, reducing agents, and the presence of Lewis acids.[1,2,3]

Recently we and other group have synthesized chiral 2-piperidineacetates, which were readily converted to chiral 2-piperidineethanols.[4,5] The 2-piperidineethanols may be utilized as chiral auxiliaries to prepare optically active compounds, since chiral amino alcohols or amino thiols have been used in many asymmetric reactions.[6] In this paper, we describe the diastereoselectivity in the reaction of chiral perhydro-2-acyl-1,3-oxazines, derived from 2-piperidineethanols, with organometallics or reducing agents.

Results and Discussion

Methyl (2*S*,5*S*)-2-[5-(*t*-butyldimethylsilyloxy)piperidin-2-yl] ethanoate or methyl (2*R*,5*S*)-2-[5-(*t*-butyldimethylsilyloxy) piperidin-2-yl]ethanoate, prepared from L-glutamate,[4,5] was reacted with $LiAlH_4$ to give (2*S*,5*S*)-2-[5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]ethan-1-ol (**1**) or (2*R*,5*S*)-2-[5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]ethan-1-ol (**2**) respectively. The condensation of phenylglyoxal monohydrate and *cis*-piperidineethanol **1** in the presence of 4Å molecular sieves gave almost one isomer of perhydro-2-benzoyl-1,3-oxazines which showed a peak at 4.86 ppm for H_{2a} in ^1H NMR spectrum. The purification of the crude mixture was attempted by column chromatography, but resulted in partial decomposition. Oxazine **3** was the major isomer, although the formation of other isomer **4a** or **4b** was not excluded.[7] By the same condensation, 1,3-oxazine **5** was obtained almost exclusively from *trans*-piperidineethanol **2** (Scheme 1).

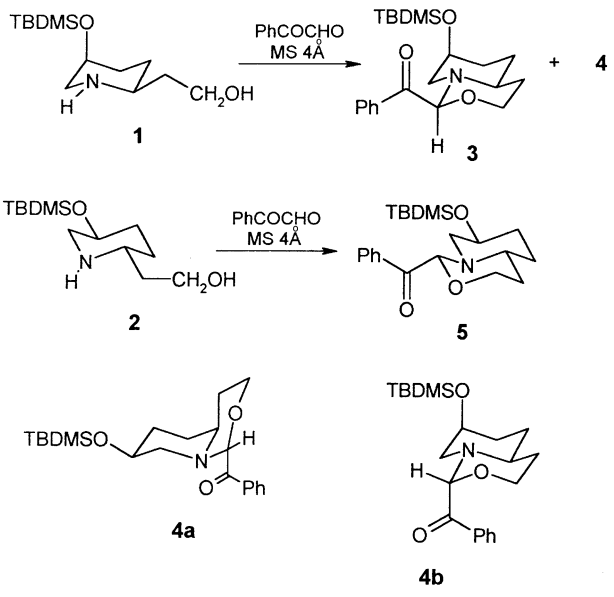
As shown in Table 1, the reaction of chiral ketooxazine **3** with Grignard reagents, organolithium reagents or reducing reagents at -78 °C gave the corresponding carbinols **6** in high diastereomeric excess. Since the alcohols were too labile to be purified by chromatography, the reaction yields and diastereomeric excess were determined by ^1H NMR spectrum of the methine protons at C_2. The chirality of the alcohol was determined by the comparison with the reported specific rotation of the corresponding α-hydroxy aldehyde which was prepared from hydroxy oxazine **6**.[3]

Unlikely with 2-acyl-1,3-oxazolidine,[3] MeMgBr or MeLi reacted with 2-acyloxazine **3** in the same stereoselection (entries 1 and 4).[1c] The cerium reagent prepared from MeMgBr and $CeCl_3$ in situ did not affect the diastereoselectivity (entry 3).[3,8] Organometallics other than MeMgBr or MeLi also proceeded in the same stereoselection, however, the diasteromeric excess decreased as the bulkiness of the reagent increases, and *t*-BuMgCl did not provide the desired product (entries 8, 11, and 12).

In the reduction of 2-acyloxazine **3**, DIBAL and $NaBH_4$ gave the same major diastereomer as those of the reactions with other organometallics (entries 13 and 14). The diastereoselectivity was the same as that of other 1,3-oxazine,[1c] but opposite to that of 1,3-oxathiane.[1b]

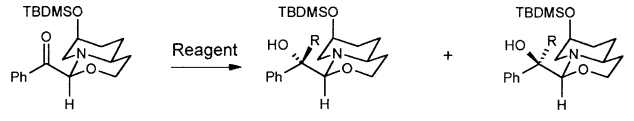
As shown in Table **2**, the reaction of oxazine **5** also proceeded with high diasteromeric excess as that of oxazine **3**. The reaction with MeMgBr, MeLi or DIBAL afforded the same stereochemistry of the major diastereomer.

In the reactions of 2-acyl-1,3-oxathianes with Grignard reagents, the facial selectivity was explained by the fact that the hard magnesium ion chelates between the carbonyl oxy-



Scheme 1

Table 1. Reaction of (2*S*,6*S*,9*S*)-2-benzoyl-9-*t*-butyldimethylsilyloxy-3-oxa-1-azabicyclo[4.4.0]decane (**3**)[a]

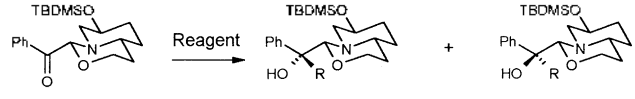


3 **6a** **6b**

Entry	Reagent	Solvent	**6a** : **6b**[b]
1	MeMgBr	Et_2O	95 : 5
2	MeMgBr	THF	95 : 5
3	MeMgBr-$CeCl_3$	THF	95 : 5
4	MeLi	Et_2O	95 : 5
5	EtMgBr	Et_2O	95 : 5
6	vinylMgBr	Et_2O	95 : 5
7	propylMgCl	Et_2O	95 : 5
8	*i*-propylMgBr	Et_2O	70 : 30
9	*n*-BuMgCl	Et_2O	95 : 5
10	*n*-BuLi	Et_2O	95 : 5
11	*t*-BuMgCl	Et_2O	-
12	*c*-pentylMgCl	Et_2O	53 : 47
13	DIBAL-H	Et_2O	95 : 5
14	$NaBH_4$	Et_2O	95 : 5

[a] The molar ratio of the reagent to compound **3** was 3, and generally the yields of the reactions were over 80%. [b] The ratio was determined by ^1H NMR spectrum of the methine proton at C_2.

Table 2. Reaction of (2*R*,6*R*,9*S*)-2-benzoyl-9-*t*-butyldimethylsilyloxy-3-oxa-1-azabicyclo[4.4.0]decane (**5**)[a]

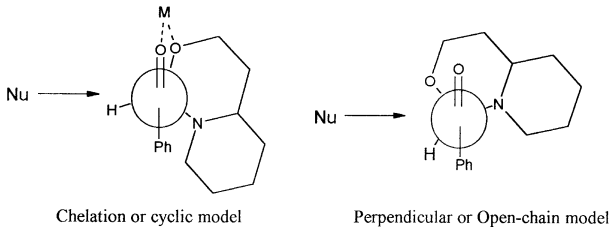


5 **7a** **7b**

Entry	Reagent	Solvent	**7a** : **7b**[b]
1	MeMgBr	Et_2O	95 : 5
2	MeLi	THF	95 : 5
3	EtMgBr	THF	95 : 5
4	DIBAL-H	Et_2O	95 : 5

[a] The molar ratio of the reagent to compound **5** was 3, and generally the yields of the reactions were over 80%. [b] The ratio was determined by ^1H NMR spectrum of the methine proton at C_2.

gen and the hard oxygen atom in preference to the soft sulfur.[1,2,7] But the preference of the oxygen to the nitrogen may not be rationalized on the basis of hardness, in case of 2-acyl-1,3-oxazines.[9a] Since the lone pair electron of the nitrogen of the tertiary amine is not quite aligned with the carbonyl oxygen, the nitrogen shoud not be effectively chelated with the metal ion. On the other hand, the chelation between the oxygen and the carbonyl oxygen is assumed to be effective, since the ether oxygen has two pairs of non-bonded electrons. In addition to these argument, the chelation of the nitrogen atom results in steric hindrance by the TBDMSO group in oxazine **3** or by other hydrogens in oxazine **5**. As a result, (*S*)-carbinol **6a** or (*R*)-carbinol **7a** was obtained from (2*S*)-2-acyloxazine **3**, or (2*R*)-2-acyloxazine **5**, respectively as a major product.



Chelation or cyclic model Perpendicular or Open-chain model

Figure 1. Chelation and Perpendicular model.

The DIBAL reduction does not proceed in accordance with chelation model. Although dipolar model was suggested in the reaction of 2-acyl-1,3-oxathiane,[1b] perpendicular or open-chain model may be operated in the case of 2-acyl-1,3-oxazine.[9] As shown in Figure 1, the tertiary amine in the ring is the largest group, and the hydride attacks the carbonyl opposite to the ring nitrogen, resulting in the same major diastereomer as Grignard reagents.

In conclusion, addition of organometallics to perhydro-2-benzoyl-1,3-oxazines proceeded with highly diastereoselective fashion to give virtually a single diastereomer. The ring oxygen atom chelates much more effectively than the ring nitrogen atom with Grignard reagents as well as organolithium reagents on the basis of cyclic (chelation) model. The reduction of the ketooxazines with DIBAL or $NaBH_4$ also gave the same stereoisomer, and may follow perpendicular (Felkin's) model, although the transition state of the reduction was not quite understood. Optically pure *cis* or *trans*-2-[5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]ethan-1-ol can be utilized as a chiral auxiliary in the preparation of chiral compounds of type RR′C(OH)X (where X=CHO, CO_2H, CH_2OH).[1,3]

Experimental Section

All chemicals were reagent grade (Aldrich Chemicl Co.) and were used as purchased without further purification. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (200 MHz) spectrometer in $CDCl_3$.

(2*S*,5*S*)-2-[5-(*t*-butyldimethylsilyloxy)piperidin-2-yl] ethan-1-ol (1). $LiAlH_4$ (0.088 g, 2.09 mmol) was added portionwise to a solution of methyl (2*S*,5*S*)-2-[5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]ethanoate (0.500 g, 1.74 mmol) in dry THF (15 mL) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was quenched with saturated NH_4Cl (5 mL) and made the alkaline with 10% aqueous K_2CO_3 (30 mL) and extracted with EtOAc (20 mL) three times. The combined organic layer was washed with brine, dried over $MgSO_4$, concentrated to give a yellow oil (0.443 g, 98%). $[\alpha]_D^{25}$ -6.5° (c=1, $CHCl_3$); ^1H NMR δ 0.01 (s, 6H, Si-CH_3), 0.85 (s, 9H, *t*Bu), 1.30-1.78 (m, 6H, H_3, H_4, H_α), 2.63-2.83 (m, 3H, H_{2e}, H_6), 3.70-3.81 (m, 3H, H_5, CH_2O); ^{13}C NMR δ -5.10, 17.8, 25.5, 27.2, 31.2, 37.2, 51.9, 57.3, 62.2, 64.4.

(2*R*,5*S*)-2-[5-(*t*-butyldimethylsilyloxy)piperidin-2-yl] ethan-1-ol (2). According to the procedure described for the synthesis of **1**, compound **2** was prepared in 95% yield

using methyl (2*R*,5*S*)-2-[5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]ethanoate . $[\alpha]_D^{25}$ -5.2° (c=1, $CHCl_3$); ^1H NMR δ 0.05 (s, 6H, Si-CH_3), 0.88 (s, 9H, *t*Bu), 1.23-1.93 (m, 6H, H_3, H_4, H_α), 2.37-2.48 (m, 1H, H_{6a}), 2.69 (m, 1H, H_{2a}), 2.97-3.05 (m, 1H, H_{6e}), 3.47-3.57 (m, 1H, H_{5a}), 3.75-3.81 (m, 2 H, CH_2O); ^{13}C NMR δ -4.80, 18.0, 25.7, 51.6, 34.0, 37.1, 53.3, 55.9, 61.6, 68.9.

(2*S*,6*S*,9*S*)-2-benzoyl-9-*t*-butyldimethylsilyloxy-3-oxa-1-azabicyclo[4.4.0]decane (3). A mixture of compound **1** (0.140 g, 0.539 mmol), phenylglyoxal monohydrate (0.076 g, 0.566 mmol) and molecular seive 4 Å in dry CH_2Cl_2 (10 mL) was refluxed overnight. After cooled, the reaction mixture was washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to short filtration through silica gel (15% EtOAc/*n*-hexane) to give ketooxazine **3** (0.172 g, 85%) as a yellow oil. ^1H NMR δ -0.25 (s, 3H, Si-CH_3), -0.15 (s, 3H, Si-CH_3), 0.74 (s, 9H, *t*Bu), 1.20-1.80 (m, 5H, H_{5a}, H_7, H_8), 2.08-2.32 (m, 2H, H_{5e}, H_{10a}), 2.50-2.70 (m, 1H, H_{10e}), 2.75-2.90 (m, 1H, H_{6a}), 3.54-3.68 (m, 1H, H_{9e}), 3.67-3.87 (m, 1H, H_{4a}), 4.20-4.34 (m, 1H, H_{4e}), 4.86 (s, 1H, H_{2a}), 7.37-7.57 (m, 3H, aromatic), 8.30 (d, J = 8.0Hz, 2H, aromatic); ^{13}C NMR δ -4.74, -4.66, 18.4, 26.1, 27.1, 28.1, 30.5, 51.3, 57.7, 67.8, 68.5, 96.5, 128.5, 130.3, 133.7, 134.7, 195.5.

(2*R*,6*R*,9*S*)-2-benzoyl-9-*t*-butyldimethylsilyloxy-3-oxa-1-azabicyclo[4.4.0]decane (5). The preparation of **5** (86%) using **2** was analogous to that of **3**. ^1H NMR δ -0.20 (s, 3H, Si-CH_3), -0.17 (s, 3H, Si-CH_3), 0.73 (s, 9H, *t*Bu), 1.24-1.97 (m, 7H, H_5, H_7, H_8, H_{10a}), 2.19 (m, 1H, H_{6a}), 2.22-2.55 (m, 1H, H_{10e}), 3.52-3.74 (m, 2H, H_{4a}, H_{9a}), 4.19-4.29 (m, 1H, H_{4e}), 4.90 (s, 1H, H_{2a}), 7.35-7.60 (m, 3H, aromatic) 8.36 (d, J = 8.0 Hz, 2H, aromatic); ^{13}C NMR δ -5.32, -5.29, 17.9, 25.6, 30.7, 31.6, 33.5, 55.4, 59.2, 67.8, 67.9, 97.7, 128.1, 130.1, 133.4, 134.1, 195.2.

General procedure for the Grignard reaction using MeMgBr. To the solution of ketone **3** (0.015 g, 0.4 mmol) in dry ether (10 mL) at -78 °C under N_2 was added dropwise 3.0 M methylmagnesium bromide in ether (0.4 mL, 1.20 mmol). After stirring for 1 h, the reaction was quenched with saturated NH_4Cl solution at -78 °C and allowed to warm to room temperature, and then EtOAc (20 mL) and brine (10 mL) were added. The organic layer was separated and the aqueous layer was further extracted with EtOAc (20 mL) twice. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give a mixture of oily carbinols (0.141 g, 95%). Crude **6a** (R = CH_3); ^1H NMR δ -0.08 (s, 3H, Si-CH_3), -0.03 (s, 3H, Si-CH_3), 0.87 (s, 9H, *t*Bu), 1.32-2.28 (m, 6H, H_5, H_7, H_8), 1.45 (s, 3H, CH_3), 2.32-2.56 (m, 2H, H_{10}), 2.77-2.89 (m, 1H, H_{6a}), 3.20-3.40 (m, 1H, H_{9e}), 3.75~3.83 (m, 1H, H_{4a}), 4.23-4.27 (m, 1H, H_{4e}), 4.33 (s, 1H, H_{2a}), 7.17-7.55 (m, 5H, aromatic); ^{13}C NMR δ -4.6, -4.4, 18.5, 26.0, 26.3, 28.6, 30.3, 31.7, 50.5, 57.2, 68.3, 68.4, 75.2, 96.3, 125.2, 126.4, 128.1, 147.3 .

Crude 7a. (R = CH_3); ^1H NMR δ -0.13 (s, 3H, Si-CH_3), 0.04 (s, 3H, Si-CH_3), 0.76 (s, 9H, *t*Bu), 1.12-1.89 (m, 7H, H_5, H_7, H_8, H_{10a}), 1.35 (s, 3H, CH_3), 2.21-2.37 (m, 1H, H_{6a}), 2.61-2.76 (m, 1H, H_{10e}), 3.46-3.68 (m, 2H, H_{4a} H_{9a}), 4.08-4.23 (m, 1H, H_{4e}), 4.09 (s, 1H, H_{2a}), 7.13-7.58 (m, 5H, aromatic); ^{13}C NMR δ -4.5, 18.4, 26.3, 30.5, 31.6, 31.8, 33.9, 57.6, 60.4, 67.2, 68.5, 75.4, 96.7, 124.5, 126.5, 128.7, 149.5.

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