HETEROCYCLES, Vol. , No. , , pp. -,

Received, , Accepted, , Published online, (Please do not delete.)

DIRHODIUM(II) TETRAKIS[*N*-BENZENE-FUSED PHTHALOYL-(*S*)-PIPERIDINONATE] AS A CHIRAL LEWIS ACID: CATALYTIC ENANTIOSELECTIVE ALDOL REACTIONS OF ACETATE-DERIVED SILYLKETENE ACETALS AND ALDEHYDES†

Takuya Washio, Seiichi Nakamura, Masahiro Anada, and Shunichi Hashimoto*

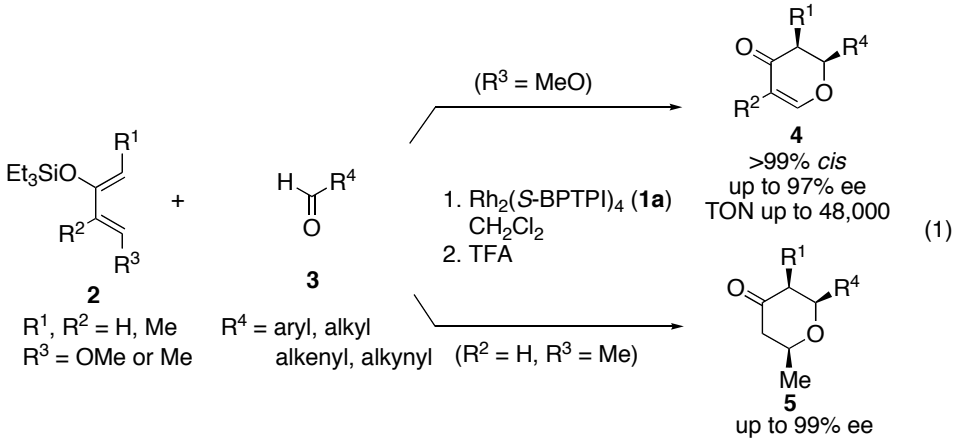
Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan
e-mail: hsmt@pharm.hokudai.ac.jp

Abstract – A first example of chiral dirhodium(II) complex-catalyzed enantioselective Mukaiyama aldol reactions is described. The aldol addition reaction of methyl acetate-derived trimethylsilylketene acetal with specific aldehydes such as benzyloxyacetaldehyde and electron-poor aromatic aldehydes is effectively catalyzed by dirhodium(II) tetrakis[*N*-benzene-fused phthaloyl-(*S*)-piperidinonate] (**1a**), providing silylated aldol adducts in up to 94% ee.

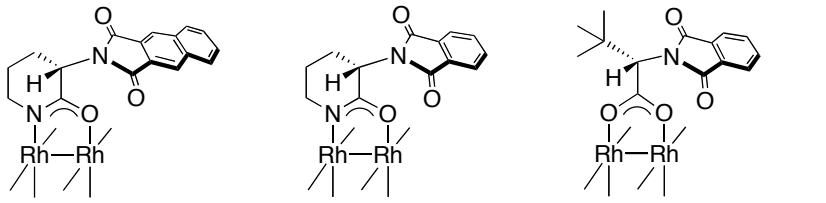
The Lewis acid-catalyzed addition of silyl enol ethers and silylketene acetals to carbonyl compounds, popularly known as the Mukaiyama aldol reaction, is one of the most powerful methods available for achieving carbon-carbon bond formation.[1] Over the past fifteen years, remarkable progress has been achieved in the development of enantioselective variants through catalysis by chiral Lewis acid complexes derived from Sn(II), Ti(IV), B, Al, Cu(II), Ag(I), and Zr(IV) with excellent levels of enantioselection.[2–10] Aside from their effectiveness in diazo decomposition,[11] dirhodium(II) complexes are now becoming recognized as a new class of chiral Lewis acid catalysts. Doyle and co-workers demonstrated that chiral dirhodium(II) carboxamidates function as effective catalysts for enantioselective hetero-Diels–Alder (HDA) reactions and [2+2] cycloaddition reactions of trimethylsilylketene with ethyl glyoxylate.[12,13] We also have disclosed that Rh_2(*S*-BPTPI)$_4$ (**1a**), a dirhodium(II) carboxamidate complex

† Dedicated to the memory of the late Dr. Kenji Koga, Professor Emeritus of the University of Tokyo.

that incorporates (*S*)-3-benzene-fused phthalimido-2-piperidinonate as chiral bridging ligands, is a highly efficient Lewis acid catalyst for *endo*- and enantioselective HDA reactions of a diverse range of aldehydes with Danishefsky-type dienes as well as with monooxygenated dienes, in which up to 99% ee and turnover numbers as high as 48,000 are achieved [eqn. (1)].[14] In an effort to extend the applicability of Rh_2(*S*-BPTPI)$_4$ in Lewis acid catalyzed reactions, we investigated the enantioselective Mukaiyama aldol reaction of acetate-derived silylketene acetals and aldehydes.



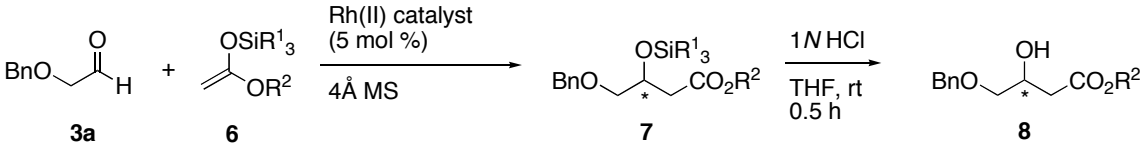
(1)



Rh_2(*S*-BPTPI)$_4$ (**1a**) Rh_2(*S*-PTPI)$_4$ (**1b**) Rh_2(*S*-PTTL)$_4$ (**1c**)

At the outset, we explored the aldol reaction of benzyloxyacetaldehyde (**3a**) and *O*-methyl *O*-trimethylsilylketene acetal (**6a**)[15] derived from methyl acetate in the presence of 5 mol % of Rh_2(*S*-BPTPI)$_4$ and pulverized 4Å molecular sieves (MS) at 0 °C. After focusing mostly on solvent effects, toluene was found to be the optimal solvent for use in this reaction, giving silylated aldol adduct (**7a**) in 75% yield with 79% ee (Table 1, Entry 1).[16] The enantioselectivity of this reaction was determined by HPLC analysis of the free aldol adduct (**8a**)[17] derived from **7a** (1*N* hydrochloric acid in THF). The preferred absolute stereochemistry of **8a** was established as *S* by its conversion to the known 3-hydroxy-γ-butyrolactone (**9**) [$[\alpha]_D^{26}$ –64.2° (*c* 1.11, EtOH), lit.,[18] $[\alpha]_D^{9}$ –85.9° (*c* 2.2, EtOH) for the (*S*)-enantiomer]. The use of ether and ethyl acetate resulted in essentially the same rate and yield as those found for toluene (6 h, 77%), but caused a marked decrease in enantioselectivity (68% ee and 52% ee, Entries 2 and 3). Somewhat surprisingly, the reaction in dichloromethane proceeded reluctantly to give (*S*)-**7a** in only modest yield and enantioselectivity (45% yield, 59% ee, Entry 4). Using toluene as the solvent, we next evaluated the abilities of other chiral dirhodium(II) complexes, Rh_2(*S*-PTPI)$_4$ (**1b**)[14,19]

Table 1. The Enantioselective Mukaiyama Aldol Reaction of Benzyloxyacetaldehyde (**3a**) and Silylketene Acetals (**6a-d**) Catalyzed by Chiral Dirhodium(II) Complexes[a)]



3a **6** **7** **8**

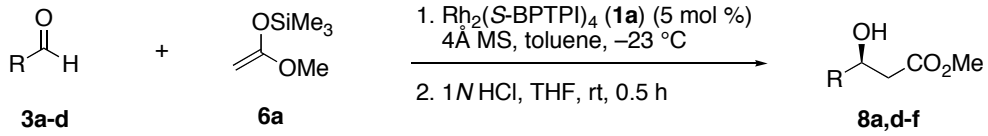
		Silylketene acetal						Aldol adduct		β-Hydroxy Ester		
Entry	Rh(II) catalyst		R^1	R^2	Solvent	Temp. (°C)	Time (h)		Yield (%)[b)]		Ee (%)[c)]	Config[d)]
1	Rh_2(*S*-BPTPI)$_4$ (**1a**)	**6a**	Me	Me	toluene	0	6	**7a**	75	**8a**	79	*S*
2	Rh_2(*S*-BPTPI)$_4$ (**1a**)	**6a**	Me	Me	Et_2O	0	6	**7a**	77	**8a**	68	*S*
3	Rh_2(*S*-BPTPI)$_4$ (**1a**)	**6a**	Me	Me	EtOAc	0	6	**7a**	77	**8a**	52	*S*
4	Rh_2(*S*-BPTPI)$_4$ (**1a**)	**6a**	Me	Me	CH_2Cl_2	0	24	**7a**	45	**8a**	59	*S*
5	Rh_2(*S*-PTPI)$_4$ (**1b**)	**6a**	Me	Me	toluene	0	6	**7a**	71	**8a**	71	*S*
6	Rh_2(*S*-PTTL)$_4$ (**1c**)	**6a**	Me	Me	toluene	0	6	**7a**	63	**8a**	18	*R*
7	Rh_2(*S*-BPTPI)$_4$ (**1a**)	**6a**	Me	Me	toluene	–23	12	**7a**	81	**8a**	86	*S*
8	Rh_2(*S*-BPTPI)$_4$ (**1a**)	**6b**	Et	Me	toluene	–23	24	**7b**	79	**8a**	68	*S*
9	Rh_2(*S*-BPTPI)$_4$ (**1a**)	**6c**	Me	Et	toluene	–23	12	**7c**	82	**8b**	66[e)]	*S*
10	Rh_2(*S*-BPTPI)$_4$ (**1a**)	**6d**	Me	^{i}Pr	toluene	–23	12	**7d**	79	**8c**	35[e)]	*S*

[a)] All reactions were performed on a 0.3 mmol scale (0.2 M) using 3 equiv. of silylketene acetal. [b)] Isolated yield.
[c)] Determined by HPLC (Daicel Chiralpak IA column followed by Daicel Chiralpak AS-H column) unless otherwise stated. [d)] See text.
[e)] Determined by HPLC (Daicel Chiralpak AD-H column).

and Rh_2(*S*-PTTL)$_4$ (**1c**),[20] derived from *N*-phthaloyl-(*S*)-piperidinone and *N*-phthaloyl-(*S*)-*tert*-leucine, respectively. Catalysis by Rh_2(*S*-PTPI)$_4$ gave (*S*)-**7a** in 71% ee (Entry 5), whereas Rh_2(*S*-PTTL)$_4$ brought about a reversal of enantioselection, giving (*R*)-**7a** in 18% ee (Entry 6). Thus we were gratified to find that the enantioselectivity was further enhanced up to 86% ee using toluene and Rh_2(*S*-BPTPI)$_4$ and a lower temperature (–23 °C) without compromising the product yield (Entry 7).[21] We also examined the steric effect of acetate-derived silylketene acetals on enantioselectivity. The use of triethylsilyl ketene acetal (**6b**) resulted in a lower enantioselectivity (68% ee, Entry 8). Varying the alkoxy substituent was also detrimental in this reaction as trimethylsilyl ketene acetals (**6c**,**d**) derived from ethyl and isopropyl acetates diminished the enantioselectivity (66% ee and 35% ee, Entries 9 and 10). These results clearly indicate that the use of the less sterically demanding silylketene acetal (**6a**) is crucial for a high level of enantioselectivity in this reaction.

With optimized conditions in hand, we then turned our attention to applying the present protocol to aldehydes other than **3a**. Some representative results are presented in Table 2. The use of electron-poor aromatic aldehydes including 4-nitrobenzaldehyde (**3b**), 2,4-dinitrobenzaldehyde (**3c**), and pentafluorobenzaldehyde (**3d**) afforded the corresponding aldol adducts (**8d**-**f**) in higher yields and enantioselectivities than those found with benzyloxyacetaldehyde (**3a**), although these reactions required much longer reaction times to reach completion (Entries 1 vs. 2-4). The highest enantioselectivity (94% ee) was achieved in the case of 4-nitrobenzaldehyde (**3b**) (Entry 2). The sense of asymmetric induction

Table 2. The Enantioselective Mukaiyama Aldol Reaction of Aldehydes (**3a-d**) and **6a** Catalyzed by Rh_2(*S*-BPTPI)$_4$[a)]



3a-d **6a** **8a,d-f**

Entry	Aldehyde		Aldol reaction	β-Hydroxy Ester			
		R	Time (h)		Yield (%)[b)]	Ee (%)	Confign
1	**3a**	$BnOCH_2$	12	**8a**	79	86[c)]	*S*
2	**3b**	4-$NO_2C_6H_4$	36	**8d**	91	94[d)]	*S*[e)]
3	**3c**	2,4-$(NO_2)_2C_6H_3$	24	**8e**	87	92[f)]	*S*[g)]
4	**3d**	C_6F_5	48	**8f**	90	88[h)]	*S*[g)]

[a)] All reactions were performed on a 0.3 mmol scale (0.2 M) using 3 equiv. of silylketene acetal. [b)] Isolated yield. [c)] Determined by HPLC (Daicel Chiralpak IA column followed by Daicel Chiralpak AS-H column). [d)] Determined by HPLC (Daicel Chiralpak AS column). [e)] Determined by its conversion to the known (*S*)-3-hydroxy-3-(4-nitrophenyl)propanoic acid. See ref 22. [f)] Determned by HPLC (Daicel Chiralpak AD-H column). [g)] Assigned by analogy. [h)] Determned by HPLC (Daicel Chiralcel OD-H column).

(nucleophlic attack from the aldehyde *si* enantioface) is consistent with the proposed model for the Rh_2(*S*-BPTPI)$_4$-catalyzed enantioselective HDA reaction,[14] which contains a hydrogen bond between the formyl hydrogen atom and the carboxamidate oxygen atom[23] in rhodium catalyst-aldehyde complexes (Figure 1). However, the present method was found to be highly sensitive to the nature of the aldehyde component, and the use of most aldehydes such as benzaldehyde, 4-methoxybenzaldehyde, cinnamaldehyde and hydrocinnamaldehyde resulted in the production of racemic aldol adducts. Thus the scope of the present Rh_2(*S*-BPTPI)$_4$ catalytic process is limited to benzyloxyacetaldehyde and aromatic aldehydes bearing strong electron-withdrawing groups.

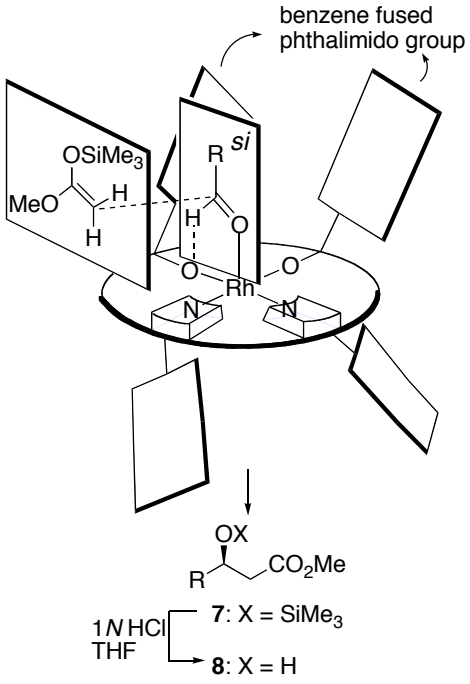


Figure 1. Plausible Stereochemical Pathway

In summary, we document the first example of enantioselective Mukaiyama aldol reactions catalyzed by a chiral dirhodium(II) complex. High levels of enantioselectivity up to 94% ee have been achieved, when Rh_2(*S*-BPTPI)$_4$ is used as a chiral Lewis acid catalyst, albeit with a limited range of silylketene acetals and aldehydes. Further studies are currently in progress to extend the utility of dirhodium(II) carboxamidate complexes as chiral catalysts for a range of Lewis acid catalyzed reactions.

EXPERIMENTAL

General. Melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300 spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). ^1H NMR spectra were recorded on JEOL JNM-EX 270 (270 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane; δ_H 0.00, $CDCl_3$; δ_H 7.26 or CD_3OD; δ_H 3.30). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet, br = broad), coupling constant and integration. ^{13}C NMR spectra were recorded on JEOL JNM-AL 400 (100 MHz) spectrometer. The following internal references were used: $CDCl_3$ (δ 77.0). Optical rotations were measured on a JASCO P-1030 digital polarimeter at the sodium D line (589 nm). EI-MS spectra were obtained on a JEOL JMS-FABmate spectrometer, operating with ionization energy of 70 eV. FAB-MS spectra were obtained on a JEOL JMS-HX 110 spectrometer. Column chromatography was carried out on Merck Kieselgel 60 (70–230 mesh) or Kanto silica gel 60 N (63–210 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualization by ultraviolet, anisaldehyde stain solution or phosphomolybdic acid stain solution. Analytical high performance liquid chromatography (HPLC) was performed on a JASCO PU-1580 intelligent HPLC pump with JASCO UV-1575 intelligent UV/VIS detector. Detection was performed at 254 nm. Chiralcel OD-H, Chiralpak IA, AS, AS-H and AD-H columns (0.46 cm × 25 cm) from Daicel were used. Retention times (t_R) and peak ratios were determined with Shimadzu C-R8A chromatopac integrator.

All non-aqueous reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Reagents and solvents were purified by standard means. *O*-Methyl-*O*-trimethylsilylketene acetal (**5a**) was prepared from methyl acetate according to the procedure of Shibasaki.[15] 4Å MS was used after pulverized and dried (150 °C, 1 mmHg, 12 h).

Typical procedure for the Mukaiyama aldol reaction (Table 1, Entry 7): Methyl (*S*)-4-benzyloxy-3-trimethylsilyloxybutyrate (7a). To an oven-dried flask equipped with a rubber septum and a Teflon-coated magnetic stirring bar were added pulverized 4Å MS (50 mg), **1a** (22 mg, 0.015 mmol, 5 mol %), **3a** (45 mg, 0.30 mmol) and toluene (1.2 mL). The resulting suspension was cooled to –23 °C under an argon atmosphere. After stirring for 10 min, a solution of **6a** (132 mg, 0.90 mmol) in toluene (0.3 mL) was added to the mixture at –23 °C, and the septum was replaced by a greased glass stopper. After 12 h of stirring at this temperature in a closed system, the reaction mixture was then filtered through a plug of Celite with EtOAc (10 mL). Filtration and concentration *in vacuo* followed by column chromatography (silica gel, 19:1 hexane/EtOAc) provided **7a** (72.0 mg, 81%) as a colorless oil; R_f = 0.35 (9:1 hexane/EtOAc); $[\alpha]_D^{24}$ –19.6° (*c* 1.01, $CHCl_3$) for 86% ee; IR (neat) ν: 1738 cm^{-1}; ^1H NMR

(270 MHz, $CDCl_3$) δ 0.10 (s, 9H, Si(CH_3)$_3$), 2.47 (dd, *J* = 7.9, 15.2 Hz, 1H, C2-*H*), 2.60 (dd, *J* = 4.6, 15.2 Hz, 1H, C2-*H*), 3.38 (dd, *J* = 5.9, 9.2 Hz, 1H, C4-*H*), 3.44 (dd, *J* = 5.3, 9.2 Hz, 1H, C4-*H*), 3.66 (s, 3H, CO_2CH_3), 4.31 (m, 1H, C3-*H*), 4.53 (s, 2H, PhCH_2O), 7.27–7.37 (m, 5H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.1 (CH_3), 40.1 (CH_2), 51.4 (CH_3), 68.4 (CH), 73.2 (CH_2), 73.9 (CH_2), 127.4 (CH), 128.2 (CH), 138.0 (C), 171.7 (C=O); HRMS (FAB) calcd for $C_{15}H_{25}O_4Si$ $(M+H)^+$ 297.1522, found 297.1516; Anal. Calcd for $C_{15}H_{24}O_4Si$: C, 60.78; H, 8.16. Found: C, 60.63; H, 8.02.

Methyl (*S*)-4-benzyloxy-3-hydroxybutyrate (8a).[17] A solution of **7a** (72 mg, 0.24 mmol) in THF (2 mL) was added in one portion to 1*N* hydrochloric acid (0.2 mL) at 23 °C. After 0.5 h of stirring at this temperature, the reaction was quenched with saturated $NaHCO_3$ solution (2 mL), and the whole was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (3 mL), and brine (2 × 3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, 3:1 hexane/EtOAc) provided **8a** (53.4 mg, 98%) as a colorless oil; R_f = 0.39 (1:1 hexane/EtOAc); $[\alpha]_D^{25}$ –9.49° (*c* 1.00, $CHCl_3$) for 86% ee; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.56 (d, *J* = 6.6 Hz, 2H, C2-*H*), 2.92 (d, *J* = 4.6 Hz, 1H, O*H*), 3.48 (dd, *J* = 5.9, 9.9 Hz, 1H, C4-*H*), 3.52 (dd, *J* = 4.6, 9.9 Hz, 1H, C4-*H*), 3.70 (s, 3H, CO_2CH_3), 4.25 (m, 1H, C3-*H*), 4.56 (s, 2H, PhCH_2O), 7.29–7.39 (m, 5H, Ar*H*). The enantiomeric excess of **8a** was determined to be 86% by HPLC with a Chiralpak IA followed by AS-H column (9:1 hexane/*i*-PrOH, 1.0 mL/min): t_R (major) = 22.8 min for (*S*)-enantiomer; t_R (minor) = 25.1 min for (*R*)-enantiomer. The absolute configuration of **8a** was determined to be *S* by chemical correlation (*vide infra*).

Determination of absolute configuration of 8a: (*S*)-3-Hydroxy-γ-butyrolactone (9).[18] A solution of (*S*)-**8a** (50 mg, 0.22 mmol, 79% ee) in MeOH (5 mL) was stirred with 10% Pd/C (10 mg) under 1 atm of H_2 at rt for 2 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, EtOAc) to afford (*S*)-**9** (22.2 mg, 99%) as a colorless oil; R_f = 0.32 (EtOAc); $[\alpha]_D^{26}$ –64.2° (*c* 1.11, EtOH) [lit.,[18] $[\alpha]_D^{9}$ –85.9° (*c* 2.2, EtOH) for (*S*)-enantiomer]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.54 (dd, *J* = 2.0, 17.8 Hz, 1H, C2-*H*), 2.76 (dd, *J* = 5.9, 17.8 Hz, 1H, C2-*H*), 2.83 (br, 1H, O*H*), 4.31 (dd, *J* = 1.3, 8.5 Hz, 1H, C4-*H*), 4.42 (dd, *J* = 4.6, 8.5 Hz, 1H, C4-*H*), 4.69 (m, 1H, C3-*H*).

Methyl (*S*)-4-benzyloxy-3-triethylsilyloxybutyrate (7b). The product was prepared following the procedure for the preparation of **7a**, using **3a** (45 mg, 0.30 mmol), silylketene acetal (**6b**) (170 mg, 0.90 mmol) and 4Å MS (50 mg). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **7b** (80.2 mg, 79%) as a colorless oil; R_f = 0.37 (9:1 hexane/EtOAc); $[\alpha]_D^{24}$

–16.7° (*c* 1.01, $CHCl_3$) for 68% ee; IR (neat) ν: 1742 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.59 (q, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$), 0.93 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 2.48 (dd, *J* = 7.9, 15.2 Hz, 1H, C2-*H*), 2.62 (dd, *J* = 4.6, 15.2 Hz, 1H, C2-*H*), 3.38 (dd, *J* = 5.9, 9.2 Hz, 1H, C4-*H*), 3.47 (dd, *J* = 4.6, 9.2 Hz, 1H, C4-*H*), 3.65 (s, 3H, CO_2CH_3), 4.31 (m, 1H, C3-*H*), 4.53 (s, 2H, $PhCH_2O$), 7.27–7.37 (m, 5H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.8 (CH_2), 6.8 (CH_3), 40.3 (CH_2), 51.5 (CH_3), 68.4 (CH), 73.3 (CH_2), 74.0 (CH_2), 127.5 (CH), 128.2 (CH), 138.0 (C), 171.9 (C=O); HRMS (FAB) calcd for $C_{18}H_{31}O_4Si$ $(M+H)^+$ 339.1992, found 339.1994.

Ethyl (*S*)-4-benzyloxy-3-trimethylsilyloxybutyrate (7c). The product was prepared following the procedure for the preparation of **7a**, using **3a** (45 mg, 0.30 mmol), silylketene acetal (**6c**) (144 mg, 0.90 mmol) and 4Å MS (50 mg). The crude product was purified by column chromatography (silica gel, 19:1 hexane/EtOAc) to provide **7c** (76.4 mg, 82%) as a colorless oil; R_f = 0.37 (9:1 hexane/EtOAc); $[\alpha]_D^{24}$ –12.4° (*c* 1.00, $CHCl_3$) for 66% ee; IR (neat) ν: 1738 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.11 (s, 9H, $Si(CH_3)_3$), 1.25 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.44 (dd, *J* = 8.5, 15.2 Hz, 1H, C2-*H*), 2.59 (dd, *J* = 4.6, 15.2 Hz, 1H, C2-*H*), 3.38 (dd, *J* = 5.9, 9.9 Hz, 1H, C4-*H*), 3.45 (dd, *J* = 5.2, 9.9 Hz, 1H, C4-*H*), 4.12 (m, 2H, $CO_2CH_2CH_3$), 4.31 (m, 1H, C3-*H*), 4.53 (s, 2H, $PhCH_2O$), 7.27–7.37 (m, 5H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.2 (CH_3), 14.3 (CH_3), 40.3 (CH_2), 60.3 (CH_2), 68.5 (CH), 73.2 (CH_2), 73.9 (CH_2), 127.5 (CH), 128.2 (CH), 138.0 (C), 171.3 (C=O); HRMS (FAB) calcd for $C_{16}H_{27}O_4Si$ $(M+H)^+$ 311.1679, found 311.1675; Anal. Calcd for $C_{16}H_{26}O_4Si$: C, 61.90; H, 8.44. Found: C, 61.82; H, 8.32.

Ethyl (*S*)-4-benzyloxy-3-hydroxybutyrate (8b).[24] The product was prepared following the procedure for the preparation of **8a** using **7c** (76 mg, 0.24 mmol). The crude product was purified by column chromatography (silica gel, 3:1 hexane/EtOAc) to provide **8b** (56.6 mg, 97%) as a colorless oil; R_f = 0.32 (2:1 hexane/EtOAc); $[\alpha]_D^{24}$ –6.63° (*c* 1.01, $CHCl_3$) for 66% ee [lit.,[24] $[\alpha]_D$ +8.0° (*c* 1.5, $CHCl_3$) for 71% ee of (*R*)-enantiomer]; ^1H NMR (270 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 2.54 (d, *J* = 6.3 Hz, 2H, C2-*H*), 2.97 (d, *J* = 4.3 Hz, 1H, O*H*), 3.50 (dd, *J* = 5.9, 9.6 Hz, 1H, C4-*H*), 3.52 (dd, *J* = 4.3, 9.6 Hz, 1H, C4-*H*), 4.16 (q, *J* = 7.3 Hz, 2H, $CO_2CH_2CH_3$), 4.23 (m, 1H, C3-*H*), 4.56 (s, 2H, $PhCH_2O$), 7.29–7.36 (m, 5H, Ar*H*). The enantiomeric excess of **8b** was determined to be 66% by HPLC with a Chiralpak AD-H column (9:1 hexane/*i*-PrOH, 1.0 mL/min): t_R (major) = 9.1 min for (*S*)-enantiomer; t_R (minor) = 9.7 min for (*R*)-enantiomer.

Isopropyl (*S*)-4-benzyloxy-3-trimethylsilyloxybutyrate (7d). The product was prepared following the procedure for the preparation of **7a**, using **3a** (45 mg, 0.30 mmol), silylketene acetal (**6d**) (157 mg, 0.90 mmol) and 4Å MS (50 mg). The crude product was purified by column chromatography (silica gel, 19:1

hexane/EtOAc) to provide **7d** (76.9 mg, 79%) as a colorless oil; R_f = 0.38 (9:1 hexane/EtOAc); $[\alpha]_D^{24}$ –4.39° (*c* 1.03, $CHCl_3$) for 35% ee; IR (neat) ν: 1732 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.11 (s, 9H, $Si(CH_3)_3$), 1.22 (d, *J* = 5.9 Hz, 6H, $CO_2CH(CH_3)_2$), 2.42 (dd, *J* = 7.9, 15.2 Hz, 1H, C2-*H*), 2.54 (dd, *J* = 4.6, 15.2 Hz, 1H, C2-*H*), 3.38 (dd, *J* = 5.9, 9.8 Hz, 1H, C4-*H*), 3.44 (dd, *J* = 5.2, 9.8 Hz, 1H, C4-*H*), 4.31 (m, 1H, C3-*H*), 4.53 (s, 2H, $PhCH_2O$), 5.00 (sep, 1H, $CO_2CH(CH_3)_2$), 7.29–7.37 (m, 5H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.2 (CH_3), 21.9 (CH_3), 40.5 (CH_2), 67.6 (CH), 68.5 (CH), 73.2 (CH_2), 73.9 (CH_2), 127.5 (CH), 128.2 (CH), 138.0 (C), 170.9 (C=O); HRMS (FAB) calcd for $C_{17}H_{29}O_4Si$ $(M+H)^+$ 325.1835, found 325.1837; Anal. Calcd for $C_{17}H_{28}O_4Si$: C, 62.92; H, 8.70. Found: C, 62.52; H, 8.55.

Isopropyl (*S*)-4-benzyloxy-3-hydroxybutyrate (8c).[25] The product was prepared following the procedure for the preparation of **8a** using **7d** (77 mg, 0.24 mmol). The crude product was purified by column chromatography (silica gel, 3:1 hexane/EtOAc) to provide **8c** (58.7 mg, 98%) as a colorless oil; R_f = 0.38 (2:1 hexane/EtOAc); $[\alpha]_D^{25}$ –3.74° (*c* 1.00, $CHCl_3$) for 35% ee [lit.,[25] $[\alpha]_D^{22}$ +9.5° (*c* 10, $CHCl_3$) for 95% ee of (*R*)-enantiomer]; ^1H NMR (270 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.3 Hz, 6H, $CO_2CH(CH_3)_2$), 2.52 (d, *J* = 6.3 Hz, 2H, C2-*H*), 3.00 (d, *J* = 4.3 Hz, 1H, O*H*), 3.48 (dd, *J* = 5.9, 9.6 Hz, 1H, C4-*H*), 3.51 (dd, *J* = 4.3, 9.6 Hz, 1H, C4-*H*), 4.23 (m, 1H, C3-*H*), 4.56 (s, 2H, $PhCH_2O$), 5.04 (sep, *J* = 6.3 Hz, 1H, $CO_2CH(CH_3)_2$), 7.29–7.37 (m, 5H, Ar*H*). The enantiomeric excess of **8c** was determined to be 35% by HPLC with a Chiralpak AD-H column (9:1 hexane/*i*-PrOH, 1.0 mL/min): t_R (major) = 7.9 min for (*S*)-enantiomer; t_R (minor) = 8.5 min for (*R*)-enantiomer.

Typical procedure for the Mukaiyama aldol reaction followed by desilylation (Table 2, Entry 2): Methyl (*S*)-3-hydroxy-3-(4-nitrophenyl)propionate (8d).[26] To an oven-dried flask equipped with a rubber septum and a Teflon-coated magnetic stirring bar were added pulverized 4Å MS (50 mg), **1a** (22 mg, 0.015 mmol, 5 mol %), **3b** (45 mg, 0.30 mmol) and toluene (1.2 mL). The resulting suspension was cooled to –23 °C under an argon atmosphere. After stirring for 10 min, a solution of **6a** (132 mg, 0.90 mmol) in toluene (0.3 mL) was added to the mixture at –23 °C, and the septum was replaced by a greased glass stopper. After 36 h of stirring at this temperature in a closed system, the reaction mixture was then filtered through a plug of Celite with EtOAc (10 mL). Concentration of the EtOAc solution gave the crude silylated aldol product, which was dissolved in THF (2 mL). This solution was added in one portion to 1*N* hydrochloric acid (0.2 mL) at 23 °C. After 0.5 h of stirring at this temperature, the reaction was quenched with saturated $NaHCO_3$ solution (2 mL), and the whole was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (3 mL), and brine (2 × 3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, 3:2 hexane/EtOAc) provided **8d** (61.5 mg, 91%) as pale yellow solid; mp 50.0–52.0 °C; R_f = 0.32 (1:1

hexane/EtOAc); $[\alpha]_D^{23}$ –37.1° (*c* 1.01, $CHCl_3$) for 94% ee; IR (KBr) ν: 3374, 1738, 1699, 1518, 1348 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.75 (d, *J* = 7.9 Hz, 1H, C2-*H*), 2.76 (d, *J* = 4.6 Hz, 1H, C2-*H*), 3.60 (d, *J* = 4.0 Hz, 1H, O*H*), 3.75 (s, 3H, CO_2CH_3), 5.24 (ddd, *J* = 4.0, 4.6, 7.9 Hz, 1H, C3-*H*), 7.57 (d, *J* = 8.6 Hz, 2H, Ar*H*), 8.22 (d, *J* = 8.6 Hz, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.7 (CH_2), 52.0 (CH_3), 69.2 (CH), 123.6 (CH), 126.3 (CH), 147.2 (C), 149.6 (C), 172.0 (C=O); HRMS (EI) calcd for $C_{10}H_{11}NO_5$ (M^+) 225.0637, found 225.0635. The enantiomeric excess of **8d** was determined to be 94% by HPLC with a Chiralpak AS column (3:1 hexane/*i*-PrOH, 1.0 mL/min): t_R (minor) = 12.7 min for (*R*)-enantiomer; t_R (major) = 16.8 min for (*S*)-enantiomer. The absolute configuration of **8d** was determined to be *S* by chemical correlation (*vide infra*).

Determination of absolute configuration of 8d: (*S*)-3-hydroxy-3-(4-nitrophenyl)propionic acid.[22] A solution of (*S*)-**8d** (45.0 mg, 0.2 mmol, 94% ee) in MeOH (2 mL) was added in one portion to 1*N* KOH solution (0.2 mL) at 23 °C. After 0.5 h of stirred at this temperature, the reaction was quenched with 1*N* hydrochloric acid (1 mL), and the whole was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (3 mL), and brine (2 × 3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, EtOAc) provided (*S*)-3-hydroxy-3-(4-nitrophenyl)propionic acid (30.0 mg, 71%) as a white solid; mp 122–127 °C; R_f = 0.39 (2:1 $CHCl_3$/MeOH); $[\alpha]_D^{23}$ –8.27° (*c* 0.50, MeOH) [lit.,[22] $[\alpha]_D$ –9.8° (*c* 0.5, MeOH) for (*S*)-enantiomer]; ^1H NMR (270 MHz, CD_3OD) δ 2.69 (d, *J* = 6.6 Hz, 2H, C2-*H*), 5.20 (t, *J* = 6.6 Hz, 1H, C3-*H*), 7.64 (d, *J* = 8.6 Hz, 2H, Ar*H*), 8.21 (d, *J* = 8.6 Hz, 2H, Ar*H*).

Methyl 3-(2,4-dinitrophenyl)-3-hydroxypropionate (8e). The product was prepared following the procedure for the preparation of **8d**, using **3c** (59 mg, 0.30 mmol), silylketene acetal (**6a**) (132 mg, 0.90 mmol) and 4Å MS (25 mg). The crude product was purified by column chromatography (silica gel, 3:2 hexane/EtOAc) to provide **8e** (70.5 mg, 87%) as a yellow solid; mp 91.5–93.0 °C; R_f = 0.34 (1:1 hexane/EtOAc); $[\alpha]_D^{24}$ +80.6° (*c* 0.89, $CHCl_3$) for 92% ee; IR (KBr) ν: 3428, 1736, 1714, 1528, 1348 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.67 (dd, *J* = 9.9, 16.5 Hz, 1H, C2-*H*), 3.00 (dd, *J* = 2.6, 16.5 Hz, 1H, C2-*H*), 3.78 (s, 3H, CO_2CH_3), 3.91 (d, *J* = 3.3 Hz, 1H, O*H*), 5.78 (ddd, *J* = 2.6, 3.3, 9.9 Hz, 1H, C3-*H*), 8.20 (d, *J* = 8.6 Hz, 1H, C6'-*H*), 8.51 (dd, *J* = 2.6, 8.6 Hz, 1H, C5'-*H*), 8.85 (d, *J* = 2.6 Hz, 1H, C3'-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.9 (CH_2), 52.3 (CH_3), 65.8 (CH), 120.0 (CH), 127.6 (CH), 130.1 (CH), 144.6 (C), 146.9 (C), 147.0 (C), 172.0 (C=O); HRMS (FAB) calcd for $C_{10}H_{11}N_2O_7$ $(M+H)^+$ 271.0566, found 271.0565. The enantiomeric excess of **8e** was determined to be 92% by HPLC with a Chiralpak AD-H column (3:1 hexane/*i*-PrOH, 1.0 mL/min): t_R = 9.5 min for major enantiomer; t_R = 11.2 min for minor enantiomer. A sample for combustion analysis was obtained by recrystallizations from 10% EtOAc

in hexane as yellow needles (>99% ee); mp 98.5–99.0 °C; Anal. Calcd for $C_{10}H_{10}N_2O_7$: C, 44.45; H, 3.73; N, 10.37. Found: C, 44.40; H, 3.75; N, 10.32. The absolute stereochemistry of **8e** was not determined.

Methyl 3-hydroxy-3-pentafluorophenylpropionate (8f). The product was prepared following the procedure for the preparation of **8d**, using **3d** (59 mg, 0.30 mmol), silylketene acetal (**6a**) (132 mg, 0.90 mmol) and 4Å MS (50 mg). The crude product was purified by column chromatography (silica gel, 6:1 hexane/EtOAc) to provide **8f** (72.9 mg, 90%) as a white solid; mp 80.0–81.0 °C; R_f = 0.26 (4:1 hexane/EtOAc); $[\alpha]_D^{23}$ –4.07° (*c* 0.95, $CHCl_3$) for 88% ee; IR (KBr) ν: 3455, 1738, 1524, 1505 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.77 (dd, *J* = 4.0, 17.2 Hz, 1H, C2-*H*), 3.15 (dd, *J* = 9.2, 17.2 Hz, 1H, C2-*H*), 3.21 (d, *J* = 5.3 Hz, 1H, O*H*), 3.75 (s, 3H, CO_2CH_3), 5.53 (ddd, *J* = 4.0, 5.3, 9.2 Hz, 1H, C3-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.1 (CH_2), 52.2 (CH_3), 62.0 (CH), 115.0 (m, C), 137.5 (dm, *J* = 253 Hz, CF), 140.8 (dm, *J* = 255 Hz, CF), 144.9 (dm, *J* = 250 Hz, CF), 171.5 (C=O); HRMS (EI) calcd for $C_{10}H_7O_3F_5$ (M^+) 270.0315, found 270.0321. The enantiomeric excess of **8f** was determined to be 88% by HPLC with a Chiralcel OD-H column (9:1 hexane/*i*-PrOH, 1.0 mL/min): t_R = 6.0 min for major enantiomer; t_R = 7.7 min for minor enantiomer. A sample for combustion analysis was obtained by recrystallizations from hexane as colorless fine needles (>99% ee); mp 84.0–84.5 °C; Anal. Calcd for $C_{10}H_7O_3F_5$: C, 44.46; H, 2.61; F, 35.16. Found: C, 44.23; H, 2.69; F, 35.04. The absolute stereochemistry of **8f** was not determined.

ACKNOWLEDGEMENTS

This research was supported, in part, by a Grant-in-Aid for Scientific Research on Priority Areas 17035002 from the Ministry of Education, Culture, Sports, Science and Technology, Japan. T.W. is grateful to JSPS for a graduate fellowship. We thank Ms. S. Oka, M. Kiuchi, A. Maeda, and H. Matsumoto of the Center for Instrumental Analysis at Hokkaido University for mass measurements and elemental analysis.

REFERENCES AND NOTES

1. (a) T. Mukaiyama, K. Narasaka, and K. Banno, *Chem. Lett.*, 1973, 1011; (b) T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, 1974, **96**, 7503.
2. For recent reviews on enantioselective Mukaiyama aldol reactions, see: (a) S. G. Nelson, *Tetrahedron: Asymmetry*, 1998, **9**, 357; (b) E. M. Carreira, 'Comprehensive Asymmetric Catalysis,' ed. by E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, Springer, Berlin, 1999, Vol. 3, Chapter 29.1; (c) M. Sawamura and Y. Ito, 'Catalytic Asymmetric Synthesis,' ed. by I. Ojima, Wiley-VCH, New

York, 2000, Chapter 8B1; (d) E. M. Carreira, 'Catalytic Asymmetric Synthesis,' ed. by I. Ojima, Wiley-VCH, New York, 2000, Chapter 8B2.

3. (a) T. Mukaiyama, S. Kobayashi, H. Uchiro, and I. Shiina, *Chem. Lett.*, 1990, 129; (b) S. Kobayashi, Y. Fujishita, and T. Mukaiyama, *Chem. Lett.*, 1990, 1455; (c) S. Kobayashi, H. Uchiro, I. Shiina, and T. Mukaiyama, *Tetrahedron*, 1993, **49**, 1761; (d) S. Kobayashi and T. Hayashi, *J. Org. Chem.*, 1995, **60**, 1098; (e) D. A. Evans, D. W. C. MacMillan, and K. R. Campos, *J. Am. Chem. Soc.*, 1997, **119**, 10859.
4. (a) T. Mukaiyama, A. Inubushi, S. Suda, R. Hara, and S. Kobayashi, *Chem. Lett.*, 1990, 1015; (b) K. Mikami and S. Matsukawa, *J. Am. Chem. Soc.*, 1994, **116**, 4077; (c) E. M. Carreira, R. A. Singer, and W. Lee, *J. Am. Chem. Soc.*, 1994, **116**, 8837; (d) G. E. Keck and D. Krishnamurthy, *J. Am. Chem. Soc.*, 1995, **117**, 2363; (e) R. A. Singer and E. M. Carreira, *J. Am. Chem. Soc.*, 1995, **117**, 12360.
5. (a) K. Furuta, T. Maruyama, and H. Yamamoto, *J. Am. Chem. Soc.*, 1991, **113**, 1041; (b) K. Furuta, T. Maruyama, and H. Yamamoto, *Synlett*, 1991, 439; (c) E. R. Parmee, O. Tempkin, S. Masamune, and A. Abiko, *J. Am. Chem. Soc.*, 1991, **113**, 9365; (d) S. Kiyooka, Y. Kaneko, and K. Kume, *Tetrahedron Lett.*, 1992, **33**, 4927.
6. E. J. Corey, C. L. Cywin, and T. D. Roper, *Tetrahedron Lett.*, 1992, **33**, 6907.
7. (a) D. A. Evans, J. A. Murry, and M. C. Kozlowski, *J. Am. Chem. Soc.*, 1996, **118**, 5814; (b) D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, and R. J. Staples, *J. Am. Chem. Soc.*, 1999, **121**, 669; D. A. Evans, C. S. Burgey, M. C. Kozlowski, and S. W. Tregay, *J. Am. Chem. Soc.*, 1999, **121**, 686.
8. (a) A. Yanagisawa, Y. Matsumoto, H. Nakashima, K. Asakawa, and H. Yamamoto, *J. Am. Chem. Soc.*, 1997, **119**, 9319; (b) M. Wadamoto, N. Ozasa, A. Yanagisawa, and H. Yamamoto, *J. Org. Chem.*, 2003, **68**, 5593.
9. (a) H. Ishitani, Y. Yamashita, H. Shimizu, and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 5403; (b) Y. Yamashita, H. Ishitani, H. Shimizu, and S. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 3292; (c) J. Kobayashi, M. Nakamura, Y. Mori, Y. Yamashita, and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 9192.
10. (a) O. Fujimura, *J. Am. Chem. Soc.*, 1998, **120**, 10032; (b) D. A. Evans, C. E. Masse, and J. Wu, *Org. Lett.*, 2002, **4**, 3375; (c) Y. Shimada, Y. Matsuoka, R. Irie, and T. Katsuki, *Synlett*, 2004, 57.
11. For recent book and review, see: (a) M. P. Doyle, M. A. McKervey, and T. Ye, 'Modern Catalytic Methods for Organic Synthesis with Diazo Compounds,' Wiley-Interscience, New York, 1998; (b)

H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861.

12. (a) M. P. Doyle, I. M. Phillips, and W. Hu, *J. Am. Chem. Soc.*, 2001, **123**, 5366; (b) M. P. Doyle, J. Colyer, *J. Mol. Catal. A*, 2003, **196**, 93; (c) M. P. Doyle, M. Valenzuela, and P. Huang, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 5391; (d) M. Valenzuela, M. P. Doyle, C. Hedberg, W. Hu, and A. Holmstrom, *Synlett*, 2004, 2425.
13. R. E. Forslund, J. Cain, J. Colyer, and M. P. Doyle, *Adv. Synth. Catal.*, 2005, **347**, 87.
14. M. Anada, T. Washio, N. Shimada, S. Kitagaki, M. Nakajima, M. Shiro, and S. Hashimoto, *Angew. Chem., Int. Ed.*, 2004, **43**, 2665.
15. K. Oisaki, Y. Suto, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 5644.
16. In the absence of 4Å MS, the aldol reaction proceeded to completion in 6 h, giving a mixture of **7a** and **8a** in 45% yield/77% ee and 32% yield/76% ee, respectively.
17. L. Shao, H. Kawano, M. Saburi, and Y. Uchida, *Tetrahedron*, 1993, **49**, 1997.
18. S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, and T. Moriwake, *Chem. Lett.*, 1984, 1389.
19. (a) S. Kitagaki, H. Matsuda, N. Watanabe, and S. Hashimoto, *Synlett*, 1997, 1171; (b) S. Kitagaki, Y. Yanamoto, H. Okubo, M. Nakajima, and S. Hashimoto, *Heterocycles*, 2001, **54**, 623.
20. (a) H. Saito, H. Oishi, S. Kitagaki, S. Nakamura, M. Anada, and S. Hashimoto, *Org. Lett.*, 2002, **4**, 3887; (b) K. Minami, H. Saito, H. Tsutsui, H. Nambu, M. Anada, and S. Hashimoto, *Adv. Synth. Catal.*, in press.
21. Although the use of 1.5 equiv of **6a** under otherwise identical conditions afforded silylated aldol adduct **7a** in 78% yield with 86% ee, the reaction required 24 h to reach completion.
22. R. F. Lowe and R. J. Stoodley, *Tetrahedron Lett.*, 1994, **35**, 6351.
23. E. J. Corey and T. W. Lee, *Chem. Commun.*, 2001, 1321.
24. A. Manzocchi, R. Casati, A. Fiecchi, and E. Santaniello, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2753.
25. S. A. Hermitage, A. Murphy, P. Nielsen, and S. M. Roberts, *Tetrahedron*, 1998, **54**, 13185.
26. M. Braun and C. Bauer, *Liebigs Ann. Chem.*, 1991, 1157.