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Highly Enantioselective Mukaiyama Aldol Reaction of α,α-Dichloro Ketene Silyl Acetal: An Efficient Synthesis of a Key Intermediate for Diltiazem

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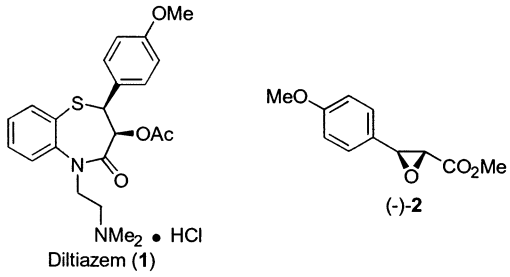
An efficient synthesis of methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (−)-**2**, a key intermediate for diltiazem (**1**), has been developed on the basis of the highly enantioselective Mukaiyama aldol reaction of *p*-anisaldehyde (**4a**) with α,α-dichloro ketene silyl acetal **5**. Thus, the reaction using a stoichiometric amount of chiral oxazaborolidinone catalyst **12a** proceeded to excellent yield (83%) and high enantioselectivity (96% ee), together with the chiral ligand **13a** in nearly quantitative recovery. The reaction using a substoichiometric amount of **12e** (20 mol %) also proceeded to excellent yield (88%), with somewhat lower enantioselectivity (77% ee). The aldol product **3a** thus obtained was easily converted to (−)-**2** in excellent yield (80%) and high optical purity (>99% ee). The highly enantioselective Mukaiyama aldol reaction with **5** catalyzed by **12a** proved to be applicable to various aldehydes. An efficient preparation of **5** from inexpensive starting materials was also described.

Introduction

Diltiazem (**1**) is one of the most potent calcium antagonists and has been used throughout the world as a remedy for angina and hypertension.[1] After methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (−)-**2** was recognized as a key intermediate for **1**, extensive research has been directed toward an efficient synthetic method of (−)-**2**.[2,3] Although a large number of synthetic approaches including the asymmetric epoxidation of methyl (*E*)-4-methoxycinnamate have been reported,[3] for reasons involving enantiomeric purity and overall efficiency, a more efficient methodology is needed. To date, an industrial synthesis of (−)-**2**, therefore, has been conducted by means of a lipase-catalyzed enantioselective hydrolysis[4] of racemic glycidate (±)-**2** in that the maximum yield cannot exceed 50%. Therefore, a route to the asymmetric synthesis of (−)-**2** has been the focus of great attention. We envisaged that the asymmetric Darzens reaction of *p*-anisaldehyde (**4a**) with methyl chloroacetate might be an efficient method. However, past examples of the Darzens reactions for the synthesis of (−)-**2** required use of a stoichiometric amount of chiral source such as chiral auxiliaries[2b,h] or an external ligand.[2f] On the other hand, recent advances in the field of the asymmetric Mukaiyama aldol reaction have enabled the use of a catalytic amount of chiral source for the reaction.[5] In this paper, we report a novel asymmetric synthesis of (−)-**2** based on the asymmetric Mukaiyama aldol reaction.[6]



For the introduction of the C-3 center of (−)-**2**, we envisioned the use of α,α-dichloro ketene silyl acetal **5** as a substrate for the asymmetric Mukaiyama aldol reaction of *p*-anisaldehyde (**4a**) (Scheme 1).[7] Generally, higher enantioselectivities are observed in the reactions

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(5) For a recent review, see: Nelson, S. G. *Tetrahedron*: *Asymmetry* **1998**, *9*, 357−389.

(6) Part of this work has been published as a preliminary communication: Imashiro, R.; Kuroda, *T. Tetrahedron Lett.* **2001**, *42*, 1313−1315.

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SCHEME 1

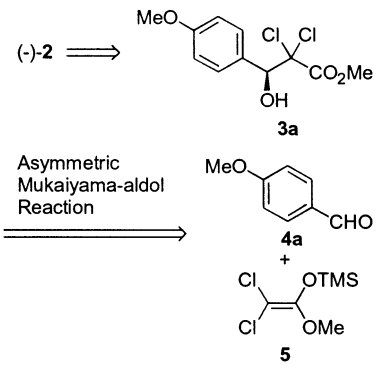
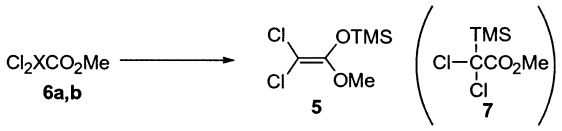


TABLE 1. Preparation of α,α′-Dichloroketene Silyl Acetal 5



entry	**6a**,**b**	X	conditions	yield (%) of **5** (**7**)
1	**6a**	H	TMSOTf−Et_3N, 10 °C to rt	20 (2)
2	**6b**	Cl	Zn−TMSCl/pentane−AcOEt, reflux	0 (0)
3	**6b**	Cl	Zn−TMSCl/THF, reflux	85 (0)

with α,α-disubstituted ketene silyl acetals than in the reactions with α-unsubstituted or α-monosubstituted ones in the asymmetric Mukaiyama aldol reaction.[8] Moreover, we expected that the reaction of **5** might proceed with high enantioselectivity, because high electronegativity and moderate bulkiness of the dichloro moiety could control its reactivity. Transformation of the resulting aldol product **3a** to the *trans*-glycidate (−)-**2** has already been reported.[9]

Results and Discussion

Preparation of α,α-Dichlorosubstituted Ketene Silyl Acetal 5. We began the present study by preparing the ketene silyl acetal **5**.[10] In our early studies, **5** was prepared from methyl dichloroacetate (**6a**), Et_3N, and TMSOTf (Table 1, entry 1). However, **5** was obtained in only poor yield with concomitant formation of the α-silyl ester isomer **7**. Next, we examined Schepin's method, which prepared the corresponding ketene silyl monothioacetal[10e] using inexpensive starting materials: methyl trichloroacetate (**6b**), zinc powder, and TMSCl. However, **5** was not obtained at all under their conditions (Table 1, entry 2). The solvent survey revealed that **5** was obtained in excellent yield (85%) using THF as a solvent (Table 1, entry 3). Moreover, **5** thus obtained was free from the concomitant formation of **7**.

Lewis Acid Catalyst Survey. Having established an efficient method for the preparation of (−)-**2**, we turned our attention to the asymmetric Mukaiyama aldol reaction. We selected boron and titanium as the less toxic metals for chiral Lewis acid catalysts to develop an industrial method. Several chiral Lewis acids, which are known to be excellent catalysts for the Mukaiyama aldol reaction with chlorine-free ketene silyl acetals, were evaluated for their usefulness in the reaction of **4a** with **5**. Carreira's Ti(IV)−Schiff base catalyst **8**[11] and Ti(IV)−BINOL complex **9**[12] gave none of the desired product **3a** (Table 2, entries 1 and 2). Commercially available (−)-DIP-chloride **10**[13] gave poor yield and selectivity (Table 2, entry 3). Next, we examined the Ti(IV) catalyst **11b**,[14] one of the Ti(IV)−TADDOLate catalysts[15] that are effective for several enantioselective reactions, and **3a** was obtained in modest yield and enantioselectivity (Table 2, entry 4). Among other catalysts examined, it was found that Kiyooka's chiral oxazaborolidinone catalyst **12a**,[16] which was easily prepared by mixing the sulfonamide **13a** obtained from D-valine with BH_3·THF complex, served as an effective catalyst for the reaction (Table 2, entry 5). From these results, we optimized the reaction parameters using this catalyst to improve the yield and enantioselectivity.

Solvent Effects. A survey of permissible solvents for this reaction was undertaken. It revealed that employment of toluene as a solvent led to a significant decline in yield (Table 3, entry 2). In solvents containing a coordinating oxygen atom, such as Et_2O and THF, the reaction afforded the product in high enantioselectivity, but the yield was low (Table 3, entries 3 and 4). The reaction using $EtNO_2$ as a solvent was least effective in terms of both yield and enantioselectivity (Table 3, entry 5).

Optimization of Ligand Structure. Next, we optimized the ligand **13a** by modifying the Ar, R^1, and R^2 groups of glycine sulfone amide.[8] While an increase in the bulkiness of R^1 led to a decrease in yield (compare entries 1 and 2, Table 4), a decrease in the bulkiness of R^1 led to a decline in both yield and enantioselectivity (compare entries 1 and 3, Table 4). Although α,α-disubstituted glycine derivative **12d** (the catalyst modifying Masamune's catalysts,[17] which are reported to be effective for the reaction of α-unsubstituted ketene silyl

(7) For examples of enantioselective Mukaiyama−aldol reactions of halogen-substituted ketene silyl acetals, see: (a) Mikami, K.; Terada, M.; Nakai, T. *Tetrahedron*: *Asymmetry* **1991**, *2*, 993−996. (b) Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271−10280. (c) Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Synlett* **1998**, 437−439. (d) Kiyooka, S.-i.; Shahid, K. A.; Hena, M. A. *Tetrahedron Lett*. **1999**, *40*, 6447−6449. (e) Kiyooka, S.-i.; Shahid, K. A. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1537−1542.

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(10) For the preparation of halogen-substituted ketene silyl acetals, see: (a) Wilcox, C. S.; Babston, R. E. *Tetrahedron Lett*. **1984**, *25*, 699−702. (b) Lion, C.; Lebbar, K.; Boukou-Poba, *J. Bull. Soc. Chim. Belg*. **1988**, *97*, 227−233. (c) Mikami, K.; Terada, M.; Nakai, T. *Tetrahedron*: *Asymmetry* **1991**, *2*, 993−996. (d) Shchepin, V. V.; Efremov, D. I.; Desyatkov, D, A. *Zh. Obschch. Khim*. **1993**, *63*, 1283−1287.

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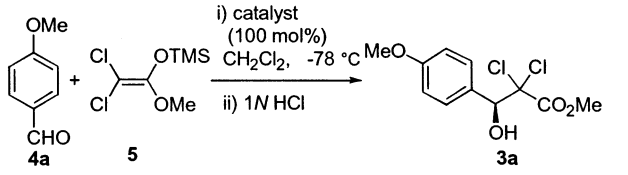
(14) (a) Haase, C.; Sarco, C. R. and DiMare, M. *J. Org. Chem*. **1995**, *60*, 1777−1787. (b) Corey, E. J.; Matsumura, Y. *Tetrahedron Lett*. **1991**, *44*, 6289−6292.

(15) For a recent review, see: Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed*. **2001**, *40*, 92−138.

(16) Kiyooka, S.-i.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem*. **1991**, *56*, 2276−2278.

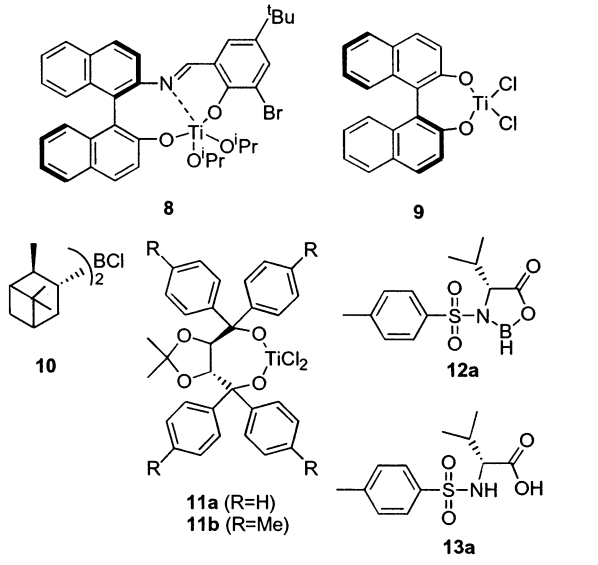
(17) (a) Parmee, E. R.: Tempkin, O.; Masamune, S. *J. Am. Chem. Soc*. **1991**, *113*, 9365−9366. (b) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett*. **1992**, *33*, 1729−1732.

TABLE 2. Effect of Catalysts on the Mukaiyama Aldol Reaction of *p*-Anisaldehyde (4a) with Ketene Silyl Acetal 5



		3a	
entry[a]	catalyst	yield[b] (%)	ee[c] (%)
1	**8**	0	
2	**9**	0	
3	**10**	28	22
4	**11b**	41	67
5	**12a**	73	96
6[d]	**12a**	83	96

[a] Reactions were carried out with **4a** (1.0 mmol) and **5** (1.1 mmol). [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral HPLC (Chiralcel OJ, *n*-hexane/*i*-PrOH = 70:30, 230 nm, 0.6 mL/min, 35 °C). The absolute configuration was determined as *S* by the retention time of HPLC. [d] 1.5 equiv of **5** was used.



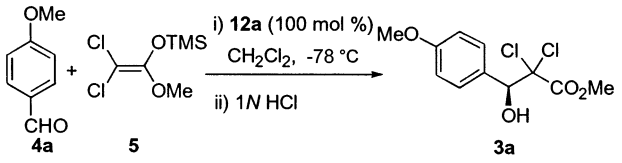
acetal) gave higher yield of **3a**, only low enantioselectivity was observed (Table 4, entry 4). While catalysts **12e** and **12f**, bearing an electron-withdrawing group in the arylsulfonyl moiety, also promoted the reaction in good yields and with high enantioselectivities (Table 4, entries 5 and 6), the reaction using **12g**, bearing an electron-donating group, brought about a significant decrease of reactivity with similar enantioselectivity (Table 4, entry 7). These differences in reactivity might be attributed to the Lewis acidity of the oxazaborolidinone due to the substitution pattern of the sulfonamides.

Synthesis of (−)-2. The aldol product **3a** thus obtained was easily converted to (−)-**2** according to the reported procedure.[2d] Thus, **3a** was reduced to monochlorohydrin **14** on treatment with Zn in AcOH, which was treated with NaOMe in MeOH to give (−)-**2** (>99% ee) in 80% yield (Scheme 2).[18]

Catalytic Reaction. To save the cost of the chiral catalyst, we examined the decrease and recovery of the

(18) Optically pure (−)-**2** was also obtained from **3a** (77% ee, Table 5, entry 2) in 58% yield after single recrystallization of the crude **2**.

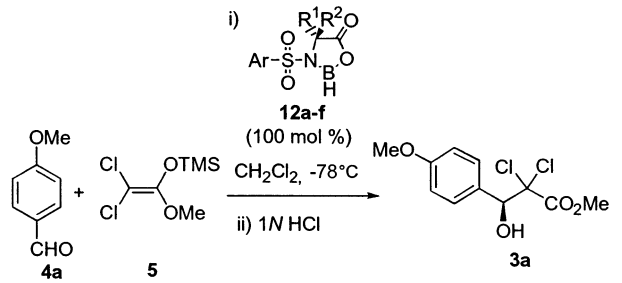
TABLE 3. Effect of Solvents on the Enantioselective Mukaiyama Aldol Reaction of *p*-Anisaldehyde (4a) with Ketene Silyl Acetal 5 Catalyzed by Oxazaborolidinone 12a



		3a	
entry[a]	solvent	yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	73	96
2	toluene	45	90
3	$EtNO_2$	34	8
4	THF	6	92
5	ether	37	93

[a] Reactions were carried out with **4a** (1.0 mmol) and **5** (1.1 mmol). [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral HPLC (Chiralcel OJ, *n*-hexane/*i*-PrOH = 70:30, 230 nm, 0.6 mL/min, 35 °C). The absolute configuration was determined as *S* by the retention time of HPLC.

TABLE 4. Effect of Oxazaborolidinone Catalysts



					3a	
entry[a]	catalyst	R^1	R^2	Ar	yield[b] (%)	ee[c] (%)
1	**12a**	*i*Pr	H	*p*-MeC_6H_4	73 (83[d])	96 (96[d])
2	**12b**	*t*Bu	H	*p*-MeC_6H_4	35	95
3	**12c**	Me	H	*p*-MeC_6H_4	41	32
4	**12d**	Et	Ph	*p*-MeC_6H_4	88	32
5	**12e**	*i*Pr	H	*o*-$NO_2C_6H_4$	78 (89[d])	93 (93[d])
6	**12f**	*i*Pr	H	*p*-$NO_2C_6H_4$	71	89
7	**12g**	*i*Pr	H	*p*-$MeOC_6H_4$	30	88
8	**12h**	*i*Pr	H	1-naphthyl	66	94

[a] Reactions were carried out with **4a** (1.0 mmol) and **5** (1.1 mmol). [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral HPLC (Chiralcel OJ, *n*-hexane/*i*-PrOH = 70:30, 230 nm, 0.6 mL/min, 35 °C). The absolute configuration was determined as *S* by the retention time of HPLC. [d] 1.5 equiv of **5** was used.

catalyst. First, we examined the reaction using substoichiometric amounts of oxazaborolidinone catalysts **12a** and **12e** (Table 5). The reaction using **12a** gave only 39% yield of **3a** and 44% ee (Table 5, entry 1). On the other hand, the reaction using **12e** proceeded to 88% yield, although a somewhat lower enantiometric excess of 77% compared with the stoichiometric reaction was observed (Table 5, entry 2). Although this reaction required a stoichiometric amount of catalyst, the greater part of it was readily recovered. Thus, acidification of the aqueous layer, followed by extraction with AcOEt, led to the recovery of the sulfonamide **13a** in 97% yield.

Substrate Generality. Encouraged by the result obtained for **4a**, reactions of **5** with various aldehydes were conducted using **12a** as a catalyst. Aromatic and α,β-unsaturated aldehydes **4b** and **4c** gave good yields

SCHEME 2

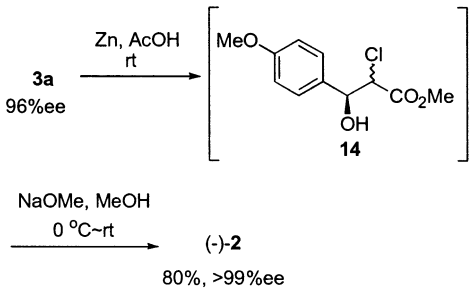
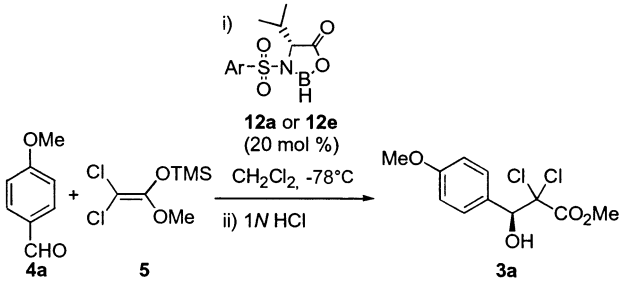


TABLE 5. Mukaiyama Aldol Reaction of *p*-Anisaldehyde (4a) with Ketene Silyl Acetal 5 Catalyzed by a Substoichiometric Amount of 12a and 12e



entry[a]	catalyst	Ar	yield[b] (%)	ee[c] (%)
1	**12a**	*p*-MeC_6H_4	39	44
2	**12e**	*o*-$NO_2C_6H_4$	88	77

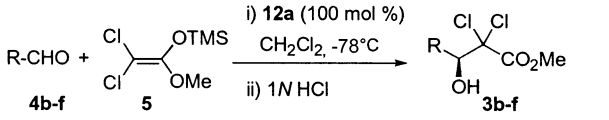
[a] Reactions were carried out with **4a** (1.0 mmol) and **5** (1.5 mmol). [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral HPLC (Chiralcel OJ, *n*-hexane/*i*-PrOH = 70:30, 230 nm, 0.6 mL/min, 35 °C). The absolute configuration was determined as *S* by the retention time of HPLC.

and high enantioselectivites of **3b** and **3c**, as was the case for **4a** (Table 5, entries 1 and 2). On the other hand, aliphatic aldehydes **4d** and **4e** afforded **3d** and **3e** in only modest yields and enantioselectivities (Table 6, entries 3 and 4). In the case of cyclohexylaldehyde (**4f**), the reaction was very slow at −78 °C, and **3f** was obtained in diminished yield and ee at higher temperature (Table 6, entry 5).

Mukaiyama Aldol Reaction with α-Monochloro-Substituted Ketene Silyl Acetal 16. We also investigated the Mukaiyama aldol reaction of **4a** with α-monochloro ketene silyl acetal **16** on consideration that the aldol product **14** could directly be converted to (−)-**2** upon cyclization. The ketene silyl acetal **16** was found to be prepared in the same manner as the preparation of **5**.[19] Unexpectedly, the reaction of **4a** with **16** using the oxazaborolidinone catalyst **12a** gave **14** in only low enantioselectity (Table 7, entry 1). Among other chiral Lewis acids examined, Ti(IV)−TADDOLate catalyst **11a** showed modest enantioselectivity (Table 7, entry 3). The optimization of aryl moiety in TADDOL ligand revealed that the *p*-tolyl-substituted catalyst **11b** afforded **14** in high diastereo- and enantioselectivity (88% de, 91% ee, Table 7, entry 4). However, due to a modest yield of **14**, no further investigations on this reaction were conducted.

(19) *E* or *Z* isomer was exclusively obtained, although the stereochemistry has yet to been determined.

TABLE 6. Mukaiyama Aldol Reaction of Aldehydes (4b−f) with Ketene Silyl Acetal 5 Catalyzed by 12a



entry[a]	aldehyde	conditions (*T* (°C), time (h))	product	yield[b] (%)	ee (%)
1	**4b**	−78, 7	**3b**	69	95[c]
2	**4c**	−78, 7	**3c**	62	92[c]
3	**4d**	−78, 7	**3d**	38	94[c]
4	**4e**	−78, 7	**3e**	42	89[d]
5	**4f**	−78 to 0, 3	**3f**	27	62[d]

[a] Reactions were carried out with **4b**−**f** (1.0 mmol) and **5** (1.1 mmol). [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral HPLC (Chiralcel OJ, *n*-hexane/*i*-PrOH = 70:30, 230 nm, 0.6 mL/min, 35 °C). The absolute configuration was deduced as *S* by the pattern of the retention time of HPLC. [d] Determined by ^1H NMR spectra of MTPA esters of alcohols **3e**−**f**. The absolute configuration was not determined.

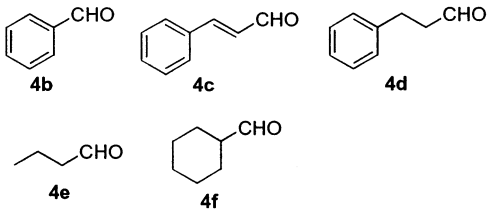
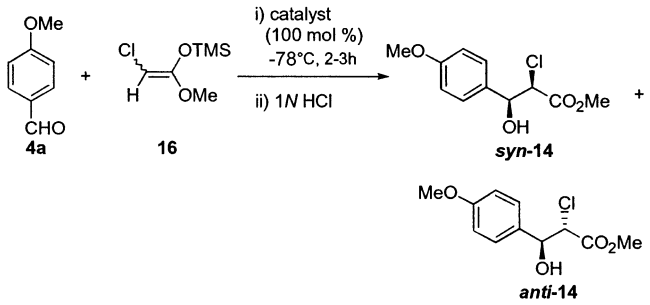


TABLE 7. Enantioselective Mukaiyama Aldol Reaction of *p*-Anisaldehyde (4a) with Ketene Silyl Acetal 16 Catalyzed by Chiral Lewis Acids 9, 11a,b, and 12a



					ee[c] (%)	
entry[a]	catalyst	solvent	yield[b] (%)	syn/anti[c]	syn	anti
1	**12a**	CH_2Cl_2	92	82/18	8[d]	43
2	**9**	CH_2Cl_2	41	50/50	3	3
3	**11a**	toluene	50	14/86	16	61
4	**11b**	toluene	53	6/94	60	91

[a] Reactions were carried out with **4a** (1.0 mmol) and **16** (1.2 mmol). [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral HPLC (Chiralcel OJ, *n*-hexane/*i*-PrOH = 70:30, 230 nm, 0.6 mL/min, 35 °C). The absolute configuration was determined as 3*S* by the retention time of HPLC. [d] 3*R* configuration.

Summary

In summary, we have achieved a novel asymmetric synthesis of (−)-**2**, a key intermediate for diltiazem, based on the chiral oxazaborolidinone-promoted Mukaiyama aldol reaction of **4a** with **5** (up to 96% ee). We also found that this reaction could be applied to some other aldehydes. Although a clear mechanistic picture of the reaction has yet to emerge,[20] the stereochemical outcome of the reaction using **12** can be explained by Corey's

model.[21] The aldol product **3a** thus obtained was easily converted to (−)-**2** by reduction and cyclization in excellent yield and high optical purity. An efficient preparation of **5** from inexpensive starting materials has also been developed. The α,α-dichloro-β-hydroxyesters **3a**−**f** thus obtained and the corresponding chiral trans glycidates are useful as versatile chiral building blocks for the synthesis of other pharmaceutical and biologically active natural products.[22]

Experimental Section

General Methods. Reagents were used as received unless otherwise stated. CH_2Cl_2 and toluene were redistilled from CaH_2 and were dried over molecular sieves (4 Å). Tetrahydrofuran (THF) was redistilled from Na and benzophenone, and was dried over molecular sieves 4 Å. Analytical TLC was preformed using precoated plates (0.25 mm) followed by visualization with UV light (254 nm), staining with a solution of phosphomolybdic acid. Melting points were measured, but uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with TMS as an internal standard.

(2,2-Dichloro-1-methoxy)vinyloxytrimethylsilane (5). To a suspension of methyl trichloroacetate (17.7 g, 100 mmol) and activated zinc powder (9.8 g, 150 mmol) in anhydrous THF (100 mL) was added TMSCl (15.2 mL, 120 mmol) at such a rate to promote gentle refluxing. Stirring was continued at ambient temperature for 30 min, and then the reaction mixture was diluted with *n*-hexane (100 mL) and filtered to remove the zinc dust. After evaporation of the solvent, the resulting solution was distilled under reduced pressure to give **4** (18.3 g, 85%): bp 64−65 °C (2 mmHg); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.64 (s, 3H), 0.30 (s, 9H); IR (film) ν 3645, 2963, 1749, 1657 cm^{-1}; MS (GCMS) *m*/*z* 214 (M^+), 216 ([M + 2]$^+$), 218 ([M + 4]$^+$).

Preparation of Sulfonamides. General Procedure. To a solution of D-valine (10.0 g, 85.4 mmol) in aqueous 1 N NaOH (171 mL, 176 mmol) was added dropwise a solution of *p*-toluenesulfonyl chloride (16.3 g, 85.4 mmol) in THF (85 mL) under ice-cooling, and the reaction mixture was stirred overnight. After evaporation of THF, the solution was washed with $CHCl_3$. The aqueous solution was acidified with aqueous 2 N HCl and extracted with AcOEt. The extracts were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. The solvent was evaporated to give the sulfonamide **13a** as a colorless solid (15.7 g, 68%).

Typical Procedure for Asymmetric Mukaiyama−Aldol Reaction of Aldehydes (4a−f) with Ketene Silyl Acetal (5) Catalyzed by Oxazaborolidinones (12a−i). To a solution of *p*-toluenesulfonamide **13a** (11 mmol, 2.98 g) in CH_2Cl_2 (100 mL) was added dropwise 1 M BH_3·THF complex in THF solution (10 mmol) at 0 °C under N_2 atmosphere. The solution was stirred at 0 °C for 0.5 h and cooled to −78 °C. A solution of aldehyde **4a** (10 mmol, 1.36 g) in CH_2Cl_2 (10 mL) and a solution of ketene silyl acetal **5** (11 mmol, 2.37 g) in CH_2Cl_2 (10 mL) were added successively to the reaction mixture at −78 °C and stirred at the same temperature for 7 h (in the reaction of **4f**, the reaction temperature was raised to 0 °C). The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with AcOEt. The extracts were washed with brine, dried over $MgSO_4$, and concentrated to dryness under reduced pressure. To the residue were added THF (40 mL) and 1 N aqueous HCl (10 mL) at rt. The reaction mixture was stirred for 0.5 h and extracted with AcOEt. The extracts were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the resulting mixture was purified by silica gel column chromatography ($CHCl_3$/hexane/AcOEt = 5:5:1) to give the aldol product **3a** (2.03 g, 73%) with 96% ee as the *S* enantiomer. The purity of **3a** was upgraded to >99% ee after recrystallization from hexanes−ether. The aqueous $NaHCO_3$ phase was acidified with aqueous HCl and was extracted with AcOEt. The extracts were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, *p*-toluenesulfonamide **13a** was recovered as a colorless solid (2.94 g, 99%).

(3*S*)-Methyl 2,2-dichloro-3-hydroxy-3-(4-methoxyphenyl)propionate (3a): yield 73%, 96% ee; mp 53 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.45 (d, *J* = 8.68 Hz, 2H), 6.90 (d, *J* = 8.86 Hz, 2H), 5.38 (s, 1H), 3.91 (s, 3H), 3.18 (br, 1H); IR (KBr) ν 3047, 2999, 2956, 2900, 2830, 1755, 1746, 1612, 1580, 1514 cm^{-1}; MS (EI) *m*/*z* 278 ([M]$^+$), 280 ([M + 2]$^+$), 282 ([M + 4]$^+$). Anal. Calcd for $C_{11}H_{12}Cl_2O_4$: C, 47.33; H, 4.33; Cl, 25.40. Found: C, 47.32; H, 4.31; C, 25.32.

(3*S*)-Methyl 2,2-dichloro-3-hydroxy-3-phenylpropionate (3b): yield 69%, 95% ee; mp 53 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.51−7.54 (m, 2H), 7.38−7.40 (m, 2H), 5.43 (d, *J* = 5.2 Hz, 1H), 3.92 (s, 3H), 3.23 (d, *J* = 5.2 Hz, 1H); IR (KBr) ν 3533, 2963, 1747 cm^{-1}; MS (EI) *m*/*z* 249 ([M]$^+$), 251 ([M + 2]$^+$), 253 ([M + 4]$^+$). Anal. Calcd for $C_{10}H_{10}Cl_2O_3$: C, 48.22; H, 4.05; Cl, 28.47. Found: C, 48.01; H, 4.25; C, 28.5.

(3*S*,4*E*)-Methyl 2,2-dichloro-3-hydroxy-5-phenyl-4-pentenoate (3c): yield 62%, 92% ee; mp 49 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.44 (d, *J* = 8.68 Hz, 2H), 7.37−7.29 (m, 3H), 6.83 (d, *J* = 15.6 Hz, 1H), 6.36 (dd, *J* = 6.29 Hz, 15.9 Hz, 1H), 4.96 (d, *J* = 6.00 Hz, 1H), 3.94 (s, 3H), 2.84 (br, 1H); IR (KBr) ν 3509, 3029, 2957, 1775, 1750 cm^{-1}; MS (EI) *m*/*z* 274 (M^+), 275 ([M + 1]$^+$), 276 ([M + 2]$^+$), 277 ([M + 3]$^+$), 278 ([M + 4]$^+$). Anal. Calcd for $C_{12}H_{14}Cl_2O_5$: C, 52.39; H, 4.40; Cl, 25.77. Found: C, 52.01; H, 4.33; Cl, 25.82.

(3*S*)-Methyl 2,2-dichloro-3-hydroxy-5-phenylpentanoate (3d): yield 38%, 94% ee; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33−7.20 (m, 5H), 4.22 (dd, *J* = 1.54 Hz, 6.44 Hz, 1H), 3.89 (s, 3H), 2.97 (m, 1H), 2.7 (br, 1H), 2.75 (dt, *J* = 8.16 Hz, 13.8 Hz, 1H), 2.20 (m,1H), 1.97 (m, 1H); MS (EI) *m*/*z* 276 (M^+), 277 ([M + 1]$^+$), 278 ([M + 2]$^+$), 279 ([M + 3]$^+$), 280 ([M + 4]$^+$); IR (film) ν 3511, 3029, 2958, 1749, 1766 cm^{-1}. Anal. Calcd for $C_{12}H_{14}Cl_2O_5$: C, 52.01; H, 5.09; Cl, 25.58. Found: C, 51.59; H, 5.01; Cl, 25.21.

(3*S*)-Methyl 2,2-dichloro-3-hydroxyhexanoate (3e): yield 42%, 89% ee; bp 72−73 °C (1.2 mmHg); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.07 (d, *J* = 4.03 Hz, 1H), 3.91 (s, 3H), 2.54 (br, 1H), 2.18 (m,1H), 1.08 (d, *J* = 6.74 Hz, 3H), 1.05 (d, *J* = 6.94 Hz, 3H); IR (film) ν 3492, 2962, 2879, 1767, 1749 cm^{-1}. Anal. Calcd for $C_7H_{12}Cl_2O_5$: C, 39.09; H, 5.62; Cl, 32.97. Found: C, 38.58; H, 5.45; Cl, 31.57.

(3*S*)-Methyl 2,2-dichloro-3-hydroxy-3-cyclohexylpropionate (3f): yield 27%, 62% ee; bp 102 °C (0.8 mmHg); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.05 (d, *J* = 4.79 Hz, 1H), 3.90 (s, 3H), 2.5 (br, 1H), 1.76−1.15 (m, 11H); IR (film) ν 3491, 2930, 2855, 1768, 1749 cm^{-1}. Anal. Calcd for $C_{10}H_{16}C_{12}O_5$: C, 47.08; H, 6.32; Cl, 27.79. Found: C, 46.76; H, 6.30; Cl, 27.41.

(2*R*,3*S*)-Methyl 3-(4-Methoxyphenyl)glycidate ((−)-2). To a solution of **3a** (1.50 g, 5.37 mmol, 96% ee) in AcOH (5.4 mL) was added activated Zn powder (387 mg, 5.91 mmol) at rt. After being stirred for 1.5 h at rt, the reaction mixture was quenched with H_2O (50 mL) and extracted with AcOEt. The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified

(20) For a theoretical study on the coordination of aldehydes to *N*-sulfonyloxazaborolidine see: Salvatella, L.; Ruiz-López, M. F. *J. Am. Chem. Soc.* **1999**, *121*, 10722−10780 and references therein.

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by silica gel column chromatography (hexane/$CHCl_3$/AcOEt = 5:5:1) to give the chlorohydrin **14** (1.17 g, 4.78 mmol) as diastereomer mixtures. To a solution of **14** in MeOH (18 mL) was added 28% NaOMe/MeOH (1.01 g, 5.26 mmol) in MeOH (6 mL) at 0 °C under N_2 atmosphere. The residue was stirred at 0 °C for 15 min and then at rt for 30 min. After being diluted with ice−water, the reaction mixture was extracted with AcOEt. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. After evaporation of the solvent, the residue was recrystallized from MeOH to give (−)-**2** as colorless crystals (894 mg, 80% yield, >99% ee): mp 87−88 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.21 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.05 (d, J = 1.7 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.51 (d, J = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 168.7, 166.2, 127.1, 126.9, 126.6, 114.3, 114.0, 57.8, 56.4, 55.2, 52.4; IR (KBr) 3029, 2965, 2843, 1748, 1614, 1587, 1519 cm^{-1}; MS (EI) m/z 208 (M^+); $[\alpha]^{24}_D$ −196 (c 1.00, MeOH). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.41; H, 5.87.

(2-Chloro-1-methoxy)vinyloxytrimethylsilane (16). To a suspension of methyl dichloroacetate (7.15 g, 50 mmol) and activated zinc powder (4.9 g, 75 mmol) in THF (50 mL) was added TMSCl (7.6 mL, 60 mmol) dropwise, and the reaction mixture was refluxed for 1 h. The mixture was diluted with *n*-hexane (50 mL) and filtrated to remove the zinc salt. After evaporation of the solvent, the resulting solution was distilled under reduced pressure to give **16** (5.62 g, 62%): bp 47−51 °C (2 mmHg); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.54 (s, 1H), 3.55 (s, 3H), 0.27 (s, 9H); IR (ATR) ν 1652 cm^{-1}; MS (GCMS) m/z 180 (M^+), 181 ($[M + 1]^+$).

Mukaiyama−Aldol Reaction of *p*-Anisaldehyde (4a) with Monochloro Ketene Silyl Acetal (16) Catalyzed by Ti(IV)−TADDOLate Catalyst (11b). To a solution of (4*S*,5*S*)-2,2-dimethyl-α,α,α′,α′-tetrakis(*p*-tolyl)-1,3-dioxolane-4,5-dimethanol (313 mg, 0.6 mmol) in toluene (5 mL) was added dropwise a solution of orthotitanic acid tetraisopropyl ester (170 mg, 0.6 mmol) in toluene (1 mL) at room temperature under argon atmosphere, and the mixture was stirred at the same temperature for 30 min. The solution was concentrated under reduced pressure at room temperature, and the resulting colorless solid was dissolved in toluene (5 mL) under argon atmosphere. To the mixture was added dropwise a solution of silicon tetrachloride (306 mg, 1.8 mmol) in toluene (1.5 mL), and the mixture was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure at room temperature to give Ti(IV)−TADDOLate catalyst **11b** as a red solid. The catalyst **11b** thus obtained was dissolved in toluene (5 mL) under argon atmosphere, and then the solution was cooled to −78 °C and was added dropwise a solution of aldehyde **4a** (68 mg, 0.5 mmol) in toluene (1 mL). After the mixture was stirred at the same temperature for 30 min, a solution of monochloro ketene silyl acetal **16** (135 mg, 0.75 mmol) in toluene (1 mL) was added dropwise, and the mixture was stirred at the same temperature for 3 h. To the reaction mixture was added a saturated aqueous sodium chloride solution (30 mL), and the mixture was extracted with AcOEt (30 mL). The aqueous layer was extracted again with AcOEt (30 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to remove the solvent. To the residue were added THF (40 mL) and 1 N aqueous HCl (10 mL) at rt. The reaction mixture was stirred for 0.5 h and extracted with AcOEt. The extracts were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the resulting mixture was purified by silica gel column chromatography (hexane/AcOEt = 8:1 to 3:1) to give 65 mg (53% yield) of **14** as colorless crystals. The ratio of 3*S* compound and 3*R* compound in the mixture is 93:7 as determined by HPLC: mp 63−65 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.94 (1H, brs), 3.81 (6H, s), 4.36 (0.94H, d, J = 8.0 Hz, erythro form), 4.42 (0.06H, d, J = 6.7 Hz, threo form), 5.01 (0.94H, d, J = 8.0 Hz, erythro form), 5.07 (0.06H, d, J = 6.7 Hz, threo form), 6.86−6.97 (2H, m), 7.25−7.28 (2H, m).

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