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A Catalytic Asymmetric Synthesis of Chiral Glycidic Acid Derivatives through Chiral Dioxirane-Mediated Catalytic Asymmetric Epoxidation of Cinnamic Acid Derivatives

Ritsuo Imashiro[†] and Masahiko Seki*[,‡]

Medicinal Research Laboratories, Tanabe Seiyaku Co., Ltd., 3-16-89, Kashima, Yodogawa-ku, Osaka 532-8505, Japan and Export & Import Group, Purchasing Department, Logistics Division, Tanabe Seiyaku Co., Ltd., 3-2-10, Dosho-Machi, Chuo-ku, Osaka 541-8505, Japan

m-seki@tanabe.co.jp

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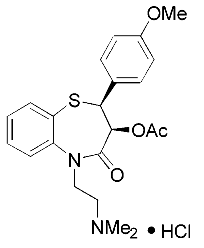
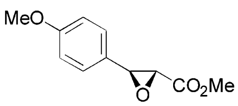
A novel and practical asymmetric synthesis of chiral glycidic acid derivatives involving methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate ((2*R*,3*S*)-**2a**), a key intermediate for diltiazem hydrochloride (**1**), was developed. Treatment of methyl (*E*)-4-methoxycinnamate ((*E*)-**3a**) with chiral dioxirane, generated in situ from a catalytic amount (5 mol %) of an 11-membered C_2-symmetric binaphthyl ketone (*R*)-**7a**, provided (2*R*,3*S*)-**2a** in 92% yield and 80% ee. Other cinnamic acid esters and amides were epoxidized by the use of the same procedure to give the corresponding chiral glycidic acid derivatives with up to 95% yield and 92% ee. Higher enantioselectivities in the asymmetric epoxidation of (*E*)-cinnamates than that of (*E*)-stilbene derivatives were observed and were proposed to be attributed to a dipole−dipole repulsion between oxygen atoms of an ester group in the cinnamates and those of the lactone moieties in the binaphthyl dioxirane.

Introduction

Diltiazem hydrochloride (**1**) is one of the most potent calcium antagonists and has been used for over 20 years as a drug for the treatment of angina and hypertension.[1] Among a number of synthetic approaches to **1**, a method utilizing methyl (2*R*,3*S*)-4-methoxyglycidate ((2*R*,3*S*)-**2a**) as a key intermediate has been recognized to be the most efficient one.[2] The chiral glycidates are key intermediates crucial for synthesizing other drugs and natural products as well.[3] While a current industrial production of (2*R*,3*S*)-**2a** has relied upon kinetic resolution of racemates (±)-**2a** through a lipase-catalyzed asymmetric hydrolysis,[4] it suffers from such drawbacks as a poor yield (42%) of (2*R*,3*S*)-**2a** as well as waste materials (ca. 200 t/year) arising from the unwanted enantiomer (2*S*,3*R*)-**2a**. A catalytic asymmetric synthesis of the chiral glycidic acid derivatives involving (2*R*,3*S*)-**2a** has therefore been highly desirable.



Diltiazem (**1**)



(2*R*,3*S*)-**2a**

While the asymmetric synthesis of the chiral glycidic acid derivatives has so far been extensively investigated,[5−9] an approach based on catalytic asymmetric epoxidation of cinnamates is considered to be the most efficient one, since the chiral glycidates can be obtained in a single step from the readily available cinnamates.[9] Jacobsen and co-

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[†] Medicinal Research Laboratories.

[‡] Export & Import Group, Purchasing Department, Logistics Division.

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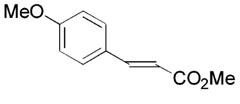
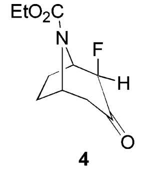
workers have reported catalytic asymmetric epoxidation of (*Z*)-cinnamates employing a chiral salen−manganese complex as the catalyst.[9a] Although excellent enantioselectivities (up to 96% ee) were achieved, the synthetic method requires poorly accessible (*Z*)-cinnamates as the starting materials, and the products are obtained as a mixture of (*E*)- and (*Z*)-epoxides. Shibasaki and co-workers have recently reported that catalytic asymmetric epoxidation of (*E*)-α,β-unsaturated carboxylic acid imidazolides, followed by the decomposition of the peroxides with MeOH, gave optically active glycidates with high yields and enantioselectivities (up to 93% ee).[9i,j] However, it requires highly toxic triphenylarsine as an additive and an expensive phenylimidazolide as the starting material.

Chiral dioxiranes, generated in situ from chiral ketones and Oxone, have been reported as the promising oxidizing reagents for asymmetric epoxidation of olefins.[9b−h,10−12] Nonetheless, the enantioselective epoxidation of α,β-unsaturated acid derivatives with chiral dioxirane still remaines a challenging issue. As the dioxiranes are electrophilic oxidants, they are generally inert to electron-deficient olefins such as α,β-unsaturated acid derivatives.[12] For instance, epoxidation of cinnamates with chiral dioxirane, derived either from α-fluoro-*N*-ethoxycarbonyltropinone (**4**)[9d] or chiral α-fluoro cyclohexanones **5**,[9f] proceeds in only moderate yields and enantioselectivities. Although Shi and co-workers have accompolished excellent enantioselectivities in the catalytic asymmetric epoxidation of cinnamates employing fructose-derived ketone **6**, yields of the chiral glycidates were only moderate to good even by the use of excess Oxone (5 equiv) and a subequimolar amount of the chiral ketone (30 mol %).[9g]

Meanwhile, Yang and co-workers have developed 11-membered C_2-symmetric biaryl ketones (*R*)-**7a**−**d** that catalyze epoxidation of various (*E*)-di- and trisubstituted olefins with high yields and high enantioselectivities.[11] We envisioned a possible use of the biaryl ketones (*R*)-**7a**−**d** as catalysts for the asymmetric epoxidation of methyl (*E*)-4-methoxycinnamate ((*E*)-**3a**) to obtain (2*R*,3*S*)-**2a**. In contrast to **4**−**6**, the catalysts (*R*)-**7a**−**d** might induce both high reactivity and enantioselectivity in the epoxidation of (*E*)-**3a** due to the presence of the two electron-withdrawing lactone moieties in (*R*)-**7a**−**d** and $\pi-\pi$ interactions between the aromatic groups in (*R*)-**7a**−**d** and (*E*)-**3a**. An enhanced stereocontrol should be expected as well on (*R*)-**7a**−**d** over **4**−**6**, since the epoxidation employing (*R*)-**7a**−**d** may proceed with homotopic ring opening of the dioxiranes, while that employing **4**−**6** must involve heterotopic cleavage. The ketones (*R*)-**7a**−**d** have an additional and significant advantage of easy preparation by using our reported procedure.[13]



(*E*)-**3a**



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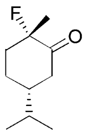

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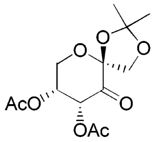

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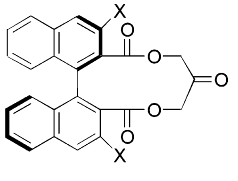
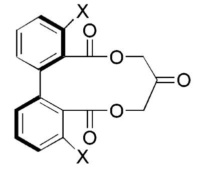


(*R*)-**7a**: X = H
(*R*)-**7b**: X = Cl



(*R*)-**7c**: X = Cl
(*R*)-**7d**: X = NO$_2$

We report herein a novel synthesis of (2*R*,3*S*)-**2a**[14] and other chiral glycidic acid derivatives through catalytic asymmetric epoxidation of cinnamaic acid derivatives with chiral C_2-symmetric biaryl ketone (*R*)-**7a** used as a catalyst. The origin of the stereocontrol in the asymmetric epoxidation will be discussed as well.

Results and Discussion

Screening of Chiral Biaryl Ketone Catalysts (*R*)-7a−d. The chiral binaphthyl ketones (*R*)-**7a**,**b** were efficiently prepared by conducting our previously reported procedure.[13c,d] Other chiral biphenyl ketones (*R*)-**7c**,**d** were synthesized according to the literature.[11c] Treatment of (*E*)-**3a** with Oxone (5 equiv) and $NaHCO_3$ (15.5 equiv) in the presence of (*R*)-**7a**−**d** (10 mol %) in DME−aq 0.4 μM Na_2EDTA [2:1, 60 volume (mL) per weight (g) of (*E*)-**3a** (v/w)] at 27 °C for 27 h provided the desired glycidate (2*R*,3*S*)-**2a** in both good yields and enantioselectivities (52−87% yield, 67−85% ee, Table 1). It should be noted

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TABLE 1. Catalytic Asymmetric Epoxidation of (*E*)-3a with Chiral Dioxiranes Generated in Situ from Catalysts (*R*)-7a−d

$$(E)\text{-}\mathbf{3a}\xrightarrow[\substack{\text{DME/H}_2\text{O 2:1 (60 v/w)}^a\\ \text{Na}_2\text{EDTA, 27 °C, 27 h}}]{\substack{\text{catalyst (10 mol\%)}\\ \text{Oxone (5 equiv)}\\ \text{NaHCO}_3\text{ (15.5 equiv)}}}(2R,3S)\text{-}\mathbf{2a}$$

entry[b]	catalyst	assay yield (%)[c]	ee (%)[c]
1	(*R*)-**7a**	87	76
2	(*R*)-**7b**	74	85
3	(*R*)-**7c**	52	67
4	(*R*)-**7d**	86	68

[a] Volume (mL) per weight (g) of (*E*)-**3a**. [b] Reactions were conducted on a 10-mmol scale. [c] Determined by HPLC analysis.

TABLE 2. Effect of Solvents in the Catalytic Aymmetric Epoxidation of (*E*)-3a with Catalyst (*R*)-7a

$$(E)\text{-}\mathbf{3a}\xrightarrow[\substack{\text{Solvent/H}_2\text{O 2:1 (15 v/w)}^a\\ \text{27 °C}}]{\substack{(R)\text{-}\mathbf{7a}\text{ (5 mol\%)}\\ \text{Oxone (1 equiv)}\\ \text{NaHCO}_3\text{ (3.1 equiv)}}}(2R,3S)\text{-}\mathbf{2}$$

entry[b]	solvent	*t* (h)[c]	assay yield (%)[d]	ee (%)[d]
1[e]	DME	2	83	78
2	DME	2	86	78
3	CH_3CN	22.5	33	72
4	$EtOCH_2CH_2OH$	4.5	67	71
5	$MeOCH_2CH_2OH$	4	62	73
6	$HOCH_2CH_2OH$	3.5	2	31
7	MeOH	21	27	63
8	^{i}PrOH	22	19	73
9	DMF	4	45	70
10	acetone	2	93	49
11	^{t}BuOMe	7	0	
12[f]	toluene	24	0	
13[f]	CH_2Cl_2	22	0	
14	1,4-dioxane	5.5	81	76
15	1,3-dioxorane	4.5	23	75

[a] Volume (mL) per weight (g) of (*E*)-**3a**. [b] Reactions were conducted on a 10-mmol scale. Oxone and $NaHCO_3$ were added portionwise every 5 min over 1.5 h. [c] Reaction time after addition of reagents. [d] Determined by HPLC analysis. [e] Na_2EDTA was added. [f] 1 mol % of Bu_4NHSO_4 was added.

that any *cis*-glycidates were not detected at all in the reaction mixture by HPLC. The binaphthyl ketones (*R*)-**7a**,**b** proved to be more effective than the biphenyl counterparts (*R*)-**7c**,**d** (Table 1, entries 1 and 2 versus entries 3 and 4). 3,3′-Dichloro-1,1′-binaphthyl ketone (*R*)-**7b** provided (2*R*,3*S*)-**2a** in higher enantioselectivity (85% ee) than the corresponding unsubstituted one (*R*)-**7a** (76% ee) (Table 1, entries 1 and 2). The stereochemical outcome is consistent with the reported epoxidation of (*E*)-stilbene derivatives.[11a−c] Because of the much higher yield in the epoxidation with (*R*)-**7a** (87%) than that with (*R*)-**7b** (74%) and the easier preparation of (*R*)-**7a** over (*R*)-**7b**, the binaphthyl ketone (*R*)-**7a** was used in the subsequent optimization.

Effect of Solvents. Screening of the solvent for the reaction was then undertaken, and the proper choice of solvents was found to be significant for obtaining good yields and enantioselectivities (Table 2). To develop a process for a practical large-scale preparation of (2*R*,3*S*)-**2a**, reduction of the amount of the reagents, catalyst, and solvent was intensively studied. The reactions were conducted with use of 1 equiv of Oxone, 3.1 equiv of $NaHCO_3$, and 5 mol % of (*R*)-**7a** in DME−H_2O. Although addition of Na_2EDTA has been reported to be essential to prevent the decomposition of Oxone with the concomitant metal in water,[15] it was not important in this reaction (Table 2, entry 1 versus entry 2), and thus Na_2EDTA was not added for further optimization. While a mixed solvent, CH_3CN−H_2O, has often been employed for the dioxirane-mediated asymmetric epoxidation, it resulted in a poor yield (33%) with a little decrease of enantioselectivity (72% ee) (Table 2, entry 3). The use of alcoholic solvents, $EtOCH_2CH_2OH$−H_2O and $MeOCH_2CH_2OH$−H_2O, led to reduction in both the yield and the enantioselectivity (Table 2, entry 4, 67% yield, 72% ee; entry 5, 62% yield, 71% ee). The use of more polar protic solvents, $HOCH_2CH_2OH$−H_2O, ^{i}PrOH−H_2O, and MeOH−H_2O, or aprotic solvent DMF−H_2O provided much poorer yields (Table 2, entry 6, 2% yield; entry 7, 27% yield; entry 8, 19% yield; entry 9, 45% yield, respectively). It is worth noteing that the reaction rate was remarkably accelarated in acetone−H_2O to provide (2*R*,3*S*)-**2a** in

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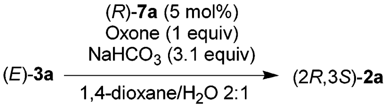
TABLE 3. Optimization of the Reaction Conditions



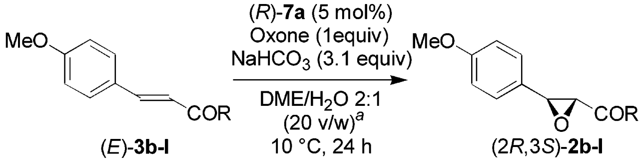
entry[a]	base (equiv)	vol of solvent (v/w)[b]	temp (°C)	addition time (h)	reaction time (h)	assay yield (%)[c]	ee (%)[c]
1[d]	$NaHCO_3$ (3.1)	15	27	1.5	5.5	81	76
2[d]	$NaHCO_3$ (4)	15	27	1.5	3.5	80	76
3[d]	$KHCO_3$ (3.1)	15	27	1.5	5.5	74	76
4[d]	K_2CO_3 (1.55)	15	27	1.5	6.5	74	78
5[d,e]	$NaHCO_3$ (3:1)	15	15−27	1.5	3.5	85	76
6[d,e]	$NaHCO_3$ (3.1)	20	15−27	1.5	5	88	77
7[f]	$NaHCO_3$ (3.1)	20	5	<0.1	48	92	80

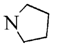
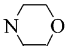
[a] Reactions were conducted on a 10-mmol scale. [b] Volume (mL) per weight (g) of (*E*)-**3a**. [c] Determined by HPLC analysis. [d] Reagents were added every 5 min over 1.5 h. [e] After addition of reagents at 15 °C, the reactions were conducted at 27 °C. [f] Reagents were added at one time.

excellent yield albeit with a moderate enantioselectivity (93%, 49% ee) (Table 2, entry 10). Even if competing epoxidation with achiral dimethyldioxirane generated in situ from acetone should take place in the reaction, the moderate enantioselectivity (49% ee) may reflect the easier formation of the dioxirane from (*R*)-**7a** than from acetone and/or the higer reactivity of the chiral dioxirane derived from (*R*)-**7a** than dimethyldioxirane. The use of biphasic systems, ^{t}BuOMe-H_2O, toluene-H_2O, and CH_2Cl_2−H_2O, did not furnish (2*R*,3*S*)-**2a** at all even in the presence of a phase transfer catalyst (Table 2, entries 11−13). The use of inexpensive 1,4-dioxane−H_2O afforded (2*R*,3*S*)-**2a** in 81% yield with 76% ee, which were comparable to the values observed in DME−H_2O. Although 1,3-dioxorane, having a similar structure to 1,4-dioxane, provided a good enantioselectivity (75% ee), the yield was poor (23%). Considering the cost together with the yield and ee, the inexpensive mixed solvent, 1,4-dioxane−H_2O, was chosen as a reaction solvent for further optimization.

Optimiztion of the Reaction Conditions. Shi and co-workers have reported that the catalytic turnover was dramatically improved upon raising the pH value in the reaction system.[10e] Addition of K_2CO_3 in place of $NaHCO_3$ was thus tested in expectation of higher basicity as well as higher solubility in H_2O than those of $NaHCO_3$. Although a slightly higher enantioselectivity of (2*R*,3*S*)-**2a** (78% ee) was obtained when K_2CO_3 was employed, the yield decreased (74%) (Table 3, entry 4). The use of $KHCO_3$, which is less basic than K_2CO_3, provided the same yield and a slightly lower enantioselectovity (74% yield and 76% ee, Table 3, entry 3). Decomposition of (2*R*,3*S*)-**2a**, Oxone, and/or chiral dioxirane under the basic conditions might result in the decrease of the yield of (2*R*,3*S*)-**2a**. While the use of an excess amount (4 equiv) of $NaHCO_3$ accelerated the epoxidation, the yield was almost the same as the case when employing 3.1 equiv of $NaHCO_3$, which is a slightly excess amount for neutralizing the acids generated from Oxone (Table 3, entry 1 versus entry 2). The reaction conditions were further optimized for attaining higher yield and higher enantioselectivity. When the addition temperature for Oxone and $NaHCO_3$ was lowered from 27 to 15 °C, the yield of (2*R*,3*S*)-**2a** was improved from 81% to 85% (Table 3, entry 1 versus entry 5). Increasing solvent volume from 15 v/w of (*E*)-**3a** to 20 v/w led to an increase of both yield and enantioselectivity, whcih is as well possibly due to an increase of the solubility of Oxone and $NaHCO_3$ (88%, 77% ee, Table 3, entry 6 versus entry 1). Although changing the reaction temperature from 27 to 5 °C resulted in a longer reaction period (48 h) to complete the reaction, the best result (92% yield and 80% ee) was achieved (Table 3, entry 7). Although the ee value of the present protocol is inferior to the result reported by Shi and co-workers (80% ee versus 92% ee), it is much superior in terms of yield (92% versus 57%), the use of a smaller amount of Oxone (1 equiv versus 5 equiv), and the lower chiral catalyst loading (5 mol % versus 30 mol %).

TABLE 4. Asymmetric Epoxidation of 4-Methoxycinnmates and 4-Methoxycinnamides

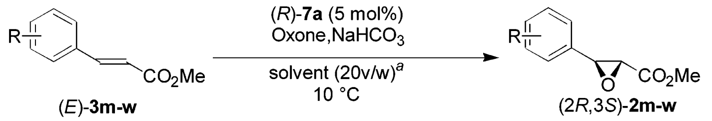


Entry	Substrate	R	Product	Assay Yield (%)[d]	ee (%)[d]
1[b]	(*E*)-**3b**	OEt	(2*R*,3*S*)-**2b**	85	77
2[c]	(*E*)-**3c**	O^{i}Pr	(2*R*,3*S*)-**2c**	85	80
3[c]	(*E*)-**3d**	O^{t}Bu	(2*R*,3*S*)-**2d**	89	77
4[c]	(*E*)-**3e**	OBn	(2*R*,3*S*)-**2e**	84	78
5[c]	(*E*)-**3f**	NH_2	(2*R*,3*S*)-**2f**	80	71
6[c]	(*E*)-**3g**	NHEt	(2*R*,3*S*)-**2g**	93	65
7[c]	(*E*)-**3h**	NHBn	(2*R*,3*S*)-**2h**	87	66
8[c]	(*E*)-**3i**	NEt_2	(2*R*,3*S*)-**2i**	80	13
9[c]	(*E*)-**3j**	NBn_2	(2*R*,3*S*)-**2j**	69	20
10[c]	(*E*)-**3k**		(2*R*,3*S*)-**2k**	79	8
11[c]	(*E*)-**3l**		(2*R*,3*S*)-**2l**	75	18

[a] Volume (mL) per weight (g) of (*E*)-**3a**. [b] Reaction was conducted on a 10-mmol scale. [c] Reactions were conducted on a 1-mmol scale. [d] Determined by HPLC analysis.

Application to the Asymmetric Epoxidation of Other Cinnamic Acid Derivatives. The asymmetric epoxidation catalyzed by (*R*)-**7a** was applied to the epoxidation of various cinnamic acid derivatives other than (*E*)-**3a**. As shown in Table 4, the bulkiness of ester moieties did not affect the yield and the enantioselectivity in the asymmetric epoxidation (Table 4, entries 1−4). Asymmetric epoxidation of cinnamamides, prepared from ammonia or primary amine, proceeded with good enan-

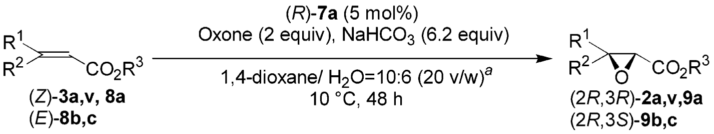
TABLE 5. Asymmetric Epoxidation of Cinnamates Carrying Various Substituents on the Phenyl Ring



entry	substrate	R	solvent[d]	Oxone (equiv)	$NaHCO_3$ (equiv)	*t* (h)	product	assay yield (%)[f]	ee (%)[f]
1[c]	(*E*)-**3m**	4-O^{t}Bu	DME/H_2O	1	3.1	24	(2*R*,3*S*)-**2m**	83	85
2[b]	(*E*)-**3n**	4-Me	DME/H_2O	1	3.1	24	(2*R*,3*S*)-**2n**	52	76
3[b]	(*E*)-**3n**	4-Me	DME/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2n**	71	75
4[b]	(*E*)-**3n**	4-Me	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2n**	95	72
5[b]	(*E*)-**3o**	4-H	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2o**	75	74
6[c]	(*E*)-**3p**	4-F	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2p**	74	72
7[c]	(*E*)-**3q**	4-Cl	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2q**	45	73
8[c]	(*E*)-**3r**	4-CO_2Me	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2r**	6	81
9[c]	(*E*)-**3s**	4-CF_3	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2s**	14	86
10[c]	(*E*)-**3t**	4-Ph	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2t**	51	91
11[c]	(*E*)-**3u**	4-^{t}Bu	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2u**	81	92
12[c]	(*E*)-**3v**	2-OMe	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2v**	55	53
13[c]	(*E*)-**3w**	3-OMe	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2w**	11	47
14[c]	(*E*)-**3x**	2,3-benzo	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2x**	55	75
15[c]	(*E*)-**3y**	3,4-benzo	1,4-dioxane/H_2O	2[e]	6.2[e]	48	(2*R*,3*S*)-**2y**	47	63

[a] Volume (mL) per weight (g) per (*E*)-**3m**−**w**. [b] Reactions were conducted on a 10-mmol scale. [c] Reactions were conducted on a 1-mmol scale. [d] The ratios 1,4-dioxane/H_2O and DME/H_2O were 10:6 and 2:1, respectively. [e] Oxone (1 equiv) and $NaHCO_3$ (3.1 equiv) were added after 24 h. [f] Determined by HPLC analysis.

TABLE 6. Asymmetric Epoxidation of (*Z*)- and Trisubstituted 3-Aryl-α,β-Unsaturated Esters



entry[b]	substrate	R^1	R^2	R^3	product	assay yield (%)[c]	ee (%)[c]
1	(*Z*)-**3a**	H	4-$MeOC_6H_4$	Me	(2*R*,3*R*)-**2a**[e]	71	16
2	(*Z*)-**3v**	H	2-$MeOC_6H_4$	Me	(2*R*,3*R*)-**2v**[e]	32	15
3	(*Z*)-**8a**	H	Ph	Et	(2*R*,3*R*)-**9a**[d]	57	26
4	(*E*)-**8b**	Ph	Me	Et	(2*R*,3*S*)-**9b**[d]	93	40
5	(*E*)-**8c**	2-thienyl	H	Me	(2*R*,3*S*)-**9c**	5	60

[a] Volume (mL) per weight (g) of the cinnamates. [b] Reactions was conducted on a 1-mmol scale. [c] Determined by HPLC analysis. [d] The absolute configurations of (2*R*,3*R*)-**9a** and (2*R*,3*S*)-**9b** were determined by comparing the optical rotations with the reported ones. [e] The absolute configurations of (2*R*,3*R*)-**2a** and (2*R*,3*R*)-**2v** were confirmed by comparing the HPLC patterns with those of (2*R*,3*R*)-**9a**.

tioselectivities (Table 4, entries 5−7). In contrast, in the case of cinnamamides, prepared from secondary amines, considerably poor enantioselectivities were observed (Table 4, entries 8−11).

The asymmetric epoxidation was further applied to the cinnamates carrying various substituents on the phenyl ring. A higher ee was obtained in the asymmetric epoxidation of (*E*)-**3m** bearing a 4-*tert*-butoxy substituent on the phenyl group, which is more bulky and has more electron-donating property than the methoxy group (Table 5, entry 1). The rate of epoxidation of (*E*)-**3n** carrying the 4-methyl group, which furnish a somewhat weak electron-donating effect, was slower and the yield of (2*R*,3*S*)-**2n** was poorer than those observed in the case of 4-alkoxy derivatives (Table 5, entry 2). Change of solvent from DME to 1,4-dioxane and further addition of Oxone (1 equiv) and $NaHCO_3$ (3.1 equiv) considerably improved the yield of (2*R*,3*S*)-**2n** (Table 5, entry 4 versus entries 2 and 3). When the 4-substituent on the phenyl group became larger (from H, fluoro, methyl, chloro, trifluoromethyl, and methoxycarbonyl phenyl to *tert*-butyl), the enantioselectivitiy elevated from 72% to 92% ee. In contrast, when a more electron-withdrawing 4-substituent (from alkyl, H, fluoro, phenyl, chloro, and trifluoromethyl to methoxycarbonyl) on the phenyl group was employed, the yield of the epoxide decreased from 95% to 6% (Table 5, entries 4−11). Substitution at the 2- or 3-position of the phenyl group reduced the yields and the enantioselectivities of the epoxides (Table 5, entries 12 and 13), while 2- or 3-naphthyl groups provided moderate enantioselectivities (Table 5, entries 14 and 15). The glycidates (2*R*,3*S*)-**2n** and (2*R*,3*S*)-**2o** are a key intermediate for a platelet aggregation inhibitor[3g] and Taxol side chain,[3a−c] respectively.

The asymmetric epoxidation of (*Z*)-cinnamates employing (*R*)-**7a** gave low to good yields and much poorer enantioselectivities compared to (*E*)-cinnamates (Table 6, entries 1−3 versus Tables 4 and 5). Trisubstituted cinnamate (*E*)-**8b** was epoxidized very rapidly to give (2*R*,3*S*)-**9b** in an excellent yield and with a moderate enantioselectivity (Table 6, entry 4). A cinnamate (*E*)-**8c** involving the 2-thienyl group provided only a trace (5%) of the epoxide (2*R*,3*S*)-**9c**, which might be attributed to easy oxidation of the sulfur atom in (*E*)-**8c** and/or (2*R*,3*S*)-**9c** under the reaction conditions (Table 6, entry 5).

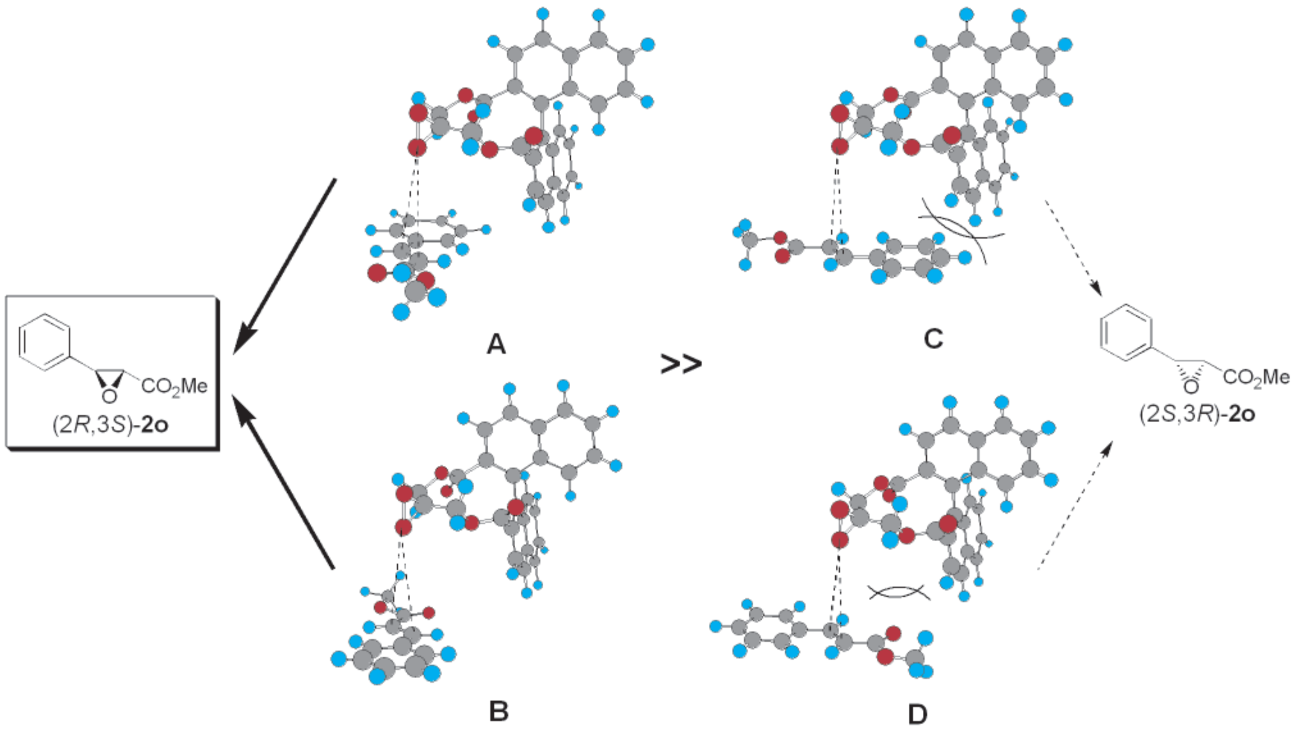


FIGURE 1. Plausible transition states for the asymmetric epoxidation of (*E*)-**3o**.

A Plausible Mechanism for the Asymmetric Epoxidation. It is reported that epoxidation of olefins by dioxiranes is mediated by an electrophilic oxygen atom transfer from dioxiranes to the nucleophilic double bond of olefins, and therefore electron-defficient olefins, especially cinnamates, are resistant to be epoxidized by the dioxiranes.[16] Despite the difficulty, we found that (*R*)-**7a** developed by Yang and co-workers can be a powerful catalyst for asymmetric epoxidation of not only cinnamates but also cinnamamides. Yang and co-workers suggested that the asymmetric epoxidation of stilbene derivatives mediated by chiral dioxirane derived from (*R*)-**7a** occurs through a spiro transition state rather than a planar one.[11c,17] On the basis of this assumption, four possible spiro transition states A−D are expected for the present reaction (Figure 1).[18] It is considered that the major (2*R*,3*S*)-enantiomers (2*R*,3*S*)-**2a**−**w** were produced through the transition states A or B in Figure 1 in that the aryl moietiy and the ester group of cinnamates may be apart from binaphthyl groups in the dioxirane. Transition state C has been claimed to be less favorable because of the steric interaction between the 4-substituent in the (*E*)-stilbenes and the 3,3′-substituents in the binaphthyl dioxiranes.[11c] The proposal was further supported by our results in that the larger the substituent at 3,3′-positions in the binaphthyl ketone or the 4-substituent on the phenyl ring of cinnamates becomes, the higher the enantioselectivities will be (Tables 1 and 5). Transition state D, which may alternatively lead to the minor product, is considered to have less steric interaction between the ester group of cinnamates and the 3,3′-substituents of the binaphthyl dioxiranes. However, it is of interest that epoxidations of 4-substituted cinnamates proceeded more enantioselectively than (*E*)-stilbenes carrying substituents at the 4-position (Scheme 1).[11c] This might be attributed to stereoelectronic effects involving a dipole−dipole repulsion[10z] between an ester group of cinnamates and lactone moieties of the binaphthyl dioxirane. In the case of cinnamamides, prepared from secondary amines, considerably poor enantioselectivities were obtained (Table 4, entries 8−11). Yang and co-workers have suggested that the existence of much larger steric sensors at the 3,3′-positions of the binaphthyl dioxirane resulted in poorer enantioselectivities and slower epoxidation.[11c] *N*,*N*-Disubstituted amides should be more sterically demanding than esters, which might be responsible for the significant decrease of the enantioselectivities and the somewhat decrease of the yields. The low enantioselectivities obtained for the (*Z*)-cinnamates might be accounted for by considering the transition states models such as Figure 1.

Conclusion

As described above, a novel and efficient asymmetric synthesis of chiral glycidic acid derivatives, involving a key intermediate for diltiazem, was accomplished through catalytic asymmetric epoxidation of cinnamates and cinnamamides with 5 mol % of chiral binaphthyl ketone

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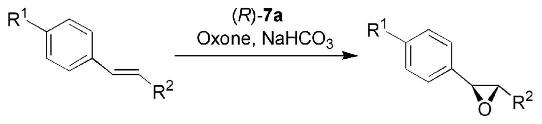
(18) The stable conformer of the dioxirane derived from (*R*)-**7a** was created as follows: The coordinates of the X-ray structure of (*R*)-**7a**, reported by Yang and co-workers, was exchanged into the corresponding dioxirane and then the stable conformer of the dioxirane was calculated by the MOPAC PM3 method.

SCHEME 1. Comparison of the Enantioselectivities in the Asymmetric Epoxidation of 4-Substituted Stilbene Derivatives with That of 4-Substituted Cinnmates Employing the Catalyst (*R*)-7a[a]



[a]R^1=H, R^2=Ph, 47% ee [a]R^1=Me, R^2=4-MeC_6H_4, 50% ee [a]R^1=Ph, R^2=4-PhC_6H_4, 87% ee [a]R^1=*t*-Bu, R^2=4-*t*-BuC_6H_4, 76% ee

[b]R^1=H, R^2=CO_2Me, 74% ee [b]R^1=Me, R^2=CO_2Me, 72% ee [b]R^1=Ph, R^2=CO_2Me, 91% ee [b]R^1=*t*-Bu, R^2=CO_2Me, 92% ee

[a] Condition a: The reactions were carried out with use of (*R*)-**7a** (10 mmol %), Oxone (5 equiv), and $NaHCO_3$ (15.5 equiv) in CH_3CN−Na_2EDTA (20:17) at room temperature. Condition b: The reactions were conducted with (*R*)-**7a** (5 mmol %), Oxone (1 equiv), and $NaHCO_3$ (3.1 equiv) in 1,4-dioxane−H_2O (10:6) at 10 °C.

(*R*)-**7a** used as a catalyst. The present method was applied to the asymmetric epoxidation of a wide variety of cinnamic acid derivatives, especially (*E*)-cinnamates and cinnamamides bearing a substituent at the 4-position of the phenyl group to give the corresponding chiral glycidic acid derivatives in up to 95% yield and 92% ee. The enhanced enantioselectivities in the epoxidation of cinnamates over stilbene derivatives can be attributed to the dipole−dipole repulsion between an ester group of cinnamates and lactone moieties of dioxiranes derived from the binaphthyl ketones.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with tetramethylsilane used as an internal standard. Optical rotations were measured at the indicated temperature with a sodium lamp (D line, 589 nm). Silica gel column chromatography was performed with Kieselgel 60 (E. Merck). Thin-layer chromatography (TLC) was carried out on E. Merck 0.25-mm precoated glass-backed plates (60 F254). Development was accomplished with 5% phosphomolybdic acid in ethanol-heat or visualized by UV light where feasible. All solvents and reagents were used as received.

(*R*)-5*H*-Dinaphtho[2,1-g:1′,2′-*i*][1,5]dioxacycloundecin-3,6,9(7*H*)-trione ((*R*)-7a). The compound (*R*)-**7a** was prepared according to our previously reported procedure.[13d] Colorless crystals; mp 300 °C dec; $[\alpha]^{25}_D$ +10.9 (*c*, 1.0, $CHCl_3$); >99% ee (Chiralcel OD, hexane/^{i}PrOH = 10:1, 1 mL/min, 40 °C, 224 nm); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.04 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.56 (dd, J = 1.5, 6.6 Hz, 2H), 7.30−7.37 (m, 2H), 7.25 (d, J = 14.1 Hz, 2H), 5.56 (d, J = 15.4 Hz, 2H), 4.20 (d, J = 15.4 Hz, 2H); MS (EI) *m*/*z* 396 (M^+); IR (KBr) ν 3550, 3430, 3050, 2970, 2925, 1755, 1730, 1593 cm^{-1}. Anal. Calcd for $C_{25}H_{16}O_5$: C, 75.71; H, 4.07. Found: C, 75.42; H, 3.99.

(*R*)-2,10-Dichlorodinaphtho[2,1-g:1′,2′-*i*]-4,8-dioxacycloundecane-3,6,9-trione ((*R*)-7b). The compound (*R*)-**7b** was prepared according to our previously reported procedure.[13c] Colorless crystals; mp 257−259 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.08 (s, 2H), 7.88 (d, J = 8.2 Hz, 2H), 7.56 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 5.57 (d, J = 15.7 Hz, 2H), 4.34 (d, J = 15.3 Hz, 2H); MS (EI) *m*/*z* 464 ($[M]^+$), 466 ($[M + 2]^+$); IR (KBr) ν 3050, 2920, 1741, 1613, 1580, 1559 cm^{-1}; $[\alpha]^{22}_D$ +92.0 (*c*, 0.100, $CHCl_3$).

(*R*)-3,19-Dichloro-9,13-dioxa-tricyclo[13.4.0.0.2,7]-nonadeca-1(15),2(7),3,5,16,18-hexane-8,11,14-trione ((*R*)-7c). The compound (*R*)-**7c** was prepared according to the literature.[11c] Yellow crystals; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.68 (dd, J = 2.7, 6.6 Hz, 2H), 7.50−7.40 (m, 4H), 5.50 (d, J = 15.4 Hz, 2H), 4.19 (d, J = 15.3 Hz, 2H), 3.39 (br, 2H).

(*R*)-3,19-Dinitro-9,13-dioxa-tricyclo[13.4.0.0.2,7]-nonadeca-1(15),2(7),3,5,16,18-hexane-8,11,14-trione ((*R*)-7d). The compound (*R*)-**7c** was prepared according to the literature.[11c] Yellow crystals; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.39 (dd, J = 1.3, 8.1 Hz, 2H), 7.88 (dd, J = 1.3, 7.8 Hz, 2H), 7.72 (t, J = 8.0 Hz, 2H), 5.51 (d, J = 15.3 Hz, 2H), 4.20 (d, J = 15.3 Hz, 2H); IR (KBr) ν 3080, 2925, 1758, 1730, 1603, 1560, 1531, 1478, 1418, 1344, 1265, 1198, 1155, 1129 cm^{-1}.

General Procedure for Cinnamates: Synthesis of (*E*)-*tert*-Butyl 4-Methoxycinnamate ((*E*)-3d). To a solution of 4-methoxycinnamic acid (2.67 g, 15 mmol) in CH_2Cl_2 (30 mL, stabilized with amylenes) was added $(COCl)_2$ (1.57 mL, 18 mmol) and DMF (3 drops) at room temperature, and the mixture was stirred at room temperature for 1 h. The mixture was evaporated and azeotroped with $CHCl_3$ (30 mL, stabilized with amylenes). To a solution of the corresponding acid chloride in CH_2Cl_2 (30 mL, stabilized with amylenes) were added ^{t}BuOH (4.30 mL, 45 mmol) and pyridine (3.84 mL, 45 mmol) successively at room temperature, and the mixture was stirred at room temperature overnight. The mixture was poured into H_2O and extracted with AcOEt. The extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 10:1) to give (*E*)-*tert*-butyl 4-methoxycinnamate ((*E*)-**3d**) (3.29 g, 94%) as colorless crystals. Mp 34−35 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (d, J = 16.0 Hz, 1H), 7.46 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.24 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H), 1.53 (s, 9H); MS (GC) *m*/*z* 234 (M^+); IR (ATR) ν 2977, 1701, 1634, 1604, 1576, 1511, 1458, 1421 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.50; H, 7.87.

(*E*)-Isopropyl 4-methoxycinnamate ((*E*)-3c): yield 98%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, J = 15.9 Hz, 1H), 7.47 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.29 (d, J = 15.9 Hz, 1H), 5.13 (hept, J = 6.3 Hz, 1H), 3.84 (s, 3H), 1.81 (d, J = 6.3 Hz, 6H); MS (GC) *m*/*z* 220 (M^+); IR (ATR) ν 2980, 1702, 1634, 1603, 1576, 1511 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.68; H, 7.27.

(*E*)-Benzyl 4-methoxycinnamate ((*E*)-3e): yield 90%; colorless crystals; mp 53−54 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, J = 15.9 Hz, 1H), 7.47 (d, J = 8.6 Hz, 2H), 7.43−7.32 (m, 5H), 6.90 (d, J = 8.6 Hz, 2H), 6.36 (d, J = 15.9 Hz, 1H), 5.24 (s, 2H), 3.83 (s, 3H); MS (GC) *m*/*z* 268 (M^+); IR (ATR) ν 2958, 2838, 1704, 1630, 1600, 1575, 1509, 1447, 1421 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.1; H, 5.96.

(*Z*)-Methyl 2-methoxycinnamate ((*Z*)-3v): yield 95%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (dd, J = 1.5, 7.6 Hz, 1H), 7.32 (dt, J = 1.5, 7.8 Hz, 1H), 7.18 (d, J = 12.6 Hz, 1H), 6.94 (dt, J = 0.8, 7.6 Hz, 1H), 6.88 (dd, J = 0.8, 8.3 Hz, 1H), 5.98 (d, J = 12.4 Hz, 1H), 3.84 (s, 3H), 3.67 (s, 3H); MS (GC) *m*/*z* 192 (M^+); IR (ATR) ν 2950, 1721, 1630, 1600, 1488, 1462, 1435 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.68; H, 6.36.

General Procedure for Cinnamamids: Synthesis of (*E*)-4-Methoxycinnamaic Acid Diethyl Amide ((*E*)-3i). To a solution of 4-methoxycinnamic acid (2.67 g, 15 mmol) in CH_2Cl_2 (30 mL, stabilized with amylenes) was added *N*,*N*-carbonyldiimidazole (2.92 g, 18 mmol) at room temperature and the mixture was stirred at room temperature for 0.5 h. To the solution was added diethylamine (5 mL) at room temperature and the mixture was stirred at room temperature for 1 h. The mixture was poured into H_2O and extracted with AcOEt. The extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to give (*E*)-4-methoxycinnamaic acid diethyl amide ((*E*)-**3i**) (2.16 g, 62%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, J = 15.2 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.70 (d, J = 15.2 Hz, 1H), 3.83 (s, 3H), 3.52−3.42 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); MS (APCI) *m/z* 234 ([M + H]$^+$); IR (ATR) ν 2973, 1644, 1595, 1509,1429 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H 8.21; N, 6.00. Found: C, 71.72; H, 8.20; N, 5.83.

(*E*)-4-Methoxycinnamic amide ((*E*)-3f): yield 73%; colorless crystals; 199−201 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.50 (d, J = 8.6 Hz, 2H), 7.45 (br, 1H), 7.36 (d, J = 15.9 Hz, 1H), 7.01 (br, 1H), 6.97 (d, J = 8.7 Hz, 2H), 6.46 (d, J = 15.9 Hz, 1H), 3.79 (s, 3H); MS (APCI) *m/z* 178 ([M + H]$^+$); IR (ATR) ν 3461, 3355, 3145, 1661, 1592, 1509, 1423 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H 6.26; N, 7.90. Found: C, 67.73; H, 6.21; H, 7.88.

(*E*)-4-Methoxycinnamic acid ethylamide ((*E*)-3g): yield 67%; colorless crystals; mp 128−129 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J = 15.7 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.26 (d, J = 15.7 Hz, 1H), 5.66 (br, 1H), 3.82 (s, 3H), 3.46−3.39 (m, 2H), 1.20 (t, J = 7.3 Hz, 3H); MS (APCI) *m/z* 206 ([M + H]$^+$); IR (ATR) ν 3293, 2965, 2877, 1664, 1653, 1604, 1575, 1537, 1513, 1422 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H 7.37; N, 6.82. Found: C, 69.91; H, 7.35; N, 6.72.

(*E*)-4-Methoxycinnamic acid benzylamide ((*E*)-3h): yield 87%; colorless crystals; mp 52 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, J = 15.2 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.36−7.26 (m, 5H), 6.87 (d, J = 8.6 Hz, 2H), 6.28 (d, J = 15.7 Hz, 1H), 5.93 (br, 1H), 4.56 (d, J = 5.8 Hz, 2H), 3.82 (s, 3H); MS (APCI) *m/z* 268 ([M + H]$^+$); IR (ATR) ν 3283, 2836, 1644, 1602, 1510, 1454, cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H 6.41; N, 5.24. Found: C, 76.39; H, 6.31; N, 5.20.

(*E*)-4-Methoxycinnamic acid dibenzylamide ((*E*)-3j): yield 73%; colorless crystals; mp 103−104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, J = 15.3 Hz, 1H), 7.42 (d, J = 8.8 Hz, 2H), 7.38−7.22 (m, 10H), 6.86 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 15.3 Hz, 1H), 4.71 (s, 2H), 4.60 (s, 2H), 3.81 (s, 3H); MS (APCI) *m/z* 358 ([M + H]$^+$); IR (ATR) ν 3000, 2929, 1644, 1595, 1573, 1509, 1492, 1454, 1437, 1421 cm^{-1}. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H 6.49; N, 3.92. Found: C, 80.46; H, 6.38; N, 3.95.

(*E*)-4-Methoxycinnamic acid pyrrolidinoamide ((*E*)-3k): yield 79%; colorless crystals; mp 117−118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, J = 15.2 Hz, 1H), 7.48 (d, J = 8.6 Hz, 2H), 6.61 (d, J = 15.2 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H), 3.64−3.58 (m, 4H), 2.05−1.97 (m, 2H), 1.93−1.86 (m, 2H); MS (APCI) *m/z* 232 ([M + H]$^+$); IR (ATR) ν 2955, 2875, 1642, 1593, 1509, 1428 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H 7.41; N, 6.06. Found: C, 72.61; H, 7.36; N, 6.01.

(*E*)-4-Methoxycinnamic acid morpholinoamide ((*E*)-3l): yield 92%; colorless crystals; mp 105−107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, J = 15.3 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 15.3 Hz, 1H), 3.88 (s, 3H), 3.84−3.72 (br, 8H); MS (APCI) *m/z* 248 ([M + H]$^+$); IR (ATR) ν 2863, 1646, 1603, 1575, 1511, 1432 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.96; H, 6.91; N, 5.75.

General Procedure for the Synthesis of Cinnamtes with 4-Substituted Phenyl Group: Synthesis of (*E*)-Methyl 3-Methoxycinnamate ((*E*)-3w). To a solution of *m*-anisaldehyde (6.81 g, 50 mmol) in AcOMe (50 mL) was added 28% NaOMe/MeOH (12.5 g, 65 mmol), and the mixture was refluxed for 3 h. The mixture was cooled to room temperature, quenched with 6 N aqueous HCl (11 mL, 66 mmol), and extracted with AcOEt. The extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 5:1) to give methyl (*E*)-3-methoxycinnamate ((*E*)-**3w**) (8.70 g, 84%) as a colorless oil. Yield 84%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, J = 15.9 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.94 (dd, J = 2.9, 8.1 Hz, 1H), 7.04 (t, J = 1.8 Hz, 1H), 6.43 (d, J = 15.9 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H); MS (GC) *m/z* 192 (M$^+$); IR (ATR) ν 2951, 1713, 1638, 1579, 1489, 1435 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.92; H, 6.33.

(*E*)-Methyl 4-*tert*-butoxycinnamate ((*E*)-3m): yield 44%; colorless crystals; mp 60−61 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, J = 15.9 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.6 Hz, 2H), 6.34 (d, J = 15.9 Hz, 1H), 3.80 (s, 3H), 1.38 (s, 9H); MS (GC) *m/z* 234 (M$^+$); IR (ATR) ν 2975, 1706, 1630, 1598, 1505, 1432 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.9; H, 7.77.

(*E*)-Methyl 4-methylcinnamate ((*E*)-3n): yield 70%; colorless crystals; mp 50−52 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, J = 16.2 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 6.40 (d, J = 16.2 Hz, 1H), 3.80 (s, 3H), 2.37 (s, 3H); MS (GC) *m/z* 176 (M$^+$); IR (ATR) ν 2948, 1702, 1632, 1606, 1515, 1435 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.07; H, 6.88.

(*E*)-Methyl 4-fluorocinnamate ((*E*)-3p): yield 85%; colorless crystals; mp 45−47 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, J = 15.9 Hz, 1H), 7.51 (m, 2H), 7.08 (t, J = 8.6 Hz, 2H), 6.37 (d, J = 15.9 Hz, 1H), 3.14 (s, 3H); MS (GC) *m/z* 180 (M$^+$); IR (ATR) ν 2956, 1705, 1632, 1599, 1509, 1435 cm^{-1}. Anal. Calcd for $C_{10}H_9FO_2$: C, 66.66; H, 5.03; F, 10.54. Found: C, 66.56; H, 5.06; F, 10.40.

(*E*)-Methyl 4-chlorocinnamate ((*E*)-3q): yield 67%; colorless crystals; mp 74−75 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, J = 15.9 Hz, 1H), 7.45 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 6.41 (d, J = 15.9 Hz, 1H), 3.81 (s, 3H); MS (GC) *m/z* 196 (M$^+$), 198 ([M + 2]$^+$); IR (ATR) ν 2952, 1702, 1634, 1592, 1490, 1432, 1407 cm^{-1}. Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 60.94; H, 4.59; Cl, 17.69.

(*E*)-Methyl 4-methoxycarbonylcinnamate ((*E*)-3r): yield 68%; colorless crystals; mp 122−123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 16.0 Hz, 1H), 7.58 (d, J = 8.3 Hz, 2H), 6.52 (d, J = 16.0 Hz, 1H), 3.93 (s, 3H), 3.83 (s, 3H); MS (GC) *m/z* 220 (M$^+$); IR (ATR) ν 2958, 1717, 1639, 1565, 1433 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.35; H, 5.43.

(*E*)-Methyl 4-trifluoromethylcinnamate ((*E*)-3s): yield 42%; colorless crystals; mp 77−79 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, J = 15.9 Hz, 1H), 7.64 (dd, J = 3.0, 8.7 Hz, 4H), 6.52 (d, J = 15.9 Hz, 1H), 3.83 (s, 3H); MS (GC) *m/z* 230 (M$^+$); IR (ATR) ν 2958, 1709, 1639, 1616, 1438, 1418 cm^{-1}. Anal. Calcd for $C_{11}H_9FO_2$: C, 57.40; H, 3.94; F, 24.76. Found: C, 57.33; H, 3.89; F, 24.41.

(*E*)-Methyl 4-phenylcinnamate ((*E*)-3t): yield 78%; colorless crystals; mp 147−148 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, J = 16.2 Hz, 1H), 7.64−7.59 (m, 6H), 7.49−7.43 (m, 2H), 7.36 (tt, J = 1.3, 7.3 Hz, 1H), 6.48 (d, J = 15.9 Hz, 1H), 3.82 (s, 3H); MS (APCI) *m/z* 239 ([M + H]$^+$); IR (ATR) ν 2945, 1711, 1635, 1600, 1487, 1437, 1409 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.63; H, 5.70.

(*E*)-Methyl 4-*tert*-butylcinnamate ((*E*)-3u): yield 65%; colorless crystals; mp 34 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 16.0 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 6.41 (d, J = 16.0 Hz, 1H), 3.80 (s, 3H), 1.33 (s, 9H); MS (GC) *m/z* 218 (M$^+$); IR (ATR) ν 2957, 1712, 1632, 1606, 1504, 1438, 1412 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.77; H, 8.42.

(*E*)-Methyl 2-methoxycinnamate ((*E*)-3v): yield 89%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, J = 16.2 Hz, 1H), 7.51 (dd, J = 1.5, 7.6 Hz, 1H), 7.35 (ddd, 1.5, 7.3, 8.8 Hz, 1H), 6.96 (dt, J = 0.8, 7.6 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.53 (d, J = 15.9 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H); MS (GC) *m/z* 192 (M$^+$); IR (ATR) ν 2951, 1713, 1639, 1579, 1489, 1435 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.43; H, 6.19.

(*E*)-Methyl 3-(1-naphthyl)-2-propenoate ((*E*)-3x): yield 69%; colorless syrup; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, J = 15.9 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.89 (t, J = 8.1 Hz, 2H), 7.76 (d, J = 7.1 Hz, 1H), 7.61−7.47 (m, 3H), 6.54 (d, J = 15.7 Hz, 1H), 3.86 (s, 3H); MS (GC) m/z 212 (M^+); IR (ATR) ν 2941, 1710, 1630, 1510, 1433 cm^{-1}. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 78.86; H, 5.58

(*E*)-Methyl 3-(2-naphthyl)-2-propenoate ((*E*)-3y): yield 69%; colorless crystals; mp 89−91 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (s, 1H), 7.88−7.82 (m, 4H), 7.67 (dd, J = 1.5, 8.6 Hz, 1H), 7.54−7.49 (m, 2H), 6.56 (d, J = 15.9 Hz, 1H), 3.84 (s, 3H); MS (APCI) m/z 213 ($[M + H]^+$); IR (ATR) ν 2961, 1712, 1646, 1505, 1435 cm^{-1}. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.03; H, 5.53.

(*E*)-Methyl 3-(3-thienyl)-2-propenoate ((*E*)-8c): yield 74%; colorless crystals; mp 48−49 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 15.9 Hz, 1H), 7.50 (dd, J = 1.3, 2.8 Hz, 1H), 7.34 (dd, J = 5.1, 8.0 Hz, 1H), 7.29 (dd, J = 1.3, 5.1 Hz, 1H), 6.27 (d, J = 15.9 Hz, 1H), 3.79 (s, 3H); MS (GC) m/z 168 (M^+); IR (ATR) ν 3096, 2948, 1702, 1634, 1436 cm^{-1}. Anal. Calcd for $C_8H_8O_2S$: C, 57.12; H, 4.79; S, 19.06. Found: C, 57.13; H, 4.61.

General Procedure of (Z)-Cinnamates: Synthesis of (*Z*)-Ethyl Cinnamate ((*Z*)-8a). To a solution of ethyl 3-phenylpropiolate (1.74 g, 10 mmol) in hexane (66 mL) and 1-hexene (33 mL) were added quinoline (2.0 g) and palladium on calcium carbonate (Lindler reagent, purchased from Aldrich, 340 mg), and the mixture was stirred under hydrogen (1 atm) at room temperature overnight. The mixture was filtered, and the filtrate was washed with 2 N aqueous HCl, H_2O, and brine successively, dried over $MgSO_4$, and evaporated. The residual mixture was purified by silica gel columun chromatography (hexane/AcOEt = 95:5) to give (*Z*)-ethyl cinnamate ((*Z*)-**8a**) as a colorless oil (1.24 g, 89%). Yield 89%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59−7.57 (m, 2H), 7.38−7.33 (m 3H), 6.95 (d, J = 12.6 Hz, 1H), 5.95 (d, J = 12.6 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H); MS (GC) m/z 192 (M^+); IR (ATR) ν 2982, 1718, 1630, 1495, 1449 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_3$: C, 74.98; H, 6.86. Found: C, 74.72; H, 7.05.

(*Z*)-Methyl 4-methoxycinnamate[9a] **((*Z*)-3a):** yield 89%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 12.9 Hz, 1H), 5.84 (d, J = 12.9 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H); MS (GC) m/z 192 (M^+); IR (ATR) ν 2951, 1717, 1601, 1509, 1442 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; N, 6.29. Found: C, 68.66; H, 6.33.

Asymmetric Epoxidation of (*E*)-3a: Synthesis of Methyl (2*R*,3*S*)-3-(4-Methoxyphenyl)glycidate ((2*R*,3*S*)-2a). To a solution of methyl (*E*)-4-methoxycinnamate ((*E*)-**2a**) (1.92 g, 10 mmol) and ketone catalyst (*R*)-**7a** (198 mg, 0.5 mmol) in a mixed solvent of 1,4-dioxane (24.4 mL) and H_2O (14.4 mL) were successively added Oxone (6.14 g, 10 mmol) and $NaHCO_3$ (2.6 g, 31 mmol) at 5 °C. The suspension was mechanically stirred at 5 °C for 48 h. The mixture was then warmed to 27 °C and stirring was continued for 2 h. The resulting suspension was treated with H_2O and the mixture was extracted three times with $CHCl_3$. The combined extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. Evaporation of the solvent provided the crude mixture of (2*R*,3*S*)-**2a** and (*R*)-**7a**. The yield and the ee value of (2*R*,3*S*)-**2a** were determined by Chiral HPLC analysis: yield 92%, 80% ee [Chiralcel OD, hexane/^{i}PrOH = 10:1, 220 nm, 40 °C, (2*R*,3*S*)-**2a** 8.1 min, (2*S*,3*R*)-**2a** 9.8 min]. The separation of (2*R*,3*S*)-**2a** and (*R*)-**7a** was accomplished by using our previously reported contituous dissolution and crystallizaition method.[14] Mp 87−88 °C; $[\alpha]^{24}_D$ −205 (c 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) 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 (200 MHz, $CDCl_3$) δ 168.7, 160.2, 127.1, 126.9, 126.6, 114.3, 114.0, 57.8, 56.4, 55.2, 52.4; IR (KBr) ν 3029, 2965, 2843, 1748, 1614, 1587, 1519 cm^{-1}. MS (EI) m/z 208 (M^+). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.14; H, 5.50.

General Procedure for Catalytic Asymmetric Epoxidation of Cinnamic Acid Derivatives: Synthesis of Ethyl (2*R*,3*S*)-3-(4-Methoxyphenyl)glycidate ((2*R*,3*S*)-2b). To a solution of methyl (*E*)-4-methoxycinnamate ((*E*)-**3a**) (206 mg, 1 mmol) and ketone catalyst (*R*)-**7a** (20 mg, 0.05 mmol) in a mixed solvent of DME (4 mL) and H_2O (2 mL) were successively added Oxone (615 mg, 1 mmol) and $NaHCO_3$ (260 mg, 3.1 mmol) at 10 °C. The suspension was stirred at 10 °C for 24 h. The mixture was then warmed to 27 °C and stirring was continued for 2 h. The resulting suspension was treated with H_2O and the mixture was extracted three times with $CHCl_3$. The combined extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified through flash NH silica gel column chromatography (AcOEt). The yield and ee of (2*R*,3*S*)-**2b** were determined by Chiral HPLC analysis: yield 85%, 77% ee [HPLC: Chiralcel OD, hexane/^{i}PrOH = 98:2, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2b** 9.6 min, (2*S*,3*R*)-**2b** 10.8 min]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.33−4.24 (m, 2H), 4.04 (d, J = 1.8 Hz, 1H), 3.81 (s, 3H), 3.50 (d, J = 1.8 Hz, 1H), 1.33(t, J = 7.1 Hz, 3H); IR (ATR) 2996, 1744, 1612, 1585, 1515, 1469, 1442, 1411 cm^{-1}; MS (EI) m/z 222 (M^+). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.93; H, 6.57.

The racemic material (±)-**2b** as standard compound was prepared as below. To a solution of (*E*)-**3b** in acetone (4 mL) and H_2O (2 mL) were successively added Oxone (1.23 g, 2 mmol) and $NaHCO_3$ (520 mg, 6.2 mmol) at room temperature, and the mixture was stirred at room temperature for 24 h. The mixture was diluted with H_2O and extracted with AcOEt. The extracts were washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 5:1) to give (±)-**2b**.

Isopropyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate ((2*R*,3*S*)-2c): yield 85%, 80% ee [HPLC: Chiralcel OG, hexane/EtOH = 99:1, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2c** 45.4 min, (2*S*,3*R*)-**2c** 40.6 min]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 5.14 (hept, J = 6.3 Hz, 1H), 4.02 (d, J = 1.8 Hz, 1H), 3.81 (s, 3H), 3.47 (d, J = 1.8 Hz, 1H), 1.31 (d, J = 6.3 Hz, 3H), 1.29 (d, J = 6.3 Hz, 3H); IR (ATR) 2982, 1742, 1614, 1517, 1440, 1409 cm^{-1}; MS (EI) m/z 236 (M^+). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.98; H, 6.76.

***tert*-Butyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate ((2*R*,3*S*)-2d):** yield 89%, 77% ee [HPLC: Chiralcel OG, hexane/EtOH = 99:1, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2d** 13.7 min, (2*S*,3*R*)-**2d** 10.5 min]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 3.97 (d, J = 1.8 Hz, 1H), 3.81 (s, 3H), 3.40 (d, J = 1.8 Hz, 1H), 1.51 (s, 9H); IR (ATR) 2990, 1733, 1612, 1515, 1434, 1402 cm^{-1}; MS (EI) m/z 250 (M^+). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.17; H, 7.20.

Benzyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate ((2*R*,3*S*)-2e): yield 84%, 78% ee [HPLC: Chiralcel OD, hexane/^{i}PrOH = 98:1, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2e** 17.7 min, (2*S*,3*R*)-**2e** 19.5 min]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.36 (m, 5H), 7.20 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.25 (q, J = 12.4 Hz, 2H), 4.06 (d, J = 1.8 Hz, 1H), 3.80 (s, 3H), 3.55 (d, J = 1.8 Hz, 1H); IR (ATR) 3379, 2941, 1727, 1613, 1586, 1515, 1442, 1405 cm^{-1}; MS (EI) m/z 284 (M^+). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.17; H, 5.74.

(2*R*,3*S*)-3-(4-Methoxyphenyl)glyidic amide ((2*R*,3*S*)-2f): yield 80%, 71% ee [HPLC: Chiralcel OJ, hexane/EtOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2f** 16.3 min, (2*S*,3*R*)-**2f** 14.5 min]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.18 (br, 1H), 6.50 (br, 1H), 4.92 (d, J = 2.0 Hz, 1H), 3.82 (s, 3H), 3.51 (d, J = 2.0 Hz, 1H); IR (ATR) 3448, 3208, 1695, 1663, 1613, 1584, 1515, 1442, 1410 cm^{-1}; MS (EI) *m/z* 193 (M$^+$). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.93; H, 5.60; N, 7.20.

(2*R*,3*S*)-3-(4-Methoxyphenyl)glyidic acid ethylamide ((2*R*,3*S*)-2g): yield 93%, 65% ee [HPLC: Chiralcel OJ-H, hexane/EtOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2g** 14.8 min, (2*S*,3*R*)-**2g** 10.6 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.19 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.22 (br, 1H), 3.82 (d, J = 2.0 Hz, 1H), 3.81 (s, 3H), 3.52 (d, J = 2.0 Hz, 1H), 3.41−3.26 (m, 2H), 1.18 (t, J = 7.3 Hz, 3H); IR (ATR) 3273, 3095, 2982, 1652, 1612, 1558, 1516 cm^{-1}; MS (APCI) *m/z* 222 ([M + H]$^+$). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.92; H, 6.72; N, 6.31.

(2*R*,3*S*)-3-(4-Methoxyphenyl)glyidic acid benzylamide ((2*R*,3*S*)-2h): yield 93%, 65% ee [HPLC: Chiralcel OJ-H, hexane/EtOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2h** 14.8 min, (2*S*,3*R*)-**2h** 10.6 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.39−7.28 (m, 5H), 7.19 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.54 (br, 1H), 4.48 (q, J = 3.0 Hz, 2H), 3.85 (d, J = 2.0 Hz, 1H), 3.81 (s, 3H), 3.59 (d, J = 2.0 Hz, 1H); IR (ATR) 3271, 1653, 1618, 1558, 1519, 1456, 1438, 1409 cm^{-1}; MS (APCI) *m/z* 284 ([M + H]$^+$). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.80; H, 6.01; N, 4.93.

(2*R*,3*S*)-3-(4-Methoxyphenyl)glyidic acid diethylamide ((2*R*,3*S*)-2i): yield 80%, 10% ee [HPLC: Chiralcel OJ-H, hexane/EtOH = 80:20, 0.5 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2i** 16.7 min, (2*S*,3*R*)-**2i** 14.7 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.25 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.03 (d, J = 2.0 Hz, 1H), 3.82 (s, 3H), 3.58 (d, J = 2.0 Hz, 1H), 3.52−3.37 (m, 4H), 1.21 (t, J = 7.0 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H); IR (ATR) 2973, 1642, 1585, 1511, 1485, 1468, 1439, 1411 cm^{-1}; MS (APCI) *m/z* 250 ([M + H]$^+$). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.48; H, 7.67; N, 5.66.

(2*R*,3*S*)-3-(4-Methoxyphenyl)glyidic acid dibenzylamide ((2*R*,3*S*)-2j): yield 69%, 20% ee [HPLC: Chiralcel OJ-H, hexane/^{i}PrOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*) 40.8 min, (2*S*,3*R*) 34.5 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.36−7.25 (m, 8H), 7.15 (d, J = 6.8 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.65 (s, 2H), 4.54 (s, 2H), 4.07 (d, J = 2.0 Hz, 1H), 3.78 (s, 3H), 3.68 (d, J = 2.0 Hz, 1H); IR (ATR) 3030, 1655, 1613, 1516, 1495, 1451 cm^{-1}; MS (APCI) *m/z* 284 ([M + H]$^+$). Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 76.39; H, 6.15; N, 3.80.

(2*R*,3*S*)-3-(4-Methoxyphenyl)glyidic acid pyrrolidinoamide ((2*R*,3*S*)-2k): yield 69%, 20% ee [HPLC: Chiralcel OJ-H, hexane/EtOH = 80:20, 0.5 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2k** 51.1 min, (2*S*,3*R*)-**2k** 46.5 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.24 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.08 (d, J = 2.0 Hz, 1H), 3.81 (s, 3H), 3.68−3.50 (m, 5H), 2.03−1.86 (m, 4H); IR (ATR) 2967, 2878, 1633, 1609, 1517, 1451 cm^{-1}; MS (APCI) *m/z* 248 ([M + H]$^+$). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.76; H, 6.90; N, 5.66.

(2*R*,3*S*)-3-(4-Methoxyphenyl)glyidic acid morpholinoamide ((2*R*,3*S*)-2l): yield 75%, 18% ee [HPLC: Chiralcel OJ-H, hexane/EtOH = 80:20, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2l** 25.8 min, (2*S*,3*R*)-**2l** 22.6 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.23 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.04 (d, J = 2.0 Hz, 1H), 3.82 (s, 3H), 3.72−3.67 (m 8H), 3.62 (d, J = 2.0 Hz, 1H); IR (ATR) 2858, 1648, 1613, 1516, 1462 cm^{-1}; MS (APCI) *m/z* 264 ([M + H]$^+$). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.09; H, 6.34; N, 5.23.

Methyl (2*R*,3*S*)-3-(4-*tert*-butoxyphenyl)glycidate ((2*R*,3*S*)-2m): yield 80%, 84% ee [HPLC: Chiralcel OD-H, hexane/EtOH = 99:1, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2m** 12.0 min, (2*S*,3*R*)-**2m** 13.7 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.19 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 4.06 (d, J = 1.8 Hz, 1H), 3.83 (s, 3H), 3.53 (d, J = 1.8 Hz, 1H), 1.35 (s, 9H); IR (ATR) 2978, 1752, 1610, 1510, 1442 cm^{-1}; MS (APCI) *m/z* 251 ([M + H]$^+$). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.91; H, 7.16.

General Procedure for Catalytic Asymmetric Epoxidation of Cinnamic Acid Derivatives: Synthesis of Mthyl (2*R*,3*S*)-3-(4-*tert*-Butylphenyl)glycidate ((2*R*,3*S*)-2u). To methyl 4-*tert*-butyl cinnamate ((*E*)-**3u**) (234 mg, 1 mmol) and ketone catalyst (*R*)-**7a** (20 mg, 0.05 mmol) in a mixed solvent of DME (2 mL) and H_2O (1 mL) were successively added Oxone (615 mg, 1 mmol) and $NaHCO_3$ (260 mg, 3.1 mmol) at 10 °C. The suspension was stirred at 10 °C for 24 h. To the mixture were added Oxone (615 mg, 1 mmol) and $NaHCO_3$ (260 mg, 3.1 mmol) at 10 °C. The mixture was stirred at 10 °C for 24 h, then warmed to 27 °C, and stirring was continued for 2 h. The resulting suspension was treated with H_2O and the mixture was extracted three times with $CHCl_3$. The combined extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified through flash NH silica gel column chromatography (AcOEt). The yield and ee of (2*R*,3*S*)-**2b** were determined by Chiral HPLC analysis: yield 81%, 92% ee [HPLC: Chiralcel OJ-H, hexane/^{i}PrOH = 90:10, 0.5 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2u** 15.7 min, (2*S*,3*R*)-**2u** 14.4 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.40 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 4.08 (d, J = 1.8 Hz, 1H), 3.83 (s, 3H), 3.53 (d, J = 1.8 Hz, 1H), 1.32 (s, 9H); IR (ATR) 2945, 2903, 1745, 1514, 1446, 1400 cm^{-1}; MS (EI) *m/z* 234 (M$^+$). Anal. Calcd for $C_{14}H_{18}O_5$: C, 71.77; H, 7.74. Found: C, 71.76; H, 7.80

Methyl (2*R*,3*S*)-3-(4-methylphenyl)glycidate ((2*R*,3*S*)-2n): yield 95%, 72% ee [HPLC: Chiralcel OJ-H, hexane/^{i}PrOH = 80:20, 0.5 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2n** 11.6 min, (2*S*,3*R*)-**2n** 10.4 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.18 (br, 4H), 4.06 (d, J = 1.8 Hz, 1H), 3.83 (s, 3H), 3.51 (d, J = 1.8 Hz, 1H), 2.36 (s, 3H); IR (ATR) 2956, 1731, 1519, 1439 cm^{-1}; MS (EI) *m/z* 168 (M$^+$). Anal. Calcd for $C_{11}H_{12}O_5$: C, 68.74; H, 6.29. Found: C, 68.45; H, 6.07.

Methyl (2*R*,3*S*)-3-phenylglycidate ((2*R*,3*S*)-2o): yield 75%, 74% ee [HPLC: Chiralcel OD-H, hexane/^{i}PrOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2o** 7.4 min, (2*S*,3*R*)-**2o** 9.1 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.39−7.35 (m, 3H), 7.30−7.26 (m, 2H), 4.10 (d, J = 1.8 Hz, 1H), 3.83 (s, 3H), 3.52 (d, J = 1.8 Hz, 1H); IR (ATR) 3037, 2956, 1753, 1497, 1460, 1441, 1417 cm^{-1}; MS (GC) *m/z* 178 (M$^+$). Anal. Calcd for $C_{10}H_{10}O_5$: C, 67.41; H, 5.66. Found: C, 67.19; H, 5.59.

Methyl (2*R*,3*S*)-3-(4-fluorophenyl)glycidate ((2*R*,3*S*)-2p): yield 74%, 72% ee [HPLC: Chiralcel OD-H, hexane/^{i}PrOH = 98:2, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2p** 9.7 min, (2*S*,3*R*)-**2p** 11.0 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.27 (dd, J = 5.1, 8.8 Hz, 2H), 7.06 (t, J = 8.8 Hz, 2H), 4.09 (d, J = 1.8 Hz, 1H), 3.86 (s, 3H), 3.48 (d, J = 1.8 Hz, 1H); IR (ATR) 2955, 1748, 1606, 1513, 1447, 1401 cm^{-1}; MS (EI) *m/z* 196 (M$^+$). Anal. Calcd for $C_{10}H_9FO_5$: C, 61.22; H, 4.62; F, 9.68. Found: C, 61.65; H, 4.52; F, 9.74.

Methyl (2*R*,3*S*)-3-(4-chlorophenyl)glycidate ((2*R*,3*S*)-2q): yield 45%, 73% ee [HPLC: Chiralcel OD-H, hexane/^{i}PrOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2q** 7.6 min, (2*S*,3*R*)-**2q** 8.8 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.35 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 4.08 (d, J = 1.8 Hz, 1H), 3.37 (s, 3H), 3.47 (d, J = 1.8 Hz, 1H); IR (ATR) 3036, 2954, 1751, 1601, 1497, 1444 cm^{-1}; MS (EI) *m/z* 212 (M$^+$), 214 ([M + 2]$^+$). Anal. Calcd for $C_{10}H_9ClO_5$: C, 56.49; H, 4.27; Cl, 16.67. Found: C, 56.29; H, 4.16; Cl, 16.27.

Methyl (2*R*,3*S*)-3-(4-methoxycarbonylphenyl)glycidate ((2*R*,3*S*)-2r): yield 6%, 81% ee [HPLC: Chiralcel OJ-H, hexane/^{i}PrOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2r** 11.0 min, (2*S*,3*R*)-**2r** 9.5 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.04 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 7.37, 2H), 4.16 (d, J = 1.8 Hz, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.51 (d, J = 1.8 Hz, 1H); IR (ATR) 2964, 1756, 1720, 1615, 1440 cm^{-1}; MS (EI) *m/z* 236 (M$^+$). Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 60.90; H, 5.00.

Methyl (2*R*,3*S*)-3-(4-trifluoromethylphenyl)glycidate ((2*R*,3*S*)-2s): yield 14%, 86% ee [HPLC: Chiralcel OJ-H, hexane/EtOH = 80:20, 0.5 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-

2s 51.1 min, (2*S*,3*R*)-**2s** 46.5 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.64 (d, $J = 8.3$ Hz, 2H), 7.42 (d, $J = 8.3$ Hz, 2H), 4.17 (d, $J = 1.8$ Hz, 1H), 3.85 (s, 3H), 3.49 (d, $J = 1.8$ Hz, 1H); IR (ATR) 2960, 1746, 1621, 1447, 1407 cm^{-1}; MS (EI) *m/z* 246 (M$^+$). Anal. Calcd for $C_{11}H_9FO_3$: C, 53.67; H, 3.68; F, 23.15. Found: C, 53.46; H, 3.56; F, 22.82.

Methyl (2*R*,3*S*)-3-(4-biphenyl)glycidate ((2*R*,3*S*)-2t): yield 51%, 91% ee [HPLC: Chiralcel OD-H, hexane/^{i}PrOH = 90:10, 1 mL/min, 254 nm, 40 °C, (2*R*,3*S*)-**2t** 7.4 min, (2*S*,3*R*)-**2t** 8.7 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.61−7.57 (m, 4H), 7.47−7.43 (m, 2H), 7.38−7.35 (m, 3H), 4.15 (d, $J = 1.8$ Hz, 1H), 3.85 (s, 3H), 3.57 (d, $J = 1.8$ Hz, 1H); IR (ATR) 3034, 1725, 1489, 1436 cm^{-1}; MS (EI) *m/z* 254 (M$^+$). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.10; H, 5.40.

Methyl (2*R*,3*S*)-3-(2-methoxyphenyl)glycidate ((2*R*,3*S*)-2v): yield 55%, 53% ee [HPLC: Chiralcel OJ-H, hexane/^{i}PrOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2v** 11.9 min, (2*S*,3*R*)-**2v** 10.4 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.30 (dt, $J = 1.8$, 8.1 Hz, 1H), 7.15 (dd, $J = 1.8$, 7.6 Hz, 1H), 6.95 (t, $J = 7.5$ Hz, 1H), 6.89 (d, $J = 8.3$ Hz, 1H), 4.43 (d, $J = 1.8$ Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.44 (d, $J = 1.8$ Hz, 1H); IR (ATR) 2948, 1740, 1603, 1589, 1495, 1437, 1417 cm^{-1}; MS (EI) *m/z* 208 (M$^+$). Anal. Calcd for $C_{11}H_{12}NO_4$: C, 63.45; H, 5.81. Found: C, 63.39; H, 5.64.

Methyl (2*R*,3*S*)-3-(3-methoxyphenyl)glycidate ((2*R*,3*S*)-2w): yield 11%, 47% ee [HPLC: Chiralcel OD-H, hexane/^{i}PrOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2w** 8.8 min, (2*S*,3*R*)-**2w** 11.0 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.29 (d, $J = 8.0$ Hz, 1H), 6.91−6.87 (m, 2H), 6.81−6.80 (m, 1H), 4.08 (d, $J = 1.8$ Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.50 (d, $J = 1.8$ Hz, 1H); IR (ATR) 2955, 1748, 1587, 1493, 1438, 1415 cm^{-1}; MS (EI) *m/z* 208 (M$^+$). Anal. Calcd for $C_{11}H_{12}NO_4$: C, 63.45; H, 5.81. Found: C, 63.20; H, 5.61.

Methyl (2*R*,3*S*)-3-(1-naphthyl)glycidate ((2*R*,3*S*)-2x): yield 55%, 75% ee [HPLC: Chiralcel OD-H, hexane/^{i}PrOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2x** 11.0 min, (2*S*,3*R*)-**2x** 13.6 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.04 (d, $J = 8.3$ Hz, 1H), 7.91 (dd, $J = 1.8$, 7.6 Hz, 1H), 7.84 (dd, 2.0, 7.3 Hz, 1H), 7.60−7.52 (m, 2H), 7.50−7.45 (m, 2H), 4.74 (d, $J = 1.8$ Hz, 1H), 3.91 (s, 3H), 3.55 (d, $J = 1.8$ Hz, 1H); IR (ATR) 2954, 1738, 1598, 1510, 1444 cm^{-1}; MS (EI) *m/z* 228 (M$^+$). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.36; H, 5.25.

Methyl (2*R*,3*S*)-3-(2-naphthyl)glycidate ((2*R*,3*S*)-2y): yield 47%, 63% ee [HPLC: Chiralcel OJ-H, hexane/^{i}PrOH = 90:10, 0.5 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**2y** 30.0 min, (2*S*,3*R*)-**2y** 25.7 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.86−7.82 (m, 4H), 7.53−7.49 (m, 2H), 7.32 (dd, $J = 1.8$, 8.6 Hz, 1H), 4.27 (d, $J = 1.8$ Hz, 1H), 3.86 (s, 3H), 3.62 (d, $J = 1.8$ Hz, 1H); IR (ATR) 2957, 1736, 1601, 1509, 1449, 1415 cm^{-1}; MS (EI) *m/z* 228 (M$^+$). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.49; H, 5.18.

Methyl (2*R*,3*R*)-3-(4-methoxyphenyl)glycidate ((2*R*,3*R*)-2a): yield 71%, 16% ee [HPLC: Chiralcel OJ-H, hexane/^{i}PrOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*R*)-**2a** 17.8 min, (2*S*,3*S*)-**2a** 20.2 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.34 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 4.22 (d, $J = 4.6$ Hz, 1H), 3.81 (d, $J = 4.6$ Hz, 1H), 3.80 (s, 3H), 3.58 (s, 3H); IR (ATR) 2998, 1749, 1611, 1584, 1515, 1442, 1401 cm^{-1}; MS (EI) *m/z* 208 (M$^+$). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.37; H, 5.78.

Methyl (2*R*,3*R*)-3-(2-methoxyphenyl)glycidate ((2*R*,3*R*)-2v): yield 57%, 26% ee [HPLC: Chiralcel OJ-H, hexane/^{i}PrOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*R*)-**2v** 13.3 min, (2*S*,3*S*)-**2v** 14.5 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.41 (dd, $J = 1.8$, 7.6 Hz, 1H), 7.30 (dt, $J = 1.8$, 7.6 Hz, 1H), 6.95 (t, $J = 7.6$ Hz, 1H), 6.84 (d, $J = 8.3$ Hz, 1H), 4.41 (d, $J = 4.6$ Hz, 1H), 3.87 (d, $J = 4.6$ Hz, 1H), 3.84 (s, 3H), 3.54 (s, 3H); IR (ATR) 2977, 1752, 1603, 1496, 1456, 1409 cm^{-1}; MS (EI) *m/z* 208 (M$^+$). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.50; H, 5.85.

Ethyl (2*R*,3*R*)-3-phenylglycidate ((2*R*,3*R*)-9a): yield 57%, 26% ee [HPLC: Chiralcel OD-H, hexane/^{i}PrOH = 99:1, 0.5 mL/min, 220 nm, 40 °C, (2*R*,3*R*)-**9a** 42.0 min, (2*S*,3*S*)-**9a** 24.6 min]; $[\alpha]^{26}_{D}$ +0.64 (*c* 1.03, CHCl$_3$) [$[\alpha]^{25}_{D}$ +25.0 (*c* 1.1, CHCl$_3$) for (2*R*,3*R*)-form]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.42 (dd, $J = 1.8$, 7.6 Hz, 2H), 7.36−7.30 (m, 3H), 4.27 (d, $J = 4.6$ Hz, 1H), 4.07−3.82 (m, 2H), 3.83 (d, $J = 4.6$ Hz, 1H), 1.02 (t, $J = 7.1$ Hz, 3H); IR (ATR) 2984, 1751, 1730, 1456 cm^{-1}; MS (EI) *m/z* 192 (M$^+$). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.53; H, 6.29.

Ethyl (2*R*,3*S*)-3-methyl-3-phenylglycidate ((2*R*,3*S*)-9b): yield 93%, 40% ee [HPLC: Chiralcel OD-H, hexane/^{i}PrOH = 98:2, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**9b** 7.8 min, (2*S*,3*R*)-**9b** 6.0 min]; $[\alpha]^{26}_{D}$ −5.81 (*c* 1.03, CHCl$_3$) [$[\alpha]^{25}_{D}$ +121.3 (*c* 1.0, CHCl$_3$) for (2*S*,3*R*)- form (96% ee)]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.39−7.30 (m, 5H), 4.35−4.26 (m, 2H), 3.46 (s, 1H), 1.77 (s, 3H), 1.33 (t, $J = 7.2$ Hz, 3H); IR (ATR) 2982, 1748, 1448 cm^{-1}; MS (EI) *m/z* 206 (M$^+$). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.81 H, 6.91.

Methyl (2*R*,3*S*)-3-(3-thienyl)glycidate ((2*R*,3*S*)-9c): yield 5%, 60% ee [HPLC: Chiralcel OD-H, hexane/^{i}PrOH = 90:10, 1 mL/min, 220 nm, 40 °C, (2*R*,3*S*)-**9c** 12.6 min, (2*S*,3*R*)-**9c** 8.8 min]; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.36−7.32 (m, 2H), 6.97 (dd, $J = 1.5$, 5.0 Hz, 1H), 4.17 (d, $J = 1.8$ Hz, 1H), 3.83 (s, 3H), 3.61 (d, $J = 1.8$ Hz, 1H); IR (ATR) 2955, 1737, 1440 cm^{-1}; MS (EI) *m/z* 184 (M$^+$). Anal. Calcd for $C_8H_8O_3S$: C, 52.16; H, 4.38; S, 17.41. Found: C, 51.77; H, 4.33.

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