Cis and Enantioselective Synthesis of 2-Oxazoline-4-carboxylates through Lewis Acid-Catalyzed Formal [3 + 2] Cycloaddition of 5-Alkoxyoxazoles with Aldehydes

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In the presence of 2 equiv of (*R*)-methylaluminum *β*-binaphthoxide, which was prepared from (*R*)-2,2′-dihydroxy-1,1′-binaphthyl and trimethylaluminum, the reaction of 5-methoxy-2-(*p*-methoxyphenyl)oxazole with benzaldehyde in MeCN gave the corresponding 2-oxazoline-4-carboxylate in high yield (89%) with high stereoselectivity (cis/trans = 92:8) and high enantioselectivity (88% ee (cis)). Under the same conditions, enantioselectivity of the cis products obtained from the reaction with para-substituted benzaldehydes was moderate. On the other hand, formal [3 + 2] cycloaddition of 5-methoxy-2-(*o*-methoxyphenyl)oxazole with benzaldehyde or para- and meta-substituted benzaldehydes successfully proceeded only in the presence of 30 mol % of (*R*)-methylaluminum *β*-binaphthoxide, which was prepared from (*R*)-2,2′-dihydroxy-1,1′-binaphthyl and 1.1−1.05 equiv of trimethylaluminum, to give *cis*-2-oxazoline-4-carboxylates in high enantioselectivity (up to 90% ee).

Introduction

2-Oxazoline-4-carboxylates are versatile building blocks in organic synthesis as masked *β*-hydroxy amino acids and 2-amino-1,3-diols. 5-Substituted 2-oxazoline-4-carboxylates have cis and trans isomers at the relative configuration of the 4- and 5-positions, and the transformation of cis and trans isomers gives *erythro*- and *threo*-*β*-hydroxy amino acids or 2-amino-1,3-diols, respectively. Furthermore, the importance of enantioselective synthesis of 2-oxazoline-4-carboxylates in modern synthetic methodology is apparent from the numerous synthetic applications using 2-oxazoline-4-carboxylates as the building blocks.[1−5] Trans isomers of 5-substituted 2-oxazoline-4-carboxylate have been selectively synthesized by the aldol reaction of isocyanoacetates with aldehydes under thermodynamic control.[1−3] For the enantioselective synthesis of *trans*-2-oxazoline-4-carboxylates, ferrocenylphosphine−gold(I) complexes were found to be the most effective catalyst in the reaction of isocyanoacetate with aldehydes.[3] However, the enantioselective synthesis of *cis*-2-oxazoline-4-carboxylates has not been reported yet.[5] Recently, we reported that regio- and stereoselective formal [3 + 2] cycloaddition of 2-aryl-5-methoxyoxazoles with aldehydes catalyzed by a stoichiometric amount of racemic methylaluminum *β*-binaphthoxide gave 2-oxazoline-4-carboxylates with high cis selectivity.[6] We also showed that tin(IV) chloride-catalyzed highly diastereoselective formal cycloaddition of 5-methoxyoxazoles with chiral *β*-alkoxyaldehydes is extremely useful for the synthesis of optically pure 2-amino-1,3,4-triols.[7] In this paper, we provide a full account of our investigation of the highly enantioselective synthesis of *cis*-2-oxazoline-4-carboxylates in the formal [3 + 2] cycloaddition of 2-aryl-5-methoxyoxazoles with aldehydes catalyzed by chiral methylaluminum *β*-binaphthoxide.[8]

Results and Discussion

Reaction of Oxazole 1a with Benzaldehyde in the Presence of a Chiral Lewis Acid. The reaction of oxazole **1a** with benzaldehyde was carried out under several conditions in the presence of chiral catalyst A, which was prepared by mixing (*R*)- or (*S*)-2,2′-dihydroxy-1,1′-binaphthyl ((*R*)- or (*S*)-BINOL) and trimethylaluminum (hexane solution) *in situ* (Scheme 1 and Table 1). We first examined the reaction under the previously reported optimum conditions for the stereoselective synthesis of racemic *cis*-2-oxazoline-4-carboxylates (Table 1, entries 1, 2, and 4).[6] After isolation of *cis*-2-oxazoline-

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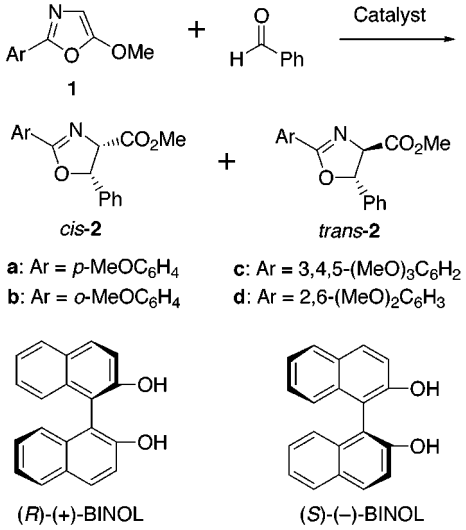
Table 1. Reaction of Oxazole 1a with Benzaldehyde[a]

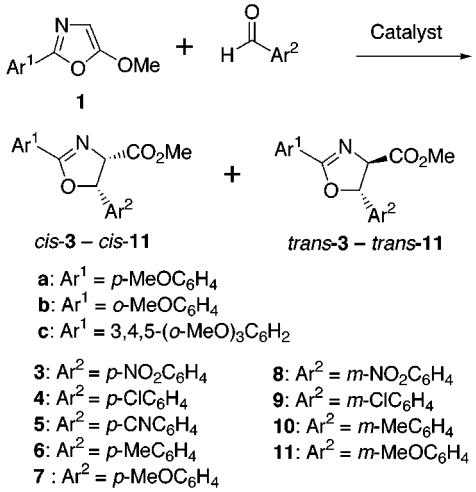
entry	catalyst (mol %)	PhCHO, equiv	solvent	*T*, °C	time, h	yield, %	cis/trans	cis, % ee[b](confign)[c]	trans, % ee[b]
1	(*R*)-BINOL + $AlMe_3$ (100)	1	CH_2Cl_2−MeCN	0	122	57	87:13	55 (4*S*,5*S*)[d]	13
2	(*S*)-BINOL + $AlMe_3$ (100)	1	CH_2Cl_2−MeCN	0	122	52	88:12	55 (4*R*,5*R*)	12
3	(*S*)-BINOL + $AlMe_3$ (200)	1	CH_2Cl_2−MeCN	0	123	64	81:19	70 (4*R*,5*R*)[e]	5
4	(*R*)-BINOL + $AlMe_3$ (200)	1	MeCN	rt	75	40	60:40	90 (4*S*,5*S*)	2
5	(*R*)-BINOL + $AlMe_3$ (200)	1	MeCN	0	76	45	87:13	86 (4*S*,5*S*)	2
6	(*R*)-BINOL + $AlMe_3$ (200)	3	MeCN	−10	89	81	92:8	88 (4*S*,5*S*)[f]	8
7	(*R*)-BINOL + $AlMe_3$ (50)	10	MeCN	−10	116	89	96:4	75 (4*S*,5*S*)	55
8	(*R*)-BINOL + $AlMe_3$ (30)	10	MeCN	−10	163	70	95:5	65 (4*S*,5*S*)	36
9	(*R*)-BINOL + $AlMe_3$ (30)	10	MeCN	−10	25[g]	31	95:5	82 (4*S*,5*S*)	ND[h]
10	(*R*)-BINOL + $AlMe_3$ (30)	10	MeCN	5	39.5	84	95:5	67 (4*S*,5*S*)	ND[h]
11	(*R*)-BINOL + $AlMe_3$ (30)	10	MeCN	rt	46	82	93:7	74 (4*S*,5*S*)	32

[a] The reaction was carried out in the presence of catalyst A, which was prepared from Me_3Al and Chiral BINOL. [b] Determined by HPLC analysis using Daicel Chiralpak AS (hexane/*i*-PrOH = 9:1, flow 0.5 mL/min). [c] See the text for determination of the configuration. [d] $[\alpha]^{21}_D = +144.5°$ (*c* 1.20, THF). [e] $[\alpha]^{19}_D = -186.4°$ (*c* 1.20, THF). [f] $[\alpha]_D^{26} = +215.2°$ (*c* 1.23, THF). [g] A solution of oxazole **1a** was added over a period of 115 h and then stirred for 25 h. [h] The % ee was not determined.

Scheme 1



Scheme 2



4-carboxylate **2a** by column chromatography, the enantiomeric excess was determined by HPLC analysis using a Daicel Chiralpak AS column. Moderate enantioselectivity (55% ee) for *cis*-**2a** was observed under the conditions by using 1 equiv of chiral catalyst A in CH_2Cl_2−MeCN (1:1) at 0 °C (Table 1, entries 1 and 2). When 2 equiv of catalyst A was used in CH_2Cl_2−MeCN (1:1), the enantioselectivity increased to 70% ee (Table 1, entry 3). Using only MeCN as the solvent showed higher enantioselectivity than that in CH_2Cl_2−MeCN (1:1) (Table 1, entries 4−6). Under the optimum conditions at −10 °C in the presence of 2 equiv of catalyst A, high yield (89%), high stereoselectivity (cis/trans = 92:8), and high enantioselectivity (88% ee (cis)) were obtained (Table 1, entry 6). It is also interesting to note that the degree of the steroselectivity (cis/trans = 98:2) and chemical yield (79%) in the presence of racemic catalyst A[6] were not inconsistent with those (cis/trans = 87:13−88:12, 52−57% yield) obtained in the presence of chiral catalyst A under the same conditions (0 °C, CH_2Cl_2−MeCN) (Table 1, entries 1 and 2). In the presence of 10 equiv of benzaldehyde in MeCN, the reaction proceeded smoothly using 30−50 mol % of chiral catalyst A. However, using catalytic amount of catalyst A resulted in lower enantioselectivity compared with that obtained using 2 equiv of catalyst A (Table 1, entries 7, 8, 10, and 11). Slow addition of a solution of oxazole **1a** in MeCN also did not give a satisfactory result in terms of chemical yield (Table 1, entry 9).

Reaction of Oxazole 1a with Para-Substituted Benzaldehyde in the Presence of Catalyst A. The reactions of oxazole **1a** with some para-substituted benzaldehydes were carried out under the conditions using 2 equiv of catalyst A in MeCN (Scheme 2, Table 2, entries 1, 4, and 8). Although these reactions proceeded in good stereoselectivity (cis/trans = 96:4−82:18), the enantiomeric excess of the cis products was moderate. To improve the enantioselectivity in the reaction with substituted benzaldehydes and to determine the amount of the catalyst, the effects of the position and number of the methoxy substituents on the 2-aryl group were investigated.

Reaction of Oxazoles 1a−d with Benzaldehyde in the Presence of Catalyst A. In the preliminary experiment, 5-methoxy-2-(*o*-methoxyphenl)oxazole **1b** reacted smoothly with benzaldehyde by using 30 mol % of catalyst A to give 2-oxazoline-4-carboxylate **2b** (cis/trans = 85:15) in 79% chemical yield and 85% ee of *cis*-**2b**. However, when the reaction was repeated several times, it was seen that it did not have reproducibility in terms of chemical yield and enantioselectivity. This might be attributed to the slight difference in the ratio of $AlMe_3$ and chiral BINOL in preparing the catalyst. The catalyst was then prepared by mixing $AlMe_3$ and (*R*)-BINOL in four different ratios from 1.2:1.0 to 1.0:1.2, and the reaction of oxazole **1b** with benzaldehyde was carried out (Table 3, entries 5−8). The use of a slight excess of $AlMe_3$ ($AlMe_3$/BINOL = 1.05:1.0−1.1:1.0) showed high yield and high enantioselectivity of *cis*-2-oxazoline-4-carboxylate **2b** (Table 3, entries 6 and 7).[9] The reaction under these

Table 2. Reaction of Oxazoles 1a−c with Substituted Benzaldehydes[a]

entry	oxazole	aldehyde	*T*, °C	time, h	product	yield, %	cis/trans	cis, % ee[b]	trans, % ee[b]
1[f,g]	**1a**	*p*-$NO_2C_6H_4CHO$	−10	20	**3a**	81	82:18	73[d]	20[d]
2	**1b**	*p*-$NO_2C_6H_4CHO$	−10	21	**3b**	83	43:57 (54:46)[c]	76[d]	31[d]
3[f]	**1c**	*p*-$NO_2C_6H_4CHO$	5	70	**3c**	74	88:12	75[d]	25[d]
4[f,g]	**1a**	*p*-ClC_6H_4CHO	−10	53	**4a**	93	87:13	51	2
5	**1b**	*p*-ClC_6H_4CHO	5	24	**4b**	89	87:13	87	13
6	**1b**	*p*-CNC_6H_4CHO	5	24	**5b**	52	71:29 (82:18)[c]	76[d]	5[d]
7[f]	**1c**	*p*-CNC_6H_4CHO	5	75	**5c**	60	90:10	75[d]	10[d]
8[f,g]	**1a**	*p*-$CH_3C_6H_4CHO$[h]	−10	168	**6a**	78	96:4	63	31
9	**1b**	*p*-$CH_3C_6H_4CHO$	5	43	**6b**	72	88:12	84	9
10	**1b**	*p*-$CH_3OC_6H_4CHO$	rt	70	**7b**	57	54:46	89	46
11[f]	**1a**	*m*-$NO_2C_6H_4CHO$	5	15	**8a**	89	90:10	82	10
12	**1b**	*m*-$NO_2C_6H_4CHO$	5	15	**8b**	85	73:27	84	11
13[f]	**1a**	*m*-ClC_6H_4CHO	5	42	**9a**	75	91:9	78	23
14	**1b**	*m*-ClC_6H_4CHO	5	42	**9b**	82	83:17	84	ND[e]
15[f]	**1a**	*m*-$CH_3C_6H_4CHO$	5	117	**10a**	61	93:7	81	25
16	**1b**	*m*-$CH_3C_6H_4CHO$	5	117	**10b**	51	88:12	88	ND[e]
17[f]	**1a**	*m*-$CH_3OC_6H_4CHO$	5	45	**11a**	66	97:3	78	33
18	**1b**	*m*-$CH_3OC_6H_4CHO$	5	45	**11b**	70	87:13	90	29

[a] The reaction was carried out in MeCN in the presence of catalyst A, which was prepared from (*R*)-BINOL and Me_3Al in a ratio of 1:1.05. [b] Determined by HPLC analysis using Daicel Chiralpak AS (hexane/*i*-PrOH = 9:1, flow 0.5 mL/min). [c] Determined by ^1H NMR analysis before chromatographic separation. [d] Determined by ^1H NMR analysis using (*R*)-BINOL as shift reagent. [e] The % ee was not determined. [f] Catalyst A was prepared from (*R*)-BINOL and Me_3Al in a ratio of 1:1. [g] Reactions were carried out with 3 equiv of aldehydes in the presence of 2 molar amounts of catalyst A in MeCN. [h] Five equiv of *p*-MeC_6H_4CHO was used.

Table 3. Reaction of Oxazoles 1a−d with Benzaldehyde[a]

entry	oxazole	catalyst, (*R*)-BINOL/$AlMe_3$	*T*, °C	time, h	product	yield, %	cis/trans	cis, % ee[b]	trans, % ee[b]
1	**1a**	1.2:1	5	72	**2a**	90	96:4	79	41
2	**1a**	1:1	5	39.5	**2a**	84	95:5	67	ND[c]
3	**1a**	1:1.1	5	23	**2a**	85	92:8	65	27
4	**1a**	1:1.2	5	23	**2a**	85	92:8	69	25
5	**1b**	1.2:1	5 to rt	68	**2b**	16	84:16	66	ND[c]
6	**1b**	1:1.05	5	27	**2b**	92	85:15	84	15
7	**1b**	1:1.1	5	49	**2b**	82	83:17	87	13
8	**1b**	1:1.2	5	23	**2b**	90	81:19	77	18
9	**1c**	1.2:1	rt	40	**2c**	35	96:4	83	54
10	**1c**	1:1	rt	42	**2c**	64	94:6	84	ND[c]
11	**1c**	1:1.1	rt	46	**2c**	63	90:10	70	27
12	**1c**	1:1.2	rt	40	**2c**	63	92:8	70	33
13	**1d**	1:1	5	50	**2d**	83	59:41	80	21

[a] The reaction was carried out in MeCN in the presence of catalyst A, which was prepared from Me_3Al and (*R*)-BINOL in the ratio listed in the table. [b] Determined by HPLC analysis using Daicel Chiralpak AS (hexane/*i*-PrOH = 9:1, flow 0.5 mL/min). [c] The % ee was not determined.

conditions also had reproducibility in terms of yields and enantioselectivity. On the other hand, utilization of 1.2 equiv of (*R*)-BINOL in preparation of the catalyst showed lower yield and enantioselectivity of cis adduct **2b**. In the case of reactions of oxazole **1a** and **1c**, however, the use of a slight excess (1.2 equiv) of (*R*)-BINOL in preparation of the catalyst showed slightly better enantioselectivity rather than by using a slight excess (1.2 equiv) of Me_3Al (Table 3, entries 1−4 and 9−12).

2-(2,6-Dimethoxyphenyl)oxazole **1d** also underwent the formal [3 + 2] cycloaddition with benzaldehyde to give the corresponding products in high yield and with good enantioselectivity of *cis*-oxazoline. However, the reaction showed lower stereoselectivity (cis/trans = 59:41).

Reaction of Oxazoles 1a,b,d in the Presence of Catalyst B, C, or D. In the presence of the catalysts having a phenyl (catalyst B) or a triphenysilyl group (catalyst C)[10] on the 3-position and a bromo group on the 6-position (catalyst D) of chiral BINOL moiety, the reactions of oxazoles **1a**,**b**,**d** with benzaldehyde were also carried out (Figure 1, Table 4, entries 2, 4−6, and 8). These catalysts, including catalyst C,[10] which is one of the best aluminum Lewis acids for asymmetric synthesis, did not exhibit better enantioselectivity than that in the presence of catalyst A. In the case of reactions using catalyst B, *trans*-2-oxazoline-4-carboxylates were predominantly produced, probably due to inhibition of the transition state that produces cis products by steric interaction of the 3-phenyl group (Table 4, entries 2, 4, and 8). Generally, the enantiomeric excess of minor *trans*-2-oxazoline-4-carboxylates by the catalyst A-catalyzed reaction was low.[11] However, in the reaction of oxazole **1a** in the presence of catalyst B, the highest enantioselectivity of *trans*-oxazoline was obtained (Table 4, entry 2).

(9) In the case of **1b**, the reaction using 2 equiv of the catalyst (−10 °C, 168 h, 35% yield) gave unsatisfactory results in terms of stereoselcetivity (cis/trans = 49:51) and enantioselectivity (cis: 62% ee), probably due to decomposition and epimerization of the product under the reaction conditions. In the presence of 20 mol % of the catalyst (Me_3Al/(*R*)-BINOL = 1:1.05), the reaction (5 °C, 45 h) did not complete (61% yield, recovered **1b**: 31%) and showed low selectivity (cis/trans = 79:21, cis: 63% ee).

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(11) This may be attributable to the concomitant formation of minor *trans*-oxazolines by Lewis acid-promoted isomerization of *cis*-oxazolines through a ring-opening-recyclization pathway involving racemization of the 4- and 5-positions.

Table 4. Reaction of Oxazoles 1a,b,d with Benzaldehyde by Using (*R*)-binol Derivatives[a]

entry	oxazole	catalyst (Ln/$AlMe_3$)	*T*, °C	time, h	product	yield, %	cis:trans	cis, % ee[b]	trans, % ee[b]
1	**1a**	A (1:1)	5	39.5	**2a**	84	95:5	67	ND[c]
2	**1a**	B (1:1)	5	25	**2a**	89	39:61	33	71
3	**1b**	A (1:1.05)	5	27	**2b**	92	85:15	84	15
4	**1b**	B (1:1.05)	5	21.5	**2b**	83	29:71	52	43
5	**1b**	C (1:1.05)	5	22	**2b**	87	66:34	64	54
6	**1b**	D (1:1.05)	5	113.5	**2b**	68	87:13	50	10
7	**1d**	A (1:1)	5	50	**2d**	83	59:41	80	21
8	**1d**	B (1:1)	5	23	**2d**	80	16:84	64	45

[a] The reaction was carried out in MeCN in the presence of the catalyst listed in the table. [b] Determined by HPLC analysis using Daicel Chiralpak AS (hexane/*i*-PrOH = 9:1, flow 0.5 mL/min). [c] The % ee was not determined.

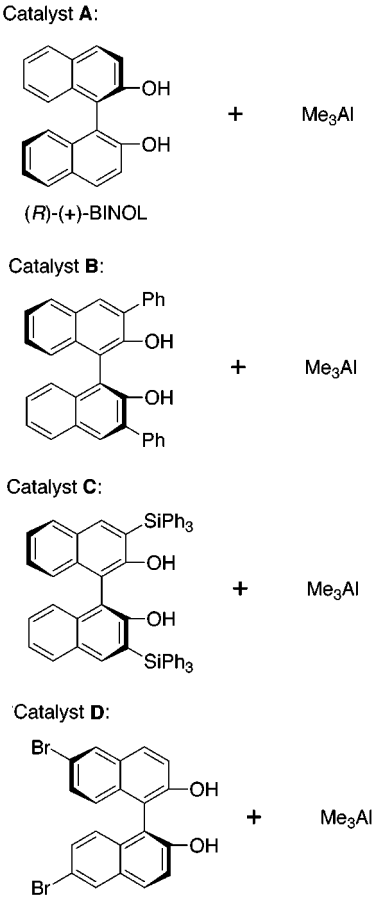


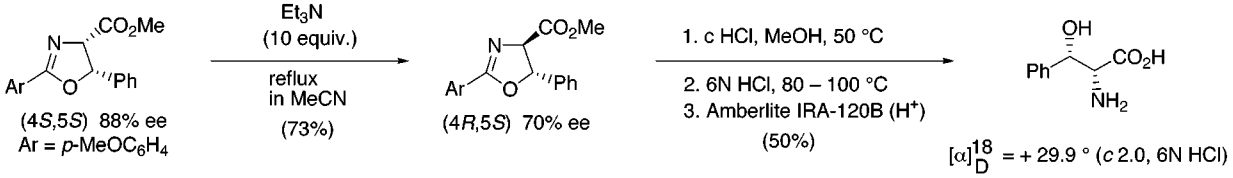
Figure 1. Catalysts A−D.

Reaction of Oxazoles 1a−c with Substituted Benzaldehyde in the Presence of Catalyst A. As described above, the highest enantioselectivity of *cis*-2-oxazoline-4-carboxylate *cis*-**2b** was obtained by the reaction of oxazole **1b** with benzaldehyde under the conditions in MeCN in the presence of about 30% of catalyst A, which was prepared by mixing $AlMe_3$ and (*R*)-BINOL in a 1.1−1.05:1.0 ratio (Table 3, entries 6 and 7). The reactions of oxazole **1b** with several kinds of para-substituted benzaldehydes were preformed under similar conditions (Table 2, entries 2, 5, 6, 9, and 10). In all cases, good enantiomeric excess of *cis*-2-oxazolines was obtained independent of the electronic character of the para substituents of the benzaldehyde derivatives. Oxazole **1c** also underwent formal [3 + 2] cycloaddition with electron-deficient para-substituted benzaldehydes to give *cis*-oxazoline-4-carboxylates in high cis and good enantioselectivity. In the reactions of oxazoles **1a** and **1b** with several kinds of meta-substituted benzaldehydes, the enantiomeric excess and cis selectivity of *cis*-oxazolines were also very high independent of the electronic character of the substituents (Table 2, entries 11−18).

Absolute Configuration of *cis*-2-Oxazoline-4-carboxylate. The absolute configuration of *cis*-2-oxazoline-4-carboxylate *cis*-**2a** was determined by the optical rotation after conversion to *threo*-*β*-phenylserine. Thus, 2-oxazoline *cis*-**2a** (88% ee) was first converted to 2-oxazoline *trans*-**2a** (70% ee) by treatment of triethylamine in MeCN under reflux in 73% yield. The resulting *trans*-**2a** was hydrolyzed by concentrated hydrochloric acid at 50 °C in MeOH and then 6 N hydrochloric acid at 80−100 °C. After treatment with Amberlite IRA-120B(H^+), *threo*-*β*-phenylserine was obtained in 50% overall yield. By comparing the optical rotation ($[\alpha]^{18}_D = +29.9°$ (*c* 2.0, 6 N HCl)) of the synthesized *threo*-*β*-phenylserine with that of the natural *threo*-*β*-phenylserine ($[\alpha]^{18}_D = -50.2 \pm 2°$ (*c* 2.0, 6N HCl)),[12] the configuration of *cis*-**2a** was determined as (4*S*,5*S*) (Scheme 3).

The Mechanism for Cis and Enantioselectivity. It has been proposed that the formal [3 + 2] cycloaddition of oxazoles with tetracyanoethylene,[13] 4-phenyl-3*H*-1,2,4-triazole-3,5-(4*H*)-dione,[14a] diethyl azodicarboxylate,[14b] nitrosobenzene,[15] and diethyl oxomalonate[16] proceeds through a stepwise pathway involving zwitterionic intermediates. According to an interpretation of the stepwise pathway, the Lewis acid activates the aldehydes by accelerating the initial attack of the oxazoles on the aldehydes in the reaction of 5-alkoxyoxazoles with aldehydes. In the catalyst A-catalyzed reaction of oxazole **1a−c** with benzaldehyde derivatives, a stable 1:1 complex of catalyst A with aldehydes may be the initial intermediate of the reaction. On the basis of the structure of this stable complex *π*, we anticipate an antiperiplanar or synclinal approach of the C4−C5 double bond of the oxazoles to the carbonyl group of complex *π* (Figure 2). In the *re*-face attack on complex *π*, the sterically less-hindered approach X, which showed the approach of

Scheme 3



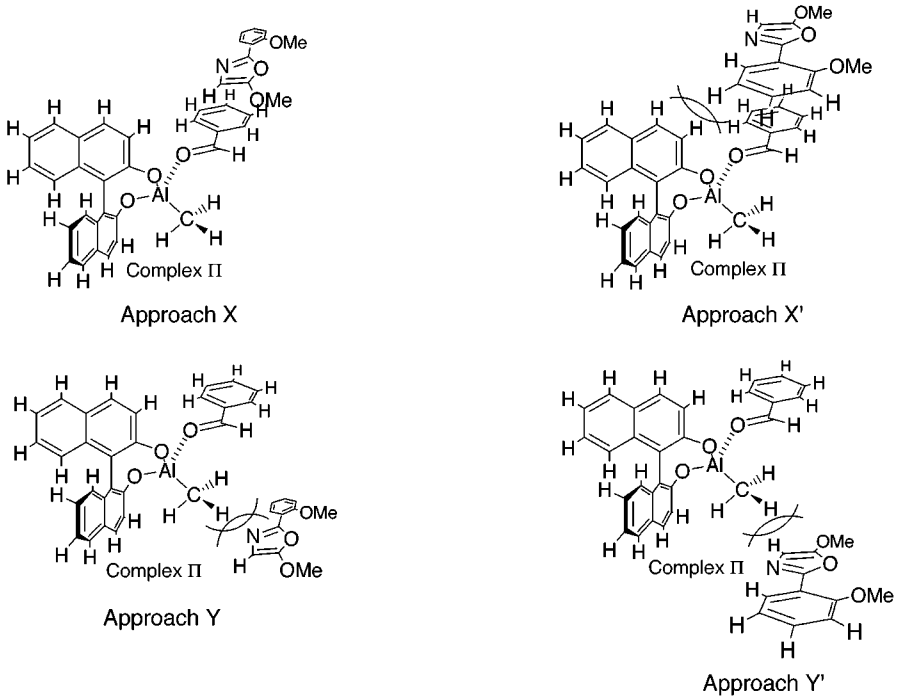


Figure 2. Approaches X, X′, Y, and Y′.

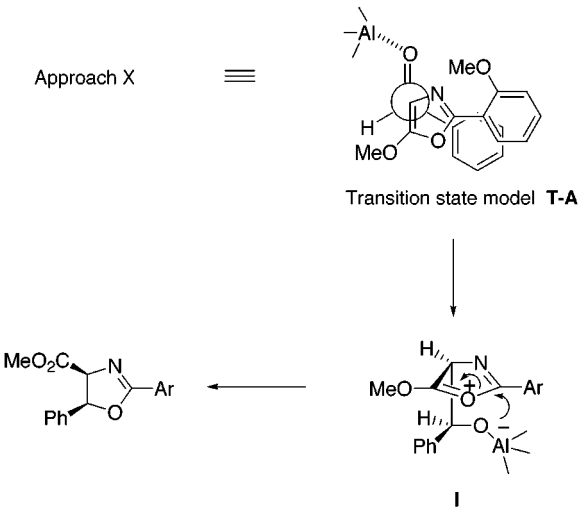


Figure 3. Postulated transition state.

oxazole **1b** as exemplified below, seems to be the most favorable. Approach X corresponds to an antiperiplanar attack of the C4−C5 double bond of the oxazoles on the carbonyl group of the aldehyde as shown in transition state model **T**−**A**, and this approach gives (4*S*,5*S*)-*cis*-2-oxazoline-4-carboxylates through a stepwise pathway involving zwitterionic intermediate I (Figure 3). Approaches such as X′ are unfavorable because of steric hindrance between the naphthyl moiety and aryl groups of the oxazoles. In the case of *si*-face attack, antiperiplanar approaches Y and Y′ seem to be much less favorable than approach X because of the steric repulsion between the methyl group of the aluminum center and the oxazoles (Figure 2).

Conclusion

We have developed new methodology for the cis and enantioselective synthesis of synthetically useful 2-oxazoline-4-carboxylates by the methylaluminum *β*-binaphthoxide-catalyzed reaction of 2-aryl-5-alkoxyoxazoles with substituted benzaldehydes. The above-described methodology has the advantage of high enantioselectivity and cis selectivity over previously reported methods for the synthesis of 2-oxazoline-4-carboxylates. Normally, the use of Lewis acids as catalysts in reactions of heterocyclic compounds is expected to have limitations in the activation and control of the reactions because the Lewis acids may form complexes with heterocyclic compounds. We believe that our success in the stereo- and enantiocontrol of formal [3 + 2] cycloaddition of 5-alkoxyoxazoles in the present work presents a new guiding principle for the use of Lewis acids for the reaction of heterocyclic compounds.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz, respectively. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were recorded at 70 eV with a direct inlet. For preparative column chromatogtaphy, Wakogel C-300 and silica gel 60 (Merck) were employed. Medium-pressure liquid chromatography was carried out using a column packed with silica gel 60 (Merck, size 0.040−0.063 mm). All reactions were carried out under an argon atmosphere in dried glassware.

Materials. MeCN and CH_2Cl_2 were purified by the method repored previously.[6,7] 5-Alkoxy-2-aryloxazoles (**1a**−**d**) were

(12) L-(−)-*threo*-*β*-Phenylserine: $[\alpha]^{18}_D = -50.2 \pm 2°$ (*c* 2.0, 6 N HCl). Vogler, K. *Helv. Chim. Acta* **1950**, *33*, 2111.

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(15) (a) Suga, H.; Ibata, T. *Chem. Lett.* **1991**, 1221. (b) Suga, H.; Shi, X.; Ibata, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1231.

(16) Suga, H.; Shi, X.; Ibata, T. *Chem. Lett.* **1994**, 1673.

synthesized from glycin methyl ester hydrochloride by the method described in the literature.[17]

2-(*p*-Methoxyphenyl)-5-methoxyoxazole (1a): pale yellow crystals (benzene−hxane); mp 80.5−82.2 °C; IR (KBr) 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 (3H, s), 3.93 (3H, s), 6.15 (1H, s), 6.93 (2H, dt, J = 8.6 Hz, 1.7 Hz), 7.80 (2H, dt, J = 8.6 Hz, 1.7 Hz). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.24; H, 5.49; N, 6.78.

2-(*o*-Methoxyphenyl)-5-methoxyoxazole (1b): colorless crystals (CH_2Cl_2−hexane); mp 66.4−69.6 °C; IR (KBr) 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (3H, s), 3.95 (3H, s), 6.25 (1H, s), 6.99−7.04 (2H, m), 7.37 (1H, ddd, J = 8.9 Hz, 7.6 Hz, 1.7 Hz), 7.84 (1H, dd, J = 7.6 Hz, 1.7 Hz). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.44; H, 5.52; N, 6.76.

2-(3,4,5-Trimethoxyphenyl)-5-methoxyoxazole (1c): pale yellow crystals (benzene-hexane); mp 107.2−109.8 °C; IR (KBr) 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (3H, s), 3.92 (6H, s), 3.95 (3H, s), 6.18 (1H, s), 7.15 (2H, s). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.93; H, 5.75; N, 5.29.

2-(2,6-Dimethoxyphenyl)-5-methoxyoxazole (1d): colorless crystals (benzene−hexane); mp 84.9−86.6 °C (from benzene−hexane); IR (KBr) 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (6H, s), 3.92 (3H, s), 6.25 (1H, s), 6.59 (2H, d, J = 8.6 Hz), 7.35 (1H, t, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ = 56.1, 58.3, 98.9, 103.8, 106.9, 131.9, 147.4, 160.0, 161.1. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.52; H, 5.62; N, 5.92.

Typical Experimental Procedure for the Reaction of Oxazoles 1b with Benzaldehyde or Substituted Benzaldehyde in the Presence of a Catalytic Amount of Catalyst A. To a solution of (*R*)-2,2′-dihydroxy-1,1′-binaphthyl (85.9 mg, 0.30 mmol) in MeCN (6 mL) was added a 1.05 M hexane solution of Me_3Al (0.30 mL, 0.315 mmol), and the resulting solution was stirred at room temperature for 1 h. After the mixture was cooled to −20 °C, a solution of oxazole **1b** (0.205 g, 1.0 mmol) and benzaldehyde or substituted benzaldehyde (10.0 mmol) in MeCN (6 mL) was added. The mixture, after being stirred at the temperature for the time cited in Tables 2 and 3, was quenched with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (30 mL × 3), the separated organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was chromatographed over silica gel using hexanes−ehtyl acetate as an eluent to give 2-oxazoline-4-carboxylate **2b**−**11b**. The cis/trans ratio was evaluated on the basis of the ^1H NMR spectrum or from the amount of the products after separation. The enantiomeric exess was determined by HPLC analysis (Dicel Chiralpak AS, hexane−^{i}PrOH, 9/1 v/v, flow rate 0.5 mL/min) or by ^1H NMR analysis using (*R*)-2,2′-dihydroxy-1,1′-binaphthyl as shift reagent after separation of cis product.

Spectroscopic data of *cis*- and *trans*-2-oxazoline-4-carboxylates **2a**, **3a**, **4a**, and **6a** were previously reported.[6]

Methyl (4*S*,5*S*)-2-(*p*-methoxyphenyl)-5-phenyl-*cis*-2-oxazoline-4-carboxylate (*cis*-2a): $[\alpha]^{26}_D$ = +215.2° (*c* 1.23, THF), 88% ee.

Methyl (4*S*,5*S*)-2-(*p*-methoxyphenyl)-5-(*p*-nitrophenyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-3a): $[\alpha]^{28}_D$ = +168.2° (*c* 1.01, $CHCl_3$), 73% ee.

Methyl (4*S*,5*S*)-2-(*p*-methoxyphenyl)-5-(*p*-chlorophenyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-4a): $[\alpha]^{28}_D$ = +64.4° (*c* 0.86, $CHCl_3$), 51% ee.

Methyl (4*S*,5*S*)-2-(*p*-methoxyphenyl)-5-(*p*-tolyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-6a): $[\alpha]^{28}_D$ = +75.5° (*c* 0.98, $CHCl_3$), 63% ee.

Methyl (4*S*,5*S*)-2-(*o*-methoxyphenyl)-5-phenyl-*cis*-2-oxazoline-4-carboxylate (*cis*-2b): pale yellow viscous oil; $[\alpha]^{25}_D$ = +241.4° (*c* 1.06, THF), 85% ee; IR (KBr) 1739, 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.23 (3H, s), 3.92 (3H, s), 5.30 (1H, d, J = 10.9 Hz), 5.93 (1H, d, J = 10.9 Hz), 7.30-7.36 (9H, m); HRMS (EI) calcd for $C_{18}H_{17}NO_4$ (M^+) 311.1158, found 311.1183.

(17) Grifanti, M.; Sein, M. L. *Ann. Chim. (Rome)* **1965**, *55*, 578.

Methyl (4*S*,5*S*)-2-(3,4,5-trimethoxyphenyl)-5-phenyl-*cis*-2-oxazoline-4-carboxylate (*cis*-2c): colorless prisms (ethyl acetate−hexane); mp 126.1−129.1 °C; IR (KBr) 1748, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.23 (3H, s), 3.92 (9H, s), 5.30 (1H, d, J = 10.9 Hz), 5.93 (1H, d, J = 10.9 Hz), 7.30-7.36 (7H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 51.68 (q), 56.33 (q), 60.96 (q), 74.16 (d), 83.04 (d), 105.97 (d), 126.37 (d), 128.30 (d), 122.01 (s), 135.90 (s), 141.49 (s), 153.15 (s), 166.42 (s), 169.52 (s); MS *m*/*z* (rel intensity) 371 (M^+, 72), 312 (77), 265 (50), 195 (base peak), 119 (28), 91 (20). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.62; H, 5.76; N, 3.76.

Methyl (4*S*,5*S*)-2-(2,6-dimethoxyphenyl)-5-phenyl-*cis*-2-oxazoline-4-carboxylate (*cis*-2d): colorless needles (benzene−hexane); mp 117.7−119.4 °C; $[\alpha]^{23}_D$ = +129.9° (*c* 0.51, $CHCl_3$), >98% ee after recrystallization; IR (KBr) 1753, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.23 (3H, s), 3.89 (6H, s), 5.38 (1H, d, J = 11.2 Hz), 5.92 (1H, d, J = 11.2 Hz), 7.31−7.49 (8H, m); ^{13}C NMR ($CDCl_3$) δ 51.6 (q), 56.1 (q), 74.2 (d), 82.6 (d), 103.9 (d), 106.9 (s), 126.9 (d), 128.0 (d), 128.5 (d), 132.0 (d), 136.4 (s), 159.1 (s), 163.6 (s), 169.5 (s). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.50; H, 5.72; N, 4.11.

Methyl (4*S*,5*S*)-2-(*o*-methoxyphenyl)-5-(*p*-nitrophenyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-3b): colorless solid (benzene-hexane); mp 136.6−139.5 °C; $[\alpha]^{23}_D$ = +124.3° (*c* 0.48, $CHCl_3$), 80% ee after recrystallization; IR (KBr) 1736, 1639, 1513, 1351, 1314 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.27 (3H, s), 3.96 (3H, s), 5.41 (1H, d, J = 10.9 Hz), 5.98 (1H, d, J = 10.9 Hz), 7.02−7.08 (2H, m), 7.49−7.59 (3H, m), 7.90 (1H, dd, J = 7.9, 2.0 Hz), 8.22 (2H, d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 51.9, 56.1, 74.5, 81.0, 111.9, 115.7, 120.5, 123.4, 127.3, 131.7, 133.4, 143.6, 147.9, 158.9, 165.7, 169.0. Anal. Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.74; H, 4.58; N, 7.81.

Methyl (4*S*,5*S*)-2-(3,4,5-trimethoxyphenyl)-5-(*p*-nitrophenyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-3c): pale yellow solid (benzene−hexane); mp 191.0−193.9 °C; IR (KBr) 1728, 1637, 1520, 1340, 1308 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28 (3H, s), 3.92 (9H, s), 5.37 (1H, d, J = 10.9 Hz), 6.01 (1H, d, J = 10.9 Hz), 7.33 (2H, s), 7.50 (2H, d, J = 8.9 Hz), 8.23 (2H, d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 51.9, 56.3, 60.9, 74.1, 81.7, 105.9, 123.4, 123.5, 127.2, 129.8, 143.1, 147.9, 153.1, 166.2, 168.9. A satisfactory analytical result was not obtained due to the instability of *cis*-**3c**.

Methyl (4*S*,5*S*)-2-(*o*-methoxyphenyl)-5-(*p*-chlorophenyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-4b): pale yellow viscous oil; $[\alpha]^{22}_D$ = +258.7° (*c* 0.34, $CHCl_3$), 87% ee; IR (neat) 1749, 1647 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.27 (3H, s), 3.94 (3H, s), 5.33 (1H, d, J = 11.2 Hz), 5.87 (1H, d, J = 11.2 Hz), 7.01−7.05 (2H, m), 7.310 (2H, s), 7.314 (2H, s), 7.47−7.50 (1H, m), 7.89 (1H, dd, J = 7.9, 2.9 Hz); ^{13}C NMR ($CDCl_3$) δ 51.8, 56.1, 74.3, 81.5, 111.9, 116.1, 120.4, 127.8, 128.4, 131.7, 133.2, 134.4, 134.8, 158.9, 165.7, 169.3; HRMS (EI) calcd for $C_{18}H_{16}NO_4Cl$ (M^+) 345.0769, found 345.0785.

Methyl (4*S*,5*S*)-2-(*o*-methoxyphenyl)-5-(*p*-cyanophenyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-5b): white amorphous solid; $[\alpha]^{22}_D$ = +234.3° (*c* 0.30, $CHCl_3$), 76% ee; IR (KBr) 2228, 1748, 1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26 (3H, s), 3.95 (3H, s), 5.38 (1H, d, J = 10.9 Hz), 5.92 (1H, d, J = 10.9 Hz), 7.02−7.07 (2H, m), 7.48−7.55 (3H, m), 7.66 (2H, d, J = 8.3 Hz), 8.22 (1H, dd, J = 7.9, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 51.9, 56.1, 74.4, 81.2, 111.9, 112.4, 115.7, 118.4, 120.4, 127.1, 131.7, 132.0, 133.4, 141.6, 158.9, 165.6, 169.0; HRMS (EI) calcd for $C_{19}H_{16}N_2O_4$ (M^+) 336.1112, found 336.1120.

Methyl (4*S*,5*S*)-2-(3,4,5-trimethoxyphenyl)-5-(*p*-cyanophenyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-5c): yellow amorphous; IR (KBr) 2229, 1745, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.27 (3H, s), 3.92 (9H, s), 5.34 (1H, d, J = 10.9 Hz), 5.95 (1H, d, J = 10.9 Hz), 7.32 (2, s), 7.43 (2H, d, J = 8.3 Hz), 7.66 (2H, d, J = 8.3 Hz). A satisfactory analytical result was not obtained due to instability of *cis*-**5c**.

Methyl (4*S*,5*S*)-2-(*o*-methoxyphenyl)-5-(*p*-tolyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-6b): yellow viscous oil; $[\alpha]^{22}_D$ = +138.4° (*c* 0.52, $CHCl_3$), 84% ee; IR (neat) 1750, 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (3H, s), 3.24 (3H, s), 3.93 (3H, s), 5.31 (1H, d, J = 10.9 Hz), 5.86 (1H, d, J = 10.9 Hz), 6.99−7.04 (2H, m), 7.14 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J = 7.9 Hz),

7.45−7.51 (1H, m), 7.90 (1H, td, J = 7.6, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 21.1, 51.6, 74.4, 82.2, 111.8, 116.4, 120.3, 126.3, 128.8, 131.7, 133.0, 133.1, 138.3, 158.9, 165.7, 169.7; HRMS (EI) calcd for $C_{19}H_{19}NO_4$ 325.1315, found 325.1337.

Methyl (4*S*,5*S*)-2-(*o*-methoxyphenyl)-5-(*p*-methoxyphenyl)-*cis*-2-oxazoline-4-carboxylate (***cis*-7b**): yellow viscous oil; $[\alpha]^{22}_D$ = +138.4° (*c* 0.52, $CHCl_3$), 89% ee; IR (neat) 1741, 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.28 (3H, s), 3.80 (3H, s), 3.94 (3H, s), 5.31 (1H, d, J = 10.9 Hz), 5.86 (1H, d, J = 10.9 Hz), 6.86 (2H, d, J = 8.9 Hz), 6.99−7.04 (2H, m), 7.26 (2H, d, J = 8.9 Hz), 7.48 (1H, d, J = 7.9 Hz), 7.89 (1H, dd, J = 7.9, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 51.7, 55.2, 56.1, 74.3, 82.1, 111.8, 113.6, 116.4, 120.3, 127.8, 131.7, 132.3, 133.0, 158.9, 159.7, 165.7, 169.7; HRMS (EI) calcd for $C_{19}H_{19}NO_5$ (M^+) 341.1264, found 341.1236.

Methyl (4*S*,5*S*)-2-(*p*-methoxyphenyl)-5-(*m*-nitrophenyl)-*cis*-2-oxazoline-4-carboxylate (***cis*-8a**): colorless needles (benzene−hexane); mp 107.5−109.8 °C; $[\alpha]^{25}_D$ = +199.5° (*c* 0.51, $CHCl_3$), 78% ee after recrystallization; IR (KBr) 1733, 1660, 1548, 1312 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.28 (3H, s), 3.89 (3H, s), 5.35 (1H, d, J = 10.9 Hz), 5.99 (1H, d, J = 10.9 Hz), 6.98 (2H, dt, J = 8.9, 2.0 Hz), 7.51−7.57 (1H, m), 7.65 (1H, d, J = 7.9 Hz), 8.04 (2H, dt, J = 8.9, 2.0 Hz), 8.19 (2H, m); ^{13}C NMR ($CDCl_3$) δ 51.9, 55.5, 74.2, 81.4, 114.0, 118.7, 121.4, 123.5, 129.4, 130.7, 132.2, 138.5, 148.1, 163.0, 166.3, 169.2. Anal. Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.69; H, 4.58; N, 7.81.

Methyl (4*S*,5*S*)-2-(*o*-methoxyphenyl)-5-(*m*-nitrophenyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-8b): colorless needles (benzene−hexane); mp 115.2−117.3 °C; $[\alpha]^{25}_D$ = +254.1° (c 0.51, $CHCl_3$), >98% ee after recrystallization; IR (KBr) 1741, 1648, 1494, 1342, 1318 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.27 (3H, s), 3.99 (3H, s), 5.40 (1H, d, J = 10.9 Hz), 6.01 (1H, d, J = 10.9 Hz), 7.01−7.07 (2H, m), 7.49−7.57 (2H, m), 7.69 (1H, d, J = 7.6 Hz), 7.87 (1H, d, J = 7.9 Hz, 8.19 (1H, dt, J = 7.9, 1.0 Hz), 8.37 (1H, s); ^{13}C NMR ($CDCl_3$) δ 51.9, 56.1, 74.3, 81.1, 111.8, 115.9, 120.5, 121.6, 123.5, 129.2, 131.7, 132.4, 133.3, 138.7, 148.2, 158.9, 166.0, 169.0. Anal. Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; 7.86. Found: C, 60.89; H, 4.62; N, 7.86.

Methyl (4*S*,5*S*)-2-(*p*-methoxyphenyl)-5-(*m*-chlorophenyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-9a): colorless needles (benzene−hexane); mp 87.5−89.8 °C; $[\alpha]^{20}_D$ = +202.2° (c 0.51, $CHCl_3$), 78% ee after recrystallization; IR (KBr) 1739, 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.30 (3H, s), 3.88 (3H, s), 5.27 (1H, d, J = 10.9 Hz), 5.86 (1H, d, J = 10.9 Hz), 6.97 (2H, dt, J = 8.9, 2.0 Hz), 7.15−7.30 (4H, m), 8.03 (2H, dt, J = 8.9, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 51.8, 55.5, 74.1, 81.9, 113.9, 119.0, 124.5, 126.4, 128.7, 129.6, 130.6, 134.3, 138.2, 162.8, 166.3, 169.4. Anal. Calcd for $C_{18}H_{16}NO_4Cl$: C, 62.52; H, 4.66; N, 4.05. Found: C, 62.65; H, 4.68; 4.04.

Methyl (4*S*,5*S*)-2-(*o*-methoxyphenyl)-5-(*m*-chlorophenyl)-*cis*-2-oxazoline-4-carboxylate (***cis*-9b**): colorless needles (benzene−hexane); mp 86.8−89.8 °C; $[\alpha]^{25}_D$ = +214.9° (c 0.51, $CHCl_3$), >98% ee after recrystallization; IR (KBr) 1741, 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.29 (3H, s), 3.96 (3H, s), 5.43 (1H, d, J = 10.9 Hz), 5.87 (1H, d, J = 10.9 Hz), 7.01−7.05 (2H, m), 7.22−7.31 (3H, m), 7.45 (1H, s), 7.50 (1H, ddd, J = 8.3, 7.6, 1.7 Hz), 7.87 (1H, dd, J = 7.9, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 51.8, 56.0, 74.4, 81.5, 111.8, 116.2, 120.4, 124.6, 126.6, 128.6, 129.4, 124.6, 126.6, 128.6, 129.4, 131.7, 133.1, 134.3, 138.3, 158.9, 165.8, 169.2. Anal. Calcd for $C_{18}H_{16}NO_4Cl$: C, 62.52; H, 4.66; N, 4.05. Found: C, 62.51; H, 4.66; N, 4.05.

Methyl (4*S*,5*S*)-2-(*p*-methoxyphenyl)-5-(*m*-tolyl)-*cis*-oxazoline-4-carboxylate (*cis*-10a): colorless prisms (benzene−hexane); mp 86.4−88.9 °C; $[\alpha]^{24}_D$ = +149.9° (*c* 0.49, $CHCl_3$), 64% ee after recrystallization; IR (KBr) 1754, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.33 (3H, s), 3.24 (3H, s), 3.87 (3H, s), 5.26 (1H, d, J = 10.9 Hz), 5.86 (1H, d, J = 10.9 Hz), 6.96 (2H, dt, J = 8.9, 2.0 Hz), 7.06−7.12 (3H, m), 7.19−7.25 (1H, m), 8.04 (2H, dt, J = 8.9, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 51.6, 55.4, 74.1, 82.9, 113.9, 119.4, 123.4, 126.9, 128.1, 129.4, 130.6, 136.0, 138.0, 162.7, 166.5, 169.8. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.35; H, 5.95; N, 4.32.

Methyl (4*S*,5*S*)-2-(*o*-methoxyphenyl)-5-(*m*-tolyl)-*cis*-2-oxazoline-4-carboxylate (***cis*-10b**): yellow viscous oil; $[\alpha]^{20}_D$ = +155.3 °C (*c* 2.35, $CHCl_3$); IR (neat) 1750, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (3H, s), 3.24 (3H, s), 3.95 (3H, s), 5.32 (1H, d, J = 10.9 Hz), 5.86 (1H, d, J = 10.9 Hz), 7.00−7.10 (2H, m), 7.12−7.23 (4H, m), 7.49 (1H, ddd, J = 7.9, 5.6, 1.7 Hz), 7.91 (1H, dd, J = 7.9, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 51.6, 56.1, 74.5, 82.3, 111.8, 116.4, 120.3, 123.2, 123.5, 128.1, 131.7, 133.0, 137.8, 158.9, 165.8, 169.0. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.14; H, 5.90; N, 4.26.

Methyl (4*S*,5*S*)-2-(*p*-methoxyphenyl)-5-(*m*-methoxyphenyl)-*cis*-2-oxazoline-4-carboxylate (*cis*-11a): colorless needles (benzene−hexane); mp 118.0−120.5 °C; $[\alpha]^{22}_D$ = +205.9° (*c* 0.51, $CHCl_3$), 80% ee after recrystallization; IR (KBr) 1751, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.28 (3H, s), 3.78 (3H, s), 3.88 (3H, s), 5.27 (1H, d, J = 10.6 Hz), 5.87 (1H, d, J = 10.6 Hz), 6.83−6.93 (3H, m), 6.96 (2H, d, J = 8.9 Hz), 7.25 (1H, t, J = 7.9 Hz), 8.04 (2H, d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 51.8, 55.3, 55.4, 74.1, 82.7, 111.8, 113.8, 114.2, 118.7, 119.3, 129.3, 130.6, 137.6, 159.5, 162.7, 166.4, 169.7. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.89; H, 5.63; N, 4.08.

Methyl (4*S*,5*S*)-2-(*o*-methoxyphenyl)-5-(*m*-methoxyphenyl)-*cis*-2-oxazoline-4-carboxylate (***cis*-11b**): pale yellow viscous oil; $[\alpha]^{23}_D$ = +199.2° (*c* 0.88, $CHCl_3$), 90% ee; IR (neat) 1747, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.27 (3H, s), 3.79 (3H, s), 3.94 (3H, s), 5.33 (1H, d, J = 10.9 Hz), 5.86 (1H, d, J = 10.9 Hz), 6.82−7.05 (5H, m), 7.25 (1H, t, J = 7.9 Hz), 7.45−7.52 (1H, m), 7.91 (1H, dd, J = 7.9, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 51.7, 55.3, 56.1, 74.4, 82.1, 111.8, 111.9, 114.1, 116.3, 118.8, 120.3, 129.2, 131.7, 133.0, 137.7, 158.9, 159.5, 165.8, 169.6. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.70; H, 5.61; 3.94.

Although a small amount of trans products could not be isolated purely or did not give satisfactry analytical data after separation by chromatograpy, these products could be characterized by ^{1}H NMR.

Methyl 2-(*o*-methoxyphenyl)-5-phenyl-*trans*-2-oxazoline-4-carboxylate (*trans*-2b): pale yellow viscous oil; IR (KBr) 1739, 1628, 1599, 1465, 1437, 1348, 1259, 1124, 1095, 1042, and 751 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s), 3.88 (3H, s), 4.84 (1H, d, J = 7.6 Hz), 5.85 (1H, d, J = 7.6 Hz), 6.98−7.03 (2H, m), 7.34−7.51 (6H, m), 7.86−7.89 (1H, m).

Methyl 2-(3,4,5-trimethoxyphenyl)-5-phenyl-*trans*-2-oxazoline-4-carboxylate (*trans*-2c): pale yellow viscous oil; ^{1}H NMR ($CDCl_3$) δ 3.86 (3H, s), 3.91 (9H, s), 4.81 (1H, d, J = 7.6 Hz), 5.88 (1H, d, J = 7.6 Hz), 7.32 (2H, s), 7.36−7.42 (5H, m).

Methyl 2-(2,6-dimethoxyphenyl)-5-phenyl-*trans*-2-oxazoline-4-carboxylate (*trans*-2d): colorless viscous oil; IR (KBr) 1741, 1664, 1595, 1477, 1435, 1306, 1257, 1223, 1174, 1113, 1055, 1030, 982, 729, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (9H, s), 4.83 (1H, d, J = 7.3 Hz), 5.89 (1H, d, J = 7.3 Hz), 7.31−7.53 (8H, m).

Methyl 2-(*o*-methoxyphenyl)-5-(*p*-nitrophenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-3b): yellow viscous oil; IR (neat) 2949, 2841, 1736, 1639, 1602, 1519, 1492, 1464, 1435, 1347, 1259, 1181, 1123, 1043, 1020, 885, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.89 (3H, s), 3.95 (3H, s), 4.79 (1H, d, J = 7.6 Hz), 5.96 (1H, d, J = 7.6 Hz), 7.00−7.06 (2H, m), 7.51 (1H, t, J = 8.6 Hz), 7.64 (2H, d, J = 8.9 Hz), 7.88 (1H, dd, J = 7.9, 1.7 Hz), 8.26 (2H, d, J = 8.9 Hz).

Methyl 2-(3,4,5-trimethoxyphenyl)-5-(*p*-nitrophenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-3c): yellow solid; IR (KBr) 2941, 1717, 1652, 1588, 1557, 1523, 1504, 1464, 1417, 1366, 1348, 1286, 1249, 1234, 1173, 1129, 1099, 1005, 847, 741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s), 3.92 (9H, s), 4.76 (1H, d, J = 7.6 Hz), 5.99 (1H, d, J = 7.6 Hz), 7.31 (2H, s), 7.58 (2H, d, J = 8.6 Hz), 8.28 (2H, d, J = 8.6 Hz).

Methyl 2-(*o*-methoxyphenyl)-5-(*p*-chlorophenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-4b): pale yellow viscous oil; ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s), 3.93 (3H, s), 4.78 (1H, d, J = 7.6 Hz), 5.82 (1H, d, J = 7.6 Hz), 6.99−7.04 (2H, m), 7.37 (4H, s), 7.45−7.51 (1H, m), 7.86 (1H, dd, J = 8.0, 1.7 Hz).

Methyl 2-(*o*-methoxyphenyl)-5-(*p*-cyanophenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-5b): pale yellow viscous

oil; ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 3.95 (3H, s), 4.72 (1H, d, J = 7.6 Hz), 5.89 (1H, d, J = 7.6 Hz), 6.92−7.09 (2H, m), 7.42−7.73 (5H, m), 7.84 (1H, d, J = 8.3 Hz).

Methyl 2-(3,4,5-trimethoxyphenyl)-5-(*p*-cyanophenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-5c): pale yellow solid; IR (KBr) 2947, 2228, 1731, 1645, 1588, 1506, 1468, 1442, 1416, 1376, 1346, 1232, 1183, 1133, 1098, 1006, 992, 851 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.89 (3H, s), 3.92 (9H, s), 4.75 (1H, d, J = 7.6 Hz), 5.89 (1H, d, J = 7.6 Hz), 7.30 (2H, s), 7.51 (2H, d, J = 8.3 Hz), 7.71 (2H, d, J = 8.3 Hz).

Methyl 2-(*o*-methoxyphenyl)-5-(*p*-tolyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-6b): pale yellow viscous oil; IR (neat) 2949, 1738, 1636, 1601, 1580, 1515, 1495, 1463, 1435, 1324, 1261, 1181, 1123, 1081, 1044, 1022, 983, 917, 757, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.36 (3H,s), 3.84 (3H, s), 3.93 (3H, s), 4.82 (1H, d, J = 7.6 Hz), 5.80 (1H, d, J = 7.6 Hz), 6.97−7.02 (2H, m), 7.20 (2H, d, J = 7.9 Hz), 7.31 (2H, d, J = 7.9 Hz), 7.43−7.50 (1H, m), 7.86 (1H, dd, J = 7.9, 2.0 Hz).

Methyl 2-(*o*-methoxyphenyl)-5-(*p*-methoxyphenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-7b): yellow viscous oil; IR (neat) 2951, 1741, 1637, 1582, 1514, 1493, 1462, 1435, 1327, 1251, 1178, 1123, 1081, 1042, 982, 832, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 3.84 (3H, s), 3.92 (3H, s), 4.83 (1H, d, J = 7.3 Hz), 5.79 (1H, d, J = 7.3 Hz), 6.92 (2H, d, J = 7.9 Hz), 6.97−7.00 (2H, m), 7.35 (2H, d, J = 7.9 Hz), 7.46 (1H, t, J = 7.9 Hz), 7.85 (1H, d, J = 7.9 Hz).

Methyl 2-(*p*-methoxyphenyl)-5-(*m*-nitrophenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-8a): yellow viscous oil; IR (neat) 2952, 1735, 1637, 1608, 1576, 1526, 1509, 1480, 1457, 1436, 1421, 1350, 1256, 1207, 1171, 1080, 1027, 842, 738, 686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 3.89 (3H, s), 4.77 (1H, d, J = 7.6 Hz), 5.97 (1H, d, J = 7.6 Hz), 6.96 (2H, dt, J = 8.0, 2.0 Hz), 7.59 (1H, t, J = 7.9 Hz), 7.74 (1H, d, J = 7.9 Hz), 8.02 (2H, dt, J = 8.9, 2.0 Hz), 8.22 (1H, ddd, J = 7.9, 2.3, 1.0 Hz), 8.27 (1H, t, J = 2.3 Hz).

Methyl 2-(*o*-methoxyphenyl)-5-(*m*-nitrophenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-8b): pale yellow viscous oil; IR (neat) 2951, 1735, 1639, 1601, 1581, 1528, 1490, 1464, 1435, 1351, 1317, 1251, 1180, 1123, 1078, 1043, 1021, 994, 757, 733, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s), 3.99 (3H, s), 4.79 (1H, d, J = 7.3 Hz), 5.98 (1H, d, J = 7.3 Hz), 7.00−7.06 (2H, m), 7.51 (1H, d, J = 7.9 Hz), 7.60 (1H, t, J = 7.9 Hz),7.77 (1H, d, J = 7.6 Hz), 7.85 (1H, d, J = 7.9 Hz), 8.22 (1H, d, J = 8.3 Hz), 8.43 (1H, s).

Methyl 2-(*p*-methoxypheny)-5-(*m*-chlorophenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-9a): pale yellow viscous oil; IR (neat) 2950, 1734, 1636, 1608, 1575, 1510, 1476, 1457, 1435, 1421, 1309, 1256, 1204, 1170, 1080, 1027, 1009, 990, 841, 789, 741, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.87 (6H, s), 4.75 (1H, d, J = 7.6 Hz), 5.84 (1H, d, J = 7.6 Hz), 6.95 (2H, dt, J = 8.6 Hz), 7.26−7.37 (4H, m), 8.01 (2H, dt, J = 8.6 Hz).

Methyl 2-(*o*-methoxyphenyl)-5-(*m*-chlorophenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-9b): pale yellow viscous oil; IR (neat) 2950, 1739, 1637, 1600, 1575, 1492, 1464, 1434, 1259, 1224, 1205, 1181, 1123, 1080, 1043, 1023, 990, 789, 755, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, s), 3.95 (3H, s), 4.78 (1H, d, J = 7.3 Hz), 5.83 (1H, d, J = 7.3 Hz), 6.99−7.04 (2H, m), 7.27−7.34 (3H, m), 7.46−7.52 (2H, m), 7.85 (1H, dd, J = 7.9, 2.0 Hz).

Methyl 2-(*p*-methoxyphenyl)-5-(*m*-tolyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-10a): pale yellow viscous oil; ^{1}H NMR ($CDCl_3$) δ 2.36 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 4.78 (1H, d, J = 7.6 Hz), 5.83 (1H, d, J = 7.6 Hz), 6.94 (2H, dt, J = 8.9, 2.0 Hz), 7.14−7.30 (4H, m), 8.01 (2H, dt, J = 8.9, 2.0 Hz).

Methyl 2-(*o*-methoxypheny)-5-(*m*-tolyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-10b): yellow viscous oil; IR (neat) 2949, 1740, 1637, 1601, 1579, 1491, 1462, 1435, 1366, 1320, 1261, 1180, 1123, 1081, 1044, 1022, 984, 792, 757, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 3.85 (3H, s), 3.93 (3H, s), 4.83 (1H, d, J = 7.6 Hz), 5.81 (1H, d, J = 7.6 Hz), 6.98−7.03 (2H, m), 7.14−7.30 (4H, m), 7.47 (1H, ddd, J = 7.9, 5.6, 2.0 Hz), 7.87 (1H, dd, J = 7.9, 2.0 Hz).

Methyl 2-(*p*-methoxyphenyl)-5-(*m*-methoxyphenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-11a): pale yellow viscous oil; ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 4.79 (1H, d, J = 7.6 Hz), 5.84 (1H, d, J = 7.6 Hz), 6.86−6.98 (5H, m), 7.26−7.31 (1H, m),8.01 (2H, d, J = 8.9 Hz).

Methyl 2-(*o*-methoxyphenyl)-5-(*m*-methoxyphenyl)-*trans*-2-oxazoline-4-carboxylate (*trans*-11b): pale yellow viscous oil; ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 3.85 (3H, s), 3.93 (3H, s), 4.83 (1H, d, J = 7.6 Hz), 5.82 (1H, d, J = 7.6 hz), 6.86−7.50 (7H, m), 7.81−7.89 (1H, m).

Conversion of 2-Oxazoline *cis*-2a to *threo*-Phenylserin. A solution of 2-oxazoline *cis*-**2a** (0.162 g, 0.520 mmol) and triethylamine (1.05 g, 1.45 mL, 10.4 mmol) in MeCN was heated under reflux for 45 h. After the solvent was removed under reduced pressure, the residue was chromatographed over silica gel using hexanes−ethyl acetate (9:1 vol /vol) as eluent to give 2-oxazoline **trans-2a** (0.118 g, 73%, 70% ee by HPLC analysis). A solution of the resulting *trans*-**2a** (0.116 g, 0.373 mmol) in concentrated HCl (2 mL) and MeOH (2 mL) was heated at 50 °C for 6 h and in 6 M HCl at 80 °C for 14 h and then 100 °C for 5 h. After extraction of the mixture with ethyl acetate (30 mL), the water layer was evaporated in vacuo. The residue was treated through Amberlite IRA-120B (H^+) to give *threo*-phenylserin (0.034 mg, 50%, $[\alpha]^{18}_D = +29.9°$ (*c* 2.0, 6 N HCl)).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of new *cis*-2-oxazoline-4-carboxylates. This material is available free of charge via the Internet at http://pubs.acs.org.

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