Tetrahedron Vol 44, No 17, pp 5253 to 5262, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00
Pergamon Press plc

ASYMMETRIC SYNTHESIS OF β-HYDROXY-α-ALKYLAMINO ACIDS BY ASYMMETRIC ALDOL REACTION OF α-ISOCYANOCARBOXYLATES CATALYZED BY CHIRAL FERROCENYLPHOSPHINE-GOLD(I) COMPLEXES

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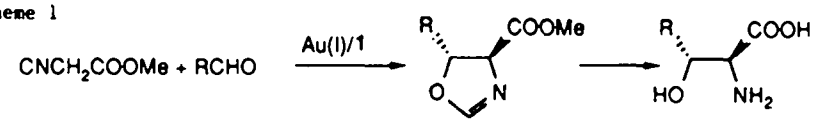
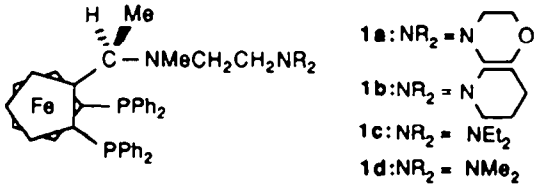
(Received in USA 23 February 1988)

Abstract: Aldol reaction of methyl α-isocyanocarboxylates (CNCH(R)COOMe: R = H, Me, Et, i-Pr) with benzaldehyde or acetaldehyde in the presence of 0.5-1.0 mol% of a chiral (aminoalkyl)ferrocenylphosphine-gold(I) complex gave optically active 4-methoxycarbonyl-4,5-dialkyl-2-oxazolines with high enantioselectivity in a quantitative yield. The oxazolines were converted into optically active β-hydroxy-α-alkylamino acid methyl esters.

In recent years we have been engaged in design and preparation of an efficient catalyst for asymmetric reactions catalyzed by chiral phosphine-transition metal complexes,[1] and found that a gold(I) complex of chiral ferrocenylphosphine ligand bearing a tertiary amino group at the end of ferrocene side chain, i.e., (R)-N-methyl-N-[2-(dialkylamino)ethyl]-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (NR_2 in 1 = morpholino (1a), piperidino (1b), diethylamino (1c), or dimethylamino (1d)), is effective for asymmetric aldol reaction of isocyanocarboxylates with aldehydes forming optically active 2-oxazoline-4-carboxylates.[2-5] We have previously reported asymmetric synthesis of β-hydroxyamino acids (up to 96% ee)[2,3] and α-alkylserines (up to 83% ee)[4] via the catalytic asymmetric aldol reaction (Scheme 1). Here we describe the reaction of methyl α-isocyanocarboxylates (CNCH(R)COOMe: R = H, Me, Et, i-Pr) with benzaldehyde and acetaldehyde forming 4-methoxycarbonyl-4,5-dialkyl-2-oxazolines which can be converted into optically active α-alkyl-β-phenylserines and α-alkylthreonines.

Scheme 1

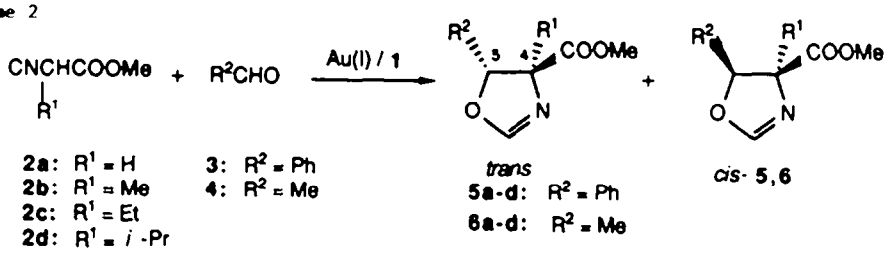




Asymmetric Aldol Reaction. Methyl α-isocyanocarboxylates 2b-d[6] were allowed to react with benzaldehyde (3) or acetaldehyde (4) in dichloromethane at 25 °C in the presence of 0.5-1.0 mol% of gold catalyst prepared in situ by mixing $[Au(c\text{-}C_6H_{11}NC)_2]BF_4$[7] and a chiral ferrocenylphosphine (R)-(S)-1[1,8] (Scheme 2). The ferrocenylphosphine ligand containing morpholino or piperidino

group at the end of the side chain is known to be superior to others in terms of enantioselectivity in the aldol reaction of methyl α-isocyanoacetate (2a).[3] The aldol reaction of α-isocyanocarboxylates 2b-d that have alkyl substituents at α position was generally slower than that of unsubstituted isocyanoacetate 2a, and it required a longer reaction time to complete the aldol reaction giving the expected 4-(methoxycarbonyl)-4,5-dialkyl-2-oxazolines. The oxazolines formed were isolated by distillation under reduced pressure, and trans and cis isomers were separated and purified by medium-pressure liquid chromatography (MPLC) or preparative GLC. The reaction conditions and results obtained are summarized in Table 1, which also contains data obtained in the reaction of 2a[2,3] for comparison.

Scheme 2



The reaction of 2b (R^1 = Me) with benzaldehyde proceeded a little more slowly than that of 2a (R^1 = H) to give 4-(methoxycarbonyl)-4-methyl-5-phenyl-2-oxazoline (5b), where the predominant isomer had trans geometry, in over 90% yield within three or four days (entries 4-7). Highest trans selectivity (93/7) and highest enantioselectivity (94% ee) were obtained with ligand 1a (entry 4). The term "trans" used here refers to the relative configuration with respect to the alkyl group at 5 position and methoxycarbonyl group at 4 position. The enantioselectivity (94% ee) for the trans isomer is comparable to that for trans-5a (entries 1 and 2). The configuration (4S,5R) of trans-5b, which was determined by palladium-catalyzed hydrogenolysis into known (S)-α-methylphenylalanine[9] (vide infra), is the same as that of trans-5a. The reaction of isocyanocarboxylate 2d (R^1 = i-Pr) was much more slower than that of 2a and 2b, a longer reaction period than 200 h being required to complete the aldol reaction at room temperature (entries 8-11), and considerable amounts of cis isomer was formed. The trans/cis ratio varied between 62/38 and 50/50 depending on the chiral ligand and reaction temperature. The trans isomer of 5d was around 90% enantiomerically pure and its configuration was (4S,5R) again. The configuration of cis isomers cis-5b and cis-5d is sensitive to the chiral ligand employed. The ligand 1a always produces (4S,5S) isomer preferentially while 1b generally produces (4R,5R) isomer preferentially.

Reaction of 2b (R^1 = Me) with acetaldehyde (4) gave 4-(methoxycarbonyl)-4,5-dimethyl-2-oxazoline (6b) as a mixture of trans and cis isomers (entries 14-16). The trans and cis geometries of oxazolines 6 derived from 4 and 2b-d were assigned by NOE measurement between substituents on 4 and 5 positions in 400 MHz ^{1}H NMR and confirmed by comparison of $[\alpha]_D$ values of cis-2-phenyloxazolines 13 derived from 6 (see Schemes 5 and 6) with those reported by Seebach.[10] The trans/cis ratio of 6b varied between 56/44 for the reaction with ligand 1a and 38/62 for the reaction with 1d. The ferrocenylphosphine with morpholino group 1a turned out to be the most selective ligand giving 86% ee for trans-6b and 54% ee for cis-6b. Other ligands, 1b and 1d, were much less stereoselective, the enantiomeric purities of trans-6b being lower than 50%. Almost the same selectivity was observed in the reaction of isocyanocarboxylate 2c (R^1 = Et) in the presence of gold-1a catalyst, which gave trans/cis ratio of 54/46 and 87% ee for trans-6c (entry 17). Reaction of 2d (R^1 = i-Pr) proceeded sluggishly to give cis oxazoline 6d predominantly (entries 18 and 19). The configurations of 6b-d were always (4S,5R) for trans isomers and (4S,5S) for cis isomers.

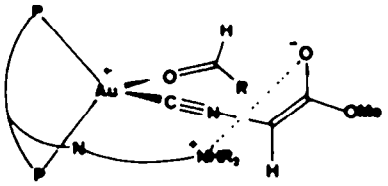
We have previously proposed[2-4] the key intermediate A for the gold-catalyzed asymmetric aldol reaction of methyl α-isocyanoacetate (2a) with aldehydes forming (4S,5R)-5-alkyloxazolines

Table 1. Asymmetric Aldol Reaction of Aldehydes 3 and 4 with Methyl Isocyanocarboxylates 2 Catalyzed by Chiral Ferrocenylphosphine (1)-Gold Complexes.[a]

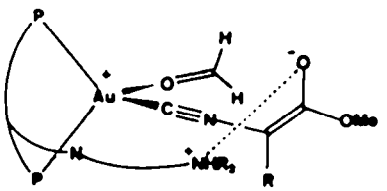
entry	aldehyde	isocyano carboxylate	ligand 1 NR_2	reaction time (h)	yield[b](%) of 5 or 6	ratio[c] of trans/cis	% ee[d] (config)[e] trans	% ee[d] (config)[e] cis
1[f]	PhCHO (3)	R^1 = H (2a)	1a 	16	93 (5a)	95/5	95 (4S,5R)	12 (4S,5S)
2[f]			1b 	16	94 (5a)	94/6	95 (4S,5R)	49 (4R,5R)
3[f]			1d NMe_2	38	91 (5a)	90/10	91 (4S,5R)	4 (4S,5S)
4		R^1 = Me (2b)	1a 	67	97 (5b)	93/7	94 (4S,5R)	53 (4S,5S)
5			1b 	43	92 (5b)	88/12	90 (4S,5R)	5 (4R,5R)
6[g]			1c NEt_2	96	90 (5b)	77/23	82 (4S,5R)	26 (4S,5S)
7			1d NMe_2	65	95 (5b)	82/18	92 (4S,5R)	44 (4S,5S)
8		R^1 = i-Pr (2d)	1a 	330	86 (5d)	62/38	88 (4S,5R)	17 (4S,5S)
9			1b 	280	86 (5d)	54/46	92 (4S,5R)	28 (4R,5R)
10[h]			1c NEt_2	100	87 (5d)	52/48	85 (4S,5R)	42 (4S,5S)
11			1d NMe_2	200	95 (5d)	50/50	88 (4S,5R)	48 (4S,5S)
12[f,i]	MeCHO (4)	R^1 = H (2a)	1a 	70	99 (6a)	89/11	89 (4S,5R)	10 (4S,5S)
13[f]			1b	16	100 (6a)	85/15	85 (4S,5R)	56 (4R,5R)
14		R^1 = Me (2b)	1a 	41	86 (6b)	56/44	86 (4S,5R)	54 (4S,5S)
15[j]			1b 	65	94 (6b)	44/56	44 (4S,5R)	6 (4S,5S)
16			1d NMe_2	94	100 (6b)	38/62	46 (4S,5R)	49 (4S,5S)
17[k]		R^1 = Et (2c)	1a 	62	92 (6c)	54/46	87 (4S,5R)	66 (4S,5S)
18		R^1 = i-Pr (2d)	1a 	260	100 (6d)	24/76	26 (4S,5R)	51 (4S,5S)
19			1b 	290	100 (6d)	22/78	35 (4S,5R)	23 (4S,5S)

[a] The reaction was carried out in dichloromethane at 25 °C. The gold catalyst (1 mol% unless otherwise noted) was prepared in situ from $[Au(c\text{-}C_6H_{11}NC)_2]BF_4$ and (R)-(S)-1. [b] Isolated yield by distillation. [c] Determined by ^1H NMR analysis. [d] Determined by ^1H NMR spectra using chiral shift reagent $Eu(hfc)_3$ or $Eu(dcm)_3$. [e] See text. [f] Reported previously in ref 2 and 3. [g] Reaction with 0.6 mol% of the catalyst at 40 °C. [h] Reaction with 0.8 mol% of the catalyst at 40 °C. [i] Reaction with 0.2 mol% of the catalyst. [j] Catalyst = 0.5 mol%. [k] Catalyst = 0.7 mol%.

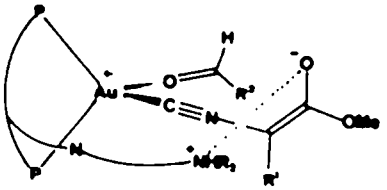
and B for that of α-substituted α-isocyanocarboxylates with formaldehyde forming (4S)-4-alkyloxazolines (see Scheme 1). It seems reasonable that the trans-(4S,5R)-oxazolines 5,6 and cis-(4S,5S)-5,6 in the present aldol reaction are formed via the intermediates C and D. In both C and D attack of the enolate of isocyanocarboxylate coordinated to gold on aldehydes takes place preferentially on the si face of the donor center of the enolate, attack on the same face of the enolate being adopted in B. Nucleophilic attack on si face of aldehydes, which is expected from A, will lead to trans-(4S,5R)-oxazolines. Sterically bulky substituent R^1 such as isopropyl on isocyanocarboxylates is likely to make C unfavorable due to steric interactions between R^1 and R^2 on the aldehyde, and then aldehydes undergo nucleophilic attack on re face, as shown in D, to produce cis-(4S,5S)-oxazolines.



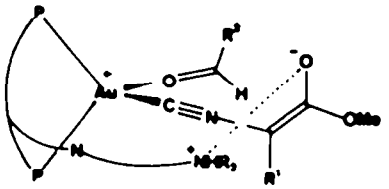
A



B



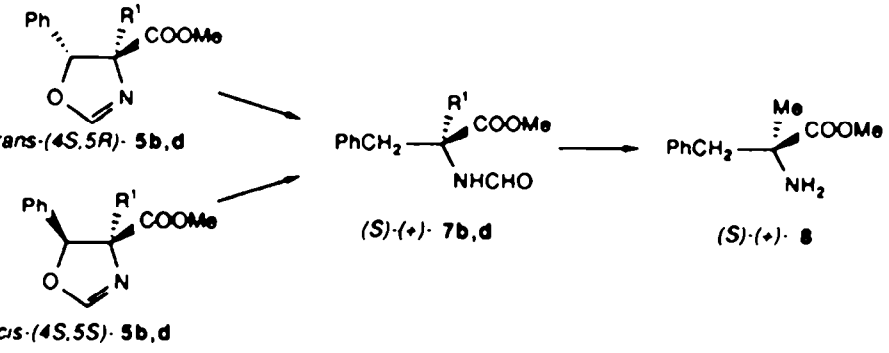
C



D

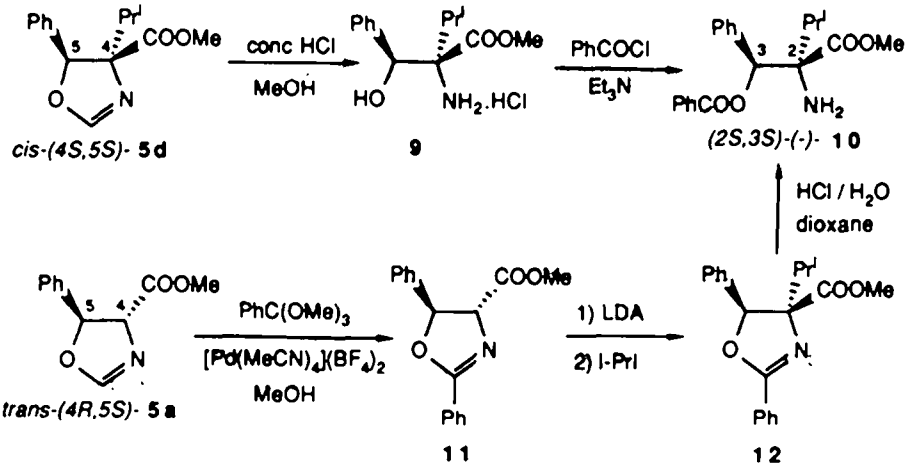
Conversion of Oxazolines into Amino Acid Derivatives and Determination of the Configuration. The oxazolines 5b and 5d, which have phenyl group at 5 position, were converted into N-formyl-amino acid methyl esters 7 by palladium-catalyzed hydrogenolysis of benzylic carbon-oxygen bond[11] (Scheme 3). Both trans-5b (82% ee, obtained in entry 6 in Table 1) and cis-5b (44% ee, entry 7) gave (+)-7b, ($[\alpha]_D^{20}$ +74.3° and +41.2°, respectively, (chloroform)), indicating that they have the same configuration at 4 position. Acidic methanolysis of (+)-7b gave known (S)-(+)-8.[9] It follows that trans-5b and cis-5b used in the transformations have absolute configurations, (4S,5R) and (4S,5S), respectively. It was also demonstrated that trans-5d and cis-5d (entry 10) have the same configuration at 4 position by the hydrogenolysis into (+)-7d.

Scheme 3



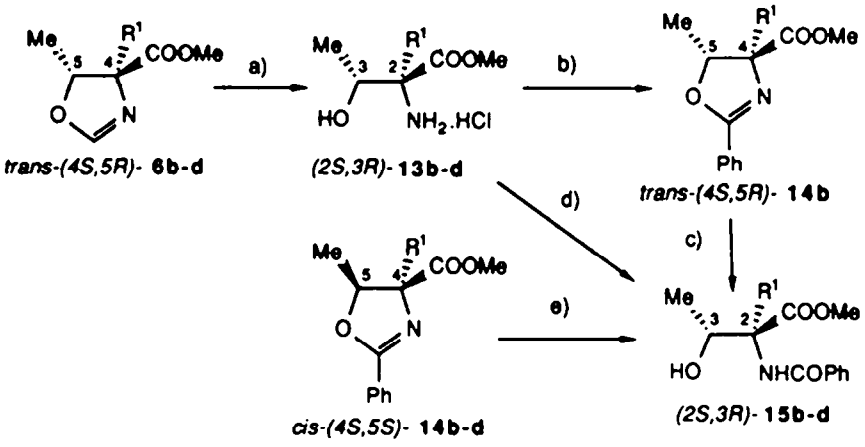
The absolute configuration of oxazoline cis-(-)-5d was determined to be (4S,5S) by comparison of optical rotation values of methyl 2-amino-2-isopropyl-3-phenyl-3-benzoyloxypropionate (10) derived from cis-5d and the authentic sample prepared via diastereoselective alkylation reported by Aebi and Seebach[12] (Scheme 4). Thus, acidic hydrolysis of cis-5d (48% ee, obtained in entry 11) with conc HCl in methanol followed by O-benzoylation of the resulting aminoalcohol 9 gave (-)-10. Treatment of (4R,5S)-4-(methoxycarbonyl)-5-phenyl-2-oxazoline (5a) (91% ee) with excess trimethyl orthobenzoate in the presence of $[Pd(MeCN)_4](BF_4)_2$ as catalyst in refluxing methanol resulted in transimidation to produce (4R,5S)-2-phenyloxazoline 11 in a good yield. Alkylation of (4R,5S)-11 according to the Seebach's procedure gave 4-isopropyloxazoline (12), though in low yield, which should have (4S,5S) configuration.[13] Hydrolysis of (4S,5S)-12 gave benzoate (-)-10 whose configuration should be (2S,3S), indicating that cis-(-)-5d has (4S,5S) configuration.

Scheme 4



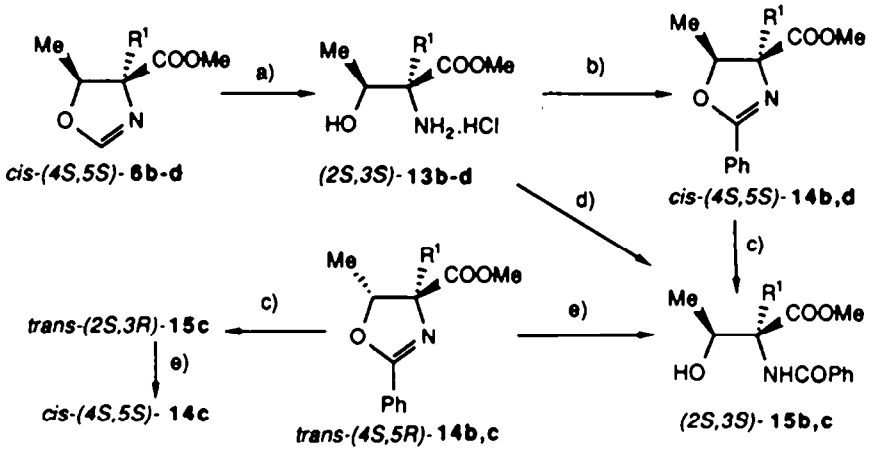
The oxazolines, trans-6 and cis-6, that have methyl group at 5 position were converted, by a sequence of reactions a, b, c, d, and e shown in Schemes 5 and 6, into cis-4-(carbomethoxy)-4-alkyl-5-methyl-2-phenyloxazolines (14) whose absolute configuration has been reported.[10] The key steps are b where reaction of aminoalcohols 13 with benzimidate affords 2-phenyloxazolines 14 with retention of configuration at both 2 and 3 positions[14] and e where reaction of benzoylaminoalcohol 15 with thionyl chloride gives 14 with inversion of configuration at 3 position.[15] The cis 2-phenyloxazolines 14b-d derived from trans oxazolines 6b-d with inversion at 5 position (Scheme 5) and those derived from cis oxazolines 6b-d with retention or with double inversion at 5 position (Scheme 6) turned out to have all (4S,5S) configuration. These results demonstrate that trans oxazolines 6b-d are (4S,5R) isomers and cis-6b-d are (4S,5S) isomers. Maximum rotation values of trans oxazolines (4S,5R)-14b and (4S,5R)-14c are calculated to be +36-37° and -28°, respectively, from the data obtained in the present transformations. The reported[10] rotation values of cis oxazolines (4S,5S)-14b and (4S,5S)-14c, both of which are contaminated with trans (4R,5S) isomers, may be corrected to -7.5° and -60°, respectively, by considering the rotation values of trans-14b and 14c. Further details are shown in Experimental section.

Scheme 5



a) conc HCl / MeOH. b) PhC(=NH)OMe / MeOH. c) i. dil HCl / H_2O. ii. $NaHCO_3$ / H_2O.
d) PhCOCl /Et_3N / $CHCl_3$. e) $SOCl_2$.

Scheme 6



Experimental

General. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. ^1H NMR spectra were measured with a JEOL JNM-MH-100 (100 MHz) or JEOL JNM-GX-400 (400 MHz) spectrometer. Enantiomeric purities by ^1H NMR analysis were determined by using a chiral shift reagent tris-(d,d-dicampholylmethanato)europium(III) [Eu(dcm)$_3$][16,17] or tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III) [Eu(hfc)$_3$][17] and measuring peak areas by cutting and weighing. A Varian Aerograph Model 920, equipped with a 20-ft column packed with Silicone DC 550 (30% on Celite) was used for isolation and purification of the products. Preparative medium-pressure liquid chromatography (MPLC) was done on a silica gel 60 prepacked Lobar (Merck) column.

Materials. Methyl isocyanocarboxylates **2a-2d** were prepared according to the literature procedure.[6] Chiral (aminoalkyl)ferrocenylphosphines **1a-c** were prepared by treatment of (R)-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl acetate[8] with 5-15 equiv of corresponding 2-(dialkylamino)ethyl-N-methylamines in refluxing methanol in a similar manner to the procedure reported for the preparation of **1d**.[8]

Asymmetric Aldol Reaction of Isocyanocarboxylates 2 with Aldehydes Catalyzed by Chiral Ferrocenylphosphine-Gold(I) Complexes. General Procedure. All the reactions were carried out under a dry nitrogen atmosphere. To a mixture of the cationic gold complex bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate[7] (27.5 mg, 0.055 mmol), 0.056 mmol of a ferrocenylphosphine **1**,

and 5.54 mmol of an isocyanocarboxylate 2 in dry dichloromethane (5.5 mL) was added benzaldehyde 3 (6.05 mmol) or acetaldehyde 4 (11.0 mmol), and the mixture was stirred at 25 °C until the reaction was completed. The completion was checked by infrared spectra of the reaction mixture and/or silica gel TLC (hexane/ethyl acetate = 2/1). Evaporation of the solvent followed by bulb-to-bulb distillation under reduced pressure gave a trans/cis mixture of oxazolines. The trans/cis ratio was determined by ^{1}H NMR studies measuring the peak areas of OCH_3 singlets, a chiral shift reagent being used to obtain high resolution for the peaks of 6. The stereoisomers of oxazolines 5 and 6 were separated by MPLC on silica gel (hexane/ethyl acetate = 1/2) and preparative GLC, respectively. The reaction conditions and results are summarized in Table 1. The enantiomeric purities of the oxazolines were determined by ^{1}H NMR studies in the presence of chiral shift reagents, $Eu(hfc)_3$ for **5b,d** and $Eu(dcm)_3$ for **6b,c,d**. The OCH_3 singlets of (4R,5S)-**5b**, (4S,5S)-**5b**, (4S,5R)-**5d**, (4S,5S)-**5d**, (4S,5R)-**6b**, (4S,5S)-**6b**, (4S,5R)-**6c**, (4S,5S)-**6c**, (4R,5S)-**6d**, and (4R,5R)-**6d** appeared at a higher field than those of their enantiomers. The ^{1}H NMR spectra and optical rotation data are shown below.

4-(Methoxycarbonyl)-4-methyl-5-phenyl-2-oxazoline (5b). (4S,5R)-**5b** (92% ee): $[\alpha]_D^{20}$ +84.5° (c 1.9, THF). ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 3H), 3.81 (s, 3H), 5.81 (s, 1H), 6.97 (s, 1H), 7.23 (s, 5H). (4S,5S)-**5b**: ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 3H), 3.11 (s, 3H), 4.14 (s, 1H), 7.08 (s, 1H), 7.23 (s, 5H). Anal. Calcd for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.67; H, 6.01; N, 6.52.

4-(Methoxycarbonyl)-4-isopropyl-5-phenyl-2-oxazoline (5d). (4S,5R)-**5d** (85% ee): $[\alpha]_D^{20}$ +2.0° (c 1.7, THF). ^{1}H NMR ($CDCl_3$) δ 0.62, 0.73 (a pair of d, J = 7 Hz, 6H), 1.99 (sept, 1H), 3.89 (s, 3H), 4.75 (s, 1H), 7.17 (s, 1H), 7.3-7.7 (m, 5H). (4S,5S)-**5d** (42% ee): $[\alpha]_D^{20}$ -35.6° (c 1.2, THF). ^{1}H NMR ($CDCl_3$) δ 0.97, 1.05 (a pair of d, J = 7 Hz, 6H), 2.40 (sept, 1H), 3.14 (s, 3H), 4.29 (s, 1H), 7.1-7.4 (m, 6H).

4-(Methoxycarbonyl)-4-methyl-5-methyl-2-oxazoline (6b). (4S,5R)-**6b** (86% ee): $[\alpha]_D^{20}$ +136.2° (c 0.8, THF). ^{1}H NMR ($CDCl_3$) δ 1.378 (s, 3H), 1.382 (d, J = 6.6 Hz, 3H), 3.786 (s, 3H), 4.839 (q, J = 6.6 Hz, 1H), 6.848 (s, 1H). (4S,5S)-**6b** (54% ee): $[\alpha]_D^{20}$ +11.1° (c 1.1, THF). ^{1}H NMR ($CDCl_3$) δ 1.271 (d, J = 6.5 Hz,3H), 1.535 (s, 3H), 3.761 (s, 3H), 4.362 (q, J = 6.5 Hz, 1H), 6.902 (s, 1H). Anal. Calcd for $C_7H_{11}O_3N$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.48; H, 7.24; N, 8.67.

4-(Methoxycarbonyl)-4-ethyl-5-methyl-2-oxazoline (6c). (4S,5R)-**6c** (87% ee): $[\alpha]_D^{20}$ +55.3° (c 0.7, THF). ^{1}H NMR ($CDCl_3$) δ 0.983 (t, J = 7.4 Hz, 3H), 1.405 (d, J = 6.7 Hz, 3H), 1.638 (dq, J = 14.8 and 7.4 Hz, 1H), 1.876 (dq, J = 14.8 and 7.4 Hz, 1H), 3.785 (s, 3H), 4.705 (q, J = 6.7 Hz, 1H), 6.884 (s, 1H). (4S,5S)-**6c** (66% ee): $[\alpha]_D^{20}$ -29.3° (c 0.5, THF). ^{1}H NMR ($CDCl_3$) δ 0.958 (t, J = 7.4 Hz, 3H), 1.255 (d, J = 6.6 Hz, 3H), 1.689 (dq, J = 14.8 and 7.4 Hz, 1H), 2.061 (dq, J = 14.8 and 7.4, 1H), 3.767 (s, 3H), 4.395 (q, J = 6.6 Hz, 1H), 6.914 (s, 1H). Anal. Calcd for $C_8H_{13}O_3N$: C, 56.13; H, 7.62; N, 8.18. Found: C, 55.84; H, 7.92; N, 7.89.

4-(Methoxycarbonyl)-4-isopropyl-5-methyl-2-oxazoline (6d). (4S,5R)-**6d** (26% ee): $[\alpha]_D^{20}$ -6.5° (c 1.0, THF). ^{1}H NMR ($CDCl_3$) δ 0.938 (d, J = 6.5 Hz, 3H), 0.942 (d, J = 6.8 Hz, 3H), 1.536 (d, J = 6.8 Hz, 3H), 2.191 (sept, 1H), 3.777 (s, 3H), 4.593 (q, J = 6.8 Hz, 1H), 6.945 (s, 1H). (4S,5S)-**6d** (51% ee): $[\alpha]_D^{20}$ -65.5° (c 0.9, THF). ^{1}H NMR ($CDCl_3$) δ 0.858 (d, J = 6.8 Hz, 3H), 0.987 (d, J = 6.7 Hz, 3H), 1.239 (d, J = 6.5 Hz, 3H), 2.198 (sept, 1H), 3.770 (s, 3H), 4.516 (q, J = 6.5 Hz, 1H), 6.919 (s, 1H). Anal. Calcd for $C_9H_{15}O_3N$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.06; H, 8.41; N, 7.61.

Hydrogenolysis of Oxazolines 5b,d to N-Formylamino Acid Methyl Esters 7b,d. The procedure reported[11] by Schöllkopf was slightly modified as follows. A mixture of 0.34 g (1.38 mmol) of (4S,5R)-**5d** (85% ee) and 40 mg of 10% Pd-C in 3.4 mL of methanol was placed in a stainless micro autoclave and magnetically stirred at 80 °C with hydrogen at 150 atm for 22 h. Evaporation of the solvent followed by preparative TLC on silica gel (hexane/ethyl acetate = 2/1) gave 0.30 g (86%) of (R)-methyl 2-formylamino-2-isopropyl-3-phenylpropionate (**7d**): $[\alpha]_D^{20}$ +79.0° (c 1.5, chloroform). ^{1}H NMR ($CDCl_3$) δ 0.93, 1.12 (a pair of d, J = 7 Hz, 6H), 2.81 (sept, 1H), 3.25 (d,

J = 14 Hz, 1H), 3.73 (s, 3H), 3.77 (d, J = 14 Hz, 1H), 6.26 (broad s, 1H), 6.82-7.32 (m, 5H), 7.94 (d, J = 2 Hz, 1H). Similarly, hydrogenolysis of (4S,5S)-5d (42% ee) gave (R)-7d ($[\alpha]_D^{20}$ +36.2° (c 0.9, chloroform)).

Treatment of (4S,5R)-5b (82% ee) with 150 atm of hydrogen in the presence of 10% Pd-C at 80 °C in a similar manner to that of 5d gave 54% yield of (S)-7b with the optical rotation of $[\alpha]_D^{20}$ +74.3° (c 1.0, chloroform). ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 3H), 3.19 (d, J = 13 Hz, 1H), 3.53 (d, J = 13 Hz, 1H), 3.76 (s, 3H), 6.48 (broad s, 1H), 6.92-7.46 (m, 5H), 8.05 (d, J = 2 Hz, 1H). Similarly, hydrogenolysis of (4S,5S)-5b (44% ee) gave (S)-7b ($[\alpha]_D^{20}$ +41.2° (c 1.2, chloroform)).

Methyl 2-Amino-2-methyl-3-phenylpropionate (8). A solution of 58 mg (26 mmol) of formamide 7b ($[\alpha]_D^{20}$ +74.3° (c 1.0, chloroform)) and 0.2 mL of conc. HCl in 2 mL of methanol was heated at 50 °C for 2 h. The mixture was stripped of solvent, made alkaline with aqueous sodium bicarbonate, and extracted with ether. Evaporation of the solvent followed by preparative TLC on silica gel (hexane/ethyl acetate = 1/1) gave 32 mg (63%) of (S)-8 ($[\alpha]_D^{20}$ +3.5° (c 1.0, ethanol)). (lit.[9] $[\alpha]_D^{20}$ -2.8° (c 1.0, ethanol) for (R)-8).

Methyl 2-Amino-2-isopropyl-3-phenyl-3-benzoyloxypropionate (10). a) Conversion of oxazoline 5d. A solution of 130 mg (0.52 mmol) of the oxazoline (4S,5S)-5d (48% ee) and 3 mL of conc HCl in 15 mL of methanol was heated at 50 °C for 3 h. Removal of the solvent under a reduced pressure gave 100% yield of the methyl ester hydrochloride 9: ^{1}H NMR (CD_3OD) δ 1.13, 1.19 (a pair of d, J = 7 Hz, 6H), 2.38 (sept, 1H), 3.71 (s, 3H), 5.27 (s, 1H), 7.40 (s, 5H). The hydrochloride 9 obtained above was treated with 0.06 mL (0.52 mmol) of benzoyl chloride, and 0.22 mL (1.6 mmol) of triethylamine in 2 mL of chloroform at 50 °C for 2.5 h. Aqueous work-up followed by preparative TLC on silica gel (hexane/ethyl acetate = 1/1) gave 18 mg (10%) of (2S,3S)-(-)-10 ($[\alpha]_D^{20}$ -33° (c 0.4, THF): ^{1}H NMR ($CDCl_3$) δ 1.05, 1.08 (a pair of d, J = 7 Hz, 6H), 2.00 (s, 2H), 2.26 (sept, 1H), 3.69 (s, 3H), 6.50 (s, 1H), 7.2-7.8, 8.1-8.4 (m, 10H).

b) Alkylation of 4-(methoxycarbonyl)-2,5-diphenyl-2-oxazoline (11). A mixture of 1.09 g (5.30 mmol) of (4R,5S)-5a (91% ee), 123 mg (0.28 mmol) of $[Pd(MeCN)_4](BF_4)_2$, and 7.2 mL (40 mmol) of trimethyl orthobenzoate in 10 mL of methanol was refluxed for 13 h. Ether was added and the mixture was washed twice with saturated sodium bicarbonate solution and stripped of solvent and low boiling compounds including trimethyl orthobenzoate. The residue was chromatographed on silica gel (MPLC) to give 924 mg (62%) of (4R,5S)-4-(methoxycarbonyl)-2,5-diphenyl-2-oxazoline (10): ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 4.78 (d, J = 7 Hz, 1H), 5.85 (d, J = 7 Hz, 1H), 7.36 (s, 5H), 7.0-7.6, 7.8-8.2 (m, 5H).

The 2-phenyloxazoline (4R,5S)-11 was subjected to the asymmetric alkylation reported by Seebach.[12] To the lithium enolate of (4R,5S)-11 (91% ee, 924 mg, 3.28 mmol) generated by treatment with 3.64 mmol of lithium diisopropylamide in 4 mL of HMPA and 20 mL of THF, was added at -62 °C 0.82 mL (8.2 mmol) of isopropyl iodide. The mixture was kept stirred at -62 °C for 8 h and at 2 °C for 14 h, and hydrolyzed with 50 mL of 50% ammonium chloride solution. Pentane extracts from the reaction mixture was washed with water, dried over anhydrous magnesium sulfate, and stripped of solvent. Repeated (three times) preparative TLC on silica gel (hexane/ethyl acetate = 3/1) of the residue gave 16 mg (1.5%) of (4S,5S)-4-(methoxycarbonyl)-4-isopropyl-2,5-diphenyl-2-oxazoline (12): ^{1}H NMR ($CDCl_3$) δ 0.99, 1.10 (a pair of d, J = 7 Hz, 6H), 2.49 (sept, 1H), 3.13 (s, 3H), 5.50 (s, 1H), 7.30 (s, 5H), 7.0-7.8, 8.0-8.4 (m, 5H). Oxazoline (4S,5S)-12 (16 mg, 0.050 mmol) was treated with 0.034 mL of 1.67 N HCl (0.050 mmol) in 1 mL of dioxane at room temperature for 18 h. The mixture was made alkaline with saturated aqueous sodium bicarbonate and extracted with ether. Evaporation of the solvent followed by preparative TLC on silica gel (hexane/ethyl acetate = 1/1) gave 12 mg (71%) of (2S,3S)-10: $[\alpha]_D^{20}$ -56° (c 0.6, THF).

Conversion of Oxazolines (4S,5R)- and (4S,5S)-6b-d into 2-Phenyloxazolines (4S,5R)- and (4S,5S)-14b-d. Typical Procedures for a) acid hydrolysis of oxazolines 6 into amino ester hydrochlorides 13, b) preparation of 2-phenyloxazolines 14 by the reaction of 13 with benzimidate, c) acid hydrolysis of 2-phenyloxazolines 14 into benzamino esters 15, d) N-acylation of 13 into benzamino esters 15, and e) preparation of 2-phenyloxazolines 14 by the reaction of 15 with

thionyl chloride, are shown below.

Procedure a. Conversion of (4S,5R)-6b into (2S,3R)-13b. A mixture of 104 mg (0.66 mmol) of (4S,5R)-**6b** (86% ee) and 1.5 mL of conc HCl in 15 mL of methanol was stirred at 50 °C for 5 h. Removal of the solvent under reduced pressure gave 112 mg (92%) of (2S,3R)-methyl 3-hydroxy-2-methyl-2-aminobutanoate hydrochloride (**13b**): $[\alpha]_D^{20}$ -7.5° (c 0.3, methanol). ^{1}H NMR (CD_3OD) δ 1.30 (d, J = 7 Hz, 3H), 1.54 (s, 3H), 3.90 (s, 3H), 4.19 (q, J = 7 Hz, 1H). In a similar manner, (4S,5R)-**6c** (87% ee), (4S,5R)-**6d** (26% ee), (4S,5S)-**6b** (54% ee), (4S,5S)-**6c** (66% ee), and (4S,5S)-**6d** (51% ee), were converted into the corresponding amino ester hydrochlorides **13**. (2S,3R)-**13c** (100% yield): ^{1}H NMR (CD_3OD) δ 0.98 (t, J = 7 Hz, 3H), 1.26 (d, J = 6 Hz, 3H), 2.03 (q, J = 7 Hz, 2H), 3.95 (s, 3H), 4.07 (q, J = 6 Hz, 1H). (2S,3R)-**13d** (95% yield): $[\alpha]_D^{20}$ -5.4° (c 1.0, methanol). ^{1}H NMR (CD_3OD) δ 1.02, 1.12 (a pair of d, J = 7 Hz, 6H), 1.27 (d, J = 7 Hz, 3H), 2.10 (m, 1H), 3.90 (s, 3H), 4.48 (q, J = 7 Hz, 1H). (2S,3S)-**13b** (93% yield): $[\alpha]_D^{20}$ +7.1° (c 0.3, methanol). ^{1}H NMR (CD_3OD) δ 1.30 (d, J = 6 Hz, 3H), 1.65 (s, 3H), 3.92 (s, 3H), 4.11 (q, J = 6 Hz, 1H). (2S,3S)-**13c** (100% yield): ^{1}H NMR (CD_3OD) δ 0.97 (t, J = 7 Hz, 3H), 1.27 (d, J = 6 Hz, 3H), 1.90 (q, J = 7 Hz, 2H), 3.86 (s, 3H), 4.22 (q, J = 6 Hz, 1H). (2S,3S)-**13d** (97% yield): $[\alpha]_D^{20}$ +1.3° (c 1.0, methanol). ^{1}H NMR (CD_3OD) δ 1.03, 1.05 (a pair of d, J = 7 Hz, 6H), 1.29 (d, J = 7 Hz, 3H), 2.35 (m, 1H), 3.85 (s, 3H), 4.18 (q, J = 7 Hz, 1H).

Procedure b. Conversion of (2S,3R)-13b into (4S,5R)-14b. The procedure reported by Moss[14] was modified as follows. A mixture of 516 mg (2.80 mmol) of the hydrochloride (2S,3R)-**13b** prepared from (4S,5R)-**6b** of 73% ee, 0.45 mL (3.3 mmol) of methyl benzimidate in 8 mL of methanol was heated to reflux for 14 h. Solvent was evaporated, saturated sodium bicarbonate solution was added to the residue, and the mixture was extracted with ether. The ether extracts were washed with brine, dried over anhydrous magnesium sulfate, and stripped of solvent. Preparative TLC on silica gel (hexane/ethyl acetate = 1/2) gave 76 mg (12%) of (4S,5R)-**14b** and 39 mg (6%) of benzamide (2S,3R)-**15b**. (4S,5R)-**14b**: $[\alpha]_D^{20}$ +26.9° (c 1.1, chloroform). ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 3H), 1.48 (d, J = 6 Hz, 3H), 3.80 (s, 3H), 5.05 (q, J = 6 Hz, 1H), 7.3-7.6, 7.9-8.1 (m, 5H). Similarly, (2S,3S)-**13b** (45% ee) and (2S,3S)-**13d** (51% ee) were converted into the corresponding 2-phenyloxazolines. (4S,5S)-**14b** (12% yield): $[\alpha]_D^{20}$ -1.3° (c 1.9, chloroform). ^{1}H NMR ($CDCl_3$) δ 1.36 (d, J = 7 Hz, 3H), 1.63 (s, 3H), 3.76 (s, 3H), 4.57 (q, J = 7 Hz, 1H), 7.3-7.7, 7.9-8.2 (m, 5H). (4S,5S)-**14d** (16% yield): $[\alpha]_D^{20}$ -45.8° (c 0.2, chloroform). ^{1}H NMR ($CDCl_3$) δ 0.91, 1.07 (a pair of d, J = 7 Hz, 6H), 1.33 (d, J = 7 Hz, 3H), 2.1-2.6 (m, 1H), 3.31 (s, 3H), 4.47 (q, J = 7 Hz, 1H), 7.1-7.8, 7.9-8.3 (m, 5H).

Procedure c. Conversion of (4S,5R)-14b into (2S,3R)-15b. A solution of 70 mg (0.30 mmol) of (4S,5R)-**14b** and 0.18 mL (0.30 mmol) of 1.7 N HCl in 1.2 mL of dioxane was stirred at room temperature for 7 h. Sodium bicarbonate (30 mg) solution was added and the mixture was stirred overnight. Water was added and ether extracts from the aqueous layer were dried over anhydrous magnesium sulfate and stripped of solvent. Preparative TLC on silica gel (hexane/ethyl acetate = 1/1) gave 60 mg (80% yield) of (2S,3R)-**15b**: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 6 Hz, 3H), 1.59 (s, 3H), 3.78 (s, 3H), 3.5 (broad s, 1H), 4.19 (q, J = 6 Hz, 1H), 7.13 (broad s, 1H), 7.2-7.6, 7.7-8.0 (m, 5H). Similarly, (4S,5S)-**14b** and (4S,5R)-**14c** were converted into benzamides (2S,3S)-**15b** and (2S,3R)-**15c** in 92% and 52% yield, respectively. (2S,3S)-**15b**: ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 6 Hz, 3H), 1.75 (s, 3H), 3.87 (s, 3H), 4.26 (q, J = 6 Hz, 1H), 4.9 (broad s, 1H), 7.3-7.7, 7.8-8.0 (m, 5H). (2S,3R)-**15c**: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.19 (d, J = 7 Hz, 3H), 1.8-2.6 (m, 2H), 3.76 (s, 3H), 4.29 (q, J = 7 Hz, 1H), 4.53 (broad s, 1H), 7.21 (s, 1H), 7.2-7.6, 7.7-8.1 (m, 5H).

Procedure d. Conversion of (2S,3R)-13c into (2S,3R)-15c. To a solution of 579 mg (2.85 mmol) of (2S,3R)-**13c** and 401 mg (2.85 mmol) of benzoyl chloride in 5 mL of chloroform was added at 0 °C 1.2 mL of triethylamine. The mixture was stirred overnight at room temperature. Removal of the solvent followed by preparative TLC on silica gel (hexane/ethyl acetate = 1/1) gave 568 mg (66%) of the benzamide (2S,3R)-**15c**. Similarly, N-benzoylation of (2S,3S)-**13c** and (2S,3R)-**13d** gave (2S,3S)-**15c** (53%) and (2S,3R)-**15d** (26%). (2S,3S)-**15c**: ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7 Hz,

3H), 1.14 (d, J = 6 Hz, 3H), 2.02 (dq, J = 14, 7 Hz, 1H), 2.69 (dq, J = 14, 7 Hz, 1H), 3.85 (s, 3H), 4.28 (q, J = 6 Hz, 1H), 5.4 (broad s, 1H), 7.3-7.6, 7.7-8.0 (m, 5H), 7.68 (s, 1H). (2S,3R)-15d (26%): ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 7 Hz, 6H), 1.26 (d, J = 7 Hz, 3H), 1.26 (s, 1H), 2.49 (sept, J = 7 Hz, 1H), 3.82 (s, 3H), 4.64 (q, J = 7 Hz, 1H), 6.54 (broad s, 1H), 7.0-8.1 (m, 5H).

Procedure e. Conversion of (2S,3R)-15b into (4S,5S)-14b. According to the procedure reported by Elliott,[15] 0.5 mL of thionyl chloride was added at -78 °C to 60 mg (0.24 mmol) of (2S,3R)-15b prepared starting with (4S,5R)-6b of 73% ee via (4S,5R)-14b. The mixture was stirred at 0 °C for 13 h, and excess of thionyl chloride was removed under reduced pressure. Sodium carbonate powder and chloroform was added, and the mixture was washed with sodium carbonate solution. The chloroform solution was dried over anhydrous magnesium sulfate. Removal of solvent followed by preparative TLC on silica gel (hexane/ethyl acetate = 1/2) gave 50 mg (81%) of (4S,5S)-14b: $[\alpha]_D^{20}$ -3.0° (c 0.5, chloroform). In a similar manner, benzamides (2S,3S)-15b (prepared from (4S,5S)-6b of 45%ee), (2S,3R)-15c (prepared from (4S,5R)-6c of 87% ee), (2S,3S)-15c (prepared from (4S,5S)-6c of 66% ee), (2S,3R)-15c (prepared from (4S,5S)-6c of 66% ee), and (2S,3R)-15d (prepared from (4S,5R)-6d of 26% ee) were converted into 2-phenyloxazolines (4S,5R)-14b (73% yield, $[\alpha]_D^{20}$ +16.2° (c 0.7, chloroform)), (4S,5S)-14c (64% yield, $[\alpha]_D^{20}$ -53.1° (c 1.1, chloroform)), (4S,5R)-14c (85% yield, $[\alpha]_D^{20}$ -18.2° (c 1.1, chloroform)), (4S,5S)-14c (85% yield, $[\alpha]_D^{20}$ -38.2° (c 1.0, chloroform)), and (4S,5S)-14d (76% yield, $[\alpha]_D^{20}$ -28.3° (c 0.3, chloroform)), respectively. (4S,5S)-14c: ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J = 7 Hz, 3H), 1.33 (d, J = 7 Hz, 3H), 2.4 (m, 2H), 3.73 (s, 3H), 4.56 (q, J = 7 Hz, 1H), 7.1-7.5, 7.8-8.1 (m, 5H). (4S,5R)-14c: ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 7 Hz, 3H), 1.48 (d, J = 7 Hz, 3H), 1.6-2.1 (m, 2H), 3.76 (s, 3H), 4.87 (q, J = 7 Hz, 1H), 7.1-7.5, 7.8-8.1 (m, 5H).

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