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ASYMMETRIC ALDOL REACTION OF α-KETOESTERS WITH ISOCYANOACETATE AND ISOCYANOACETAMIDE CATALYZED BY A CHIRAL FERROCENYLPHOSPHINE-GOLD(I) COMPLEX

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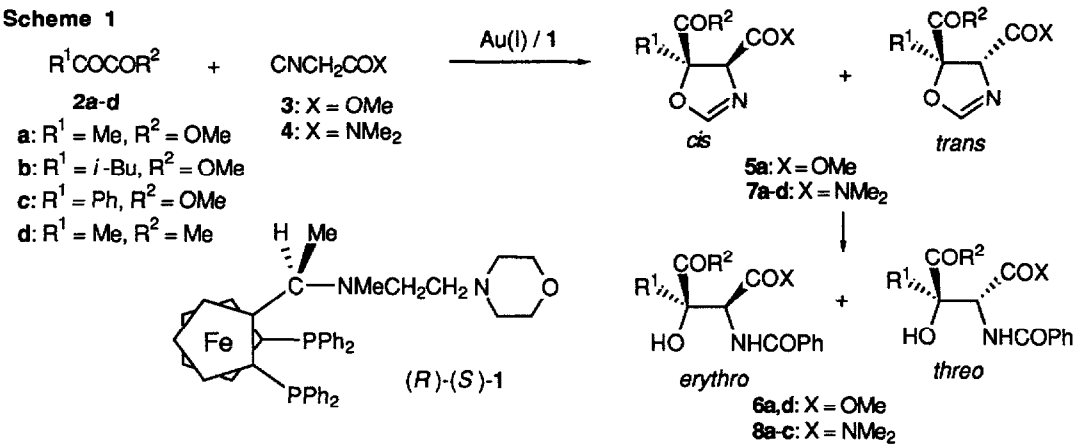
Summary: Asymmetric aldol reaction of α-ketoesters (RCOCOOMe: R = Me, *i*-Bu, Ph) with methyl isocyanoacetate or *N,N*-dimethyl-α-isocyanoacetamide in the presence of 1 mol% of a chiral (aminoalkyl)ferrocenylphosphine-gold(I) catalyst proceeded with high enantioselectivity to give corresponding oxazolines of up to 90% ee, which were converted into optically active β-alkyl-β-hydroxyaspartic acid derivatives.

We have found that the gold(I) complex coordinated with an optically active ferrocenylphosphine ligand bearing 2-(dialkylamino)ethylamino side chain is an effective catalyst for the asymmetric aldol type reaction of α-isocyanocarboxylates ($CNCHRCOOMe$),[1-3] carboxamides ($CNCH_2CONR_2$),[4] and phosphonates ($CNCH_2P(O)(OR)_2$)[5] with aldehydes producing optically active oxazolines, and applied the catalytic asymmetric reaction to the synthesis of β-hydroxyamino acids and their derivatives, e. g., β-alkylserines,[1,4] α-alkylserines,[3] sphingosines,[2] and (1-aminoalkyl)phosphonic acids.[5] Here we report the asymmetric synthesis of β-alkyl-β-hydroxyaspartic acids[6] through the gold(I)-catalyzed asymmetric aldol reaction of α-ketoesters with isocyanoacetate and amide.

Asymmetric aldol reaction of β-ketoesters **2** with methyl isocyanoacetate (**3**) or *N,N*-dimethyl-α-isocyanoacetamide (**4**)[7] was carried out in essentially the same manner as that of aldehydes (Scheme 1). Thus, to a solution of 40.0 mg (0.055 mmol) of ferrocenylphosphine ligand **1**, 25.0 mg (0.050 mmol) of $[Au(cyclo\text{-}C_6H_{11}NC)_2]BF_4$, and 0.96 g (9.7 mmol) of methyl

Scheme 1



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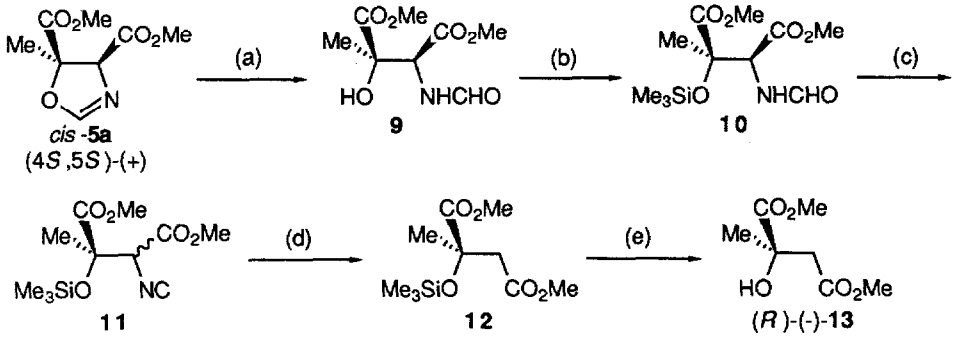
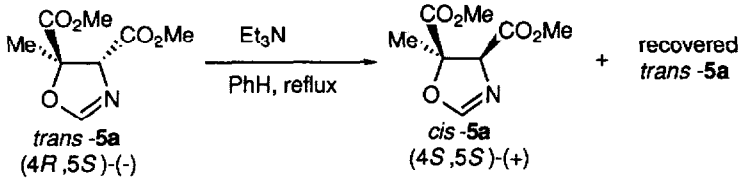
isocyanoacetate (**3**) in 5 mL of dry dichloromethane was added under nitrogen 1.06 g (10.4 mmol) of methyl 2-oxopropanoate (**2a**), and the mixture was stirred at 25 °C for 12 h. Evaporation of the solvent followed by bulb-to-bulb distillation (ca. 120 °C/0.3 mmHg) gave 1.75 g (90% yield) of 5-methyl-4,5-dicarbomethoxy-2-oxazoline (**5a**) which consisted of *cis* and *trans* isomers in a ratio of 73/27. The isomers were isolated by silica gel column chromatography (Kusano, CPS-223L-1, ethyl acetate) to give isomerically pure *cis*-**5a** ($[\alpha]_D^{20}$ +153° (*c* 0.9, THF)) and *trans*-**5a** ($[\alpha]_D^{20}$ -69.2° (*c* 1.0, THF)) in 59% and 25% yield (based on **3**), respectively. The oxazolines were converted into dimethyl 3-methyl-3-hydroxy-2-benzoylaminobutanedioate (**6a**) by treatment with conc HCl in methanol (at 50 °C for 1 h) followed by *N*-benzoylation with benzoyl chloride and triethylamine in chloroform. The enantiomeric purities of **6a** were determined to be 82% ee for *erythro* isomer and 33% ee for *threo* isomer by HPLC analysis with chiral stationary phase column (Sumitomo Chemical Co., Sumipax OA-series, hexane/dichloroethane/ethanol). The *cis*-**5a** was converted into known (*R*)-(-)-dimethyl 3-hydroxy-3-methylbutanedioate (**13**)[8] ($[\alpha]_D^{20}$ -23.7° (*c* 1.1, chloroform)) by a sequence of reactions[9] including deamination via isonitrile **11**,[10] which is shown in Scheme 2.[11] It follows that (+)-*cis*-**5a** has the configuration of (4*S*,5*S*). Treatment of (-)-*trans*-**5a** with triethylamine in refluxing benzene for 18 h resulted in the epimerization at C-4 position giving (+)-*cis*-**5a** ($[\alpha]_D^{20}$ +57.7° (*c* 0.8, THF)), together with recovered (-)-*trans*-**5a** (*cis*-**5a**/*trans*-**5a** = 1/1), indicating that the configuration of (-)-*trans*-**5a** is (4*R*,5*S*).

Scheme 2



(a) AcOH / H_2O, THF, r.t., 14 h (97%). (b) BSA, DMF, 80 °C, 3 h (87%). (c) $POCl_3$, Et_3N, r.t., 2 h (97%). (d) $HSnBu_3$, AIBN, PhH, reflux, 21 h (66%). (e) (i) 6 N HCl, reflux, 12 h. (ii) CH_2N_2, ether, r.t. (**%).



A higher enantio- and *cis*-selectivity was observed in the reaction of *N*,*N*-dimethyl-α-isocyanoacetamide (**4**) with **2a**.[12] The oxazoline **7a**, which was shown by ^1H NMR analysis to be formed in a quantitative yield and to consist of *cis* and *trans* isomers in a ratio of 88/12,

Table 1. Asymmetric Aldol Reaction of α-Ketoesters 2 with Isonitriles 3 and 4 Catalyzed by Chiral Ferrocenylphosphine [(*R*)-(*S*)-1]-Gold(I) Complex.[a]

α-ketoester 2	isonitrile 3 or 4	time (h)	yield[b] of oxazoline	ratio[c] of *cis*/*trans*	yield[d] and % ee[e] of benzamide
MeCOCOOMe (2a)	$CNCH_2COOMe$ (3)	12	90% (5a)	73/27	*erythro*-6a: – 82% ee (4*S*,5*S*)
					threo-6a: – 33% ee (4*R*,5*S*)
2a	$CNCH_2CONMe_2$ (4)	20	– (7a)	88/12	*erythro*-8a: 67%, 90% ee (4*S*,5*S*)[f]
					threo-8a: 11%, 36% ee (4*S*,5*R*)
i-BuCOCOOMe (2b)	4	68	– (7b)	79/21	*erythro*-8b: 71%, 76% ee[g]
					threo-8b: 11%, 84% ee[h]
PhCOCOOMe (2c)	4	108	– (7c)	80/20	*erythro*-8c: 42%, 42% ee[i]
					threo-8c: 17%, 74% ee[j]
MeCOCOMe (2d)	4	39	92% (7d)	51/49	*erythro*-6d: 37%, 75% ee[k]
					threo-6d: 28%, 74% ee[l]

[a] The reaction was carried out in dichloromethane at 25 °C. The gold catalyst was prepared in situ from $[Au(c\text{-}C_6H_{11}NC)_2]BF_4$ and (*R*)-(*S*)-1. 2/3/catalyst = 1.1/1.0/0.005. 2/4/catalyst = 1.1/1.0/0.01. [b] Isolated yield by bulb-to-bulb distillation. [c] Determined by ^1H NMR analysis of the crude reaction product. [d] Isolated yield by MPLC (Kusano, CPS-223L-1, hexane/ethyl acetate = 1/2). [e] Determined by HPLC analysis of benzamide 6 or 8 with a chiral stationary phase column (Sumitomo Chemical Co., Sumipax OA series, hexane/dichloroethane/-ethanol as eluent). OA-2000 x 2 (100/20/1) for *threo*-6a, *erythro*-8a, *threo*-8c, and *threo*-6d. OA-2000I (100/20/1) for *erythro*-6a and *threo*-8a. OA-2000I (150/20/1) for *erythro*-6d. OA-2200 x 2 (250/20/1) for *erythro*-8c. OA-4100 x 2 (150/25/1) for *erythro*- and *threo*-8b. [f] $[\alpha]_D^{20}$ -155° (*c* 1.0, chloroform). [g] $[\alpha]_D^{20}$ -94.0° (*c* 1.0, chloroform). [h] $[\alpha]_D^{20}$ -4.8° (*c* 0.7, chloroform). [i] $[\alpha]_D^{20}$ -93.7° (*c* 1.0, chloroform). [j] $[\alpha]_D^{20}$ +3.8° (*c* 0.6, chloroform). [k] $[\alpha]_D^{20}$ +3.0° (*c* 0.8, chloroform). [l] $[\alpha]_D^{20}$ +49.4° (*c* 0.8, chloroform).

was converted into benzamide **8a** by treatment with conc HCl in methanol at 50 °C for 1 h followed by the *N*-benzoylation. The enantiomeric purities of *erythro*-**8a** and *threo*-**8a**, which were readily separated by silica gel chromatography, were found to be 90% ee and 36% ee, respectively. Acidic methanolysis of **7a** under drastic conditions (conc HCl in methanol at reflux for 40 h) followed by the *N*-benzoylation gave diesters **6a** as main products, together with small amounts of **8a**. Reaction of α-ketoesters **2b,c** and 2,3-butanedione (**2d**) with isocyanoacetamide **4** also proceeded with the (*R*)-(*S*)-**1**/Au(I) catalyst to give corresponding oxazolines **7b-d** with high enantioselectivity. The diastereoisomers were separated and characterized as *N*-benzoyl-β-alkyl-β-hydroxyaspartic acid derivatives **8b**, **8c**, and **6d**. The reaction conditions and results for the asymmetric aldol reactions are summarized in Table 1.[13]

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9 **9**: $[\alpha]_D^{20}$ -32.6° (*c* 0.9, chloroform). **12**: $[\alpha]_D^{20}$ +5.74° (*c* 1.2, chloroform).

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11 Acidic hydrolysis of *cis*-**5a** (1. 6 N HCl at 80 °C. 2. propylene oxide/EtOH) followed by recrystallization from H_2O/EtOH (1/2) gave 65% yield of *erythro*-(2*S*,3*S*)-3-methyl-3-hydroxy-2-aminobutanedioic acid hemihydrate ($[\alpha]_D^{20}$ -7.1° (*c* 1.1, H_2O). Mp 210 °C (dec)).

12 The higher selectivity of the acetamide has also been observed in the reaction with aldehydes (ref. 4), though the role of amide group remains to be clarified.

13 ^{1}H NMR (δ $CDCl_3$/TMS, 200 MHz) for new compounds are shown below. *cis*-**5a**: 1.72 (s, 3 H), 3.75 (s, 6 H), 4.59 (d, *J* = 2.0 Hz, 1 H), 7.01 (d, *J* = 2.0 Hz, 1 H). *trans*-**5a**: 1.56 (s, 3 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 5.01 (d, *J* = 2.0 Hz, 1 H), 7.02 (d, *J* = 2.0 Hz, 1 H). *erythro*-**6a**: 1.47 (s, 3 H), 3.62 (s, 1 H), 3.73 (s, 3 H), 3.90 (s, 3 H), 5.41 (d, *J* = 9.6 Hz, 1 H), 6.89 (d, *J* = 9.6 Hz, 1 H), 7.4-7.65, 7.8-8.0 (m, 5 H). *threo*-**6a**: 1.57 (s, 3 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 4.00 (s, 1 H), 5.21 (d, *J* = 9.6 Hz, 1 H), 7.05 (d, *J* = 9.6 Hz, 1 H), 7.4-7.6, 7.7-7.9 (m, 5 H). *cis*-**7a**: 1.64 (s, 3 H), 2.93 (s, 3 H), 3.23 (s, 3 H), 3.78 (s, 3 H), 4.85 (d, *J* = 2.0 Hz, 1 H), 6.98 (d, *J* = 2.0 Hz, 1H). *trans*-**7a**: 1.56 (s, 3 H), 3.03 (s, 3 H), 3.17 (s, 3 H), 3.84 (s, 3 H), 5.32 (d, *J* = 2.0 Hz, 1 H), 7.06 (d, *J* = 2.0 Hz, 1 H). *erythro*-**8a**: 1.39 (s, 3 H), 2.95 (s, 3 H), 3.24 (s, 3 H), 3.79 (s, 3 H), 5.38 (s, 1 H), 5.55 (d, *J* = 10.0 Hz, 1 H), 6.89 (d, *J* = 10.0 Hz, 1 H), 7.4-7.6 (m, 3 H), 7.83 (deformed d, *J* = 8.0 Hz, 2 H). *threo*-**8a**: 1.50 (s, 3 H), 2.98 (s, 3 H), 3.23 (s, 3 H), 3.88 (s, 3 H), 4.13 (s, 1 H), 5.41 (d, *J* = 10.0 Hz, 1 H), 7.4-7.6 (m, 4 H), 7.82 (deformed d, *J* = 8.0 Hz, 2 H). *cis*-**7b**: 0.90, 0.98 (a pair of d, *J* = 6.3 Hz, 6 H), 1.6-2.1 (m, 3 H), 2.93 (s, 3 H), 3.20 (s, 3 H), 3.77 (s, 3 H), 4.83 (d, *J* = 1.8 Hz, 1 H), 7.00 (d, *J* = 1.8 Hz, 1 H). *trans*-**7b**: 0.87, 0.95 (a pair of d, *J* = 6.3 Hz, 6 H), 1.6-1.9 (m, 3 H), 3.03 (s, 3 H), 3.20 (s, 3 H), 3.82 (s, 3 H), 5.17 (d, *J* = 1.8 Hz, 1 H), 7.12 (d, *J* = 1.8 Hz, 1 H). *erythro*-**8b**: 0.83, 0.93 (a pair of d, *J* = 6.4 Hz, 6 H), 1.6-1.8 (m, 3 H), 2.93 (s, 3 H), 3.25 (s, 3 H), 3.77 (s, 3 H), 5.17 (s, 1 H), 5.46 (d, *J* = 10.0 Hz, 1 H), 6.91 (d, *J* = 10.0 Hz, 1 H), 7.4-7.6 (m, 3 H), 7.82 (deformed d, *J* = 6.6 Hz, 2 H). *threo*-**8b**: 0.84, 0.96 (a pair of d, *J* = 6.2 Hz, 6 H), 1.6-1.9 (m, 3 H), 2.97 (s, 3 H), 3.28 (s, 3 H), 3.88 (s, 3 H), 4.02 (s, 1 H), 5.40 (d, *J* = 9.8 Hz, 1 H), 7.4-7.6 (m, 4 H), 7.81 (deformed d, *J* = 6.4 Hz, 2 H). *cis*-**7c**: 3.00 (s, 3 H), 3.27 (s, 3 H), 3.76 (s, 3 H), 5.32 (d, *J* = 1.8 Hz, 1 H), 7.16 (d, *J* = 1.8 Hz, 1 H), 7.25-7.75 (m, 5 H). *trans*-**7c**: 2.49 (s, 3 H), 3.08 (s, 3 H), 3.85 (s, 3 H), 5.90 (d, *J* = 1.8 Hz, 1 H), 7.25-7.75 (m, 6 H). *erythro*-**8c**: 3.01 (s, 3 H), 3.39 (s, 3 H), 3.75 (s, 3 H), 5.94 (d, *J* = 10.0 Hz, 1 H), 6.56 (s, 1 H), 6.72 (d, *J* = 9.2 Hz, 1 H), 7.25-7.7 (m, 5 H). *threo*-**8c**: 2.77 (s, 3 H), 3.16 (s, 3 H), 3.81 (s, 3 H), 5.75 (s, 1 H), 5.88 (d, *J* = 9.4 Hz, 1 H), 7.2-7.8 (m, 6 H). *cis*-**7d**: 1.47 (s, 3 H), 2.37 (s, 3 H), 2.90 (s, 3 H), 3.19 (s, 3 H), 4.89 (d, *J* = 1.8 Hz, 1 H), 7.04 (d, *J* = 1.8 Hz, 1 H). *trans*-**7d**: 1.42 (s, 3 H), 2.30 (s, 3 H), 3.01 (s, 3 H), 3.19 (s, 3 H), 5.24 (d, *J* = 1.8 Hz, 1 H), 7.10 (d, *J* = 1.8 Hz, 1 H). *erythro*-**6d**: 1.40 (s, 3 H), 2.47 (s, 3 H), 3.70 (s, 3 H), 4.31 (s, 1 H), 5.44 (d, *J* = 9.6 Hz, 1 H), 7.04 (broad d, *J* = 9.6 Hz, 1 H), 7.4-7.65, 7.8-7.95 (m, 5 H). *threo*-**6d**: 1.51 (s, 3 H), 2.36 (s, 3 H), 3.82 (s, 3 H), 4.57 (s, 1 H), 5.25 (d, *J* = 9.8 Hz, 1 H), 6.94 (broad d, *J* = 9.8 Hz, 1 H). **9**: 1.43 (s, 3 H), 3.57 (broad s, 1 H), 3.72 (s, 3 H), 3.87 (s, 3 H), 5.26 (d, *J* = 10.0 Hz, 1 H), 6.42 (broad d, *J* = 10.0 Hz, 1 H), 8.38 (d, *J* = 1.0 Hz, 1 H). **10**: 0.14 (s, 9 H), 1.44 (s, 3 H), 3.69 (s, 3 H), 3.79 (s, 3 H), 5.22 (d, *J* = 9.8 Hz, 1 H), 6.24 (broad d, 1 H), 8.37 (d, *J* = 1.2 Hz, 1 H). **11** (a mixture of diastereoisomers): For major isomer 0.18 (s, 9 H), 1.65 (s, 3 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 4.76 (s, 1 H). For minor isomer 0.18 (s, 9 H), 1.58 (s, 3 H), 3.81 (s, 6 H), 4.63 (s, 1 H). **12**: 0.14 (s, 9 H), 1.52 (s, 3 H), 2.79 (AB q, *J* = 14.8 Hz, $\Delta\nu$ = 0.15 ppm, 2 H), 3.66 (s, 3 H), 3.75 (s, 3 H).

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