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ASYMMETRIC ALDOL REACTION OF α-ISOCYANOACETAMIDES WITH ALDEHYDES CATALYZED BY A CHIRAL FERROCENYLPHOSPHINE-GOLD(I) COMPLEX

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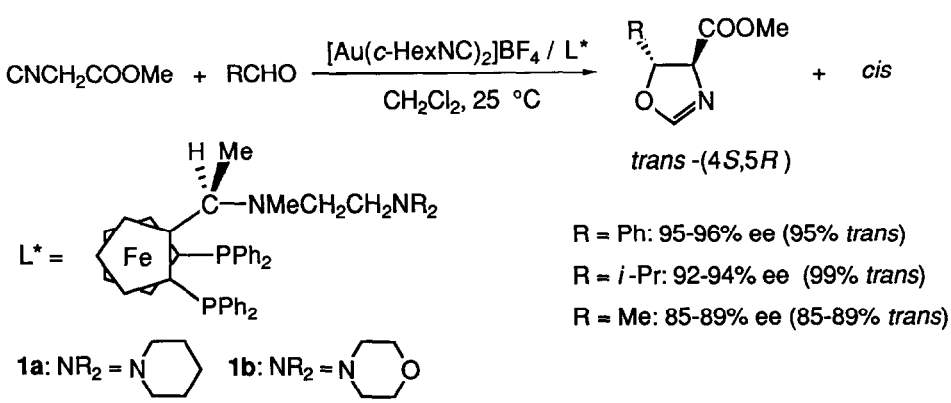
Summary: Aldol reaction of N,N-dialkyl-α-isocyanoacetamides with primary alkyl aldehydes in the presence of 0.5-1 mol% of a chiral (aminoalkyl)ferrocenylphosphine-gold(I) catalyst proceeded with high enantio- and diastereoselectivity to give trans-5-alkyl-2-oxazoline-4-carboxamides of up to 98.6% ee, which were converted into optically active threo-β-hydroxyamino acids.

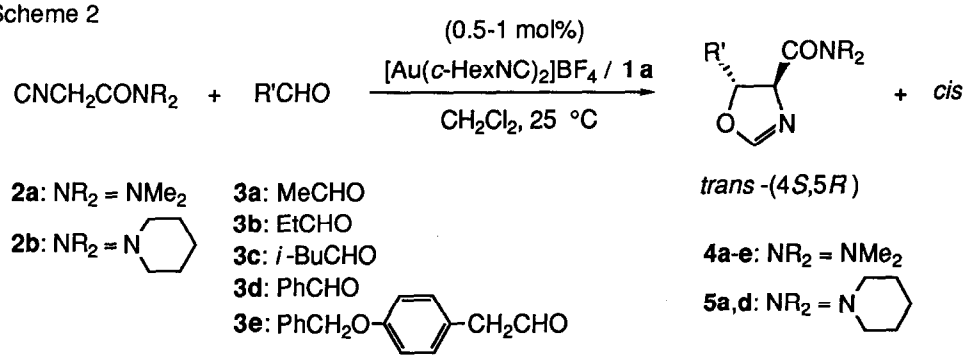
We have studied on catalytic asymmetric aldol reaction of methyl α-isocyanocarboxylates with aldehydes forming optically active 4-methoxycarbonyl-2-oxazolines which can readily be hydrolyzed to β-hydroxyamino acids,[1] and found that high stereoselectivity is achieved by use of a gold(I) catalyst coordinated with a chiral ferrocenylphosphine ligand containing 2-(piperidino)ethylamino **1a** or 2-(morpholino)ethylamino **1b** group on the ferrocene side chain.[2,3] The gold-catalyzed reaction of α-isocyanoacetate is especially stereoselective with aromatic aldehydes and secondary alkyl aldehydes such as isobutyraldehyde giving trans-oxazolines of about 95% ee, but the stereoselectivity is not so high with aldehydes of sterically less hindered alkyls (Scheme 1). Thus, the oxazoline produced from acetaldehyde was found to have at most 89% enantiomeric purity for trans isomer and the ratio of 89/11 for trans/cis isomers. Here we report the use of N,N-dialkyl-α-isocyanoacetamides which improves both enantio- and trans-selectivity in the aldol reaction with primary alkyl aldehydes.

Scheme 1



N,N-Dialkyl-α-isocyanoacetamides **2a** and **2b** were prepared by the reaction of methyl α-isocyanoacetate with dimethylamine and piperidine, respectively, in methanol.[4] Asymmetric aldol reaction of amide **2** with aldehydes was carried out in essentially the same manner as that of the methyl ester[1,2] (Scheme 2). Thus, to a solution of 37.2 mg (0.052 mmol) of ferrocenylphosphine ligand **1a**, 25.1 mg (0.050 mmol) of $[Au(cyclo\text{-}C_6H_{11}NC)_2]BF_4$, and 1.12 g (10.0 mmol) of N,N-dimethyl-α-isocyanoacetamide (**2a**) in 5 mL of dry dichloromethane was added under nitrogen 1.1 mL (20 mmol) of acetaldehyde (**3a**). The mixture was stirred at 25 °C for 40 h, and materials with low boiling points were removed under reduced pressure. ^1H NMR analysis of the residue indicated that the trans/cis ratio of 5-methyl-2-oxazoline-4-(N,N-dimethyl)carboxamide (**4a**)[5] is 91/9. Silica gel column chromatography (Merck, Lobar) of the crude products with ethyl acetate as eluent gave 1.32 g (85% yield) of trans-**4a** $[\alpha]_D^{20}$ +439° (c 1.0, THF). A part of trans-oxazoline **4a** was converted into 3-hydroxy-2-(3,5-dinitrobenzoylamino)butanamide **7a** by treatment with conc HCl in methanol followed by N-acylation of the aminoamide hydrochloride **6a** with 3,5-dinitrobenzoyl chloride and triethylamine in chloroform, and the enantiomeric purity was determined to be 98.6% ee by HPLC analysis of **7a** with a chiral stationary phase column (Sumitomo Chemical Co., Sumipax OA-4500, hexane/dichloroethane/ethanol = 25/10/1). Hydrolysis of the oxazoline to threonine was effected by heating 6.6 mmol of trans-**4a** with 6 mL of 6 N hydrochloric acid at 100 °C for 40 h in a sealed tube. Dehydrochlorination[6] by treatment with propylene oxide (3 mL) in ethanol (6 mL) gave 74% yield of L-threonine ($[\alpha]_D^{20}$ -27.9° (c 2.0, H_2O)).[7] The absolute configuration of trans-**4a** is (4S,5R), same as that of oxazolines formed in the reaction of methyl isocyanoacetate.[1,2]

Scheme 2



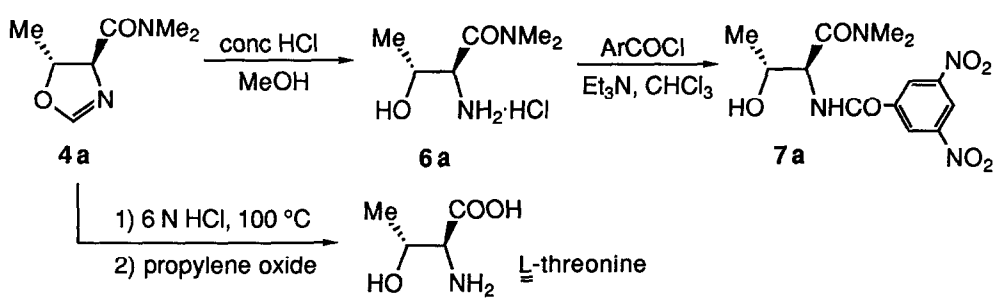
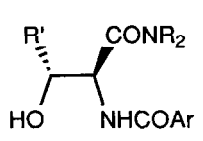


Table 1. Asymmetric Aldol Reaction of α-Isocyanoacetamides (**2**) with Aldehydes (**3**) Catalyzed by Chiral Ferrocenylphosphine [(*R*)-(*S*)-**1a**]-Gold(I) Complex.[a]

entry	isonitrile 2	aldehyde 3	time (h)	yield (%)[b] of trans	ratio[c] of trans/cis	% ee[d] trans	$[\alpha]_D^{20}$ (c 1.0–1.5, THF)
1[e]	$CNCH_2CONMe_2$ (**2a**)	CH_3CHO (**3a**)	40	85 (**4a**)	91/9	98.6	+439°
2[e]		CH_3CH_2CHO (**3b**)	40	84 (**4b**)	95/5	96.3	+419°
3		$(CH_3)_2CHCH_2CHO$ (**3c**)	6	92 (**4c**)	94/6	97.3	+379°
4		PhCHO (**3d**)	25	74 (**4d**)	94/6	94.1	+318°
5		*p*-BnO-C_6H_4-CH_2CHO (**3e**)	80	84 (**4e**)	>95/5	94.5	+248°
6[e]	$CNCH_2CON$ (**2b**)	CH_3CHO (**3a**)	20	84 (**5a**)	94/6	96.1	+402°
7		PhCHO (**3d**)	50	73 (**5d**)	95/5	93.9	+279°
8[f]	$CNCH_2COOMe$	CH_3CHO (**3a**)	15	(100)[h]	85/15	85	
9[g]		$(CH_3)_2CHCH_2CHO$ (**3c**)	16	(99)[h]	96/4	87	
10[f]		PhCHO (**3d**)	17	(94)[h]	94/6	95.5	

[a] The reaction was carried out in dichloromethane at 25 °C. The gold catalyst was prepared in situ from bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate, $[Au(RNC)_2]BF_4$, and (*R*)-*N*-methyl-*N*-[2-(1-piperidino)ethyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine [(*R*)-(*S*)-**1a**]. **3**/**2**/catalyst = 1.1/1.0/0.005–0.01, unless otherwise noted. [b] Isolated yield by silica gel chromatography (Lobar Si 60, eluted with ethyl acetate). [c] Determined by ^1H NMR analysis of the crude reaction product. [d] Determined by HPLC analysis of *N*-acyl derivatives of β-hydroxy-α-aminoamides, which were obtained by treatment of the oxazolines **4** or **5** with conc HCl in MeOH, with a chiral stationary phase column (Sumitomo Chemical Co., Sumipax OA series). *N*-3,5-Dinitrobenzoyl derivatives **7** with OA-4500 for **4a**,b and **5a**, *N*,*O*-bis(3,5-dinitrobenzoyl) derivatives **8** with OA-4500 for **4d** and **5d**, and *N*,*O*-dibenzoyl derivatives **9** with OA-2000 for **4c**,**e**. [e] **3**/**2** = 2.0/1.0. [f] Reported previously in ref 2. [g] (*R*)-(*S*)-**1b** was used. [h] Yield of trans/cis mixture.



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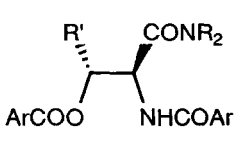

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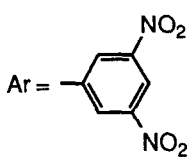

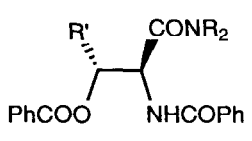

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The results obtained for the aldol reaction of isocyanoacetamides **2** with aldehydes are summarized in Table 1,[8] which also contains data obtained for the reaction of isocyanoacetate for comparison. Use of amide **2a** achieved high enantioselectivity (>96% ee) in the reaction with primary alkyl aldehydes, propionaldehyde (**3b**) and isovaleraldehyde (**3c**) as well as acetaldehyde (**3a**) (entries 1-3). With methyl isocyanoacetate these aldehydes gave lower % ee (entries 8 and 9). Aldol reaction of piperidine amide **2b** also proceeded with high stereoselectivity to give trans-oxazoline **5a** of 96.1% ee in trans/cis ratio of 94/6 (entry 6). The stereoselectivity was not improved in the reaction with benzaldehyde (entries 4, 7, and 10), i. e., both amides **2a,b** and the methyl ester gave the corresponding oxazolines of about 95% ee.

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5 ^{1}H NMR ($CDCl_3$). trans-**4a**: δ 1.39 (d, J = 6.5 Hz, 3 H), 2.97 (s, 3 H), 3.24 (s, 3 H), 4.34 (dd, J = 7 and 2 Hz, 1 H), 5.26 (quint, J = 6.5 Hz, 1 H), 6.78 (d, J = 2 Hz, 1 H). cis-**4a**: δ 1.26 (d, J = 6 Hz, 3 H), 2.93 (s, 3 H), 3.03 (s, 3 H), 4.90 (quint, J = 6 Hz, 1 H), 5.06 (dd, J = 10 and 2 Hz, 1 H), 6.94 (d, J = 2 Hz, 1 H).

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8 ^{1}H NMR (δ $CDCl_3$) for oxazolines **4** and **5**. trans-**4b**: 0.99 (t, J = 7 Hz, 3 H), 1.63 (q, J = 7 Hz, 2 H), 2.98 (s, 3 H), 3.25 (s, 3 H), 4.38 (dd, J = 7 and 2 Hz, 1 H), 5.13 (q, J = 7 Hz, 1 H), 6.80 (d, J = 2 Hz, 1 H). trans-**4c**: 0.95, 0.97 (a pair of d, J = 6 Hz, 6 H), 1.15-2.0 (m, 3H), 2.97 (s, 3 H), 3.24 (s, 3 H), 4.32 (dd, J = 8 and 2 Hz, 1 H), 5.22 (dt, J = 8 and 6 Hz, 1 H), 6.75 (d, J = 2 Hz, 1 H). trans-**4d**: 3.00 (s, 3 H), 3.19 (s, 3 H), 4.19 (dd, J = 8 and 2 Hz, 1 H), 6.18 (d, J = 8 Hz, 1 H), 6.99 (d, J = 2 Hz, 1 H), 7.34 (broad s, 5 H). cis-**4d**: 2.48 (s, 3 H), 2.70 (s, 3 H), 5.32 (dd, J = 10 and 2 Hz, 1 H), 5.62 (d, J = 10 Hz, 1 H), 7.22 (d, J = 2 Hz, 1 H), 7.34 (broad s, 5 H). trans-**4e**: 2.97 (s, 3 H), 3.17 (s, 3 H), 4.64 (dd, J = 8 and 2 Hz, 1 H), 5.02 (s, 2 H), 6.06 (d, J = 8 Hz, 1 H), 6.88 (d, J = 9 Hz, 2 H), 6.89 (d, J = 2 Hz, 1 H), 7.17 (d, J = 9 Hz, 2 H), 7.31 (broad s, 5 H). trans-**5a**: 1.39 (d, J = 7 Hz, 3 H), 1.2-2.0 (m, 6 H), 3.3-4.0 (m, 4 H), 4.32 (dd, J = 7.5 and 2 Hz, 1 H), 5.31 (quint, J = 7 Hz, 1 H), 6.80 (d, J = 2 Hz, 1 H). trans-**5d**: 1.3-1.9 (m, 6 H), 3.3-3.9 (m, 4 H), 4.67 (dd, J = 8 and 2 Hz, 1 H), 6.21 (d, J = 8 Hz, 1 H), 6.98 (d, J = 2 Hz, 1 H), 7.30 (broad s, 5 H).

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