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ASYMMETRIC ALDOL REACTION OF α-ISOCYANOCARBOXYLATES WITH PARAFORMALDEHYDE CATALYZED BY CHIRAL FERROCENYLPHOSPHINE-GOLD(I) COMPLEXES: CATALYTIC ASYMMETRIC SYNTHESIS OF α-ALKYLSERINES

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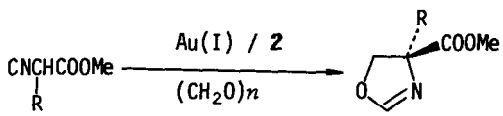
Summary: Aldol reaction of methyl α-isocyanocarboxylates (CNCH(R)COOMe: R = H, Me, Et, i-Pr, Ph) with paraformaldehyde in the presence of 1 mol% of a chiral (aminoalkyl)ferrocenylphosphine-gold(I) complex gave optically active 4-alkyl-2-oxazoline-4-carboxylates (up to 83% ee) which were readily hydrolyzed to α-alkylserines.

There has been intense interest recently in biological activity of α-alkylserines[1] such as α-methylserine and considerable efforts have been devoted to developing efficient methods for the synthesis of optically active α-alkylserines.[2,3] They have been prepared by hydroxy- or benzyloxymethylation of lithiated bis(lactim) ethers prepared from optically active amino acids,[2] or alkylation of a lithiated optically active oxazolidine derived from serine.[3] Previously we have reported that chiral (aminoalkyl)ferrocenylphosphine-gold(I) complexes catalyze the asymmetric aldol reaction of an isocyanoacetate with aldehydes to produce optically active 5-alkyl-2-oxazoline-4-carboxylates with high enantio- and diastereoselectivity.[4] Here we wish to describe the asymmetric synthesis of optically active α-alkylserines which can be achieved by the gold(I)-catalyzed asymmetric aldol reaction of α-isocyanocarboxylates with formaldehyde.

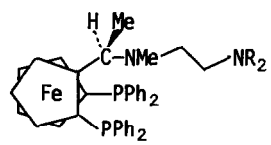
Methyl α-isocyanocarboxylates **1a-e** were prepared by dehydration of the corresponding N-formylamino acid methyl esters according to the reported procedure.[5] We have examined several (aminoalkyl)ferrocenylphosphine ligands for the gold-catalyzed aldol reaction of the isocyanocarboxylates with paraformaldehyde and found that those bearing dimethylamino (**2a**) or piperidino group (**2b**) at the terminal position of the ferrocene side chain[4,6] are more effective than others to give optically active methyl 4-alkyl-2-oxazoline-4-carboxylates (**3a-e**) with high enantioselectivity (Scheme 1).

Scheme 1



1a: R= H
1b: R= Me
1c: R= Et
1d: R= i-Pr
1e. R= Ph

3a-e

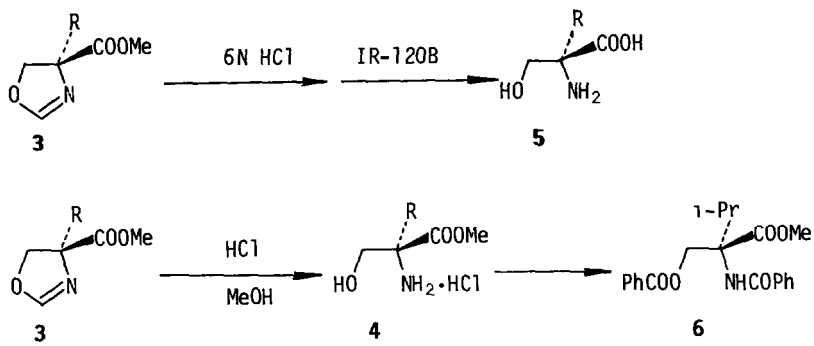


2a: NR_2= NMe_2
2b: NR_2= N

A typical procedure is given for the reaction of methyl 2-isocyano-3-methylbutyrate (**1d**). To a mixture of 25.1 mg (0.050 mmol) of bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate,[7] 37.2 mg (0.051 mmol) of (R)-N-methyl-N-[2-(piperidino)ethyl]-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine ((R)-(S)-**2b**), 0.18 g (6.0 mmol) of paraformaldehyde in 5 ml of dry dichloromethane was added 0.706 g (5.00 mmol) of **1d**, and the mixture was stirred under nitrogen at 25 °C for 70 h. Evaporation of the solvent followed by bulb-to-bulb distillation (ca. 100 °C/0.5 mmHg) gave 0.826 g (97% yield) of 4-isopropyl-4-(methoxycarbonyl)-2-oxazoline (**3d**) ($[\alpha]_D^{20}$ +100.4° (c 1.1, THF)), whose enantiomeric purity was determined to be 81% by ^{1}H NMR spectra using chiral europium shift reagent Eu(dcm)$_3$.

Reaction of other α-isocyanocarboxylates also proceeded under similar conditions to produce oxazolines **3**[8] in high yields. The results are summarized in Table 1. The enantiomeric purities of 57-70% ee were obtained in the reaction of **1a-c** with the ferrocenylphosphine **2b**. Comparable stereoselectivity was observed with the ligand **2a**. The oxazolines **3** were readily converted into methyl α-alkylserinate hydrochlorides (**4**) and α-alkylserines (**5**) (Scheme 2). Thus, the hydrolysis of **3a** (44% ee), **3b** (63% ee), **3c** (66% ee), and **3d** (81% ee) with 6 N hydrochloric acid at 80 °C for 6 h followed by treatment with ion exchange column (Amberlite IR-120B, H^+ form) gave (S)-serine (**5a**) ($[\alpha]_D^{20}$ -2.0° (c 5.5, H_2O)),[9] (S)-α-methylserine (**5b**) ($[\alpha]_D^{20}$ +3.3° (c 1.0, H_2O)),[10] (S)-α-ethylserine (**5c**) ($[\alpha]_D^{20}$ -3.3° (c 1.0, 5 N HCl)),[11] and (S)-α-isopropylserine (**5d**) ($[\alpha]_D^{20}$ +7.8° (c 1.0, H_2O)), respectively, in a quantitative yield. The oxazoline **3d** (81% ee) was converted into N,O-dibenzoyl-α-isopropylserine methyl ester (**6**) ($[\alpha]_D^{20}$ +2.9° (c 0.9, chloroform)) via **4d** ($[\alpha]_D^{20}$ +2.2° (c 0.4, methanol)) by acidic hydrolysis in methanol (conc. HCl, MeOH, 50 °C, 3 h) followed by dibenzoylation (PhCOCl, Et_3N, DMAP, THF reflux), and the configuration of (+)-**3d** was determined to be (S) by comparison of the optical rotation with that of authentic sample prepared by Seebach's method.[3,12]

Scheme 2



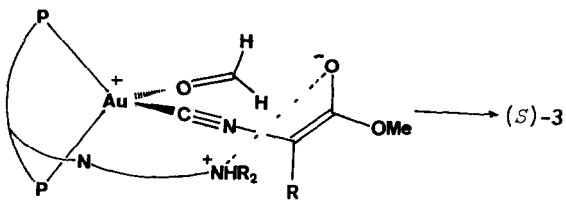
In our previous studies[4] on the asymmetric aldol reaction of methyl isocyanoacetate with aldehydes, we have proposed that the terminal amino group on the side chain of ferrocenylphosphine ligands abstracts one of the active hydrogens of isocyanoacetate coordinated with gold to form ammonium enolate and the formation of the ion pair is responsible for the high stereoselectivity. The present asymmetric aldol reaction with formaldehyde where the stereoselectivity is concerned only with the enantioface differentiation of the enolate of α-isocyanocarboxylates, is considered to proceed via the intermediate **A** or **B**. The absolute configuration (S) of the products (**3a-d**) indicates that the hydroxymethylation occurred preferentially from

Table 1. Asymmetric Aldol Reaction of Methyl α-Isocyanocarboxylates (1) with Paraformaldehyde Catalyzed by Chiral Ferrocenylphosphine-Gold(I) Complexes.[a]

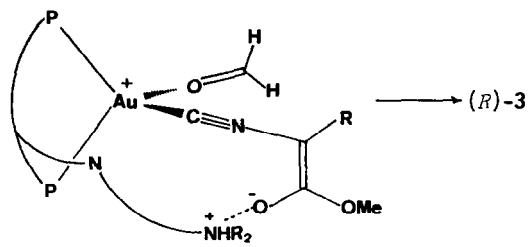
entry	R in CNCH(R)COOMe (1)	NR_2 in ligand 2	reaction time (h)	yield[b](%) of 3	% ee[c] (config)[d]	$[\alpha]_D^{20}$ (c in THF)
1	H (1a)	NMe_2 (2a)	20	99	52 (S)	
2	H (1a)	N⟨⟩ (2b)	20	89	44 (S)	+134.4° (1.2)
3	Me (1b)	NMe_2 (2a)	40	100	64 (S)	
4	Me (1b)	N⟨⟩ (2b)	40	95	63 (S)	+96.7° (1.4)
5	Et (1c)	NMe_2 (2a)	50	89	70 (S)	
6	Et (1c)	N⟨⟩ (2b)	50	89	66 (S)	+81.9° (1.3)
7	i-Pr (1d)	NMe_2 (2a)	70	99	71 (S)	
8	i-Pr (1d)	N⟨⟩ (2b)	70	96	81 (S)	+100.4° (1.1)
9	Ph (1e)	NMe_2 (2a)	90	75	67[e]	+160.1° (1.3)

[a] The reaction was carried out in dichloromethane at 25 °C. The gold catalyst (1 mol%) was prepared in situ from $[Au(c\text{-}C_6H_{11}NC)_2]BF_4$ and (R)-(S)-2. [b] Isolated yield by distillation. [c] Determined by ^1H NMR spectra using chiral shift reagent $Eu(dcm)_3$ or $Eu(hfc)_3$. [d] Determined by converting oxazolines 3 into known α-alkylserines (see text). [e] The configuration has not been determined. Acidic hydrolysis of 3e in methanol gave methyl α-phenylserinate hydrochloride (4e) of $[\alpha]_D^{20}$ -24.9° (c 1.2, methanol).

the si face of the donor center of the enolate of isocyanocarboxylate in **A**. It is interesting that the enolates of all the isocyanocarboxylates (1a-d) reacted on the si face irrespective of the steric bulkiness of the substituent R on **1**. It may be concluded that the reaction face of the enantiotopic enolate is determined mainly by the attractive interaction forming ammonium enolate rather than by steric repulsions between the substituents on the enolate and the chiral ligand.



A



B

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8 ^{1}H NMR ($CDCl_3$) spectra for 3 are as follows. 3a: δ 3.84 (s, 3H), 4.3-5.0 (m, 3H), 7.00 (d, J = 2 Hz, 1H). **3b**: δ 1.26 (s, 3H), 3.49 (s, 3H), 3.68 (d, J = 9 Hz, 1H), 4.30 (d, J = 9 Hz, 1H), 6.56 (s, 1H). 3c: δ 0.90 (t, J = 7 Hz, 3H), 1.89 (q, J = 7 Hz, 2H), 3.78 (s, 3H), 4.04 (d, J = 9 Hz, 1H), 4.56 (d, J = 9 Hz, 1H), 6.88 (s, 1H). **3d**: δ 0.85 and 0.88 (a pair of d, J = 7 Hz, 6H), 2.32 (sept, J = 7 Hz, 1H), 3.79 (s, 3H), 4.13 (d, J = 9 Hz, 1H), 4.57 (d, J = 9 Hz, 1H), 6.92 (s, 1H). **3e**: δ 3.75 (s, 3H), 4.26 (d, J = 9 Hz, 1H), 5.18 (d, J = 9 Hz, 1H), 7.06 (s, 1H), 7.2-7.6 (m, 5H).

9 The reported rotation for (S)-**5a** is $[\alpha]_D^{20}$ -6.83° (c 10, H_2O): Beilstein, **4**, 505.

10 The reported rotation for (R)-**5b** is $[\alpha]_D^{20}$ -5.8° (c 0.3, H_2O): Ref. 2a. See also Ref. 1a, 2b, and 3a.

11 The reported rotation for (S)-5c is $[\alpha]_D^{25}$ -6.5° (c 1.0, 5 N HCl). Ref. 1a and N. Takamura, S. Terashima, K. Achiwa, and S. Yamada, Chem. Pharm. Bull., **15**, 1776 (1967).

12 The alkylation of the lithium enolate of methyl (2R,4S)-2-t-butyl-3-formyloxazolidine-4-carboxylate derived from (S)-serine with isopropyl iodide according to the reported procedure[3] gave low yield (1%) of a 4-isopropyloxazolidine that should have (4S) configuration. Hydrolysis with conc. HCl in methanol followed by dibenzoylation gave (S)-**6** ($[\alpha]_D^{20}$ +3.0° (c 1.2, chloroform)).

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