Tetrahedron Letters,Vol.28,No.49,pp 6215-6218,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ASYMMETRIC ALDOL REACTION OF AN ISOCYANOACETATE WITH ALDEHYDES CATALYZED BY CHIRAL FERROCENYLPHOSPHINE-GOLD(I) COMPLEXES: DESIGN AND PREPARATION OF NEW EFFICIENT FERROCENYLPHOSPHINE LIGANDS

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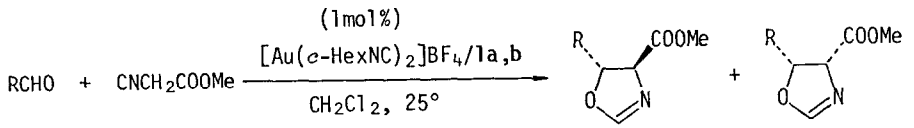
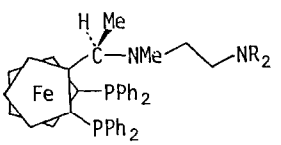
Summary: An optically active ferrocenylphosphine ligand containing 2-(morpholino)ethylamino or 2-(piperidino)ethylamino group on the ferrocene side chain was effective for the gold-catalyzed aldol reaction of methyl isocyanoacetate with aldehydes to give optically active 4-methoxycarbonyl-5-alkyl-2-oxazolines (up to 96% ee) with high enantio- and diastereoselectivity in a quantitative yield.

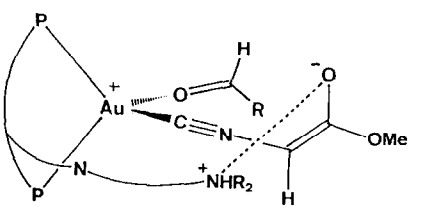
We have previously shown that a gold(I) complex of chiral ferrocenylphosphine ligand bearing a tertiary amino group at the end of ferrocene side chain, i.e., (R)-N-methyl-N-[2-(dialkylamino)ethyl]-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (NR_2 = NMe_2 (**1a**) or NEt_2 (**1b**)), is an effective catalyst for the aldol reaction of methyl isocyanoacetate with aldehydes to produce optically active 4-methoxycarbonyl-5-alkyl-2-oxazolines with high enantio- and diastereoselectivity[1] (Scheme 1), and proposed that the terminal amino group abstracts one of the active hydrogens of isocyanoacetate coordinated with gold to form ammonium enolate (intermediate **A**) and the formation of the ion pair will bring about high stereoselectivity by the enhanced steric interactions.[1] On the basis of the proposed mechanism, appropriate modification of the terminal amino group is expected to increase the selectivity by steric and/or electronic factors. Here we report that the ferrocenylphosphine ligand containing morpholino or piperidino group at the end of ferrocene side chain improved the stereoselectivity giving rise to the oxazolines of up to 96% ee.

Scheme 1





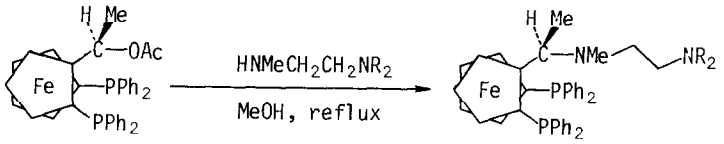
1a: NR_2= NMe_2
1b: NR_2= NEt_2



A

A series of chiral (aminoalkyl)ferrocenylphosphines **1** were prepared by treatment of (R)-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl acetate[2] with 5-15 equiv of 2-(dialkylamino)ethyl-N-methylamines[3] in refluxing methanol (Scheme 2). They have dibutylamino (**1c**), di-i-propylamino (**1d**), pyrrolidino (**1e**), piperidino (**1f**), 1-azacycloheptyl (**1g**), morpholino (**1h**), and N-methylpiperazino (**1i**) groups at the terminal position of the ferrocene side chain.[4] It has been proved that the terminal amino nitrogen should be located four atoms away from the ferrocenylmethyl position for high stereoselectivity.[1]

Scheme 2



1c: NR_2= N(*n*-Bu)$_2$ **1d**: NR_2= N(*i*-Pr)$_2$ **1e**: NR_2= 

1f: NR_2=  **1g**: NR_2=  **1h**: NR_2= 

1i: NR_2= 

The ferrocenylphosphines **1c-i** were examined for stereoselectivity in the gold-catalyzed reaction of methyl isocyanoacetate with acetaldehyde (**2a**) (Scheme 3) which has given only a modest optical yield with the chiral ligands so far used.[1] The enantiomeric purities of the oxazolines **3a** and the ratio of trans and cis isomers were dependent strongly on the structure of the terminal amino group (entries 1-9 in Table 1), indicating that the amino group is playing a key role in the stereoselection. The highest selectivity was obtained in the reaction with the ferrocenylphosphine containing morpholino group **1h**, which gave trans-**3a** of 89% ee with 89% trans selectivity (entry 8). The ferrocenylphosphine ligand containing piperidino group (**1f**) showed the second highest selectivity for the reaction of acetaldehyde (entry 6). A little lower stereoselectivity was observed in the reaction with **1e** and **1g**, which have five- and seven-membered ring amines, respectively (entries 5 and 7). The acyclic dialkylamino groups on the side chain, such as dimethylamino-, diethylamino-, dibutylamino-, and di-i-propylamino, gave **3a** of low enantiomeric purity, i.e., at most 72% ee (entries 1-4). It may be concluded that the cyclic amino groups are more effective than the acyclic ones and

Scheme 3

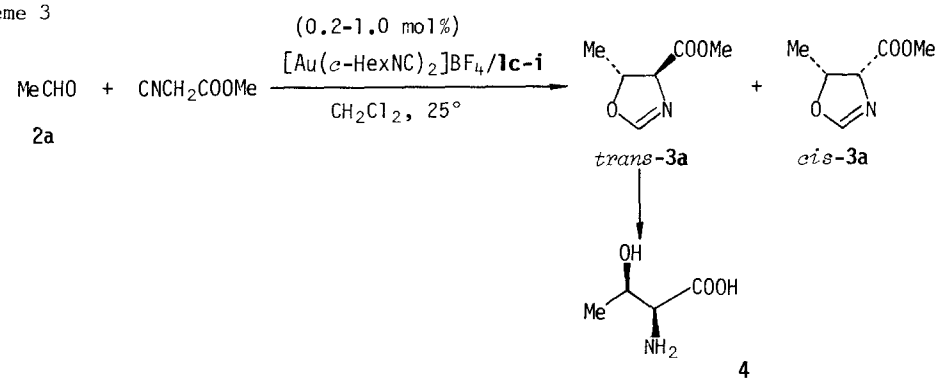
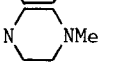
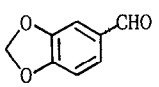


Table 1. Asymmetric Aldol Reaction of Aldehydes **2** with Methyl Isocyanoacetate Catalyzed by Chiral Ferrocenylphosphine-Gold Complexes.[a]

entry	aldehyde **2**	ligand **1** NR_2	yield[b](%) of **3**	ratio[c] of trans/cis	% ee[d] (configuration)[e] trans-**3**	cis-**3**
1	MeCHO (**2a**)	**1a** NMe_2	94	78/22	37 (4S,5R)	0
2[f]		**1b** NEt_2	100	84/16	72 (4S,5R)	44 (4R,5R)
3		**1c** $N(n\text{-}Bu)_2$	100	78/22	71 (4S,5R)	40 (4R,5R)
4		**1d** $N(i\text{-}Pr)_2$	99	70/30	55 (4S,5R)	68 (4R,5R)
5		**1e** 	83	87/13	74 (4S,5R)	18 (4R,5R)
6		**1f** 	100	85/15	85 (4S,5R)	56 (4R,5R)
7		**1g** 	100	86/14	80 (4S,5R)	38 (4R,5R)
8[g]		**1h** 	99	89/11	89 (4S,5R)	10 (4S,5S)
9		**1i** 	85	89/11	83 (4S,5R)	50 (4R,5R)
10[f]	i-PrCHO (**2b**)	**1b** NEt_2	99	98/2	90[h](4S,5R)	——
11		**1f** 	99	99/1	94 (4S,5R)	——
12		**1h** 	100	99/1	92 (4S,5R)	——
13[f]	n-PrCH=CHCHO (**2c**)	**1a** NMe_2	97	80/20	81[h](4S,5R)	0
14		**1h** 	85	87/13	92 (4S,5R)	47 (4R,5R)
15[f]	PhCHO (**2d**)	**1a** NMe_2	91	90/10	91[h](4S,5R)	4 (4S,5S)
16[f]		**1b** NEt_2	98	89/11	93[h](4S,5R)	49 (4R,5R)
17		**1f** 	94	94/6	95 (4S,5R) (95.5)[i]	49 (4R,5R)
18		**1h** 	93	95/5	95 (4S,5R) (95.2)[i]	12 (4S,5S)
19	 (**2e**)	**1h** 	86	95/5	96 (4S,5R)	0

[a] The reaction was carried out in dichloromethane at 25 °C for 10-40 h. 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 $Eu(dcm)_3$. The OCH_3 singlet of the major enantiomer of trans-**3** always appeared at a higher field than that of the minor one. [e] See ref 1. [f] Reported previously in ref 1. [g] Reaction with 0.2 mol% of the catalyst. [h] The % ee values which were corrected by re-examination of the ^1H NMR studies are different from those reported in ref 1. [i] The oxazoline **3d** was converted into 4-(methoxycarbonyl)-2,5-diphenyl-2-oxazoline, and the % ee was determined by HPLC analysis with a chiral stationary phase column (Sumipax OA-4100).

the six-membered ring system is most effective among the cyclic amino groups. The optically active trans-(4S,5R)-**3a** thus obtained was converted into L-threonine[5,6] (**4**) by treatment with 6N hydrochloric acid at 80 °C for 1 h.[7]

The high efficiency of the ferrocenylphosphine ligands **1h** and **1f** was also observed in the aldol reaction of several other aldehydes. The enantiomeric purities of the trans oxaxolines obtained in the reaction of isobutyraldehyde (**2b**) and 2-hexenal (**2c**) were over 92% ee (entries 11, 12 and 14). In the previous studies,[1] both of the aldehydes gave the oxazolines of lower enantiomeric purity with the ligand **1a** or **1b** (entries 10 and 13). It should be noted that the trans selectivity was also improved by using the ligand **1h** or **1f**. Benzaldehyde (**2d**) and piperonal (**2e**) produced the corresponding trans oxazolines of 95%-96% ee in over 95% trans selectivity (entries 17 and 19).

The stereoselectivity attained here is among the highest for asymmetric carbon-carbon bond forming reactions,[8,9] especially for catalytic asymmetric reactions.[10] Now we are in a position to be able to synthesize optically active β-hydroxyamino acids and their derivatives by this highly selective catalytic aldol reaction.

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3 Most of the 2-(dialkylamino)ethyl-N-methylamines were prepared by N-methylation (HCOOEt and then $LiAlH_4$/THF) of the corresponding commercially available 2-(dialkylamino)ethylamines.

4 The chemical yields of ferrocenylphosphines **1c-i** and their specific rotations ($[\alpha]_D^{25}$ (c 0.2-0.4, chloroform)) are as follows. **1c**: 83%, -297°. **1d**: 77%, -295°. **1e**: 69%, -325°. **if**: 77%, -333°. **1g**: 81%, -298°. **1h**: 84%, -325°. 1i: 73%, -305°.

5 Starting with trans-(4S,5R)-**3a** of 86% ee, optically pure L-threonine ($[\alpha]_D^{21}$ -28.5° (c 2.2, H_2O)) (ref 6) was obtained in 60% yield by recrystallization (80% ethanol) of the crude product.

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(Received in Japan 19 August 1987)