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The gold(I)-catalyzed aldol reaction utilizing chiral ferrocenylamine ligands: synthesis of *N*-benzyl-substituted ligands

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Abstract

The synthesis and characterization of (*R*)-*N*-{2-[(*R*)-*N*-2-hydroxy-1-propyl-*N*-benzyl]aminoethyl}-*N*-benzyl-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl amine (**9**) and selected carbamate esters is described. The stereoselectivity of the gold(I)-catalyzed reaction of benzaldehyde with methyl isocyanoacetate was compared using the *N*-benzyl-substituted *versus* the corresponding *N*-methyl-substituted ferrocenylamine ligands. The lower diastereo- and enantioselectivity obtained using the *N*-benzyl-substituted ferrocenylamine ligands is consistent with the transition-state model proposed for the stereoselective step of the gold(I)-catalyzed aldol reaction utilizing ferrocenylamine ligands possessing both central and planar chirality.

Introduction

The development of synthetic methodology that preferentially leads to the formation of a single enantiomer of a targeted chiral compound is today a topic of fundamental importance [1]. Of particular importance are C–C bond-forming reactions whose diastereo- and enantioselectivity are derived from the use of catalytic quantities of chiral transition-metal catalysts [2].

Recently, Ito and Hayashi described an elegant synthesis of oxazolines by a gold(I)-catalyzed aldol reaction in the presence of chiral ferrocenylamine ligands possessing both central and planar chirality [3]. For example, the reaction of **1** with **2** catalyzed by the *in situ* formed catalyst between bis(cyclohexyl isocyanide) gold(I) tetrafluoroborate [4] (**3**) and (*R*)-(*S*)-**4** gave predominately the *trans*-oxazoline **5** in 91% enantiomeric excess (e.e). Quite recently, we reported that the planar and central chirality in **4** can act in either a cooperative or noncooperative manner in controlling the stereoselectivity of the reaction [5]. Chiral cooperativity (internal

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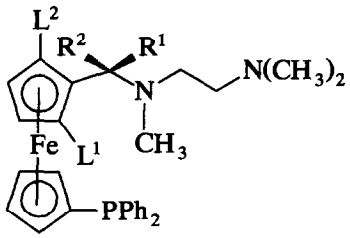
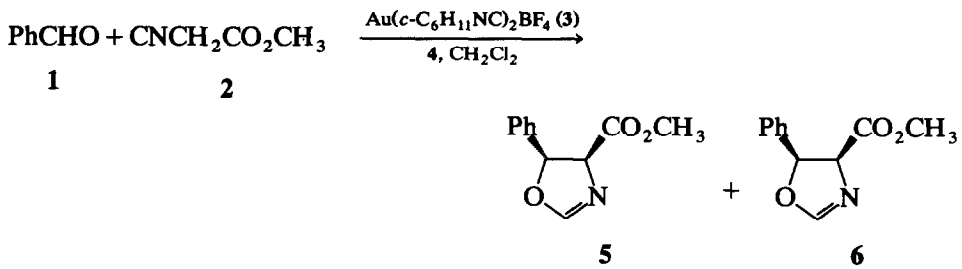


(*R*)-(*S*)-**4**: $R^1 = CH_3$; $R^2 = H$; $L^1 = PPh_2$; $L^2 = H$
(*S*)-(*R*)-**4**: $R^1 = H$; $R^2 = CH_3$; $L^1 = H$; $L^2 = PPh_2$
(*R*)-(*R*)-**4**: $R^1 = CH_3$; $R^2 = H$; $L^1 = H$; $L^2 = PPh_2$
(*S*)-(*S*)-**4**: $R^1 = H$; $R^2 = CH_3$; $L^1 = PPh_2$; $L^2 = H$



Scheme 1.

cooperativity of chirality) thus refers to individual chirotopic segments of the ligand molecule that act in a cooperative manner to promote a particular diastereo- and enantioselectivity in product formation. The notion of internal cooperativity of chirality is conceptually analogous to the strategy of double stereodifferentiation (here labeled external cooperativity of chirality) advocated by Masamune [6].

Although the effect upon product stereoselectivity of either changing the steric requirements of [7] or adding stereocenters to [8] the terminal tert-amine group of (*R*)-(*S*)-**4** is known, a change in the substitution of the internal (bonded to the α-carbon atom) *N*-methyl group has not been reported. The mechanistic model of the stereoselective transition state (TS) proposed suggests that a change in substitution at this nitrogen atom should significantly alter product stereoselectivity [3,5b,9]. We report herein a study to test this contention.

Results and discussion

The previously reported methodology from our laboratory [8] for the preparation of chiral ferrocenylamines with additional stereocenters suggested a facile method for the synthesis of an *N*-benzyl-substituted ferrocenylamine. Additionally, the previously prepared *N*-methyl-substituted analoges were available for direct comparison as ligands in the gold(I)-catalyzed aldol reaction [8].

The reaction of an excess of the *N*,*N*-dibenzyl-substituted diamine **7** with (*R*)-propylene oxide (**8**) gave the chiral aminoalcohol **9**. The reaction of **9** with the

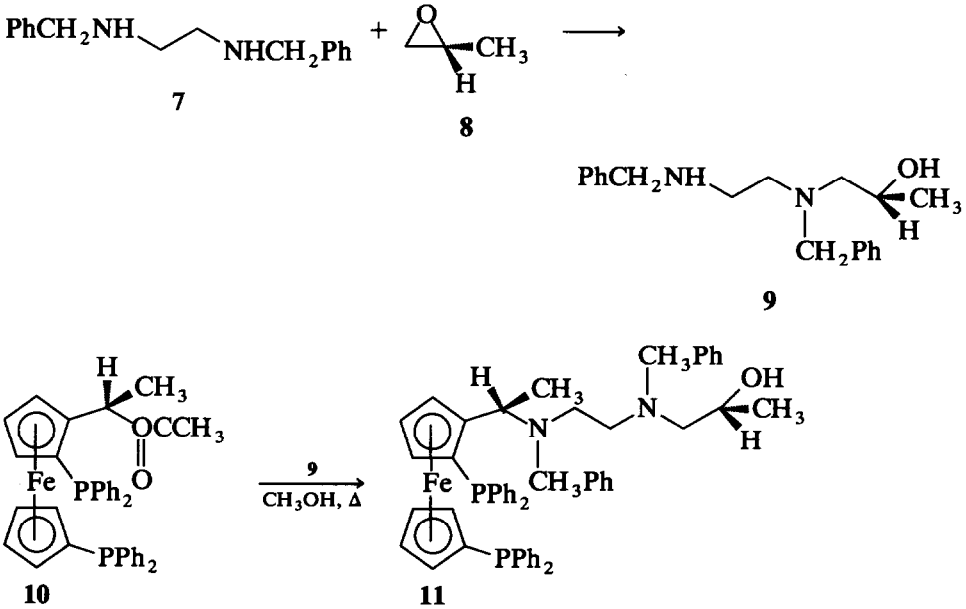
Table 1

Comparison of product stereoselectivity in the gold(I)-catalyzed aldol reaction of **1** and **2** obtained using *N*-benzyl and *N*-methyl-substituted ferrocenylamine ligands

Entry	Ligand	*N*-Substituent	Yield [a]	% *trans* [e.e.]-**5** [b,c]	% *cis* [e.e.]-**6** [b,c]
1	(*R*,*R*,*S*)-**12**	Benzyl	33	67 [26 (4*S*,5*R*)]	33 [11 (4*R*,5*R*)]
2	(*R*,*R*,*S*)-**15**	Methyl	84	90 [96 (4*S*,5*R*)]	10 [40 (4*R*,5*R*)]
3	(*R*,*R*,*R*,*S*)-**13**	Benzyl	44	64 [16 (4*S*,5*R*)]	36 [8 (4*R*,5*R*)]
4	(*R*,*R*,*R*,*S*)-**16**	Methyl	88	90 [95 (4*S*,5*R*)]	10 [34 (4*R*,5*R*)]
5	(*R*,*R*,*S*,*S*)-**14**	Benzyl	35	68 [15 (4*S*,5*R*)]	32 [6 (4*R*,5*R*)]
6	(*R*,*R*,*S*,*S*)-**17**	Methyl	96	89 [95 (4*S*,5*R*)]	11 [35 (4*R*,5*R*)]

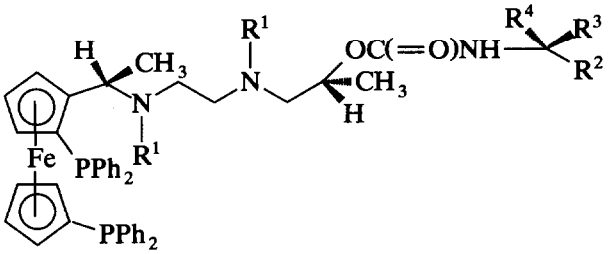
[a] Distilled isolated yields. [b] Enantiomer in e.e. in parentheses. [c] Error in e.e. estimated to be ±3%.

ferrocenyl acetate **10** [10] gave the hydroxy-functional ligand **11** (36%, column chromatographed). The reaction of **11** with 1-octadecyl isocyanate using dibutyltin dilaurate as a catalyst gave (*R*,*R*,*S*)-**12** (73% column chromatographed [11*]. The catalyzed reaction of **11** with either (*R*)- or (*S*)-1-naphthylethyl isocyanate was slow and the reaction was conveniently carried out in a Paar bottle at 100°C to give (*R*,*R*,*R*,*S*)-**13** and (*R*,*R*,*S*,*S*)-**14** both in 89% yield (column chromatographed).



The *N*-benzyl ligands **12**–**14** and the previously reported corresponding *N*-methyl derivatives **15**–**17** [8] were evaluated as ligands in the gold(I)-catalyzed aldol reaction of **1** with **2** (Table 1). Both the low diastereo- and enantioselectivity obtained using the *N*-benzyl derivatives **12**–**14** are striking when compared with the corresponding *N*-methyl derivatives **15**–**17**. The diastereoselectivities obtained using the *N*-benzyl derivatives **12**–**14** are similar to that obtained in the gold(I)-catalyzed aldol reaction in the absence of a chiral ferrocenylamine ligand [7].

* Reference number with asterisk indicates a note in the list of references.



(*R*,*R*,*S*)-**12**: $R^1 = PhCH_2$; $R^2 = 1\text{-}C_{17}H_{35}$; $R^3 = R^4 = H$
(*R*,*R*,*R*,*S*)-**13**: $R^1 = PhCH_2$; $R^2 = CH_3$; $R^3 = 1$-naphthyl; $R^4 = H$
(*R*,*R*,*S*,*S*)-**14**: $R^1 = PhCH_2$; $R^2 = CH_3$; $R^3 = H$; $R^4 = 1$-naphthyl
(*R*,*R*,*S*)-**15**: $R^1 = CH_3$; $R^2 = 1\text{-}C_{17}H_{35}$; $R^3 = R^4 = H$
(*R*,*R*,*R*,*S*)-**16**: $R^1 = CH_3$; $R^2 = CH_3$; $R^3 = 1$-naphthyl; $R^4 = H$
(*R*,*R*,*S*,*S*)-**17**; $R^1 = CH_3$; $R^2 = CH_3$; $R^3 = H$; $R^4 = 1$-naphthyl

A reasonable explanation of the results obtained is that the increased steric requirements of the *N*-benzyl substituents adversely affect the geometry required for high e.e. in the stereoselective TS. The less than optimal geometry obtained, which may adversely affect the abstraction of an isocyanoester proton by the terminal nitrogen atom, is also reflected in a reducted yield of product [5b].

Experimental

*1-[*N*-[2-Benzylamino)ethyl]-*N*-benzyl]amino-(*R*)-(−)-2-propyl alcohol (**9**)*

To a solution of 120.0 g (0.5 mol) of **7** in 75 mL of methyl alcohol at 30°C was added dropwise over a 3 h period, 4.15 g (71 mmol) of (*R*)-(+)-**8**. The solvent was removed *in vacuo* and the residue was distilled to give 5.7 g (27%) of a colorless liquid, b.p. 150–170°C (0.005 mm). $[\alpha]_D^{22}$ −59.40 [c = 0.623, $CHCl_3$]. IR (neat): ν 3300 (OH, NH) cm^{-1}. ^1H NMR ($CHCl_3$): δ 1.09 (d, 3 H), 2.24–2.86 (complex overlapping m, CH_2, 6 H), 3.66 (AB q, Ph*CH*$_2$, 2 H), 3.69 (s, Ph*CH*$_2$, 2 H), 3.80 (m, CH, 1 H). MS (DP): *m/e* 280 (M − 18).

*(*R*)-*N*-[2-[(*R*)-*N*-2-Hydroxy-1-propyl-*N*-benzyl]aminoethyl]-*N*-benzyl-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl amine (**11**)*

A mixture of 3.20 g (5 mmol) of **10**, 5.50 g (18 mmol) of the (*R*)-(−)-**9**, and 50 mL of methyl alcohol was heated at reflux for 18 h. The solvent was removed *in vacuo* and the residue was dissolved in 20 mL of diethyl ether. The ether solution was extracted with water (3 × 100 mL) and the organic phase was dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified three times by chromatography (SiO_2, diethyl ether eluent, SiO_2, dichloromethane eluent, followed by SiO_2, dichloromethane diethyl ether (9:1) eluent) to give 1.56 (36%) of a yellowish-orange viscous liquid. $[\alpha]_D^{22}$ −347.04 [c = 0.423, $CHCl_3$]. IR ($CHCl_3$): ν 3400 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.97 (d, CH_3, 3 H), 1.30 (d, CH_3, 3 H), 1.55 (br s, OH, 1 H), 1.87–2.39 (complex overlapping m, CH_2, 6 H), 3.25 (m, O*CH*, 1 H), 3.34 (AB q, PhCH_2, 2H), 3.37 (m, CpH, 1 H), 3.42 (m, PhCH_2, 2H), 3.72 (m, CpH, 1 H), 3.86 (m, CpH, 1 H), 4.04 (m, CpH, 1 H), 4.11 (m, CpH, 1 H), 4.26 (dq, CpCH, 1 H), 4.34 (m, CpH, 2 H),

6.70–7.57 (complex m, 30 H). Anal. Found: C, 75.2; H, 6.4; N, 3.3. $C_{55}H_{56}FeN_2OP_2$ calc.: C, 75.2; H, 6.4; N, 3.2%.

(R)-N-{2-[(R)-N-2-Hydroxy-1-propyl-N-benzyl]aminoethyl}-N-benzyl-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl amine, N-1-octadecylcarbamic acid ester (12)

To a solution of 439 mg (0.5 mmol) of **11** in 20 mL of tetrahydrofuran (THF) was added sequentially 295 mg (1 mmol) of n-octadecyl isocyanate and 5 mg of dibutyltin dilaurate. The reaction mixture was stirred for 20 h at room temperature. Any insoluble precipitate was removed by filtration and the solvent was removed *in vacuo*. The residue was purified twice by chromatography (neutral alumina activity IV, dichloromethane eluent followed by SiO_2, dichloromethane diethyl (19:1) eluent) to give 430 mg (73%) of a viscous yellowish-orange liquid, $[\alpha]_D^{22}$ −236.57 [c = 0.402, $CHCl_3$]. IR ($CHCl_3$): ν 3440 (NH), 1710 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.89 (t, CH_3, 3 H), 1.03 (d, CH_3, 3 H), 1.27 (complex overlapping m, CH_2, 33 H), 1.45 (m, $NHCH_2CH_2$, 2 H), 1.88 (m, 1 H), 2.02–2.42 (complex overlapping m, 5 H), 3.12 (dt, C(=O)$NHCH_2$, 2 H), 3.39 (overlapping m, CpH and $PhCH_2$, 5 H), 3.74 (m, CpH, 1 H), 3.82 (m, CpH, 1 H), 4.06 (s, CpH, 1 H), 4.11 (s, CpH, 1 H), 4.22 (dq, $CpCHCH_3$, 1 H), 4.34 (m, CpH, 2 H), 4.38 (s, CpH, 1 H), 4.51 (t, NH, 1 H), 4.71 (m, CHO, 1 H), 6.70–7.53 (complex m, 30 H). Anal. Found: C, 75.7; H, 8.0; N, 3.6. $C_{74}H_{93}FeN_3O_2P_2$ calc.: C, 75.7; H, 8.0; N, 3.6%.

(R)-N-[2-[(R)-N-2-Hydroxy-1-propyl-N-benzyl[aminoethyl]-N-benzyl-1-[(S)-1',2-bis-(diphenylphosphino)ferrocenyl]ethyl amine, N-(R)-(−)-1-(1-naphthyl)ethylcarbamic acid ester (13)

By the procedure used to prepare **12**, compound **13** was prepared from 439 mg (0.5 mmol) of **11**, 197 mg (1 mmol) of (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate and 5 mg of dibutyltin dilaurate in 20 mL of THF (20 h at 100°C in pressure apparatus). The residue was purified twice by chromatography (neutral alumina activity IV, dichloromethane eluent followed by SiO_2, dichloromethane diethyl ether (19:1) eluent) to give 480 mg (89%) of a viscous yellowish-orange liquid. $[\alpha]_D^{22}$ −256.96 [c = 0.395, $CHCl_3$]. IR ($CHCl_3$): ν 3430 (NH), 1705 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.08 (d, 3 H), 1.34 (d, 3 H), 2.15 (d, 3 H), 2.17–2.51 (complex overlapping m, 10 H), 3.41 (m, CpH, 1 H), 3.54 (m, CpH, 1 H), 3.66–4.68 (complex overlapping m, 9 H), 7.05–7.52 (complex m, 37 H). Anal. Found: C, 75.8; H, 6.4; N, 3.9. $C_{68}H_{67}FeN_3O_2P_2$ calc.: C, 75.9; H, 6.3; N, 3.9%.

(R)-N-[2-(R)-N-2-Hydroxy-1-propyl-N-benzyl]aminoethyl]-N-benzyl-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl amine, N-(S)-(+)-1-(1-naphthyl)ethylcarbamic acid ester (14)

By the procedure used to prepare **12**, compound **14** was prepared from 439 mg (0.5 mmol) of **11**, 197 mg (1 mmol) of (*S*)-(+)-1-(1-naphthyl)ethyl isocyanate and 5 mg of dibutyltin dilaurate in 20 mL of THF (20 h at 100°C in a Parr bottle). The residue was purified twice by chromatography (neutral alumina activity IV, dichloromethane eluent followed by SiO_2, dichloromethane diethyl ether (19:1) eluent) to give 480 mg (89%) of a viscous yellowish-orange liquid. $[\alpha]_D^{22}$ −263.42 [c = 0.421, $CHCl_3$]. IR ($CHCl_3$): ν 3430 (NH), 1705 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.07 (d, 3 H), 1.23 (d, 3 H), 1.56 (d, 3 H), 1.84 (m, 1 H), 1.97–2.34 (complex overlapping m, 5 H), 3.34 (overlapping m, CpH and $PhCH_2$, 5 H), 3.72

(m, CpH, 1 H), 3.81 (m, CpH, 1 H), 4.04 (m, CpH, 1 H), 4.07 (s, CpH, 1 H), 4.19 (m, Cp*CH*CH_3, 1 H), 4.31 (m, CpH, 2 H), 4.73 (m, 1 H), 5.84 (br s, NH, 1 H), 5.66 (m, 1 H), 6.61–8.17 (complex m, 37 H). Anal. Found: C, 75.5; H, 6.4; N, 4.0. $C_{68}H_{67}FeN_3O_2P_2$ calc.: C, 75.9; H, 6.3; N, 3.9%.

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11 The *R,S* nomenclature of Cahn–Ingold–Prelog is used in all cases to specify the absolute configuration. In key numbers, the absolute configurations of the stereogenic C-atoms are specified first and starting from the stereogenic C-atom in the ferrocenylamine side-chain closest to the cyclopentadienyl ring and proceeding outwards; the last stereochemical descriptor always refers to the planar chirality of the ferrocenylamine ligand. In all cases reported in this paper, stereogenic C-atoms are also chirotopic.