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ASYMMETRIC SYNTHESIS: MODIFICATION OF CHIRAL FERROCENYLAMINE LIGANDS FOR THE GOLD(I)-CATALYZED ALDOL REACTION

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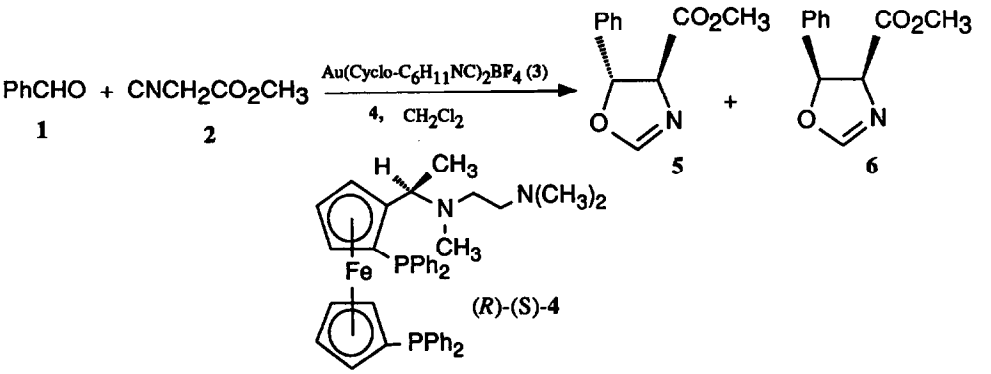
Summary: The synthesis of a chiral ferrocenylamine ligand, (*R*)-(*S*)-**11**, with a modifiable ester group is described. High diastereo- and enantioselectivity were obtained in the gold(I)-catalyzed aldol reaction using (*R*)-(*S*)-**11** as a ligand.

The formation of a single enantiomer of a targeted chiral compound is today a topic of fundamental importance. Particularly challenging is the development of methodology for enantioselective C-C bond formation with a chiral transition-metal catalyst.[1]

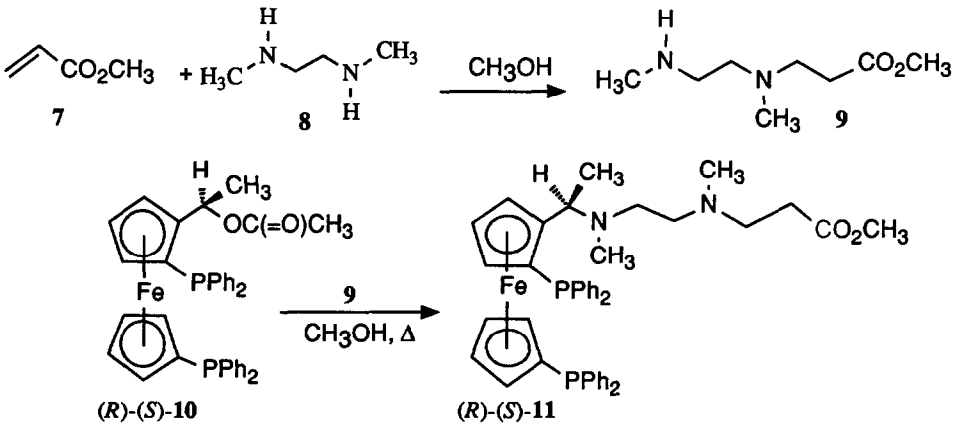


Quite recently, Ito and Hayashi reported an elegant diastereo- and enantioselective gold(I)-catalyzed aldol reaction using chiral ferrocenylamine ligands.[2] The reaction of **1** with **2** using the complex formed *in situ* from bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate,[3] **3**, and (*R*)-(*S*)-**4** gave predominately the *trans*-oxazoline **5** in 91 % enantiomeric excess (ee). Although Hayashi has reported studies on the effect of modifying the terminal amine functionality upon product stereoselectivity[4], a simple procedure has not been reported that allows the modification of the chiral side chain for both mechanistic studies involving additional chiral centers and the preparation of supported catalysts. As part of our studies on the mechanism of the gold(I)-catalyzed aldol reaction[5], methodology for the modification of the chiral ferrocenylamine alkyl side chain that maintains the required position of the terminal nitrogen atom necessary for high product enantioselectivity was developed.

The 1,4-conjugate addition reaction of methyl acrylate, **7**, with an excess of N,N'dimethylethylene-

diamine, **8**, gave the aminoester **9** (80 % distilled). The reaction of **9** with the ferrocenylamine acetate (*R*)-(*S*)-**10**[6] in methyl alcohol at reflux temperature gave the ester-functional derivative (*R*)-(*S*)-**11** (14 % column chromatographed)[7].

The gold(I)-catalyzed reaction of **1** with **2** using (*R*)-(*S*)-**11** as a ligand gave a 89:11 *trans*-to-*cis* oxazoline ratio. The ee's of the (4*S*, 5*R*)-*trans*-**5** and (4*R*, 5*R*)-*cis*-**6** oxazolines obtained were 92 % and 1 %, respectively[8]. The diastereo- and enantioselectivity obtained using (*R*)-(*S*)-**11** as a ligand in the



gold(I)-catalyzed aldol reaction for the *trans*-oxazoline product was identical within experimental error as that obtained using (*R*)-(*S*)-**4**. We have previously observed that the *cis*-oxazoline product is more sensitive to changes in the steric requirements of either the substrate or ligand, and this sensitivity is reflected in the lower ee of **6** obtained using (*R*)-(*S*)-**11**.[5d,9] Mechanistic studies on the gold(I)-catalyzed aldol reaction using derivatives of (*R*)-(*S*)-**11** are being pursued in our laboratory.

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7. **9**: bp 47 °C (0.003 mm); IR (neat) ν 3320 (NH), 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49 (br s, NH, 1 H), 2.24 (s, NCH_3, 3 H), 2.44 (s, NCH_3, 3 H), 2.49 (complex m, 4 H), 2.64 (t, 2 H), 2.71 (t, 2 H), 3.69 (s, OCH_3, 3 H). Anal. Calcd for $C_8H_{18}N_2O_2$: C, 55.2; H, 10.4; N, 16.1. Found: C, 55.0; H, 10.3; 16.5. **11**: $[\alpha]^{22}_D$ - 305.64 [c = 0.337, $CHCl_3$]; IR ν 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, 3 H), 1.67 (s, 3 H), 1.75 (complex m, 2 H), 2.05 (s, 3 H), 2.20-2.57 (complex overlapping m, 6 H), 3.49 (m, 1 H), 3.62 (m, 1 H), 3.67 (s, OCH_3, 3 H), 3.96 (m, 1 H), 4.06 (m, 2 H), 4.16 (dq, Cp*CH*, 1 H), 4.36 (m, 2 H), 7.00-7.52 (complex m, 20 H). Anal. Calcd for $C_{44}H_{48}FeN_2O_2P_2$: C, 70.0; H, 6.4; N, 3.7. Found: C, 69.9; H, 6.6; N, 3.8
8. (a) For a general procedure for the gold(I)-catalyzed aldol reaction, see reference 5b. (b) Only one enantiomer of the *trans* and *cis* oxazoline is illustrated.
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