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NMR STUDIES OF THE GOLD(I)-CATALYZED ASYMMETRIC ALDOL REACTION OF ISOCYANOACETATE

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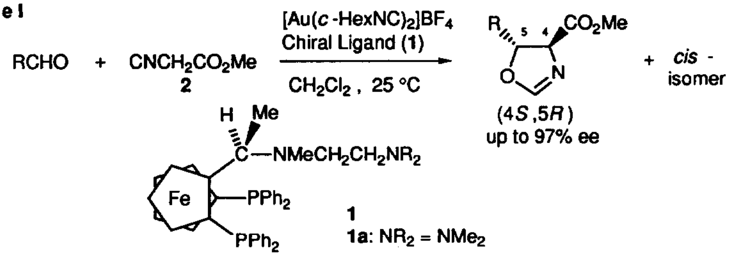
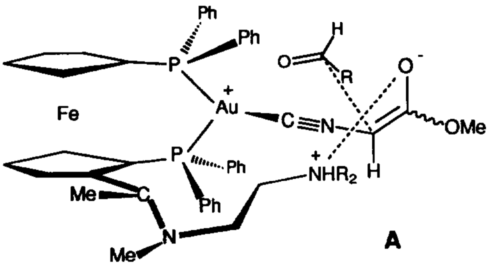
Summary: A ferrocenylphosphine-silver-isocyanoacetate complex was investigated as a model compound for catalytic species in gold-catalyzed aldol reaction. $^1H\{^1H\}$ NOE studies of the silver complex indicated that terminal amino group of pendant side chain of the ferrocenylphosphine ligand is located close to active hydrogens of isocyanoacetate coordinated.

We have previously reported the gold-catalyzed asymmetric aldol reaction of isocyanoacetates with aldehydes (Scheme I)[1] and related asymmetric reactions.[2] It was proposed that the terminal amino group of pendant side chain of ferrocenylphosphine ligand (**1**) participates in the formation of enolate of the isocyanoacetate coordinated with gold and the participation permits a favorable arrangement of enolate and aldehyde on the gold at the stereodifferentiating transition state to bring about high stereoselectivity (transition state A).[1a-c] Here we wish to report our NMR studies which support the participation of the terminal amino group.

Scheme I



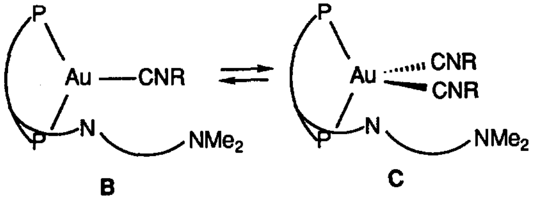
1
1a: $NR_2 = NMe_2$



A

The ^{31}P NMR of a solution prepared by mixing [Au(c-HexNC)$_2$]BF$_4$ and one equiv of **1a** in CD_2Cl_2/CH_2Cl_2 gave AB quartet with large P-P coupling (171 Hz) in the temperature range between 20 and -60 °C (δ 33.4 at -60 °C). A new species which gave a new AB quartet at higher field (δ 11.3, J_{P-P} = 107 Hz) at -95 °C was observed upon addition of 50 equiv of cyclohexyl isocyanide. These observations indicate that a tri-coordinate gold complex chelated by bisphosphine (**B**) is a major species in the presence of small excess of cyclohexyl isocyanide and the bisphosphine-gold complex adopts the tetra-coordinate structure (**C**) when cyclohexyl isocyanide is present in a high concentration (Scheme II).[3-6] Although the low affinity of isocyanide to gold made further structural analysis of the tetra-coordinate species very difficult, it was found that a silver version gives a good model of tetra-coordinate gold complex. Thus, a CD_2Cl_2 solution of AgOTf-**1a**-**2** (1:1:2) gave ^{31}P NMR signals consisting of two sets of double AB quartets (δ -5.6) of almost the same intensities at -95 °C. The signals can be assigned to two unequivalent phosphorous atoms coordinated with silver, AB quartet due to the P-P coupling (ca. 80 Hz) splitting by the coupling between ^{107}Ag-P (ca. 300 Hz) and ^{109}Ag-P (ca. 340 Hz). Variable temperature ^1H NMR studies directly indicated the presence of two unequivalent isocyanoacetates coordinated with the silver-bisphosphine complex ($CNCH_2CO_2Me$; δ 4.49, J_{AB} = 22 Hz and δ 4.84, J_{AB} = 18 Hz at -95 °C). Exchange of the two isocyanoacetates at the coordination site is faster than NMR time scale over -75 °C (δ 4.62, J_{AB} = 19 Hz at -40 °C).

Scheme II



$^1H\{^1H\}$ nuclear Overhauser effect (NOE) and ^1H NMR chemical shift studies of the solution gave more detailed structure of the tetra-coordinate silver complex, whose molecular drawings and selected NOEs are shown in Figure 1.[7] Irradiation of the methyl protons of dimethylamino group at the terminal of the pendant side chain gave rise to a fairly large NOEs at methylene protons (8.6%)[8] and methoxy protons (5.4%) of 2. These NOE enhancements together with other NOEs relating to the pendant[9] are sufficient to prove that the pendant directs toward the reaction site locating the terminal amino group close to methylene hydrogens of an isocyanoacetate (Figure 1a). The conformation of the side chain may be caused by an attractive interaction between the amino group and the methylene hydrogens. The mode of distortion between two Cp rings and the dihedral angle determined by N-C(sp3)-C(Cp)-C(Cp)[10] was estimated by NOEs illustrated in Figure 2a and 2b, respectively. The face-edge orientation of four phenyl groups of chiral ligand[11] was determined by NOEs relating to their ortho protons (Figure 1b).[12] Chemical shifts of the side chain protons are in good agreement with the structure: H5 (δ 1.42) and methyl proton H7 (δ 0.82) are remarkably shielded by Ph1 and Ph3, respectively, while H3 (δ 2.49) is deshielded by Ph3.

^{1}H NMR spectra (CD_2Cl_2) of **1a** coordinated with gold in the presence of 20 equiv of 2 are similar to those of **1a** in the tetra-coordinate silver complex. The similarity suggests that silver in Figure 1 may be replaced by gold. Present studies intensely suggest that the interaction of terminal amino group with the enolate not only controls the arrangement of enolate but also makes the chiral environment rigid raising the enantiofacial selectivity of aldehyde, which approaches the enolate avoiding steric hindrance of Ph4.

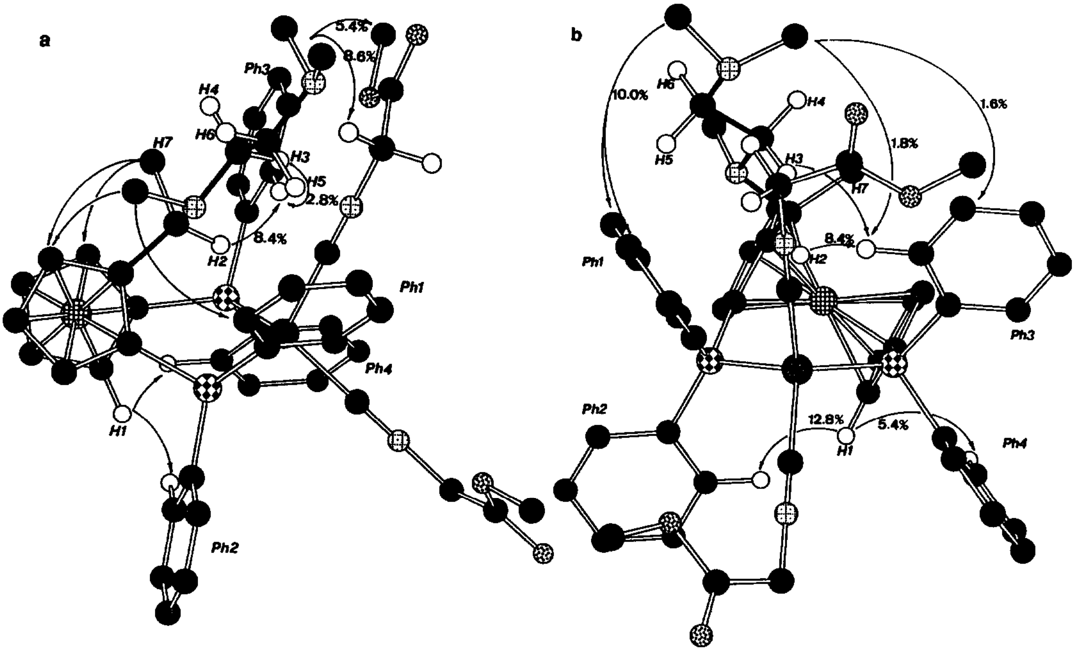


Figure 1. Molecular drawings viewed from two directions and selested $^1H\{^1H\}$ NOEs of the silver complex in a CD_2Cl_2 solution of silver(I) triflate, ferrocenylphosphine (**1a**), and isocyanoacetate (**2**) (1:1:2).

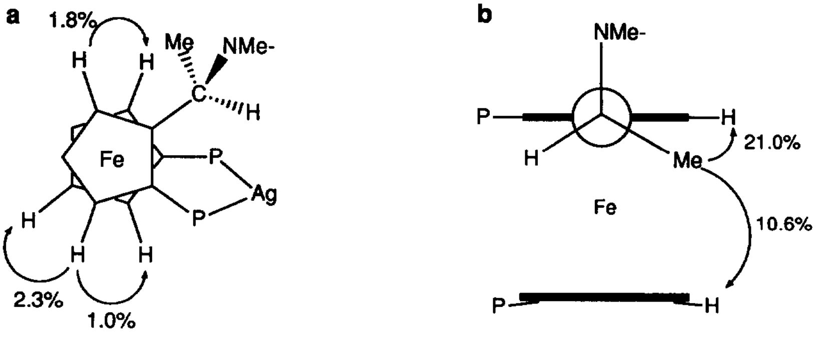


Figure 2. NOEs indicating the mode of distortion between two Cp rings and dihedralangle distinguished by N-C(sp3)-C(Cp)-C(Cp).

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2 a) Y. Ito, M. Sawamura, M. Kobayashi, T. Hayashi, Tetrahedron Lett., **29**, 6321 (1988). b) M. Sawamura, Y. Ito, T. Hayashi, Tetrahedron Lett., **30**, 2247 (1989). c) Y. Ito, M. Sawamura, H. Hamashima, T. Emura, T. Hayashi, Tetrahedron Lett., **30**, 4681 (1989).

3 All experiments reported here were performed in the absence of aldehyde because the complexes appeared to be too dynamic to observe in the presence of aldehyde. Addition of benzaldehyde did not cause detectable change of ^1H NMR spectra of a ferrocenylphosphine-gold complex, indicating that aldehyde is hardly coordinated with gold.

4 An infrared spectroscopic experiment supported these assignment. IR spectra of a solution of $[Au(\underline{c}\text{-}HexNC)_2]BF_4$ and **1a** (1/1) in CH_2Cl_2 gave a pair of strong sharp bands at 2147 and 2200 cm^{-1}. These bands should be assigned to isocyano stretching vibrations of free isocyanide and isocyanide of **B**, respectively.

5 Tetra-coordinate gold complexes $[AuL_4]^+$ (L = R_3P, RNC) are known in the literatures: a) M. T. Mays, P. A. Vergnano, J. Chem. Soc. Dalton Trans., 1112 (1979). b) C. B. Colburn, W. E. Hill, C. A. McAuliffe, R. V. Parish, J. Chem. Soc. Chem. Commun., 218 (1979). c) P. G. Jones, ibid, 1031 (1980). d) R. C. Elder, E. H. K. Zeiher, M. Onady, R. R. Whittle, ibid, 900 (1981). e) A. Sacco, M. Freni, Gazz. Chim. Ital., *86*, 195 (1956).

6 For a review on gold(I) coordination chemistry: Puddephatt, R. J. In Comprehensive Coordination Chemistry, G. Wilkinson, Ed.; Pergamon: Oxford, Vol. 5, pp 861 (1987).

7 Each NOE enhancement is calculated as a total of enhancements of all equivalent protons.

8 Four methylene protons of two molecules of 2 are equivalent at the experimental condition (20 °C), but the NOE must be caused by only the isocyanide closer to the pendant.

9 The discrimination between *H3*, *H4* and *H5*, *H6* was performed by the deuteration of *H5* and *H6*.

10 The role of central chirality of the side chain on ferrocene has been mentioned by Pastor and Togni: S. D. Pastor, A. Togni, J. Am. Chem. Soc., **111**, 2333 (1989).

11 While the face-edge orientation of four aromatic rings on chiral bisphosphines chelated to transition metals has often been discussed concerning mechanisms of catalytic asymmetric reactions, the present studies provide the first demonstration of the face-edge orientation *in solution*. For previous discussions of face-edge orientation of chiral ligands see: a) J. M. Brown, P. L. Evans, Tetrahedron, **44**, 4916 (1988), and references cited therein. b) P. B. Mackenzie, J. Whelan, B. Bosnich, J. Am. Chem. Soc., **107**, 2046 (1985). c) D. H. Farrar, N. C. Payne, J. Am. Chem. Soc., **107**, 2054 (1985).

12 Two ortho (or meta) protons on each phenyl group are observed as equivalent protons, since the rotation around P-C(Ph) bond is faster than NMR time scale at 20 °C.

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