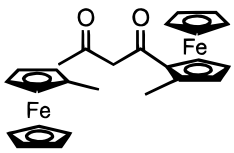
A BMPD−Yttrium Isopropoxide Complex: Highly Efficient Chiral Lewis Acid Catalyst for Asymmetric Silylcyanation

Atsushi Abiko* and Guo-qiang Wang

Kao Institute for Fundamental Research, Kao Corporation, Ichikai-machi, Haga-gun, Tochigi, 321-34, Japan

Received February 9, 1996

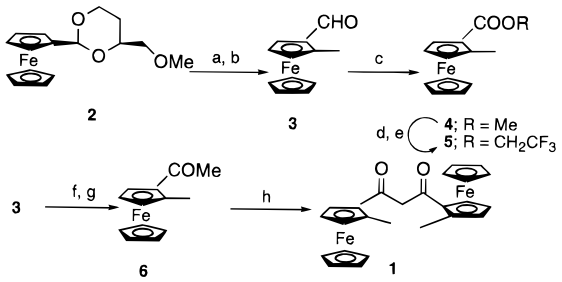
Excellent enantioselectivity has been achieved for various chiral Lewis acid-catalyzed asymmetric reactions; however, the major disadvantage of these processes is the low turnover number of the catalyst.[1] Usually, 5−20 mol % of the catalyst is required, and few catalysts are effective below 1 mol % of the catalyst loading, which makes chiral Lewis acid catalysts unattractive for practical use. We have discovered that a 1:1 complex of (*R,R*)-BMPD [1,3-bis(2-methylferrocenyl)propane-1,3-dione] (**1**) and yttrium isopropoxide, prepared *in situ*, is a remarkable catalyst for asymmetric silylcyanation. In the presence of 0.2 mol % of the catalyst, the reaction of benzaldehyde and TMSCN proceeded in 95% yield with 87% ee. The turnover number of 500 for this catalyst is remarkably high for chiral Lewis acid-catalyzed asymmetric reactions.



BMPD **1**
[(*R,R*)-Bis-(2-methylferrocenyl)-propane-1,3-dione]

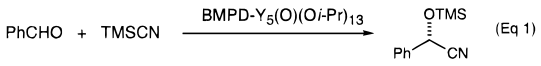
Although 1,3-dicarbonyl compounds have been among the most popular ligands for metals,[2] their chiral modification has received little attention. Most of the known chiral 1,3-dicarbonyl ligands are derived from camphor, and a limited number of synthetic applications of their metal complexes have been reported. Only a few asymmetric catalytic reactions of a metal−chiral 1,3-dicarbonyl compound complex have exhibited good enantioselectivity, such as the use of Eu(hfc)$_3$ and related complexes as catalysts for the hetero Diels−Alder reaction[3] and the use of Cu(hfc)$_2$ as a catalyst for asymmetric cyclopropanation.[4] BMPD, a new chiral 1,3-dicarbonyl compound, was designed to affect asymmetric induction on the basis of the C_2 symmetry of the ligand and of the chiral ferrocene for various asymmetric catalytic reactions. Retrosynthetic analysis shows that **1** could be prepared by the condensation of an enantiopure acetylferrocene and an ester of enantiopure ferrocenecarboxylic acid of the same sense, both of which could be obtained from the same formylferrocene. Thus, (*R*)-2-methylformylferrocene was prepared using Kagan's protocol.[5] *ortho*-Metalation of the chiral acetal **2** with *t*-BuLi followed by alkylation with iodomethane and then hydrolysis afforded (*R*)-2-methylformylferrocene (**3**)[6] in 90% yield, which was shown to be 94%ee by HPLC analysis of the corresponding methyl ester **4**[7] on a chiral column (Chiralcel OD, with Hex:*i*-PrOH = 10:1). The Claisen condensation of **6**[8] to lead **1** was problematic but was achieved efficiently (in 80% yield) with the use of the trifluoroethyl ester **5** and potassium hydride in THF. Pure (*R,R*)-**1**,[mp 150−151 °C; $[\alpha]^{23}_D$ −75.8 (c = 0.80, $CHCl_3$); FAB MS m/z 468 (M^+). Anal. Calcd for $C_{25}H_{24}O_2Fe_2$: C, 64.14; H, 5.17. Found: C, 63.93; H, 5.23] was obtained after recrystallization from dichloromethane and hexane to remove the meso-isomer (Scheme 1).

Scheme 1[a]



[a] Key: (a) *t*-BuLi, MeI, ether; (b) H_3O^+, 90% from **2**; (c) MnO_2, HCN, MeOH, 85%; (d) NaOH, EtOH, 97%; (e) CF_3CH_2OH, DCC, DMAP, 90%; (f) MeMgBr, THF; (g) MnO_2, benzene, 75% from **3**; (h) KH, THF, **5**, then recrystallization, 80%.

After a brief survey of the catalytic activity of the metal complexes derived from BMPD for asymmetric reactions, we have found that the complex prepared *in situ* from the ligand and Y$_5$(O)(O-*i*-Pr)$_{13}$[9,10] catalyzed the silylcyanation of benzaldehyde with remarkable efficiency (eq 1).[11] The optimized reaction procedure for the asymmetric silylcyanation using 1 mol % of the catalyst is as follows (Table 1 entry 1). A solution of Y$_5$(O)(O-*i*-Pr)$_{13}$ (12.3 mg, 0.01 mmol) and (*R,R*)-BMPD (23.4 mg, 0.05 mmol, 1 equiv compared to yttrium) in CH_2Cl_2 (2 mL) was stirred at room temperature for 1 h. One fifth of the benzaldehyde (106 mg, 1.0 mmol) was added at *room temperature*, and the reaction was stirred for 3 min. Then the reaction mixture was cooled to −78 °C, and TMSCN (150 mg, 1.5 mmol) was added. The remaining benzaldehyde (424 mg, 4 mmol) and TMSCN (600 mg, 6.0 mmol)[12] were added in three portions in every 20 min.



(1) Yamamoto, H.; Maruoka, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: Weinheim, 1993; pp 413−440.
(2) *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1987; Vol. 2, Chapter 15.4.
(3) (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716. (b) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451.
(4) Matlin, S. A.; Lough, W. J.; Chan, L.; Abram, D. M. H.; Zhou, Z. *J. Chem. Soc., Chem. Commun.* **1984**, 1038.
(5) Riant, O.; Samuel, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835.
(6) Schlögl, K.; Fried, M.; Falk, H. *Monatsh. Chim.* **1964**, *95*, 576.
(7) Falk, H.; Schlögl, K.; Steyrer, W. *Monatsh. Chim.* **1966**, *97*, 1029.
(8) Marquarding, D.; Burghard, H.; Ugi, I.; Urban, R.; Klusacek, H. *J. Chem. Res. Synop.* **1977**, 82.
(9) (a) Poncelet, O.; Sartain, W. J.; Hubert-Pfalzgraf, L. G.; Folting, K.; Caulton, K. G. *Inorg. Chem.* **1989**, *28*, 263. (b) Bradley, D. C.; Chudzynska, H.; Frigo, D. M.; Hammond, M. E.; Hursthouse, M. B.; Mazid, M. A. *Polyhedron* **1990**, *5*, 719. The commercial "Y(O-*i*-Pr)$_3$" (purchased from Soekawa Chemical Co.) was usually a mixture of an oligomeric Y(O-*i*-Pr)$_3$ and Y$_5$(O)(O-*i*-Pr)$_{13}$ with a variable ratio, from which pure Y$_5$(O)(O-*i*-Pr)$_{13}$ was obtained by recrystallization from *i*-PrOH. The complex prepared from the oligomeric Y(O-*i*-Pr)$_3$ afforded the same results, but the complex formed rather slowly (14 h at room temperature).
(10) With 5 mol % of the isolated Y(BMPD)$_3$ complex, the silylcyanation of benzaldehyde afforded silylated cyanohydrin in 75% yield with 25% ee after 14 h at −78 °C. Y(BMPD)$_3$ was prepared by the reaction of $YCl_3 \cdot nH_2O$ and 3BMPD in the presence of KOH (3 equiv) in aqueous EtOH in 85% yield: mp 260 °C dec; $[\alpha]^{23}_D$ −61.1 (c = 0.90, $CHCl_3$); FAB MS m/z 1491 (M^+); ^{1}H NMR δ 6.20 (s, 3H).
(11) North, M. *Synlett* **1993**, 807.

0022-3263/96/1961-2264$12.00/0

Table 1. Catalytic Asymmetric Silylcyanation of Aldehydes[a]

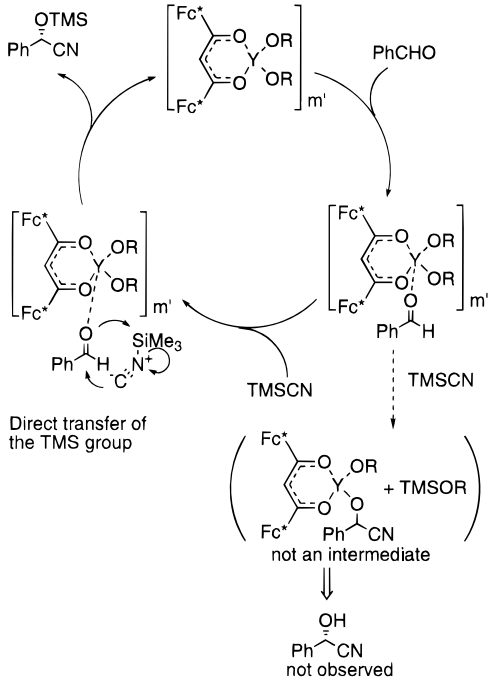
entry	aldehyde	catalyst (mol %)	$[\alpha]^{23}_D$ (c in $CHCl_3$)	confign	% ee
1	benzaldehyde	1	−39.1 (0.80)	S[c]	90
2	benzaldehyde[b]	0.2	−38.6 (2.21)	S[c]	87
3	*p*-tolualdehyde	1	−47.2 (1.60)	S[d]	91
4	*p*-phenylbenzaldehyde	1	−33.3 (0.72)	S[e]	90
5	*p*-methoxybenzaldehyde	1	−38.3 (1.86)	S[d]	84
6	*p*-fluorobezaldehyde	1	−30.7 (1.50)	S[e]	81
7	*m*-phenoxybenzaldehyde	1	−13.6 (1.80)	S[f]	79
8	*p*-cyanobenzaldehyde	1	−11.2 (1.00)	S[d]	30
9	pivalaldehyde	1	5.8 (1.65)	R[d]	49
10	cyclohexanecarboxyaldehyde	1	6.8 (1.70)	R[c]	49

[a] The reaction was carried out under the optimized conditions. See text. Chemical yields are over 95%. [b] The substrates were added during 5 h. [c] Minamikawa, H.; Hayakawa, S.; Yamada, T.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379. [d] Matthews, B. R.; Jackson, W. R.; Jayatilake, G. S.; Willshire, C.; Jacobs, H. A. *Aust. J. Chem.* **1988**, *41*, 1697. [e] Absolute stereochemistry was estimated by analogy. [f] $[\alpha]_D$ in benzene. Danda, H.; Nishikawa, H.; Otaka. K. *J. Org. Chem.* **1991**, *56*, 6740.

The reaction mixture was stirred for another 30 min and poured into a mixture of 1 N HCl and THF. The hydrolytic workup followed by chromatographic purification afforded (*S*)-(−)-α-hydroxyphenylacetonitrile: 650 mg, 98%; $[\alpha]^{23}_D$ −39.1 (c = 0.80, $CHCl_3$); 90% ee.[13] Comparison of various ratios of ligand and yttrium clearly showed a 1:1 ratio to be optimum.[14] Dichloromethane was found to be the solvent of choice.[14] Pretreatment of the complex with benzaldehyde at room temperature was necessary for high enantioselectivity and resulted in the formation of benzyl alcohol (1.5 equiv compared to the ligand) *via* a Meerwein−Ponndorf−Verley (MPV) reaction. Addition of benzaldehyde at −78 °C, followed by TMSCN, afforded the product with 35% ee, and the MPV reaction did not occur.[15] At higher temperatures, the selectivity of the reaction was significantly decreased. A 25% ee was achieved at 0 °C. The results of the catalytic asymmetric silylcyanation are summarized in Table 1. Using optimized conditions, the reaction was complete within 2 h with 1 mol % of the catalyst to afford the product in 98% yield with 90% ee (entry 1, Table 1). *As little as 0.2 mol % of the catalyst gave comparable results using the slow addition technique* (entry 2, Table 1). Aromatic aldehydes generally afforded higher ee except for those with electron-withdrawing substituents. For aliphatic aldehydes the sense of the enantioselection was reversed with low selectivity (entries 9 and 10, Table 1).

Although we have no information about the structure of the catalyst, it is possible to comment about the mechanism of the catalyst turnover. During the course of the reaction, all the cyanohydrin was silylated, even

Scheme 2



in the presence of excess aldehyde. This suggests that the silylcyanohydrin was formed from an aldehyde and TMSCN *via* the isocyanosilane form[16] by the mechanism like a "silatropic ene reaction," [17] not by the stepwise silylation of the intermediate yttrium derivative of the cyanohydrin (Scheme 2).

In summary, BMPD demonstrates the potential for chiral 1,3-dicarbonyl compounds as ligands in asymmetric catalytic reactions. The remarkably high catalytic activity of the BMPD−yttrium isopropoxide complex shows the possibility of a practical application of a chiral Lewis acid catalyst. Studies on the structure of the catalyst and the further application of the catalyst system for other reactions are continuing in our laboratory.

Supporting Information Available: Experimental procedures and characterization data (6 pages).

JO960271L

(12) One equivalent (to the catalyst) of the TMSCN was consumed to silylate the alcohol, which was produced upon complexation of yttrium isopropoxide with BMPD.

(13) Enantiomeric purity was determined by HPLC analysis (μ-Porasil, Hex:EtOAc = 20:1) after conversion to the corresponding (*R*)-MTPA ester.

(14) BMPD:yttrium = 0.8:1, 61% ee; 1:1, 90% ee; 1.2:1, 69% ee; 1.5:1, 59% ee; 2:1, 74% ee; 3:1, 48% ee. Solvent, % ee: CH_2Cl_2, 90% ee; toluene, 75% ee; ether, 70% ee; THF, 38% ee; EtCN, 0% ee.

(15) Complexation in the presence of benzyl alcohol (2 equiv, rt, 1 h) or treatment (rt, 1 h) of the complex, prepared by the usual manner, with benzyl alcohol (2 equiv) followed by the addition of benzaldehyde and TMSCN *at −78 °C* gave the cyanohydrin with 40 and 35% ee, respectively. However, complexation in the presence of benzyl alcohol (2 equiv, rt, 1 h) followed by the treatment with benzaldehyde *at room temperature* gave the cyanohydrin with 81% ee after the reaction with TMSCN at −78 °C. The structure change might be accompanied by the MPV reaction and responsible for the high selectivity.

(16) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, Heidelberg, New York, 1983; p 7.

(17) Mikami, K.; Matsukawa, S. *J. Am Chem. Soc.* **1994**, *116*, 4077.