

Catalytic Asymmetric Mannich-Type Reactions Using a Novel Chiral Iron Complex

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This paper is dedicated to Professor Roger Sheldon on the occasion of his 60th birthday.

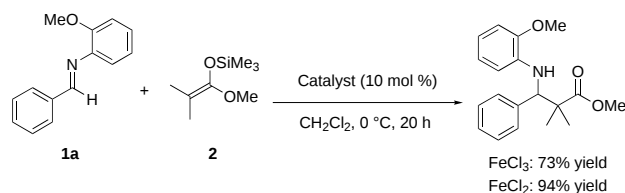
Abstract: Catalytic asymmetric Mannich-type reactions using a novel chiral iron complex have been developed. The reactions proceeded smoothly in the presence of a catalyst prepared from iron(II) chloride, a BINOL derivative, and *i*-Pr₂NEt. The desired products were obtained in good yield with good to high enantioselectivity, when 3,3'-I₂BINOL was employed as a chiral ligand. A protic additive such as methanol facilitated the reactions effectively.

Keywords: asymmetric catalysis; iron; Lewis acid; Mannich reaction

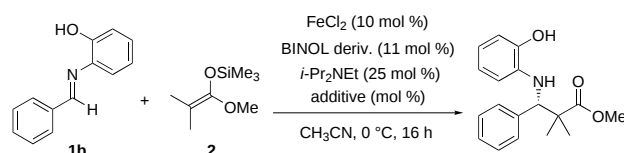
While iron is one of the most abundant elements in nature, it is less harmful and readily accessible, and environmentally benign processes using iron compounds as catalysts or reagents are expected. Indeed, applications of iron compounds to organic synthesis have been investigated, and several useful synthetic reactions using iron compounds have already been reported.^[1] In the field of asymmetric synthesis, although some chiral iron complexes have been employed,^[2] the use of chiral iron complexes as chiral Lewis acids is limited. In 1991, Corey et al. reported an enantioselective Diels–Alder reaction using an iron chloride/chiral bisoxazoline complex as a Lewis acid catalyst.^[3] Khier et al., Kündig et al., and Kanemasa et al. also developed chiral iron catalyst systems in asymmetric Diels–Alder reactions, independently.^[4,5,6] On the other hand, although activation of azomethine compounds using a catalytic amount of a chiral Lewis acid and successive nucleophile addition provide an efficient method for the preparation of optically active nitrogen-containing compounds, few examples of chiral iron catalysts that activate azomethine compounds effectively have been reported.^[7] In the course of our study to search for efficient chiral catalysts, it was revealed that iron chlorides showed promising catalytic activity in achiral Mannich-type reactions of imines with silicon enolates (ketene silyl acetals, for example, Scheme 1).^[8]

Here, we report a novel chiral iron complex, which is successfully used in asymmetric Mannich-type reactions.

For realizing high asymmetric induction, the choice of suitable chiral ligands and substrates is an important factor. Imines prepared from aldehydes and *o*-amino-phenol seemed to form effective bidentate chelation with a metal and provide an excellent asymmetric environment. We have already reported that chiral zirconium complexes prepared from zirconium alkoxide and 1,1'-binaphthalene-2,2'-diol (BINOL) derivatives were effective for the activation of imines, and that high reactivity and diastereo- and enantioselectivity were observed in several zirconium-catalyzed asymmetric reactions.^[9,10] We decided to employ BINOL derivatives as chiral ligands in this reaction. When FeCl₂, a BINOL derivative, and an alkylamine such as diisopropylethylamine (*i*-Pr₂NEt) were combined, significant chiral induction was observed (Table 1, run 1). For solvents, acetonitrile gave the best results. We then chose substituents at the 3,3'-positions of the BINOL derivatives which would give significant effects on the asymmetric environment around Fe. Methyl groups introduced at the 3,3'-positions worked well to improve enantioselectivity; however, the yield was still not satisfactory (run 2). Next we employed the BINOLs containing electron-withdrawing groups at the 3,3'-positions. It was interesting to find that the iodo group gave the best result, and that the selectivity was increased to 56% ee (run 5).^[11] To improve the enantioselectivity, we carried out further investigations and found that a protic additive gave positive effects on both reactivity and selectivity. It is noted that two equivalents of water to the catalyst slightly improved the selectivity



Scheme 1. Catalytic Mannich-type reactions using iron chlorides.

Table 1. Development of a chiral iron catalyst.


Run	BINOL deriv.	additive [mol %]	Yield [%]	ee [%]
1	(<i>R</i>)-BINOL	—	25	46
2	(<i>R</i>)-3,3'-Me ₂ BINOL	—	23	50
3	(<i>R</i>)-3,3'-Cl ₂ BINOL	—	31	38
4	(<i>R</i>)-3,3'-Br ₂ BINOL	—	63	37
5	(<i>R</i>)-3,3'-I ₂ BINOL	—	62	56
6 ^[a]	(<i>R</i>)-3,3'-I ₂ BINOL	—	68	3
7	(<i>R</i>)-3,3'-I ₂ BINOL	H ₂ O (20)	69	61
8	(<i>R</i>)-3,3'-I ₂ BINOL	MeOH (100)	73	68

^[a] 2,6-Lutidine was used instead of *i*-Pr₂NEt.

(run 7), and that addition of an excess amount of methanol enhanced the rate of the reaction dramatically (run 8).^[12]

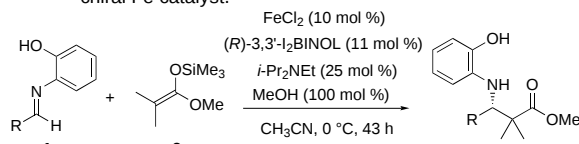
We then investigated reactions of other imines, and the results are summarized in Table 2. In most cases, the reactions proceeded smoothly to afford the desired products in good yields with good to high enantioselectivity. In particular, the imine **1c** prepared from 1-naphthaldehyde (run 2) and the imine **1d** from *o*-tolualdehyde gave high enantioselectivity, indicating that the asymmetric environments created were affected by the substituents at the *ortho*-position of the benzaldehyde moieties.

In conclusion, we have developed a novel chiral iron catalyst system, which was effective for Mannich-type reactions of imines with a ketene silyl acetal. Remarkable rate enhancement was observed by addition of protic additives such as methanol. Further investigations to survey the scope and limitation of this system as well as to apply it to other reactions are in progress.

Experimental Section

Typical Procedure for the Reaction of the Imine Derived from Benzaldehyde in the Presence of Methanol

Dried acetonitrile was degassed by a freeze-thawing method under reduced pressure before use. Under an argon atmosphere, to a suspension of anhydrous iron(II) chloride (0.040 mmol) and (*R*)-3,3'-diiodo-1,1'-binaphthalene-2,2'-diol (3,3'-I₂BINOL, 0.044 mmol) in acetonitrile (0.4 mL) was added *i*-Pr₂NEt (0.10 mmol) in acetonitrile (0.3 mL) at 0 °C, and the whole was stirred for 2 h at the same temperature. To this mixture, MeOH (0.40 mmol) in acetonitrile (0.3 mL) was

Table 2. Catalytic asymmetric Mannich-type reactions using the chiral Fe catalyst.


Run	R	Yield [%]	ee [%]
1	 (1b)	83	66
2	 (1c)	76	84
3	 (1d)	74	82
4	 (1e)	76	62
5	 (1f)	82	65
6	 (1g)	76	46

added, and the whole was stirred for additional 1 h. Then the imine **1b** (0.40 mmol) in acetonitrile (0.5 mL) and a ketene silyl acetal **2** (0.48 mmol) in acetonitrile (0.5 mL) were successively added. The mixture was stirred for the times indicated in the Tables, and saturated aqueous NaHCO₃ was added to quench the reaction. After addition of dichloromethane, the organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The organic layers were combined and dried over anhydrous Na₂SO₄. After filtration and concentration under reduced pressure, the residue was treated with THF/1 N HCl (20:1) for 1 h at 0 °C. Then the solution was made basic with saturated aqueous NaHCO₃ solution. After usual work-up, the crude product was purified by preparative thin layer chromatography (benzene/ethyl acetate, 10:1) to afford the desired Mannich adduct. The optical purity was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD, hexane/*i*-PrOH = 9/1).

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References and Notes

- [1] Reviews: a) H.-J. Knölker, A. Braier, D. J. Brocher, S. Cammerer, W. Frohner, P. Gonser, H. Hermann, D.

- Herzberg, K. R. Reddy, G. Rohde, *Pure Appl. Chem.* **2001**, 73, 1075; b) W. A. Donaldson, *Current Organic Chemistry* **2000**, 4, 837; c) H.-J. Knölker, *Chem. Rev.* **2000**, 100, 2941; d) K. Ruck-Braun, M. Mikulas, P. Amrhein, *Synthesis* **1999**, 727; e) T. Kauffmann, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 386; f) B. Meunier, *Chem. Rev.* **1992**, 92, 1411; g) D. Astruc, *Chem. Met.-Carbon Bond* **1987**, 4, 625.
- [2] Reviews: a) J. P. Collman, Z. Wang, *Chemtracts* **1999**, 12, 229; b) S. G. Davies, *Aldrichimica Acta* **1990**, 23, 31.
- [3] E. J. Corey, N. Imai, H.-Y. Zhang, *J. Am. Chem. Soc.* **1991**, 113, 728.
- [4] N. Khiar, I. Fernández, F. Alcudia, *Tetrahedron Lett.* **1993**, 34, 123.
- [5] a) E. P. Kündig, B. Bourdin, G. Bernardinelli, *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1856; b) M. E. Bruin, E. P. Kündig, *Chem. Commun.* **1998**, 2635; c) E. P. Kündig, C. M. Saudan, F. Viton, *Adv. Synth. Catal.* **2001**, 343, 51; d) Quite recently, asymmetric 1,3-dipolar cycloaddition using a chiral Fe catalyst was reported, see: F. Viton, G. Bernardinelli, E. P. Kündig, *J. Am. Chem. Soc.* **2002**, 124, 4968.
- [6] a) S. Kanemasa, Y. Oderaotoshi, H. Yamamoto, J. Tanaka, E. Wada, D. P. Curran, *J. Org. Chem.* **1997**, 62, 6454; b) S. Kanemasa, Y. Oderaotoshi, S. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada, *J. Am. Chem. Soc.* **1998**, 120, 3074.
- [7] Whiting et al. have reported catalytic asymmetric aza-Diels–Alder reactions using a chiral iron-bisoxazoline complex, see: S. Bromidge, P. C. Wilson, A. Whiting, *Tetrahedron Lett.* **1998**, 39, 8905.
- [8] Unpublished results; Hossain et al. have reported that a cyclopentadienyliron complex works as a Lewis acid to activate imines in the preparation of aziridines, see: a) M. F. Mayer, M. M. Hossain, *J. Org. Chem.* **1998**, 63, 6839; b) M. Redlich, S. J. Mahmood, M. F. Mayer, M. M. Hossain, *Synth. Commun.* **2000**, 30, 1401; c) M. F. Mayer, Q. Wang, M. M. Hossain, *J. Organometallic Chem.* **2001**, 630, 78.
- [9] a) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, 119, 7153; b) S. Kobayashi, M. Ueno, H. Ishitani, *J. Am. Chem. Soc.* **1998**, 120, 431; c) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, 122, 8180; d) S. Kobayashi, Y. Hasegawa, H. Ishitani, *Chem. Lett.* **1998**, 1131; e) H. Ishitani, T. Kitazawa, S. Kobayashi, *Tetrahedron Lett.* **1999**, 40, 2161; f) S. Kobayashi, S. Komiyama, H. Ishitani, *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 979; g) S. Kobayashi, K. Kusakabe, S. Komiyama, H. Ishitani, *J. Org. Chem.* **1999**, 64, 4220; h) S. Kobayashi, K. Kusakabe, H. Ishitani, *Org. Lett.* **2000**, 2, 1225; i) H. Ishitani, S. Komiyama, S. Kobayashi, *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 3186; j) H. Ishitani, S. Komiyama, Y. Hasegawa, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, 122, 762; k) T. Gastner, H. Ishitani, R. Akiyama, S. Kobayashi, *Angew. Chem. Int. Ed. Engl.* **2001**, 40, 1896.
- [10] Wulff et al. also reported catalytic asymmetric Mannich-type reactions of imines prepared from *o*-aminophenol using a chiral Zr-VAPOL complex, see: S. Xue, S. Yu, Y. Deng, W. D. Wulff, *Angew. Chem. Int. Ed. Engl.* **2001**, 40, 2271.
- [11] 3,3'-I₂BINOL was an effective ligand in Zr-catalyzed asymmetric aldol reactions, see: a) H. Ishitani, Y. Yamashita, H. Shimizu, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, 122, 5403; b) Y. Yamashita, H. Ishitani, H. Shimizu, S. Kobayashi, *J. Am. Chem. Soc.* **2002**, 124, 3292.
- [12] In some metal-catalyzed asymmetric reactions, water affected the yields and selectivities, see: S. Ribe, P. Wipf, *Chem. Commun.* **2001**, 299.