Chiral 2-(1-Dimethylaminoethyl)ferrocenecarbaldehyde as an Effective Catalyst for Asymmetric Alkylation of Aldehydes with Dialkylzinc

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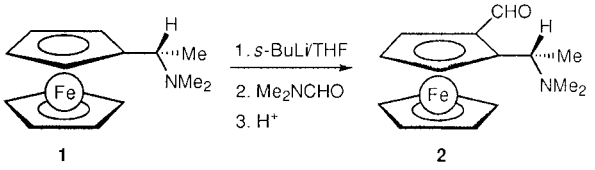
Abstract: The chiral ferrocenecarbaldehyde bearing an amino group was used as a ligand of diethylzinc in the asymmetric alkylation of aldehydes. It effectively catalyzed the reaction with either aromatic, straight chain or branched aliphatic aldehydes to afford chiral alcohols in good yields with high enantiomeric excess (up to 93 % ee).

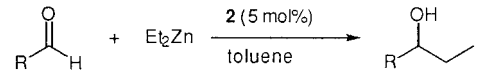
Planar chiral ferrocenes are of current interest as ligands and chiral building blocks in asymmetric synthesis.[1] The unique structure of ferrocenes allows one to design a variety of chiral substituted ferrocenes. Well-designed chiral ferrocenes may produce high stereoselectivities during organic reactions. Chiral ferrocenecarbaldehydes have recently been reported by Kagan et al. as precursors for ligands of transition metal catalysts in asymmetric organic synthesis.[2] We would like to now report the catalytic ability of the chiral ferrocenecarbaldehyde bearing an amino group (**2**) as a chelating ligand of dialkylzinc during the alkylation of aldehydes.



1 2

Scheme 1

The chiral 2-(1-dimethylaminoethyl)ferrocenecarbaldehyde (**2**) was readily prepared by the *ortho*-lithiation of the (2-(*S*)-dimethylaminoethyl)ferrocene (**1**) using *s*-BuLi and the subsequent reaction with dimethylformamide (Scheme 1).[3] We used **2** as a catalyst for the ethylation of aldehydes with diethylzinc. As shown in Table 1, the reaction smoothly proceeded in toluene at 0 °C to give the corresponding alcohol in good to excellent yields with high enantiomeric excess (ee) values (up to 93 % ee) (Scheme 2). The reaction of benzaldehyde with (*S,R*)- and (*R,S*)-(**2**) gave the (*R*)- and (*S*)-isomers of 1-phenyl-1-propanol, respectively (runs 1-2). A slight difference in the ee values between 4-methoxy- and 4-nitrobenzaldehyde suggests that the reaction is not be affected by an electronic factor (runs 3-4). With either the aromatic, the straight chain or branched aliphatic aldehyde, the stereoselective alkylation successfully produced the corresponding alcohol in high optical purity.



Scheme 2

It is well established that asymmetric alkylation of aldehydes with dialkylzinc needs a certain catalyst such as a Lewis acid, a sulfonamide, and an amino alcohol including a ferrocenyl amino alcohol.[4] It is interesting that the aldehyde works as a catalyst in the reaction: the catalyst employed here was an amino aldehyde not an amino alcohol. We then examined the origin of the catalytic activity of **2**. The results of the reaction with benzaldehyde using ferrocene compounds as catalysts are summarized in Table 2. Simple ferrocenecarbaldehyde did not catalyze the reaction (run 1). The parent aminoferrocene (**1**) showed poor catalytic activity giving a low yield (29%) and ee (7 %) value of the product (run 2). These results suggest that both the formyl and amino groups are required for high catalytic and high asymmetric induction abilities. The trick of the reaction may be shown by the following experimental results. The ferrocene-carbaldehyde (**2**) was alkylated with diethylzinc without catalyst to give the ferrocenyl alcohol (**3**) after hydrolysis with high diastereoselectivity (>99 de) (Scheme 3).[5] The ferrocenyl alcohol (**3**) also worked as an effective catalyst for the highly enantioselective ethylation with diethylzinc (run 3). The actual catalyst, therefore, should be the zinc ferrocenyl alkoxide. High diastereoselective alkylation of **2** with dialkylzinc was the key point of the reaction.[6] The advantage of this method is that the reaction can conveniently be carried out using **2** itself as a catalyst without isolation of a diastereomerically pure ferrocenyl amino alcohol.[7] The use of chiral ferrocene-carbaldehyde bearing the oxazoline (**4**)[8] or acetal (**5**)[2] group as a catalyst resulted in a low yield with a low ee value (runs 4-5).

Table 1. Ethylation of Aldehydes with Diethylzinc Catalyzed by (*S,R*)-**2**

run	aldehyde	yield [%][a]	ee [%][b]	config.
1	benzaldehyde	94	91	*R*
2[c]	benzaldehyde	92	87	*S*
3	4-methoxybenzaldehyde	97	93	*R*
4	4-nitrobenzaldehyde	88	91	-[d]
5	1-naphthaldehyde	91	88	*R*
6	ferrocenecarbaldehyde	90	81	*R*
7	cinnamaldehyde	85	80	*R*
8	3-phenylpropanal	88	83	*R*
9	pentanal	85	80	*R*
10	isobutyraldehyde	73	81	*R*
11	cyclohexanecarbaldehyde	87	82	*R*
12	pivaldehyde	55	80	*R*

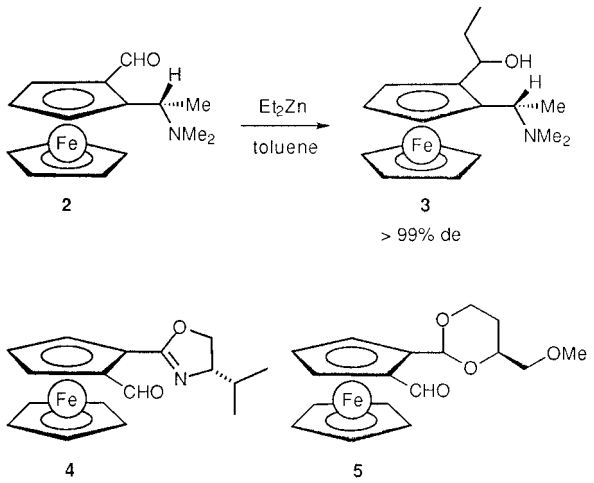
[a]Isolated yield after PTLC. [b]Determined by HPLC using Daicel Chiralcel OD column (*i*-PrOH/hexane = 10/90) and/or by GC using Astec Chiraldex B-PH chiral capillary column. [c](*R,S*)-**2** was used as the catalyst. [d]Not determined

Table 2. Ethylation of Benzaldehydes with Diethylzinc Catalyzed by Ferrocene Compounds

run	ferrocene catalyst	yield [%][a]	ee [%][b]	config.
1	ferrocenecarbaldehyde	0	-[c]	-
2	(*S*)-**1**	29	7	*S*
3	**3** (>99% de)	90	90	*R*
4	(*S,S*)-**4**	11	30	*S*
5	(*S,S*)-**5**	5	-[c]	-

[a]Isolated yield after PTLC. [b]Determined by GC using Astec Chiraldex B-PH chiral capillary column. [c] Not determined

The general procedure for the ethylation of aldehyde with diethylzinc catalyzed by **2** is as follows. In a two-neck 50 mL round-bottom flask containing a magnetic stirrer bar was placed **2** (14.3 mg, 0.05 mmol, 5 mol %) under nitrogen. Dry toluene (5.0 mL) was then added to the flask followed by the addition of 1.0 mol/l hexane solution of Et_2Zn (1.5 mL, 1.5 mmol) at 0 °C. After 30 min, benzaldehyde (100 mg, 1.0 mmol) was added to the resulting solution at 0 °C and stirred for 15 h. The reaction was quenched by the addition of diluted HCl. The aqueous



Scheme 3

layer was extracted with two portions of diethyl ether (20 mL), washed with brine and dried ($MgSO_4$); the ferrocenyl amino alcohol (**3**) was extracted into an acidic aqueous solution. The GC/MS analysis of the ethereal solution revealed the presence of 1-phenyl-1-propanol. After evaporation of the solvent, the product was isolated by preparative TLC (hexane/ethyl acetate = 5/1) (127.9 mg, 0.94 mmol, 94% yield). Enantiomeric excess was determined by HPLC analysis using a Daicel Chiralcel OD column and/or by GC with a chiral capillary column (Astec Chiraldex B-PH, 30 m). The absolute configuration was determined by chiroptical comparison with literature values.[4,7,9]

References and notes

(1) For reviews, a) *Ferrocenes*; Togni, A.; Hayashi, T., Eds.; VCH: Weinheim, 1995. b) Kagan, H. B.; Riant, O. *In Advances in Asymmetric Synthesis Vol 2*; Hassner, A., Ed.; JAI: London, 1997; pp189-235. c) Togni, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1475. d) Kagan, H. B.; Diter, P.; Gref. A.; Guillaneux, D.; Masson-Szymczak, A.; Rebiere, F.; Riant, O.; Samuel, O.; Tauden, S. *Pure&Appl. Chem.* **1996**, *68*, 29.

(2) Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. B. *J. Org. Chem*. **1997**, *62*, 6733.

(3) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc*. **1970**, *92* 5389. Analytical data for **2**: red solid; mp = 64-66 °C dec. $[\alpha]_D^{28}$ = 168.4 (c = 0.77, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (d, 3H, *J* = 6.8 Hz), 2.08 (s, 6H), 4.23 (s, 5H), 4.5-4.8 (m, 3H), 10.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 40.3, 55.5, 68.5, 69.3, 70.3, 71.2, 72.3, 91.5, 193.2; IR (KBr) $\nu_{C=O}$ = 1671cm^{-1}. Anal. Calcd for $C_{15}H_{19}FeNO$: C, 63.17; H, 6.72; N, 4.91. Found: C, 63.15; H, 6.74; N, 6.69.

(4) For reviews, a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. b) Butsugan, Y.; Araki, S.; Watanabe, M. *In Ferrocenes*; Hayashi, T.; Togni, A. Eds.; VCH: Weinheim, **1995**; pp143-168. c) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC: Boca Raton, 1996. d) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley; New York, **1994**; Chap 5.

(5) Analytical data for **3**: red oil; $[\alpha]_D^{25}$ = -35.3 (c = 0.33, $CHCl_3$). IR (KBr) ν_{OH} = 3172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, 3H, *J* = 7.4 Hz), 1.21 (d, 3H, *J* = 6.6 Hz), 1.6-1.7 (m, 1H), 1.8-2.0 (m, 1H), 2.07 (s, 6H), 3.94 (s, 5H), 3.9-4.2 (m, 3H), 4.60 (dd, 1H, *J* = 3.2, 9.6 Hz); ^{13}C NMR ($CDCl_3$) δ 7.0, 11.3, 26.8, 38.5, 57.1, 65.2, 66.3, 67.0, 69.0, 69.5, 89.0, 91.3. Anal. Calcd for $C_{17}H_{25}FeNO$: C, 64.77; H, 7.99; N, 4.44. Found: C, 64.81; H, 7.96; N, 4.41.

(6) Taudien, S.; Riant, O.; Kagan, H. B. *Tetrahedron Lett*. **1995**, *36*, 3513. Highly diastereoselective addition of organometallic reagents to chiral ferrocenecarbaldehydes will be reported in due course.

(7) Trapping of α-lithio ferrocene of **1** with an aldehyde gives a diastereomeric mixture of a ferrocenyl amino alcohol with a low diastereomeric excess. Battelle, L. F.; Bau, R.; Oyakawa, R. T.; Ugi, I. K. *J. Am. Chem. Soc*. **1973**, *95*, 482; Watanabe, M.; Araki, S.; Butugan, Y.; Uemura, *J. Org. Chem*. **1991**, *56*, 2218.

(8) Samakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem*. **1995**, *60*, 10; Richard, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, 74; Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79. Analytical data for **4**: orange solid; mp = 78-80 °C dec.; $[\alpha]^{25}_D$ = -1105 (c = 0.75, MeOH). IR (KBr) $\nu_{C=O}$ = 1673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, 3H, *J* = 6.8 Hz), 0.97 (d, 3H, *J* = 6.6 Hz), 1.77 (sextet, 1H, *J* = 6.6 Hz), 3.9-4.0 (m, 1H), 4.05 (t, 1H, *J* = 5.2 Hz), 4.22 (s, 5H), 4.66 (m, 1H), 4.90 (m, 2H), 10.6 (m, 1H); ^{13}C NMR ($CDCl_3$) δ18.3, 18.6, 32.6, 69.7, 70.2, 72.6, 73.1, 74.8, 78.8, 163.8, 195.3. Anal. Calcd for $C_{17}H_{19}FeNO_2$: C, 62.79; H, 5.89; N, 4.31. Found: C, 62.75; H, 5.94; N, 4.35.

(9) Kitajima, H.; Ito, K.; Aoki, Y. and Katsuki, T. *Bull. Chem. Soc. Jpn*. **1997**, *70*, 207.