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Enantioselective Synthesis of 1-Metallocenylalkanols by Catalytic Asymmetric Alkylation of Metallocenecarboxaldehydes with Dialkylzincs

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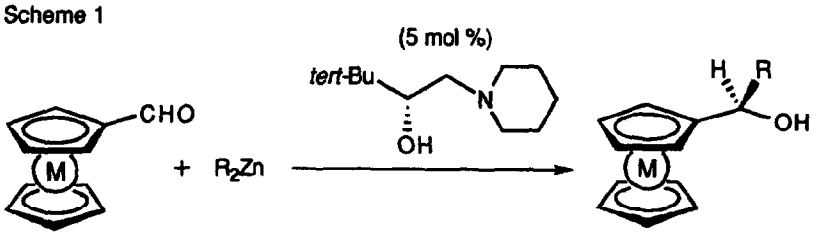
Abstract: Reaction of ferrocenecarboxaldehyde and ruthenocenecarboxaldehyde with diethylzinc or dimethylzinc in the presence of 5 mol % of (*R*)-3,3-dimethyl-1-piperidino-2-butanol proceeded with high enantioselectivity to give (*R*)-1-ferrocenylpropanol (>96% ee), (*R*)-1-ferrocenylethanol (>99% ee), (*R*)-1-ruthenocenylpropanol (96% ee), and (*R*)-1-ruthenocenylethanol (90% ee) in over 84% yield. The (*R*)-1-metallocenylalkanols were converted into the corresponding (*R*)-1-metallocenyl-*N*,*N*-dimethylamines.

Metallocenes of Group 8 metals are of interest because of their unique features. In particular, the optically active ferrocenes whose chirality is due to the ferrocene planar chirality have been widely used in asymmetric catalysis as chiral ligands.[2,3] The planar chiral ferrocenes have been conveniently prepared through the diastereoselective ortholithiation of optically active *N*,*N*-dimethyl-1-ferrocenylethylamine,[4] which is obtained by optical resolution of the racemic amine[4,5] and there have been reported only a few convenient methods for the asymmetric synthesis of optically active ferrocenes.[6] Asymmetric alkylation of aldehydes with alkylzinc reagents in the presence of a catalytic amount of chiral β-aminoethanols is known to be one of the most efficient methods for the preparation of optically active alcohols.[7,8] We report here the use of the asymmetric alkylation for the synthesis of 1-ferrocenylalkanols and their ruthenocene analogs (Scheme 1), which can serve as precursors of 1-metallocenyl-*N*,*N*-dimethylamines.

Scheme 1



1: M = Fe
2: M = Ru

3a: M = Fe, R = Et
3b: M = Fe, R = Me
4a: M = Ru, R = Et
4b: M = Ru, R = Me

Table 1. Catalytic Asymmetric Alkylation of Metallocenecarboxaldehydes with Dialkylzincs in the Presence of (*R*)-3,3-Dimethyl-1-piperidino-2-butanol[a]

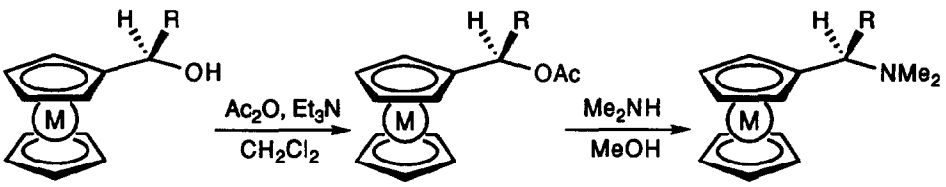
entry	aldehyde	R_2Zn	solvent	temp (°C)	time (days)	product (%)[b]	% ee (config.)	$[\alpha]_D^{20}$[c]
1	**1** (Fe)	Et_2Zn	toluene/hexane[d]	–5	2	**3a** (96)	>96[e]	–57.5
2	**1** (Fe)	Me_2Zn	toluene/hexane[d]	–5	2	**3b** (0)	–	–
3	**1** (Fe)	Me_2Zn	toluene/hexane[d]	20	3	**3b** (75)	79[f]	–23.0
4	**1** (Fe)	Me_2Zn	Et_2O	20	7	**3b** (96)	>99[f] (*R*)	–31.1[g]
5	**2** (Ru)	Et_2Zn	toluene/hexane[d]	–8	5	**4a** (99)	96[e]	–49.0
6	**2** (Ru)	Me_2Zn	Et_2O	20	12	**4b** (17)	75[h]	–
7	**2** (Ru)	Me_2Zn	Et_2O/benzene[d]	20	14	**4b** (84)	90[h]	–24.0
8	**2** (Ru)	Me_2Zn	Et_2O/toluene[d]	20	7	**4b** (40)	80[h]	–

[a] All reactions were carried out under argon atmosphere. Aldehyde/R_2Zn/aminoalcohol = 1/1.1/0.05. [b] Isolated yield by column chromatography. [c] *c* 0.5-1.1 in benzene. [d] 1/1. [e] Determined by ^1H NMR analysis in the presence of Eu(hfc)$_3$. [f] Determined by optical rotation. [g] At 25 °C. [h] Determined by HPLC analysis of its 3,5-dinitrophenylcarbamate ester with chiral stationary phase column, Sumichiral OA-1100.

A solution of ferrocenecarboxaldehyde (**1**) in toluene was allowed to react with 1 M solution of diethylzinc in hexane under argon atmosphere in the presence of 5 mol % of (*R*)-3,3-dimethyl-1-piperidino-2-butanol.[7] The reaction at –5 °C was completed in 2 days to give 96% yield of 1-ferrocenylpropanol (**3a**)[9] ($[\alpha]_D^{20}$ –57.5 (*c* 1.0, benzene)). The enantiomeric purity of **3a** was determined to be over 96% ee by ^1H NMR analysis in the presence of optically active shift reagent Eu(hfc)$_3$ (entry 1 in Table 1). The methylation of **1** with dimethylzinc under similar conditions was much slower than the ethylation, no methylation being observed in the reaction at –5 °C in the mixed solvent system consisting of toluene and hexane (entry 2). The methylation at 20 °C for 3 days gave (*R*)-1-ferrocenylethanol (**3b**)[10] of 79% optical purity in 75% yield (entry 3). Diethyl ether was found to be a solvent of choice for the asymmetric methylation of **1**. Thus, the methylation in diethyl ether at 20 °C gave 96% yield of (*R*)-**3b**, whose optical rotation $[\alpha]_D^{25}$ –31.1 (*c* 1.0, benzene) is larger than the value reported for optically pure (*R*)-**3b** ($[\alpha]_D^{25}$ –30.5 (*c* 1.1, benzene))[10] (entry 4). The enantioselectivity observed here is much higher than the methylation of **1** in the presence of (–)-DAIB which gave (*S*)-**3b** of 81% ee.[7d]

Ruthenocenecarboxaldehyde (**2**)[11] was also examined for the enantioselective alkylation in the presence of (*R*)-3,3-dimethyl-1-piperidino-2-butanol. The reaction of **2** with diethylzinc in toluene/hexane (1/1) proceeded with high enantioselectivity to give a quantitative yield of 1-ruthenocenylpropanol (**4a**)[12] ($[\alpha]_D^{20}$ –49.0 (*c* 1.0, benzene)), whose enantiomeric purity determined by ^1H NMR analysis using Eu(hfc)$_3$ was 96% (entry 5). The methylation of ruthenocenecarboxaldehyde **2** with dimethylzinc in ether carried out in a similar manner to the methylation of ferrocene analog **1** was very slow, only 17% yield of 1-ruthenocenylethanol (**4b**)[13] was obtained in the reaction at 20 °C for 12 days (entry 6). The slow rate of the methylation is due mainly to the low solubility of the aldehyde **2** in ether at the low temperature. The use of mixed solvent system, ether/benzene (1/1) or ether/toluene (1/1), which dissolve the aldehyde **2**, improved the conversion and enantioselectivity (entries 7 and 8). Thus, the reaction in ether/benzene at 20 °C for 14 days gave 84% yield of **4b** ($[\alpha]_D^{20}$ –24.0 (*c* 0.5, benzene)), whose enantiomeric purity was 90%. The enantiomeric purity of **4b** was determined by HPLC analysis of its carbamate ester, obtained by treatment of **4b** with 3,5-dinitrophenyl

Scheme 2



3,4

5a: M = Fe, R = Et
5b: M = Fe, R = Me
6a: M = Ru, R = Et
6b: M = Ru, R = Me

isocyanate, with chiral stationary phase column, Sumichiral OA-1100. The absolute configuration of new optically active 1-metallocenylalkanols obtained here, (–)-1-ferrocenylpropanol (**3a**), (–)-1-ruthenocenylpropanol (**4a**), and (–)-1-ruthenocenylethanol (**4b**), is assumed to be all *R* from the *R* configuration of the known alcohol (–)-**3b**, since the asymmetric alkylation of aromatic aldehydes with diethylzinc and dimethylzinc catalyzed by a chiral aminoalcohol have always produced the alcohols of the same configuration.[7,8]

It has been reported that (*R*)-1-ferrocenylethanol (**3b**) can be readily converted into (*R*)-*N*,*N*-dimethyl-1-ferrocenylethylamine (**5b**) without racemization, by acetylation of the alcohol followed by amination of the resulting acetate with dimethylamine.[5,10] The nucleophilic substitution reaction at the ferrocenylmethyl position has been known to proceed with complete retention of configuration via the 1-ferrocenylethyl cation, which is readily formed and has high configurational stability.[10] The acetylation-amination reactions of (*R*)-1-metallocenylalkanols obtained above according to the reported procedures[10] gave the corresponding optically active dimethylamines **5** and **6** in over 80% yield (Scheme 2): (*R*)-**5a**:[14] ($[\alpha]_D^{20}$ –43.8 (*c* 1.0, benzene)). (*R*)-**5b**: ($[\alpha]_D^{25}$ +14.2 (*c* 1.0, ethanol), literature[4,10] for (*S*)-**5b**, $[\alpha]_D^{25}$ –14.1 (*c* 1.6, ethanol)). (*R*)-**6a**:[15] ($[\alpha]_D^{20}$ +13.2 (*c* 1.0, benzene)). (*R*)-**6b**:[16] ($[\alpha]_D^{20}$ +22.1 (*c* 1.8, benzene)). The enantiomeric purity of the amines should be the same as the starting alcohols. The procedures for the conversion of (*R*)-**5b** into ferrocenylphosphine ligands such as (*R*)-(*S*)-BPPFA have been already established,[2,17] and (*R*)-1-ruthenocenyl-*N*,*N*-dimethylamines **6** are convenient starting compounds for the preparation of chiral ruthenocenylphosphines,[18] which will be described elsewhere in due course.

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References and Notes

1 On leave from Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, China.

2 For reviews: (a) Hayashi, T.; Kumada, M. *Acc. Chem. Res.* **1982**, *15*, 395. (b) Hayashi, T. *Pure Appl. Chem.* **1988**, *60*, 7.

3 (a) Hayashi, T.; Sawamura, M.; Ito, Y. *Tetrahedron* **1992**, *48*, 1999. (b) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586. (c) Hayashi, T.; Yamazaki, A. *J. Organomet. Chem.* **1991**, *413*, 295, and references cited therein.

4 Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389.

5 A kinetic resolution of 1-ferrocenylethanol by esterification with lipase has been reported: Boaz, N. W. *Tetrahedron Lett.* **1989**, *30*, 2061.

6 David, D. M.; Kane-Maguire, L. A. P.; Pyne, S. G. *J. Chem. Soc. Chem. Commun.* **1990**, 888.

7 (a) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877. (b) Hayashi, M.; Kaneko, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1991**, 25. (c) Hayashi, M.; Miwata, H.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1167. (d) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19. (e) Soai, K.; Hirose, Y.; Sakata, S. *Tetrahedron Asymmetry* **1992**, *3*, 677.

8 For Reviews: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (b) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49.

9 For **3a**: ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.3 Hz, 3 H), 1.61-1.70 (m, 2 H), 1.99-2.03 (m, 1 H), 4.12-4.26 (m, 5 H), 4.18 (s, 5 H). ^{13}C NMR ($CDCl_3$) δ 10.3, 30.9, 65.1, 67.2, 67.6, 67.8, 68.2, 71.0, 94.2. IR (neat): 3436, 1106, 1002 cm^{-1}. Anal. Calcd for $C_{13}H_{16}OFe$: C, 63.96; H, 6.61. Found C, 63.95; H, 6.69. (*R*)-**3a** and (*S*)-**3a** have been briefly reported: Harada, A.; Saeki, K.; Takahashi, S. *Carbohydrate Research* **1989**, *192*, 1.

10 Gokel, G.; Marquarding, D.; Ugi, I. K. *J. Org. Chem.* **1972**, *37*, 3052.

11 Ruthenocenecarboxaldehyde (**2**) was prepared in 78% yield from ruthenocene according to the reported procedures: Kamiyama, S.; Suzuki, T. M.; Kimura, T.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 909.

12 For **4a**: ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.3 Hz, 3 H), 1.58-1.75 (m, 2 H), 1.93 (d, *J* = 3.3 Hz, 1 H), 4.15-4.26 (m, 5H), 4.20 (s, 5 H). IR (neat): 3468, 1101, 998 cm^{-1}. Anal. Calcd for $C_{13}H_{16}ORu$: C, 53.97; H, 5.57. Found: C, 54.00; H, 5.59.

13 For **4b**: ^{1}H NMR ($CDCl_3$) δ 1.34 (d, *J* = 6.3 Hz, 3 H), 1.44 (d, *J* = 5.0 Hz, 1 H), 4.28 (dq, *J* = 5.0 and 6.3 Hz, 1 H), 4.53-4.68 (m, 4 H), 4.61 (s, 5 H). IR (KBr): 3244, 1101, 996 cm^{-1}. Anal. Calcd for $C_{12}H_{14}ORu$: C, 52.35; H, 5.13. Found: C, 52.41; H, 5.13.

14 For **5a**: ^{1}H NMR ($CDCl_3$) δ 1.10 (t, *J* = 7.3 Hz, 3 H), 1.66-1.75 (m, 2 H), 2.00 (s, 6 H), 3.25 (dd, *J* = 10.9 and 3.3 Hz, 1 H), 4.01-4.12 (m, 4 H), 4.11 (s, 5 H). ^{13}C NMR ($CDCl_3$) δ 12.3, 24.4, 40.5, 65.0, 66.9, 67.1, 67.4, 69.3, 68.5. IR (KBr): 1446, 1227, 1105, 988 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NFe$: C, 66.44; H, 7.81; N, 5.16. Found: C, 66.04; H, 7.70; N, 5.14.

15 For **6a**: ^{1}H NMR ($CDCl_3$) δ 0.98 (t, *J* = 7.3 Hz, 3 H), 1.52-1.85 (m, 2 H), 2.10 (s, 6 H), 3.02 (dd, *J* = 10.1 and 4.1 Hz, 1 H), 4.45-4.83 (m, 4 H), 4.51 (s, 5 H). IR (KBr): 2815, 2773, 1101, 991 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NRu$: C, 56.94; H, 6.69; N, 4.43. Found: C, 56.99; H, 6.81; N, 4.35.

16 For **6b**: ^{1}H NMR ($CDCl_3$) δ 1.27 (d, *J* = 6.9 Hz, 3 H), 2.17 (s, 6 H), 3.32 (q, *J* = 6.9 Hz, 1 H), 4.47-4.55 (m, 4 H), 4.51 (s, 5 H). IR (KBr): 2819, 2777, 1101, 999 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NRu$: C, 55.61; H, 6.33; N, 4.63. Found: C, 55.58; H, 6.22; N, 4.65.

17 Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138.

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