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Asymmetric dihydroxylation reactions leading to novel chiral ferrocene derivatives

Walther G. Jary and Judith Baumgartner *

Institute for Organic Chemistry, Technical University of Graz, Stremayrgasse 16, A-8010 Graz, Austria

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Abstract

Several ferrocenyl alkenes were used as starting materials for asymmetric dihydroxylation reactions. Although they turned out to be unreactive employing Sharpless' standard conditions, by systematic variation of the reaction conditions the desired novel ferrocenyl diols could be obtained in good yields and in enantiomeric excesses up to >99%.

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1. Introduction

Metallocenes, especially those of the group 8 metals, are of interest because of their unique features.[1] In particular, optically active ferrocenes have been widely used in asymmetric catalysis as chiral ligands.[2] Currently, all asymmetric syntheses of ferrocene derivatives bearing side chain chirality known so far are made by the reduction of ferrocenyl ketones to chiral secondary alcohols or using chiral cyclopentadienyl alkanols as the starting material.[3] Their reduction can be accomplished by using chemical procedures[4] or microorganisms and enzymes.[5] Recently we had a need for ferrocene derivatives bearing chiral vicinal hydroxy groups in the side chain. Surprisingly there are no such derivatives reported in the literature up to now. We therefore decided to synthesize ferrocenes bearing a double bond in the side chain and transform them via the Sharpless dihydroxylation procedure to the desired diols.

2. Results

Conversion of the ferrocenyl alkenes **1**, **3**, **5**, and **7** under standard Sharpless dihydroxylation conditions[6] (3 equiv. of $K_3Fe(CN)_6$ and K_2CO_3, 1 mol% of $K_2OsO_2(OH)_4$ and $(DHQD)_2PHAL$ in *t*BuOH:H_20 (1:1) at 0°C) does not proceed at all and the starting materials could be recovered after

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* Corresponding author. Tel: ++43(316)873-8248; fax: ++43(316)873-8740; e-mail: judith@orgc.tu-graz.ac.at

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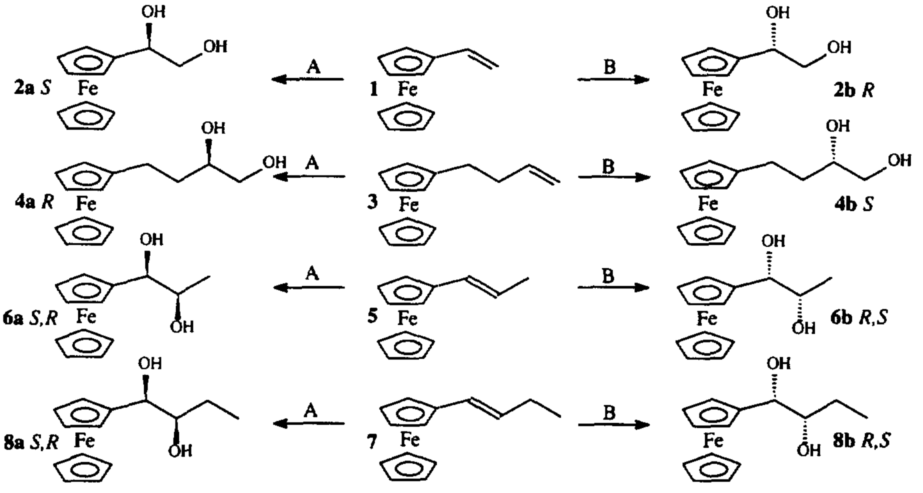
48 hours unchanged (Scheme 1). First variations of these conditions (Table 1, entries 1–4) yielded the diols, however, in very poor yields and ees. We decided to use vinylferrocene **1** and homoallylferrocene **3** as starting materials for further improvement of the reaction,[7] because it is known from the literature that vinylsubstrates are difficult to handle in this reaction.[8]



Ligand used: A: $(DHQD)_2PHAL$ or $(DHQD)_2PYR$; B: $(DHQ)_2PHAL$ or $(DHQ)_2PYR$.

Scheme 1.

Improvement could be achieved by addition of acetone, in which the starting materials are more soluble, thus leading to increased reaction rates (entries 5 and 14). In the case of vinylferrocene we obtained better yields in solvent mixtures of acetone and water without any alcohol addition. In accordance to Sharpless' observation[8] the change from $(DHQD)_2$–PHAL to $(DHQ)_2PHAL$ shows a dramatic drop in ee, but only in the case of **1**[9] (entries 6–9) and not with **3** (entries 15–17). The first surprise was an increase in both ee and yield by performing the reactions at room temperature (entry 8). Doubling the amount of ligand led to an ee of 72% (entry 9). The same reaction running at 0°C gave only 15% yield and showed an ee of about 5%. The change from ligands based on phthalazine to those based on pyrimidine in acetonitrile–water mixtures and an additional increase of the osmate concentration gave the first good results (entries 10–13).

In the case of compound **3** variations of temperature, amount of ligand and osmate were not very effective (entries 16–23). Only a change of solvent led to slightly better results (entries 14–16). Remarkably, in this case the change of the ligand from $(DHQD)_2PYR$ to $(DHQ)_2PYR$ increased the ee (entries 19–22) which is contrary to the published results.[10] The mixture of acetonitrile–water as a solvent also worked better in the case of $(DHQD)_2PHAL$. Entry 23 shows that the reaction running at 50°C yielded an ee of 56%. In comparison the same reaction at room temperature gave 48% ee. At the begining of our studies we tried to decrease the reaction times by the addition of methanesulfonamide[10] without success. With these results it was possible to figure out the best reaction conditions for compound **5** (entries 24–28) and **7** (entries 29 and 30). The very short reaction times of three hours for these conversions are worth mentioning.

Table 1

Entry	Starting material	Solvent	Equivalent $K_3Fe(CN)_6$ and K_2CO_3	Ligand [mol%]	mol% $K_2OsO_2(OH)_4$	Time [h]	Temp [°C]	Yield. [%]	ee and product
1	**1**	*t*BuOH/H_2O = 1:1	7.8	$(DHQD)_2$PHAL [7]	5	24	0	12	**0%,2a**
2	**3**	*t*BuOH/H_2O = 1:1	7.8	$(DHQD)_2$PHAL [7]	5	12	0	33	**50%, 4a**
3	**5**	*t*BuOH/H_2O = 1:1	7.8	$(DHQD)_2$PHAL [7]	5	12	20	46	**44%, 6a**
4	**7**	*t*BuOH/H_2O = 1:1	7.8	$(DHQD)_2$PHAL [7]	5	12	20	51	**50%, 8a**
5	**1**[a]	Acetone/*t*BuOH/H_2O = 1:0.5:0.5	7.8	$(DHQD)_2$PHAL [15]	3.3	24	0	25	5%, **2a**
6	**1**[a]	Acetone/H_2O = 1:1	7.8	$(DHQD)_2$PHAL [15]	3.3	48	0	35	16%, **2a**
7	**1**[a]	Acetone/H_2O = 1:1	7.8	$(DHQ)_2$PHAL [15]	3.3	48	0	35	3%, **2b**
8	**1**[a]	Acetone/H_2O = 1:1	7.8	$(DHQ)_2$PHAL [15]	3.3	24	20	54	24%, **2b**
9	**1**	Acetone/H_2O = 1:1	7.8	$(DHQD)_2$PHAL [30]	3.3	48	20	70	72%, **2a**
10	**1**	CH_3CN/H_2O = 1:1	3	$(DHQD)_2$PYR [10]	4	23	20	61	93%, **2a**
11	**1**	CH_3CN/H_2O = 1:1	3	$(DHQ)_2$PYR [10]	4	23	20	52	87%, **2b**
12	**1**	CH_3CN/H_2O = 1:1	3	$(DHQ)_2$PYR [10]	10	3	20	87	84%, **2b**
13	**1**	CH_3CN/H_2O = 1:1	3	$(DHQD)_2$PYR [10]	10	23	20	79	96%, **2a**
14	**3**	Aceton/*t*BuOH/H_2O = 1:0.5:0.5	7.8	$(DHQD)_2$PHAL [15]	3.3	24	0	50	53%, **4a**
15	**3**	Acetone/H_2O = 1:1	7.8	$(DHQD)_2$PHAL [15]	3.3	24	0	99	59%,**4a**
16	**3**[a]	Acetone/*t*BuOH/H_2O = 1:0.5:0.5	7.8	$(DHQ)_2$PHAL [15]	3.3	24	0	24	57%, **4b**
17	**3**[a]	Acetone/H_2O = 1:1	7.8	$(DHQ)_2$PHAL [15]	3.3	24	0	54	46%, **4b**
18	**3**	Acetone/H_2O = 1:1	7.8	$(DHQD)_2$PHAL [30]	3.3	48	20	38	5%, **4a**
19	**3**	CH_3CN/H_2O = 1:1	3	$(DHQD)_2$PYR [10]	4	12	20	61	**49%, 4a**
20	**3**	CH_3CN/H_2O = 1:1	3	$(DHQ)_2$PYR [10]	4	12	20	71	**13%, 4b**
21	**3**	CH_3CN/H_2O = 1:1	3	$(DHQD)_2$PYR [10]	10	12	20	61	**49%, 4a**
22	**3**	CH_3CN/H_2O = 1:1	3	$(DHQ)_2$PYR [10]	10	12	20	71	13%,**4b**
23	**3**	CH_3CN/H_2O = 1:1	3	$(DHQD)_2$-PHAL [10]	10	5	50	75	56%, **4a**
24	**5**	CH_3CN/H_2O = 1:1	3	$(DHQD)_2$PHAL [10]	4	3	20	78	36%, **6a**
25	**5**	CH_3CN/H_2O = 1:1	3	$(DHQD)_2$PYR [10]	4	3	20	99	97%, **6a**
26	**5**	CH_3CN/H_2O = 1:1	3	$(DHQ)_2$PYR [10]	4	3	20.	98	**86%, 6b**
27	**5**	CH_3CN/H_2O = 1:1	3	$(DHQD)_2$PYR [10]	10	23	20	79	**84%, 6a**
28	**5**	CH_3CN/H_2O = 1:1	3	$(DHQ)_2$PYR [10]	10	3	20	99	**97%, 6b**
29	**7**	CH_3CN/H_2O = 1:1	3	$(DHQD)_2$PYR [10]	10	3	20	76	93%, **8a**
30	**7**	CH_3CN/H_2O = 1:1	3	$(DHQ)_2$PYR [10]	10	3	20	75	93%, **8b**

[a] Addition of 12 mol% $MeSO_2NH_2$.

3. Discussion

The ferrocene derivatives used seem to behave differently from all substrates investigated to date in the AD-reaction. The amount of ligand and osmate used was previously thought to have no influence on the enantioselectivity of the reaction.[10] In this case it was a crucial factor. The same shall apply to the concentration of $K_3Fe(CN)_6$, K_2CO_3 and the kind of solvent used. Raising the temperature from 0°C to 20°C led to much better results in terms of yield and ee. A further increase of the reaction temperature seems not to affect the outcome. On adding a further recrystallisation step the ee could be raised to >99%. The change from ligands based on phthalazine to those on pyrimidine did not result in a different absolute configuration of the resulting diol.[11] The absolute configuration of compound **2b**[†] was determined by anomalous X-ray diffraction to be *R* which is in accordance to the Sharpless prediction model.

[†] The X-ray crystallographic data are deposited at the Cambridge Crystallographic Data Centre under the No.: CCDC-101031. They are available under: telefax: ++1223/336 033; e-mail: deposit@chemcrys.cam.ac.uk.

4. Experimental section

4.1. General information

NMR spectra were recorded on Bruker MSL 300, or Varian Gemini 200 spectrometers. *J* Values are measured in hertz. Multiplicities in ^{13}C spectra were determined by DEPT experiments. Melting points were recorded on a Tottoli apparatus (Buechi) and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 341 spectrometer with a quartz cuvette (5 cm long and with a volume of 3.4 ml). The given rotation values were always measured from the reaction which gave the best ees. Flash chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck). Enantiomeric excess was determined on a HPLC (Chiral PAK AD (250 cm×2.5 mm); flow: 0.40 ml min^{-1}; detection: 215 nm; eluent: 2-propanole:*n*-hexane=1:9; room temperature). $K_3Fe(CN)_6$ was obtained from Riedel de Haean.

4.2. General procedure

The amounts of reagents and the kind of solvents (50 ml) are given in Table 1. The typical procedure is given for a 100 mg scale. To a homogenous solution of $K_3Fe(CN)_6$, K_2CO_3, the ligand $K_2OsO_2(OH)_4$ was added and the mixture stirred until the osmate had dissolved. The starting material was added slowly, dropwise, to prevent the build up of precipitate. After the reaction was complete, 0.7 g of Na_2SO_3 was added and the solution stirred for an additional 20 minutes. The reaction mixture was extracted three times with ethyl acetate (each 15 ml). The combined organic layers were dried with Na_2SO_4 and the solvent removed in vacuo. Flash chromatography gave the pure product.

*4.3. 1-[((1S)-cis-1,2-Dihydroxy)ethyl]ferrocene **2a** and 1-[((1R)-cis-1,2-dihydroxy)ethyl]ferrocene **2b***

2: Yellow crystals; retention time: 33.2 (*S*); 22.8 (*R*); HRMS: calculated for $C_{12}H_{14}FeO_2$: 264.03428; found: 264.03428; ^1H-NMR (300 MHz, d_6-DMSO) δ 3.38 (m, 1H), 3.77 (m, 1H), 4.31 (m, 2H), 4.39 (br. s, 6H), 4.43 (m, 1H), 4.54 (dt, *J*=4.2 Hz, 1H), 4.81 (t, *J*=5.8 Hz, 1H, D_2O changeable), 4.96 (d, *J*=5.2 Hz, 1H, D_2O changeable); ^{13}C-NMR (300 MHz, d_6-DMSO) δ 66.4 (t), 66.8 (d), 67.2 (d), 67.3 (d), 68.6 (d), 70.2 (d), 90.7 (s). **2a**: Mp: 98–100°C; $[\alpha]_D^{20}$=+23.8 (c=0.38, CH_2Cl_2); recrystallisation from acetonitrile–water yielded >99% ee: mp: 101–103°C; $[\alpha]_D^{20}$ +23.6 (c=0.36, CH_3OH). **2b**: Mp: 101–103°C; $[\alpha]_D^{20}$=−23.3 (c=0.10, CH_3OH).

*4.4. 1-[((3R)-cis-3,4-Dihydroxy)butyl]ferrocene **4a** and 1-[((3S)-cis-3,4-dihydroxy)butyl]ferrocene **4b***

4: Yellow crystals; retention time: 31.5 (*R*); 26.2 (*S*); HRMS: calculated for $C_{14}H_{18}FeO_2$: 274.06558; found: 274.06558; ^1H-NMR (300 MHz, $CDCl_3$) δ 1.66 (m, 2H), 1.78 (br. s, 1H, D_2O changeable), 2.54–2.37 (m, 3H, 1H, D_2O changeable), 3.48 (m, 1H), 3.69 (m, 2H), 4.06–4.12 (m, 9H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 25.9 (t), 34.7 (t), 67.0 (t), 67.8 (d), 68.4 (d), 68.7 (d), 69.1 (d), 72.1 (d), 89.1 (s). **4a**: Mp: 77–82°C; $[\alpha]_D^{20}$=+0.85 (c=2.76, CH_2Cl_2). **4b**: Mp: 88–90°C; $[\alpha]_D^{20}$=−2.05 (c=0.25, CH_2Cl_2).

*4.5. 1-[((1S,2R)-cis-1,2-Dihydroxy)propyl]ferrocene **6a** and 1-[((1R,2S)-cis-1,2-dihydroxy)propyl]ferrocene **6b***

6: Yellow crystals; retention time: 34.8 (1*S*,2*R*); 21.5 (1*R*,2*S*); HRMS: calculated for $C_{13}H_{16}FeO_2$: 260.04993; found: 260.04993; ^1H-NMR (200 MHz, $CDCl_3$) δ 1.07 (d, *J*=6.3 Hz, 3H), 2.39 (br. s, 1H), 2.68 (br. s, 1H), 3.66 (dt, *J*=6.4 Hz, 2H), 4.06 (d, *J*=6.6 Hz, 1H), 4.18–4.25 (m, 9H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 18.8 (q), 64.9 (d), 68.1 (d), 68.3 (d), 68.6,(d), 68.8 (d), 71.9 (d), 74.6, (d), 89.8 (s). **6a**: Mp: 69–71°C; $[\alpha]_D^{20}$=+73.1 (c=0.14, CH_2Cl_2). **6b**: Mp: 50–52°C; $[\alpha]_D^{20}$=−68.1 (c=0.21, CH_2Cl_2).

*4.6. 1-[((1S,2*R*)-*cis*-1,2-Dihydroxy)butyl]ferrocene **8a** and 1-[((1*R*,2S)-*cis*-1,2-dihydroxy)butyl]ferrocene **8b***

8: Orange oil; retentions time: 45.8 (1*S*,2*R*); 27.1 (1*R*,2*S*); HRMS: calculated for $C_{14}H_{18}FeO_2$: 274.06558; found: 274.06558; ^{1}H-NMR δ 0.93 (t, *J*=7.4 Hz, 3H), 1.40 (m, 2H), 2.52 (br. d, *J*=2.9 Hz, 1H), 2.76 (br. s, 1H), 3.42 (m, 1H), 4.15–4.31 (m, 10H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 10.3 (q), 26.1 (t), 65.4 (d), 68.3 (d), 68.4 (d), 68.8 (d), 72.9 (d), 76.8 (d), 90.8 (s). **8a**: $[\alpha]_D^{20}$=+72.7 (c=1.50, CH_2Cl_2). **8b**: $[\alpha]_D^{20}$=−62.5 (c=0.54, CH_2Cl_2).

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References

1. A. Togni, T. Hayashi, Ferrocenes, VCH Verlagsgesellschaft mbH. Weinheim, Germany, 1995.
2. For reviews see: (a) T. Hayashi, M. Kumada; *Acc. Chem. Res.*; **1982**, *15*, 395–401. (b) T. Hayashi; *Pure Appl. Chem.*; **1988**, *60*, 7–12.
3. L. Schwink, S. Vettel, P. Knochel; *Organometallics*; **1995**, *14*, 5000–5001.
4. For reviews see: (a) K. Soai, S. Niwa; *Chem. Rev.*; **1992**, *92*, 833–856. (b) R. Noyori, M. Kitamura; *Angew. Chem. Int. Ed. Engl.*; **1991**, *30*, 49–70.
5. For a review see: A. D. Ryabov; *Angew. Chem. Int. Ed. Engl.*; **1991**, *30*, 931–941.
6. H. Becker, M. A. Soler, K. B. Sharpless; *Tetrahedron*; **1995**, *51*, 1345–1376
7. First results were presented on the "9th IUPAC Symposium on Organometallic Chemistry (OMCOS 9)", 20–25 July 1997; in Göttingen, Germany.
8. H. Becker, K. B. Sharpless; *Angew. Chem. Int. Ed. Engl.*; **1996**, *35*, 448–450.
9. Preparation of diol is reported in the racemic form: S. I. Goldberg, W. D. Loeble; *J. Org. Chem.*; **1968**, *33*, 2971–2973.
10. H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless; *Chem. Rev.*; **1994**, *94*, 2483–2547.
11. K. P. M. Vanhessche, K. B. Sharpless; *J. Org. Chem.*; **1996**, *61*, 7978–7979.