

PII: S0957-4166(97)00097-9

Synthesis of chiral bis(oxazolinyl)biferrocene ligands and their application to Cu(I)-catalyzed asymmetric cyclopropanation

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Abstract: Homochiral bis(oxazolinyl)biferrocene ligands, which have both planar and central chirality, are synthesized from oxazolinylferrocenes through a diastereoselective directed lithiation followed by an oxidative dimerization. Asymmetric cyclopropanation of styrene with diazoacetates in the presence of 5 mol% CuOTf-bis(oxazolinyl)biferrocene complexes gives 2-(phenyl)cyclopropane carboxylates in up to 99% ee. © 1997 Elsevier Science Ltd

The malonic acid-derived chiral bis(oxazoline) compounds have been successfully used as N,Nchelates in several important transition metal catalyzed reactions. For example, highly enantioselective catalytic reactions such as cyclopropanation¹ and aziridination² of olefins, the Diels-Alder reaction,³ and the asymmetric allylic substitution reaction⁴ have been developed employing bis(oxazoline) 1-metal (Cu, Mg, Fe, Pd, etc.) complexes. The effectiveness of the bis(oxazoline) ligands in the metal catalyzed reactions has led to the development of other structural analogs.⁵ Among them, the bis(oxazoline) ligand of the copper catalyst 2 developed by Corey and co-workers^{5a} is notable since it provides a wider bite angle for the metal chelation than the malonic acid-derived ones. In an intramolecular cyclopropanation reaction, the copper catalyst 2 afforded a pronounced enantioselectivity compared to the Cu(I)-1 complexes. Encouraged by the result, we embarked on the development of new bis(oxazoline) ligands endowed with a wide bite angle for the metal chelation as depicted in 3. Here we wish to report an efficient synthesis of new homochiral bis(oxazolinyl)biferrocene ligands, and their application as N,N-chelates in the copper catalyzed cyclopropanation of styrene with diazoacetates.



The synthesis of bis(oxazoline) **5a** was started from oxazolinylferrocene **4a**. Diastereoselective lithiation of **4a**⁶ followed by in situ conversion to the corresponding ferrocenylcopper intermediate and subsequent oxidative dimerization under an oxygen atmosphere readily gave only (S,S,pS,pS)-**5a** in 52% yield. The bis(oxazoline) **5b** was similarly synthesized from **4b** in 59% yield. The silylated bis(oxazolines) **6** were synthesized from the dimerized product **5b**: lithiation of **5b** followed by quenching with trialkylsilylchloride led to **6a** (58%) and **6b** (46%), respectively (Scheme 1). It was difficult to determine the substitution site of the silyl groups (via ortho- vs possible remote lithiation)

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by spectroscopic methods. Also, it was not possible to get single crystal of the silvlated compounds suitable for X-ray crystallography. Therefore, we synthesized **6c** from **5b** by the same sequence in 59% yield using benzophenone instead of trialkylsilvlchloride. The compound **6c** readily crystallized. By analogy with the X-ray crystal structure of **6c**,⁷ it was assumed that ortho lithiation directed by the oxazoline group also occurred in the syntheses of **6a** and **6b**. Both bis(oxazolinyl)biferrocene **5** and **6** have planar chirality as well as carbon-centered chirality.⁸





The utility of bis(oxazolines) 5 and 6 as chiral ligands was studied in the copper catalyzed cyclopropanation of styrene with diazoacetates.⁹ Initial experiments indicated that the cyclopropanation at 25°C gave higher enantioselectivity than the reaction at higher temperature (55°C). A temperature variable ¹H NMR study for the copper catalyst generated by mixing CuOTf $0.5C_6H_6$ and the bis(oxazoline) ligand in CDCl₃ at the temperature range from 20 to 60°C did not show any change. It was of interest that when an equimolar mixture of CuOTf-bis(oxazoline) 5 (or 6) was stirred at 55°C for 2 h before the addition of substrates, the overall yields were increased (10-20%) relative to the case without warming the catalyst, even though the actual cyclopropanation reaction was carried out at 25°C. In this case, there was no appreciable change in the selectivities. The ratio of trans-7 and cis-7 was determined by ¹H NMR analysis, and their ees were determined by HPLC or GC analysis using chiral stationary phase columns. Representative results are summarized in Table 1. Comparing ligands 5a and 5b in the cyclopropanation, the catalytic reaction with 5a was much slower and less enantioselective than the reaction with 5b (entry 1 vs 2). The trans/cis selectivity as well as their enantioselectivity were dependent on the ester group of the diazoacetate used, as already demonstrated by others.¹ When *l*-menthyl diazoacetate was used, 73% ee for trans-7 and 84% ee for cis-7 (trans/cis=81:19) was observed in the cyclopropanation reaction with ligand 5b. It is of interest that ligands 6a and **6b** with silvl groups that are remote from the metal chelating site produce better enantioselective catalytic systems in comparison with 5b. The catalytic reaction of *l*-menthyl diazoacetate using ligand 6a gave trans-7 and cis-7 with 90% and 99% ee, respectively; however, a lower enantioselectivity was observed in the cyclopropanation with ligand 6b that has the sterically more demanding triethylsilyl group. The introduction of the silvl substituents adjacent to the oxazoline rings may restrict their free rotation, hence less flexible bis(oxazoline)-copper complexes form in comparison with those without the silvl groups. This conformational stability and possible additional steric congestion by the interaction of the silvl with the oxazoline groups may cause the increase in the enantioselection. The trans/cis selectivity and enantioselectivity observed with our bis(oxazoline)-CuOTf complexes show a similar trend as those observed with the 2,2'-bis(oxazolyl)-1,1'-binaphthyls-CuOTf complexes of Hayashi and co-workers¹⁰ that would have a similarly wide bite angle as 2.

In summary, we have synthesized new ferrocene-based bis(oxazoline) compounds which are shown to be potentially useful chiral ligands in the asymmetric cyclopropanation. A study on the scope and limitation of the catalysts in the cyclopropanation reaction and application of the ligands in other catalytic asymmetric reactions are undergoing.

$PH + N_2CHCO_2R + \frac{CuOTf-5 \text{ or } 6}{1,2-\text{dichloroethane}} + H + H + CO_2R + H + CO_2R + H + CO_2R + CO_2$						
Entry	Ligand	Diazoacetate R =	Yield ^b	trans:cis d	%ee ^e	
			(%) of 7		trans	cis
1	5a	Ethyi	47 ^c	66:34	1.7 ^t	27
2	5b	Ethyl	49	67:33	40	73
3	5b	tert-Butyl	31	73:27	37	62
4	5b	d-Menthyl	56	87:13	59	49
5	5b	/-Menthyl	63	81:19	73	84
6	6a	Ethyl	58	66:34	70	83
7	6a	tert-Butyl	36	74:26	73	90
8	6a	d-Menthyl	63	88:12	87	86
9	6a	/-Menthyl	64	77:23	90	99
10	6b	Ethyl	52	61:39	62	74

Table 1. Asymmetric cyclopropanation of styrene with diazoacetates catalyzed by copper(I)-bis(oxazolinyl)biferrocenes^a

^a The reaction was carried out in the presence of 5 mol% of the copper (I) catalyst that was preheated at 55 °C for 2 h. ^b Isolated yield of a mixture of trans-7 and cis-7. ^c The reaction was carried out at 45 *C. ^d The ratio of trans-7/cis-7 was determined by ¹H NMR anaylsis. ^e Determined by HPLC [Chiralcel® OJ column for 7 (R = Et)] and GC [Chiraldex G-TA for cis-7 (R = t-Bu), HP-1 column for 7 (R = d- and +menthyl)] analysis: In the case of the trans-7 (R = t-Bu), it was converted to the corresponding ethyl ester for the ee determination. ¹ (S,S)-Isomer was obtained in slight excess: In other cases, (1R,2R)trans-7 and (1R, 2S)-cis-7 were the major enantiomers, as depicted in the figure.

Acknowledgements

The author (K. H. Ahn) wishes to express sincere thanks to Professor E. J. Corey at the Department of Chemistry, Harvard University, for his generous support and guidance during the visiting research. The author also thanks M. Grogan and Dr F. Xu at the same department for their help and discussions. The financial support by the Korea Research Foundation for the visiting research is gratefully acknowledged. This work was partially supported by the Ministry of Education sponsoring the Basic Science Research Institute (BSRI-96-3437), Korea.

References

- 1. (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. Tetrahedron Lett. 1990, 31, 6005. (b) Lowenthal, R. E.; Masamune, S. Tetrahedron Lett. 1991, 32, 7373. (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. J. Am. Chem. Soc. 1991, 113, 726. (d) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. Helv. Chim. Acta 1991, 74, 232.
- 2. Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. J. Am. Chem. Soc. 1993, 115, 5328.
- 3. (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. J. Am. Chem. Soc. 1991, 113, 728. (b) Corey, E. J.; Ishihara, K. Tetrahedron Lett. 1992, 33, 6807.
- 4. Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. Tetrahedron 1992, 48, 2143.
- 5. (a) Gant, T. G.; Noe, M. C.; Corey, E. J. Tetrahedron Lett. 1995, 36, 8745. (b) Tokunoh, R.; Tomiyama, H.; Sodeoka, M.; Shibasaki, M. Tetrahedron Lett. 1996, 37, 2449. (c) Harm, A. M.;

Knight, J. G.; Stemp, G. Synlett 1996, 677. (d) Bedekar, A. V.; Andersson, P. G. Tetrahedron Lett. 1996, 37, 4073.

- 6. (a) Sammakia, T.; Latham, H. A.; Schaad, D. R. J. Org. Chem. 1995, 60, 10. (b) Ahn, K. H.; Cho, C.-W.; Baek, H.-H.; Park, J.; Lee, S. J. Org. Chem. 1996, 61, 4937 and references cited therein.
- 7. Unpublished results.
- 8. Physical and spectral data for the synthesized ligands: (S,S,pS,pS)-5a: mp 54–55°C; $[\alpha]_D^{26}$ –480.8 (c 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.78-4.81 (m, 4H), 4.39 (t, 2H, J=2.6 Hz), 4.28 (s, 10H), 4.14 (dd, 2H, J=8.9, 7.8 Hz), 3.70-3.85 (m, 4H), 1.62-1.68 (m, 2H), 1.00 (d, 6H, J=6.7 Hz), 0.86 (d, 6H, J=6.7 Hz); 13 C NMR (75 MHz, CDCl₃) δ 165.63, 85.23, 76.72, 73.07, 72.27, 70.92, 70.04, 68.33, 33.58, 19.91, 18.96; MS (FAB) m/z 593 (M+1); Anal. Calcd for C₃₂H₃₆Fe₂N₂O₂: C, 64.89; H, 6.13; N, 4.73. Found: C, 65.15; H, 6.17; N, 4.48. (*S*,*S*,*pS*)-5b: mp 216–217°C (dec); $[\alpha]_{D}^{26}$ – 1040.9 (c 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.79 (dd. 2H, J=2.5, 1.6 Hz), 4.74 (dd, 2H, J=2.2, 1.6 Hz), 4.38 (dd, 2H, J=2.5, 2.2 Hz), 4.36 (s, 10H), 4.01 (d, 4H, J=8.6 Hz), 3.73 (t, 2H, J=8.6 Hz), 0.88 (s, 18H); 13 C NMR (75 MHz, CDCl₃) δ 164.58, 84.80, 77.29, 76.72, 72.49, 70.57, 67.97, 67.60, 34.07, 26.42 (two Cp ring protons H-5 and H-6 overlapp); MS (FAB) m/z 621 (M+1); Anal. Calcd for C₃₄H₄₀Fe₂N₂O₂: C, 65.82; H, 6.50; N, 4.52. Found: C, 65.61; H, 6.34; N, 4.43. (S,S,pS,pS)-6a: oil; $[\alpha]_{p}^{27}$ -370.0 (c 1.30, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.84 (d, 2H, J=2.4 Hz), 4.30 (s, 10H), 4.22 (d, 2H, J=2.4 Hz), 4.04 (dd, 2H, J=9.3, 8.5 Hz), 3.79 (dd, 2H, J=8.9, 8.5 Hz), 3.66 (dd, 2H, J=9.3, 8.9 Hz), 0.77 (s, 18H), 0.27(s, 18H); ¹³C NMR (75 MHz, CDCl₃) δ 164.72, 89.58, 78.93, 76.80, 76.71, 74.03, 73.31, 70.59, 67.92, 33.54, 26.42, 0.80; MS (FAB) m/z 765 (M); Anal. Calcd for C₄₀H₅₆Fe₂N₂O₂Si₂: C, 62.82; H, 7.38; N, 3.66. Found: C, 62.68; H, 7.23; N, 3.53. (S,S_pS_pS) -**6b**: oil; $[\alpha]_D^{27}$ -350.4 (c 1.07, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.85 (d, 2H, J=2.37 Hz), 4.31 (s, 10H), 4.22 (d, 2H, J=2.37 Hz), 4.02 (dd, 2H, J=9.5, 8.5 Hz), 3.77 (dd, 2H, J=8.8, 8.5 Hz), 3.64 (dd, 2H, J=9.5, 8.8 Hz). 0.81–1.03 (m, 30H), 0.77 (s, 18H); ¹³C NMR (75 MHz, CDCl₃) δ 165.01, 89.29, 78.45, 77.23, 76.66, 74.65, 71.57, 70.67, 67.97, 33.63, 26.42, 8.45, 5.19; MS (FAB) m/z 849 (M); Anal. Calcd for C46H68Fe2N2O2Si2: C, 65.08; H, 8.07; N, 3.30. Found: C, 65.24; H, 7.89; N, 3.17.
- 9. For a review: Doyle, M. P. In Catalytic Asymmetric Synthesis; Ojima, I., Ed.; VCH: New York, 1993; p 63.
- 10. Uozumi, Y.; Kyota, H.; Kishi, E.; Kitayama, K.; Hayashi, T. Tetrahedron: Asymmetry 1996, 7, 1603.

(Received in Japan 5 February 1997)