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

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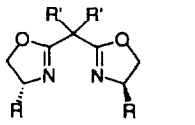
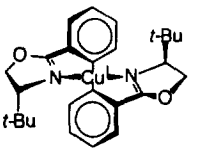
Abstract: Homochiral bis(oxazolinyl)biferrocene ligands, which have both planar and central chirality, are synthesized from oxazolinylferrocenes through a diastereoselective directed lithiation followed by an oxidative dimerization. Asymmetric cyclopropanation of styrene with diazoacetates in the presence 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,N*-chelates in several important transition metal catalyzed reactions. For example, highly enantioselective catalytic reactions such as cyclopropanation[1] and aziridination[2] of olefins, the Diels–Alder reaction,[3] and the asymmetric allylic substitution reaction[4] 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.

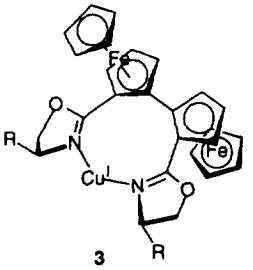


R = *i*-Pr, *t*-Bu, Ph, etc
R' = Me, H

1



2



3

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*$_p$*S*,$_p$*S*)-**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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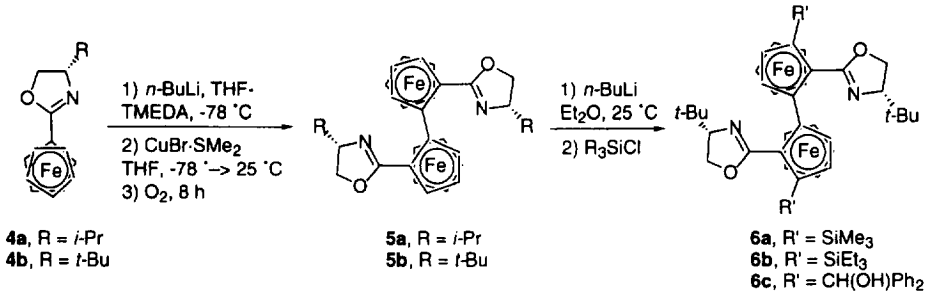
by spectroscopic methods. Also, it was not possible to get single crystal of the silylated compounds suitable for X-ray crystallography. Therefore, we synthesized **6c** from **5b** by the same sequence in 59% yield using benzophenone instead of trialkylsilylchloride. The compound **6c** readily crystallized. 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]



4a, R = *i*-Pr
4b, R = *t*-Bu

5a, R = *i*-Pr
5b, R = *t*-Bu

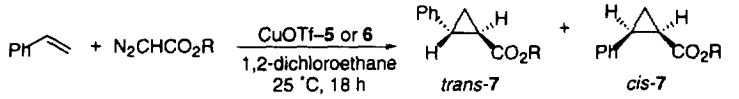
6a, R' = $SiMe_3$
6b, R' = $SiEt_3$
6c, R' = $CH(OH)Ph_2$

Scheme 1.

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 ^{1}H NMR study for the copper catalyst generated by mixing CuOTf·0.5C_6H_6 and the bis(oxazoline) ligand in $CDCl_3$ 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 ^{1}H 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 silyl 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 silyl 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 silyl groups. This conformational stability and possible additional steric congestion by the interaction of the silyl 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-workers[10] 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.

Table 1. Asymmetric cyclopropanation of styrene with diazoacetates catalyzed by copper(I)–bis(oxazolinyl)biferrocenes[a]



Entry	Ligand	Diazoacetate R =	Yield[b] (%) of **7**	*trans:cis*[d]	%ee[e] *trans*	%ee[e] *cis*
1	**5a**	Ethyl	47[c]	66:34	1.7[f]	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**	*l*-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**	*l*-Menthyl	64	77:23	90	99
10	**6b**	Ethyl	52	61:39	62	74

[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 ^{1}H 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 *l*-menthyl)] analysis: In the case of the *trans*-**7** (R = *t*-Bu), it was converted to the corresponding ethyl ester for the ee determination. [f] (*S,S*)-Isomer was obtained in slight excess: In other cases, (1*R*,2*R*)-*trans*-**7** and (1*R*, 2*S*)-*cis*-**7** were the major enantiomers, as depicted in the figure.

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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, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{32}H_{36}Fe_2N_2O_2$: C, 64.89; H, 6.13; N, 4.73. Found: C, 65.15; H, 6.17; N, 4.48. (*S*,*S*,*pS*,*pS*)-**5b**: mp 216–217°C (dec); $[\alpha]_D^{26}$ −1040.9 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{34}H_{40}Fe_2N_2O_2$: 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; $[\alpha]_D^{27}$ −370.0 (*c* 1.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{40}H_{56}Fe_2N_2O_2Si_2$: 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, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{46}H_{68}Fe_2N_2O_2Si_2$: C, 65.08; H, 8.07; N, 3.30. Found: C, 65.24; H, 7.89; N, 3.17.
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