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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 385–388

The synthesis and application of novel C_2-symmetric chiral *N,N,O,O* bisoxazoline ligands with a ferrocene backbone

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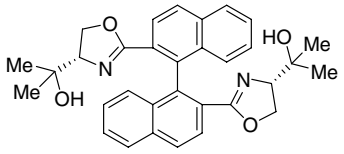
Received 1 September 2006; revised 12 November 2006; accepted 14 November 2006
Available online 4 December 2006

Abstract—Novel C_2-symmetric bisoxazoline ligands **5** with a ferrocene backbone and a hydroxyl group at the substituent of the oxazoline ring were designed and prepared. With these ligands, up to 94% ee was obtained for the alkylation of arylaldehyde with diethylzinc.

Chiral oxazoline ligands derived from readily available amino acids have found widespread use in metal-catalyzed asymmetric reactions.[1] The synthesis and application of novel bisoxazoline ligands with a chiral backbone such as 1,3-dioxolane,[2] ferrocene[1j,3] and biaryl[4] had received much attention in the past decades. C_2-symmetric bisoxazoline ligands **1** and **2** with an axis-fixed and -unfixed biaryl backbone, respectively, were developed previously and it was found that these kind of ligands afforded excellent enantioselectivity in the asymmetric alkylation of benzaldhyde with diethylzinc.[5] On the other hand, the other types of ligands **3** and **4** possessing both planar chirality and central chirality were prepared by selective lithiation of bisoxazoline ferrocene followed by the reaction with electrophilic attack.[6] Both ligands **3** and **4** showed that the ferrocene backbone had great effect on the enantioselectivity and catalytic activity. So it is expected that some interesting and effective asymmetric inductions may be found by the combination of ferrocene backbone and the easily introduced hydroxyl group in the substituent of the oxazoline ring. Here, we wish to report the preparation of the novel C_2-symmetric bisoxazoline ligands **5** with a ferrocene backbone bearing a hydroxyl group in the substituent of the oxazoline ring, and their application in the asymmetric alkylation of arylaldehyde with diethylzinc.



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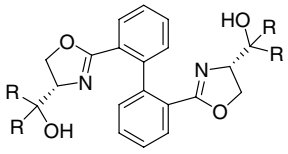

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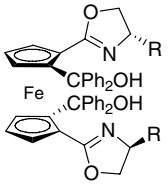
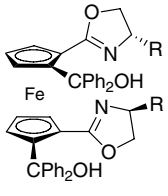
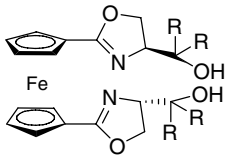


3 (**a**: R=*i*-Pr, **b**: R=*t*-Bu)



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



5 (**a**: R=H, **b**: R=Me, **c**: R=Et, **d**: R=Ph)

Ligand **5** was synthesized easily from 1,1′-ferrocenedicarboxylic acid dichloride and L-serine methyl ester hydrochloride through the intermediates **6** and **7** as shown in Scheme 1. Thus, in the presence of triethylamine, 1,1′-ferrocenedicarboxylic acid dichloride reacted with L-serine methyl ester hydrochloride to give amide compound **6** with a yield of 92%. Then, the hydroxyl group of **6** was activated by Burgess Reagent [(methoxycarbonylsulamoyl)-triethylammonium hydroxide inner

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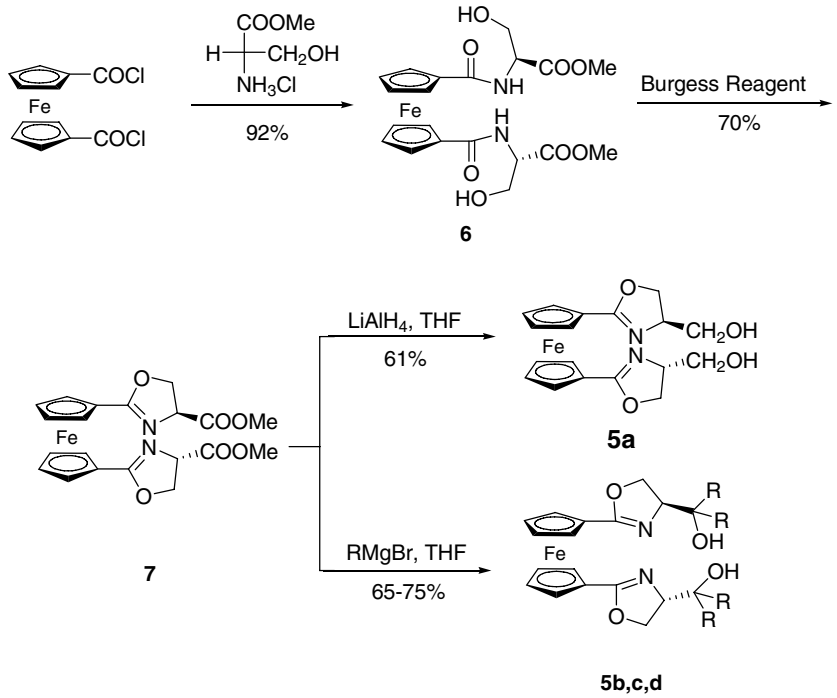
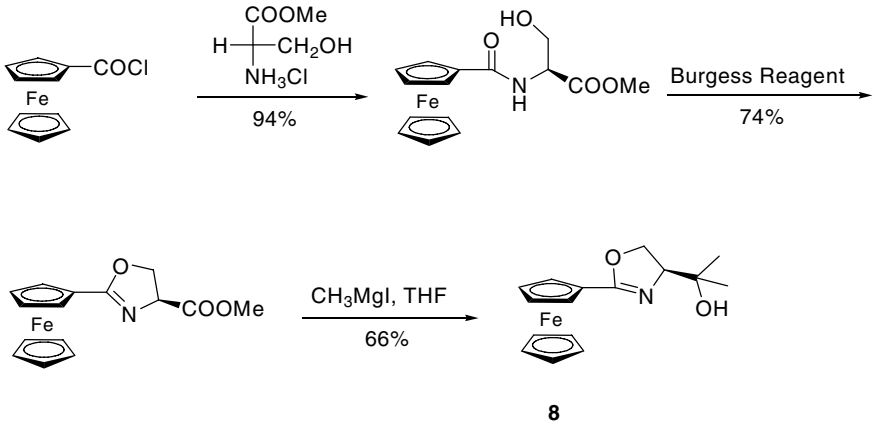
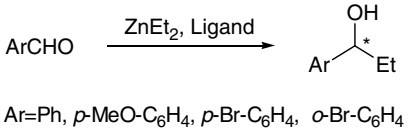
doi:10.1016/j.tetlet.2006.11.088



Scheme 1.



Scheme 2.



Scheme 3.

salt] and the formation of oxazoline ring was carried out to afford bisoxazoline compound **7** in 70%.[5,7] Finally, reduction of **7** with $LiAlH_4$ at room temperature for 6 h afforded the desired ligand **5a** bearing a hydroxyl group in the yield of 61%.[8] While treating **7** with Grignard reagent in THF at 0 °C afforded other analogous ligands **5b–d** in the yields of 65–75%.[9]

The C_1-symmetric monooxazoline ligand **8**[10] was also synthesized in the same way with the overall yield of 46% in three steps (Scheme 2).

With the present new kinds of bisoxazoline ligands in hand, we investigated their performance in zinc(II)—catalyzed asymmetric alkylation of arylaldehyde with diethylzinc (Scheme 3, Tables 1–3). The alkylation of benzaldehyde with diethylzinc using ligand **5b** was first examined.[5]

The effect of solvent on the catalytic reaction with **5b** as a ligand (Table 1, entries 1–3) was examined at first. It was shown that when the solvent was toluene, it gave the best result of 87% ee. When using THF and dichloromethane instead of toluene, the value of enantiomeric excess decreased to 81% and 79%, respectively. The effect of the temperature to the reaction was also investigated (entries 4–5). It was observed that lower temperatures gave higher enantioselectivity. At room temperature, the ee value was only 74%. While the temperature was reduced to −25 °C, the enantioselectivity

Table 1. Zn(II)-catalyzed asymmetric alkylation of benzaldehyde with diethylzinc[a]

Entry	Ligand	Solvent	Conditions (°C/h)	Yield[b] (%)	% ee[c] (config)[d]
1	**5b**	Toluene	0/48	93	87 (*R*)
2	**5b**	THF	0/48	77	81 (*R*)
3	**5b**	DCM	0/48	86	79 (*R*)
4	**5b**	Toluene	rt/24	92	74 (*R*)
5	**5b**	Toluene	−25/144	40	94 (*R*)

[a] The reactions were carried out with 2.2 equiv of $ZnEt_2$ and 10 mol % of ligand.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD–H column.
[d] Determined by comparing the sign of its optical rotation with the literature data.

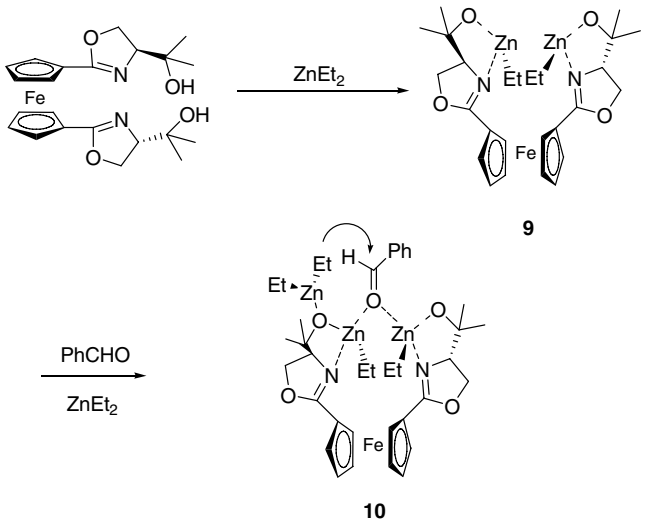
Table 2. Zn(II)-catalyzed asymmetric alkylation of benzaldehyde with diethylzinc using different ligands[a]

Entry	Ligand	Conditions (°C/h)	Yield[b] (%)	% ee[c] (config)[d]
1	**5a**	0/48	92	79 (*R*)
2	**5b**	0/48	93	87 (*R*)
3	**5c**	0/48	86	45 (*R*)
4	**5d**	0/48	86	41 (*R*)
5	**8**	0/48	89	20 (*R*)
6[e]	**3a**	0/24	25	70 (*R*)
7[e]	**4a**	0/24	68	83 (*R*)
8[e]	**3b**	0/24	63	91 (*R*)
9[e]	**4b**	0/8	97	93 (*R*)

[a] The reaction was carried out with 2.2 equiv of $ZnEt_2$ and 10 mol % of ligand in toluene.
[b] Isolated yield.
[c] Determined by HPLC using OD–H column.
[d] Determined by comparing the sign of its optical rotation with the literature data.
[e] See Ref. 6.

was enhanced to 94% although the reaction proceeded very slowly and only 40% isolated yield of chiral alcohol was obtained even after 6 days.

Then the effect of the bulkiness of ligand was investigated. As shown in Table 2, the ligand **5b** with the methyl as substituted group showed high catalytic activity and enantioselectivity for asymmetric reaction (entry 2). When the bulkiness became much larger by changing methyl to ethyl and phenyl, the enantioselectivities were dramatically decreased to 45% and 41%, respectively (entries 3–4). Ligand **5a** with no substituted groups also showed good catalytic activity, although the enantioselectivity was a little lower than the ligand **5b**. It could



Scheme 4.

be concluded that the bulkiness of ligand has great effect on catalytic enantioselectivity. In sharp contrast, however, the reaction with the C_1-symmetric monooxazoline ligand **8** resulted in a low enantiomeric excess [20% ee (*R*)] (entry 5) under the identical conditions. Furthermore, we compared the enantioselectivity of ligands **3** and **4** possessing both planar chirality and central chirality with ligands **5**, which are easier to be prepared, and have much simple structures than **3** and **4**.[6] Ligand **5b** showed higher enantioselectivity than ligands **3a** and **4a** having *iso*-propyl groups and similar enantioselectivity with ligands **3b** and **4b** having *tert*-butyl groups in the oxazoline ring (entries 6–9).

The ligand **5b** was then used as the catalyst for the addition of diethylzinc to the other aromatic aldehydes (Scheme 3, Table 3). The reactions were performed using 10 mol % of the catalyst in toluene at 0 °C. With regard to the additions to the aldehydes, electronic effects of the aromatic ring substituents did not seem to have great influence in this case. Bearing a strong electron donating substituted group such as methoxyl in the *para*-position of the benzene ring, it afforded a better enantioselectivity (92% ee, entry 2), although the reaction rate was a little lower. When the substituent group on the benzene ring was changed to electron withdrawing group such as bromo, the value of enantiomeric excess was decreased to 83%. On the other hand, it was shown that the steric hindrance played an important role in determining the degree of the enantioselectivity of the reaction: *ortho*-

Table 3. Zn(II)-catalyzed asymmetric alkylation of several kinds of arylaldehydes with diethylzinc[a]

Entry	Ligand	Aldehyde	Conditions (°C/h)	Yield[b] (%)	% ee (config)[c]
1	**5b**	C_6H_5CHO	0/48	93	87 (*R*)
2	**5b**	*p*-MeO–C_6H_4CHO	0/96	92	92[d] (*R*)
3	**5b**	*p*-Br–C_6H_4CHO	0/48	95	83[e] (*R*)
4	**5b**	*o*-Br–C_6H_4CHO	0/48	93	66[d] (*R*)

[a] The reaction was carried out with 2.2 equiv of $ZnEt_2$ and 10 mol % of ligand in toluene.
[b] Isolated yield.
[c] Determined by comparing the sign of its optical rotation with literature data.
[d] Determined by HPLC using chiral AD–H column.
[e] Determined by HPLC using chiral OJ–H column.

substituted benzaldehyde gave lower enantiomeric excess than their *para*-substituted analogues (entries 3–4).

By comparing the results from C_2-symmetric bisoxazoline ligand **5b** and the C_1-symmetric one **8**, we could suggest that the reaction catalyzed by *N*,*N*,*O*,*O* ligand **5b** may proceed in a catalytic mechanism totally different from that of the *N*,*O* ligand **8**. Similar to the binuclear aluminum catalytic mechanism[11] and binuclear zinc catalytic mechanism[5,12] reported before, a plausible mechanism was presented as shown in Scheme 4. A binuclear zinc intermediate **9** might be formed, followed by the coordination with arylaldehyde and additional diethylzinc to form complex **10**. Then, the coordinated diethylzinc attacked the carbonyl group stereoselectively to afford the corresponding chiral alcohol from the back of benzaldehyde for less steric hindrance. It was interesting to observe that the C_2-symmetric bisoxazoline ligands **5c**,**d** with bulkier substituent groups gained much lower enantiomeric excess than ligands **5a**,**b** with smaller substituent groups, which might be caused by the unmatching of the catalyst and substrate.

In summary, a series of novel bioxazoline ligands with a ferrocene backbone were synthesized, and their ability to catalyze the asymmetric alkylation of arylaldehyde with diethylzinc was also studied. The *N*,*N*,*O*,*O* ligand **5b** with the methyl as substituent groups showed the best catalytic activity and enantioselectivity. A possible binuclear zinc catalytic mechanism was proposed finally.

Acknowledgements

This work was partly supported by the Excellent Young Teachers Program of MOE, PR China and the National Natural Science Foundation of China (No. 20572070).

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8. Data for **5a**: mp 188 °C (decomposed). $[\alpha]_D^{25}$ +161.8 (*c* 0.5 MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (d, 2H, $J = 12.4$ Hz), 4.14 (d, 2H, $J = 12.4$ Hz), 4.20–4.25 (m, 2H), 4.26 (br s, 2H), 4.41 (dd, 2H, $J =$ 8.0, 11.2 Hz), 4.54 (t, 2H, $J = 8.0$ Hz), 4.59 (br s, 2H), 4.69 (br s, 2H), 4.82 (br s, 2H). HRMS: (MALDI) Calcd for $C_{18}H_{20}FeN_2O_4$ $[M+H]^+$: 385.0845. Found: 385.0864.
9. Data for **5b**: mp 83–85 °C. $[\alpha]_D^{25}$ +15.8 (*c* 0.075 MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 6H), 1.38 (s, 6H), 4.10 (t, 2H, $J = 9.6$ Hz), 4.28 (t, 2H, $J = 8.0$ Hz), 4.37 (br s, 2H), 4.39 (br s, 2H), 4.44 (br s, 2H), 4.70 (br s, 4H). HRMS: (MALDI) Calcd for $C_{22}H_{28}FeN_2O_4$ $[M+H]^+$: 441.1471. Found: 441.1486. Data for **5c**: mp 104–105 °C. $[\alpha]_D^{25}$ −101.5 (*c* 0.36 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 6H, $J = 7.6$ Hz), 0.97 (t, 6H, $J = 7.6$ Hz), 1.35 (q, 4H, $J = 7.2$ Hz), 1.54 (q, 4H, $J = 7.2$ Hz), 4.22 (dd, 2H, $J = 8.4$, 10.8 Hz), 4.32 (d, 2H, $J = 0.8$ Hz), 4.34 (d, 2H, $J = 0.8$ Hz), 4.35 (br s, 2H), 4.44 (br s, 2H), 4.65 (br s, 2H), 4.70 (br s, 2H). HRMS: (MALDI) Calcd for $C_{26}H_{36}FeN_2O_4$ $[M+H]^+$: 497.2097. Found: 497.2098. Data for **5d**: mp 198–199 °C. $[\alpha]_D^{25}$ −395.3 (*c* 0.36 $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (t, 2H, $J = 8.4$ Hz), 3.87 (t, 2H, $J = 8.4$ Hz), 4.29 (br s, 2H), 4.54 (br s, 2H), 4.60 (br s, 2H), 4.71 (br s, 2H), 5.21 (t, 2H, $J = 8.4$ Hz), 7.04 (t, 2H, $J = 7.2$ Hz), 7.18 (t, 4H, $J = 7.6$ Hz), 7.22 (t, 2H, $J = 7.2$ Hz), 7.30 (t, 4H, $J = 7.6$ Hz), 7.37 (d, 4H, $J =$ 7.2 Hz), 7.59 (d, 4H, $J = 7.2$ Hz). HRMS: (MALDI) Calcd for $C_{42}H_{36}FeN_2O_4$ $[M+Na]^+$: 711.1917. Found: 711.1916.
10. Data for **8**: mp 85–87 °C. $[\alpha]_D^{25}$ +96.5 (*c* 1.05 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.34 (s, 3H), 4.10 (dd, 1H, $J = 8.0$, 10.0 Hz), 4.21 (s, 5H), 4.27 (t, 1H, $J = 8.0$ Hz), 4.34 (br s, 1H), 4.37 (br s, 2H), 4.33–4.39 (m, 1H), 4.77 (br s, 1H), 4.80 (br s, 1H). HRMS: (MALDI) Calcd for $C_{16}H_{19}FeNO_2$ $[M+H]^+$: 314.0838. Found: 314.0857.
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