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Asymmetric Induction of Chiral 1,1′-Bis(oxazolinyl)ferrocenes as Ligands in Metal-Catalyzed Cyclopropanation and Diels-Alder Reactions

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Abstract: Four chiral 1,1'-bis(oxazolinyl)ferrocenes(**1a-1d**) have been prepared and used as ligands in the copper catalyzed asymmetric cyclopropanation of styrene with ethyl diazoacetate (EDA) and the magnesium catalyzed Diels-Alder reaction between 3-acryloyl-2-oxazolidinone and cyclopentadiene. Enantioselectivities up to 24% and 41%, respectively, for cyclopropanation and Diels-Alder reaction were observed.

Keywords: Asymmetric induction, 1,1'-bis(oxazolinyl)ferrocene, ligand, cyclopropanation, Diels-Alder reaction.

Bis(oxazoline) ligands[1] have been successfully used in a variety of metal-catalyzed asymmetric reactions, such as cyclopropanation, allylic oxidation reactions, *etc*; Chiral ferrocene derivatives[2] have also been proved as effective ligands in numerous asymmetric reactions, for example, chiral ferrocenylphosphines exhibited high enantioselectivity for the reduction of olefins, Heck reactions and Aldol reactions of aldehydes. These results stimulated us to study the behaviour the bis(oxazoline) ligands incorporating ferrocenes. In this letter, the syntheses of four novel ferrocene-based chrial bisoxazolines **1a-1d** are reported and the application of these compounds as ligands in Lewis acid catalyzed asymmetric cyclopropanation and Diels-Alder reaction has been investigated.

The ligands were synthesized from 1,1'-bis(chlorocarbonyl)ferrocene (**2**) and (*S*)-β-amino alcohols according to Ikeda's procedure[3] (**Scheme 1**), and the new compounds were confirmed by ^{1}H and ^{13}C NMR, IR and elemental analysis[4].

In order to evaluate the chiral inducing ability of the prepared ligands **1a-1d**, the copper-catalyzed cyclopropanation of styrene with ethyl diazoacetate (EDA) was carried out (Scheme **2**). The enantiomeric excess (*ee*) of the *trans*-products was determined by capillary GC after conversion via the acid to *l*-(-)-menthyl ester[5], while the *ee* of the *cis*-isomers was determined through the corresponding methyl ester by GC with a chiral stationary phase column (2,6-di-O-pentyl-3-O-valeryl-β-cyclodextrin, 17 m×0.25 mm × 0.31 μm) [6].

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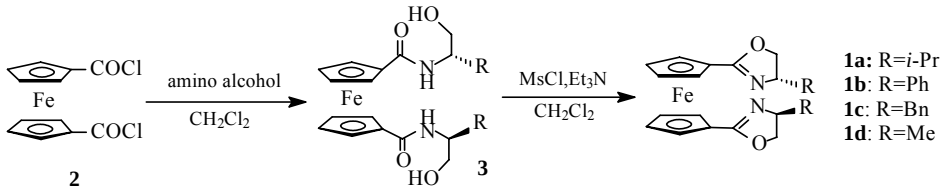
Scheme 1



Scheme 2

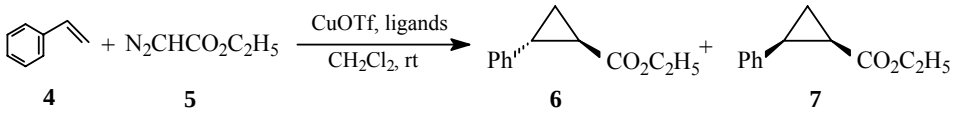


Table 1 Asymmetric cyclopropanation of styrene with ligands **1a**-**1d**[a]

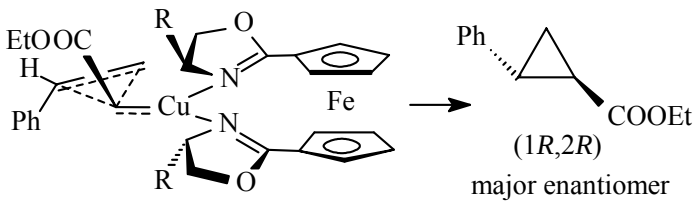
Ligand	Reaction time	Yield[b](%)	*trans:cis*[c]	%*ee* (configuration)[d]	
				trans	*cis*
1a	34 h	61	59:41	13(1*R*,2*R*)	24(1*R*,2*S*)
1b	18 h	78	68:32	5 (1*R*,2*R*)	3 (1*R*,2*S*)
1c	12 days	46[e]	57:43	8 (1*R*,2*R*)	9 (1*R*,1*S*)
1d	40 h	78	59:41	5 (1*R*,2*R*)	8 (1*R*,1*S*)

[a] All reactions were carried out in CH_2Cl_2 with 5 mol% ligand, 5 mol% $(CuOTf)_2C_6H_6$, and 5~8 equiv of styrene at rt. [b]Isolated yield based on EDA after purification by flash chromatography. [c]Determined by CGC with a SE-30 column. [d]Correlated to Pfaltz's results in ref 3. [e]The reaction was not completed yet.

The results summarized in **Table 1** showed that all the ligands had some extent of asymmetric induction. The relatively highest enantioselectivity was observed with ligand **1a**, which gave 24% *ee* for the *cis*-product **6**, but the other three ligands had only weak asymmetric induction.

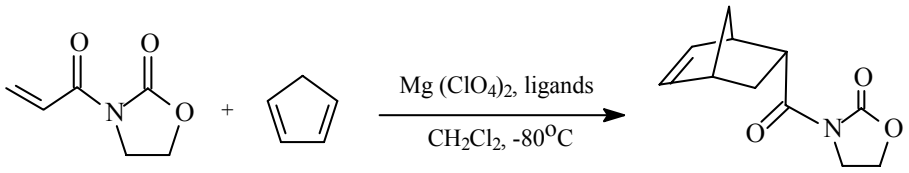
The observed enantioselectivity can be interpreted using a copper carbenoid structure as outlined in **Figure 1**. The attack of the carbenoid center from its *Re* face is more favourable due to lesser repulsive interaction built-up between the alkyl and carboxylic ester. If *Si* face of styrene approaches this favourable side of carbenoid center , the major product is *trans*-(1*R*,2*R*)enantiomer. Analogous approach of this type has been proposed by Singh[7].

Figure 1



The enantioselectivity of the four ligands 1a-1d has also been tested in the typical Diels-Alder reaction between cyclopentadiene and N-acryloyl-1,3-oxazolidinine-2- one[8] (Sheme 3). The catalysts were prepared *in situ* from 1a-1d and magnesium perchlorate.The *endo:exo* ratio was determined by ^{1}H NMR, and the enantioselectivity of the *endo* adduct was determined by HPLC with a chiral Daicel OD-H column.

Scheme 3



8 **9** **10** (2*R* -endo)

From the data in **table 2**, it is evident that all the four ligands exhibited some extent of asymmetric induction to Diels-Alder reaction. The ligand **1a** was found to be the most efficient one among the four ligands which gave the cycloadducts with high *endo:exo* selectivity (92:8) and 41% *ee* (2*R*) for the *endo* isomer(Entry **1**). While other three ligands **1b**, **1c** and **1d** exhibited low degree enantioselectivity(Entries **2**-**4**).

Table 2 Diels-Alder reaction between **8** and cyclopentadiene with ligands **1a**-1d [a]

Entry	Ligand	Conversion [b]	*endo:exo* [b]	*ee* (%) (configuration) [c]
1	**1a**	94%	92:8	41 (2*R*-endo)
2	**1b**	100%	77:23	8 (2*S*-endo)
3	**1c**	98%	84:16	3 (2*R*-endo)
4	**1d**	98%	85:15	1 (2*R*-endo)

[a]All reactions were run in CH_2Cl_2 with 11 %mol ligand and 10 %mol metal at -80℃ for 24~48 hr. [b]Determined by ^{1}H NMR. [c]Determined by chrial HPLC with 10% *i*-PrOH in hexane as elution at 210 nm. [c]Correlated to the literature 7 according to the HPLC peaks orders.

The mechanism of the asymmetric induction could be explained using a reactive species: a tetrahedral bis(oxazoline)-Mg(II)-dienophile complex proposed by Corey[9] for Mg(II)-catalyzed Diels-Alder reaction. Of particular interest, the ligand **1b** having phenyl substituent on the oxzolinyl rings showed the opposite sense of asymmetric induction compared to other three ligands, the main enantiomer obtained was (*S*)-*endo*-**10** (Entry **2**). This special result had also been observed and studied theoretically by Evans[10] and Jorgensen[11].

References and Notes

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4. The constants of the prepared ligands **1a** and **1b** are identical to the literature 3, the constants of **1c** and **1d** are as follows.**1c**: reddish crystal, yield 65%. mp 97~99℃. $[\alpha]_D^{29}$ -59.9 (*c* 2.0, $CHCl_3$). IR(KBr, cm^{-1}): 3010, 2900, 1650, 1480, 1450, 1375, 1275, 1120, 1020, 965, 825, 700. ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.69 (dd, 2H, *J* = 9.2, 13.7 Hz, PhCH), 3.22 (dd, 2H, *J* = 4.6, 13.7 Hz, PhH), 4.05 (dd, 2H, *J* = 7.2, 8. 2 Hz, OCH), 4.24 (dd, 2H, *J* = 8.3, 17.4 Hz, OCH), 4.33 (m, 4H, FcH), 4.42 (m, 2H, NCH), 4.74 (m, 4H, FcH), 7.28 (m, 10H, PhH). ^{13}C NMR (300 MHz, δ ppm, $CDCl_3$): 165.5, 138.0, 129.2, 128.5, 126.5, 72.0, 71.9, 71.6, 71.4, 70.6, 70.5, 67.8, 41.7. Anal. calcd. for $C_{30}H_{28}FeN_2O_2$: C, 71.44; H, 5.60; N, 5.55; Found: C, 71.00;H, 5.67; N, 5.43. **1d**: brown crystal, yield 68%, mp. 79~80℃.$[\alpha]_D^{29}$ -39.9 (*c* 2.0, $CHCl_3$). IR (KBr,cm^{-1}): 3075, 2945, 2900, 1650, 1480, 1440, 1380, 1345, 1295, 1250, 1120, 1025, 960, 825, 730. ^1H NMR (300 MHz, δ ppm, $CDCl_3$): 1.33 (d, 6H, *J* = 6.6 Hz, CH_3), 3.87 (t, *J* = 7.8 Hz, 2H, OCH), 4.23 (m, 2H, NCH), 4.36 (br s, 4H, FcH), 4.45(dd, 2H, *J* = 7.9, 9.1 Hz, OCH), 4.76(t, 4H, FcH). ^{13}C NMR (300 MHz, δ ppm, $CDCl_3$): 164.8, 73.7, 71.9, 71.8, 71.7, 70.6, 70.5, 61.9, 21.4. Anal. calcd. for $C_{18}H_{20}FeN_2O_2$: C, 61.38; H, 5.72; N, 7.84; Found: C, 61.23; H, 5.49; N, 7.84.
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