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Synthesis of imine–amine type of chiral ligands and their application in the asymmetric cyclopropanation of olefins with diazoacetates

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Abstract—Novel chiral ligands **1**, which possess both imine and amine moieties, were prepared from readily available homochiral materials. Copper complexes of **1** were prepared in situ and used in the asymmetric cyclopropanation of olefins with alkyl diazoacetates to give cyclopropanecarboxylates, inducing e.e. values of up to 87%. The size of the chelate ring in the copper complexes influenced the enantioselectivity of the reaction. © 2001 Published by Elsevier Science Ltd.

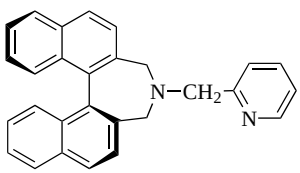
1. Introduction

Since the first example of copper-catalyzed enantioselective cyclopropanation reported by Nozaki et al. in 1966,[1] various optically active copper complexes have been synthesized and used as catalysts for the asymmetric cyclopropanation of olefins with diazo esters. The highly enantioselective copper catalysts included Cu–Schiff base,[2] Cu–semicorrin,[3] Cu–bisoxazoline,[4] Cu–bipyridine,[5] Co–bis(dioxime),[6] Cu–binaphthyldiimine[7] and Cu–pinene-[5,6]-bipyridine[8] complexes. However, the chiral ligands in these copper catalysts are limited to either imine alcohols or bisimine type functionalities. These ligands are soft bases and their complexes with highly reduced transition metals are stabilized mainly by back-bonding of metal electrons to the ligand. Kanemasa et al. have demonstrated that C_2-symmetric secondary 1,2-diamines, which are strongly basic ligands, also show excellent asymmetric induction in the cyclopropanation reactions.[9] In the course of our studies on the design of new *N*-containing chiral ligands, we became interested in chiral bis-nitrogen ligands which possess both imine and amine moieties. Herein, we wish to report the synthesis of new ligands **1** bearing *N*-heterocycles and a chiral azepine moiety as the first example of imine–amine type of chiral ligands and their application in the copper-catalyzed asymmetric cyclopropanation reaction.

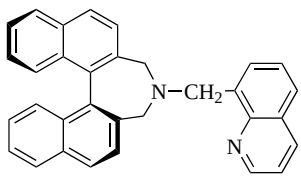
2. Results and discussion

2.1. Ligand syntheses

To synthesize the desired chiral imine–amine type ligands **1**, we have developed two practical synthetic routes outlined in Scheme 1. In one approach (route A), ligands **1a** and **1b** were directly obtained by treatment of (*S*)-2,2′-dibromomethyl-1,1′-binaphthyl **2**[10] with 2-aminomethylpyridine and 8-aminomethylquinoline in one step with high yield (95% for **1a** and 90% for 1**b**). In an alternative route (route B), ligands **1a** and **1b** were prepared by alkylation of (*S*)-3,5-dihydro-4*H*-dinaphth[2,1-c:1′,2′-e]azepine **3**[11] with 2-bromomethylpyridine and 8-bromomethylquinoline. The yields are also very high (97% for **1a** and 91% for **1b**).



1a



1b

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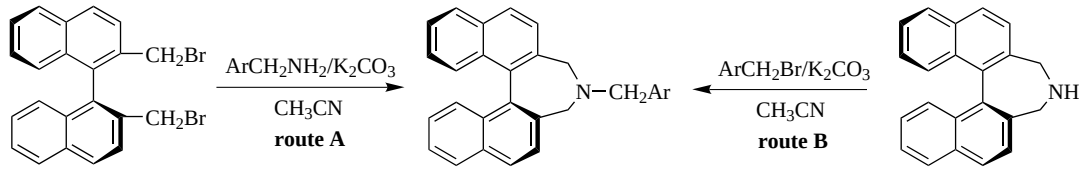


2 **1a** Ar = 2-pyridinyl **1b** Ar = 8-quinolinyl **3**

Scheme 1.

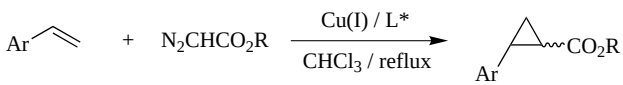
2.2. Enantioselective cyclopropanation

The asymmetric cyclopropanation reaction was carried out by slow addition of diazoacetate to a refluxing solution of olefins in chloroform containing copper catalyst prepared in situ from $[Cu(OTf)\cdot(C_6H_6)_{0.5}]$ and the ligand **1**. No reaction occurred in refluxing dichloromethane. The examination of catalyst loading showed that 1.0 mol% of catalyst was necessary to complete the reaction, and no differences in the diastereoselectivity and the enantioselectivity have been found when up to 4.0 mol% of catalyst was used. The results are summarized in Table 1.

Variation in the structure of the diazoacetate has a great influence on the diastereoselectivity and enantioselectivity. For example, when the R group in the diazoacetate is changed from ethyl to the bulkier dicyclohexylmethyl or L-menthyl in the cyclopropanation of styrene (entries 1–6) both *trans*/*cis* ratios and enantioselectivities increased significantly. The best result was observed with L-menthyl diazoacetate, where 87% e.e. for the *trans*- and 83% e.e. for the *cis*-isomer (*trans*/*cis* = 82:18) were obtained. This is consistent with the trend previously reported in the asymmetric cyclopropanation with other copper-catalysts.[12] The decrease in e.e. for the product obtained on reaction with D-menthyl diazoacetate in entries 7 and 8 may be explained by a mismatching of the stereotopic interaction between ligand and the ester group in the carbenoid intermediate. The cyclopropanation of different olefins was also examined. Substituted styrenes, especially those bearing an electron-withdrawing substituent, showed lower enantioselectivity than styrene itself (entries 9–14 versus 5 and 6).

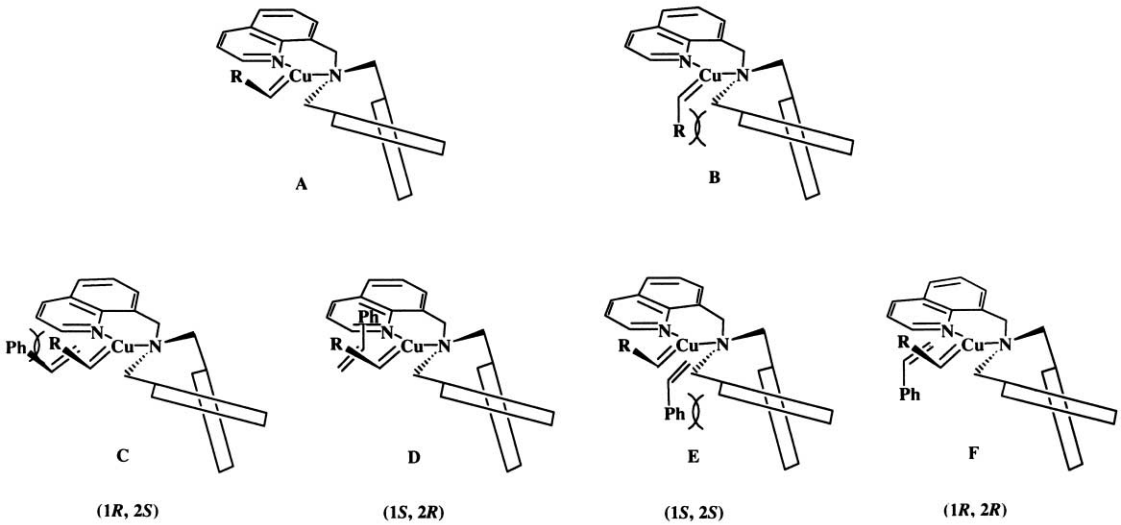
To explain the sense of asymmetric induction of our new ligands, a working model has been proposed as shown in Scheme 2. It is known that the copper–ligand complex first reacts with alkyl diazoacetate to form a metal–carbene complex, which then is attacked by the olefin to give the cyclopropane product. The steric interactions between the substituents of the ligand and the ester group in the carbenoid intermediate determine the direction of the approach of the olefin and thus control the stereochemistry of the product.[13] The com-

Table 1. Enantioselective cyclopropanation of olefins with diazoacetates



Entry	Ligand	Ar	R	Yield (%)[a]	*cis*/*trans*[b]	% e.e. (*cis*)[c]	% e.e. (*trans*)[c]
1	**1a**	Ph	Et	61	37:63	36	40
2	**1b**	Ph	Et	60	28:72	43	45
3	**1a**	Ph	DCM[d]	61	18:82	71	63
4	**1b**	Ph	DCM	54	16:84	80	83
5	**1a**	Ph	L-Menthyl	56	23:77	77	74
6	**1b**	Ph	L-Menthyl	60	18:82	83	87
7	**1a**	Ph	D-Menthyl	61	23:77	39	46
8	**1b**	Ph	D-Menthyl	64	19:81	47	51
9	**1a**	4-MePh	L-Menthyl	60	22:78	65	66
10	**1b**	4-MePh	L-Menthyl	62	29:71	77	72
11	**1a**	4-MeOPh	L-Menthyl	54	29:71	73	64
12	**1b**	4-MeOPh	L-Menthyl	55	28:72	75	65
13	**1a**	4-ClPh	L-Menthyl	36	31:69	42	46
14	**1b**	4-ClPh	L-Menthyl	39	28:72	64	49

[a] Isolated yield.
[b] Measured by GC with a capillary column (HP-1, 30 m×0.32 mm ID).
[c] Determined by GC analysis using capillary columns HP-1 (30 m×0.32 mm ID) and CP-SIL 24CB (30 m×0.25 mm ID) (for entries 1–4, after re-esterification with (−)-menthol). The absolute configurations, (1*S*,2*R*) for the *cis*-isomers and (1*R*,2*R*) for the *trans*-isomers were determined by chiroptical comparison with the published values.[12c]
[d] Dicyclohexylmethyl diazoacetate.



Scheme 2.

parison of steric repulsion between the ligand and the ester group connected to the carbenoid center showed that the intermediate **A** is more stable than intermediate **B**. For simplicity, we will only consider the intermediate **A** in the following discussion. There are four possible approaches for the styrene to the reaction center of **A**, two (**C** and **D**) lead to *cis*-products, and another two (**E** and **F**) provide *trans*-products. Although the *trans*/*cis* ratio of the product appears to be determined exclusively by the nature of the olefin and the diazoacetate, the enantioselectivity is dependent on the interactions of the ester group of the carbenoid, the ligand and the olefin. In the case of the formation of *cis*-cyclopropane, approach **D** is considered to suffer from less steric repulsion as compared with approach **C**, leading to a *cis* product with (1*S*,2*R*)-configuration. Similarly, the approach **F** suffers from less steric hindrance than approach **E**, providing the *trans* product with (1*R*,2*R*)-configuration. The absolute configuration of both *cis*- and *trans*-isomers of cyclopropanation products obtained from the experiments agrees with the above discussion.

It is noteworthy that the reactions with **1a** were invariably less enantioselective than the corresponding reactions with **1b**. Ligands **1a** and **1b** have similar electronic properties, but the copper complexes formed in the reaction have different chelate ring size. The ligand **1a**, upon coordination, forms a five-membered chelate ring, while ligand **1b** forms a six-membered ring. Because of the consequent increase in the bite angle, the substituents of ligand **1b** will be closer to the metal center and the ester group in the intermediate, resulting in a more efficient interaction. Thus, the reaction with **1b** showed relatively high enantioselectivity. A similar trend in the effect of chelate ring size on the enantioselectivity has also been observed in the asymmetric cyclopropanations with pyridinyl–oxazoline and quinolinyl–oxazoline ligands.[14]

3. Conclusion

In summary, two new chiral imine–amine type ligands have been successfully synthesized and were used as chiral ligands in the copper-catalyzed asymmetric cyclopropanation. Moderate to good enantioselectivities and diastereoselectivities have been provided. The scope and limitations of this type of ligand system in asymmetric cyclopropanation and their applications in other metal-catalyzed asymmetric reactions are now under investigation in our laboratory.

4. Experimental

4.1. General

Melting points were measured with a Yanaco MP-500 apparatus and uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-P200 instrument using tetramethylsilane as an internal standard in deuterochloroform. IR spectra were obtained as KBr plates on a Shimadzu 435 spectrophotometer. Mass spectra were measured on a VG-7070E spectrometer using a solid probe at 70 eV. Elemental analyses (C, H, N analyses) were carried out on a Yanaco MT-3 analyzer. Chloroform was distilled over calcium sulfate. Acetonitrile was distilled over calcium hydride.

4.2. Syntheses of the ligands

4.2.1. (*S*)-3,5-Dihydro-4-(2-pyridinylmethyl)dinaphth[2,1-c:1′,2′-e]azepine 1a. General procedure (route A): A mixture of (*S*)-2,2′-dibromomethyl-1,1′-binaphthyl **2** (3.10 g, 7.04 mmol), 2-aminomethylpyridine (0.91 g, 8.44 mmol) and K_2CO_3 (2.14 g, 15.49 mmol) was dissolved in dry acetonitrile (30 mL) and stirred at room temperature for 24 h. The mixture was then diluted with dichloromethane (30 mL), filtered and evaporated to dryness under reduced pressure. The crude product

obtained was purified by silica gel column chromatography to give **1a** as a white solid (2.58 g, 95% yield). Mp 197–198°C. $[\alpha]_D^{20}$ +235.4 (*c* 1.0, CH_2Cl_2); IR (KBr): 2977.0, 2926.0, 2820.3, 1588.8, 1432.5, 1148.0, 1053.0, 819.1, 750.5 cm^{-1}. ^1H NMR: δ (ppm) 3.28 (d, $J=12.2$ Hz, 2H), 3.68 (d, $J=12.2$ Hz, 2H), 3.74 (d, $J=14.0$ Hz, 1H), 3.87 (d, $J=14.0$ Hz, 1H), 7.20–7.96 (m, 15H), 8.75 (dd, $J=5.2$ and 1.8 Hz, 1H). MS (EI): 294(100), 295(38), 265(27), 252(11), 93(74), 92(16). Anal. calcd for $C_{28}H_{22}N_2$: C, 87.01; H, 5.73; N, 7.26. Found: C, 87.15; H, 5.74; N, 7.10%.

4.2.2. (*S*)-3,5-Dihydro-4-(8-quinolinylmethyl)dinaphth-[2,1-c:1′,2′-e]azepine 1b. White solid, 90% yield. Mp 98–99°C. $[\alpha]_D^{20}$ +215.2 (*c* 1.0, CH_2Cl_2). IR (KBr): 3049.0, 2926.0, 2802.0, 1590.0, 1496.0, 1128.6, 1039.1, 819.5, 752.1 cm^{-1}. ^1H NMR: δ (ppm) 3.34 (d, $J=12.0$ Hz, 2H), 3.76 (d, $J=12.2$ Hz, 2H), 4.20 (d, $J=14.6$ Hz, 1H), 4.62 (d, $J=14.6$ Hz, 1H). MS (EI): 436(4), 295(40), 294(100), 277(19), 265(29), 252(10), 157(10), 143(75), 115(10). Anal. calcd for $C_{32}H_{24}N_2$: C, 88.04; H, 5.54; N, 6.42. Found: C, 87.89; H, 5.56; N, 6.40%.

General procedure (route B): A mixture of (*S*)-3,5-dihydro-4*H*-binaphth[2,1-c:1′,2′-e]-azepine **3** (401 mg, 1.36 mmol), 8-bromomethylquinoline (302 mg, 1.36 mmol) and K_2CO_3 (207 mg, 1.50 mmol) was dissolved in dry acetonitrile (10 mL) and stirred at room temperature for 18 h. The mixture was then diluted with dichloromethane (20 mL), filtered and evaporated to dryness under reduced pressure. The crude product obtained was purified by silica gel column chromatography to give **1b** as a white solid (539 mg, 91%). Similarly, ligand **1a** was prepared in 97% yield.

4.3. General procedure for copper-catalyzed cyclopropanation

To a two-neck round-bottomed flask were added $Cu(OTf)\cdot(C_6H_6)_{0.5}$ (5.0 mg, 0.02 mmol), chloroform (20 mL) and ligand (0.04 mmol) under nitrogen. The solution was stirred at room temperature for 2 h and filtered through a syringe-tip filter (0.45 μm). After addition of the alkene (10 mmol), the solution was heated to reflux, and diazoacetate (2 mmol) in chloroform (15 mL) was slowly added over 4 h at the refluxing temperature. The resulting mixture was stirred under reflux for an additional 2 h. The mixture was then worked up by removing the solvent and the crude product obtained was purified by silica gel column chromatography (petroleum ether/EtOAc). All the cyclopropanes obtained are known compounds and were characterized by ^1H NMR. Diastereoselectivities (*cis*:*trans* ratio) of cyclopropanation products were measured by GC with a capillary column (HP-1, 30 m×0.32 mm ID). The enantiomeric excesses of cyclopropanes in entries 1–4 in Table 1 were determined, after re-esterification with (–)-menthol, by GC analysis with a capillary column (HP-1, 30 m×0.32 mm ID). For entries 9–12 in Table 1, enantiomeric excesses were determined by GC analysis using a capillary column CP-SIL 24CB (30 m×0.25 mm ID).

Acknowledgements

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