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Tetrahedron: *Asymmetry* 16 (2005) 727–731

Chiral C_2-symmetric ligands containing two binaphthyl units linked by 2,2′-bipyridyl bridge in asymmetric catalysis

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Received 1 December 2004; accepted 17 December 2004
Available online 26 January 2005

Abstract—The catalytic activities of new chiral C_2-symmetric ligands **1**–**4** in the asymmetric alkylation of aromatic aldehydes with diethylzinc to give 1-arylpropanols are studied. In most cases, the yields were good and enantioselectivities up to 87% were observed. Copper-catalyzed cyclopropanation proceeded with ⩽51% enantioselectivity and ~3:1 *trans*/*cis*-diastereoselectivity.

1. Introduction

Recently, Shibasaki et al. reported a novel class of linked BINOL ligands, in which two BINOL units are linked by carbon, oxygen or sulfur bridges. These ligands introduced new possibilities for multifunctional asymmetric catalysis.[1–3] Phenylenebis(ethynyl)-tethered bis-BINOL ligands have also been reported as enantioselective catalyst.[4] Introduction of an appropriate tether between two binaphthyl units would stabilize a dimeric structure, allowing us to study the enantioselectivity of the dimeric form.[5–13] Enantioselective addition of diethylzinc to aldehydes is one of the most reliable methods to prepare chiral alcohols[14–16] and also a standard reaction to test the reactivity and enantioselectivity of newly designed chiral ligands. BINOL and its derivatives have been widely employed as enantioselective catalysts in this reaction.[17] They can conduct the highly enantioselective synthesis of a variety of chiral alcohols. But limitation has also been identified, in most cases, the reaction requires the use of both Et_2Zn and $Ti(O^iPr)_4$. Therefore, the search of efficient catalysts continues for the enantioselective addition of diethylzinc to aldehydes. In asymmetric, transition metal catalyzed reaction, ligands with sp^2 nitrogen(s) as the coordinating atom(s) constitute an important class.[18–20] Over the past 15 years, chiral C_2-symmetric bidentate *N*,*N*-coordinating ligands such as bis-oxazolines,[21–25] sermicorrins,[26–29] and 2,2′-bipyridines[30–35] have been reported to be highly efficient catalysts in a number of asymmetric reactions. Bolm et al. reported C_2-symmetric bipyridylalcohol ligands and high asymmetric induction has been achieved in additions of diethylzinc to aldehydes in the presence of those ligands.[36] We have synthesized a series of new C_2-symmetric chiral bipyridyl ligands **1**–**4** in which two binaphthyl units are linked by 2,2′-bipyridyl (Fig. 1). The procedures of synthesis of these ligands have been described previously.[37] Herein, we report our results of an efficiently enantioselective diethylzinc addition to aromatic aldehydes catalyzed by bis-BINOLs **1c** and **2b** and **4c** in the absence of $Ti(O^iPr)_4$. The evaluation of these chiral ligands as chiral directors in asymmetric copper(I)-catalyzed cyclopropanation[38] of styrene with a diazoester is also described.

2. Results and discussion

2.1. Enantioselective addition of diethylzinc to aromatic aldehydes

The containing hydroxyl groups C_2-symmetric bipyridine ligands **1c**, **2b**, and **4c** were synthesized via deprotected of MOM protected ligands with conc HCl in MeOH–THF.[37] We tested their properties as catalysts for the addition of diethylzinc to benzaldehyde (Scheme 1). The reaction was conducted at room temperature in toluene by the sequential treatment of Et_2Zn with a chiral ligand and benzaldehyde (Table 1). As the results summarized in Table 1 show, compound **2b** gave the highest enantioselectivity among the three ligands (entry

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doi:10.1016/j.tetasy.2004.12.015

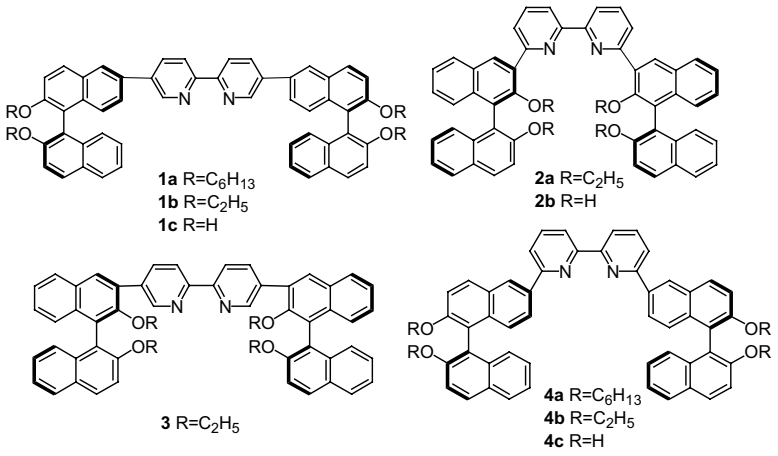
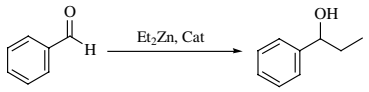


Figure 1. Chiral C_2-symmetric ligands (*R*,*R*)-**1**–**4**.



Scheme 1.

3). The low enantioselectivity of compounds **1c** and **4c** indicated that the BINOLs tethered by bipyridyl at the 3-position are more suitable for this reaction than at 6-position. In ligands **1c** and **4c**, the hydroxy groups are far away from the pyridine nitrogens, to prevent the formation of a chelate zinc complex. This led to low enantioselectivity. We then explored the conditions for the use of ligand **2b** in the reaction of diethylzinc with benzaldehyde. From Table 1, it is clear that the yields of the isolated 1-phenyl-1-propanol are good and the enantioselectivities obtained are also satisfactory in all cases. Solvents have a significant effect on both the rate and enantioselectivity of the reaction. THF (entry 7), CH_2Cl_2 (entry 8) and CH_3CN (entry 9) decreased the enantioselectivity and also the rate. Low temperature leads to a slight increase in asymmetric induction from 82% to 86% ee but had only a small effect on the rate for (*R*,*R*)-**2b** (entry 4). Changing the amount of catalyst from 2% to 8% has a slight effect on the enantioselectivity (entries 5, 6). With (*R*,*R*)-**2b** being the best ligand, other aldehydes were also tested (Table 2). Several observations were noticed: in most cases, chemical yields of alcohols and enantioselectivities were lower than benzaldehyde; enantioselectivity up to 87% ee was observed as for 1-naphthaldehyde; all reactions required longer time for completion; not all substrates favor the (*R*)-configuration isomer for (*R*,*R*)-**2b**.

2.2. Asymmetric cyclopropanation catalyzed by Cu(I) complexes

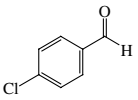
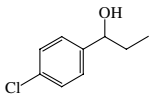
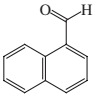
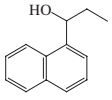
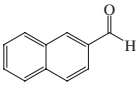
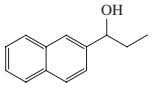
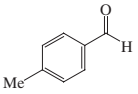
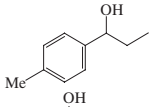
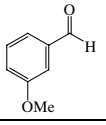
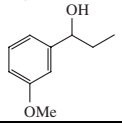
To explore further the scope of these chiral ligands, we have briefly studied the cyclopropanation of styrene with ethyl diazoacetate as the metallocarbene source (Scheme 2). Following previous reports,[43–49] we first generated Cu(II) complexes from $(TfO)_2Cu$ (1 mol%) and the respective ligands **1a**,**b**,**4a**,**b**,**2a**, and **3**, which were reduced in situ with phenylhydrazine to the corresponding Cu(I) species. The reaction was carried out in CH_2Cl_2 in the presence of the catalyst via a slow addition of the diazoacetic ester over a period 3 h (Table 3). From Table 3 we obviously found that (*R*,*R*)-**2a** has the best catalytic activity among the six ligands.

Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by ligands **1c**,**4c**,**2b**[a]

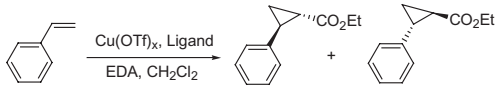
Entry	Catalyst	Solvent	Time (h)[b]	Temp (°C)	Yield (%)[c]	Ee (%)[d]
1	(*R*,*R*)-**1c**	Toluene	24	22	82	66(*R*)
2	(*R*,*R*)-**4c**	Toluene	24	22	77	59(*R*)
3	(*R*,*R*)-**2b**	Toluene	12	22	88	82(*R*)
4	(*R*,*R*)-**2b**	Toluene	12	0	90	86(*R*)
5[e]	(*R*,*R*)-**2b**	Toluene	24	22	98	80(*R*)
6[f]	(*R*,*R*)-**2b**	Toluene	24	22	95	86(*R*)
7	(*R*,*R*)-**2b**	THF	24	22	66	54(*R*)
8	(*R*,*R*)-**2b**	CH_2Cl_2	24	22	63	44(*R*)
9	(*R*,*R*)-**2b**	CH_3CN	24	22	46	48(*R*)

[a] Reactions were run with 5 mol% ligands unless otherwise stated.
[b] Reactions were monitored by GC.
[c] Isolated yield after chromatography.
[d] Determined by GC analysis using a chiral column (Chrompack Chirasil-DEX-CB column) or by HPLC analysis using a chiral column (OD-H column). Absolute configuration was determined by comparing the sign of specific rotation.[39–42]
[e] Reactions were run with 2 mol% catalyst.
[f] Reactions were run with 8 mol% catalyst.

Table 2. Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by ligand **2b**[a]

Substrate	Product	Time (h)[b]	Yield (%)[c]	Ee (%)[d]
		48	56	16(*R*)
		48	71	87(*S*)
		48	85	45(*R*)
		48	62	54(*S*)
		48	65	74(*R*)

[a] Reactions were run with 5 mol% ligands unless otherwise stated.
[b] Reactions were monitored by GC.
[c] Isolated yield after chromatography.
[d] Determined by GC analysis using a chiral column (Chrompack Chirasil-DEX-CB column) or by HPLC analysis using a chiral column (OD-H column). Absolute configuration was determined by comparing the sign of specific rotation.



Scheme 2.

The results demonstrated that reactivities of the Cu complexes of **1**–**4** as catalysts in asymmetric cyclopropanation correlate with the shape of the chiral cavity of these ligands. Molecular models of ligand complexes **2a**-**M** and **4b**-**M** (Fig. 2) reveal important features concerning the shape of the chiral cavity. The cavities of **1a**,**b**,**4a**, and **b** have a relatively wide 'entrance' (in these ligands binaphthyl unit is linked by bipyridyl at the 6-position), whereas ligand **3** is narrower, which brings the OR groups closer to the metal. By contrast, the entrance of **2a** is narrower than that in the previous ligands (ligands **3** and **2a** binaphthyl units linked by bipyridyl at the 3-position). So in these ligands, the narrow entrance contributes to the asymmetric induction. Low temperature leads to an increase in asymmetric induction from 39% to 51% ee (*trans*) but has little effect on either the *trans*/*cis* selectivity on the rate for (*R*,*R*)-**2a** (entries 3 and 7). The amount of catalyst has almost no effect on either the *trans*/*cis* selectivity or enantioselectivity (entries 8 and 9). On prolonging the reaction time from 3 h to 12 h, the yield of product was increased, giving the product in 99% yield (entry 10). Practically identical results were obtained with the Cu(I) complex generated directly from (*R*,*R*)-**2a** and $(CuOTf)_2{\cdot}C_6H_6$ (entries 11 and 12).

Table 3. Asymmetric cyclopropanation of styrene with ethyl diazoacetate catalyzed by Cu complexes of chiral ligands

Entry	Ligand	X	Mol (%)	Time (h)	Temp (°C)	Yield (%)	*trans*/*cis*[a]	Ee (*trans*)[b,c]
1	(*R*,*R*)-**1a**	2	1	3	20	72	67/33	4(1*S*,2*S*)
2	(*R*,*R*)-**1b**	2	1	3	20	95	66/34	15(1*S*,2*S*)
3	(*R*,*R*)-**2a**	2	1	3	20	94	62/38	39(1*S*,2*S*)
4	(*R*,*R*)-**3**	2	1	3	20	90	67/33	31(1*S*,2*S*)
5	(*R*,*R*)-**4a**	2	1	3	20	92	62/38	6(1*S*,2*S*)
6	(*R*,*R*)-**4b**	2	1	3	20	92	65/35	16(1*S*,2*S*)
7	(*R*,*R*)-**2a**	2	1	3	0	75	64/36	51(1*S*,2*S*)
8	(*R*,*R*)-**2a**	2	2	3	20	87	60/40	39(1*S*,2*S*)
9	(*R*,*R*)-**2a**	2	5	3	20	88	68/32	40(1*S*,2*S*)
10	(*R*,*R*)-**2a**	2	1	12	20	99	64/36	42(1*S*,2*S*)
11	(*R*,*R*)-**2a**	1	1	3	20	78	72/28	35(1*S*,2*S*)
12	(*R*,*R*)-**2a**	1	1	3	0	82	60/40	48(1*S*,2*S*)

[a] Determined by GC.
[b] Determined by chiral GC (Chirasil-DEX CB).
[c] Absolute configuration was (1*S*,2*S*) by comparison of specific rotations with the values in the literature.[50]

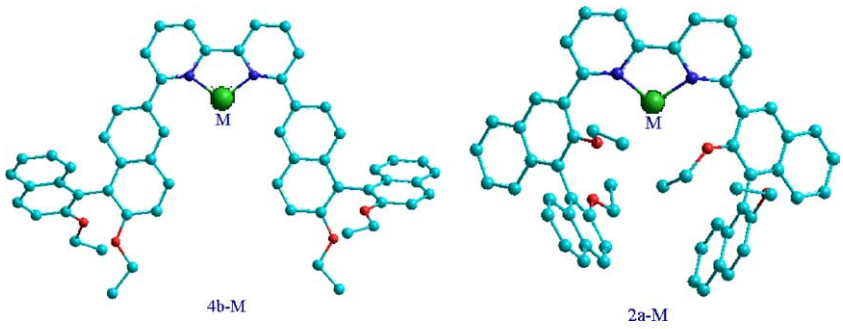


Figure 2. 3D representation of **4b-M** and **2a-M**.

3. Conclusions

In conclusion, a series of new chiral bis-binaphthyls linked by 2,2′-bipyridine ligands **1**–**4** has been applied in the catalytic asymmetric alkylation of aromatic aldehydes with diethylzinc and copper-catalyzed cyclopropanation. In the enantioselective addition of diethylzinc to aldehydes, enantiomeric excesses of up to 87% were observed. In copper-catalyzed cyclopropanation, the cyclopropanes could be obtained in moderate *trans*/*cis* selectivity and enantioselectivity. New catalysts have been shown to be promising in the above two types of asymmetric catalytic reactions. We are continuing our efforts on the use of these ligands in other catalytic asymmetric reactions.

4. Experimental

GC measurements were carried out on a Shimadzu GC-2010A instrument. HPLC utilized a Shimadzu LC-6AD pump, a Shimadzu SPD-10A UV dectector, and Shimadzu Class-VP system controller software. Chem 3D model derived from the software Hyperchem 7.5 of Hyper cube, Inc. Products were purified by column chromatography on silica gel (100–200 mesh). Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise stated. THF was distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. CH_3CN and CH_2Cl_2 were dried over calcium hydride.

4.1. General procedure for the addition of diethylzinc to aldehydes

Chiral ligand (0.05 mmol, 5 mol%) in dry toluene (1.0 mL) was cooled to 0 °C and 1 M diethylzinc in hexane (1.5 mmol, 1.5 mL) was added slowly. The mixture was allowed to stir at room temperature for 30 min. Freshly distilled aldehyde (1 mmol) was added and the reaction was monitored by GC. After the reaction was completed, it was quenched by addition of 2 M HCl (5 mL). The layers were separated and aqueous layer was extracted with ether (three times by 20 mL). The combined organic layers were dried by Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography. Enantiomeric excesses for the products were determined by chiral GC with Chirasil-DEX CB or by HPLC analysis using a chiral column (OD-H column).

4.2. General procedure for asymmetric cyclopropanation catalyzed by Cu(I) complexes

A solution of the ligand (0.06 mmol) and $(TfO)_2Cu$ (18 mg, 0.05 mmol) in dichloromethane (5 mL) was stirred under nitrogen atmosphere at 20 °C for 1 h. The solution was filtered through glass wool under nitrogen, and to the filtrate were successively added phenylhydrazine (5.9 μL, 0.06 mmol) and styrene (1 mL, 8.74 mmol). A solution of ethyl diazoacetate (3–5 mmol) in dichloromethane (3 mL) was added dropwise over a period of 3 h using a syringe pump. The mixture was stirred for 12 h and concentrated in vacuum. The ratio of *trans* and *cis* isomers was determined by capillary GC. Separation of the isomers was performed by chromatography on a silica gel column with hexane/ethyl acetate (20:1). Enantiomeric excesses for the products were determined by chiral GC with Chirasil-DEX CB.

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