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Enantioselective conjugate addition of diethylzinc to cyclic enones catalyzed by chiral copper complexes containing a new phosphorus ligand with an H_8-binaphthoxy moiety

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Abstract

A new chiral phosphorus amidite ligand with an H_8-binaphthoxy moiety was synthesized and applied to the copper-catalyzed asymmetric conjugate addition of diethylzinc to cyclic enones with high enantioselectivity. The results gave support to the generality of the advantage of the sterically more demanding H_8-binaphthyl backbone in biaryl chiral ligands.

1. Introduction

Conjugate addition reactions of carbon nucleophiles to α,β-unsaturated compounds are widely used in organic synthesis for carbon–carbon bond formation.[1,2] It is therefore not surprising that major efforts have been devoted to the establishment of synthetic methods for asymmetric conjugate additions and several successful examples of the stoichiometric or catalytic stereoselective 1,4-addition to enones have been developed.[2–4] While the catalytic enantioselective conjugate additions with chiral Ni(II) and Zn(II) complexes of chiral amino alcohols are of substantial interest, these catalysts showed enantioselectivity only for acyclic enones and the reactivity was low. Alexakis and co-workers reported the first example of copper-catalyzed enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one with low enantioselectivity (32% e.e.).[5] Recently, Feringa et al.[6] reported an efficient copper(II) catalyst system containing trivalent ligand **1** which is capable of facilitating conjugate addition of readily available diethylzinc reagents to cyclic enones with high enantioselectivity. On the other hand, based on the studies on the asymmetric titanium-catalyzed alkylation of aldehydes with trialkylaluminum or diethylzinc, we have established the generality of the advantage of the sterically more demanding H_8-binaphthyl

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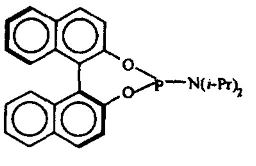
Table 1
The solvent effect on the conjugate addition of diethylzinc to 2-cyclohexen-1-one catalyzed by $Cu(OTf)_2$–2 complex

Entry	Solvent	Conversion (%)	E.e. (%)
1	Toluene	100	73
2	Benzene	100	67
3	Dichloromethane	100	82
4	Diethyl ether	100	64
5	THF	62.3	26

3 : $Cu(OTf)_2$: 2: Et_2Zn = 1 : 0.05 : 0.11 : 1.5; -20°C; 3.0 hours. 100% selectivity was observed in all cases.

backbone in a variety of catalytic reactions.[7] In this paper we wish to report a more efficient chiral ligand **2**, which contains an H_8-binaphthoxy moiety in the copper-catalyzed conjugate addition of diethylzinc to cyclic enones.



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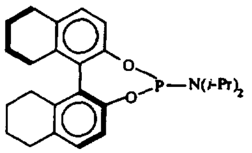

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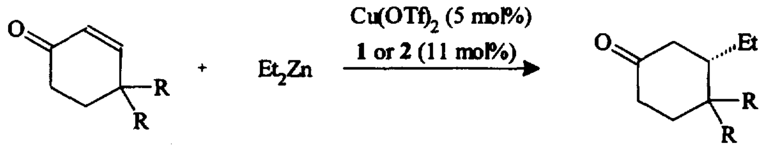

R = H, 3
R = CH_3, 4

2. Results and discussion

On the basis of our previous studies of the comparison of BINOL and H_8-BINOL complexes,[7] it is of interest to find out whether the partially hydrogenated trivalent phosphorus ligand **2** is more effective than **1** in the conjugate addition of dialkylzinc to enones. Our initial efforts were concentrated on the synthesis of chiral ligand **2** and the application of it in the Cu(II)-catalyzed conjugate addition of diethylzinc to 2-cyclohexen-1-one. We are pleased to find that the Cu(II) complex containing chiral ligand **2** indeed gave higher enantioselectivity (73% e.e.) than the complex containing chiral ligand **1** (64% e.e.) in the same reaction under the same reaction conditions.

This result encouraged us to investigate the factors governing the rate and enantioselectivity of the reaction. A profound solvent effect was observed in this study and the results are summarized in Table 1. In aprotic solvents, the reaction proceeded smoothly with high reactivity and moderate to high enantioselectivity. However, in protic solvents, both reactivity and enantioselectivity were low. The highest enantioselectivity was observed in dichloromethane.

The effect of reaction temperature on the enantioselectivity was also examined. Like many other similar reactions, the higher enantioselectivity was obtained at a lower reaction temperature (Table 2). When the reaction temperature was lowered from 20°C to −40°C, the enantioselectivity increased from

Table 2
The effect of reaction temperature on the conjugate addition of diethylzinc to 2-cyclohexen-1-one catalyzed by $Cu(OTf)_2$–**2** complex

Entry	Temperature (°C)	Conversion (%)	E.e. (%)
1	20	100	73
2	0	100	78
3	-20	100	82
4	-40	100	85

3 : $Cu(OTf)_2$: 2 : Et_2Zn = 1 : 0.05 : 0.11 : 1.5; 3.0 hours; dichloromethane as solvent. 100% selectivity was observed in all cases.

73% e.e. to 85% e.e. To our knowledge, this is the most promising result in the conjugate addition of diethylzinc to 2-cyclohexen-1-one.

Another example of cyclic enone, 4,4-dimethyl-2-cyclohexen-1-one **4**, was also converted smoothly to the 1,4-adducts with high enantiomeric excesses. A comparison of the asymmetric conjugate addition of diethylzinc to cyclic enones catalyzed by copper complexes containing chiral ligands **1** and **2** is summarized in Table 3. The experimental data clearly indicates that the trivalent phosphorus ligand **2** was more effective than **1** in the conjugate addition of diethylzinc to cyclic enones.

Table 3
A comparison of the conjugate addition catalyzed by copper complexes with chiral ligands **1** and **2**[a]

Entry	Enone	Ligand (L*)	Conversion (%)[b]	E.e. (%)[b]
1	3	2	100 (100)	82 (71)
2	3	1	100 (100)	68 (63)
3	4	2	92.3 (95.0)	88 (85)
4	4	1	91.2 (94.7)	81 (80)

[a] Enone : $Cu(OTf)_2$: L* : Et_2Zn = 1 : 0.05 : 0.11 : 1.5; -20°C; 3.0 hours; dichloromethane as solvent. 100% selectivity was observed in all cases. [b] The data in the brackets were obtained under the following conditions: Enone : $Cu(OTf)_2$: L* : Et_2Zn = 1 : 0.03 : 0.065 : 1.5; -15°C; 3.0 hours; toluene as solvent.

These results again give supporting evidence for the generality of the advantage of the sterically more demanding H_8-binaphthyl backbone in chiral ligands for enantioselective catalytic reactions.

In conclusion, we have developed a new chiral phosphorus amidite ligand which gave good e.e.'s for the copper(II)-catalyzed conjugate addition of diethylzinc to cyclic enones. Further studies on other reactions with this ligand are in progess.

3. Experimental section

All experiments were carried out under a nitrogen atmosphere. Except as specified, commercial reagents were used as received without further purification. All solvents used were dried using standard, published methods and were distilled before use.

3.1. Preparation of (S)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthylphospinite-diisopropylamidite (S)-2

A solution of (*S*)-2,2′-dihydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (882 mg, 3 mmol) in toluene (25 mL) was added to a solution of freshly distilled PCl_3 (270 μL, 3 mmol), Et_3N (860 μL, 6 mmol), and toluene (5 mL) at −60°C. The reaction mixture was stirred for 2 hours, warmed to room temperature, and then filtered. The filtrate was cooled to −40°C and was treated with a 2.0 M solution of lithium diisopropyl amide (1.5 mL, 3 mmol) for 3 hours. The reaction mixture was warmed to ambient temperature and was filtered, concentrated, and purified by recrystallization to give the pure product (*S*)-**2** in 95% yield. The analytical data for (*S*)-**2** are as follows: m.p.: 123–125°C; $[\alpha]_D$=+178.6 (c=1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, CD_3OD) δ: 7.06–6.88 (m, 4H); 3.29–3.27 (m, 2H); 2.85–2.2.74 (m, 4H); 2.70–2.58 (m, 2H); 2.36–2.20 (m, 2H); 1.81–1.71 (m, 6H); 1.59–1.52 (m, 2H); ^{13}C-NMR (101 MHz, CD_3OD) δ: 149.9, 149.1, 149.0, 138.2, 137.5, 134.1, 132.7, 129.8, 129.7, 129.6, 129.4, 128.9, 128.6, 128.2, 127.9, 126.2, 125.9, 125.6, 119.3, 119.0, 44.8, 44.7, 29.5, 29.4, 28.1, 28.0, 26.0, 24.9, 23.2, 23.1, 22.9; ^{31}P-NMR (162 MHz, toluene) δ: 149.36 ppm; HRMS calculated for $C_{26}H_{34}O_2NP$ M^+: 423.233, found: 423.237.

3.2. A typical procedure for the catalytic conjugate addition of diethylzinc to 2-cyclohexen-1-one

A solution of $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) and (*S*)-**2** (9.0 mg, 0.021 mmol) in 2 mL dichloromethane was stirred for 1.0 hour. The solution was cooled to −20°C and 2-cyclohexen-1-one (32 μL, 0.33 mmol) and a 1.0 M toluene solution of diethylzinc (0.5 mL, 0.5 mmol) were added. After stirring for 3.0 hours at −15°C, the solution was mixed with 2.0 mL water and 0.2 mL 1.0 M hydrochloric acid solution, and the product was extracted with 5.0 mL ethyl acetate. The conversion and enantioselectivity were determined by GLC with a Chiraldex G-PN capillary column.

Acknowledgements

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