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Highly efficient and enantioselective cyclopropanation of styrene with diazoacetates using a new copper-(Schiff-base) catalyst

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Abstract

A new copper-(Schiff-base) complex, derived from (*S*)-2-amino-1,1-di(3,5-di-*t*-butylphenyl)propanol, 2-hydroxy-5-nitrobenzaldehyde and copper acetate monohydrate, was used as an efficient catalyst for the cyclopropanation of styrene with diazoacetates, affording ees of up to 98%. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Catalytic asymmetric cyclopropanation of diazoacetates with olefins has attracted much attention.[1] Catalysts containing various metals and optically active ligands have been employed, and styrene has been used as a benchmark olefin for this reaction. High enantioselectivities have been achieved by using Cu-(Schiff-base),[2] Co-dioximate,[3] and copper complexes with a C_2 symmetry, such as Cu-semicorrin,[4] Cu-bisoxazoline,[5] Cu-bipyridine,[6] Ru-(bisoxazolinyl)pydridine,[7] Rh_2(5S-MEPY)$_4$,[8] etc.,[9,10] as catalysts. Although a Cu-(Schiff-base) complex emerged 30 years ago as the first catalyst for the asymmetric cyclopropanation of styrene,[11] this kind of catalyst is not as effective as the catalysts which have appeared over the last decade.[4–10] However, there has been a renaissance of this kind of catalyst in recent years. For example, Co(III)-Salen complexes were found by Fukuda and Katsuki and a cobalt complex, MPAC, by Yamada et al. to be efficient catalysts for the asymmetric cyclopropanation of styrene with *t*-butyl diazoacetate.[12,13] Yamada et al. also reported that nitrogen-containing cyclic compounds such as *N*-methylimidazole could be used as effective additives to accelerate this reaction and to improve the enantioselectivity.[13] However, the effectiveness of these catalysts is unknown when a small alkyl diazoacetate is employed, since, as a general rule, a higher enantioselectivity is achieved when a

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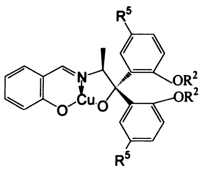
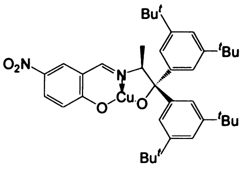
diazoacetate containing a bulkier alkyl group is used. On the other hand, Cu-(Schiff-base) complexes are not as effective as Co-Salen complexes with a C_2 symmetry in catalyzing the asymmetric cyclopropanation of styrene, although Cu-(Schiff-base) catalysts have achieved great successes in the cyclopropanation of trisubstituted olefins with various diazoacetates, which is one of the greatest achievements in asymmetric catalysis. For example, for the reaction of styrene with *l*-menthyl diazoacetate catalyzed by S-1648[2b], 79% ee and 81% ee for *cis* and *trans* products, respectively, were obtained. This was the best result in the asymmetric cyclopropanation of styrene catalyzed by Cu-(Schiff-base) complexes before 1999. Very recently, Cai et al. reported that copper-(Schiff-base) complexes were efficient for the asymmetric cyclopropanation of styrene by changing the size of the alkoxyl group of Aratani's catalyst.[15]

In the widely exploited mechanism for the catalytic asymmetric cyclopropanation, a carbene–copper intermediate is proposed. The steric interaction of this intermediate with an olefin during electrophilic attack controls the regioselectivity in the metallacyclobutane formation and the ee of the cyclopropane derivatives. Therefore, substituents on the ligand are of great importance for the enantioselectivity. Based on this consideration, we synthesized a new Schiff-base ligand and a new Cu-(Schiff-base) complex. Here we report the application of this new copper (Schiff-base) on the reaction of styrene with diazoacetates. The ee reached 98% when *i*-butyl diazoacetate was used. This catalyst is different from the catalysts reported in other studies in that it has 3,5-dialkyl substituents rather than a 2-alkoxyl and a 5-alkyl substituent.[2,15]



Aratani's catalyst



Catalyst in this work

2. Results and discussion

The reaction was first carried out with 1,2-dichloroethane as the solvent, and an ee up to 89% was obtained. The choice of the solvent was not limited to 1,2-dichloroethane. As shown in Table 1, many solvents, in addition to 1,2-dichloroethane, were tested for this reaction and high ee values were obtained in most solvents. In particular, good yields and excellent enantioselectivities were obtained when benzene, nitrobenzene, chlorobenzene, hexane, THF, nitroethane and ethyl acetate were used. Generally, the ee values were higher than 88% for the *cis*-isomer and higher than 75% for the *trans*-isomer. These results are quite different from those over most copper catalysts reported before, which give higher ees for the *trans*-isomer than for the *cis*-isomer. It is also found that acetonitrile, acetone and pyridine were ineffective under the same conditions. When pyridine was employed as the solvent, no cyclopropyl derivatives were detected at 40°C. Increasing the temperature to 80°C only resulted in a very low yield of the product, and the configuration of the dominant isomer in the *trans*-isomers became inverted when pyridine was used. A similar phenomenon was reported by Nakamura et al. when Co-dioximate was used as the catalyst and some nitrogen-containing compounds were used as the additives.[3] Acetonitrile and pyridine have strong coordinating abilities and may coordinate with metal ions and change

Table 1
The effect of solvents on the asymmetric cyclopropanation of styrene

Entry	Solvent	Yield (%)[a]	*cis*/*trans*[a]	ee%[a] (*cis*)[c]	ee%[a] (*trans*)[d]
1	dichlorothane	63.4	42.5/57.5	89.1	80.5
2	$PhNO_2$	65.4	46.9/53.1	90.5	79.5
3	Benzene	51.6	44.1/55.9	88.0	76.4
4	hexane	39.6	47.1/52.9	90.1	86.0
5	THF	52.9	43.7/56.3	90.6	76.8
6	PhCl	55.1	45.2/54.8	88.0	74.4
7	$EtNO_2$	66.4	47.3/52.7	91.9	80.7
8	EtOAc	52.3	45.8/54.2	90.6	78.2
9	CH_3CN	5.8	41.7/58.3	35.1	26.1
10	acetone	7.6	36.5/63.5	37.6	25.3
11	Py,40℃	0	/	/	/
12	Py, 80℃	3.1	41.3/58.7	7.0	7.4

Reaction conditions: 1 mmol of ethyl diazoacetate, 1.0 ml of styrene, 1 mol% of catalyst (based on diazoacetate), 3.0 ml of solvent, 40℃.

a: Determined by GC analysis (permethyl β -cyclodextrin chiral capillary column, 30m× 0.25 mm ID, 0.25 μ m film, column temp. 130℃).

b: Determined by the comparison of GC elution order of the enantiomers with authentic sample prepared according to the literature.

c: 1R,2S as the major enantiomer.

d: 1R,2R as the major enantiomer except 1S, 2S as the major enantiomer in entry 12.

the transition state of the products, so that ee values of the products change dramatically when these two solvents are employed. The low ee values obtained with acetone as the solvent may be due to the exchange reaction occurring between the catalyst and the large excess of acetone, which may give rise to copper salicylaldehydate, an achiral catalyst. The low yield with acetone as the solvent may be explained by the side reaction of the diazoacetate with acetone.

It is worth noting that our results are different from the results recently reported by Cai et al., i.e. high ees were achieved for cyclopropanation in a solvent with a strong polarity, such as acetonitrile and DMF, in Cai's work.[15]

Secondary interactions among ligand–metal–substrate are of importance in some asymmetric catalytic reactions such as hydrogenation.[16] All efficient copper-(Schiff-base) catalysts used in asymmetric cyclopropanation so far have a similar structure in that they have alkoxyphenyl groups as substituents. Whether an alkoxyphenyl group is essential or not to achieve a high ee has not been reported. In contrast to those catalysts derived from chiral aminoalcohols reported so far, the catalyst in this work does not contain alkoxyl groups and gives high ees. This demonstrates that an alkoxyl group in an aminoalcohol is not vital for this reaction. Thus, the secondary interactions among the alkoxyl group–copper–olefin do not play a crucial role in the catalytic process. The substituent(s) in the aminoalcohol affects the enantioselectivity only via steric repulsion rather than by electronic effects or coordination.

A higher yield can be obtained at a higher temperature, as shown in Table 2. However, a lower ee was obtained on increasing the temperature. Enantiomeric excesses of 93 and 84% for the *cis* and *trans* products, respectively, were obtained at 0°C, but only with low yields. According to these data, the preferable temperature range for this reaction is 20 to 60°C. A similar dependence of the yield on the temperature was observed in the early days with achiral catalysts as well as with chiral catalysts,[15,17,18] and discussion has been made on this phenomenon.[17] This catalyst is highly effective, as shown in Table 3. An ee of 51% could be obtained when only 0.1 mol% of the catalyst was used.

Table 2
The influence of temperature on the reaction of styrene

Entry	Temp.(℃)	Yield (%)	*cis*/*trans*	ee of *cis*[a]	ee of *trans*[b]
1	0	25.2	47.2/52.8	93.1	83.6
2	25	57.0	47.0/53.0	92.9	83.7
3	40	63.4	42.5/57.5	89.1	80.5
4	60	63.9	45.2/54.8	89.0	74.5
5	80	87.2	42.8/57.2	83.3	71.2
6	100	85.6	37.9/62.1	53.7	37.2

Reaction conditions: 1 mmol of ethyl diazoacetate, 1.0 ml of styrene, 1mol% of catalyst, 3.0 ml of 1,2-dichloroethane as the solvent.

a: 1R,2S as the major enantiomer.

b: 1R,2R as the major enantiomer.

Table 3
The influence of the amount of catalyst on the reaction of styrene

Entry	Amt of cat.(mol%)	Yield (%)	*cis*/*trans*	ee of *cis*[a]	ee of *trans*[b]
1	1	87.2	42.8/57.2	83.3	71.2
2	0.1	87.0	35.8/64.2	51.4	31.3
3	0.01	63.0	36.7/63.3	19.4	8.8
4	0.001	61.0	31.1/68.9	7.0	0.3
5	0.0001	17.1	38.0/62.0	/	/

Reaction conditions: the same as that in Table 2 except the amount of catalyst used and the running at 80℃.

a: 1R,2S as the major enantiomer.

b: 1R,2R as the major enantiomer.

A bulky group in the diazoacetate favors the enantioselectivity and diastereoselectivity. When *i*-butyl diazoacetate was used, the ees reached 98 and 85% for the *cis* and *trans* products, respectively (Table 4). On the other hand, when *l*-menthyl diazoacetate was used, 95 and 98% ees for the *cis*- and *trans*-esters, respectively, were obtained. These are much higher than the results

Table 4
The influence of alkyls in diazoacetate on the reaction of styrene

Entry	RDA	*cis*/*trans*	ee of *cis*[a]	ee of *trans*[b]
1	MeDA	52.4/47.6	89.1	81.6
2	EtDA	47.0/53.0	92.9	83.7
3	^{n}BuDA	47.8/52.2	88.9	78.1
4	^{i}BuDA	45.0/55.0	98.0	85.5
5	^{t}BuDA	27.9/62.1	/	/
6	*l*-MentDA	23.9/76.1	95.0	98.0

Reaction conditions: 1 mmol of diazoacetate, 1.0 ml of styrene, mol% of catalyst, 3.0 ml of 1,2-dichloroethane, 25℃.

a: 1R,2S as the major enantiomer.

b: 1R,2R as the major enantiomer.

reported in the literature using other copper-(Schiff-bases) as the catalysts.[2,14] It is worth noting that when methyl diazoacetate is used, there are more of the *cis*-isomers in the product than of the *trans*-isomers, which is rarely observed in the cyclopropanation of styrene.

This catalyst was also applied to the asymmetric cyclopropanation of other olefins, and the results are listed in Table 5. An ee of 85% was achieved for the reaction of 1,1-diphenylethene. Higher diastereoselectivities were obtained with 1-octene and allyl bromide as the olefins, whereas lower diastereoselectivities were obtained when vinyl acetate and 2-methyl-1-pentene were employed, and the enantioselectivities were not as high as with styrene.

Table 5
Asymmetric cyclopropanation of some other olefins

Olefin	*cis*/*trans*	ee% of *cis*	ee% of *trans*
1-Octene	36.6/73.4	41.7	-
Allyl bromide	28.9/71.1	-	-
Vinyl acetate	53.9/46.1	39.5	17.9
Diphenylethene		85.4 (1R)	
2-Me-1-pentene	47.4/52.6	-	47.9

Reaction conditions: 1 mmol of ethyl diazoacetate, 1.0 ml of olefin, 1 mol% of catalyst, 3.0 ml of 1,2-dichloroethane, 40℃.

In conclusion, the new catalyst in this work is efficient for the asymmetric cyclopropanation of styrene.

3. Experimental

Unless otherwise stated, all reactions were carried out under an argon atmosphere. Optical rotations were measured by a SEPA-200 high sensitivity polarimeter. NMR spectra were recorded by a Bruker DRX-400 NMR spectrometer with a BBI probe. The yields and ee values were determined by GC analyses with a chiral capillary column (30×0.25 mm permethyl cyclodextrin, ID, 0.25 μ film) at 130°C. Configurations of phenylcyclopropanecarboxylate were determined with a GC by comparing the GC elution order of the enantiomers with an authentic sample prepared according to the literature.

3.1. (S)-2-Amino-1,1-di(3,5-di-t-butylphenyl)propanol

At 0°C, 1.5 g (10.8 mmol) of methyl ester hydrochloride of L-alanine was added with vigorous stirring to a Grignard reagent derived from 13.8 g (50.2 mmol) of 3,5-di-*t*-butylbromobenzene and 1.40 g (57.6 mmol) of magnesium. The mixture was refluxed overnight and then cooled to room temperature. A saturated aqueous solution (50 ml) of ammonium chloride was added to the cooled mixture and the organic phase was separated. The aqueous phase was extracted with 3×50 ml of chloroform. The combined organic solution was washed with aqueous sodium bicarbonate and saturated brine, then dried and concentrated. The residue was purified with a silica gel column and ether–petroleum ether as the eluent and 2.30 g of the product was obtained. Yield 42.8%, $[\alpha]_D = -40.61$ (*c* 1.108, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.49–7.44 (m, 2H), 7.36–7.34 (m, 2H), 7.22–7.19 (m, 2H), 4.12 (q, 1H), 2.16 (s, br, 3H), 1.31 (s, 9H), 1.30 (s, 9H), 1.28 (s, 9H), 1.28 (s, 9H), 1.25 (d, 1H), 0.94 (d, 3H).

3.2. The Schiff-base

A solution of 0.289 g (0.641 mmol) of (*S*)-2-amino-1,1-di(3,5-di-*t*-butylphenyl)propanol and 0.103 g (0.616 mmol) of 2-hydroxy-5-nitrobenzaldehyde[19] were dissolved in 10 ml of ethanol and the mixture was stirred for 6 h. Most of the ethanol was removed in vacuo and the residue was purified by a chromatographic column to give 0.365 g of pure Schiff-base, yield 97.8%. Mp 138–139°C; $[\alpha]_D = +85.5$ (*c* 0.994, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 14.55 (s, 1H), 8.01 (dd, $J_1 = 9.48$ Hz, $J_2 = 2.68$ Hz, 1H), 7.92 (d, $J = 2.76$ Hz, 1H), 7.75 (s, 1H), 7.32 (d, $J = 6.64$ Hz, 2H), 7.28 (s, 2H), 7.21 (d, $J = 6.32$ Hz, 1H), 6.63 (d, $J =$ Hz, 2H), 4.52 (m, 1H), 3.53 (s, br, 1H), 1.42 (d, $J = 6.52$ Hz, 3H), 1.28 (s, 18H), 1.18 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 173.6, 163.7, 150.5,150.4, 143.0, 142.1, 136.8, 129.7, 128.8, 121.2, 121.1, 120.8, 120.6, 114.9, 80.8, 68.9, 34.9, 34.9, 31.5, 31.4, 16.3.

3.3. The catalyst

The Schiff-base was dissolved in 30 ml of ethanol and 0.139 g (6.95 mmol) of copper acetate monohydrate solution was added to the above solution. The mixture was stirred and an aqueous sodium hydroxide solution was added, and stirring was continued for 1 h. Water (50 ml) was added to the mixture and the mixture was extracted with 3×10 ml of benzene. After the solution was washed with water, dried and the benzene removed in vacuo, the catalyst was obtained. Yield 74.6%, $[\alpha]_D = -290$ (*c* 0.100, C_6H_6).

3.4. Cyclopropanation

Under an argon atmosphere, a few drops of a solution of 0.114 g (1.00 mmol) of ethyl diazoacetate in 2.0 ml of solvent was added to a mixture of 6.0 mg (0.01 mmol) of the catalyst, 1.0 ml of styrene and 2.0 ml of the solvent at 80°C to initiate the reaction. After the mixture was cooled to 40°C, the rest of the diazoacetate solution was added slowly and the mixture was stirred for another 4 h after all the diazoacetate was added. The solvent was removed in vacuo and passed through a short silica gel column to remove the catalyst, then analyzed by GC (permethyl β-cyclodextrin chiral capillary column, 30×0.25 mm ID, 0.25 μ film, column temperature 130°C) using the internal method with ethyl adipate as a standard. Configurations of the enantiomers were determined by comparison of the GC elution order with an authentic sample prepared according to the literature.

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