An easily recoverable and efficient catalyst for heterogeneous cyclopropanation of olefins

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Abstract

The cyclopropanation of olefins with alkyl diazoacetates were carried out by copper complexes of Schiff bases, derived from chitosan and substituted salicylaldehydes, as the catalysts. The catalysts showed high activity and up to 56% e.e. was achieved under optimal conditions; moreover, the catalysts could be easily recovered and reused after the reaction.
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1. Introduction

Catalytic cyclopropanation of olefins with diazo-compounds has been one of the most efficient ways to obtain chiral cyclopropanes [1–6], which are of high value in biological and medicinal chemistry [7–11]. In the last four decades, many catalytic systems to promote these kinds of reactions have been proved successful on a laboratory scale but few have been industrialized. Due to the inherent advantages of heterogeneous catalyst over homogeneous catalyst [12–15], a great deal of efforts have been devoted to the development of chiral heterogeneous catalyst which can promote enantioselective organic reactions. Up to now, most of the heterogeneous catalysts were devised by immobilizing chiral metal complexes onto solid supports with or without covalent bonds, many of which showed good catalytic activity but low to moderate enantioselectivity when being used for catalytic cyclopropanation reactions [16–22].

Chitosan is the N-deacetylated derivative of chitin, which is easily obtained from crab or shrimp naturally abundant in the seas. Chitosan has many good properties of natural polymers, such as biocompatibility, biodegradability, non-toxicity, etc., which make it an environmental friendly material [23,24]. Furthermore, it has high percentage of nitrogen and potential chiral sites in its molecular framework. In our previous work, we reported that Schiff base copper complexes derived from chitosan and substituted salicylaldehydes were efficient catalysts for the cyclopropanation of styrene [25]. In this paper, we furthered our study by altering the copper content in the catalysts and using other diazoacetates. Additionally, other olefins than styrene as substrate were also studied. The catalysts were synthesized according to the route in Scheme 1. Chitosan and salicylaldehyde or substituted salicylaldehydes were stirred in methanol, giving the Schiff

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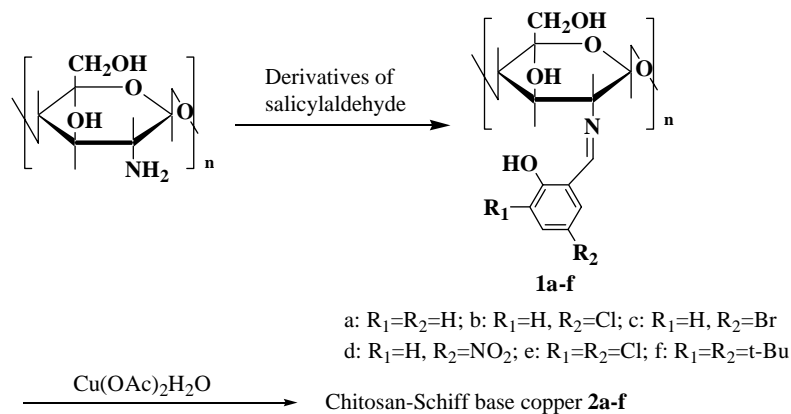
Scheme 1. Procedure for synthesis of the chitosan-Schiff base copper(II) complexes (**2a**–**2f**).
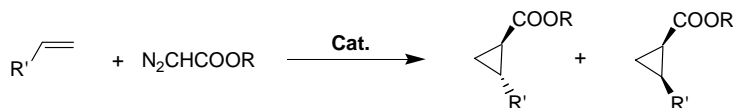
Scheme 2. Cyclopropanation of olefins with diazoacetates.

base. Coordinating the Schiff base with copper salt resulted in the dark-green Schiff base copper complexes, which were then used as catalysts to promote the cyclopropanation of olefins with alkyl diazoacetates (Scheme 2).

2. Experimental

2.1. Materials and analysis

Ethyl diazoacetate and 2,5-dimethyl-2,4-hexadiene were purchased from Fluka. *t*-Butyl acetoacetate was purchased from Acros. *t*-Butyl diazoacetate was synthesized from *t*-butyl acetoacetate as described in the literature [27]. Other reagents were of analytical grade and were used as received.

Atomic absorption results were obtained on a WFX-10 atomic absorption spectrometer. The reaction products of cyclopropanation were analyzed by a GC–MS (Agilent 6890N GC/5973 MS) system. The yield, the ratio of *cis* and *trans* isomer, and the e.e. values were determined by gas chromatography on a HP 5890 II GC with a SE-54 capillary column and a HP 6890GC with a CP-Chirasil-Dex CB capillary column (25 m × 0.25 mm, 0.25 μm i.d.).

2.2. Preparation of the chitosan-Schiff base (*1a*–*1f*)

1.9 g chitosan and 30 mmol salicylaldehyde derivatives were refluxed in 30 ml methanol and 3 ml acetic acid for 10 h. After the completion of reaction, the chitosan-Schiff base supports were collected by filtration, washed with ethanol and acetone, respectively, and dried under vacuum.

2.3. Preparation of the chitosan-Schiff base copper(II) catalysts (*2a*–*2f*)

Chitosan-Schiff bases and $Cu(OAc)_2 \cdot H_2O$ were added with different N/Cu ratio in 20 ml ethanol and refluxed for 10 h. After the reaction, the chitosan-Schiff base copper(II) catalysts were collected by filtration, washed with water and ethanol. The chitosan-Schiff base copper(II) catalysts were dried under vacuum. The copper content of the catalysts was determined by atomic absorption spectroscopy.

2.4. Cyclopropanation reaction

Under an argon atmosphere, a few drops of 0.5 mmol of diazoacetate in 2 ml of 1,2-dichloroethane was added to a mixture of 5 mol% (based on copper) catalyst, 8 mmol of olefin and 1 ml of 1,2-dichloroethane at 80 °C to initiate the reaction. After the mixture was cooled to 60 °C, the rest of the diazoacetate solution was added over 1.5 h by a syringe pump, the mixture was stirred for another 1.5 h after the addition was complete, and then the mixture was filtrated. The catalyst was recovered for further reactions.

3. Results and discussion

The reaction was first carried out between ethyl diazoacetate and styrene catalyzed by complex **2a** with a different copper content. The results are summarized in Table 1. As can be seen in Table 1, the catalysts showed high catalytic activity, a good yield about 80% being achieved. With the decrease in the copper content, the e.e. of both isomers changed gradually. We deduced that when the complex contained higher copper, there must be some uncoordinated copper just absorbed on the solid surface, lowering the enantioselectivity of the reaction. The highest enantioselectivity was obtained when the copper content was around 4.4%, which led to 20.7% e.e. for *cis* isomer and 10.0% e.e. for *trans* isomer (entry 5). Further lowering the copper content might lead to a condition of inadequate active metal centers, and for that reason, the complex could not induce the reaction

efficiently. In the following study, the copper content of the complexes was kept constant at about 4.4%.

Because the chitosan-Schiff base copper complex is insoluble in most organic solvent, it can be separated by filtration when the reaction finished, and after being washed with 1,2-dichloroethane for several times, it can be reused. The results are shown in Table 2, from which one can see, after five runs of reactions, the catalyst still retained its high catalytic activity.

Inspired by the above results, we decided to continue the study of these kinds of catalysts for cyclopropanation of styrene by introducing functional groups into the salicylaldehyde moiety and bulky group into the diazoacetate. The results are summarized in Table 3. When the reaction was carried out between styrene and ethyl diazoacetate, neither the electron-withdrawing nor the bulky substituents on the salicylaldehyde moiety of the catalysts had much influence on the yield and e.e. of both *cis* and *trans* isomers (entries 1, 3, 5, 7, 9 and 11). However, using *t*-butyl diazoacetate instead of ethyl diazoacetate resulted in a dramatic increase in e.e. for both the *cis* and *trans* isomers. On the other hand, a big drop in the yield was observed, which indicated that the bulky *t*-butyl group made it more difficult to form metal carbene species by the reaction between the *t*-butyl diazoacetate and the chitosan-Schiff base copper complexes. It is noteworthy that these kinds of catalysts are different from those in the previous report [26] in that the introduction of electron-withdrawing substituents to the salicylaldehyde moiety of the catalysts had a negative effect on the enantioselectivity of the reaction between styrene and *t*-butyl diazoacetate. This effect can be seen by comparing entry 2 and

Table 1

Cyclopropanation of styrene with ethyl diazoacetate catalyzed by complex **2a** with different copper content[a]

Entry	Cu (%)	Yield[b] (%)	*cis:trans*	e.e. of *cis*[c] (%)	e.e. of *trans*[d] (%)
1	16.5	81.3	37.2:62.8	8.1	2.8
2	12.4	79.1	37.5:62.5	10.6	2.8
3	11.0	82.5	37.1:62.9	9.6	4.5
4	7.8	84.3	37.1:62.9	17.4	7.2
5	4.4	81.5	35.3:64.7	20.7	10.0
6	2.8	78.3	35.9:64.1	18.6	4.6

[a] Reactions were carried out at 60 °C in 1,2-dichloroethane with 5 mol% catalyst.
[b] The yields were based on ethyl diazoacetate.
[c] 1*S*, 2*R* as the major enantiomer.
[d] 1*S*, 2*S* as the major enantiomer.

Table 2

Cyclopropanation of styrene with ethyl diazoacetate using recycled catalyst **2a** (copper content is 4.4%)[a]

Entry	Recycle no.	Yield[b] (%)	cis:trans	e.e. of cis[c] (%)	e.e. of trans[d] (%)
1	Fresh	81.5	35.3:64.7	20.7	10.0
2	1	80.1	35.5:64.5	19.0	8.6
3	2	82.4	36.3:63.7	16.9	9.3
4	3	79.6	35.8:64.2	16.9	7.2
5	4	77.3	35.6:64.4	15.8	5.9

[a] Reaction conditions are the same as in Table 1.
[b] The yields were based on ethyl diazoacetate.
[c] 1*S*, 2*R* as the major enantiomer.
[d] 1*S*, 2*S* as the major enantiomer.

Table 3

Cyclopropanation of styrene with $N_2CHCOOR$ catalyzed by chitosan-Schiff base copper(II) complexes (**2a**–**2f**) [a]

Entry	Catalyst	R	Yield[b] (%)	cis:trans	e.e. of cis (%)	e.e. of trans (%)
1	**2a**	Et	81.5	35.3:64.7	20.7	10.0
2[c]	**2a**	t-Bu	43.2	26.1:73.9	43.0	26.1
3	**2b**	Et	86.3	36.2:63.8	19.1	2.8
4[c]	**2b**	t-Bu	38.8	26.8:73.2	42.8	24.0
5	**2c**	Et	83.7	36.7:63.3	16.7	2.2
6[c]	**2c**	t-Bu	35.1	26.6:73.4	33.6	20.3
7	**2d**	Et	81.7	36.3:63.7	11.2	4.4
8[c]	**2d**	t-Bu	36.2	28.1:71.9	22.3	10.8
9	**2e**	Et	78.3	36.0:64.0	15.8	4.1
10[c]	**2e**	t-Bu	37.0	28.8:71.2	33.6	23.4
11	**2f**	Et	77.6	30.2:69.8	20.0	8.7
12[c]	**2f**	t-Bu	32.5	23.7:76.3	55.8	37.0

[a] Reaction conditions are the same as in Table 1 except *t*-butyl diazoacetate (R = *t*-Bu) was used in even entries instead of ethyl diazoacetate (R = Et).
[b] The yields were based on $N_2CHCOOR$.
[c] The absolute configuration of the products was not identified.

entries 4, 6, 8 and 10. The highest enantioselectivity was obtained with catalyst **2f** bearing two *t*-butyl groups on the salicylaldehyde moiety, which led to 55.8% e.e. for *cis* isomer and 37.0% e.e. for *trans* isomer (entry 12). The results lead to the conclusion that the steric effect is more remarkable than the electronic effect in improving the enantioselectivity of the reaction promoted by the chitosan based catalyst.

Table 4

Cyclopropanation of various olefins with $N_2CHCOOR$[a]

Substrates	R	Yield[b] (%)	cis:trans	e.e. of cis (%)	e.e. of trans (%)
1-Heptene	Et	82.6	33.4:63.6	25.5	15.4
	t-Bu	66.3	29.0:71.0	56.3	42.9
1-Octene	Et	88.4	34.9:63.1	22.1	13.5
1-Nonene	Et	86.3	34.5:63.5	27.9	15.5
	t-Bu	58.7	30.6:69.4	51.3	37.7
α-Methyl styrene	Et	77.7	44.1:55.9	18.5	27.5
2,5-Dimethyl-2,4-hexadiene	Et	65.1	45.5:54.5	11.0	10.1

[a] Reaction conditions are the same as in Table 1 and the absolute configuration of the products was not identified.
[b] The yields were based on $N_2CHCOOR$.

In addition, the complex **2f** was also applied to the cyclopropanation of other olefins with diazoacetates. The results are summarized in Table 4, when 1-heptene and 1-octene as well as 1-nonene were used as the substrates, high yields were achieved; moreover, the e.e. values were higher than when styrene was used. Compared with the reaction between styrene and *t*-butyl diazoacetate, a better yield of 66.3% was attained when the reaction was carried out between 1-heptene and *t*-butyl diazoacetate. An e.e. of 27.5% for the *trans* isomer was achieved for the reaction of α-methyl styrene, whereas low yield and enantioselectivity was obtained when 2,5-dimethyl-2,4-hexadiene was employed as a substrate.

4. Conclusion

In conclusion, we have developed a series of easily recoverable and efficient catalysts for the cyclopropananion of olefins with alkyl diazoacetates based on natural polymer chitosan. The substituents on the salicylaldehyde moiety of the catalysts showed obvious effects on the enantioselectivities of the reaction between olefins and *t*-butyl diazoacetate. The optimization of the catalyst is still underway in our laboratory.

Acknowledgements

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