Chinese Chemical Letters Vol. 16, No. 3, pp 331-334, 2005
http://www.imm.ac.cn/journal/ccl.html

Asymmetric Intramolecular Cyclopropanation Induced by (β-Diketone)-copper Complex

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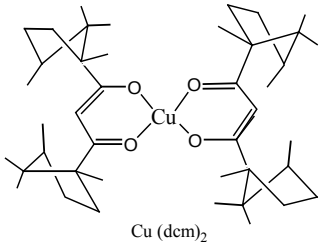
Abstract: Asymmetric intramolecular cyclopropanation of allylic diazoacetate was investigated using a chiral (β-diketone)-copper complex as catalyst, excellent yield and enantioselectivity were achieved. Some factors influencing enantioselectivity were discussed.

Keywords: Intramolecular, cyclopropanation, asymmetric catalysis, (β-diketone)-copper.

In recent years, synthesis of chiral bicyclic or polycyclic compounds with a cyclopropane moiety by asymmetric intramolecular cyclopropanation has been an attractive subject [1, 2]. M. P. Doyle and *et al.* found that intramolecular cyclopropanation of allylic diazoacetates could be catalyzed by chiral dirhodium(II) carboxamidates with high enantioselectivity[3]. However, these same synthetically useful transformations have not been examined using chiral copper(II) complex with C_2-symmetric ligands. We have previously reported a chiral β-diketone complex $Cu(dcm)_2$ as a chiral catalyst in the asymmetric cyclopropanation of styrene with diazoacetate[4], high enantioselectivities have been achieved.

In this work we further applied this chiral copper (II) complex as the catalyst for the enantioselective intramolecular cyclopropanation of allylic diazoacetates.

Scheme 1



$Cu(dcm)_2$

Results and Discussion

The choice of the solvent was not limited to benzene. As shown in **Table 1**, many solvents were tested for the reaction of allylic diazoacetate **2d** and high ee value were

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obtained in some solvents such as hexane, THF, chlorobenzene. It was also found that acetone, acetoneitrile and pyridine were ineffective under the same conditions.

A high yield can be obtained at a higher temperature, as shown in **Table 2**. However, a lower ee value was obtained upon increasing the temperature for the reaction of allylic diazoacetate **2d**. Enantiomeric excess of 94.6% was obtained at 0℃, but the yield was low (9.4 %). According to these data, the preferable temperature range for this reaction is 60 or 80℃.

This catalyst is highly effective, as shown in **Table 3**. The reaction could be carried out with 0.01 mol % catalyst loading, affording 47% yield of product with 43.1% ee in the case of **2d**.

To evaluate the effectiveness of the chiral catalyst $Cu(dcm)_2$ in inducing the enantioselective cyclization of alllylic diazoacetates, we initiated a series of exploratory experiments. The allylic diazoacetates **2a~2f** were prepared by the reaction of the corresponding allylic alcohols **1a~1f** with glyoxylic acid chloride p-toluene sulfonyl hydrazone according to the procedure reported by Corey and Myers5 as shown by **Scheme 2**. The reaction of cyclopropanation was carried out with benzene as the solvent, the results are collected in **Table 4.** It was found that excellent enantioselectivities were obtained when R_3=H, R_1=R_2=O-MePh or Ph, while R_1=R_2=H, R_3 changes from H to CH_3 or Ph, the enantioselectivities decreased significantly. So, bulky groups

Table 1 The effect of solvent on the asymmetric cyclopropanation reaction of **2d** [a].

Entry	Solvent	Yield (%)	ee(%) [b]
1	hexane	71	84.6
2	THF	69	86.7
3	chlorobenzene	64	91.6
4	acetone	32	27.4
5	acetonitrile	36	37.6
6	pyridine	19	16.7

a. Reactions were performed in refluxing solvents using 1 mol % of catalyst.
b. Determined by HPLC with a Chiraldex G-TA column.

Table 2 The influence of temperature on the asymmetric cyclopropanation reaction of **2d**.

Entry	Temp.(℃)	Yield (%)	ee (%)
1	0	9.4	94.6
2	25	19.3	93.8
3	40	36.8	93.2
4	60	47	92.1
5	80	62	91.2
6	100	59.3	71.7

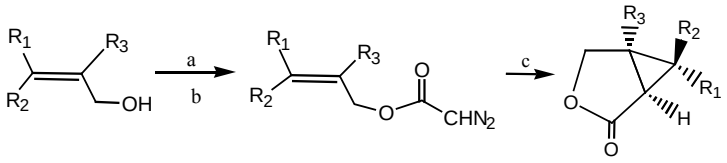
Reactions were performed in benzene using 1mol % of catalyst.

Table 3 The influence of the amount of catalyst on the asymmetric cyclopropanation of **2d**.

Entry	Amt of Cat. (mol%)	Yield (%)	ee (%)
1	2	62.4	91.4
2	1	62	91.2
3	0.1	53	73.6
4	0.01	47	43.1
5	0.001	19.6	15.7

Reaction conditions: the same as that in **Table 1** except the amount of catalyst used.

Scheme 2



1a~1f **2a~2f** **3a~3f**

a) $MeC_6H_4SO_2NHN{=}CHCOCl$, b) $C_6H_5NMe_2$, c) $Cu(dcm)_2$

Table 4 Enantioselective intramolecular cyclopropation of **2a~2f** catalyzed by $Cu(dcm)_2$.

product	R_1	R_2	R_3	Yield (%)	Ee (%)
3a	H	H	H	79.0	54.4
3b	CH_3	CH_3	H	80.0	72.3
3c	H	H	CH_3	71.4	46.8
3d	Ph	Ph	H	62.0	91.2
3e	*O*-MePh	*O*-MePh	H	56	93.4
3f	H	H	Ph	69.6	37.7

Reactions were performed in refluxing benzene using 1mol % of catalyst.

in R_1 and R_2 favored the enantioselectivity and substitution at the proximal position of the double bond appeared to be disadvantageous for the enantioselectivity.

In conclusion, the catalyst of $Cu(dcm)_2$ is found to be efficient for the asymmetric intramolecular cyclopropanations of some allylic diazoacetates.

Experimental

Allylic diazoacetates **2a~2f** were prepared by the procedure of reference[5].

3.3-Diphenyl-2-propen-1-yl diazoacetate(**2d**): ^{1}HNMR ($CDCl_3$, δ ppm): 7.53~7.29 (m, 10H), 6.47~6.36 (m, 1H), 4.93~4.81(d, 2H, J=7.2), 4.81(br s, 1H); IR 1703.5 (C=O) cm^{-1}. ^{13}CNMR($CDCl_3$, δ ppm): 167.8, 138.9, 136.1, 129.5, 128.9, 127.4, 125, 66.4, 46.3; Anal. Calcd. for $C_{17}H_{14}O_2N_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.59; H, 5.11; N, 10.01.

3.3-D-*O*-mephenyl-2-propen-1-yldiazoacetate (**2e**): ^{1}HNMR ($CDCl_3$, δ ppm): 7.62~7.29 (m, 8H), 6.51~6.42 (m, 1H), 4.96~4.82(d, 2H, J=7.5), 4.83(br s, 1H), 2.43(s, 6H); IR 1698.7 (C=O) cm^{-1}; ^{13}CNMR($CDCl_3$, δ ppm): 168.8, 141.9, 139.3, 131.6, 130.5, 128.7, 126.8, 66.8, 46.7, 28.6; Anal. Calcd. for $C_{19}H_{18}O_2N_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.31; H, 5.86; N, 9.32.

2-Phenyl-2-propen-1-yl diazoacetate (**2f**): ^{1}HNMR ($CDCl_3$, δ ppm): 7.42~7.23(m, 5H), 5.33~5.21 (d, 2H, J=12.5), 4.631(s, 2H), 4.79(br s, 1H); IR 1699.3 (C=O) cm^{-1}; ^{13}CNMR($CDCl_3$, δ ppm): 166.9, 141.9, 138.1, 128.7, 127.6, 126.3, 124.2, 66.9, 46.1. Anal. Calcd for $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.39; H, 4.87; N, 13.76.

3-Oxabicyclo[3.1.0]hexan-2-one (**3a**) was obtained from[6] cycligation of **2a~2f** in 79% yield. Enantiomer separation on a 30 m Chiraldex G-TA column operated at 80℃ for 2 min and then programmed to 150℃ at 1℃/min: 45 min for (1R, 5S)-**3a** enantiomer, 47 min for (1S, 5R)-**3a** enantiomer, 54.4%ee, $[\alpha]_D^{20}$ +34.6°(c 1, $CHCl_3$), 55.8% ee based on a report of (1R, 5S) **-3a,** $[\alpha]_D^{20}$ +62(c 2.5, $CHCl_3$)[6].

6.6-Dimethyl-3-oxabicyclo[3.1.0]hexan-2-one **3b** was obtained in 80% yield. Enantiomer separation on a 30 m Chiraldex G-TA column operated at 163℃: 14 min for (1S, 5R)-**3b** enantiomer, 20 min for (1R, 5S)-**3b** enantiomer, 72.3%ee, $[\alpha]_D^{25}$ +64.8(c 2, $CHCl_3$), 74.8% ee based on 98% optically pure (1S, 5R)-**3b,** $[\alpha]_D^{23}$ +85(c 1.96, $CHCl_3$) [6].

5-Methyl-3-oxabicyclo[3.1.0]hexan-2-one **3c** was obtained in 71.4% yield. Enantiomer separation on a 30 m Chiraldex G-TA column operated at 120℃: 25 min for (1S, 5R)-**3c** enantiomer, 26 min for (1R, 5S)-**3c** enantiomer, 46.8%ee, $[\alpha]_D^{25}$ -26.7(c 0.9, $CHCl_3$), 50% ee based on 99.5% optically pure (1R, 5S)-**3c,** $[\alpha]_D^{23}$ -53(c 0.9, $CHCl_3$)[6].

6.6-Diphenyl-3-oxabicyclo[3.1.0]hexan-2-one **3d** was obtained in 62% yield. Enantiomer separation on a 30 m Chiraldex G-TA column operated at 158℃: 89 min and 94 min for two enantiomers, 91.2% ee, $[\alpha]_D^{23}$-110(c 0.5, $CHCl_3$). It absolute configuretion was not determined. ^{1}HNMR($CDCl_3$, δ ppm): 7.52~7.27(m, 10H, C_6H_5), 4.50(dd, 2H, J=9.5, 4.7 Hz, OCH_2), 2.64(dd, 1H,J=7.2, 4.3Hz, CHC=O), 2.45~2.39 (m, 1H, CH); IR 1762.7(C=O)cm^{-1}. ^{13}C NMR($CDCl_3$, δ ppm): 168.8, 138.9, 131.2, 130.5, 128.9, 71.4, 31.6, 29.6, 28.3; Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.43; H, 5.52.

6,6-Di-*O*-mephenyl-3-oxabicyclo[3.1.0]hexan-2-one **3e** was obtained in 56% yield. Enantiomer separation on a 30 m Chiraldex G-TA column operated at 164℃: 73 min and 80 min for two enantiomers, 93.4% ee, $[\alpha]_D^{23}$ -126.c 0.5, $CHCl_3$). It absolute configuretion was not determined. ^{1}H NMR($CDCl_3$, δ ppm): 7.47~7.19(m, 10H, C_6H_5), 4.43(dd, 2H, J=9.3, 4.5 Hz, OCH_2), 2.53(dd, 1H,J=7.0, 4.1Hz, CHC=O), 2.47~ 2.39 (m, 1H, CH), 2.37 (s, 6H, CH_3); IR 1788.6 (C=O) cm^{-1}; ^{13}C NMR($CDCl_3$, δ ppm): 167.9, 140.3, 132.1, 130.5, 129.8, 72.6, 31.4, 29.8, 29.1, 28.5; Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.98; H, 7.95; Found: C, 81.83; H, 7.81.

5-Phenyl-3-oxabicyclo[3.1.0]hexan-2-one **3f** was obtained in 69.6% yield. Enantiomer separation on a 30 m Chiraldex G-TA column operated at 144℃: 70 min and 76 min for two enantiomers, 37.7% ee, $[\alpha]_D^{23}$ 65.6(c 1, $CHCl_3$). It absolute configuration was not determined. ^{1}HNMR($CDCl_3$, δ ppm): 7.67~7.34 (m,5H, C_6H_5), 4.63~4.24 (m, 2H, OCH_2), 1.81~1.89 (m, 1H, CH C=O), 1.31(dd, 1H, J=8.9, 4.1 Hz), 1.16 (dd, 1H J=4.1, 2.7 Hz); IR 1783.5 (C=O) cm^{-1}; ^{13}CNMR($CDCl_3$, δ ppm): 168.9, 140.1, 131.1, 130.2, 129.5, 72.6, 33.4, 29.8, 28.9; Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 7.64. Found: C, 75.99; H, 7.52.

Acknowledgement

This work is supported by the National Natural Science Foundation of China and the Department of Education Excellent Teachers Foundation.

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Received 8 March, 2004