Heterogeneous Catalysis

DOI: 10.1002/ange.201300468

Highly Stereoselective Cyclopropanation of α,β-Unsaturated Carbonyl Compounds with Methyl (Diazoacetoxy)acetate Catalyzed by a Chiral Ruthenium(II) Complex**

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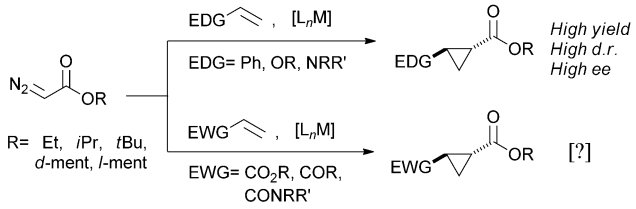
Transition-metal-catalyzed asymmetric cyclopropanation of olefins with diazoacetates is a highly useful synthetic transformation for the construction of optically active cyclopropane frameworks, which are important structures because of their appearance in a wide variety of biologically active molecules.[1] Therefore, during the past two decades, various catalytic systems have been developed for the highly diastereo- and enantioselective cyclopropanation reactions.[2] In particular, good stereocontrolled syntheses of cyclopropane derivatives have been achieved using copper,[3] rhodium,[4] ruthenium,[5] and recently cobalt[6] as catalysts. However, despite these considerable advances, only a few catalytic systems can catalyze the asymmetric cyclopropanation of electron-deficient olefins, such as α,β-unsaturated carbonyl compounds.[2e,5d,6e,f] Because of the electrophilic nature of the metal–carbene intermediate obtained by the reaction of metal complexes and diazoacetate, electron-rich olefins are generally preferred as reactants (Scheme 1).

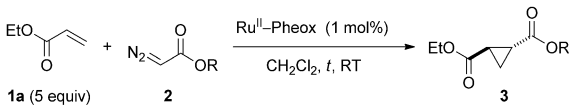


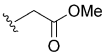
Scheme 1. Transition-metal-catalyzed asymmetric cyclopropanation.

Among several previous reports, the D_2-symmetric chiral porphyrin Co^{II}-based catalysts are the most efficient catalytic systems for asymmetric cyclopropanation of electron-deficient olefins, as previously reported by Zhang and coworkers.[6e] Because the resulting optically active dicarbonyl cyclopropane compounds were found to be very important synthetic intermediates for various applications,[7] the development of a general and efficient catalytic system for the cyclopropanation of α,β-unsaturated carbonyl compounds is highly desirable. This prompted us to explore highly efficient catalytic systems that can promote the asymmetric cyclopropanation of α,β-unsaturated carbonyl compounds with diazoacetates to give the corresponding dicarbonyl cyclopropanes in high yields and with excellent diastereoselectivity and enantioselectivity.

Because we recently reported that the complex Ru^{II}-Pheox is extremely efficient in asymmetric inter- and intramolecular cyclopropanation,[8] the cyclopropanation of ethyl acrylate **1a** with various diazoacetates **2** catalyzed by Ru^{II}-Pheox was examined. The results are shown in Table 1.

Table 1: Screening of various diazoacetates.[a]



Entry	R	Diazo **2**	*t*	Yield **3** [%][c]	*trans*/*cis*[d]	*ee* [%][e]
1	Et	EDA **2a**	1 min	15	>99:1	–
2[b]	Et	EDA **2a**	12 h	45	>99:1	99
3		SDA **2b**	1 min	25	>99:1	87
4[b]		SDA **2b**	12 h	52	>99:1	88
5		ADA **2c**	1 min	30	>99:1	99
6[b]		ADA **2c**	12 h	52	>99:1	99
7		MDA **2d**	1 min	46	>99:1	96
8[b]		MDA **2d**	12 h	75	>99:1	96

[a] Reaction conditions: ethyl acrylate **1a** (1.0 mmol) and diazoacetate **2** (0.2 mmol) in the presence of Ru^{II}-Pheox (1 mol%). [b] Diazoacetate **2** diluted in CH_2Cl_2 was slowly added for 11 h by using a syringe pump. [c] Yield of isolated product. [d] Determined by NMR spectroscopy. [e] Determined by chiral-phase HPLC analysis.

Although the yield was very low when the reaction was carried out with ethyl diazoacetate (EDA) for 1 min, the yield was enhanced to 45% by the slow addition of diazo compound (Table 1, entries 1 and 2). The corresponding dicarbonyl cyclopropane was obtained with excellent *trans*-selectivity (>99:1) and enantioselectivity (99% *ee*). Succinimidyl diazoacetate (SDA) **2b** increased the yield to 52%; however, the enantioselectivity decreased to 88% *ee* (Table 1, entry 4). Next, we focused our efforts on ketone- or ester-

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[**] This work was supported by a Grant-in-Aid for Scientific Research (C) (No. 20550137) from the Japan Society for the Promotion of Science.

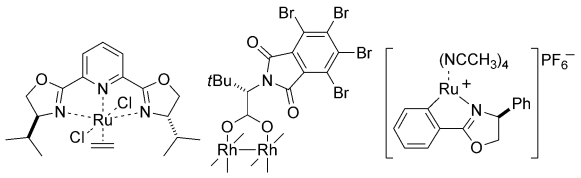
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201300468.

functionalized diazoacetates, such as acetonyl diazoacetate (ADA) **2c**[9] and methyl (diazoacetoxy)acetate (MDA) **2d**,[10] which have never been used before as carbene sources in the cyclopropanation. Although ADA **2c** gave the desired product in moderate yield (52%), both the diastereoselectivity and enantioselectivity were very high (d.r. > 99:1, 99% *ee*, respectively; Table 1, entry 6). Surprisingly, when MDA **2d** was used as the carbene source in the cyclopropanation, the desired product was obtained in high yield (75%) with excellent diastereoselectivity (> 99:1) and enantioselectivity (96% *ee*; Table 1, entry 8). We envisioned that the carbonyl moiety on the functional group could have played an important role as an electron-donating group after the coordination between the carbonyl group and the ruthenium metal center as described previously,[8b] which may generate the nucleophilic carbene complex intermediate. Therefore, higher electron-donating group such as ester could further increase the nucleophilicity of the carbene intermediate, resulting in highly reactive cyclopropanation.

Encouraged by the results obtained with the Ru^{II}-Pheox catalyst, we investigated the cyclopropanation of ethyl acrylate **1a** with MDA **2d** catalyzed by commonly used catalysts, such as $Cu(OAc)_2$, $[Rh_2(OAc)_4]$, and $Pd(OAc)_2$. The results are shown in Table 2. No products were detected when the reaction was carried out employing the $Cu(OAc)_2$ catalyst (Table 2, entries 1 and 2). However, the desired product could be obtained in low yield with high diastereoselectivity (> 99:1) when $[Rh_2(OAc)_4]$, and $Pd(OAc)_2$ were used (Table 2, entries 3 and 4). The chiral $[RuCl_2(pybox\text{-}ip)(C_2H_4)]$ catalyst,[2d] which was synthesized by Nishiyama's group and broadly used in cyclopropanation, was also unproductive (Table 2, entries 5 and 6). The chiral $[Rh_2(S\text{-}TBPTTL)_4]$ catalyst, reported by Hashimoto and co-workers,[11] gave the desired product in moderate yield (49%) and high diastereoselectivity (> 99:1); however, the enantioselectivity was very low (19% *ee*) (Table 2, entry 7). The Ru^{II}-Pheox catalyst further improved the enantioselectivity to 98% *ee* when the reaction was conducted at lower temperature (0°C). Conversely, the enantioselectivity was slightly decreased to 90% *ee* at higher temperature (Table 2, entries 9 and 10).

With the optimal reaction conditions established, substrate typologies were investigated. Initially, as summarized in Table 3 (entries 1–7), we examined the cyclopropanation of a series of α,β-unsaturated esters with MDA **2d** or ADA **2c**. Ethyl and methyl acrylate gave the corresponding bicarbonyl cyclopropane products in higher yield and enantioselectivity than the reaction with bulky phenyl and benzyl acrylates. The cyclopropanation of α-methyl substituted acrylate gave a cyclopropane product **3d** with little change in the yield

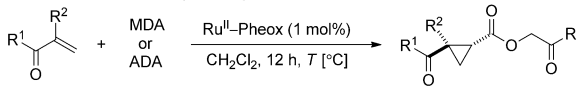
Table 2: Screening of various catalysts.

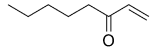
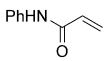
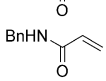
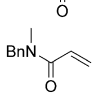


Entry	Catalyst	X (mol%)	*T* [°C]	Yield [%][a]	*trans*/*cis*[b]	*ee* [%][c]
1	$Cu(OAc)_2$	1	RT	0	–	–
2	$Cu(OAc)_2$	5	40	0	–	–
3	$[Rh_2(OAc)_4]$	5	RT	9	> 99:1	–
4	$Pd(OAc)_2$	5	RT	23	> 99:1	–
5	$[RuCl_2(pybox\text{-}ip)(C_2H_4)]$	3	RT	0	–	–
6	$[RuCl_2(pybox\text{-}ip)(C_2H_4)]$	3	40	0	–	–
7	$[Rh_2(S\text{-}TBPTTL)_4]$	1	RT	49	93:7	19
8	Ru^{II}-Pheox	1	RT	75	> 99:1	96
9	Ru^{II}-Pheox	1	0	43	> 99:1	98
10	Ru^{II}-Pheox	1	40	52	> 99:1	90

[a] Yield of isolated product. [b] Determined by NMR spectroscopy. [c] Determined by chiral-phase HPLC analysis.

Table 3: Ru^{II}-Pheox-catalyzed asymmetric cyclopropanation of various α,β-unsaturated carbonyl compounds with MDA or ADA.

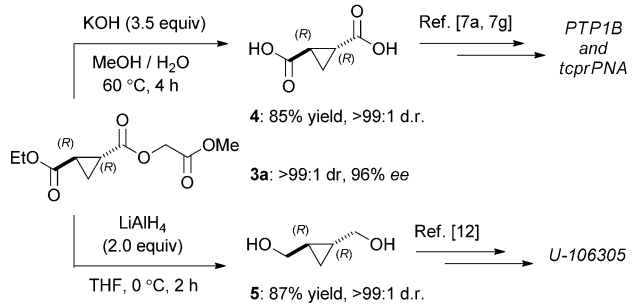


Entry	Alkene **1**	Diazo **2**	*T* [°C]	Yield [%][a]	**3**	*trans*/*cis*[b]	*ee* [%][c]
1		MDA	RT	75	**3a**	> 99:1	96
2		ADA	RT	52	**3b**	> 99:1	99
3		MDA	RT	66	**3c**	> 99:1	96
4		MDA	RT	56	**3d**	> 99:1	96
5		MDA	RT	55	**3e**	> 99:1	93
6		MDA	RT	50	**3f**	> 99:1	94
7		MDA	RT	61	**3g**	97:3	94
8		MDA	RT	75	**3h**	> 99:1	96
9		MDA	RT	73	**3i**	> 99:1	94
10		MDA	RT	87	**3j**	> 99:1	98
11		MDA	RT	55	**3k**	> 99:1	93
12		MDA	40	87	**3l**	> 99:1	84
13		ADA	40	74	**3m**	> 99:1	94
14		MDA	40	70	**3n**	> 99:1	88
15		MDA	40	57	**3o**	> 99:1	92

[a] Yield of isolated product. [b] Determined by NMR spectroscopy. [c] Determined by chiral-phase HPLC analysis.

while maintaining the same diastereoselectivity and enantioselectivity as obtained with nonsubstituted acrylate on the α position (Table 3, entry 4). Surprisingly, cyclic ester substrate such as 2-methylenebutyrolactone could also be cyclopropanated to give spiro[2.4]heptane **3g** in good yield (61%) and with high diastereoselectivity and enantioselectivity (Table 3, entry 7). Next, the aliphatic and aromatic α,β-unsaturated ketones were examined (Table 3, entries 8–11). The reactions proceeded smoothly and produced the **3h–3j** products in high yields with excellent diastereoselectivity and enantioselectivity. In particular, the highest yield (87%) and enantioselectivity (98% *ee*) were obtained when bulky phenyl vinyl ketone was used as a substrate (Table 3, entry 10). However, in the case of cyclopropanation with benzyl vinyl ketone, lower yield and enantioselectivity were obtained (Table 3, entry 11). Notably, the cyclopropanation of α,β-unsaturated amides could not proceed under the optimal reaction temperature. By increasing the temperature to 40 °C, the desired products were formed in high yields with excellent diastereoselectivity (> 99:1) while the enantioselectivities decreased due to the higher temperature (Table 3, entries 12–15).

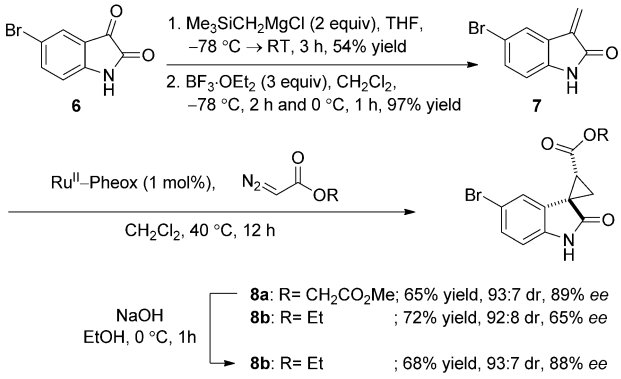
To demonstrate the utility of this general and highly stereoselective bicarbonyl cyclopropane synthesis, we prepared the 1,2-cyclopropane dicarboxylic acid and 1,2-cyclopropane dimethanol, which are key intermediates in the reported syntheses of PTP1B,[7a] tcprPNA,[7g] and U-106305[12] from dicarbonyl cyclopropane **3a** (Scheme 2). The optically



Scheme 2. Preparation of 1,2-cyclopropane dicarboxylic acid and 1,2-cyclopropane dimethanol.

active 1,2-cyclopropane dicarboxylic acid intermediate **4** can be easily synthesized by the hydrolysis of **3a** with KOH giving 85% yield and high diastereoselectivity (d.r. > 99:1). Furthermore, we successfully synthesized the 1,2-cyclopropane dimethanol intermediate **5** in 87% yield with high diastereoselectivity (d.r. > 99:1) by the reduction of **3a** with $LiAlH_4$. As the (1*R*,2*R*) configuration of 1,2-cyclopropane dicarboxylic acid and 1,2-cyclopropane dimethanol were confirmed by the comparison of their optical rotation,[12b,13] the absolute configuration of dicarbonyl cyclopropane **3a** was also determined to be (1*R*,2*R*).

Encouraged by the efficiency of the Ru^{II}-Pheox-catalyzed asymmetric cyclopropanation of methyl (diazoacetoxy)acetate **2d** with α,β-unsaturated carbonyl compounds, we sought to examine the utility of this method for the enantioselective total synthesis of an oxindole containing unique spiro cyclopropane **8b**, which was reported to be useful as HIV-1 nonnucleoside reverse transcriptase inhibitor by He and co-workers in 2006[14] (Scheme 3). We used 5-bromoisatin **6** as



Scheme 3. Total synthesis of HIV-1 nonnucleoside reverse transcriptase inhibitor **8b**.

the starting material and initiated a Peterson olefination to produce the corresponding 5-bromo-3-methyleneindolin-2-one **7** in good yield. We then performed the asymmetric cyclopropanation of **7** with MDA catalyzed by Ru^{II}-Pheox under the optimized conditions. The reaction proceeded smoothly to give the expected product **8a** in good yield with high diastereoselectivity (93:7) and enantioselectivity (89% *ee*). Subsequent hydrolysis of **8a** can be easily carried out to generate the desired spiro cyclopropane oxindole **8b** in 68% yield with high diastereoselectivity (93:7) and enantioselectivity (88% *ee*). Notably, the asymmetric cyclopropanation of **7** with EDA **2a** also gave the **8b** product in high yield with high diastereoselectivity, even though the enantioselectivity was decreased to 65% *ee*. This novel synthetic route represents a significant improvement in terms of diastereoselectivity efficiency reported till date. Moreover, it also established the first enantioselective total synthesis of spiro cyclopropane oxindole **8b**.

To summarize, we have developed a Ru^{II}-Pheox-catalyzed asymmetric cyclopropanation of α,β-unsaturated carbonyl compounds with ketone- or ester-functionalized diazoacetates. The use of MDA as a carbene source was found to be crucial for the Ru^{II}-Pheox-catalyzed cyclopropanation of electron-deficient olefins, giving the corresponding dicarbonyl cyclopropane products in high yields with excellent diastereoselectivity (up to > 99:1) and enantioselectivity (up to 99% *ee*). Furthermore, we have also successfully utilized the dicarbonyl cyclopropane product to synthesize the optically active 1,2-cyclopropane dicarboxylic acid and 1,2-cyclopropane dimethanol, which are useful as intermediates for the synthesis of various bioactive compounds. Moreover, this catalytic system is very important because it can be exploited to produce the spiro cyclopropane oxindole **8b**, which is an HIV-1 nonnucleoside reverse transcriptase inhibitor.

Experimental Section

General procedure for the cyclopropanation reaction: A solution of diazoester (0.2 mmol) in CH_2Cl_2 (2 mL) was slowly added to a mixture of Ru^{II}-Pheox catalyst (1.3 mg, 0.002 mmol) and α,β-unsaturated carbonyl compounds (1.0 mmol) in CH_2Cl_2 (1 mL) for 11 h under an argon atmosphere at room temperature. After the completion of the addition, the reaction mixture was then stirred for 1 h at room temperature. Upon completion, solvent was removed and the residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane to give the desired product. The *trans*/*cis* ratio was determined from the crude ^1H NMR spectra, and the *ee* value was determined by chiral HPLC analysis.

Received: January 18, 2013
Revised: March 15, 2013
Published online: April 16, 2013

Keywords: asymmetric cyclopropanation · carbenes · methyl (diazoacetoxy)acetate · ruthenium · α,β-unsaturated carbonyl compounds

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