Highly Enantioselective Intramolecular Cyclopropanation of Alkenyl Diazo Ketones Using Ru(salen) as Catalyst

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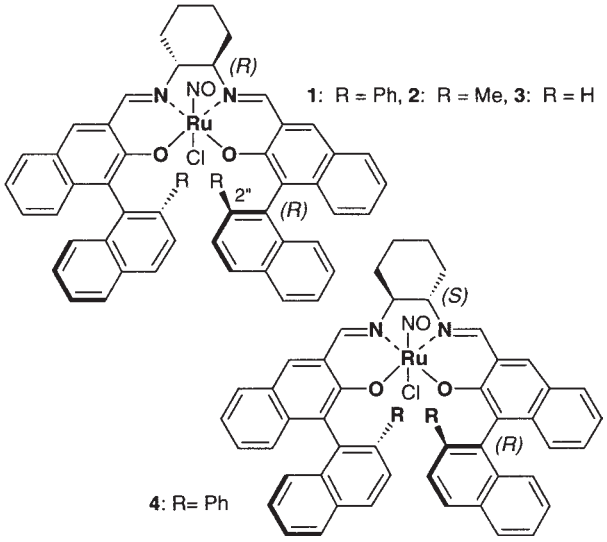
Intramolecular cyclopropanation of alkenyl diazoketones was found to proceed in a highly enantioselective manner by using optically active (nitroso)(salen)ruthenium(II) complex **1** as the catalyst under photo-irradiation.

Transition metal-mediated reactions of olefins and diazo compounds are highly practical methods for cyclopropane formation and a variety of catalysts have been developed for stereocontrol of the reactions.[1] Today, both *trans*- and *cis*-selective intermolecular cyclopropanations have been achieved in a highly enantioselective manner.[1–3] Intramolecular cyclopropanation, especially the cyclopropanation of alkenyl diazoester and diazoamide compounds, has also been achieved with high enantioselectivity by using Cu-,[4] Rh-,[5,6] Ru-,[7] and Co-complexes[8] as catalysts. Intramolecular cyclopropanation of alkenyl diazoketone substrates have also been extensively studied.[4b,9–14] Of the catalysts examined, Cu(semicorin)[9] and Cu[bis(oxazoline)s],[4b,10] showed modest to high enantioselectivity (up to 95% ee), depending on the substrates used. Recently, Pérez-Pietro et al. reported that rhodium complex bearing a unique *o*-metallated aryl phosphine ligand was an efficient catalyst for this type of reaction: cyclopropanations giving [4.1.0]heptan-2-one derivatives with the catalyst show enantioselectivity up to 95% ee, while the reactions giving [3.1.0]hexan-2-one derivatives show enantioselectivity up to 80% ee.[15] Further elaboration of the cyclization of alkenyl diazoketone substrates is strongly required. The difficulty in stereocontrol of intramolecular cyclopropanation of alkenyl diazoketones has been attributed to the transition state conformation: the alkenyl moiety is forced to approach the carbenoid center away from the chiral auxiliary.[14] Another reason is that carbenoid intermediates derived from diazoketones are more reactive, therefore less selective, than those derived from diazoesters.[16]

We have demonstrated that optically active (nitroso)(salen)-ruthenium complex [hereafter, denoted as Ru(salen)] **1** is an efficient catalyst for highly *cis*- and enantio-selective intermolecular cyclopropanation reaction under photo-irradiated conditions.[17] Recently, we have also discovered that slightly modified Ru(salen)s (**2** and **3**) catalyze the cyclization of *trans*-substituted allyl α-diazoacetates with good to high enantioselectivity.[7c]

With these results, we were intrigued by intramolecular cyclopropanation of alkenyl diazoketones.

We first examined the cyclization of (*E*)-1-diazo-6-phenyl-5-hexen-2-one using complex **3** as the catalyst under photo-irradiated conditions (Table 1, entry 1). However, the enantioselectivity was only moderate (58% ee). We next examined the cyclization using complexes **1**, **2**, and **4** as the catalysts and found



that excellent enantioselectivity as well as high chemical yield was obtained when the complex **1** was used as the catalyst (entry 3). Although the detailed mechanism of asymmetric induction is unclear at present, we assume that the 2″-phenyl substituent of **1** protrudes toward the incoming alkenyl moiety of the carbenoid intermediate and efficiently regulates its orientation.

Although enantioselectivity of the reaction with complex **4** was poor, it is noteworthy that the sense of enantioselection by **4** is opposite to the sense of enantioselection by complexes **1–3**. These results suggest that the approach of the olefinic unit of diazo compound is mainly dictated by the chirality of the diamine part, which has a strong influence on the conformation of the salen ligand.[18]

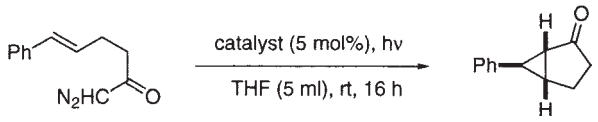


Table 1. Intramolecular cyclopropanation of (*E*)-1-diazo-6-phenyl-5-hexen-2-one

Entry	Catalyst	Yield/%	% ee[a]	elution order[b]
1	**3**	62	58	+
2	**2**	60	44	+
3	**1**	78	94	+
4	**4**	81	12	−

[a]Determined by HPLC analysis using chiral column (Daicel Chiralcel OD-H, hexane:isopropanol = 9 : 1). [b]Plus sign means that the major enantiomer is eluted fast and minus sign means that the minor enantiomer is eluted fast.

With the promising result, we focused our attention to cyclopropanation of diazoketones of different types (Table 2). The cyclization of trisubstituted alkenyl diazoketones also proceeded with high enantioselectivity (entries 1 and 2). These results indicated that non-conjugated alkenyl diazoketones can be good substrates for the present cyclization. The reaction of the alkenyl diazoketone bearing an alkynyl substituent also showed high enantioselectivity (entry 3). The presence of (*Z*)-phenyl group somewhat reduced the enantioselectivity (79% ee) of the cyclization (entry 4). Thus, good to high enantioselectivity was attained in all the reactions examined. Furthermore, it is worth to note that the presence of bulky *E*-substituent (R^1) seems to favorably affect enantioselectivity of the reaction (cf. Table 1, entry 3 and Table 2, entries 1–3).[19]

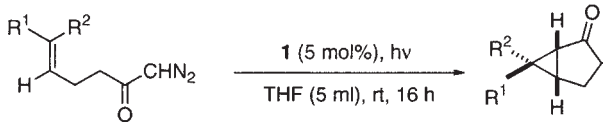


Table 2. Intramolecular cyclopropanation of alkenyl diazoketones with **1** as the catalyst

Entry	R^1	R^2	Yield/%	% ee
1	$(CH_3)_2CH(CH_2)_2$	CH_3	72	93[a]
2	CH_3	CH_3	65	87[b]
3	PhC≡C	H	82	84[c]
4	H	Ph	62	79[d]

[a]Determined by GLC analysis using a 30 m × 0.25 mm Chiral Supelco β-DEX column [column temperature: 130 °C for 70 min, then programmed to 180 °C at 5 °C/min, and 180 °C for 30 min): 76.53 min (minor enantiomer), 77.31 min (major enantiomer)]. [b]Determined by GLC analysis using a 30 m × 0.25 mm Chiral Supelco β-DEX column [column temperature: 90 °C for 30 min, then programmed to 110 °C at 2 °C/min, and 110 °C for 30 min): 41.38 min (minor enantiomer), 41.94 min (major enantiomer)]. Absolute configuration was determined to be 2*R*, 3*S* by comparing the reported specific optical rotation: $[\alpha]_D^{24} + 45$ (c 0.2 chloroform) (87% ee), [Lit. (Ref. 11) $[\alpha]_D^{23} - 34.3$ (c 1.0 chloroform) for 2*S*, *3R*-isomer (63% ee)]. [c]Determined by HPLC analysis using chiral column (Daicel Chiralcel OJ-H, hexane : isopropanol = 3 : 1). [d]Determined by HPLC analysis using chiral column (Daicel Chiralcel OJ-H, hexane : isopropanol = 20 : 1).

In conclusion, we were able to demonstrate the high potentiality of a suitably designed Ru-salen complex as the catalyst for asymmetric intramolecular cyclopropanation of alkenyl diazoketones under photo-irradiated conditions.

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References and Notes

1 For a recent review, see: a) M. P. Doyle, "Catalytic Asymmetric Synthesis," ed. by I. Ojima, Wiley-VCH, New York (2000), Chap. 5, p 191. b) A. Pfaltz, K. M. Lydon, A. M. McKervey, A. B. Charette, and H. Level, "Comprehensive Asymmetric Catalysis," ed. by E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, Springer, Berlin (1999), Chap. 16.
2 M. P. Doyle and M. N. Protopopova, *Tetrahedron*, **54**, 7919 (1998).
3 T. Niimi, T. Uchida, R. Irie, and T. Katsuki, *Adv. Synth. Catal.*, **343**, 79 (2001).
4 a) M. P. Doyle, C. S. Peterson, Q.-L. Zhou, and H. Nishiyama, *J. Chem. Soc., Chem. Commun.* **1997**, 211. b) M. P. Doyle, C. S. Peterson, and D. L. Parker, Jr., *Angew. Chem., Int. Ed. Engl.*, **35**, 1334 (1996).
5 a) M. P. Doyle, R. E. Austin, A. S. Bailey, M. P. Dwyer, A. B. Dyatkin, A. V. Kalinin, M. M. Y. Kwan, S. Liras, C. J. Oalmann, R. J. Pieters, M. N. Protopopova, C. E. Raab, G. H. Roos, Q.-L. Zhou, and S. F. Martin, *J. Am. Chem. Soc.*, **117**, 5763 (1995). b) M. P. Doyle, A. B. Dyatkin, A. V. Kalinin, D. A. Rupper, S. F. Martin, M. R. Spallar, and S. Liras, *J. Am. Chem. Soc.*, **117**, 11021 (1995).
6 a) H. M. L. Davies and B. D. Doan, *Tetrahedron Lett.*, **37**, 3967 (1996). b) H. M. L. Davies and B. D. Doan, *J. Org. Chem.*, **64**, 8501 (1999).
7 a) S.-B. Park, K. Murata, H. Matsumoto, and H. Nishiyama, *Tetrahedron: Asymmetry*, **6**, 2487 (1995). b) C.-M. Che, J.-S. Huang, F.-W. Lee, Y. Li, T.-S. Lai, H.-L. Kwong, P.-F. Teng, W.-S. Lee, W.-C. Lo, S.-M. Peng, and Z.-Y. Zhou, *J. Am. Chem. Soc.*, **123**, 4119 (2001). c) B. Saha, T. Uchida, and T. Katsuki, *Synlett*, **2001**, 114. d) I. J. Munslow, K. M. Gillespie, R. J. Deeth, and P. Scott, *Chem. Commun.*, **2001**, 1638.
8 T. Uchida, B. Saha, and T. Katsuki, *Tetrahedron Lett.*, **42**, 2521 (2001).
9 C. Piqué, B. Fähndrich, and A. Pfaltz, *Synlett*, **1995**, 491.
10 a) R. Tokunoh, H. Tomiyama, M. Sodeoka, and M. Shibasaki, *Tetrahedron Lett.*, **37**, 2449 (1996). b) P. Müller and C. Boléa, *Synlett*, **2000**, 826.
11 G.-S. Kim, W.-C. Cho, and H. K. Ahn, *Tetrahedron*, **55**, 10079 (1999).
12 W.-S. Park, H.-J. Son, G.-S. Kim, and H. K. Ahn, *Tetrahedron: Asymmetry*, **10**, 1903 (1999).
13 D.-J. Cho, S.-J. Jeon, H.-S. Kim, C.-S. Cho, S.-C. Shim, and T.-J. Kim, *Tetrahedron: Asymmetry*, **10**, 3833 (1999).
14 M. P. Doyle, M. Y. Eismont, and Q. L. Zhou, *Russ. Chem. Bull.*, **46**, 955 (1997).
15 a) M. Barberis, J. Pérez-Prieto, S.-E. Stribia, and P. Lahuerta, *Org. Lett*, **3**, 3317 (2001). b) M. Barberis, J. Pérez-Prieto, K. Herbst, and P. Lahuerta, *Organometallics*, **21**, 1667 (2002). Although the enantioselectivity of the cyclopropanation giving [3.1.0]hexan-2-one has been reported to be 87% in Ref. 15a, it has been reported to be 74% in Ref. 15b.
16 P. Müller and E. Maitreiean, *Collect. Czech. Chem. Commun.*, **64**, 1807 (1999).
17 T. Uchida, R. Irie, and T. Katsuki, *Tetrahedron*, **56**, 3501 (2000).
18 T. Katsuki, *Adv. Synth. Catal.*, **34**, 131 (2002).
19 Typical experimental procedure: (Nitroso)(salen)ruthenium complex **1** (4.9 mg, 5 μmol) was dissolved in 4 ml of THF under N_2. To this mixture was added a THF solution (1 ml) of (*E*)-1-diazo-6-phenyl-5-hexen-2-one (20 mg, 0.1 mmol) dropwise over a period of 12 h using a syringe pump under irradiation of incandescent light. The reaction mixture was stirred for another 4 h and concentrated in vacuo. The residue was chromatographed on silica gel using hexane and ethyl acetate (11 : 1) as eluent to yield bicyclic ketone (13.5 mg) in 78% yield. The enantiomeric excess of the product was determined as described in the footnote a of Table 1.