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Highly stereoselective Ru(II)–Pheox catalyzed asymmetric cyclopropanation of terminal olefins with succinimidyl diazoacetate†

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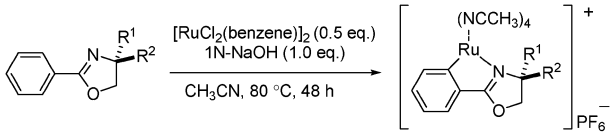
The Ru(II)–Pheox complex is an efficient catalyst for the intermolecular cyclopropanation of various terminal olefins with succinimidyl diazoacetate. This catalytic system can perform under mild conditions, and the desired cyclopropane products are obtained in high yields with excellent diastereoselectivity and enantioselectivity.

Optically active cyclopropane derivatives play an important role in natural product synthesis and are valuable synthetic intermediates in organic and pharmaceutical chemistry.[1] After the pioneering work by Nozaki *et al.*,[2] significant efforts have been devoted to the development of transition-metal-catalyzed asymmetric cyclopropanation of alkenes with diazoesters, and many excellent results have been reported.[3] Nevertheless, the challenge to develop the catalytic systems still remains, with easy manipulation and under convenient conditions, from the viewpoint of practicality while still affording high yield and high stereoselectivity. Among the various reported catalytic systems,[3] only a few can catalyze asymmetric cyclopropanation under practically desirable conditions (carried out at room temperature and without slow addition of diazoesters) while affording high diastereoselectivity and enantioselectivity. In 2009, Zhang *et al.* reported the general synthesis of optically active cyclopropyl carboxamide derivatives *via* cyclopropanation of terminal olefins with succinimidyl diazoacetate (N_2CHCO_2Su) in the presence of a Co(II)–porphyrin catalyst under practically desirable conditions.[4] Although the cyclopropanation by using this catalyst afforded excellent *trans*-diastereoselectivity, moderate yields (50–90%) and good enantioselectivity (in most cases 89–95% ee) in reaction time of two days were achieved. In addition, the porphyrin ligand is expensive and time-consuming; further, an additive such as DMAP is necessary to control the enantioselectivity. These drawbacks prompted us to explore a simple and highly efficient catalyst that can promote the cyclopropanation of a wide range of olefins with diazo reagents and afford the desired product in excellent yields and high stereoselectivity.

Recently, we reported the efficient use of a novel macroporous polymer-supported chiral Ru(II)–Pheox catalyst in inter- and intramolecular cyclopropanation reactions.[5] Despite the high reactivity, enantioselectivity, and reusability of our macroporous catalyst, the development of a highly *trans*-stereoselective carbene transfer process that can proceed effectively in the presence of this catalyst under mild conditions remains a challenge. Herein, we report a highly stereoselective Ru(II)–Pheox catalyzed asymmetric cyclopropanation of olefins with succinimidyl diazoacetate as the carbene source. Ru(II)–phenyloxazoline complexes (Ru(II)–Pheox) **2a** and **2b** were synthesized in high yield from inexpensive, commercially available benzoyl chloride and amino alcohols (Scheme 1).[6]

Initially, we compared the activity of the symmetric Ru(II)-*dm*-Pheox catalyst **2a** with that of the popularly used Cu and Rh metals in the intermolecular cyclopropanation of styrene with succinimidyl diazoacetate **4**. The results are shown in Table 1. No product was formed when the reaction was carried out at room temperature in the presence of the Cu catalyst (copper powder) (entry 5), but the desired product could be isolated in 63% yield when the temperature was increased to 45 °C and 20 mol% Cu was used (entry 6). $Rh_2(OAc)_4$ gave the desired product in good yield (82%) in less than 1 min, but the diastereoselectivity was low (74 : 26) (entry 7). Interestingly, **2a** afforded succinimidyl 2-phenyl cyclopropylcarboxylate **5** in very high yield (99%) and excellent *trans* diastereoselectivity (>99 : <1) in less than 1 min at room temperature (entry 4). Dichloromethane was found to be the solvent of choice.

Encouraged by the results obtained with **2a**, we prepared the chiral catalyst Ru(II)-*Ph*-Pheox complex **2b** and used it for the asymmetric cyclopropanation. We compared the catalytic efficiency of **2b** at room temperature with that of $RuCl_2$((*S*),(*S*)pybox-ip)(C_2H_4) **6**,[7] which was synthesized by Nishiyama's group and broadly used in cyclopropanation reactions.[3d]



1a; R^1=R^2= CH_3
1b; R^1=H, R^2= Ph

2a; R^1=R^2= CH_3, 89% yield
2b; R^1=H, R^2= Ph, 82% yield

Scheme 1

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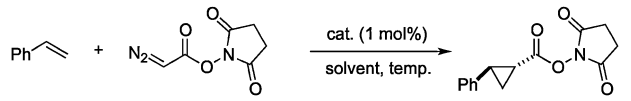
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for Ru(II)–Pheox catalysts and products. See DOI: 10.1039/c2cc32706f

Table 1 Optimization of reaction conditions[a]



3 (5 equiv.) **4** (N_2CHCO_2Su) **5**

Entry	Cat.	Solvent	Temp. (°C)	Time	Yield[b] (%)	*trans* : *cis*[c]	ee[d] (%)
1	**2a**	CH_3CN	25	24 h	73	>99 : <1	—
2	**2a**	THF	25	<1 min	81	>99 : <1	—
3	**2a**	Acetone	25	<1 min	89	>99 : <1	—
4	**2a**	CH_2Cl_2	25	<1 min	99	>99 : <1	—
5	Cu (powder)	CH_2Cl_2	25	48 h	0	—	—
6[e]	Cu (powder)	CH_2Cl_2	45	48 h	63	59 : 41	—
7	$Rh_2(OAc)_4$	CH_2Cl_2	25	<1 min	82	74 : 26	—
8[f]	**6**	CH_2Cl_2	25	48 h	87	>99 : <1	87
9	**2b**	CH_2Cl_2	25	<1 min	98	>99 : <1	95
10	**2b**	CH_2Cl_2	0	15 min	99	>99 : <1	98
11	**2b**	CH_2Cl_2	−10	30 min	97	>99 : <1	99

[a] Reactions were carried out under an argon atmosphere on a 0.2 mmol scale with a cat./N_2CHCO_2Su/styrene molar ratio of 0.01 : 1 : 5. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] After reduction to alcohols, as confirmed by chiral HPLC using a Chiralcel OD-H column. [e] With 20 mol% catalyst. [f] With 5 mol% catalyst.

2b gave higher product yields and enantioselectivity within a very short time than did $RuCl_2((S),(S)$pybox-ip$)(C_2H_4)$ (Table 1, entries 8 and 9). Pleasingly, enantioselectivity was improved to 99% by decreasing the temperature to −10 °C (Table 1, entry 11).

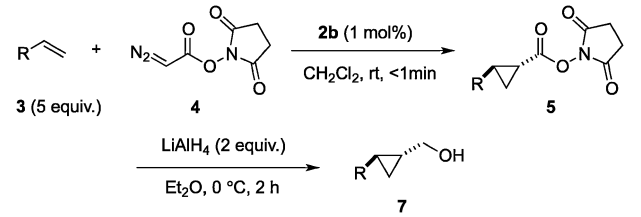
To gain further insight into the catalytic activity of **2b**, we studied the **2b**-catalyzed intermolecular cyclopropanation of various terminal olefins with succinimidyl diazoacetate under the optimized conditions and subsequent reduction of the cyclopropane derivatives into valuable cyclopropylmethanol derivatives,[8] as shown in Table 2. Electron-donating (*o*-, *m*-, and *p*-positions) and electron-withdrawing styrene derivatives (Table 2, entries 1, 3, 5, 7, 9, and 11) could be easily cyclopropanated with succinimidyl diazoacetate **4** in less than 1 min and without any further additive to afford the desired products in excellent yields (92–98%) and >99% *trans*-diastereoselectivity. Further, no side products resulting from dimerization of the diazo compound were observed.

Subsequent reduction of compounds **5a–f** could be easily carried out to afford the corresponding cyclopropylmethanol derivatives with superior enantioselectivity (91–99% ee).

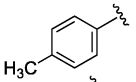
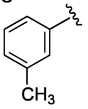
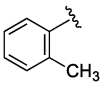
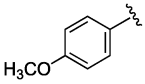
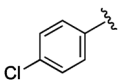
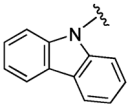
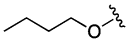
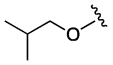
Other substrates such as *N*-vinyl carbazole and *n*-butyl- and isobutyl vinyl ethers also afforded the corresponding products in high yields, with excellent diastereoselectivity and enantioselectivity after reduction. In all the cases, the alcoholic cyclopropane products were obtained in a total yield of 66–89% with excellent enantioselectivity (91–99% ee).[9]

The preferred prochiral face for the attack of the Ru–carbene species by styrene is chosen on the basis of the vacant metal coordination site and the less crowded steric space, as shown in Scheme 2. The seven-member ring formed as a result of coordination between the succinimidyl carbonyl group and the Ru metal center prevented the attack from the G direction, while the bulky phenyl group prevented the Si-face attack. In addition, attack from the H and F directions was prevented by

Table 2 Ru(II)-*Ph*-Pheox catalyzed asymmetric cyclopropanation of various olefins with succinimidyl diazoacetate and subsequent reduction of the corresponding cyclopropane derivatives



3 (5 equiv.) **4** **5** **7**

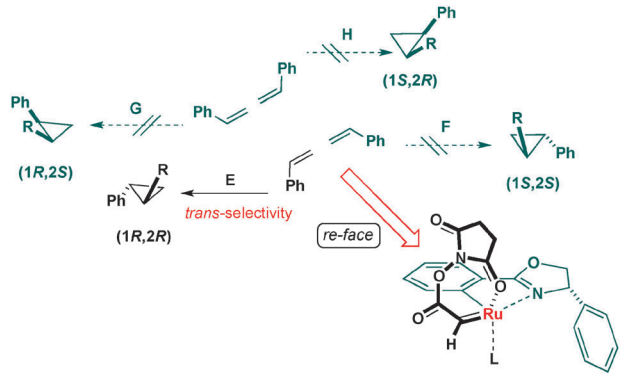
Entry	R	Product	Yield[a] (%)	*trans* : *cis*[b]	ee[c] (%)
1		**5a**	98	>99 : <1	—
2		**7a**	78[e]	>99 : <1	95
3		**5b**	95	>99 : <1	—
4		**7b**	78[e]	>99 : <1	99
5		**5c**	97	>99 : <1	—
6		**7c**	84[e]	>99 : <1	91
7		**5d**	92	>99 : <1	—
8		**7d**	67[e]	>99 : <1	91
9		**5e**	98	>99 : <1	—
10		**7e**	79[e]	>99 : <1	92
11		**5f**	92	>99 : <1	—
12		**7f**	75[e]	>99 : <1	99
13		**5g**	99	>99 : <1	—
14[d]		**7g**	89[e]	>99 : <1	98
15		**5h**	94	>99 : <1	—
16		**7h**	66[e]	>99 : <1	99[f]
17		**5i**	94	>99 : <1	—
18		**7i**	81[e]	>99 : <1	99[f]

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis. [c] Determined by chiral HPLC using Chiralcel OD, OD-H, or OK columns. [d] THF was used as a solvent. [e] Total yield of two steps. [f] Determined by benzoylation using benzoyl chloride (see ESI).

the succinimidyl and phenyl rings, respectively. The previous explanation led us to understand the high *trans*-selectivity of this reaction.[10]

From the abovementioned observations and the atom economy point of view, we state that our Ru(II)–Pheox catalysts offer the following advantages: (a) low cost of preparation; (b) mild reaction conditions (the reaction proceeds rapidly at room temperature without the need for slow addition of the diazo reagent); (c) non-requirement of further additives; (d) the shortest possible reaction time (less than 1 min); (e) low catalyst loading; and (f) excellent yields, enantioselectivity, and diastereoselectivity (92–99%, 99% in most cases, and >99 : <1, respectively).

In conclusion, we have established a protocol for the highly stereoselective Ru(II)–Pheox catalyzed asymmetric cyclo propanation of terminal olefins with (N_2CHCO_2Su). The reaction can be carried out smoothly under practically desirable conditions,



Scheme 2

and succinimidyl cyclopropylcarboxylates in significantly enhanced yields, diastereoselectivity, and enantioselectivity can be obtained. Subsequent reduction of these cyclopropane products readily affords the corresponding cyclopropylmethanol derivatives with superior enantioselectivity.

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Notes and references

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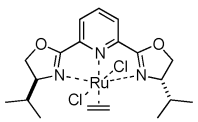
6 See the ESI† for the detailed explanation.

7 The structure of the $RuCl_2((S),(S)$pybox-ip$)(C_2H_4)$ catalyst, which was synthesized by Nishiyama's group



6: $RuCl_2((S),(S)$pybox-ip$)(C_2H_4)$

8 (*a*) J. Pietruszka and T. Wilhelm, *Synlett*, 2003, 1698; (*b*) J. M. Vega-Pérez, I. Periñán, C. Palo-Nieto, M. Vega-Holm and F. Iglesias-Guerra, *Tetrahedron: Asymmetry*, 2010, **21**, 81; (*c*) N. Koyata, T. Miura, Y. Akaiwa, H. Sasaki, R. Sato, T. Nagai, H. Fujimori, T. Noguchi, M. Kirihara and N. Imai, *Tetrahedron: Asymmetry*, 2009, **20**, 2065.

9 All the racemic product versions were prepared in high yields and >99% *trans*-selectivity (see ESI†).

10 Experiments with other diazo compounds are being carried out for comparing the results with those obtained for the succinimidyl diazoacetate and thus clarifying the importance of the carbonyl group.