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A new chiral ruthenium complex for catalytic asymmetric cyclopropanation

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Abstract—A new chiral ruthenium complex **6**, featured with an *N*,*O*-mixed polydentate ligand, was synthesized and characterized. This ruthenium complex showed high efficiency in catalytic cyclopropanations of alkenes with diazoacetates. High *trans*/*cis* selectivity and enantioselectivity (up to 96%) were achieved with the readily accessible ethyl diazoacetate as the reagent.

Metal-catalyzed asymmetric cyclopropanation remains of great interest due to its versatile applications in synthetic organic chemistry.[1] Although several excellent metal catalysts such as Cu-salicylaldimine,[2a] Cu-semicorrin,[2b] Cu-bisoxazoline,[2c] and chiral dirhodium system,[2e–f] have been developed for asymmetric intermolecular or intramolecular cyclopropanations, the development of new catalysts in terms of low catalyst loading, high diastereoselectivity, good enantioselectivity, and the use of readily accessible and cheap diazo compounds, remains an important goal. Several successful chiral Ru catalysts have also been developed for intermolecular cyclopropanation of olefins and diazoacetates. Among them are Nishiyama's Ru Pybox system,[3] Katsuki's Ru salen system,[4] and Scott's Ru Schiff-base complex.[5] Herein we wish to report a novel and efficient chiral ruthenium catalyst **6** for intermolecular cyclopropanation of olefins with diazoacetates. Low catalyst loading (1 mol%), good *trans*/*cis* selectivity (90/10), and high enantioselectivities (up to 96%) have been achieved with the readily available ethyl diazoacetate as the reagent. Possible interaction between the esters of carbenes and the hydroxyl groups in **6** is a novel feature of our catalytic system.

In the course of exploring ligands with a well-defined chiral environment, we designed an *N*,*O*-mixed polydentate ligand **3**. This ligand can be directly prepared from chiral 2-amino-2′-hydroxy-1,1′-binaphthyl **1** (NOBIN)[6] and 2,6-pyridinedimethanal **2** (Scheme 1). By refluxing the mixture of **1** and **2** in *i*-propanol in the presence of 4 Å molecular sieves, ligand **3** was obtained in 75% yield with a high purity (>95%).[7] We hoped to make ruthenium complex **4** through the reaction of $[Ru^{II}Cl_2(p\text{-cymene})]_2$, pyridine, and ligand **3** in *i*-propanol. However, our results showed that a different air-stable Ru complex **5** was formed. The structure of **5** was characterized by NMR and MS analysis, and its naphthol protons were also examined by H-D exchange.[8] We envisioned that the scaffold of **5** might be good for catalytic cyclopropanation reaction. However, **5** showed no reactivity for cyclopropanation of styrene and ethyl diazoacetate at room temperature. In order to make an active Ru catalyst for cyclopropanation, we employed bulkier pyridine derivatives for the preparation of Ru catalysts. Surprisingly, when we used 2,6-dichloropyridine or 2-chloropyridine as the base and methanol as the solvent, a purple precipitate was formed (Scheme 2). This precipitate was identified to have no pyridine moiety according to its ^1H NMR spectrum, while one mol equivalent of methanol was observed. We thus assumed that the structure of the precipitate was a methanol-coordinated Ru complex **6**.[9] To further corroborate the assignment, **6** was treated with pyridine in dichloromethane solution, leading to the formation of Ru complex **5**. It is noteworthy that 2,6-dichloropyridine or 2-chloropyridine did not exchange with the coordinated methanol of **6** in the reaction to form pyridine coordinated Ru complex like **5**. We consider that this could be attributed to the steric effect of the substituted pyridines. The steric bulk of the ligand **3** might only allow the coordination of unhindered pyridine to the ruthenium atom. Complex **6** is stable under N_2 atmosphere and can be stored for a long time. No sign of decomposition was observed according to its NMR after it was stored under N_2 for 6 months.

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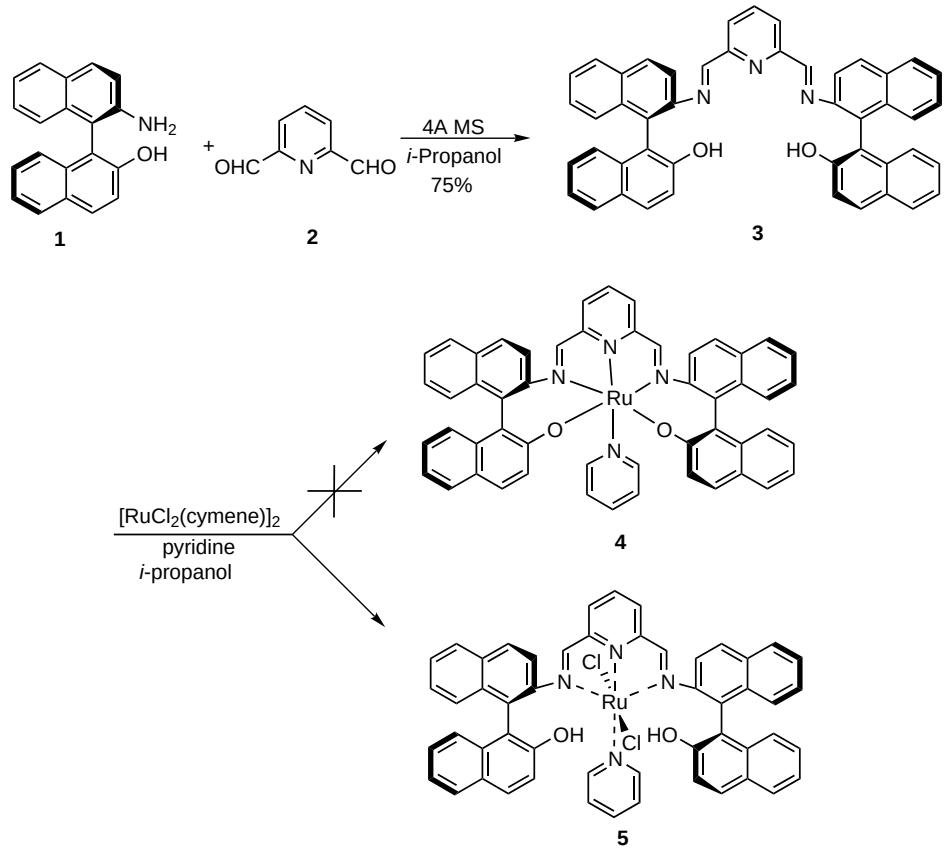
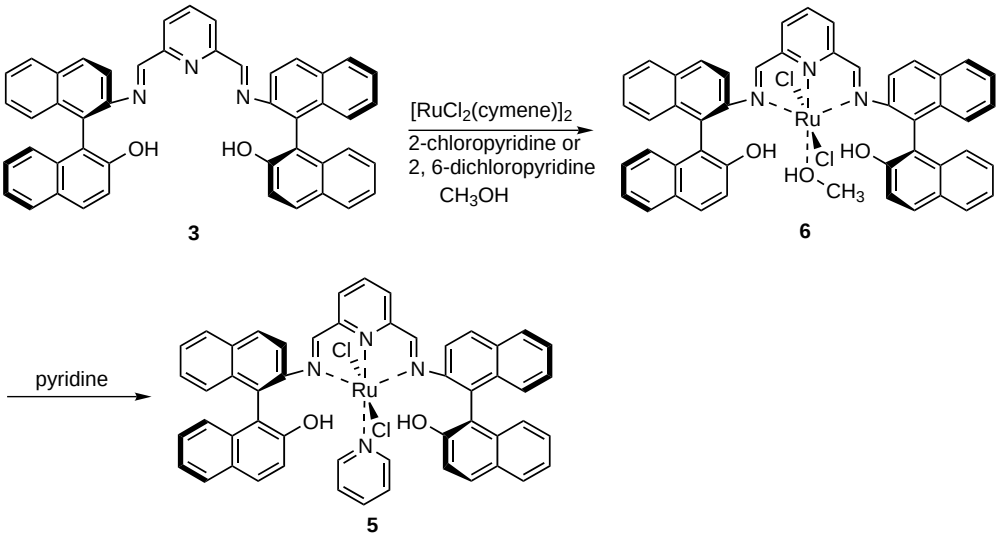


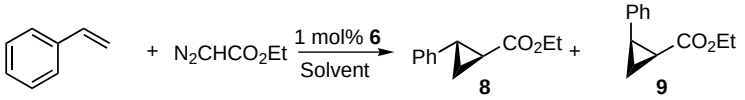
Scheme 1.



Scheme 2.

The Ru complex **6** was then tested for catalytic cyclopropanation reaction. It is found that **6** is a highly active catalyst for cyclopropanation of styrene with ethyl diazoacetate. In the presence of 1 mol% of **6**, the cyclopropanation proceeded smoothly to afford 2-phenylcyclopropanecarboxylates **8** and **9** in high yields. *trans*/*cis* Selectivity and enantioselectivity were solvent dependent (Table 1). High selectivities were observed with a non-coordinated solvent. In CH_2Cl_2, the best *trans*/*cis* selectivity (90:10) and enantioselectivity (*trans* ee: 97%; *cis* ee: 90%) were achieved (entry 1). We thus employed CH_2Cl_2 as the solvent to screen different diazoacetates (Table 2). It is well documented that bulkier diazoacetates such as *tert*-butyl diazoacetate or menthyl diazoacetate give better enantioselectivity in most intermolecular cyclopropanations.[1a] However, bulkier diazoacetates eroded the yield as well as the enantioselectivity in our system (entry 7 versus entries

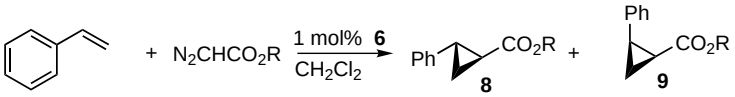
Table 1. Solvent effect in cyclopropanation of styrene with ethyl diazoacetate



Entry	Solvent	Ratio (*trans:cis*)	Ee (%)	
			trans	*cis*
1[a]	CH_2Cl_2	90:10	97	90
2	$ClCH_2CH_2Cl_2$	88:12	96	87
3	Toluene	89:11	95	85
4	THF	83:17	64	5

[a] Ethyl diazoacetate was added in one portion; yields were not determined.

Table 2. Asymmetric cyclopropanation of styrene and diazoacetate with **6** as the catalyst



Entry	R	Yield (%)	Ratio (*trans:cis*)	Ee (%)	
				trans	*cis*
5[a]	Me	85	85:15	88	56
6	Et	88	90:10	96	83
7	*i*-Pr	88	95:5	90	63
8	*t*-Bu	75	97:3	86	54
9	(−)-Menthyl	66	95:5[b]	58	44
10	(+)-Menthyl	76	96:4[b]	85	4

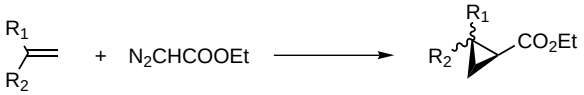
[a] All reactions were carried out under the following conditions unless otherwise specified: styrene (5 mmol), diazoacetate (0.6 mmol, 0.5N in CH_2Cl_2), catalyst **1** (6 μmol), CH_2Cl_2 (1 mL), 20–25°C, ca. 4 h for addition of diazoacetate then stirring for 4–8 h. Isolated yields. The *cis*/*trans* ratios and ee's were determined by Chiral GC column (beta dex 120, 30 m), the % ee's were determined with the corresponding ethyl ester. Absolute configuration: (1*S*,2*S*) for *trans*, (1*S*,2*R*) for *cis*.

[b] The ratios were determined by ^1H NMR.

8–10). Ethyl diazoacetate turned out to be the best in terms of yield and enantioselectivity although the *trans*/*cis* ratio was lower than other sterically hindered esters.

We thus used ethyl diazoacetate as the carbene source to react with olefin substrates. As shown in Table 3, Ru complex **6** showed a broad substrate scope for electron-rich, electron-poor, aromatic, and aliphatic olefins. High ee's (93–83%) were obtained for *trans* cyclopropanation products. While enantioselectivities were comparable, yield for an electron-rich olefin was higher than that for an electron-poor olefin since more carbene dimerization products were formed in the latter case[10] (entries 11 and 12). An aliphatic olefin also provided

Table 3. Results of cyclopropanation of olefins with ethyl diazoacetate catalyzed by **6**



Entry[a]	Olefin	R_1	R_2	Yield (%)	Ratio (*trans:cis*)	Ee (%)	
						trans	*cis*
11	**10**	H	*p*-Cl-Ph	45	90:10	92	70
12	**11**	H	*p*-MeO-Ph	78	87:13	86	69
13	**12**	H	2-Naphthyl	78	90:10	83	72
14	**13**	H	n-C_5H_{11}	45	83:17	91	86
15	**14**	CH_3	Ph	82	47:53	93	93

[a] Cyclopropanation of these olefins were carried out under the conditions used for entry 5.

high ee's, although the yield was moderate (entry 13). Good yield and excellent ee's were also obtained for α-methyl styrene (entry 14).

In conclusion, we have discovered a new and efficient chiral ruthenium catalyst **6**, which has been successfully applied in catalytic asymmetric cyclopropanation. It is noteworthy that high ee's have been reached for *trans* cyclopropanation products with the easily accessible and cheap ethyl diazoacetate as the reagent and low catalyst loading (1 mol%) has been achieved. Since NOBIN can be easily prepared and resolved, our ruthenium catalyst **6** is potentially practical for the synthesis of a variety of chiral cyclopropane compounds. Further studies are focused on structural modifications of the ruthenium complex as well as its applications for other asymmetric reactions and this progress will be reported in due course.

Acknowledgements

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7. Small impurity is the mono Schiff base product, which is not removable via recrystallizations.
8. Spectra data for **5**: ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 8.85 (d, 6.4 Hz, 2H), 7.94 (d, 8.1 Hz, 2H), 7.86 (d, 8.6 Hz, 4H), 7.77 (s, 2H), 7.73 (m, 1H), 7.48 (m, 8H), 7.38 (dt, 8.3 Hz, 1.2 Hz, 2H), 7.31 (dt, 6.8 Hz, 1.2 Hz, 2H), 7.21 (m, 6H), 7.19 (t, 6.5 Hz, 2H), 7.03 (t, 1H), 6.82 (m, 4H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 167.3, 162.32, 157.0, 151.7, 147.7, 136.9, 134.3, 133.6, 130.8, 130.6, 129.3, 129.2, 128.9, 128.4, 128.2, 128.1, 127.7, 127.6, 126.4, 125.7, 125.0, 124.7, 124.6, 124.5, 124.2, 122.9; MS (ESI) m/z 921 (M^++1), 885 (M^+−Cl), 849 (M^+−2Cl). HRMS calcd for $RuC_{52}N_4H_{36}O_2Cl$ 885.1582, found: 885.1619.
9. Spectra data for **6**: ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 8.39 (d, 8.6 Hz, 2H), 8.08 (d, 8.9 Hz, 2H), 8.00 (d, 8.1 Hz, 2H), 7.92 (m, 4H), 7.81 (d, 8.8 Hz, 2H), 7.53 (t, 7.0 Hz, 2H), 7.39 (m, 4H), 7.29 (t, 7.3 Hz, 2H), 7.19 (dd, 8.4 Hz, 12.4 Hz, 4H), 7.10 (d, 8.4 Hz, 2H), 6.97 (t, 7.9 Hz, 1H), 6.86 (d, 7.3 Hz, 2H), 6.39 (s, 2H), 3.98 (s, 1H), 3.37 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 166.1, 164.1, 151.6, 148.7, 136.8, 134.4, 133.8, 130.9, 130.4, 129.6, 129.3, 128.9, 128.2, 127.8, 127.3, 126.8, 125.8, 125.6, 125.3, 124.9, 124.5, 123.5, 121.7, 51.2; MS (ESI) m/z 888 (M^++CH_3CN−CH_3OH−Cl), 847 (M^+−CH_3OH−Cl). HRMS calcd for $RuC_{49}N_4H_{34}O_2Cl$ 847.1424, found: 847.1380.
10. Formation of fumarate and maleate as the carbene dimerization product is a general phenomenon in metal catalyzed cyclopropanation of olefins with diazoacetate.