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Asymmetric cyclopropanation of styrene with ethyl diazoacetate using a N_2P_2-ligand ruthenium(II) catalyst: axial ligand controlled enantioselectivity

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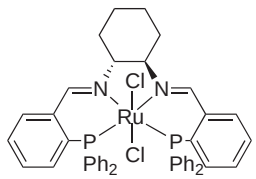
Abstract—The N_2P_2–Ru(II) complex **1**, activated by silver triflate, exhibited good catalytic activity but low enantioselectivity in the asymmetric cyclopropanation of styrene with ethyl diazoacetate. *N*-Donor additives were introduced into the activated system as axial ligands to improve the *ee*'s for this reaction. Up to 90% *ee* for *cis*-isomers was achieved by using 2,4,6-collidine as an additive.

Catalytic asymmetric cyclopropanation of olefins with diazoacetate esters has been one of the most important methodologies for the formation of chiral cyclopropane compounds.[1] Various optically active *N*- and *N*,*O*-donor ligands, such as Schiff bases,[2] semicorrins,[3] bisoxazolines,[4] Py-box[5] and bipyridines,[6] etc., have been employed successfully in the reaction. However, there are only a couple of reports on the testing of *P*- or *N*,*P*-donor ligands in the reaction,[7–11] and low *ee*'s were observed in most cases. Recently, Noyori reported the N_2P_2–Ru(II) complex **1** and employed it as a catalyst precursor in the asymmetric transfer hydrogenation of aromatic ketones with potassium 2-propoxide as cocatalyst.[12a] In this paper, the complex was used as the catalyst precursor for the asymmetric cyclopropanation of styrene with ethyl diazoacetate by using AgOTf as an activating agent and an achiral *N*-donor additive as an axial ligand. In the presence of 2,4,6-collidine, up to 90% *ee* for *cis*-isomers was achieved.



The N_2P_2-Ru(II) Complex **1**

In the distorted octahedral structure of the N_2P_2–Ru(II) complex **1**,[12] the Ru–Cl bond in the axial position is so stable that it cannot be broken during the cyclopropanation to form a coordinatively unsaturated species catalyzing the decomposition of the diazoacetate ester. According to the literature method, silver salts, especially silver triflate, were used as activating agents for similar catalysts to precipitate out part or all of the chloride anions.[8,13] Therefore, two silver salts, AgOTf and $AgBF_4$, were used in this reaction to activate the complex **1**, and the results using these activated catalysts are summarized in Table 1.

After being activated by AgOTf, the catalyst showed very good catalytic activities (entries 2–6 in Table 1 versus entry 1). However, the *ee*'s were not so high, and it seemed that the solvents used in the catalyst activation obviously affected the enantioselectivities of the cyclopropanation products (entries 2 and 4 versus entries 3 and 5). Better results were obtained by using 4 equiv. of AgOTf as activating agent, and *cis*-isomers were favored in the product. In contrast to the use of AgOTf as an activating agent, $AgBF_4$ gave a 70% *ee*, but the chemical yield was only 7%.

It is well known that some *N*-donor additives can improve enantioselectivity in asymmetric cyclopropanation catalyzed by the salen/salen-like ligand–metal complexes.[14,15] Herein, we also tried to introduce some *N*-donor additives into the activated catalyst system as axial ligands. The results are listed in Table 2.

Et_3N was used in our initial attempt, which resulted in a remarkable improvement of the *ee*'s. Using 6 or 12 equiv. of Et_3N, about 80% *ee* for *cis*-isomers was achieved at room temperature.

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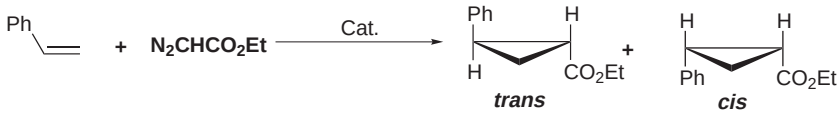
Table 1. Asymmetric cyclopropanation of styrene with ethyl diazoacetate using AgOTf or $AgBF_4$ as an activating agent[a]



Entry	Additive	Ag:Ru	Solvent	Temp. (°C)	Yield[b] (%)	*cis*:*trans*[d]	% *ee*[c,d] (*cis*)	% *ee*[c,e] (*trans*)
1	–	–	–	25	0	–	–	–
2	AgOTf	2:1	CH_2Cl_2	25	95	55:45	0	0
3	AgOTf	2:1	CH_2Cl_2/styrene	25	98	57:43	10	17
4	AgOTf	4:1	CH_2Cl_2	25	97	60:40	0	0
5	AgOTf	4:1	CH_2Cl_2/styrene	25	97	62:38	40	5
6	AgOTf	4:1	CH_2Cl_2/styrene	0	69	60:40	51	31
7	$AgBF_4$	4:1	CH_2Cl_2/styrene	25	7	88:12	70	0

[a] Complex **1** (83 mg, 0.01 mmol) and 2 or 4 equiv. of AgOTf were mixed with 2 mL of CH_2Cl_2 and with (or without) 2 mL of styrene in a 25 mL Schlenk tube. The mixture was stirred at room temperature overnight, and then, the precipitate was filtered off. Ethyl diazoacetate (57 mg, 0.5 mmol) in 5 mL of CH_2Cl_2 was added to the solution containing the catalyst and styrene at the selected temperature in 6 h by a syringe pump and stirred for another 8 h. The catalyst-free sample was analyzed by GC.

[b] Determined by GC with diethyl adipate as internal standard.

[c] The *ee*'s for the cyclopropanation product and the ratio of *trans*- and *cis*-isomers were determined by capillary GC using a chiral column (cyclodex-β, 2,3,6-M, 30 m×0.25 mm i.d.), and the configuration of the four isomers was determined by comparing the GC elution order with authentic sample prepared according to the literature.

[d] 1*R*,2*S* as the major enantiomer.

[e] 1*R*,2*R* as the major enantiomer.

Table 2. Asymmetric cyclopropanation of styrene with ethyl diazoacetate in the presence of some *N*-donor additives[a,b]

Entry	Additive	Additive:Ru (mol/mol)	Temp. (°C)	Yield (%)	*cis*:*trans*	% *ee* (*cis*)[c]	% *ee* (*trans*)[d]
1	Et_3N	2:1	25	67	60:40	47	13
2	Et_3N	6:1	25	49	69:31	80	46
3	Et_3N	12:1	25	40	76:24	81	34
4	Et_3N	24:1	25	41	61:39	68	10
5	2-Picoline	12:1	25	8	62:38	71	11
6	2,6-Lutidine	12:1	25	50	70:30	79	70
7	2,4,6-Collidine	12:1	25	81	70:30	82	79
8	2,4,6-Collidine	12:1	0	55	64:36	90	73
9	2,6-Dichloropyridine	12:1	25	61	73:27	14	33
10	2-Chloro-6-picoline	12:1	25	42	57:43	63	68
11	2-Bromopyridine	12:1	25	53	77:23	84	26
12	3-Bromopyridine	12:1	25	0	–	–	–
13	Imidazole	12:1	25	0	–	–	–
14	*N*-Methylimidazole	12:1	25	Trace	–	–	–
15	Pyridine	12:1	25	0	–	–	–

[a] Reaction conditions: 0.5 mmol of ethyl diazoacetate, 2 mL of styrene, 2 mol% catalyst prepared in situ (based on the diazoacetate), and 12 equiv. of additive were added.

[b] The exchange of Cl/OTf was carried out in 2 mL of CH_2Cl_2 at 25°C. Then, the precipitate was filtered off, and the selected additive was introduced into the solution and stirred for 2 h.

[c] 1*R*,2*S* as the major enantiomer.

[d] 1*R*,2*R* as the major enantiomer.

Under the optimum reaction conditions, based on Et_3N as an additive, other *N*-donor additives, including imidazole, *N*-methyl imidazole and a series of pyridine derivatives, were examined.

As shown in entries 5–15, the *ee*'s of around 80–85% are obtained by using 2,6-lutidine, 2,4,6-collidine and α-bromopyridine as additives, while imidazole, *N*-methylimidazole, pyridine and 3-bromopyridine cause the deactivation of the catalyst. Among the additives, 2,4,6-collidine gave a fairly high yield at room temperature (81% yield, entry 7). Lower temperature, 0°C, was attempted in the presence of 2,4,6-collidine, and a good *ee*, up to 90% for the *cis*-isomers, was achieved (entry 8).

In summary, we have reported an effective catalyst system for the asymmetric cyclopropanation of styrene and ethyl diazoacetate using the N_2P_2–Ru(II) complex **1** as precursor. After being activated by AgOTf, good catalytic activities were observed. With the introduction of some *N*-donor additives as axial ligands, good enantioselectivity of the reaction (around 80–90% *ee*) was achieved.

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