Cyclopropanation

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Asymmetric Cyclopropanation of Alkenes with Dimethyl Diazomalonate Catalyzed by Chiral Diene–Rhodium Complexes**

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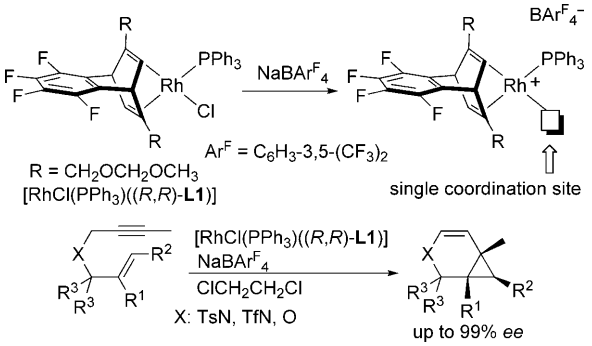
Chiral dienes have been recently developed as ligands for transition metal complexes that displayed highly efficient and enantioselective carbon–carbon bond formations.[1] A breakthrough reaction that makes use of chiral dienes is the asymmetric addition of organometallic reagents to electron-deficient alkenes and related compounds, and is catalyzed by the corresponding rhodium complexes.[2,3] Herein we report a new application of chiral diene ligands into rhodium-catalyzed asymmetric cyclopropanation of alkenes with dimethyl diazomalonate.

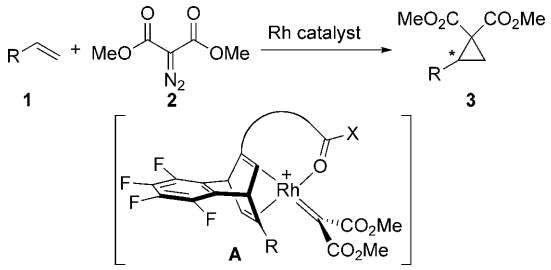
Dirhodium(II) carboxamidates and carboxylates have been developed as catalysts for the asymmetric cyclopropanation of alkenes with diazo compounds, and new catalytic systems that are capable of high enantioselectivity for a wider range of substrates have also been reported.[4] Several types of chiral bridging ligands of the dirhodium(II) catalysts have been used to achieve high catalytic activity and enantioselectivity. Monomeric Cu,[5] Ru,[6,7] Co,[7] and Ir[8] complexes coordinated with chiral ligands are another class of successful catalysts for asymmetric cyclopropanation. A bis(oxazoline) rhodium(II) complex was reported as a rare monomeric rhodium catalyst for the asymmetric cyclopropanation of alkenes with ethyl diazoacetate.[9,10]

There have been many successful reports on the asymmetric cyclopropanation of alkenes with diazo compounds,[11–13] but the reaction with metal carbenes of malonate groups remains to be developed although the enantioenriched cyclopropane *gem*-diesters are very useful in total synthesis.[14] Diazomalonate derivatives are substantially less reactive toward the transition-metal-mediated decomposition leading to metal–carbene species.[15] In the cyclopropanation reaction with diazomalonates the enantioselectivity was generally low, and the highest *ee* value reported to date was 50% in the asymmetric cyclopropanation with dimethyl diazomalonate catalyzed by a chiral dirhodium(II) carboxamidate.[11b] The difficulty in enantiocontrol with symmetrical alkyl diazomalonates is attributed to the lack of enantioface differentiation of the symmetrically substituted metal-carbene moiety, and thus the asymmetric cyclopropanation with metal carbenes of malonate groups is realized only by an efficient enantioface recognition by the approaching alkenes.[12a]

We recently reported that a rhodium(I) complex coordinated with triphenylphosphine and a chiral diene ligand based on a tetrafluorobenzobarrelene (tfb) skeleton[16] efficiently catalyzes the asymmetric cycloisomerization of 1,6-enynes, where the active cationic rhodium species has a stereochemically controlled single coordination site on the rhodium center for electrophilic activation of the alkyne moiety (Scheme 1).[16c] We focused on a similar type of rhodium(I) catalyst bearing a single coordination site for the decomposition of dimethyl diazomalonate (**2**) to generate the rhodium-carbene **A** in the asymmetric cyclopropanation of alkenes (Scheme 2). Our newly designed rhodium catalyst involves a chelating chiral diene moiety and a carbonyl oxygen as an intramolecularly coordinating functional group.



Scheme 1. The cationic rhodium complex coordinated with a chiral diene and PPh_3 in the asymmetric cycloisomerization of 1,6-enynes.



Scheme 2. Asymmetric cyclopropanation catalyzed by chiral diene–rhodium complexes.

Several chiral rhodium(I) catalysts were tested to estimate their catalytic activity and enantioselectivity in the cyclopropanation of styrene (**1a**, 5 equiv) with dimethyl diazomalonate (**2**) in toluene at 60 °C for 24 hours (Table 1). The

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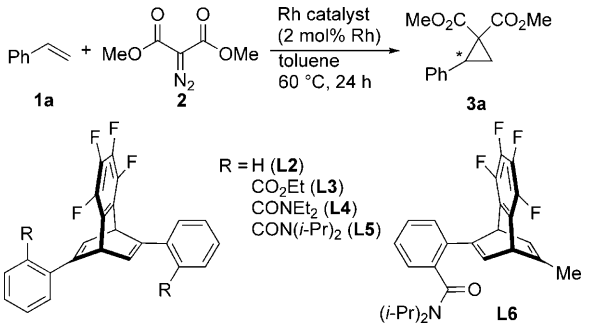
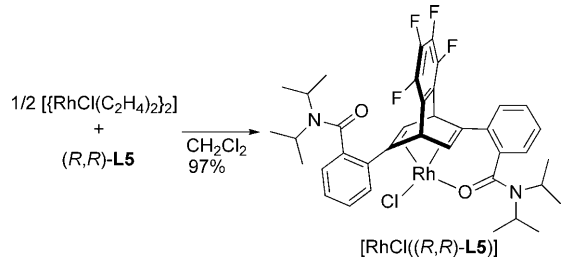
Table 1: Rhodium-catalyzed asymmetric cyclopropanation of styrene **1a**.[a]



Entry	Rhodium catalyst	Yield [%][b]	*ee* [%][c]
1	[{RhCl((*R*)-binap)}$_2$]	0	–
2	[{RhCl((*R*)-binap)}$_2$]/NaBAr$^F_4$	0	–
3	[RhCl(PPh$_3$)((*R*,*R*)-**L1**)]/NaBAr$^F_4$	4[d]	–[e]
4	[{RhCl((*R*,*R*)-**L2**)}$_2$]	3[d]	–[e]
5	[{RhCl((*R*,*R*)-**L2**)}$_2$]/NaBAr$^F_4$	11	6 (*S*)
6[f]	[{RhCl((*R*,*R*)-**L2**)}$_2$]/NaBAr$^F_4$	11[d]	–[e]
7	[RhCl(C$_2$H$_4$)$_2$]$_2$/(*R*,*R*)-**L3**/NaBAr$^F_4$	64	33 (*S*)
8	[RhCl(C$_2$H$_4$)$_2$]$_2$/(*R*,*R*)-**L4**/NaBAr$^F_4$	70	39 (*S*)
9	[RhCl(C$_2$H$_4$)$_2$]$_2$/(*R*,*R*)-**L5**/NaBAr$^F_4$	81	75 (*S*)
10	[RhCl(C$_2$H$_4$)$_2$]$_2$/(*S*,*S*)-**L6**/NaBAr$^F_4$	76	43 (*R*)
11	[RhCl((*R*,*R*)-**L5**)]/NaBAr$^F_4$	84	83 (*S*)
12	[RhCl((*R*,*R*)-**L5**)]	3[d]	–[e]
13[g]	[RhCl((*R*,*R*)-**L5**)]/NaBAr$^F_4$	86	89 (*S*)
14[g,h]	[RhCl((*R*,*R*)-**L5**)]/NaBAr$^F_4$	62	84 (*S*)

[a] Reaction conditions: rhodium catalyst (2 mol% of Rh), **1a** (5 equiv), **2** (0.50 M), with or without NaBAr$^F_4$ (4 mol%) in toluene at 60°C for 24 h. Rh/L = (1.0:1.1) in entries 7–10. [b] Yield of isolated product. [c] Determined by HPLC analysis with chiral stationary phase column (Chiralcel OD-H). [d] Determined by ^{1}H NMR. [e] Not determined. [f] For 48 h. [g] At 40°C for 48 h. [h] Reaction of 1.2 equiv of styrene.

rhodium/bisphosphine catalyst [{RhCl((*R*)-binap)}$_2$][17] (2 mol% Rh) had no catalytic activity for the formation of cyclopropane diester **3a** with or without NaBAr$^F_4$ (4 mol%) (Ar^F = 3,5-bis(trifluoromethyl)phenyl), which was used for the generation of cationic complexes (Table 1, entries 1 and 2). The [RhCl(PPh$_3$)((*R*,*R*)-**L1**)]/NaBAr$^F_4$ catalyst, which efficiently catalyzes the asymmetric cycloisomerization of 1,6-enynes (Scheme 1), gave only 4% yield of **3a** (Table 1, entry 3). The rhodium catalyst coordinated with phenyl substituted tfb ligand **L2** [{RhCl((*R*,*R*)-**L2**)}$_2$][16a] was also inactive for the present reaction (Table 1, entry 4). Although the cationic Rh^I/**L2** catalyst gave an 11% yield of **3a** (Table 1, entry 5), the *ee* value of **3a** was low (6% *ee*) and the catalyst lost its catalytic activity, resulting in 11% yield of **3a** even after a prolonged reaction time (48 hours; Table 1, entry 6).[18] In contrast, newly designed chiral diene ligands **L3**–**L6** bearing an ester or an amide group at the *ortho* position of the phenyl ring were found to display high catalytic activity (Table 1, entries 7–10). Thus, the reaction in the presence of [{RhCl(C$_2$H$_4$)$_2$}$_2$], (*R*,*R*)-**L3** (2 mol% of Rh, Rh/**L3** = 1.0/1.1), and NaBAr$^F_4$ gave 64% yield of **3a** with 33% *ee* (Table 1, entry 7). The use of **L4** substituted with (diethylamido)phenyl groups also gave **3a** in 70% yield with 39% *ee* (Table 1, entry 8). Higher enantioselectivities were observed by using **L5**, which contains 2-(diisopropylamido)phenyl groups and produced **3a** in 81% yield with 75% *ee* (Table 1, entry 9). It is remarkable that the use of C_1-symmetric **L6** substituted with a methyl and a 2-(amido)phenyl group gave **3a** in 76% yield (Table 1, entry 10). These results indicate that the presence of one amide group on the ligand is responsible for the high catalytic activity. The use of isolated monomeric rhodium–diene complex [RhCl((*R*,*R*)-**L5**)] (Scheme 3, see below)



Scheme 3. Synthesis of [RhCl((*R*,*R*)-**L5**)].

combined with NaBAr$^F_4$ led to higher enantioselectivity compared with that generated in situ and gave **3a** in 84% yield with 83% *ee* (Table 1, entry 11). In the absence of NaBAr$^F_4$, the complex [RhCl((*R*,*R*)-**L5**)] had no catalytic activity, indicating that an active single coordination site on a cationic rhodium is essential for the catalytic activity (Table 1, entry 12). The reaction proceeded well even at 40°C to give **3a** in 86% yield with 89% *ee* (Table 1, entry 13). The cyclopropanation of 1.2 equiv of styrene also proceeded, although a slight decrease of the yield and *ee* value was observed (62% yield with 84% *ee*; Table 1, entry 14). The absolute configuration of **3a** produced by use of (*R*,*R*)-**L5** was determined to be (*S*)-(−) by comparison of its specific rotation with the value reported previously.[19]

We succeeded in the determination of the structure of the chloro rhodium complex [RhCl((*R*,*R*)-**L5**)] by X-ray crystallographic analysis (Scheme 3 and Figure 1a).[20] A rhodium(I) center of [RhCl((*R*,*R*)-**L5**)] is coordinated with a diene moiety and a carbonyl oxygen on the benzene ring together with a chloride ligand. The ^{1}H NMR spectrum ($CDCl_3$) of the complex [RhCl((*R*,*R*)-**L5**)] had signals corresponding to two non-equivalent vinylic groups (δ = 2.95 and 4.03 ppm) and two bridgehead protons (δ = 5.55 and 5.99 ppm), which indicates that the complex is not a chloro-bridged dimer but

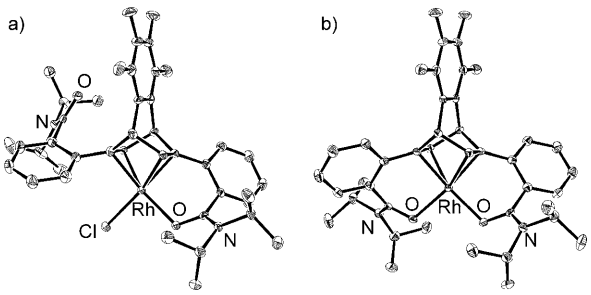
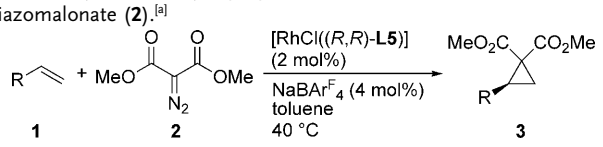


Figure 1. a) ORTEP of [RhCl((*R*,*R*)-**L5**)] (ellipsoids set at 50% probability level; hydrogen atoms omitted for clarity). b) ORTEP of [Rh((*R*,*R*)-**L5**)PF$_6$] set at 50% probability level. The PF_6^- counterion and the hydrogen atoms are omitted for clarity.

has a monomeric C_1-symmetric form in solution. The cationic complex [Rh((*R*,*R*)-**L5**)PF_6] was also isolated by the reaction of [RhCl((*R*,*R*)-**L5**)] with $AgPF_6$, and it was characterized by X-ray crystallographic analysis (Figure 1b).[21] A rhodium center of the cationic complex is coordinated with two carbonyl oxygen atoms to provide a C_2-symmetric square planar structure.

Table 2 summarizes the results obtained for the reactions of several alkenes **1** with dimethyl diazomalonate (**2**), which were carried out in the presence of [RhCl((*R*,*R*)-**L5**)] (2 mol%) and $NaBAr^F_4$ (4 mol%) at 40°C. The cyclopropanation of styrene derivatives bearing a variety of substituents on the benzene rings gave the corresponding cyclopropane diesters in good yields, with enantioselectivities ranging from 80 to 90% *ee* (Table 2, entries 2–7). The reaction of α-methylstyrene (**1h**) gave 62% yield of **3h** with modest enantioselectivity (57% *ee*; Table 2, entry 8). Both the yield and the enantioselectivity were low in the reaction of 4-phenylbut-1-ene (**1i**) (Table 2, entry 9).

Table 2: Asymmetric cyclopropanation of alkenes **1** with dimethyl diazomalonate (**2**).[a]



1 **2** **3**

Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph (**1a**)	86 (**3a**)	89 (*S*)
2	2-MeC_6H_4 (**1b**)	78 (**3b**)	88 (*S*)
3	3-MeC_6H_4 (**1c**)	79 (**3c**)	87 (*S*)
4	4-MeC_6H_4 (**1d**)	76 (**3d**)	88 (*S*)
5	4-$MeOC_6H_4$ (**1e**)	96 (**3e**)	80 (*S*)
6	4-ClC_6H_4 (**1f**)	64 (**3f**)	90 (*S*)
7	4-$CF_3C_6H_4$ (**1g**)	57 (**3g**)	87 (*S*)
8	[α-methylstyrene, **1h**]	62 (**3h**)	57
9	$PhCH_2CH_2$ (**1i**)	14 (**3i**)	29

[a] Reaction conditions: [RhCl((*R*,*R*)-**L5**)] (2 mol%), **1** (1.00 mmol), **2** (0.20 mmol), $NaBAr^F_4$ (4 mol%), toluene (0.4 mL) at 40°C. For 48 h (entries 1, 4, and 6), and 72 h (other entries). [b] Yield of isolated product. [c] Determined by HPLC analysis.

In summary, we have developed new chiral diene ligands for rhodium-catalyzed asymmetric cyclopropanation of alkenes with dimethyl diazomalonate. The intramolecular coordination of the diene moiety and the carbonyl oxygen on the ligand to the rhodium(I) center was found to be important for high catalytic activity.

Experimental Section

$NaBAr^F_4$ (7.4 mg calculated as dihydrate, 0.0080 mmol) was added to a solution of [RhCl((*R*,*R*)-**L5**)] (3.1 mg, 0.0040 mmol), styrene (**1a**) (104.2 mg, 1.00 mmol), and dimethyl diazomalonate (**2**) (31.6 mg, 0.200 mmol) in toluene (0.4 mL), and the mixture was stirred at 40°C for 48 h. The mixture was filtered though a short silica gel column with ethyl acetate, and the eluate was concentrated on a rotary evaporator. The residue was subjected to preparative TLC on silica gel with hexane/ethyl acetate (3:1) to give **3a** (40.1 mg, 0.171 mmol, 86%).

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[18] In entries 1–6 and 12 of Table 1, a significant amount of unreacted **2** was observed by ^{1}H NMR spectroscopy of the crude mixture (for example, 86% for entry 5 and 77% for entry 6).

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[20] CCDC 775834 ([RhCl((*R*,*R*)-**L5**)]) and 775847 ([Rh((*R*,*R*)-**L5**)PF_6]) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] The cationic complex [Rh((*R*,*R*)-**L5**)PF_6] also catalyzed the asymmetric cyclopropanation of **1a** with **2** in 1,2-dichloroethane (owing to the low solubility of the complex) to give **3a** in 69% yield with 71% *ee*.

