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Highly *cis*-Selective Cyclopropanations with Ethyl Diazoacetate Using a Novel Rh(I) Catalyst with a Chelating N-Heterocyclic Iminocarbene Ligand

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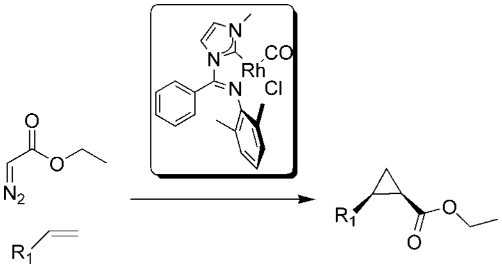
ABSTRACT



A structurally characterized Rh(I) iminocarbene complex (N,C)Rh(CO)Cl is activated with AgOTf to act as a highly *cis*-selective catalyst for the cyclopropanation of substituted styrenes and other alkenes with ethyl diazoacetate (11 examples, 10−99% yield, up to >99% *cis*-selectivity).

Cyclopropanes are important substructures in many biologically active compounds.[1−3] Metal-catalyzed cyclopropanation reactions are well-known, and the most common catalytic method of obtaining cyclopropanes involves transfer of a carbene moiety from a diazocarbonyl compound to an olefin. In such a reaction, two new stereogenic centers are formed, leading to two diastereomeric products.

One challenge in intermolecular cyclopropanation reactions can be to control which diastereomer is formed, especially with commonly used carbonyl diazo compounds like the commercially available ethyl diazoacetate. Many catalysts have been developed that are selective for formation of the thermodynamically favored *trans*-isomer.[4−12]

There are, however, only few reports on *cis*-selective catalysts for this type of reaction.[13−19] Among these is a Cu(I) homoscorpionate catalyst that gives very good yields and high *cis*-selectivity in the reaction between ethyl diazoacetate and styrene.[20] Ru[21−25] and Co−salen[26] complexes have been reported to display high *cis*-selectivities with ethyl diazoacetate. Recently, Co[27] and Ir−salen[28] complexes give

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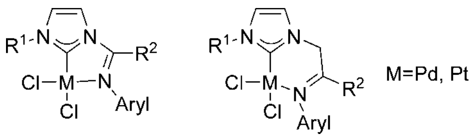


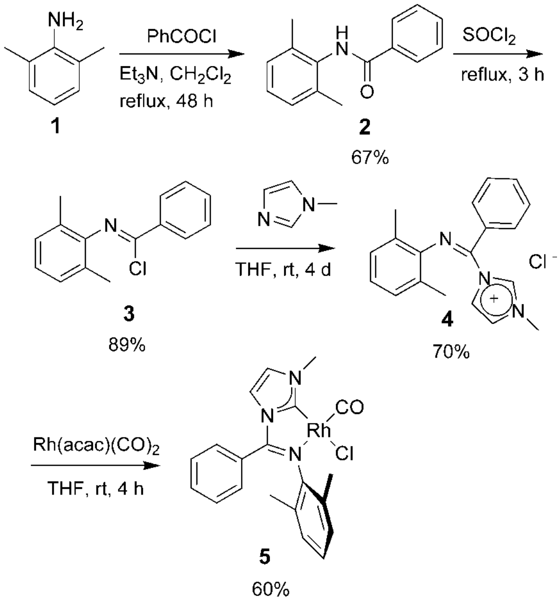
Figure 1. Iminocarbene ligands and complexes previously reported.

very high *cis*-selectivities with *tert*-butyl diazoacetate.

Among the Rh-based catalysts that are reported to be useful for cyclopropanation reactions, there are a few that give good *cis*-selectivities but rather low yields.[29−33] We here report the synthesis of a novel Rh(I) complex **5** with a chelating N-heterocyclic iminocarbene ligand and the use of this complex in cyclopropanation reactions.

Arduengo's report on stable N-heterocyclic carbenes (NHC's)[34,35] triggered the use of such species as ligands for organometallic complexes. NHC−metal complexes are excellent catalysts for a wide range of chemical transformations.[36−38] We have previously reported the synthesis of five- and six-membered ring chelate complexes of Pd and Pt with N-heterocyclic iminocarbene ligands of the types shown in Figure 1.[39−41]

Scheme 1



The related Rh(I) complex **5** was synthesized as shown in Scheme 1. Iminoimidazolium salt **4** was synthesized in good yields by the previously reported method.[42]

The new Rh(I) complex **5** was obtained by reacting the imidazolium salt **4** with commercially available Rh(acac)(CO)$_2$, as described by Gade and co-workers for a related NHC−oxazole Rh(I) complex.[43] The ^{13}C NMR spectrum of **5** exhibited a characteristic doublet for the carbene carbon at δ 185.9 with $J(^{103}\mathrm{Rh}-^{13}\mathrm{C}) = 58$ Hz. The IR $\nu_{\mathrm{C=N}}$ absorption of the imine was lowered by 54 cm^{-1} compared to that of **4**. These data strongly suggest that the iminocarbene ligand has formed a κ^2(C,N) chelate at Rh. This was verified by an X-ray structure analysis of **5** (Figure 2).

Some Au and Cu complexes with NHC ligands show good reactivity in cyclopropanation reactions.[44,45] In view of the fact that certain Rh complexes also catalyze such reactions,[29−33] we decided to subject our novel Rh(I) complex **5** to cyclopropanation conditions.

The reaction between ethyl diazoacetate (EDA) and styrene was chosen as the initial test system (Table 1). The EDA was added in one portion without sign of carbene dimerization under cyclopropanation conditions. When **5** was mixed with EDA and styrene in dichloromethane, essentially no reaction was observed. Activation of **5** with silver triflate

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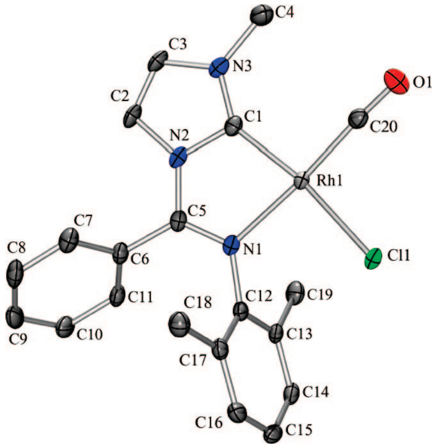


Figure 2. ORTEP drawing of **5** (hydrogens omitted for clarity, ellipsoids at 50% probability). Selected bond lengths (Å) and angles (deg): Rh−N(1), 2.131(2); Rh−Cl, 2.3665(6); Rh−C(1), 1.953(2); Rh−C(20), 1.813(3); C(5)−N(1), 1.293(3); C(5)−N(2), 1.386(3); C(1)−Rh−C(20), 97.39(11); C(20)−Rh−Cl, 90.38(8); Cl−Rh−N(1), 93.40(6); N(1)−Rh−C(1), 78.53(9).

Table 1. Cyclopropanation of Styrene with Ethyl Diazoacetate under Different Conditions[a]

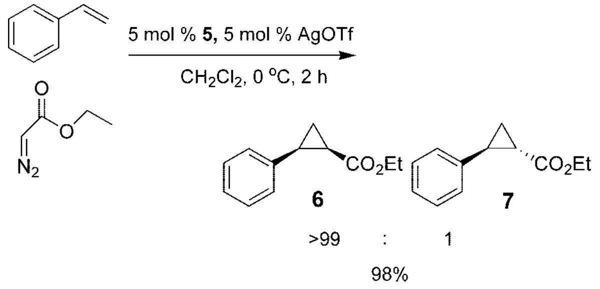
entry	mol % **5**	equiv styrene	mol % AgOTf	T/°C	time/h	yield %[b] (*cis*:*trans*)[c]
1	0	10	5	20	16	n.r.
2	1	10	0	20	48	trace
3	1	10	1	0	48	50 (92:8)
4	2.5	10	2.5	0	3	89 (94:6)
5	5	1	5	20	19	21 (75:25)
6	5	2.5	5	0	24	47 (95:5)
7	5	5	5	0	2	98 (>99:1)
8	5	10	5	20	3	96 (92:8)
9	5	10	5	0	2	98 (>99:1)

[a] Reaction conditions: 1.00 mmol EDA and given quantities of **5**, AgOTf, and styrene in 20 mL of dichloromethane. Number of equiv of styrene, mol % **5**, and mol % AgOTf refer to molar quantity of EDA used. [b] Isolated yield. [c] *cis*:*trans* ratio determined by ^{1}H NMR and GLC.

(AgOTf) in dichloromethane at room temperature for 20 min before addition of styrene and EDA gave the *cis*- and *trans*-cyclopropanes **6** and **7** in 96% isolated yield with a high diastereomeric ratio, 92:8, in favor of the *cis*-isomer **6**. A control experiment in which silver triflate (but no **5**) was added resulted in no decomposition of the diazo compound, no carbene dimerization, and no cyclopropanation. Our Rh complex **5** is therefore required for the *cis*-selective cyclopropanation of styrene. We surmise that the role of the AgOTf activation is to generate a cationic species with a vacant coordination site, which is responsible for the catalytic action. Alternative activation methods are under investigation.

The highest *cis*-selectivities and yields were achieved when the reaction temperature was lowered to 0 °C. The yield was now 98%, and the diastereomeric ratio was >99:1 in favor of the *cis*-isomer (Scheme 2). This is among the highest *cis*-selectivities that have ever been reported in such a reaction.

Scheme 2



The scope of the catalytic reaction was explored with a range of alkenes (Table 2). All reactions were conducted with 5 mol % of **5** and AgOTf and a 5-fold excess of alkene at 0 °C. The catalyst exhibits excellent reactivity and selectivity with *p*-substituted styrenes and 1-vinyl naphthalene (entries 1−4).

Table 2. Cyclopropanation of Different Alkenes to Examine the Scope of the Catalyst[a]

entry	alkene	yield[b] (%)	*cis:trans*[c]
1	styrene	98	>99:1
2	*p*-methoxystyrene	99	>99:1
3	*p*-chlorostyrene	99	>99:1
4	1-vinylnaphthalene	94	>99:1
5	indene	98	98:2
6	cyclopentene	98	99:1
7	cyclohexene	36	96:4
8	1,4-cyclohexadiene	91	79:21
9	1-octene	60	78:22
10	α-methylstyrene	38	66:44
11	1,1-diphenylethene	10	-
12	*trans*-β-methylstyrene	0	-
13	*cis*-stilbene	0	-

[a] Reaction conditions: 0.050 mmol **5**, 0.050 mmol AgOTf, 5.0 mmol alkene, 1.00 mmol EDA in 20 mL of dichloromethane under an Ar atmosphere at 0 °C. See Supporting Information for further details. [b] Isolated yield based on EDA limiting reagent. [c] Determined by ^{1}H NMR and GLC.

Some cyclic and aliphatic alkenes were also tested. The catalyst displays remarkably high reactivity and selectivity with cyclopentene, indene, and cyclohexene (Table 1, entries 5−7). To the best of our knowledge, these are the highest *cis*-selectivities that have ever been reported with these alkenes in reactions with ethyl diazoacetate.

The reaction with 1,4-cyclohexadiene forms cyclopropanes in good yield with moderate diastereoselectivity (entry 8). No C−H insertion products were seen in this experiment despite the fact that cyclohexadiene is a good substrate for Rh-mediated carbene insertion into the allylic C−H bonds.[46] With 1-octene (entry 9), the selectivity and the reactivity drops somewhat, although a good *cis*-selectivity still persists.

With disubstituted alkenes, the yields are lower, and the diastereoselectivity is poorer (Table 1, entries 10−13). During these reactions, formal carbene dimerization is observed. These results suggest that the catalyst is quite sensitive to steric hindrance at the alkene.

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In summary, we have synthesized a novel Rh(I) complex bearing a chelating N-heterocyclic iminocarbene ligand. This complex gives excellent yields and remarkably high *cis*-diastereoselectivities in cyclopropanation reactions between styrene and ethyl diazoacetate. The catalyst gives similarly excellent to good results with monosubstituted aromatic alkenes and cyclic alkenes. The catalytic system is under continuing investigation in our laboratories, and we hope that mechanistic studies will shed light on the mode of the catalytic action which in turn may lead to even better and more selective catalysts.

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Supporting Information Available: Characterization data and ^{1}H NMR of cyclopropanes, characterization and ^{1}H NMR, ^{13}C NMR, COSY, and NOESY spectra of Rh complex **5**, crystal data for **5**, and structural data in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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