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# Enantiocontrol in the intermolecular cyclopropanation reaction catalyzed by dirhodium(II) complexes with *ortho*-metalated aryl phosphine ligands

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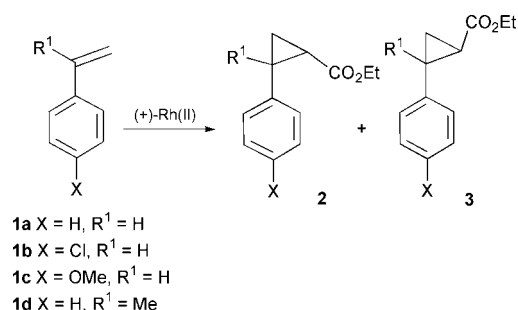
(*P*) and (*M*) dirhodium(II) complexes with *ortho*-metalated aryl phosphines are assessed as chiral catalysts in the enantioselective cyclopropanation of styrenes by ethyl diazoacetate; enantioselectivities up to 91% and up to 87%, respectively, for *cis*- and *trans*-2-arylcyclopropanecarboxylates are observed.

A great deal of effort is presently being devoted to the development of new chiral catalysts to induce enantiocontrol in carbene transfer reactions.<sup>1–3</sup> The catalytic reaction of ethyl diazoacetate with styrene is a model reaction with which stereo- and enantioselectivity for intermolecular cyclopropanation is measured and catalytic effectiveness is determined. Chiral copper catalysts,<sup>4–8</sup> especially those with bis-oxazoline ligands and ruthenium catalysts,<sup>9</sup> have been found to induce the highest levels of enantiocontrol. Thus, enantioselectivities up to 99% for ethyl 2-phenylcyclopropanecarboxylates have been obtained in the cyclopropanation of styrene with ethyl diazoacetate catalyzed by Cu catalysts. In general, chiral dirhodium(II) catalysts do not provide high enantioselectivities; there is a remarkable exception in chiral azetidine-4-carboxylate-ligated dirhodium(II) catalysts.<sup>10</sup> They produce enantioselectivities up to 76 and 52% ee, respectively, for **2a** and **3a** (Scheme 1).<sup>†</sup>

Dirhodium(II) catalysts of general formula Rh<sub>2</sub>(O<sub>2</sub>CR)<sub>2</sub>(PC)<sub>2</sub>, containing two *ortho*-metalated aryl phosphines (PC) in a head to tail arrangement,<sup>11</sup> (Fig. 1), have backbone chirality and they can be isolated as pure enantiomers by conventional resolution methods.<sup>12</sup> Until now, all approaches to the design of enantiomerically pure Rh(II) catalysts have depended on the attachment of enantiomerically pure ligands to the dirhodium core.

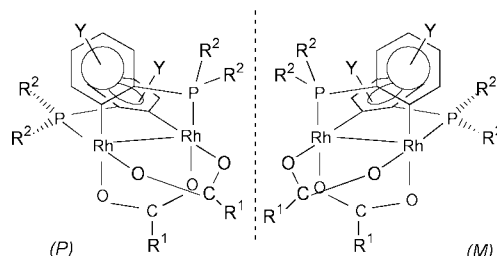
The racemic Rh<sub>2</sub>(O<sub>2</sub>CR)<sub>2</sub>(PC)<sub>2</sub> compounds have been used in intramolecular processes.<sup>13,14</sup> Those with high electron-withdrawing carboxylate groups (CF<sub>3</sub>CO<sub>2</sub>) have shown the best selectivity values.

We now report, from results obtained with a series of Rh(II) catalysts, Rh<sub>2</sub>(O<sub>2</sub>CCF<sub>3</sub>)<sub>2</sub>(PC)<sub>2</sub>, that they induce low diastereoselectivity in the intramolecular cyclopropanation of styrenes **1a–1d** (Scheme 1), but both cyclopropane diastereoisomers are obtained with high optical purity.



Scheme 1 Catalyzed cyclopropanation of styrenes.

Use of catalysts **4–8** for cyclopropanation of styrene with ethyl diazoacetate gave the results reported in Table 1 (Fig. 1). Catalysts **4–7** showed low diastereoselectivity in the obtention of both diastereoisomers, **2a** and **3a**. However, all of them induced high asymmetry in the cyclopropanation of styrene; those catalysts with a more basic phosphine (catalysts **4–6** compared to **7**) led to the best ee values. The influence of the olefin on enantioselectivity was studied using styrenes of varying nucleophilicity (Table 2). Product yields were higher with the more nucleophilic olefins **1c** and **1d**. However, no remarkable differences on diastereo- and enantioselectivity were found for catalysts **4–7**. These results confirm that degradation to an achiral rhodium catalyst is not a major competing pathway.



Rh	Phosphine Ar <sub>3</sub> P (Ar)	R <sup>1</sup>	R <sup>2</sup>	Y
<b>4</b>	C <sub>6</sub> H <sub>5</sub>	CF <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H
<b>5</b>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	CF <sub>3</sub>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>
<b>6</b>	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub>	CF <sub>3</sub>	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>
<b>7</b>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	CF <sub>3</sub>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	F
<b>8</b>	C <sub>6</sub> H <sub>5</sub>	C(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H

Fig. 1 List of Rh(II) catalysts with *ortho*-metalated aryl phosphine ligands.

Table 1 Asymmetric cyclopropanation of styrene catalyzed by the (*M*)-enantiomer

Rh	Yield % <sup>a</sup>	% ee			Configuration	
		<b>2a/3a<sup>b</sup></b>	<b>2a<sup>c</sup></b>	<b>3a<sup>c</sup></b>	<b>2a<sup>d</sup></b>	<b>3a<sup>d</sup></b>
<b>4</b>	55	48:52	91	87	1 <i>S</i> , 2 <i>R</i>	1 <i>S</i> , 2 <i>S</i>
<b>5</b>	40	61:39	87	75	1 <i>S</i> , 2 <i>R</i>	1 <i>S</i> , 2 <i>S</i>
<b>6</b>	36	51:49	88	81	1 <i>S</i> , 2 <i>R</i>	1 <i>S</i> , 2 <i>S</i>
<b>7</b>	71	47:53	74	74	1 <i>S</i> , 2 <i>R</i>	1 <i>S</i> , 2 <i>S</i>
<b>8</b>	94	43:57	39	6	1 <i>R</i> , 2 <i>S</i>	1 <i>R</i> , 2 <i>R</i>

<sup>a</sup> Cyclopropanation yield based on ethyl diazoacetate. <sup>b</sup> Determined by GC analysis. <sup>c</sup> Ee values were based on GC analysis with a 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-beta-CDX column. <sup>d</sup> Configuration was determined by correlation of the sign of the rotation of polarized light with that of the known enantiomer (ref. 15).

**Table 2** Influence of the olefin on enantioselectivity in the cyclization catalyzed by (*M*)-**4**

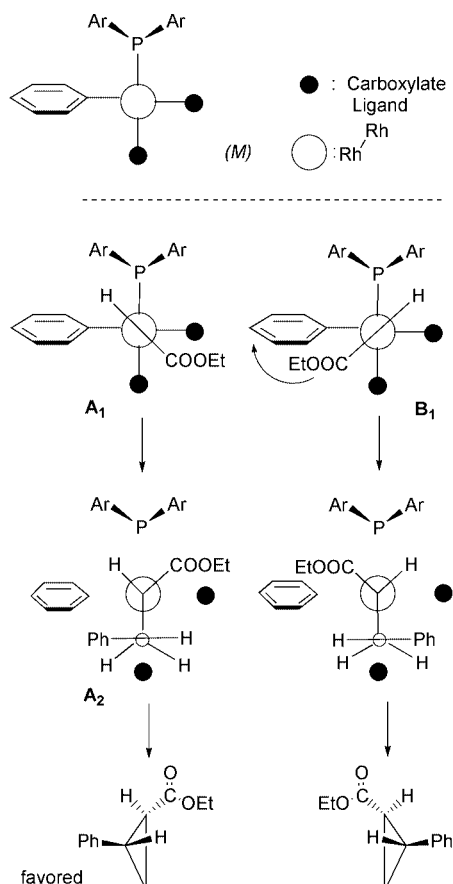
Olefin	Yield %	% ee		
		2/3	2	3
<b>1a</b>	55	48:52	91	87
<b>1b</b>	62	49:51	86	— <sup>a</sup>
<b>1c</b>	88	51:49	— <sup>a</sup>	85
<b>1d</b>	90	51:49	84	— <sup>a</sup>

<sup>a</sup> Not determined.

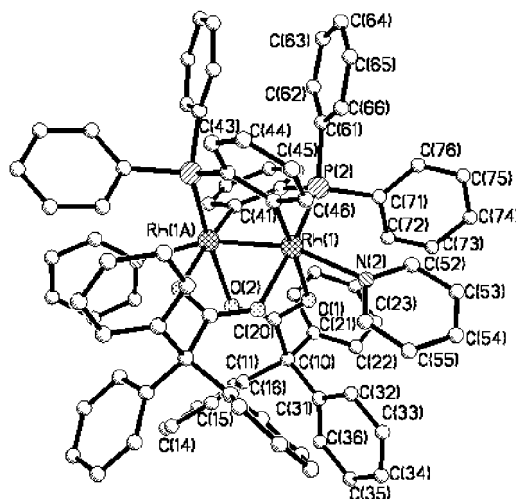
We suggest that the olefin approaches to the carbenoid through its less substituted carbon and also that the carbene transfer to olefin occurs through an early transition state. The interaction between the carbenoid ester group (CO<sub>2</sub>Et) and the olefinic substituents (R, Ar) would be weak in such a case. These two mechanistic details, altogether, could explain the low influence of the olefin on diastereoselectivity observed in our experiments.

A tentative rationale for the observed high ee values for both stereoisomers, and for the sense of asymmetric induction in the cyclopropanation of styrenes with Rh(II) catalysts **4–7** is based on the model depicted in Fig. 2 for the *M*-catalyst. The non-metalated aryl substituents of the phosphorus atom protrude into the region where carbene transfer takes place, thereby limiting the possible orientations of the coordinated carbene and favoring those orientations placing the ester group at the less sterically demanding quadrants (orientation **A**<sub>1</sub> and **B**<sub>1</sub> in Fig. 2). The cyclopropanation step, **A**<sub>1</sub> → **A**<sub>2</sub> appears to be more favored than **B**<sub>1</sub> → **B**<sub>2</sub>, since in the latter, a repulsive interaction builds up between the ester group and the metalated aryl group at some level of the process.

Additional evidence supporting such a model was obtained from the crystal structure determination of the enantiomerically pure catalyst (*M*)-**8** having bulky carboxylate ligands



**Fig. 2** Model transition state for the reaction of styrene catalyzed by the (*M*)-enantiomer.



**Fig. 3** Molecular view of the complex Rh<sub>2</sub>[(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>CCO<sub>2</sub>]<sub>2</sub>[(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>(C<sub>6</sub>H<sub>4</sub>)P]<sub>2</sub> [(*M*)-**8**]. Selected distances (Å) are Rh(1)–Rh(1A) = 2.5587(7), Rh(1)–O(2) = 2.151(3), Rh(1)–O(1) = 2.164(3), Rh(1)–P(2) = 2.280(13), Rh(1)–N(2) = 2.302(4). Selected angles (°) are C(41)–Rh(1)–O(2) = 88.08(15), O(2)–Rh(1)–O(1) = 85.65(12), O(2)–Rh(1)–P(2) = 171.46(9), N(2)–Rh(1)–Rh(1A) = 162.02.

[(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>CCO<sub>2</sub>] (Fig. 3). In this case two relevant observations are made: the enantioselectivity was much lower (almost zero for one of the diastereoisomers) and there was a reversal of induction. These two facts may be attributed to increased steric interactions in the area of the carboxylate ligands, due to the higher steric requirements of the [(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>CCO<sub>2</sub>] in **8** compared to (CF<sub>3</sub>CO<sub>2</sub>) in **4–7**, that make a carbenoid intermediate **A**<sub>1</sub> less favored than **B**<sub>1</sub> (Fig. 2). Additional studies oriented to confirm the reliability of the model depicted in Fig. 2 are in progress.

In summary, results indicate a high chiral recognition in the intermolecular cyclopropanation of styrenes showed by these dirhodium(II) compounds. The ee values clearly exceed those previously observed with other Rh(II) catalysts for this particular intermolecular reaction.

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† CCDC 155434. See <http://www.rsc.org/suppdata/cc/b0/b010145c/> for crystallographic files in .cif format.

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