

# Highly enantioselective and cis-diastereoselective cyclopropanation of olefins catalyzed by ruthenium complexes of (iminophosphoranyl)ferrocenes

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**Abstract**—Chiral (iminophosphoranyl)ferrocenes (**1** and **2**) are highly efficient ligands to achieve high diastereoselectivity (up to 95/5 dr in favor of the cis-isomer) as well as enantioselectivity (up to 99% ee) in Ru-catalyzed asymmetric cyclopropanation of various olefins. Reversal in diastereoselectivity is found as a function of metal-to-ligand ratio in the reaction of styrene.

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Asymmetric cyclopropanation of olefins with alkyl diazoacetates catalyzed by chiral transition metal complexes is well-established due to the frequent occurrence of cyclopropanes in natural products as well as their importance as valuable synthetic intermediates.<sup>1</sup> As such, a great number of catalysts are known. Pd-, Rh-, and Cu-based systems incorporating chiral nitrogen donors such as salicylaldimines, semicorrins, oxazolines, polypyrazoles, azaferrocenes, and ferrocenylamines are among the most efficient in terms of enantioselectivity.<sup>2,3</sup> Yet, the simultaneous formation of two stereocenters in olefin cyclopropanation requires the control of both diastereo- and enantioselectivities, and has so far remained as a great challenge. Almost all catalytic systems developed so far favor *trans*-selectivity.<sup>2–4</sup> In contrast, the development of methodology favoring *cis*-selectivity has rather been slow,<sup>5</sup> and limited success has been made only in non-asymmetric cyclopropanation with Rh-, Fe-, and Cu-based catalysts.<sup>6–8</sup> Recently, Mezzetti has demonstrated that high enantioselectivity with *cis*-selectivity can be achieved by some Ru–salen complexes.<sup>9</sup> More recently, an immobilized dirhodium(II) compound has also been reported to give high *cis*-selectivity.<sup>10</sup>

We have recently reported the synthesis of chiral ferrocene-based iminophosphoranes (**1** and **2**, Chart 1) and demonstrated that they can serve as a new class of practical ligands for Pd-catalyzed allylic alkylation of allyl acetates and Rh- and Ir-catalyzed hydrogenation of various olefins.<sup>11,12</sup> In particular, these new ligands exhibit exceptionally high enantioselectivity (up to 99% ee) in the Rh-/Ir-catalyzed hydrogenation of olefins regardless of the type of functional groups and of substitution.<sup>12</sup> We anticipated that **1** and **2** should act as tightly binding chelates and thus would be capable of stabilizing metal centers involved in catalytic cycles, even in rather low oxidation states.<sup>13,14</sup> Furthermore, as sterically demanding and robust chelates, they are supposed to accomplish higher asymmetric induction in other reactions as well. We now wish to report a successful expansion of **1** and **2** as ligands in Ru-catalyzed asymmetric cyclopropanation of various olefins.

In the first set of experiments to benchmark the potential of our ligands, we performed cyclopropanation of

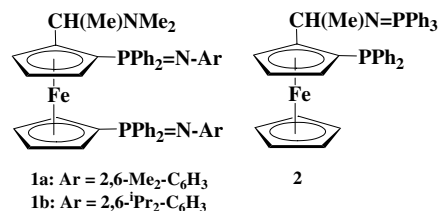


Chart 1.

**Keywords:** Asymmetric cyclopropanation; (Iminophosphoranyl)ferrocenes; Ruthenium catalysts; cis-Diastereoselection.

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**Table 1.** Cyclopropanation of styrene with EDA as a function of metal<sup>a</sup>

Entry	Metal	Yield <sup>b</sup> (%)	% dr <sup>b</sup> (trans/cis)	% ee <sup>c</sup> (trans/cis)
1	Ru(DMSO) <sub>4</sub> Cl <sub>2</sub>	64	15:85	01:99
2	Ru(PPh <sub>3</sub> ) <sub>3</sub> Cl <sub>2</sub>	82	50:50	99:28
3	Rh(PPh <sub>3</sub> ) <sub>3</sub> Cl	65	53:47	12:99
4	RhCl <sub>3</sub> ·xH <sub>2</sub> O	67	30:70	20:78
5	Pd(OAc) <sub>2</sub>	78	58:42	30:99
6	Pd <sub>2</sub> (dba) <sub>3</sub>	90	85:15	45:90
7	Cu(OTf) <sub>2</sub>	81	85:15	48:99

<sup>a</sup> Reaction conditions: [M] = 2 mol%; [M]:[L\*] = 1:1; L\* = (S, R)-**1a**.

<sup>b</sup> GC yield.

<sup>c</sup> Determined by chiral GC and absolute configuration by comparison with the literature values.

styrene with ethyl diazoacetate (EDA) as a function of metal (Eq. 1). Typical experimental procedure is as described in Ref. <sup>15</sup> and the results are illustrated in Table 1.

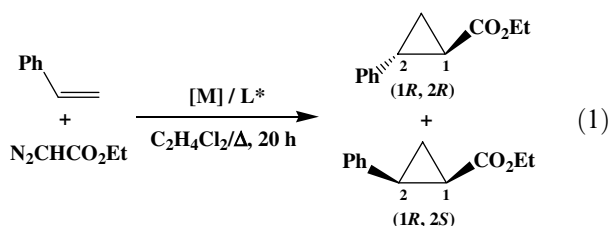


Table 1 shows that **1a** forms very effective catalysts in situ with a series of metal complexes to give cyclopropanated products in high chemical yields with excellent enantioselectivities up to 99% ee in most cases. The degree of and the preference for diastereoselectivity show dependency on the metal as well as the type of metal, the observations being little surprising as judged from the literature. The most characteristic feature of Table 1, however, is that Ru(DMSO)<sub>4</sub>Cl<sub>2</sub> and RhCl<sub>3</sub>·xH<sub>2</sub>O are quite unique in that they exhibit high cis preference. In addition, when the comparison is made between the two complexes, the former is the choice of preference as far as enantioselectivity is concerned. In fact, Ru(DMSO)<sub>4</sub>Cl<sub>2</sub> results in a quantitative enantiomeric excess for the major cis-diastereomer (entry 1).

Having established the role of Ru(DMSO)<sub>4</sub>Cl<sub>2</sub> in stereoselectivity, we decided to explore the reaction further by varying the type of ligands and the metal-to-ligand ratio. Indeed, Table 2 shows that Ru(DMSO)<sub>4</sub>Cl<sub>2</sub>-catalyzed cyclopropanation of styrene is a function of ligand. Most characteristically, all three ligands exhibit high enantioselectivities for both diastereomers in all but one set of experimental conditions (entry 3). In addition, **1a** draws a special attention in that it prefers cis-diastereoselection when the metal-to-ligand ratio is 1:1, while **1b** and **2** act on the contrary under the same condition (entries 3 and 5). At the same time, it should be noted that dramatic reversal in diastereoselectivity is observed with a change in the metal-to-ligand ratio. For instance, cis-diastereoselection found with **1a** undergoes reversal to yield a trans-diastereomer with doubling

**Table 2.** Ruthenium-catalyzed asymmetric cyclopropanation of styrene as a function of ligand and metal-to-ligand ratio<sup>a</sup>

Entry	[L]	[M]:[L]	Yield <sup>b</sup> (%)	% dr <sup>b</sup> (trans/cis)	% ee <sup>c</sup> (trans/cis)
1	<b>1a</b>	1:1	64	15:85	01:99
2		1:2	97	70:30	99:72
3	<b>1b</b>	1:1	74	88:12	33:31
4		1:2	74	09:91	99:91
5	<b>2</b>	1:1	79	53:47	97:99
6		1:2	60	30:70	99:99

<sup>a</sup> Reaction conditions: catalyst (M) = Ru(DMSO)<sub>4</sub>Cl<sub>2</sub>; [M] = 2 mol%; absolute configuration of L = (S, R); solvent = dichloroethane; reaction temperature = 70 °C.

<sup>b</sup> GC yield.

<sup>c</sup> Determined by chiral GC and absolute configurations determined by comparison with the literature values.

the relative concentration of ligand (entries 1 and 2). Also conspicuous is concomitant reversal in enantioselectivity as well with **1a**. Although a little less dramatic with **1b** and **2**, such reversal in stereoselectivity as a function of the metal-to-ligand ratio can be clearly seen in an opposite manner (entries 3–6). All-in-all, to the best of our knowledge, reversal in stereoselectivity as a function of the metal-to-ligand ratio such as observed here in cyclopropanation reactions has never been reported so far.

In order to investigate the scope of applicability of **1** and **2** as ligand in Ru-catalyzed cyclopropanation, we have employed a series of olefins as illustrated in Table 3. The table demonstrates that **1a** is a versatile ligand to achieve high asymmetric induction (up to 97/3 dr and 99% ee) for all olefins employed. It is quite remarkable to note that such high values of % de and % ee are com-

**Table 3.** Ru-catalyzed asymmetric cyclopropanation of olefins<sup>a</sup>

Entry	Olefin	[M]:[L]	Yield <sup>b</sup> (%)	% dr <sup>b</sup> (trans/cis)	% ee <sup>c</sup> (trans/cis)
1	<b>Bu</b>	1:1	79	16:84	92:94
2		1:2	88	37:63	66:96
3	<b>Hex</b>	1:1	73	48:52	28:73
4		1:2	45	28:72	74:98
5	<b>Ph</b>	1:1	78	26:74	95:98
6		1:2	75	05:95	97:93
7	<b>Ph</b>	1:1	37	19:81	98:80
8		1:2	42	67:33	99:92
9	<b>Et<sub>3</sub>Si</b>	1:1	90	91:09	98:99
10		1:2	73	94:06	96:98
11	<b>Ph</b>	1:1	69	97:03	66:99
12		1:2	40	73:27	98:92

<sup>a</sup> The same reaction conditions as adopted in Table 2; catalyst precursor prepared in situ from Ru(DMSO)<sub>4</sub>Cl<sub>2</sub> and (S, R)-**1a**.

<sup>b</sup> GC yield.

<sup>c</sup> Determined by chiral GC and absolute configurations determined by comparison with the literature values.

parable to or in some cases even better than those obtained with well-established ligands such as bisoxazolines, semicorrins, and azaferrocenes.<sup>2–4</sup> Simple terminal alkyl olefins, which are difficult to cyclopropanate, are also catalyzed efficiently. Overall, *cis*- is profoundly observed with all olefins except in the case of triethylvinylsilane and indene. The reversal in diastereoselectivity observed with styrene (Table 2) is not found with other olefins as observed from the table. Lastly, *trans*- or *cis*-preference seems to depend not only on the metal-to-ligand ratio but also on the nature of olefins.

In summary, we have demonstrated that chiral (imino-phosphoranyl)ferrocenes such as **1** and **2** are very powerful ligands to exhibit high *cis*-selectivity as well as enantioselectivity (up to 99% *dr* and *ee*) in Ru-catalyzed asymmetric cyclopropanation of a range of olefins with EDA. They are comparable to or better than well-known ligands such as bisoxazolines, semicorrins, and azaferrocenes in terms of asymmetric induction. Further advantage of employing **1** and **2** lies in the fact that the control of diastereo- as well as enantioselectivity may be feasible by a little structural change in the ligand or by varying the metal-to-ligand ratio as demonstrated in the reactions of styrene derivatives.

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15. Representative procedure for asymmetric cyclopropanation is as follows: The catalyst (0.05 mmol) was generated in situ by dissolving equimolar amounts of the ligand and  $\text{Ru}(\text{DMSO})_4\text{Cl}_2$  in dichloroethane (10 mL). This solution was mixed with the olefin substrate (10 equiv). To the reaction mixture at 70 °C was added slowly  $\alpha$ -ethyl diazoacetate (2.5 mmol) diluted in dichloroethane (10 mL) over a period of 15 h with a syringe pump. After the addition was complete, the solvent and excess olefin were

removed under vacuum. The oily residue was passed through a short silica gel column and the products were collected. The diastereomeric excess (% de) was determined by GC equipped with CBP-10 on a Acme 6000E GC. The enantiometric excess (% ee) was determined by GC equipped with Chiraldex BPH on a Acme 6000E GC. The absolute configuration of enantiomer was determined by comparison of their specific rotation with previous reports.