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Highly Enantioselective Synthesis of Cyclopropylphosphonates Catalyzed by Chiral Ruthenium Porphyrins

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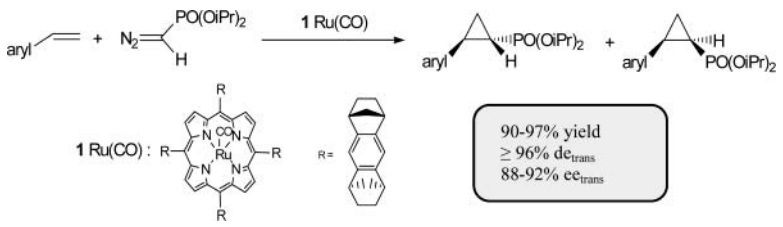
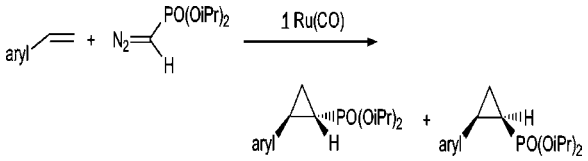
ABSTRACT



The asymmetric addition of diisopropyl diazomethylphosphonate to styrene derivatives was carried out by using chiral ruthenium porphyrins as catalysts. The reaction proceeded under mild conditions and gave *trans*-cyclopropylphosphonates with good yields and high ee's (up to 92%). A progressive increase for stereochemical effectiveness exists between enantiomeric excess and the number of chiral goups linked to ruthenium porphyrins.

Cyclopropylphosphonate derivatives have been the focus of interest for chemists because of their possible biological activities.[1] They were found to be potent inhibitors of alanine racemase and aminocyclopropanecarboxylate deaminase,[2] potential insecticides,[3] competitive antagonists for the *N*-methyl-D-aspartate receptor,[4] and many other biological applications have also been suggested.[5−7] Cyclopropylphosphonates are also very convenient intermediates for the synthesis of diphenylmethylene-cyclopropane derivatives[8] by the Wadsworth−Emmons reaction. Although a number of routes to cyclopropylphosphonates have been described in the literature, such as cyclopropanation with copper catalysts[3,9,10] or with rhodium complexes,[11] only two examples of catalytic enantioselective intermolecular cyclopropanation have been reported using rhodium complexes[12] but with an aryldiazomethylphosphonate and ruthenium complexes with a low enantiomeric excess (33%).[13] In this paper, we describe a general method for the highly enantioselective synthesis of cyclopropylphosphonates using D_4-symmetric ruthenium porphyrin (eq 1).[14] We also present the synthesis of a series



of chiral ruthenium porphyrins wherein each porphyrin bears,

(1) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1−67.
(2) Erion, M. D.; Walsh, C. T. *Biochemistry* **1987**, *26*, 3417−3425.
(3) Reid, J. R.; Marmor, R. S. *J. Org. Chem.* **1978**, *43*, 999−1001.
(4) Dappen, M. S.; Pellicciari, R.; Natalini, B.; Monahan, J. B.; Chiorri, C.; Cordi, A. A. *J. Med. Chem.* **1991**, *34*, 161−168.
(5) Hanessian, S.; Cantin, L. D.; Roy, S.; Andreotti, D.; Gomtsyan, A. *Tetrahedron Lett.* **1997**, *38*, 1103−1106.
(6) Hah, J. H.; Gil, J. M.; Oh, D. Y. *Tetrahedron Lett.* **1999**, *40*, 8235−8238.
(7) Duquenne, C.; Goumain, S.; Jubault, P.; Feasson, C.; Quirion, J. C. *Org. Lett.* **2000**, *2*, 453−455.
(8) Lewis, R. T.; Motherwell, W. B.; Shipman, M.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1995**, *51*, 3289−3302.
(9) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379−1385.
(10) Lewis, R. T.; Motherwell, W. B. *Tetrahedron Lett.* **1988**, *29*, 5033−5036.
(11) Zaragoza, F. *Tetrahedron* **1997**, *53*, 3425−3439.
(12) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 2117−2120.
(13) Paul-Roth, C.; De Montigny, F.; Rethoré, G.; Simonneaux, G.; Gulea, M.; Masson, S. *J. Mol. Catal. A: Chem.* **2003**, *201*, 79−91.

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at least, a chiral group (containing norbornane groups fused to the central benzene ring) and a spirobifluorenyl group for future polymerization. After ruthenium insertion, all of the chiral complexes are tested for asymmetric cyclopropanation of styrenes, showing the increasing effect of the number of chiral sites on the ee.

The first D_4-symmetric metalloporphyrin was prepared by Halterman and Jan.[14] The key feature in their preparation was the development of an efficient synthesis of a C_2-symmetric benzaldehyde that contains two norbornane groups fused to the central benzene ring (Figure 1). A D_2-symmetric

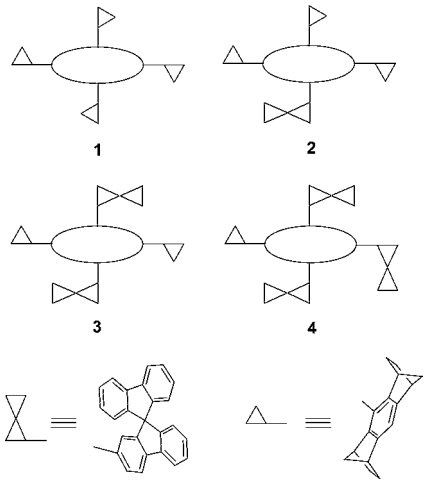
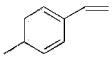
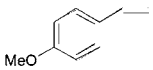
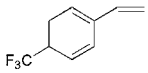
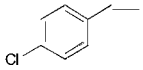


Figure 1. Schematic representation of the chiral porphyrins **1**, **2**, **3**, and **4**.

version with this aldehyde was reported later by the same authors.[15] Using a manganese chloride complex as a catalyst, epoxidation of aromatic substituted alkenes yielded up to 76% ee.[16] Frauenkron and Berkessel[17] and Che et al.[18,19] independently reported later that the ruthenium complex of the same chiral porphyrin **1** (Figure 1) can be used to catalyze the cyclopropanation of styrene with ethyl diazoacetate. This reaction is particularly interesting because the enantiomeric excesses are quite high (90%).

To evaluate the reactivity of the diazophosphonate, its ruthenium-catalyzed decomposition was examined in the presence of styrene in dichloromethane at room temperature by using **1**-RuCO as catalyst (Table 1). The cyclopropane was formed with good yield (97%), high diastereoselectivity, and high enantioselectivity for the *trans* isomer (90%). We also investigated the cyclopropanation of *para*-substituted

Table 1. Asymmetric Cyclopropanation of Styrene Derivatives with Diisopropyl Diazomethylphosphonate (DAMP) Catalyzed by **1**-Ru(CO)[a]

	substrate	T(°C)	Yield[b] (%)	trans/cis ratio	ee_{trans}[e]	ee_{cis}[e]
1[c]		25	97	96/4	90	34
2[d]		25	93	99/1	87	23
3[d]		25	96	97/3	90	23
4[d]		25	90	95/5	92	5
5[d]		25	92	97/3	88	27

[a] Reactions were performed in CH_2Cl_2 for 2 h with a catalyst/diazo/substrate molar ratio of 1:200:1000. [b] Isolated yields based on DAMP. [c] Determined by chiral GC (see Supporting Information). [d] Determined by chiral HPLC (see Supporting Information). [e] Undetermined absolute configuration.

styrenes (Table 1). As shown in the Table 1, *para*-substitution (*p*-Y-styrene, Y = Me, MeO, CF_3, and Cl) does not have a significant effect upon the enantioselectivity of styrene cyclopropanation. A similar effect was noted with asymmetric cyclopropanation with ethyl diazoacetate using a different chiral ruthenium catalyst.[20]

To get more information on the stereochemistry of these catalytic reactions, preparation of the carbene complex was first undertaken. Reaction of the chiral carbonyl ruthenium complex **1**-RuCO with excess of diisopropyl diazomethylphosphonate in dichloromethane results in the displacement of the CO ligand and generation of the dark brown carbene complex **5** in 82% yield (Figure 2). The carbene complex was stable enough to be purified by chromatography on silica

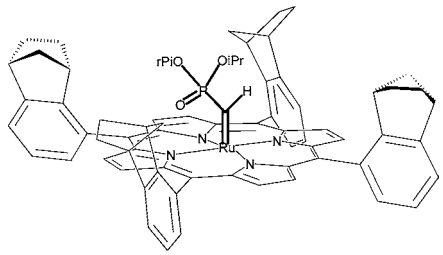


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Figure 2. Schematic representation of the ruthenium carbene complex **5**, showing only the upper face of the porphyrin ring.

(14) Halterman, R. L.; Jan, S. T. *J. Org. Chem.* **1991**, *56*, 5253−5254.
(15) Halterman, R. L.; Mei, X. *Tetrahedron Lett.* **1996**, *37*, 6291−6294.
(16) Halterman, R. L.; Jan, S. T.; Nimmons, H. L.; Standlee, D. J.; Khan, M. A. *Tetrahedron* **1997**, *53*, 11257−11276.
(17) Berkessel, A.; Kaiser, P.; Lex, J. *Chem. Eur. J.* **2003**, *9*, 4746−4756.
(18) Che, C. M.; Huang, J. S.; Lee, F. W.; Li, Y.; Lai, T. S.; Kwong, H. L.; Teng, P. F.; Lee, W. S.; Lo, W. C.; Peng, S. M.; Zhou, Z. Y. *J. Am. Chem. Soc.* **2001**, *123*, 4119−4129.
(19) Cheung, W. H.; Zheng, S. L.; Yu, W. Y.; Zhou, G. C.; Che, C. M. *Org. Lett.* **2003**, *5*, 2535−2538.

gel. The proton-decoupled ^{13}C NMR spectrum shows a typical low-field signal for the carbene carbon at 284.1 ppm as a doublet due to coupling with phosphorus ($J_{CP} = 180$ Hz) and the ^{1}H NMR spectrum spectrum reveals a doublet at 15.3 ppm ($J_{PH} = 46$ Hz).

The postulate of possible metallocarbenes as active intermediates in cyclopropanation reactions prompted us to investigate the catalytic activity of **5** toward diazomethylphosphonate addition to styrene in comparison to those of **1**-RuCO and the rutheniumdioxo congener.[21] As shown in Table 2, very similar diastereoselectivity and enantioselectivity were observed for the three complexes, suggesting the formation of **5** during the catalytic reaction with a possible solvent molecule in axial position, the final metal products being essentially the carbene metal complex **5** and traces of **1**-RuCO.

Table 2. Cyclopropanation of Styrene with Diazomethylphophonate Catalyzed by **1**-RuCO, **5**, and Dioxoruthenium Complex[a]

	1-Ru(CO)	**1**-RuO_2	**5**
yield (%)[c]	97	94[b]	96
trans/*cis* ratio	96/4	99/1	99/1
ee_{trans} (%)[d]	90	84	89

[a] Reactions were performed in CH_2Cl_2 48 h with a catalyst/diazo/substrate molar ratio of 1:200:1000. [b] Time reaction of 5 days. [c] Isolated yields based on DAMP. [d] Determined by chiral GC (see Supporting Information).

We have recently shown that stable metalloporphyrin, showing good electroactivity (thickness >100 μm) can be prepared by oxidative electropolymerization of metalloporphyrin complexes bearing spirobifluorene groups. Thus polymerization of Ru spirobifluorenylporphyrins leads to very efficient catalysts that can be easily recovered and reused. We anticipate that these heterogeneous catalytic systems would be potentially applicable to practical organic synthesis with a special focus on asymmetric catalysis using chiral polymers. As a chiral extension of our previous work on polymers,[22] the spirobifluorenyl group was designed to allow polymerization and the chiral group for asymmetric induction.

The key feature in our preparation was to use a one-flask method for preparing all chiral *meso*-substituted porphyrins, bearing one, two, three, and four chiral substituents. Two different methods were undertaken. First, it is well-known that the condensation of aryldipyrrylmethanes with benzaldehyde leads to a scrambling.[23,24] Thus, reaction of 9,9′-spirobifluorenyldipyrromethane and dimethanoanthracene-9-carbaldehyde led to a mixture of four porphyrins, bearing four (**1**), three (**2**), two (**3**), and one (**4**) chiral group, with low yield (total yield <10%), whereas only **3** was expected without any scrambling. An alternate route to these chiral porphyrins is also possible through a mixed-aldehyde condensation of spirobifluorene aldehyde, chiral aldehyde, and pyrrole. This second method gave a mixture of the different porphyrins porphyrins **1** (10%), **2** (18%), and **3** (8%), which were isolated by chromatography. The detailed synthesis of the corresponding ruthenium complexes **2**-RuCO, **3**-RuCO, and **4**-RuCO, bearing three, two, and one chiral groups, respectively, is described in Supporting Information.

We then investigated the cyclopropanation reaction using diazomethylphosphonate and diazoacetate with the complexes **2**-RuCO, **3**-RuCO, and **4**-RuCO (Figure 1), the results being reported in Table 3. Surprisingly, complex **2**-RuCO bearing only three chiral groups catalyzed the cyclopropanation reaction, yielding cyclopropylphosphonates with a moderate decrease of the ee by comparison with those obtained with **1**-RuCO. For example, the ee decreased from 90% to 77% for styrene at 25 °C (Table 3, entries 2 and 4). Thus the stereochemical effect of the loss of the D_4 symmetry was not so dramatic. Furthermore, replacing two chiral groups by two spirobifluorene groups yields the complex **3**-RuCO, which catalyzed the cyclopropanation of styrene with 66% ee (Table 3, entry 6). Similar effects were observed using ethyl diazoacetate instead of diazomethylphosphonate.

Table 3. Asymmetric Cyclopropanation of Styrene with Ethyl Diazoacetate (EDA) or Diisopropyl Diazomethylphosphonate (DAMP) Catalyzed by Ruthenium Carbonyl Porphyrins **1**-Ru(CO), **2**-Ru(CO), **3**-Ru(CO), and **4**-Ru(CO)[a]

	catalyst	diazo	*T* (°C)	yield[b] (%)	*trans*/*cis* ratio	ee_{trans}[c]	ee_{cis}[c]
1	1-Ru(CO)	EDA	25	96	95/5	87[d]	4
2		DAMP		97	96/4	90[e]	34
3	2-Ru(CO)	EDA	25	95	93/7	65	3
4		DAMP		65	96/4	77	27
5	3-Ru(CO)	EDA	25	94	90/10	41	8
6		DAMP		55	95/5	66	8
7	4-Ru(CO)	EDA	25	96	90/10	25	2
8		DAMP		13	90/10	33	3

[a] Reactions were performed in CH_2Cl_2 for 2 h with EDA and 48 h for DAMP with a catalyst/diazo/substrate molar ratio of 1:200:1000. [b] Isolated yields based on EDA or DAMP. [c] Determined by chiral GC (see Supporting Information). [d] Configuration (1*S*,2*S*). [e] Undetermined absolute configuration.

Thus, introducing three chiral groups on the porphyrin ring removes only part of the chiral steric hindrance. Because we do not have an X-ray structure determination of complexes **2**-RuCO, **3**-RuCO, and **4**-RuCO, the reason for their difference on enantioselectivity with styrene remains unclear, but a progressive decrease of the chiral cavity above the active center during the formation of the carbene ruthenium complex seems to affect progressively the degree of the prochiral-face recognition. In all the cases, the major isomer

(20) Galardon, E.; Roué, S.; Le Maux, P.; Simonneaux, G. *Tetrahedron Lett.* **1998**, *39*, 2333−2334.
(21) Lai, T. S.; Zhang, R.; Cheung, K. K.; Kwong, H. L.; Che, C. M. *J. Chem. Soc., Chem. Commun.* **1998**, 1583−1584.
(22) Poriel, C.; Ferrand, Y.; Le Maux, P.; Rault-Berthelot, J.; Simonneaux, G. *Chem. Commun.* **2003**, 2308−2309.
(23) Wallace, D. M.; Leung, S. H.; Senge, O. M.; Smith, K. M. *J. Org. Chem.* **1993**, *58*, 7245−7257.
(24) Lindsey, J. S. *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 1, pp 46−118.

is the *anti*-cyclopropane with the (1*S*,2*S*) configuration. A similar result is observed for asymmetric cyclopropanation of styrene with diisopropyl diazophosphonate, the absolute configuration of the major isomer being not known.

In summary, the asymmetric cyclopropanation of diazomethylphosphonates catalyzed by chiral ruthenium porphyrins occurs in a highly stereoselective manner. Additionally, a progressive increase for stereochemical effectiveness exists between enantiomeric excess and the number of chiral goups in cyclopropanation reaction catalyzed by optically active ruthenium porphyrins bearing spirobifluorene groups. Electropolymerization of **2**-RuCO and **3**-RuCO and investigation of the catalytic properties of the resulting chiral polymers are currently underway in our laboratory and will be reported in due course.

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Supporting Information Available: Synthetic details and characterization of all ruthenium complexes, as well as general procedure for cyclopropanation and determination of enantioselectivity. This material is available free of charge via the Internet at http://pubs.acs.org.

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