DIRHODIUM(II) TETRAKIS[3(*S*)-PHTHALIMIDO-2-PIPERIDINONATE]: A NOVEL DIRHODIUM(II) CARBOXAMIDATE CATALYST FOR ASYMMETRIC CYCLOPROPANATION†

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Abstract – Dirhodium(II) tetrakis[3(*S*)-phthalimido-2-piperidinonate] catalyzes cyclopropanation of α-methylstyrene with *d*-menthyl diazoacetate to give *d*-menthyl (1*S*,2*S*)-2-methyl-2-phenylcyclopropanecarboxylate of 90% de.

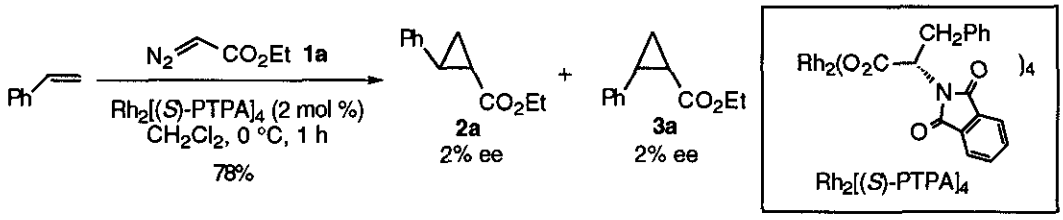
The design and development of asymmetric catalysts to induce a high level of enantioselection in carbon-carbon bond forming reactions have been the subject of intensive investigations in organic synthesis.[1] Our efforts in this area have led to the development of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate], Rh_2[(*S*)-PTPA]$_4$, for intramolecular C-H insertion reactions of α-diazocarbonyl compounds,[2] the efficacy of which has been demonstrated by the construction of optically active cyclopentanone, 2-indanone, and 2-azetidinone derivatives with up to 95% ee, and also rationalized by evaluating an asymmetric environment at the rhodium(II) carbene center featured by the two protruding phthalimido walls. As a logical extension of our efforts directed toward the development of dirhodium(II)-catalyzed enantioselective carbene transformations,[3] our interest was centered on asymmetric cyclopropanation reactions.

Since the pioneering work of Nozaki and Noyori[4] with chiral Cu-salicylaldimine complexes as catalysts in 1966, there have been devised a tremendous number of asymmetric cyclopropanation catalysts including cobalt,[5] copper,[6] ruthenium,[7] and rhodium[8] complexes of rationally designed chiral ligands. Of these catalysts, chiral copper catalysts bearing C_2-symmetric nitrogen ligands[9] such as semicorrine,[6c] bis(oxazoline),[6d,e] bis(imidazoline)[6f] and bipyridines[6g] have prsoven to be by far the most successful for asymmetric cyclopropanations of various olefins with achiral diazoacetates (up to 99% ee), while dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(*S*)-carboxylate],[8c] Rh_2[5(*S*)-MEPY]$_4$, the rhodium catalyst of choice developed by Doyle offers a notable advantage for the intramolecular asymmetric cyclopropanations of allylic and homoallylic diazoacetates[8d] but neither with the corresponding alkenyl-diazoketones[8b] nor with intermolecular cyclopropanations as above.[8a] We now wish to introduce

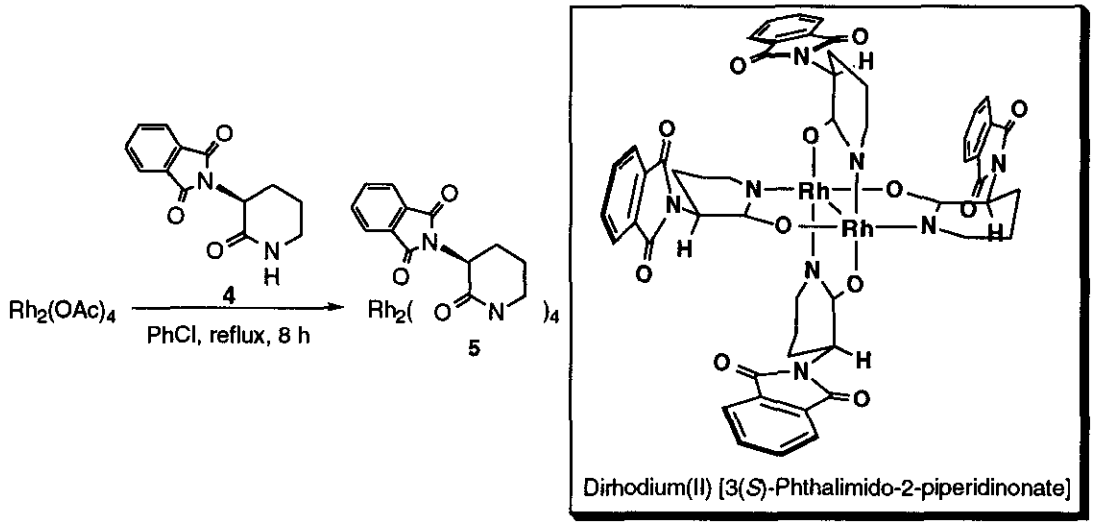
† Dedicated to the memory of the late Dr. Yoshio Ban, Professor Emeritus of Hokkaido University.

dirhodium(II) tetrakis[3(*S*)-phthalimido-2-piperidinonate] as one of a new family of dirhodium(II) catalysts, the potentiality of which is described herein.

At the outset, Rh_2[(*S*)-PTPA]$_4$ was applied to cyclopropanation of styrene with ethyl diazoacetate (**1a**). In the presence of 2 mol % of the catalyst, the reaction proceeded smoothly (CH_2Cl_2, 0 °C, 1 h) to give ethyl *trans*- and *cis*-2-phenylcyclopropanecarboxylates (**2a**) and (**3a**) in a ratio of 55:45 and with very low enantioselectivities (2% ee each).[10] On this disappointing result, we speculated that a reactivity of

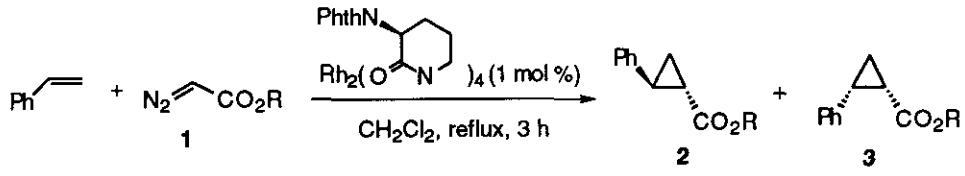


the rhodium(II) carbene complex, a putative reactive intermediate, might be too high to exhibit enantioselectivity. In this respect, it has recently been disclosed that electronic effects as well as steric influences of the bridging ligands of dirhodium(II) catalysts can switch site- or chemoselectivities in competitive carbene transformations.[11] We thus reasoned that dirhodium(II) carboxamidate catalysts would generate less reactive but more discriminating carbene complexes for olefins than those derived



from dirhodium(II) carboxylate catalysts through a stronger backbonding from rhodium to the carbene carbon.[12] To this end, we chose 3(*S*)-phthalimido-2-piperidinone (**4**)[13] as the bridging ligands, in which the phthalimido group was expected to serve as an enantiocontroller from the previous studies.[2] Dirhodium(II) tetrakis[3(*S*)-phthalimido-2-piperidinonate] (**5**)[16] was prepared by ligand exchange between $Rh_2(OAc)_4$ and **4** under the conditions of Doyle,[8c] the spectroscopic data of which demonstrated that two oxygen and two nitrogen donor atoms were bonded to each octahedral rhodium in a *cis* configuration as expected from Doyle's Rh_2[5(*S*)-MEPY]$_4$.[8c]

Table 1. Asymmetric Cyclopropanation of Styrene with Alkyl Diazoacetates Catalyzed by Dirhodium(II) Tetrakis[3(*S*)-phthalimido-2-piperidinonate]



entry	diazoacetate **1** R	*trans*-cyclopropane **2**[a] % yield	$[\alpha]^{22}_D$ deg (*c*, $CHCl_3$)	% ee[c]	*cis*-cyclopropane **3**[b] % yield	$[\alpha]^{22}_D$ deg (*c*, $CHCl_3$)	% ee[c]
1	**1a** Et	31	+46.1° (1.12)	17	19	+3.0° (1.24)	28
2	**1b** Bu^t	37	+163.7° (1.03)	61	34	+10.3° (1.03)	51
3	**1c** $CHPr^i_2$	42	+126.2° (1.06)	69	18	+8.2° (1.14)	75
4	**1d** $CMePr^i_2$	57	+139.5° (1.04)	68	35	+17.4° (0.34)	52
5	**1e** *l*-menthyl	32	+77.7° (1.00)	73	30	-54.4° (1.07)	79
6	**1f** *d*-menthyl	57	+222.6° (1.13)	89	22	+48.2° (1.00)	83

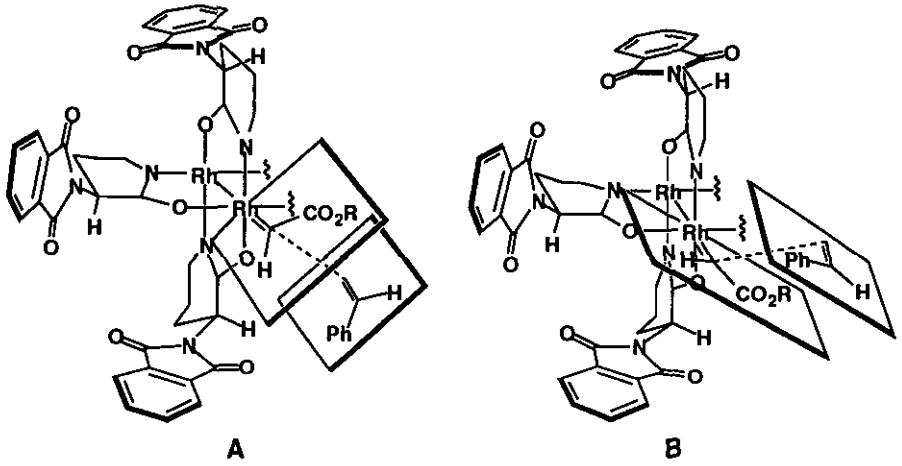
[a] The absolute configurations of **2** were determined to be 1*S*,2*S* by comparison of the sign of optical rotation of the corresponding alcohol with that of the known compound.[6e] [b] The absolute configurations of **3** were determined to be 1*S*,2*R* by comparison of the sign of optical rotation of the corresponding alcohol with that of the known compound: T. Aratani, Y. Nakanishi, and H. Nozaki, *Tetrahedron*, *1970*, **26**, *1675*. [c] Determined by hplc (Daicel Chiralcel OJ) after conversion into the corresponding alcohol.

Asymmetric cyclopropanation reaction was performed by addition of a solution of the diazoacetate (**1**) (0.85 mmol) in CH_2Cl_2 (2 ml) through a syringe pump over 3 h to a refluxing CH_2Cl_2 (2 ml) solution of the catalyst (**5**) (1 mol %) and 5 equiv of styrene. After a standard work-up, the corresponding *trans*- and *cis*-2-phenylcyclopropanecarboxylates (**2**) and (**3**) were separated by silica gel column chromatography, which were reduced with $LiAlH_4$ to the corresponding known alcohols to determine the preferred absolute configurations and enantioselectivities. The results are summarized in **Table 1**, which demonstrates several characteristic features of this novel catalyst.

As might be expected, the catalyst (**5**) exhibited even higher enantioselectivities with **1a** than Rh_2[(*S*)-PTPA]$_4$ (entry 1). It has been well recognized that enantioselectivities and *trans*/*cis* ratios in catalytic asymmetric cyclopropanation can be improved with an increase in the steric bulk of the ester alkyl group of diazoacetates.[5-9] With respect to the enantioselectivities, the general trend was observed with the ethyl, *tert*-butyl, and 2,4-dimethyl-3-pentyl diazoacetates (**1a-c**) (entries 1-3). However, with the more sterically demanding 2,3,4-trimethyl-3-pentyl diazoacetate (**1d**),[8a] further enhancement of enantioselectivities could not be attained (entry 4). On the other hand, the *trans*/*cis* selectivities were modest in every case, with the *trans*-isomer slightly favored, as suggested by those with Rh_2[5(*S*)-MEPY]$_4$ and its congeners.[8a,e,f] The use of the enantiomeric menthyl diazoacetates (**1e,f**) resulted in a slight effect on double stereodifferentiation, in which the matched pair incorporating *d*-menthyl diazoacetate (**1f**) improved the enantioselectivity to 89%, the highest value reported to date for this reaction with the dirhodium(II) catalysts.[8a,e,f]

The stereochemical outcome of the present cyclopropanation may be explained by the operational model proposed originally by Pfaltz[6c] and a little later by Doyle[8b,c] with asymmetric cyclopropanations

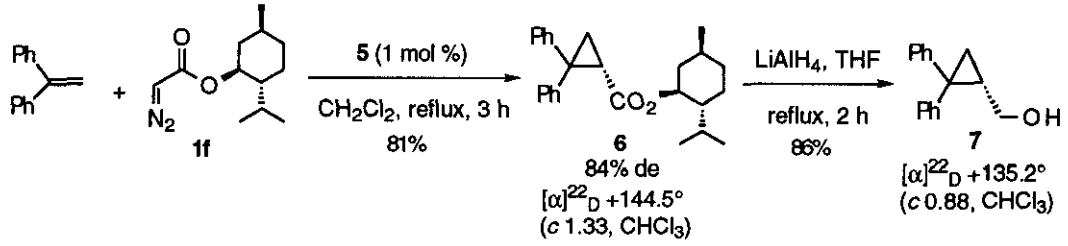
catalyzed by (semicorrinato)copper(I) complex and $Rh_2[5(S)\text{-MEPY}]_4$, respectively.[17] The chiral environment around the rhodium(II) center can be divided into four quadrants, of which two are occupied by the protruding phthalimido group at the stereogenic center of the piperidinonate ligands. In consequence, the putative rhodium(II) carbene intermediates (**A**) and (**B**) can be presented as two low-



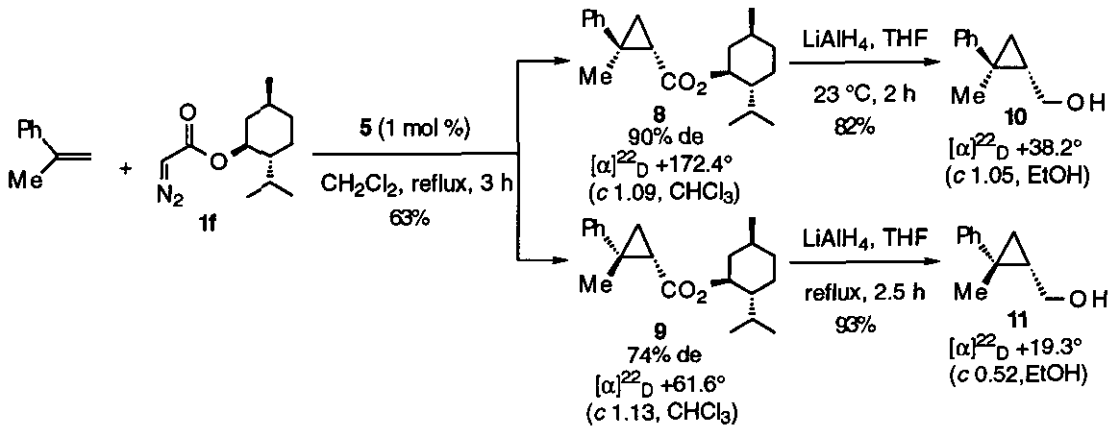
A **B**

energy conformations, in which the ester group is accommodated in the less crowded quadrant. The rhodium(II) carbene (**A**) allows the attack of styrene predominantly at the less congested *si*-face, in which the *p* orbital of the carbene interacts with the less substituted center of styrene so that the more substituted end points far away from the rhodium atom, leading to the formation of the *trans*-cyclopropane with the observed (1*S*,2*S*)-configuration. When the attack of styrene to the less hindered *re*-face of the rhodium(II) carbene (**B**) takes place, a repulsive steric interaction builds up between the ester group and the phthalimido group during pyramidalization of the involved carbon centers. Therefore, this pathway *via* **B** is disfavored. With regard to the *trans*/*cis* ratios, modest selectivities may be understood by assuming that the present cyclopropanation has early transition state and so the steric interaction between the ester group and the phenyl substituent is weak.

The asymmetric cyclopropanation catalyzed by **5** can be extended to 1,1-disubstituted olefins, in which the stereochemical outcome is predictable based on the above model. The cyclopropanation of 1,1-



diphenylstyrene with *d*-menthyl diazoacetate (**1f**) under the foregoing conditions furnished *d*-menthyl (*S*)-2,2-diphenylcyclopropanecarboxylate (**6**) in 81% yield and in 84% de.[18] With α-methylstyrene, the *trans*-cyclopropane (**8**) of 90% de and the *cis*-cyclopropane (**9**) of 74% de were obtained in 40% and 23% yields, respectively.[19]



In conclusion, we have demonstrated that dirhodium(II) tetrakis[3(*S*)-phthalimido-2-piperidinonate] (**5**) is a highly promising chiral catalyst for asymmetric cyclopropanation reactions. Further studies on the scope and potency of this catalyst are currently in progress.

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