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Design and Synthesis of a [2.2]Paracyclophane-based Planar Chiral Dirhodium Catalyst and its Applications in Cyclopropanation Reaction of Vinylarenes with α-Methyl-α-Diazo Esters

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Abstract: A planar chiral dirhodium paddlewheel complex $Rh_2(S_p\text{–PCP})_4$ based on the [2.2]paracyclophane has been synthesized for the challenging cyclopropanation of venylarene derivatives with *tert*-butyl α-diazo propionates. The homobimetallic rhodium catalyst relies on the high steric demand and rigidity of [2.2]paracyclophane that favors the cyclopropanation of 1-aryl substituted, 1,1-disubstituted and benzannulated alkenes over β-hydride migration at room temperature with high diastereoselectivity.

Keywords: Catalyst Design; Bimetallic Catalysts; Chiral dirhodium(II) complexes; Cyclopropanation; Planar Chirality; [2.2]Paracyclophane

Rhodium(II) paddlewheel complexes are exceptionally powerful catalysts that have wide synthetic applications in metal-carbene transformations. It includes the formation of diverse cyclophanes which are important motifs in bioactive natural products and pharmaceuticals by employing diazo compounds with alkenes.[1] The intermediate rhodium carbenoid precursors react in a vast range of transformations including cyclopropanation,[1d,2] cyclopropenation,[1a,3] X–H (X=C, Si, N, O, S) insertion,[4] and ylide transformations[4d,5] with high chemoselectivity. Various dirhodium tetracarboxylate complexes have been shown to be effective catalysts for highly site-selective and stereoselective C–H bond functionalization of a wide range of useful substrates.[4a,6] Combined with the ease of access to diazo compounds, their structural and synthetic versatility as well as scalability, makes them ideal intermediates for late-stage modifications.[4d,7]

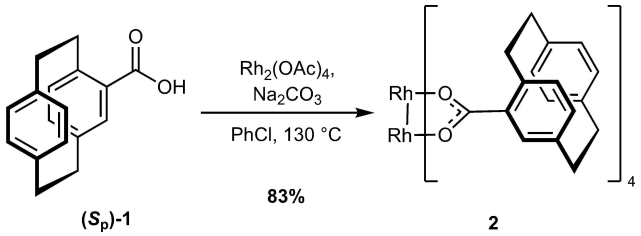
Advancing the catalyst design, a variety of metal-mediated reactions involving diazo compounds have been reported in literature.[4e,8] Tailoring catalytic reactivity of dirhodium complexes, by tuning of the carboxylate ligands around the reaction center, with a particular emphasis on selectivity, new efficient rhodium-based catalyst systems have been previously explored.[9] The goal is to gain a more general catalytic and synthetic utility, where a wide scope of alkenes and diazo compounds is tolerated. Significant progress has been made in recent years. Yet, the task remains a longstanding challenge.[2c,10] However, an exception has been the selective transformation involving α-alkyl-substituted α-diazo compounds. The propensity of the intermediate carbene to undergo β-hydride

migration has precluded these compounds from a general application in intermolecular reactions for a long time.[3d,11]

To overcome this challenge, crucial effects of sterically demanding different ligands in dirhodium complexes in combination with low reaction temperature has also been demonstrated. Taking this into consideration, the use of α-alkyl-substituted α-diazo compounds has become more general and led to the development of diastereo- and enantioselective systems.[2e,3c,12] Even though a large number of carboxylate-ligands for dirhodium complexes has been investigated, mostly effecting cyclopropanation and C–X insertion in a stereoselective manner, the element of planar chirality has never been explored, so far. Dirhodium complexes based on ferrocene as ligand and their catalytic applications in intramolecular C–H insertion reactions have been investigated previously.[13] The huge success of planar chiral ferrocenyl ligands represented by the JosiPhos family, and the [2.2]paracyclophane (PCP) based PhanePhos being the most prominent example of ligands, show that introducing planar chirality is a viable alternative to the most conventional, central chirality and offers new opportunities for the development of efficient catalyst systems.[14] Nonetheless, compared to central and axial chirality, the research on planar chirality is lagging behind.

Herein, we present the design and first synthesis of the planar chiral dirhodium(II) paddlewheel complex $Rh_2(S_p\text{–PCP})_4$ bearing [2.2]paracyclophane carboxylate ligands and its catalytic applications in cyclopropanation reaction of vinylarenes with α-methyl-α-diazo esters.

Our research group and others have previously demonstrated a series of novel [2.2]paracyclophane-based planar chiral systems and their applications as a useful class of catalysts and ligands to facilitate synthetically important various selective asymmetric transformations.[15] The unique "bent and battered" structure of the [2.2]paracyclophane possesses a configurationally distorted and rigid structure with inherently high steric demand.[14b,16] Our group has been particularly interested to explore whether incorporation of the planar chiral PCP scaffold in rhodium(II) paddlewheel complexes, with its distorted and rigid core, would improve catalytic activity towards cyclopropanation with α-alkyl-substituted α-diazo compounds. Enantiomerically pure (S_p)-4-carboxy [2.2]paracyclophane (***S*$_p$-1**, S_p-PCP) was obtained from the enantiomerically pure aldehyde[15d] *via* Pinnick oxidation. Carboxylic acid ***S*$_p$-1** was used for the preparation of the new planar chiral dirhodium complex, $Rh_2(S_p\text{–PCP})_4$ (**2**, Scheme 1) *via* equatorial ligand exchange by heating a mixture of the ligand **(*S*$_p$)-1** and rhodium(II) acetate in a Soxhlet extractor filled with sodium carbonate. After purification on silica gel,



Scheme 1. Synthesis of the PCP-based planar-chiral dirhodium complex $Rh_2(S_p\text{–PCP})_4$ (**2**).

greenish $Rh_2(S_p\text{–PCP})_4$ complex was isolated in 83% yield.

The dirhodium(II) paddlewheel complex consists of four equatorial μ_2-ligands (PCP) and two axial ligands (as cocrystallized water molecules). Whereby the most interesting feature of the $Rh_2(S_p\text{–PCP})_4$, is the positioning of the [2.2]paracyclophane ligands in the complexes (Figure 1). For the dirhodium(II) catalyst, to transfer chiral information towards the final product, the space above (α-face) and below (β-face) of the O–Rh–O planes has to be sterically restricted.[1d] In case of $Rh_2(S_p\text{–PCP})_4$, the equatorial ligands adopt a distorted C_2 symmetry around the dirhodium core,

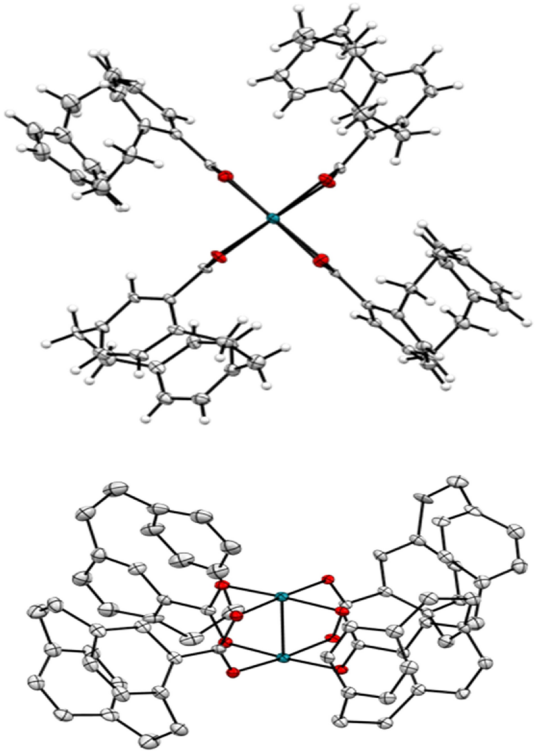
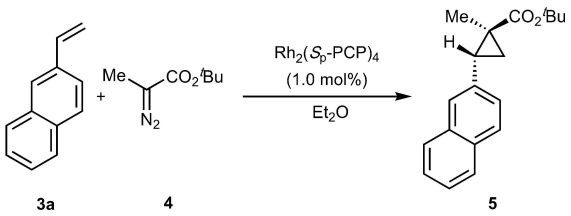


Figure 1. Top-view (top) and side-view (bottom) of the crystal structure of $Rh_2(S_p\text{–PCP})_4$ (**2**). Cocrystallized H_2O molecules are omitted for clarity, displacement parameters are drawn at 30% probability level. The absolute configuration was determined crystallographically.

whereby the [2.2]paracyclophane bridge heads point out of the O–Rh–O plane. This creates a chiral and sterically restricted space above the rhodium center, leaving the *α*-face unrestricted.

We envisioned the [2.2]paracyclophane dirhodium complex **2** for the cyclopropanation reaction of different alkenes with *α*-alkyl-substituted *α*-diazo compounds (Scheme 2). Previously, cyclopropanation with *tert*-butyl *α*-diazopropionate catalyzed by dirhodium (II)tetrakis[*N*-tetrabromophthaloyl-(*S*)-*tert*-leucinate] Rh_2(*S*-TBPTTL)$_4$ has been demonstrated, provide the corresponding cyclopropanes with good yields and with high diastereoselectivity.[17] We employed 2-vinylnaphtalene (**3a**) as test substrate and after optimization using Rh_2(S_p-PCP)$_4$ (1.0 mol%) and *tert*-butyl *α*-diazopropionate (**4**, 2.0 equiv.) in diethyl ether gave the best results, affording the cyclopropane product **5a** in 74% yield (see supporting information, Table 1). In every case of the optimization, the product was obtained with a d.r. > 99:1. Here, a high selectivity of the catalyst over *β*-hydride migration was observed at room temperature. For a high selectivity of a dirhodium catalyst in the formation of the cyclopropanation product over *β*-hydride migration, low temperature and sterically demanding carboxylate ligands proved vital. The counterintuitive finding that bulky ligands favor the cyclopropanation reaction may be rationalized with substrate-ligand interactions.[18] The reaction was unsuccessful with higher substituted diazo compounds. Ethyl, *n*-propyl, benzyl, and *i*-propyl groups in *α*-position did not lead to any product formation, even if the reaction was conducted at −78 °C. The propensity of *α*-alkyl-*α*-diazo esters to undergo *β*-hydride migration is inversely proportional to the degree of substitution. With increased substitution, the C–H bond strength decreases. Lower reaction temperature stabilizes the carbene intermediate, but also lowers its chemical reactivity. We assume that at lower temperatures, the *β*-hydride migration still prevails, so that the cyclopropanation product is not formed.

The temperature profile of the reaction was examined very closely. Previous reports have shown a higher resilience of the rhodium carbene intermediate against *β*-hydride migration at lower temperatures.[3c,d,11a] Reducing the reaction temperature to 0 °C and to −25 °C led to a considerably longer reaction time until all of the diazo compound **4** was consumed. A decrease in yield of the cyclopropanation product was observed in both cases, whereas the formation of the elimination product was the dominating pathway. Most likely this is due to a reduced reactivity of the carbene intermediate, favoring the faster *β*-elimination over the cyclopropanation pathway. The use of equimolar amounts of the diazo compound **4** led to reduction in yield, whereas a higher excess did not lead to a significant further increase.



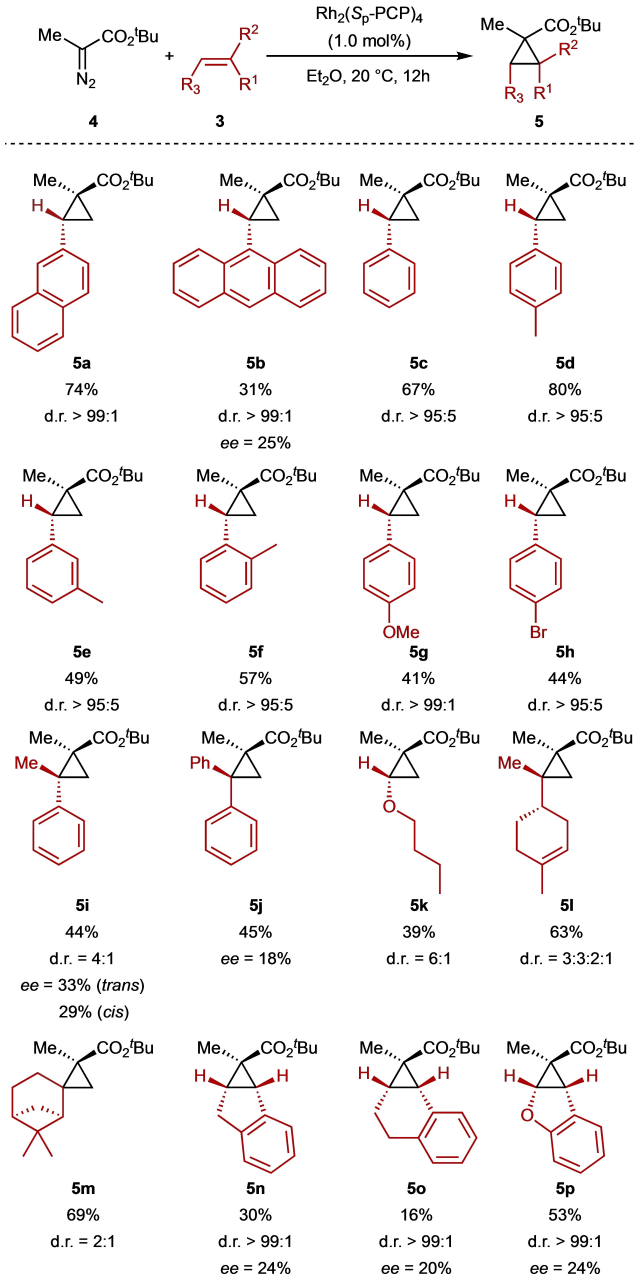
3a 4 5

Scheme 2. Rh_2(S_p–PCP)$_4$ catalyzed cyclopropanation reaction of 2-vinylnaphtalenene (**3a**) with *tert*-butyl *α*-diazopropionate **4** employing Rh_2(S_p–PCP)$_4$ (**2**).

With the optimized reaction conditions in hands, a variety of terminal alkene components were screened (Scheme 3). Generally, a high diastereoselectivity (d.r. > 95:5) and, with few exceptions, no notable enantioselectivity was observed. The lack of additional sterically demanding groups on the PCP-scaffold leaves the *β*-face of the catalyst mostly unrestricted. This site is more accessible to form the carbene intermediate from the diazo compound and reacts with most of the alkenes without enantioselectivity. For the cyclopropanation of styrene derivatives (**3c**–**3h**) good to high yields were obtained. The steric and electronic effects on the cyclopropanation was investigated using styrene derivatives with a methyl substituent in *para*- (**5d**) *meta*- (**5e**) and *ortho*- (**5f**) position. Here, the electron donating character of the methyl group increases the yield, especially when in case of *para*-position and gave the product **5d** with 80% yield. The electron donating effect in *ortho*-position compensates better for the competing steric hinderance, than in *meta*-position, which is shown by the product yields in 57% and 49%, respectively.

An exception to the high diastereoselectivity are compounds **5i**, **5l** and **5m** derived from 1,1-disubstituted alkenes. An additional substituent in *α*-position led to the construction of two quaternary carbon centers at once which gave the products **5i** and **5j** in a good yield and in the case of **5i** with a d.r. of 4:1. Attempts to cyclopropanate 1,2-disubstituted alkenes (*cis* and *trans*) as well as trisubstituted alkenes were not successful. In the case of the *α*-substituted alkenes **5i** and **5j**, a comparatively higher enantioselectivity up to 31% was observed. The cyclopropanated cyclic alkenes were obtained with 24% *ee*. No notable enantioselectivity was observed for monosubstituted alkene derivatives under these reaction conditions. The exception to this is the bulky 9-vinyl anthracene derivative product **5b** which was obtained with 25% *ee*.

Of particular note is that *n*-butyl vinyl ether (**5k**) and the *α*,*α*-alkyl disubstituted alkenes (*R*)-limonene (**3l**) and (−)-*α*-pinene (**3m**) were also effectively cyclopropanated in high yields and with a d.r. of 3:3:2:1 and 2:1, respectively. Other alkyl substituted alkenes such as 1-octene, vinylcyclohexene, and 3-



Scheme 3. Synthetic scope of the cyclopropanation employing different alkenes (0.20 M, 0.42 mmol) employing $Rh_2(S_p\text{-PCP})_4$ (**2**, 1.0 mol%) and **4** (0.40 M, 0.83 mmol) in diethyl ether. The d.r. was determined *via* GC-MS of the crude reaction mixture. All yields refer to the average isolated yield from two experiments.

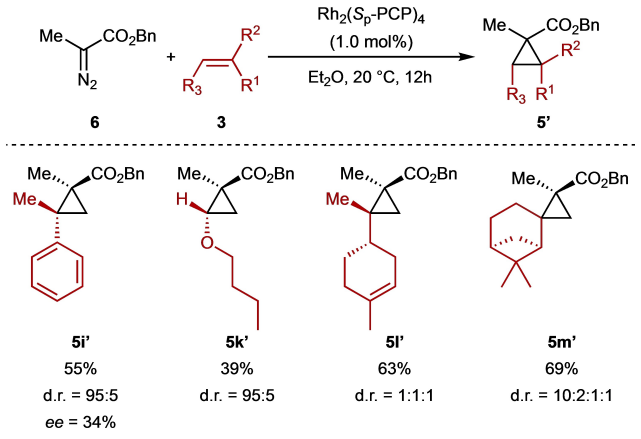
butenylbenzene on the other hand were unreactive. The cyclopropanation reaction of these substrates is considerably slower than the competing 1,2-hydrogen shift and no product was formed. The reaction of cyclic alkenes was successful with annulated benzene derivatives such as indene (**3 n**), dialin (**3 o**) and benzofuran (**3 p**). In these cases, the cyclopropanation gave a single diastereoisomer with low to moderate yield. The more reactive indene (**3 n**) led to a higher yield than dialin (**3 o**) and even though benzofuran (**3 p**), being an aromatic heterocycle, gave the cyclopropanation product in an even higher yield compared to indene (**3 n**).

The cyclopropanation of heterocyclic substrates (see supporting information, 2-vinylpyridine, 4-vinylpyrididine, chromen-2-one and 3,4-dihydro-2*H*-pyrane) was unsuccessful. In case of 2- and 4-vinylpyridine, a color change of the reaction mixture to purple and orange, respectively, was observed (supporting information, Figure 70). This indicates an axial coordination to the dirhodium core,[19] which may cause a deactivation of the complex and inhibiting the cyclopropanation reaction. The lack in reactivity chromen-2-one and dihydropyran may be related to the electron deficiency of double bonds, thus favoring the faster hydride shift of the carbenoid intermediate over the cyclopropanation reaction.

To improve the diastereoselectivity for the substrates **5 i**, **5 k**, **5 l**, and **5 m**, benzyl diazopropionate (**6**) was tested instead of employing *tert*-butyl diazopropionate (Scheme 4). Diastereomeric ratios of up to 95:5 were found for compounds **5 i'** and **5 k'**. A higher ratio was also observed in the case of the pinene substrate **5 l'**, whereas (*R*)-limonene (**3 l**), was obtained with lower diastereoselectivity. These differences between the *tert*-butyl and benzyl ester probably result from favorable π- π interactions of the benzyl group with the catalyst.

The molecular structure of the compounds **5 j** and **5 n** (Figure 2) were further confirmed by single crystal X-ray crystallography. In case of **5 n**, the absolute configuration was determined crystallographically.

Tailoring the planar chiral rhodium(II) paddlewheel complexes *via* PCP ligand design, with particular emphasis on improving selectivity, a comprehensive



Scheme 4. Cyclopropanation of selected alkenes (0.20 M, 0.42 mmol) employing $Rh_2(S_p\text{-PCP})_4$ (**2**, 1.0 mol%) and **6** (0.40 M, 0.83 mmol) in diethyl ether. The d.r. was determined via GC-MS of the crude reaction mixture. All yields refer to the average isolated yield from two experiments.

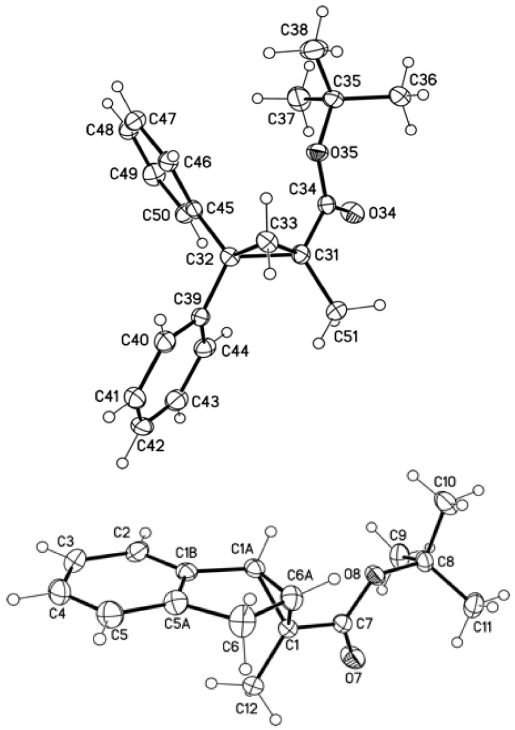


Figure 2. Molecular structure of (*rac*)-**5 j** (top) and 1*S*,1a*R*,6a*R*-**5 n** (bottom, displacement parameters are drawn at 50% probability level).

exploratory work is currently in progress. Additional insights into mechanism could be obtained benefiting from *in-silico* computational design and transition state modeling that might assist in obtaining high regio-, diastereo-, and enantioselective control. We also believe that the $Rh_2(S_p\text{–PCP})_4$ complex will inspire and aid in the design and exploration of new bimetallic complexes for different applications, such as developing new chiral NMR auxiliaries for enantiodifferentiation and chiral recognition.[20] We are currently progressing in this direction.

In summary, a conceptually novel planar-chiral dirhodium complex $Rh_2(S_p\text{–PCP})_4$ based on the [2.2] paracyclophane scaffold was synthesized. The $Rh_2(S_p\text{–PCP})_4$ complex proofed viable as a highly diastereoselective catalyst for the cyclopropanation of a variety of terminal alkenes with *tert*-butyl-functionalized *α*-diazopropionate. The reaction occurs with a high preference for the formation of the cyclopropanation product at room temperature over a 1,2-hydride shift. The catalytic protocol provides an attractive and easy access to cyclopropane building blocks containing an all-carbon quaternary stereogenic center.

Experimental Section

Dirhodium(II) tetrakis [(S_p)-[2.2]paracyclophane-4-carboxylate] (2). Rhodium (II) acetate (180 mg, 407 µmol, 1.00 equiv.) and (S_p)-4-carboxy[2.2]paracyclophane (616 mg, 2.40 mmol, 6.00 equiv.) in anhydrous chlorobenzene (75 mL) was heated to reflux under argon atmosphere in a Soxhlet extraction apparatus. The extraction thimble was charged with potassium carbonate that had been dried at 155 °C for 24 h. A new thimble containing potassium carbonate was introduced every 24 h. After 72 h, the solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (silica, *n*-pentane /CH_2Cl_2/THF, 4:4:1). The title compound (408 mg, 337 µmol, 83%) was obtained as a green solid. ^{1}H NMR (500 MHz, THF-d_8, ppm) $\delta = 7.04$ (d, $J = 2.0$, 4H, H_{Ar}), 6.44 (dd, $J = 7.8$, 2.0, 4H, H_{Ar}), 6.31 (qd, $J = 7.8$, 2.0, 12H, H_{Ar}), 6.21 (dd, $J = 7.8$, 1.8, 4H, H_{Ar}), 6.11 (dd, $J = 7.7$, 1.7, 4H, H_{Ar}), 4.08 (ddd, $J = 11.9$, 9.2, 2.2, 4H, H_{PC}), 2.98 (ddd, $J = 14.3$, 10.2, 6.7, 8H, H_{PC}), 2.93–2.77 (m, 16H, H_{PC}), 2.74–2.63 (m, 4H, H_{PC}); ^{13}C NMR (126 MHz, THF-d_8, ppm) $\delta = 187.4$ (C_q, 4 C, *C*O), 141.6 (C_q, 4 C, C_{Ar}), 140.7 (C_q, 4 C, C_{Ar}), 140.0 (C_q, 4 C, C_{Ar}), 139.7 (C_q, 4 C, C_{Ar}), 136.4 (+, 4 C, CH, C_{Ar}), 135.8 (+, 4 C, CH, C_{Ar}), 135.8 (+, 4 C, CH, C_{Ar}), 135.2 (C_q, 4 C, C_{Ar}), 133.6 (+, 4 C, CH, C_{Ar}), 133.4 (+, 4 C, CH, C_{Ar}), 133.0 (+, 4 C, CH, C_{Ar}), 132.6 (+, 4 C, CH, C_{Ar}), 37.3 (–, 4 C, CH_2), 36.1 (–, 4 C, CH_2), 36.0 (–, 4 C, CH_2), 35.7 (–, 4 C, CH_2); IR (ATR, cm^{-1}) $\tilde{\nu} = 2922$ (w), 2850 (w), 1647 (m), 1595 (w), 1568 (m), 1551 (m), 1432 (w), 1409 (s), 1374 (vs), 1319 (w), 1248 (w), 1203 (w), 1181 (w), 1082 (w), 1040 (w), 907 (w), 884 (w), 873 (w), 800 (m), 785 (m), 715 (m), 677 (m), 626 (w), 534 (m), 506 (s); HRMS (ESI$^+$, [M]$^+$, $C_{68}H_{60}O_8Rh_2$) calc.: 1210.2398; found: 1210.2397; EA (C $_{68}H_{60}O_8Rh_2$ + $C_4H_8O_2$, 1299.1, %) calc.: C 66.57, H 5.28; found C 66.33, H 5.52

General Procedure for the Cyclopropanation of Alkenes. In a sealable vial, the corresponding alkene (415 µmol, 1.00 equiv.) and $Rh_2(S_p\text{–PCP})_4$ (5.00 mg, 4.20 µmol, 1.00 mol%) were dissolved under argon atmosphere in dry diethyl ether (2.1 mL, 0.20 M) at 20 °C. To this solution *tert*-butyl 2-diazopropanoate (130 mg, 190 µL, 0.83 mmol, 2.00 equiv.) in diethyl ether (3.1 mL, 0.40 M) was added at a rate of 0.5 mL/h, then stirred for 12 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to obtain the corresponding cyclopropyl compound.

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