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Regioselective and Room-Temperature Carbon–Carbon Bond Activation of Cyclopropanes by Rhodium(II) Porphyrin

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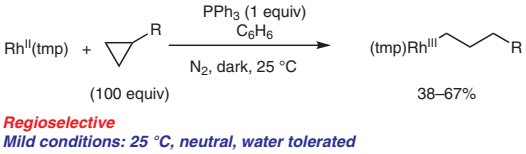

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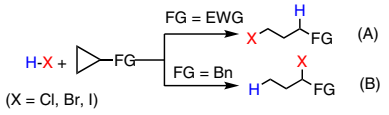
Abstract Regioselective carbon–carbon bond activation of cyclopropanes by Rh^{II}(tmp) (tmp = 5,10,15,20-tetramesitylporphyrinato dianion) was achieved at room temperature under neutral conditions to yield corresponding rhodium–porphyrin alkyls. This reaction can tolerate water, and functional groups are compatible.

Key words regioselective, CCA, cyclopropanes, rhodium(II) porphyrin

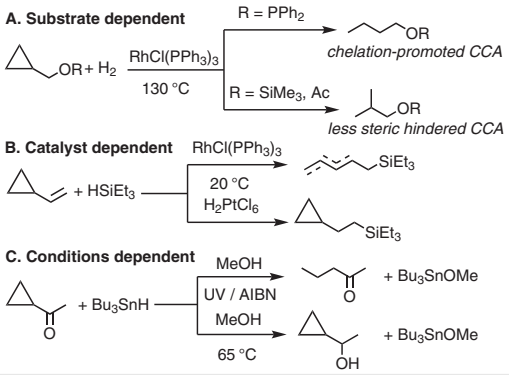
Cyclopropanes are important starting materials for versatile 3-carbon linear and branched building blocks for organic synthesis. The utility of cyclopropanes in organic chemistry arises from their unique structural and electronic characteristics. The resemblance of cyclopropane chemistry to that of carbon–carbon double bonds provides numerous synthetic possibilities such as addition to carbon–carbon bonds, which results in ring cleavage. The ring strain-release energy (ca. 26.5 kcal/mol)[1] associated with ring cleavage can provide a major driving force to achieve carbon–carbon bond activation (CCA) for various skeletal and chemical transformation.

Polar reagents such as hydrogen halide add to the C–C bonds of cyclopropanes for direct ring cleavage in conventional organic reactions without catalyst. Monosubstituted cyclopropanes undergo 1,3-addition of hydrogen halide to cyclopropanes to give linear *n*-propyl halides, while the regioselectivity of the halide atom is highly dependent on the substituted functional groups (Scheme 1).[2] Cyclopropanes with an electron-withdrawing group (FG = $COCH_3$, COPh, COOH, CN) undergo nucleophilic attack with halide at the less substituted carbon (Scheme 1, A). However, nucleophilic attack by halide to benzyl cyclopropane occurs at the more substituted carbon (Markovnikov addition, Scheme 1, B).



Scheme 1 Substrate dependent regioselectivity for the addition of HX to cyclopropanes

The direct addition of nonpolar reagents such as hydrogen gas, tin hydride, and silane to cyclopropanes in neutral conditions is more difficult than that of polar ones. Transition-metal catalysts often affect the reaction regioselectivity.[3] Chirik has reported the rhodium-catalyzed ring-opening hydrogenation of cyclopropanes. H_2 is added to cyclopropanes to give a linear propane through 1,3-addition, for phosphine-containing chelating substrates or a branched propane through 1,2-addition to nonchelating substrates (Scheme 2, A).[4]



Scheme 2 Selectivity for addition of nonpolar species to cyclopropanes

Besides substrates, catalysts also control the chemo- and regioselectivity of the addition to cyclopropanes. The addition of triethylsilane to vinyl cyclopropane catalyzed by the Wilkinson complex affords the 1,3-addition cyclopropyl ring product without reaction at the double bond, which is in contrast with the H_2PtCl_6-catalyzed reaction giving the 1,2-addition product at the double bond (Scheme 2, B).[5]

Furthermore, the radical addition of nonpolar reagents to cyclopropane is highly dependent on reaction conditions. Upon irradiation with ultraviolet light or initiation by AIBN, tributyltin hydride adds to cyclopropyl phenyl ketone to afford the 1,3-addition ring-opening product. However, cyclopropyl phenyl ketone is reduced thermally by tributyltin hydride to give the cyclopropylcarbinol (Scheme 2, C).[6] Therefore, the chemoselective and regioselective addition of nonpolar reagents to cyclopropane remains to be defined.

Our group has focused on the study of the selective aliphatic carbon–carbon bond activation mediated by rhodium–porphyrin complexes for the past 16 years.[7] Rh^{II}(por) (por = porphyrinato dianion) (Figure 1) exists as the metalloradical with Rh^{II} bearing an odd electron at the dz^2 frontier molecular orbital. For the sterically less hindered porphyrins, such as ttp (ttp = 5,10,15,20-tetratolylporphyrinato dianion) or oep (oep = octylethylporphyrinato dianion), dimerization of Rh^{II}(por) occurs to afford $[Rh^{II}(por)]_2$.[8] With the bulky porphyrin tmp ligand, Rh^{II}(tmp) is monomeric in nature. Rh(por)H is a nonpolar reagent due to the mainly covalent Rh–H bond. Previously, we have reported the Rh^{II}(ttp)-catalyzed 1,2-addition of Rh(ttp)H to the C–C bond of cyclooctane to afford the ring-opening product of Rh(ttp)(*n*-octyl) (Scheme 3).[9] Therefore, as part of our long-term interest, we now report the regioselective room-temperature CCA of cyclopropanes by the metalloradical

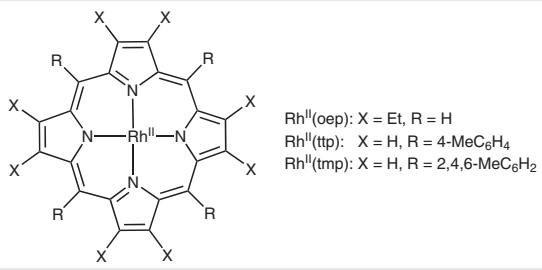
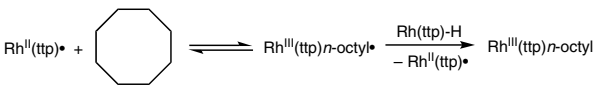


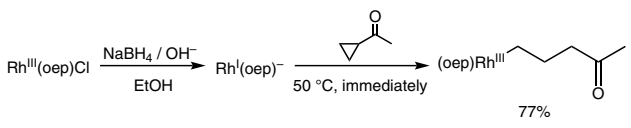
Figure 1 Structures of rhodium–porphyrin complexes

Rh^{II}(tmp) to afford linear ring-opening products through 1,3-addition under neutral conditions.

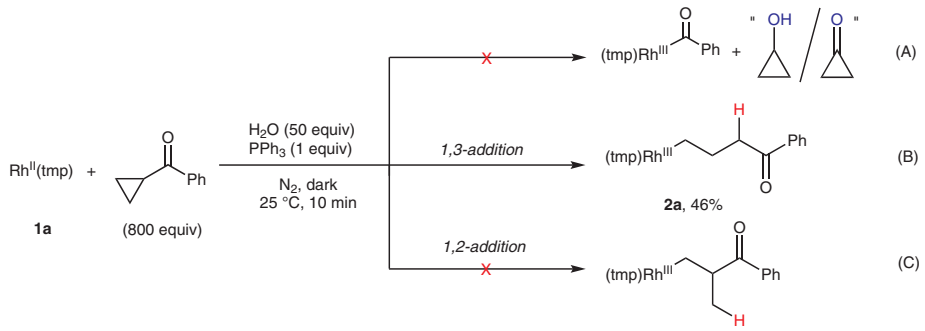
In the course of our continuing research on room-temperature C(CO)–C(α) bond activation of isopropyl ketones,[10] we initially aimed to realize the C(CO)–C(α) bond activation of cyclopropyl phenyl ketone by Rh(tmp)OH, which could be generated by the reaction of Rh^{II}(tmp) (**1a**) with H_2O (Scheme 4, pathway A). To our surprise, we have discovered cyclopropyl phenyl ketone underwent chemoselective and regioselective CCA of the cyclopropyl group without C(CO)–C(α) cleavage in the presence of H_2O. The cyclopropyl ring was cleaved in neutral conditions at 25 °C in 10 minutes to give the linear 1,3-addition product Rh(tmp)$CH_2CH_2CH_2$COPh (**2a**) in 46% yield (Scheme 4, pathway B), and the branched 1,2-addition product was not observed (Scheme 4, pathway C). Since the pK_a of Rh(ttp)H is about 11,[11] the more electron-rich Rh^{I}(tmp)$^-$ would hardly form under neutral conditions. Therefore, it distinguishes in mechanism from the reported ring-cleavage reaction of cyclopropane derivatives with performed Rh^{I}(oep)$^-$ anion (Equation 1).[12] We then further explored the substrate scope and conducted mechanistic studies of this chemical transformation.



Scheme 3 Rh^{II}(ttp)-catalyzed 1,2-addition of Rh(ttp)H to cyclooctane



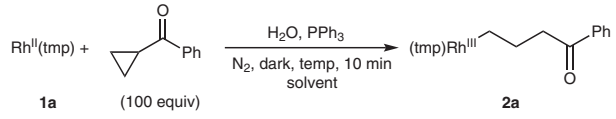
Equation 1



Scheme 4 Discovery of selective CCA of cyclopropane

Cyclopropyl phenyl ketone was used as the model compound to optimize the reaction conditions. When the reaction temperature was increased from 25 °C to 50 °C, the product yield of Rh(tmp)$CH_2CH_2CH_2$COPh (**2a**) ranged from 46–52%, which did not change significantly (Table 1, entries 1 and 2). Lowering the substrate loading from 800 equivalents in solvent-free conditions to 100 equivalents in acetone, the reaction also proceeded to give Rh(tmp)$CH_2CH_2CH_2$COPh (**2a**) in 48% yield (Table 1, entry 3). In contrast to the C(O)–C bond activation of ketones,[10] where the addition of H_2O promotes the reaction yield, H_2O was not necessary for the ring opening of cyclopropanes. The product was obtained in a similar yield of 44% without water added (Table 1, entry 4). However, it also demonstrated that this transformation could tolerate water. It has been reported that the promoter ligand PPh_3 can increase the product yield.[13] The yield of Rh(tmp)$CH_2CH_2CH_2$COPh (**2a**) was indeed reduced to 24% in the absence of PPh_3 (Table 1, entry 5). Coordinated PPh_3 of (PPh_3)Rh^{II}(tmp) is shown to increase the electron density on rhodium and then promote the odd electron to a higher energy level, thus increasing its reactivity.[13] Since we did not observe any effect of H_2O on rate and yield (Table 1, entries 3 and 4), we further investigated the reaction in benzene. The reaction proceeded even better in benzene solvent to afford Rh(tmp)$CH_2CH_2CH_2$COPh (**2a**) in 52% yield (Table 1, entry 5).

Table 1 Optimization of Conditions



1a (100 equiv) **2a**

Entry	Temp (°C)	H_2O loading	PPh_3 loading	Solvent	Yield (%)
1	25	50	1	solvent-free[a]	46
2	50	50	1	solvent-free[a]	52
3	25	50	1	acetone	48
4	25	0	1	acetone	44
5	25	0	0	acetone	24
6	25	0	1	benzene	52

[a] 800 equiv of cyclopropyl phenyl ketone were added.

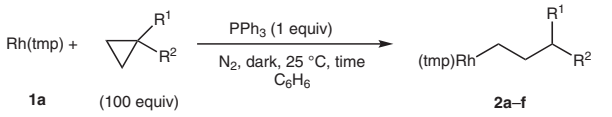
As Rh(tmp)H is generated by the reaction of of Rh^{II}(tmp) with H_2O,[14] deuterated-water-labeling experiment was carried out to investigate whether the H source of the CCA product of cyclopropanes is from water. However, the reaction yielded no d_1-enriched product (Equation 2). This result corroborates that H_2O was not necessary in the CCA of cyclopropanes. As the ketone substrate has been shown to be the H atom donor in our reported photocatalytic C(CO)–C(α) bond activation of ketones,[15] we rationalize the substrate, likely the weak α-C–H bond of cyclopropyl phenyl ketone, is the H atom source.

1a (100 equiv) **2a**, 41%

Equation 2

With the optimized reaction conditions, Rh^{II}(tmp) **1a** reacted with both polar and nonpolar cyclopropanes at 25 °C under neutral conditions to generate the regioselective 1,3-addition products with Rh(tmp) at the less substituted carbon (Table 2). The reactivity of cyclopropyl methyl ketone and cyclopropyl phenyl ketone is similar, and after 10 minutes, the corresponding products Rh(tmp)$CH_2CH_2CH_2C(O)CH_3$ (**2b**) and Rh(tmp)$CH_2CH_2CH_2$C(O)Ph (**2a**) were obtained in 51% and 52% yield, respectively (Table 2, entries 1 and 2). Cyclopropyl cyanide also gave Rh(tmp)$CH_2CH_2CH_2$CN (**2c**) in 45% yield in 10 minutes at room temperature (Table 2, entry 3). The reaction between Rh^{II}(tmp) (**1a**) and cyclopropyl benzene (Table 2, entry 4) was slower than that of ketones and cyanide, and Rh(tmp)$CH_2CH_2CH_2$Ph (**2d**) was obtained in 42% yield after 2 hours. When the substituted functional group was changed from ketone to ester, the reactivity of cyclopropane decreased with 38% yield of Rh(tmp)$CH_2CH_2CH_2$COOEt (**2e**) formed after 4 days (Table 2, entry 5). However, diethyl cyclopropane-1,1-dicarboxylate reacted much faster to give the ring-opening CCA product of Rh(tmp)$CH_2CH_2CH(COOEt)_2$ (**2f**) in 67% after 10 minutes (Table 2, entry 6).

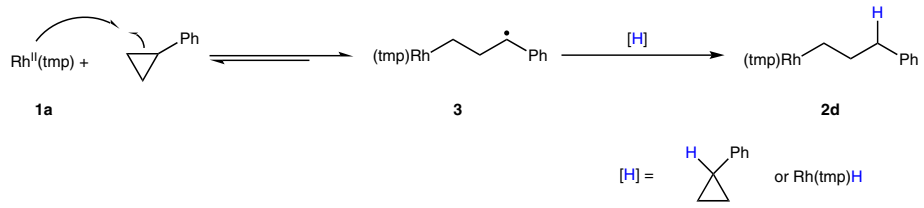
Table 2 Substrate Scope



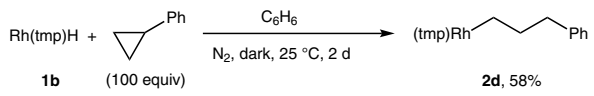
1a (100 equiv) **2a–f**

Entry	R^1	R^2	Time	Yield (%)
1	H	C(O)Ph	10 min	**2a** 52
2	H	$C(O)CH_3$	10 min	**2b** 51
3	H	CN	10 min	**2c** 45
4	H	Ph	2 h	**2d** 42
5	H	COOEt	4 d	**2e** 38
6	COOEt	COOEt	10 min	**2f** 67

Since the reaction products **2a–f** are the formal 1,3-addition products of Rh(tmp)H to the cyclopropanes, we then examined the reaction of cyclopropyl benzene with Rh(tmp)H (**1b**) in benzene solvent. Rh(tmp)H (**1b**) indeed reacted with cyclopropyl benzene at 25 °C to afford Rh(tmp)$CH_2CH_2CH_2$Ph (**2d**) in 58% yield after 2 days, which was much slower than that of Rh^{II}(tmp) (**1a**, Equation 3).



Scheme 5 Proposed mechanism of Rh^{II}(tmp)-catalyzed ring opening of cyclopropane



Equation 3

As Rh(tmp)H is known to contain a small amount of Rh^{II}(tmp) in equilibrium in solution,[16] we therefore propose the reaction mechanism operates with a Rh^{II}(tmp)-catalyzed 1,3-addition of Rh(tmp)H into the C–C bond of cyclopropane, analogous to the Rh^{II}(ttp)-catalyzed 1,2-addition of Rh(ttp)H into the C–C bond of cyclooctane (Scheme 3).[9]

The relationship between substrate and the reaction rate as well as the product yield also validates this proposal. The attack of Rh^{II}(tmp) to cyclopropane generates a Rh(tmp) propyl carbon centered radical. The radical stability is correlated to the corresponding C–H bond-dissociation energy of substituted propane. Table 3 shows the α-C–H bond dissociation energy of selected propane analogues.[17] The reaction rate and yield of various cyclopropanes indeed increase with decreasing C–H bond-dissociation energy except that of cyclopropyl benzene, possibly due to the larger steric hindrance of the phenyl group.

Table 3 α-C–H Bond-Dissociation Energy (BDE) of Selected Propane Analogues

Compound	C–H bond BDE (kcal/mol)
H-CH(CH$_3$)C(O)Ph	92.9
H-CH(CH$_3$)C(O) CH$_3$	92.3
H-CH(CH$_3$)CN	94.0
H-CH(CH$_3$)Ph	85.4
H-CH(CH$_3$)COOEt	95.6
H-C(CH$_2$CH$_3$)(COOEt)$_2$	91.5

The slower CCA of cyclopropyl benzene with Rh(tmp)H than that of Rh^{II}(tmp) further suggests the attack of Rh^{II}(tmp) at the carbon center is the rate-determining step, followed by the rapid exothermic H atom abstraction.

On the basis of the above results and earlier reports,[9,15,16] Scheme 5 shows the proposed reaction mechanism for the ring opening of cyclopropyl benzene by Rh^{II}(tmp) (**1a**) to afford the 1,3-addition product Rh(tmp)CH$_2$CH$_2$CH$_2$Ph (**2d**). Initially, Rh^{II}(tmp) (**1a**) cleaves the C–C bond of the cyclopropyl group to afford the benzyl carbon centered stabilized radical **3**. Then the radical **3** abstracts a hydrogen atom from the substrate[15] or from the weak Rh(tmp)H (**1b**) bond[9] to generate the 1,3-addition product Rh(tmp)CH$_2$CH$_2$CH$_2$Ph (**2d**).

In summary, we have discovered the room-temperature, regioselective, metalloradical-catalyzed ring-opening CCA of both polar and nonpolar cyclopropanes by Rh^{II}(tmp)/PPh$_3$ to afford 1,3-addition products in moderate yields.[18] The reaction is water tolerant and functional-group compatible. Further studies are ongoing.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589129.

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(18) **Typical Procedure for Rh(tmp)$CH_2CH_2CH_2$COPh (2a)**
To the benzene solution of Rh^{II}(tmp) (**1a**, 0.00445 mmol) PPh_3 (1.2 mg, 0.00458 mmol) was added, and the reaction mixture was stirred at 25 °C. After 10 min, the benzene solvent was removed by vacuum evaporation and then degassed cyclopropyl phenyl ketone (65 µL, 0.465 mmol) and benzene (430 µL) were added. The mixture was then stirred under nitrogen at 25 °C for 10 min. Excess solvent was removed, and the dark red crude product was then purified by column chromatography on silica gel eluting with hexane/CH_2Cl_2 (1:1) to give the reddish purple solid of Rh(tmp)$CH_2CH_2CH_2$COPh (**2a**, 2.4 mg, 0.00233 mmol, 52% yield). *Rf* = 0.64 (hexane/CH_2Cl_2 = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = –4.73 (dt, 2 H, $^2J_{Rh-H}$ = 2.8 Hz, $^3J_{HH}$ = 8.1 Hz), –3.76 (quint, 2 H, *J* = 8.0 Hz), 0.18 (t, 3 H, *J* = 7.6 Hz), 1.82 (s, 12 H), 1.92 (s, 12 H), 2.63 (s, 12 H), 6.81 (d, 2 H, *J* = 7.8 Hz), 7.03 (t, 2 H, *J* = 7.5 Hz), 7.28 (s, 4 H), 8.50 (s, 8 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 12.85 (d, $^1J_{Rh-C}$ = 28.5 Hz), 21.60, 21.68, 21.84, 23.62, 36.24, 119.74, 127.40, 127.83,,127.85, 128.06, 130.79, 132.34, 135.83, 137.53, 138.51, 139.08, 139.12, 142.69, 197.52. HRMS (MALDI-MS): *m/z* calcd for $[M]^+$ ($C_{66}H_{63}N_4ORh$): 1030.4051; found: 1030.4064.