Carbenes

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Rhodium(III)-Catalyzed Transannulation of Cyclopropenes with *N*-Phenoxyacetamides through C–H Activation**

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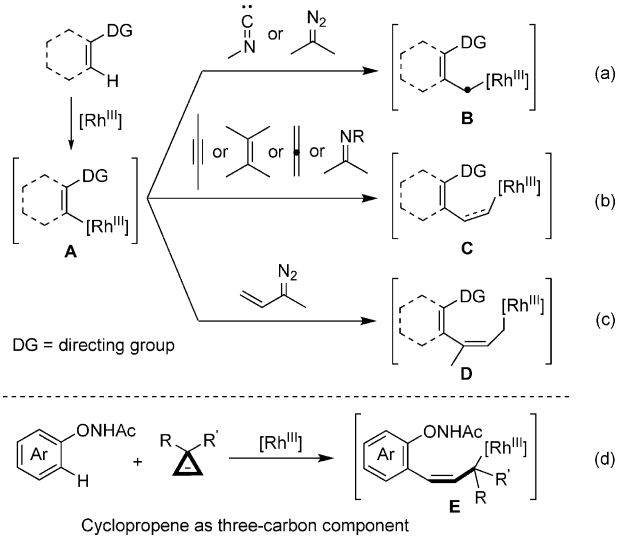
Abstract: *An efficient rhodium(III)-catalyzed synthesis of 2H-chromene from N-phenoxyacetamides and cyclopropenes has been developed. The reaction represents the first example of using cyclopropenes as a three-carbon unit in rhodium(III)-catalyzed C(sp^2)–H activations.*

Transition-metal-catalyzed activation of C–H bonds has attracted considerable attention and significant progress has been achieved.[1] Among the various directing-group-assisted C–H bond-activation systems developed recently, the rhodium(III)-catalyzed reactions have been demonstrated as effective transformations with remarkable diversity.[1b,g,i,2] As summarized in Scheme 1, these transformations start from the directing-group-assisted C–H activation, thus generating the rhodium(III) intermediate **A**, from which the reactions may be categorized into three different types according to the number of carbon units in the coupling partners participating in the reaction. In the one-carbon insertion (Scheme 1 a), either isonitriles[3] or diazo compounds[4] are employed as the substrates. The insertion of a one-carbon unit into the Rh–C bond generates the benzyl rhodium(III) species **B**. In the case of two-carbon unit insertion, which forms the rhodium(III) intermediate **C** (Scheme 1 b), a wide range of unsaturated components, including alkynes,[5] alkenes,[1,6] allenes,[7] imines,[8] and isocyanates,[9] have been explored as the substrates.

For the three-carbon insertion, to the best of our knowledge there have been only two examples documented in the literature. Cui and co-workers used vinyldiazo compounds as the three-carbon components, thus generating the benzyl allyl rhodium(III) intermediate **D** through rhodium(III) carbene migratory insertion (Scheme 1 c).[10] More recently, Yu and Li have used cyclopropenones as coupling partners in rhodium-(III)-catalyzed C–H activation.[11]



Scheme 1. Rhodium(III)-catalyzed C(sp^2)–H activation.

Although significant progress has been made in rhodium-(III)-catalyzed C–H activation, it is still highly desirable to further expand this type of reaction. It is known that cyclopropenes can also be used as vinyl metal carbene precursors.[12] These highly strained unsaturated compounds are excellent three-carbon units for organic synthesis. The metal carbene species generated through ring opening undergo typical carbene transformations, such as cyclopropanation,[13] C–H insertion,[14] olefin metathesis,[15] and other related rearrangement reactions.[16] Rovis and co-workers have recently reported a rhodium(III)-catalyzed synthesis of isoquinolones from amides and activated cyclopropenes through C–H activation.[17] Although to our knowledge this is the first example using cyclopropenes as a coupling partner in transition-metal-catalyzed C–H activation, it is categorized as the type shown in Scheme 1 b where the cyclopropene serves as an alkene, and the sp^3-carbon atom of the cyclopropene does not participate in the newly formed ring structure.

In connection to our interest in both catalytic carbene transformations and C–H bond activation, we herein report a rhodium(III)-catalyzed C–H bond activation of *N*-phenoxyacetamide with cyclopropenes, which are utilized as three-carbon component to form the intermediate **E** (Scheme 1 d). This reaction employs an oxidizing directing group, which contains an N–O bond, and has recently been developed by Liu, Lu, and co-workers.[5f,6d] The transformation provides an efficient method for the synthesis of 2*H*-chromene[18] with good yields and broad substrate scope.

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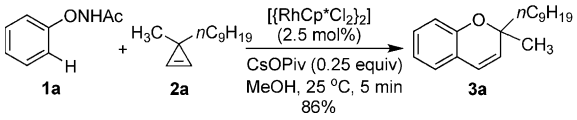
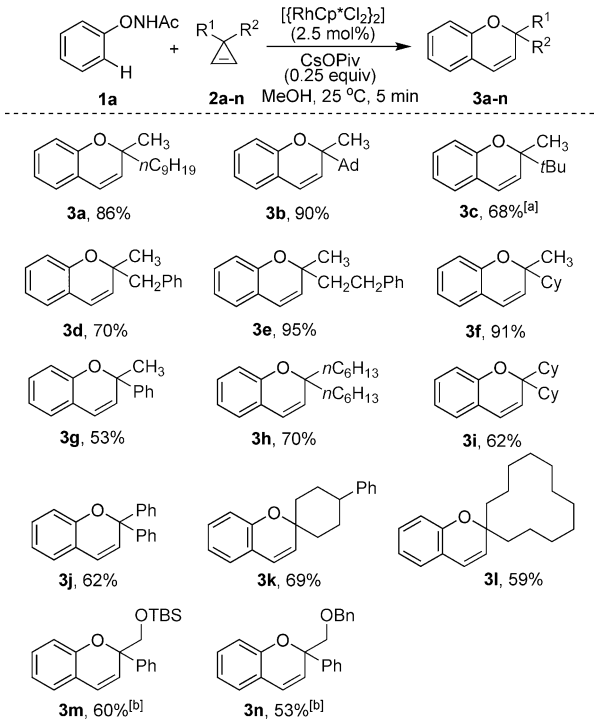
At the outset, *N*-phenoxyacetamide (**1a**)[19] and cyclopropene (**2a**) were used as the substrates to investigate this reaction. Through extensive optimization of the reaction conditions, the 2*H*-chromene product **3a** could be obtained in 86% yield under the following reaction conditions: **1a** (0.1 mmol), **2a** (0.13 mmol), [{RhCp*Cl$_2$}$_2$] (2.5 mol%), CsOPiv (0.25 equiv), MeOH (2 mL), 25°C, 5 min [Eq. (1); Cp* = C$_5$Me$_5$, Piv = pivaloyl].[20]



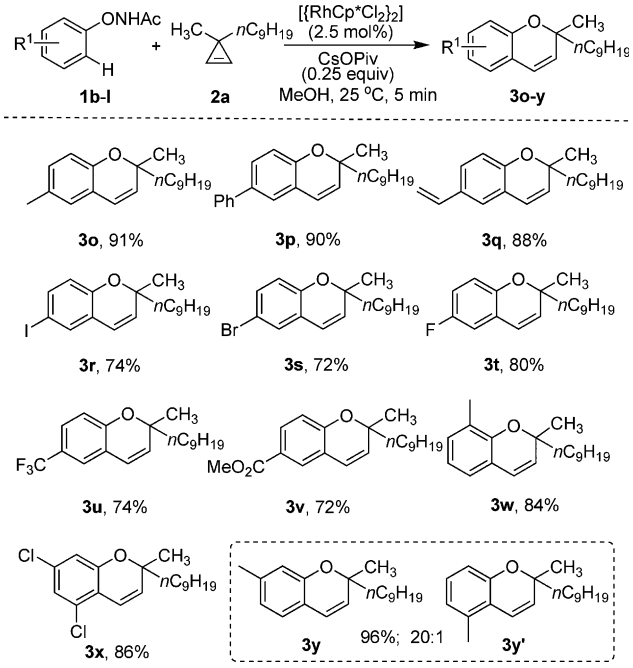
(1)

We next proceeded to study the scope of the reaction. A series of 3,3-disubstituted cyclopropenes (**2a–n**) were first examined (Scheme 2). It was found that the reaction was affected by the steric bulk of the substituents on the sp^3-carbon atom of the cyclopropene. When one of the substituents is a methyl group, the reaction results in moderate yields (**3a–g**). The alkyl-substituted cyclopropene **2h** could also give the corresponding product **3h** in decent yield. However, cyclopropenes substituted with more bulky groups, and spirocyclopropenes afforded the corresponding products in low yields (**3i, j** and **3k, l**, respectively). Notably, cyclopropenes bearing a heteroatom could also participate in the reaction. Moreover, the reactions with the siloxymethyl-substituted cyclopropene **2m** and benzyloxymethyl-substituted cyclopropene **2n** proceeded smoothly, albeit with prolonged reaction times (**3m**, **n**).



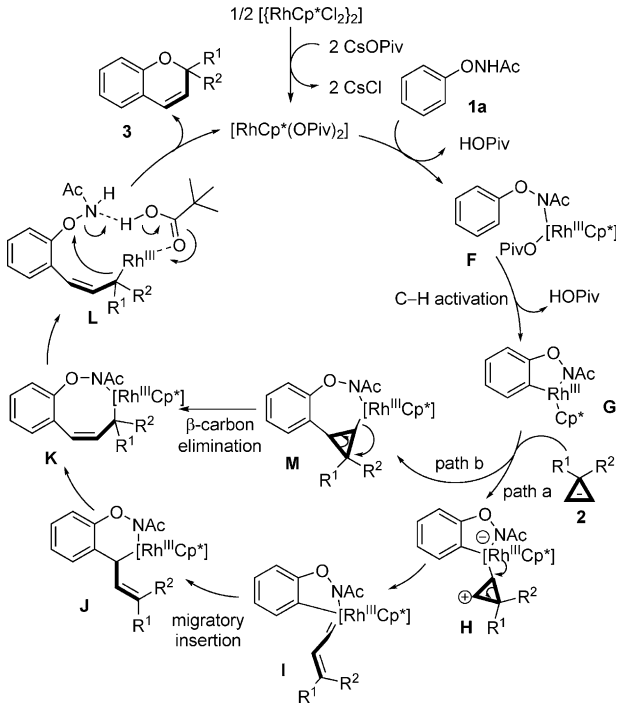
Scheme 2. Scope with respect to the cyclopropenes. If not otherwise noted, the reactions were carried out with **1a** (0.20 mmol), **2a–n** (0.26 mmol), [{RhCp*Cl$_2$}$_2$] (2.5 mol%), and CsOPiv (0.25 equiv) in MeOH (4 mL) at 25°C for 5 min under air. Yields are those of the products isolated after column chromatography. [a] Cyclopropene was added as a solution in pentane (0.3 M). [b] The reactions were carried out with **1a** (0.36 mmol), **2m**, **n** (0.20 mmol) at 25°C for 10 min under air. Ad = adamantyl, TBS = *tert*-butyldimethylsilyl.

Next, the scope with respect to the *N*-phenoxyacetamides was studied (Scheme 3). To our delight, various substituents on the aromatic ring were tolerated and good to excellent yields of the corresponding 2*H*-chromene products could be obtained. Electronic effects do not significantly affect the outcomes of the reaction. For the substrates substituted with electron-withdrawing groups, the desired product **3v** could be obtained in 72% yield. It is noteworthy that vinyl, iodo, bromo, and chloro substituents are tolerated under the reaction conditions, and is beneficial for further transformations through coupling reactions (**3q–s**, **3x**). In the case of a *meta*-substituted substrate, **3y** was detected as the major product by ^{1}H NMR spectroscopy, and resulted from activation of the C–H bond in the position *para* to the methyl group, thus suggesting that the reaction is sensitive to steric effects and occurs at the less-hindered site.

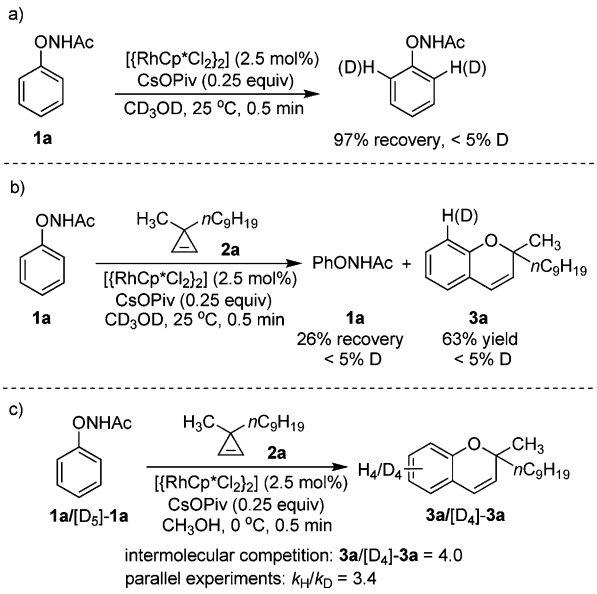


Scheme 3. Scope with respect to the *N*-phenoxyacetamides. Reactions were carried out with **1b–l** (0.20 mmol), **2a** (0.26 mmol), [{RhCp*Cl$_2$}$_2$] (2.5 mol%), and CsOPiv (0.25 equiv) in MeOH (4 mL) at 25°C for 5 min under air. Yields are those of the products isolated after column chromatography.

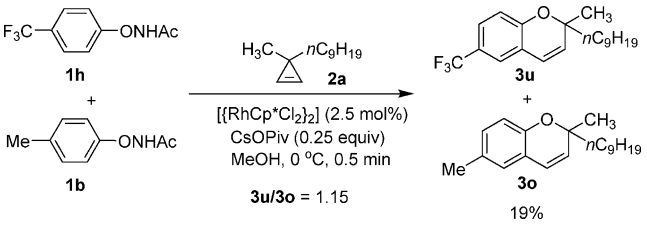
We propose a plausible mechanism as depicted in Scheme 4. The reaction commences with anion exchange to generate an active catalyst, [Cp*Rh(OPiv)$_2$], which coordinates to **1a** to form the intermediate **F**. Subsequent C–H bond cleavage results in the formation of the rhodacyclic intermediate **G**, from which two possible pathways may be followed. In path a, the cyclopropene is activated by **G** to



Scheme 4. Proposed reaction mechanism.



Scheme 5. Deuterium exchange and KIE experiments.



Scheme 6. Competition experiment.

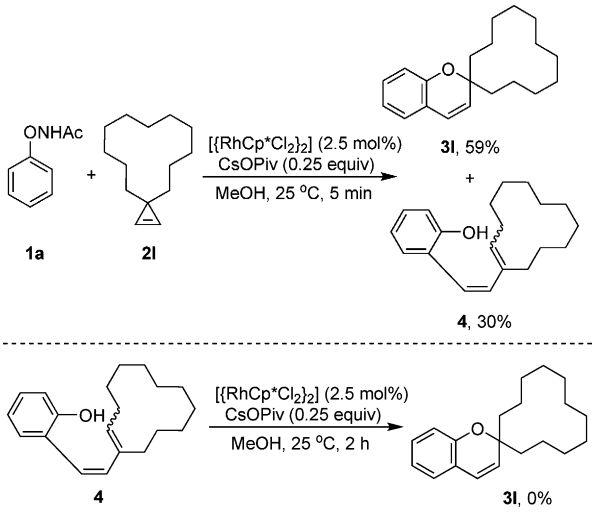
generate the intermediate **H**, from which ring opening occurs to form the rhodium(III) carbene **I**. Rhodium(III) carbene migratory insertion from **I** affords the rhodacyclic intermediate **J**. Next, the eight-membered rhodacyclic intermediate **K** is generated through 1,3-allylic migration, followed by intramolecular substitution to form the C–O bond and break the N–O bond with the aid of acid.[5f] Finally, the product **3** is formed along with the regeneration of the rhodium(III) catalyst. Alternately, the reaction may follow path b. The double bond of cyclopropene first inserts into the Rh–C bond of **G**. Then, β-carbon elimination from **M** gives the rhodacyclic intermediate **K**, which undergoes the process as shown above to afford **3**.

To gain insight into the reaction mechanism, a series of experiments were carried out (Schemes 5–8). First, **1a** was treated with [{RhCp*Cl_2}$_2$] and CsOPiv in CD_3OD (Scheme 5a). After stirring for 0.5 minutes, 97% of **1a** was recovered and no deuterium incorporation was observed. When the reaction was conducted with **1a** and **2a** in CD_3OD for 0.5 minutes, deuterium incorporation was not observed in either the recovered **1a** or the product **3a** (Scheme 5b). These results suggest that under the reaction conditions the C–H bond activation step is largely irreversible. The kinetic isotope effects (KIE) were determined at 0 °C because of the high conversion when carrying out the reaction at 25 °C. An evident primary KIE value was observed (4.0 determined by intermolecular competition and 3.4 determined by parallel reaction, both at low conversion), thus indicating that the C–H bond-cleavage process is presumably the rate-determining step (Scheme 5c).

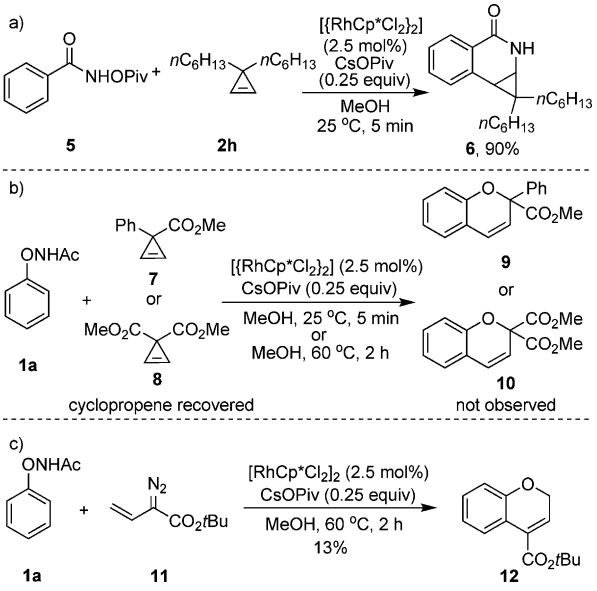
Subsequently, competition experiments of equimolar amounts of **1h** and **1b** under the standard reaction conditions with **2a** was carried out (Scheme 6). The ratio of the products indicates that the electron-deficient **1h** is only slightly more reactive. The lack of significant electronic preference suggests that concerted metalation deprotonation (CMD) may be responsible for the C–H activation.[1e]

It has been noted that in one case a 1,3-diene is observed as the byproduct (Scheme 2; **3l**), thus suggesting the possibility that the 2*H*-chromene products may be formed through ring closure of 1,3-dienes. To verify such speculations, we isolated the the byproduct 1,3-diene **4** in 30% yield when *N*-phenoxyacetamide (**1a**) and spiro-cyclopropene (**2l**) were used as the substrates in the reaction (Scheme 7). Subsequently, **4** was submitted to the standard reaction conditions. None of the ring-closure product **3l** was identified. This result is contradictory to the speculation that 1,3-dienes are the reaction intermediates. The generation of 1,3-diene is likely associated with the steric bulk of R^1 and R^2, which would slow down the conversion of **K** into **L** in the catalytic cycle shown in Scheme 4. The 1,3-diene byproduct is formed through β-hydride elimination from **K**.

Additional experiments have been carried out to identify the effect of the substrate structure on the reaction (Scheme 8). When *O*-pivaloyl benzhydroxamine (**5**) was employed as the coupling partner in the reaction with **2h** under the standard reaction conditions, the cyclopropane product **6** was isolated in 90% yield (Scheme 8a). The result, which is consistent with those reported by Hyster and



Scheme 7. Rhodium(III)-catalyzed reaction of **1a** and **2l**.



Scheme 8. Rhodium(III)-catalyzed reaction with various substrates.

Rovis,[17] suggests that the directing group plays the crucial role in determining the reaction path.

Next, with **1a** as the coupling partner the reaction with either the cyclopropene **7** or **8** was investigated (Scheme 8b). The reactions gave neither the expected product **9** nor **10**. The results may be interpreted as follows: In path a of the mechanism, **H** is destabilized because of the electron-withdrawing ester substituents, while in the path b, the carbonyl group of the ester substituent may stabilize the intermediate **M** through coordination with rhodium, thus making β-carbon elimination unfavorable.[21] Lastly, the vinyldiazoester **11** was subjected to the reaction as a three-carbon component,[10] and the anticipated product **12** was obtained, albeit in low yield (Scheme 8c). This result supports path a of the mechanism shown in Scheme 4. However, further studies are necessary to unambiguously confirm the proposed reaction mechanisms.

In summary, we have demonstrated the use of cyclopropene as the three-carbon unit in rhodium(III)-catalyzed C–H bond activation. An efficient rhodium(III)-catalyzed synthesis of 2*H*-chromene from *N*-phenoxyacetamides and cyclopropenes through C–H activation has been developed. The reaction proceeds under mild reaction conditions at room temperature and does not need external oxidants. A wide range of substrates are tolerated in this transformation, and various products can be obtained in good to excellent yields.

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