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2*H*-Chromene-3-carboxylic Acid Synthesis via Solvent-Controlled and Rhodium(III)-Catalyzed Redox-Neutral C−H Activation/[3 + 3] Annulation Cascade

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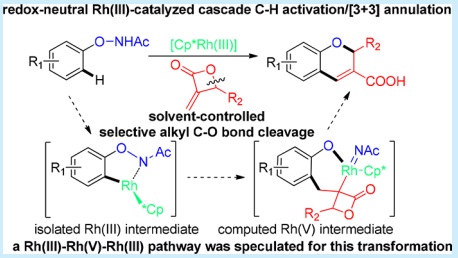
Supporting Information

ABSTRACT: An efficient and redox-neutral synthesis of 2*H*-chromene-3-carboxylic acids from *N*-phenoxyacetamides and methyleneoxetanones has been realized via a solvent-controlled and rhodium(III)-catalyzed C−H activation/unusual [3 + 3] annulation sequence. This transformation represents the first example of using an α-methylene-β-lactone unit as the three-carbon source in transition-metal-catalyzed C−H activations through selective alkyl C−O bond cleavage. Synthetic applications and mechanistic details, including further derivatization of 2*H*-chromene-3-carboxylic acids, the isolation and identification of a five-membered rhodacycle, as well as the theoretical studies for reasoning a plausible Rh(III)−Rh(V)−Rh(III) process, have also been discussed.



Transition-metal-catalyzed cascade C−H activation/annulations have emerged as a powerful and straightforward synthetic strategy for the one-pot assembly of many important structural motifs, such as ubiquitous nitrogen-containing heterocycle scaffolds, in an atom-economic fashion.[1] In general, the compulsive use of a combination of traditional directing groups (DGs) and stoichiometric amounts of external oxidants is required to achieve the above regioselective C−H activation/annulation reactions, which to some extent hindered their synthetic applications.

To conquer the aforementioned limitation, recently, the development of an autocleavable oxidizing directing group (ODG) that acts simultaneously as both the DG and internal oxidant and then to be incorporated into the structural backbone of the product or transformed into a highly valuable functional group has received intensive research focus in this hot area.[2] As a result, several versatile ODGs have stood out[2−13] thus far, of which O-NHAc played a particularly prominent role. Followed by the pioneering work from the research group of Lu,[4] to date, Glorius,[5] Wang,[6] You,[7] Zhao,[8] Liu,[9] Rovis,[10] Zhou,[11] us,[12] and others[13] have made significant progress in O-NHAc-directed C−H functionalization reactions. However, by reviewing these notable achievements, some important issues remain to be addressed in terms of substrate scope and reaction mode. Indeed, previous O-NHAc-directed C−H functionalization reactions are mostly limited to the employment of diazo compounds,[6a,9a,11,12a] alkenes,[4b,5a−c,6b,9b,10,13a] and alkynes[4a,c,d,8a,13d] as the coupling partners, and the simple alkylation, direct alkenylation, or classical annulation mode were frequently observed. Accordingly, a fairly limited and oxygen-involved product class was obtained through the O−N bond cleavage. Clearly, more efforts are still needed to explore new, redox-neutral and O-NHAc-directed transition-metal-catalyzed cascade C−H activation/annulations for direct synthesis of other key structural motifs such as 2*H*-chromene, for which, to the best of our knowledge, there has been only one elegant Rh(III)-catalyzed example documented in the literature using highly strained unsaturated cyclopropenes as the three-carbon components.[6b]

On the other hand, more recently, Howell's group disclosed a highly selective Pd-catalyzed ring opening of methyleneoxetanones with amines to give β-hydroxy amides through an acyl C−O bond cleavage pathway (Scheme 1, eq 1).[14] Almost simultaneously, Li's group also revealed a Rh(III)-catalyzed C−H allylation of (hetero)arenes with methyleneoxetanones to deliver acrylic acid derivatives via *ortho*-C−H activation, followed by selective olefin insertion and β-oxygen elimination (unusual alkyl C−O bond cleavage pathway) (Scheme 1, eq 2).[15]

Inspired by these developments, and in consideration of the reactivity of *N*-phenoxyacetamide substrates in C−H functionalization reactions, we reasoned that a promising transition-metal-catalyzed cascade C−H activation/annulation between *N*-phenoxyacetamides and methyleneoxetanones can be reached under proper reaction conditions as the highly reactive and negatively charged phenol species is easy to produce via *ortho*-C−H alkenylation of the α-methylene part/the cleavage of

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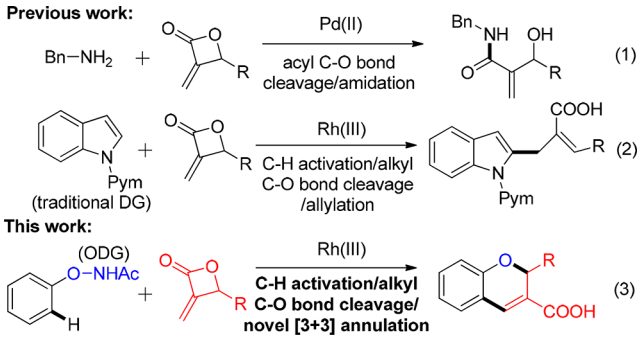
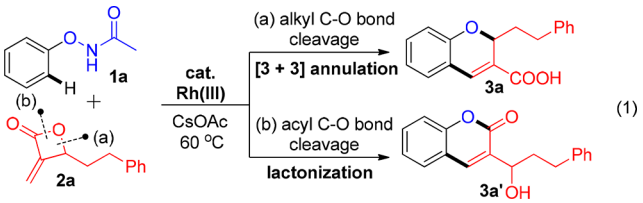
Scheme 1. Transition-Metal-Catalyzed C−H Functionalization with Methyleneoxetanones



the O−N bond, which undergoes a cyclization with a β-lactone moiety via acyl and/or alkyl C−O cleavage and subsequent intramolecular nucleophilic attack. On the basis of our efforts, we now report the first solvent-controlled and Rh(III)-catalyzed redox-neutral C−H activation, followed by an unusual [3 + 3] annulation of *N*-phenoxyacetamides with methyleneoxetanones via selective alkyl C−O bond cleavage, leading to direct and efficient access to a 2*H*-chromene-3-carboxylic acid framework with excellent regioselectivity (Scheme 1, eq 3).

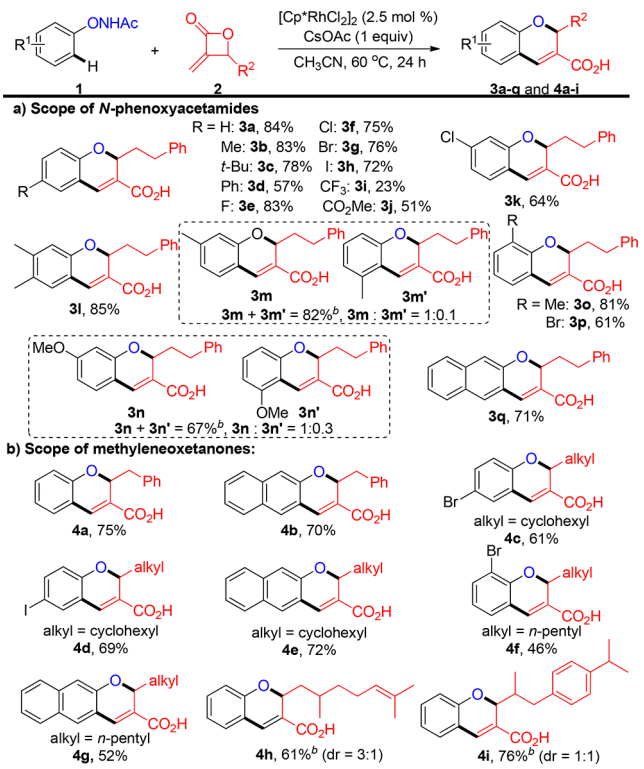
We commenced our exploration with optimization studies on the coupling of *N*-phenoxyacetamide **1a** with methyleneoxetanone **2a** (eq 1; see the Supporting Information (SI) for



details). The desired 2*H*-chromene-3-carboxylic acid **3a** was delivered with 42% isolated yield under the initial conditions, in which 1,4-dioxane was employed as the solvent. Control experiments confirmed that both $[Cp^*RhCl_2]_2$ and CsOAc were indispensable for the reaction outcome. Very interestingly, changing the solvent 1,4-dioxane to MeOH gave an improved yield of **3a** (60%) along with a lactonization byproduct **3a′** (the ratio of **3a**/**3a′** = 6/1), indicating that two different ring-opening pathways of β-lactone were simultaneously involved in MeOH, probably due to competing alkyl C−O and acyl C−O bond cleavages in β-lactone.[16] Moreover, these results revealed that the solvent played a key role in controlling the reaction process and the selectivity. Considering the unusual [3 + 3] annulation mode for direct construction of the valuable 2*H*-chromene core, in which very few transition-metal-catalyzed protocols[6b,17] have been reported for its synthesis, we were thus interested to further optimize the related reaction parameters for this transformation, with the ultimate aim of improving the yield and the selectivity toward the formation of **3a**. After a number of trials, we found that the desired product **3a** was solely obtained in 84% isolated yield via selective alkyl C−O bond cleavage. Encouraged by these results, we thus identified the following conditions for subsequent studies: **1a** (0.2 mmol), **2a** (1.5 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), and CsOAc (1.0 equiv) in MeCN at 60 °C for 24 h under an atmosphere of air.

With the reaction conditions established, we first explored the scope of *N*-phenoxyacetamides, and the results are summarized in Scheme 2a. We found that the developed Rh(III)-catalyzed system proved to be broadly applicable, thus furnishing the

Scheme 2. Scope of Substrates[a,b]



[a]Reaction conditions: **1** (0.2 mmol, 1 equiv), **2** (0.3 mmol, 1.5 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), and CsOAc (1 equiv) in CH_3CN (0.1 M) at 60 °C for 24 h without exclusion of air or moisture; isolated yields were reported. [b]Contained an inseparable mixture of isomers; the ratio was determined by ^1H NMR.

corresponding 2*H*-chromene-3-carboxylic acids in moderate to good yields. We found that the electrical property of the substituent played a crucial role in the reaction because *N*-methoxybenzamides bearing the electron-withdrawing group (the range of yields from 23 to 76%) gave yields relatively lower than those bearing the electron-donating group (the range of yields from 67 to 85%). Importantly, various substitutions, including many useful functional groups such as halogens (**3e**−**h**, **3k**, and **3p**), trifluoromethyl (**3i**), and ester (**3j**) either at the *para*- (**3b**−**g**), *meta*- (**3k**−**n**), or *ortho*- (**3o**,**p**) position, were fully tolerated. Of note, substrate **1k** bearing the chloro functional group at the *meta*-position provided the desired product **3k** with exclusive regioselectivity toward the less-hindered site, whereas the *meta*-methyl- and methoxy-substituted derivatives all gave a mixture of regioisomers with different ratios (**3m**/**3m′** = 1:0.1, **3n**/**3n′** = 1:0.3), revealing that the nature of the substituent at the *meta*-position had a clear effect on determining the reaction outcome and the regioselectivity. This protocol could be extended to polyaromatic diphenyl and naphthalene substrates, giving the predicted products **3d** and **3q** in decent isolated yields.

To better probe the scope of the reaction, several methyleneoxetanones bearing substituents of different types and natures such as alkyl, alkenyl, cycloalkyl, and aryl were further investigated (Scheme 2b). Gratifyingly, the reaction showed good compatibility with these substrates to deliver the

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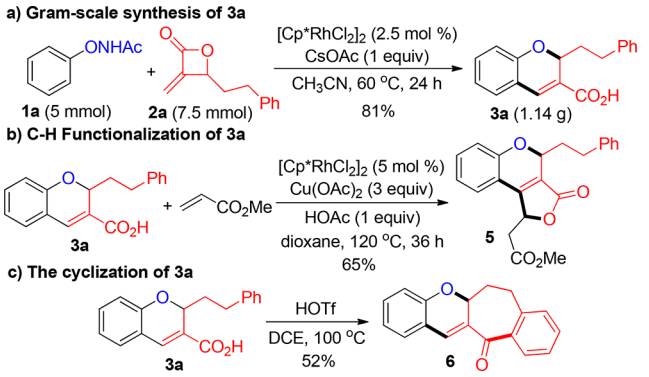
corresponding [3 + 3] annulation products in synthetically useful yields. In particular, the two methyleneoxetanone substrates, derived from the well-known and FDA-approved food flavors citronellal and cyclamen aldehyde, also worked well, affording the desired products **4h** and **4i** in good yields, which further demonstrated the versatility of the developed Rh(III)-catalyzed [3 + 3] annulation.

To demonstrate the synthetic application potentiality, gram-scale synthesis of product **3a** was performed under the optimized conditions, and a decent yield of 81% was isolated smoothly (Scheme 3a). Additionally, two representative

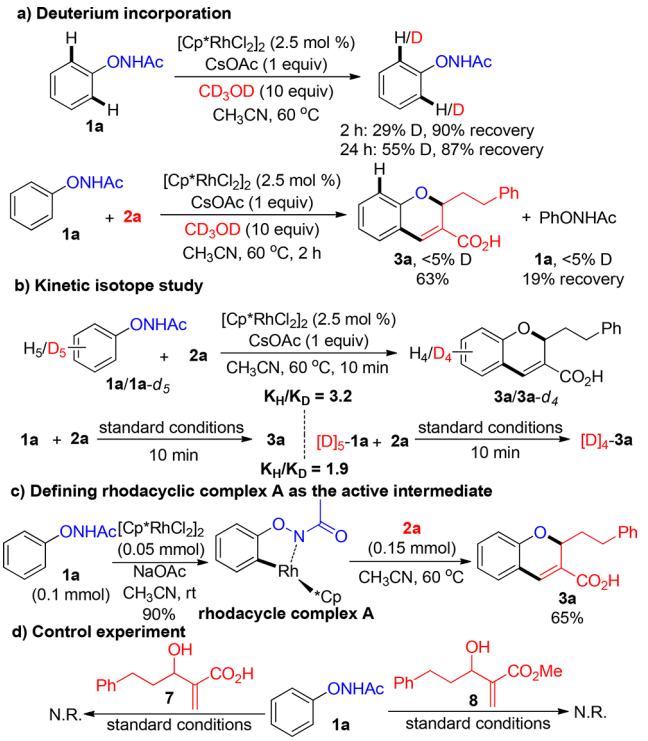
Scheme 3. Gram-Scale Synthesis and Derivatization of 3a



derivatization reactions have been carried out to explore the synthetic transformation of the obtained 2*H*-chromene-3-carboxylic acid products. As illustrated in Scheme 3b, further C−H functionalization of **3a** with methyl acrylate afforded an intriguing scaffold, 1*H*-furo[3,4-*c*]chromen-3(4*H*)-one derivative **5** in 65% yield. In addition, treatment of **3a** with HOTf at 100 °C resulted in intramolecular cyclization to deliver the interesting tetracyclic product **6** in 52% yield (Scheme 3c).

To further cast light on the reaction mechanism, a series of experimental investigations were conducted (Scheme 4). First, the reversibility of the C−H activation was defined by removing the methyleneoxetanone substrate and running the reaction in deuterated methanol. As shown in Scheme 4a, ^{1}H NMR analysis showed approximately 29 and 55% deuteration at the *ortho*-positions of the recovered *N*-phenoxyacetamide **1a** after 2 or 24 h, respectively, revealing that the C−H activation process was reversible. Second, carrying out the same reaction in the presence of **2a** led to no deuterium incorporation in product **3a** and unreacted **1a**, suggesting that the reaction rate of the migratory insertion of **2a** was far faster than that of the C−H bond activation step. Then, the isotope-labeling experiment was performed to further probe the C−H activation process (Scheme 4b). Both results from a competitive experiment and two parallel, side-by-side reactions showed that significant kinetic isotope effect was involved based on two rate constants, thus suggesting that the C−H cleavage might be related to the rate-determining step. Moreover, to capture the potential intermediates, we first treated $[Cp^*RhCl_2]_2$ with **1a**, and the five-membered rhodacyclic complex **A** was smoothly obtained. As predicted, complex **A** displayed good activity in the next stage of the stoichiometric reaction (Scheme 4c), which provided clear evidence that C−H activation was involved in the catalytic cycle, and also revealed that the rhodacyclic complex **A** species should act as one of the active intermediates for this transformation. Finally, two control experiments were carried

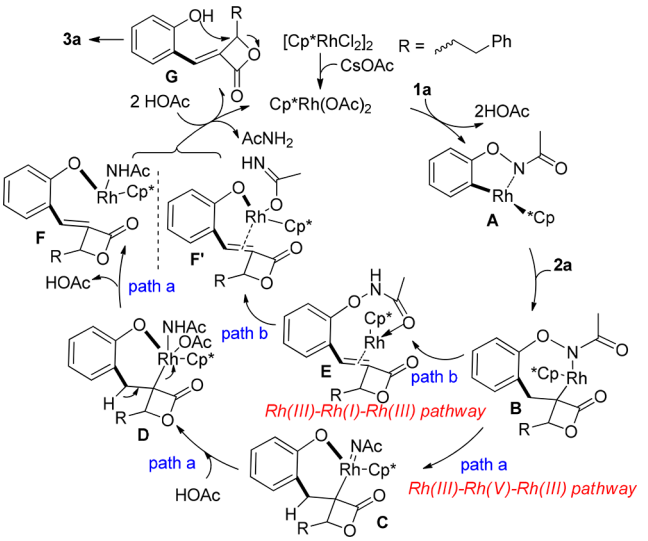
Scheme 4. Experimental Mechanistic Studies



out to define the role of the β-lactone moiety and the reaction sequence with regard to the olefination and the ring opening. As demonstrated in Scheme 4d, no reaction was monitored when 2-carboxyl allylic alcohol **7** and its ester form **8** were treated with **1a** under standard conditions, showing that a four-membered β-lactone moiety was crucial for the reaction outcome and also implying that its ring-opening step should occur after the C−H activation/olefination reaction.

On the basis of these experimental results and literature precedents, we proposed the plausible mechanism of this reaction in Scheme 5. First, the reactive acetate Rh catalyst was generated through a ligand exchange, followed by the coordination with the N atom of **1a** and *ortho*-C−H activation

Scheme 5. Proposed Mechanism



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of the directing group to yield the five-membered rhodacycle intermediate **A**. Subsequent regioselective migratory insertion of the α-methylene moiety of **2a** into the Rh−C bond of **A** forms the seven-membered intermediate **B**. Then, both the Rh(III)−Rh(I)−Rh(III) and the Rh(III)−Rh(V)−Rh(III) pathways are possible, mainly depending upon the oxidation of Rh by the O−N bond.[5a] Thus, in pathway a, an oxidative addition of Rh(III) into the O−N bond produces the six-membered Rh(V) species **C**, followed by HOAc-assisted addition and subsequent anti-β-H elimination to give the intermediate **F**. Alternatively, β-H elimination of **B** provides the ring-opening Rh(I) species **E**. Then, intramolecular oxidative addition of Rh(I) into the O−N bond affords **F′** (pathway b). Finally, protonation of **F′** regenerates the active catalyst and delivers the intermediate **G**, which undergoes a classical intramolecular S_N2-type nucleophilic substitution reaction along with the alkyl C−O bond cleavage to release the product **3a**.

To further confirm which pathway is more feasible for this transformation, DFT calculations were performed with Gaussian 09 by selecting the isolated rhodacycle **A** as the starting point (see the SI for details). The results demonstrate that rhodacycle **A** proceeds via a Rh(III)−Rh(V)−Rh(III) pathway to give the **INT-5** (intermediate **F**) with an overall 41.9 kcal/mol exothermicity (pathway a), in which **TS-2** and **TS-3** are used as the transition states with a free energy of 21.8 and 27.6 kcal/mol, respectively. However, in pathway b, a higher free energy barrier is required to overcome a Rh(III)−Rh(I)−Rh(III) pathway (**TS-2′** = 26.4 kcal/mol; **TS-3′** = 30.1 kcal/mol). Moreover, a low overall exothermicity of 28.3 kcal/mol is involved from **A** to **INT-5′** (intermediate **F′**). Taken together, the results reveal that pathway b is clearly disfavored in comparison to the pathway a.

In summary, we have developed, for the first time, a mild solvent-controlled and rhodium(III)-catalyzed redox-neutral cascade C−H activation/unusual [3 + 3] annulation of diverse *N*-phenoxyacetamides for the one-pot synthesis of a 2*H*-chromene-3-carboxylic acid framework with broad substrate tolerance and good functional group compatibility, in which methyleneoxetanones were employed as an innovative three-carbon source through selective alkyl C−O bond cleavage of the β-lactone moiety. The synthetic utilities of the obtained products have also been successfully exemplified by the gram-scale synthesis of the products and subsequent derivatization reactions for the one-pot construction of interesting 1*H*-furo[3,4-*c*]chromen-3(4*H*)-one derivatives and tetracyclic compounds. Through a set of experimental investigations together with the theoretical calculations, an active five-membered rhodacycle intermediate has been established, and a tandem C−H activation/olefination/intramolecular S_N2-type nucleophilic substitution process employing the Rh(III)−Rh(V)−Rh(III) pathway to turn over the catalytic cycle has also been deduced rationally. Further studies on understanding the reaction mechanism and exploring the new type of reaction modes of methyleneoxetanones are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01477.

Experimental procedures, characterization of products, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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