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# Divergent Construction of Diverse Scaffolds through Catalyst-Controlled C–H Activation Cascades of Quinazolinones and Cyclopropenones

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**Abstract:** A transition-metal-catalyzed C–H activation cascade strategy to rapidly construct diverse quinazolinone derivatives in a one-pot manner is reported. The catalysts play an important role in the different transformations. Additionally, the procedure is scalable, proceeds with high efficiency and good chemo-/regio-selectivity, and tolerates a range of functional groups.

Quinazolinone moiety is an ubiquitous in biological materials and natural products,[1] which have shown broad bioactivity, such as anticancer,[2] antibacterial,[3] anti-diabetes,[4] hypnotic,[5] sedative,[6] and analgesics activity[7] (Figure 1A). Therefore, chemical workers have devoted themselves to synthesizing such kind of structures and derivatives.[8] Over the past decades, metal-catalyzed C–H activation has emerged as a powerful strategy for the step-economical construction of a wide variety of value-added arenes.[9] In particular, high-valent $Rh^{III}$[10] and $Ru^{II}$[11] complexes have stood out as highly efficient catalysts for the construction of C–C bonds by C–H activation. With the rapid development of transition-metal-catalyzed C–H activation, quinazolinone, the natural nitrogen-containing scaffold, has been used as a directing group (DG) to assist metal-catalyzed *ortho*-C–H activation progress.[12] For example, Cui demonstrated a $Pd^{II}$-catalyzed reaction of quinazolinones with alkynes, leading to fused poly-heterocycles.[12b] Then, constructing dihydroisoquinoline-fused quinazolinone scaffolds through a $Ru^{II}$-catalyzed C–H allylation/hydroamination cascade was reported by Jana.[12c] Besides, through the $Rh^{III}$-catalyzed cascade, Szostak successfully developed a strategy for the synthesis of isoquinolino[1,2-b]quinazolines from 2-arylquinazolinones and sulfoxonium ylides (Figure 1B).[13]

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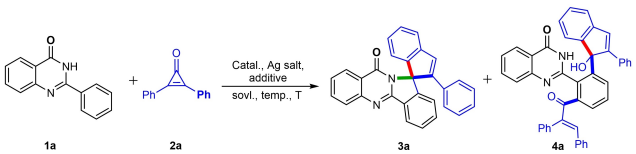
Cyclopropenone, the smallest strained aromatic ring, has been employed as privileged chemical building blocks to construct complicated molecules in the C–H activation field.[14] Representative synthetic works included the construction of cyclopentene spiroisoindolinones developed by Wu,[14b] and the synthesis of chalcones reported by Li.[14c] Our group has also been interested in this kind of moiety for a long time.[14d–f] For example, we have already reported a divergent synthesis of chalcones, quinolones and indoles through C–H activation.[14d] Given in the significant bioactivity of quinazolinones, we envisaged the possibility of transition-metal-catalyzed C–H activation using cyclopropenones as building blocks to constitute a new route to quinazolinone derivatives. We commenced our study by choosing 2-phenylquinazolin-4-(3*H*)-one **1a** and diphenylcyclopropenone **2a** as the model substrates under the catalysis of metal catalysts. Transition metals, like Rh, Ir, Ru, Co, were used respectively (Table 1, entries 1–4). To our delight, a spiro-fused heterocycle-containing product **3a** was obtained when employing $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst. Polycyclic structures fused at a central carbon are of great interest due to their appealing conformational features and

**Table 1.** Optimization of conditions.[a]




| | Catalyst | Additives | Solvent | Yield [%][b] 3a | 4a |
|---|---|---|---|---|---|
| 1 | $[IrCp^*Cl_2]_2$ | – | $CH_2Cl_2$ | – | – |
| 2 | $[Ru(p\text{-cymene})Cl_2]_2$ | – | $CH_2Cl_2$ | 41 | – |
| 3 | $CoCp^*(CO)I_2$ | – | $CH_2Cl_2$ | – | – |
| 4 | $Pd(OAc)_2$ | – | $CH_2Cl_2$ | – | – |
| 5 | $[RhCp^*Cl_2]_2$ | – | $CH_2Cl_2$ | 6 | 5 |
| 6 | $Ru(bpy)_3Cl_2 \cdot 6H_2O$ | – | $CH_2Cl_2$ | – | – |
| 7 | Grubb's catalyst | – | $CH_2Cl_2$ | – | – |
| 8 | $RuCl_3$ | – | $CH_2Cl_2$ | – | – |
| 9 | $[Ru(p\text{-cymene})Cl_2]_2$ | PivOK | $CH_2Cl_2$ | – | – |
| 10 | $[Ru(p\text{-cymene})Cl_2]_2$ | AdCOOH | $CH_2Cl_2$ | 64 | – |
| **11** | **$[Ru(p\text{-cymene})Cl_2]_2$** | **AdCOOH** | **DCE** | **84** | – |
| 12[c] | $[RhCp^*Cl_2]_2$ | – | TFE | – | 12 |
| 13[c,d,e] | $[RhCp^*(OAc)_2]$ | – | TFE | – | 75 |
| **14**[e,d,f,g] | **$[RhCp^*(OAc)_2]$** | – | **TFE** | – | **81** |

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.21 mmol), Catalyst (5 mol%), $AgSbF_6$ (30 mol%), Additive (2.0 equiv.), Solvent (2.0 mL), at 130 °C for 24 h; [b] Isolated yields; [c] 3.0 equiv. of **2a**, 100 °C; [d] 48 h; [e] 10 mol% Catalyst, without $AgSbF_6$; [f] 4.0 equiv. of **2a**; [g] 110 °C.

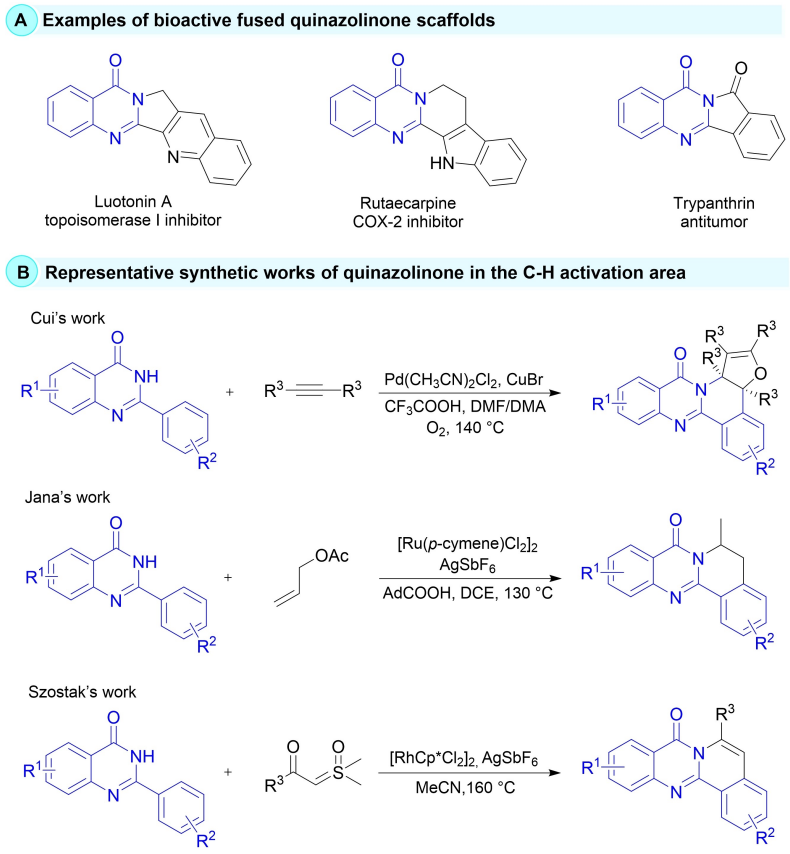



**Figure 1.** Quinazolinones and their C–H activation research.

their structural implications in biological system and organic materials.[15] These rapid [4+1] and [1+4] cycloadditions are attractive and step-economical process for the construction of a spiral heterocycle. Therefore, a series of optimal experiments were carried out to improve the yield of **3a**. We speculated that Ru-catalyst might play a crucial role in the transformation.

The tests of other Ru catalysts were followed, and the results revealed that $[Ru(p\text{-cymene})Cl_2]_2$ remained the best one (Table 1, entries 5–7). $[Ru(p\text{-cymene})Cl_2]_2$ and Ag salts were proved to be indispensable in the following investigation (see the Supporting Information for details). Subsequently, various acid additives were examined to improve the yield.[16] Among various additives we tested, AdCOOH could give a better yield of 63%. When the temperature of the reaction was increased to 130 °C and DCE was employed as the solvent, the reaction could proceed in high efficiency, furnishing **3a** in the best yield (84%). Thus, the reaction conditions in entry 11 were selected as the optimal conditions.

It is worth noting that when $[RhCp^*Cl_2]_2$ was employed as the catalyst, a new product was detected (Table 1, entry 5). By analyzing the structure data, we found it was an unsymmetrical difunctionalized product containing an indenol moiety and a chalcone side. Then, we started to screen the reaction conditions. When using TFE as the solvent, the yield could be improved. To reduce interference caused by self-coupling product from **2a** catalyzed by Ag salts, we tried to use active $[RhCp^*(OAc)_2]$, which needs no anion exchange with the Ag salts at the beginning of the C–H activation, as the catalyst.[17] As expected, the yield of **4a** could be improved under the catalysis of $[RhCp^*(OAc)_2]$. Thus, we successfully developed a reaction that could selectively construct the sequential unsymmetrical twofold C–H activation product under the optimum conditions: **1a** (0.1 mmol), **2a** (0.4 mmol), $[RhCp^*(OAc)_2]$ (10 mol%), TFE (2.0 mL) at 110 °C for 48 h.

After the efficient methods were developed for the synthesis of **3a** and **4a**, the substrate scope of the Ru- and Rh-catalyzed reactions between quinazolinones and cyclopropenones were examined (Figure 2). Generally, the synthesis of products **3** was found to be efficient for a wide range of substrates. 2-Phenylquinazolin-4-(3*H*)-one containing substituents on the *para*-site of the benzene ring such as methyl, isopropyl, *tert*-butyl, and trifluoromethyl could be efficiently converted into spiro-fused heterocycles **3a**–**3j** in high yields. Both electron-donating and -withdrawing groups were compatible with these conditions. Significantly, this protocol was readily scaled up to produce grams of spiro-fused quinazolinones, highlighting its industrial application foreground (**3i**). When the *meta*-site of the benzene ring was occupied by the methoxy group, trifluoromethoxy group and chlorine group, the compounds could be given on the side with less steric hindrance (**3l**–**3n**). However, when the methoxy group turned to the *ortho*-site of the benzene ring, the corresponding

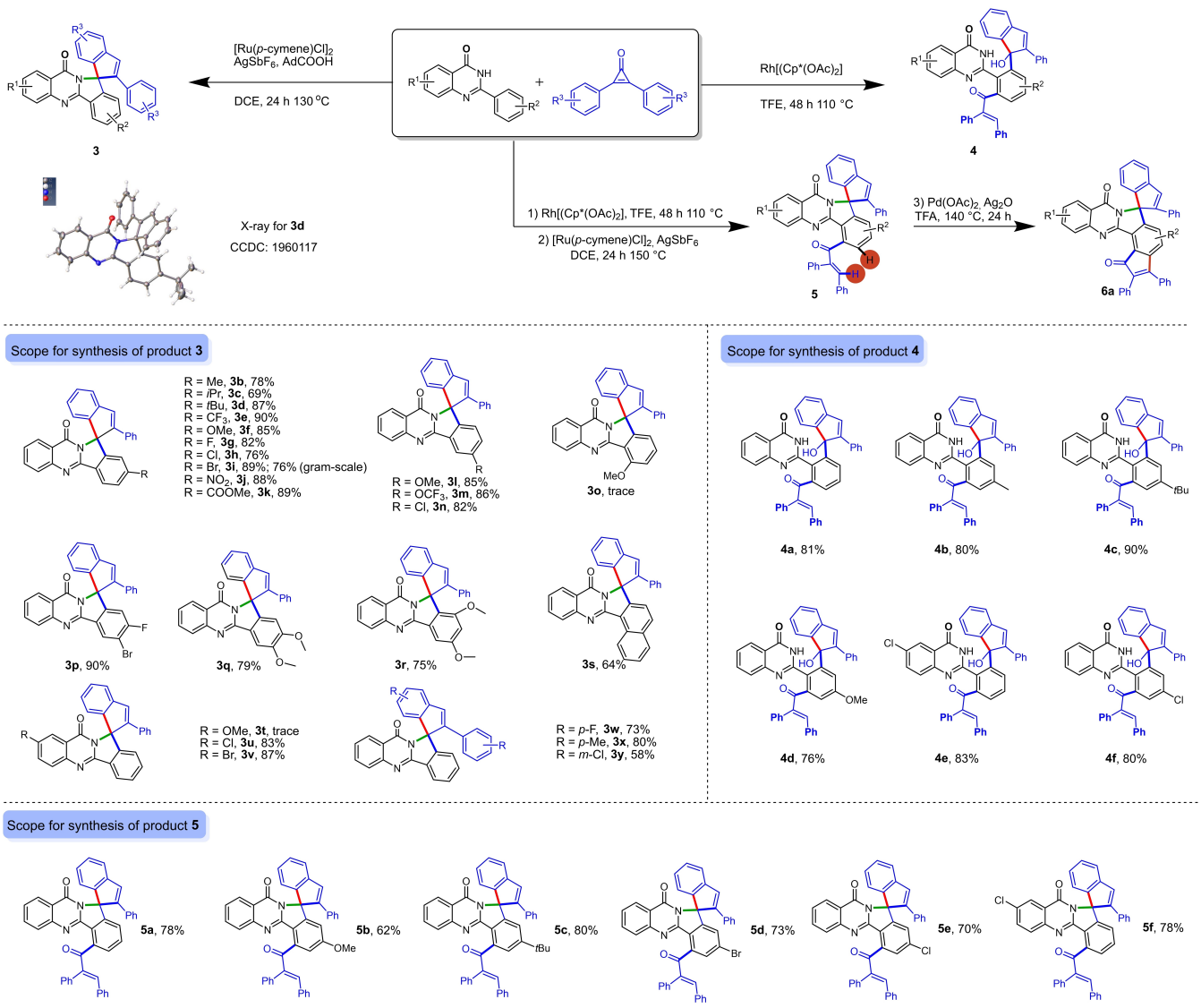



**Figure 2.** The substrate scope of the reactions.

product **3o** could not be detected. Compared with the previous compounds we got, it may be caused by the steric hindrance (**3f** and **3l**). Bis-substituted quinazolinone and 2-naphthylquinazolin-4-(3*H*)-one were tolerated as well, providing the corresponding products **3p**–**3s** in good yields. Electron-donating group substituted groups were proved to be sluggish to take part in the transformation compared with the electron-withdrawing substituted ones (**3t**–**3v**). We also tried to examine the scope of cyclopropenones, and the results suggested that substituted cyclopropenone could bear the conditions to form corresponding products **3w**–**3y**. The scope for the synthesis of compound **4** was next assessed with different substituted quinazolinones (Figure 2). Products **4a**–**4f** could also be generated in a high efficiency when 2-phenylquinazolin-4-(3*H*)-one was substituted by other groups.

Considering the indenol moiety of **4a**, we anticipated that the structure could undergo dehydration way to form a compound containing a spiro-fused ring. When the separated product **4a** reacted under the optimal conditions for constructing **3a**, we could obtain the desired product **5a** (Figure 2). Elevating the temperature to 150 °C, **5a** could be obtained in 78% yield. The transformation could also be achieved in a slightly lower yield through a two-step one-pot manner.

We hoped that the chalcone chain in **5a** could couple with the *meta*-site C–H bond of the benzene ring and occur a direct functionalization to form an indanone derivative product **6a**. It would be a valuable attempt for synthesis of indanone derivatives, which are important moiety of some widely used biological products.[18] Moreover, the challenging research on intramolecular C–C coupling reactions through the activation of two C–H bonds directed by a functional group are not fully explored.[19] After the screening of reaction conditions (see the Supporting Information for details), we found that **5a** could be transformed into **6a** in a moderate yield under the catalysis of

$Pd(OAc)_2$ (Figure 2). Notably, the efficient one-pot synthesis of tetra-substituted product **6a** starting from **1a** and **2a** could be smoothly implemented, albeit involving sequential activation of five C–H bonds.

To reveal how the product **3a** and **4a** were synthesized, some preliminary mechanism studies were conducted (Figure 3). H/D exchange between **1a** and $CD_3OD$ was firstly performed, and the starting material was recovered with 59% deuteration at the *ortho* positions, indicating the reversibility of C–H activation in the absence of cyclopropenones (Figure 3a). Another *ortho*-H/D exchange was observed in the NMR spectrum when treating [$D_5$]-**1a** with **2a** under the standard conditions, again confirming that the initial *ortho*-ruthenation was reversible (Figure 3b). Moreover, the competition reaction determined the reaction slightly favored the electron-donating quinazolinones (Figure 3c). Finally, the competitive and parallel kinetic isotope effects were measured. The $k_H/k_D$ and $P_H/P_D$ values were 3.3 and 6.1, respectively, thus suggesting that the *ortho*-C–H cleavage of **1a** was probably involved in the rate-limiting step (Figure 3d).

Based on mechanism experiments and the reported C–H activation works,[12c,14g,20] a plausible mechanism was illustrated in Figure 4. Initial anion exchange affords the active $[MLX_2]$ species, which likely involves the coordination of the nitrogen atom of **1a** to the metal center, followed by reversible displacement of aromatic C–H bond to form five-membered metal-cycle **A**. Intermolecular oxidative addition by cyclopropenone then generates an intermediate **C**. Subsequent reductive elimination and intramolecular C–H activation then lead to the formation of an intermediate **D**. When using $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst and AdCOOH as the additive, the intermediate **E** is produced from **D** by an intramolecular nucleophilic attack. Oxidative addition gives ruthenium/π-allylic intermediate **F**, which undergoes reductive elimination to offer the product **3a**. Meanwhile, the $Ru^{II}$ catalyst is regenerated for a next catalysis cycle. Under the catalysis of $[RhCp^*(OAc)_2]$, the intermediate **D** goes through the same intramolecular nucleophilic attack pathway to form an intermediate product with an indenol moiety, followed by Rh-catalyzed *ortho*-C–H activation to selectively form an intermediate **G**. The other cyclopropenone suffers the oxidative addition/reductive elimination way to form a stable chelation intermediate **H**, which retards the further synthesis of the second indenol moiety. Finally, the disubstituted product **4a** is obtained by the release of the active Rh catalyst and protonation.

In summary, we have developed a divergent C–H activation cascade reaction strategy to rapidly construct structurally different scaffolds from 2-arylquinazolin-4-(3*H*)-one and cyclopropene-

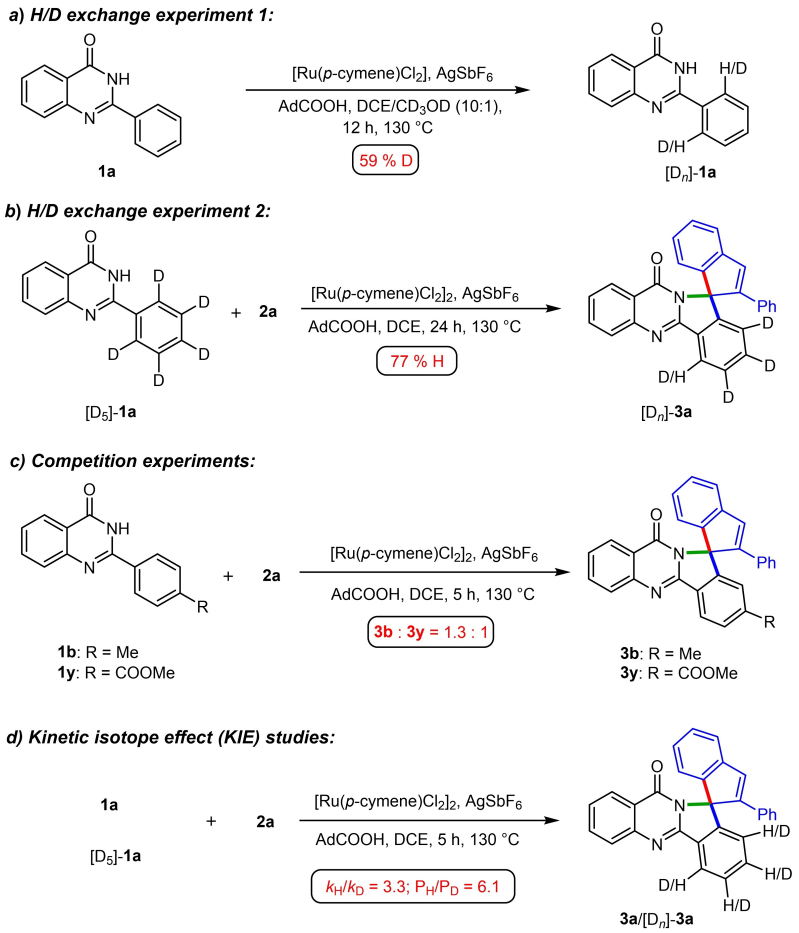



**Figure 3.** Mechanistic studies.

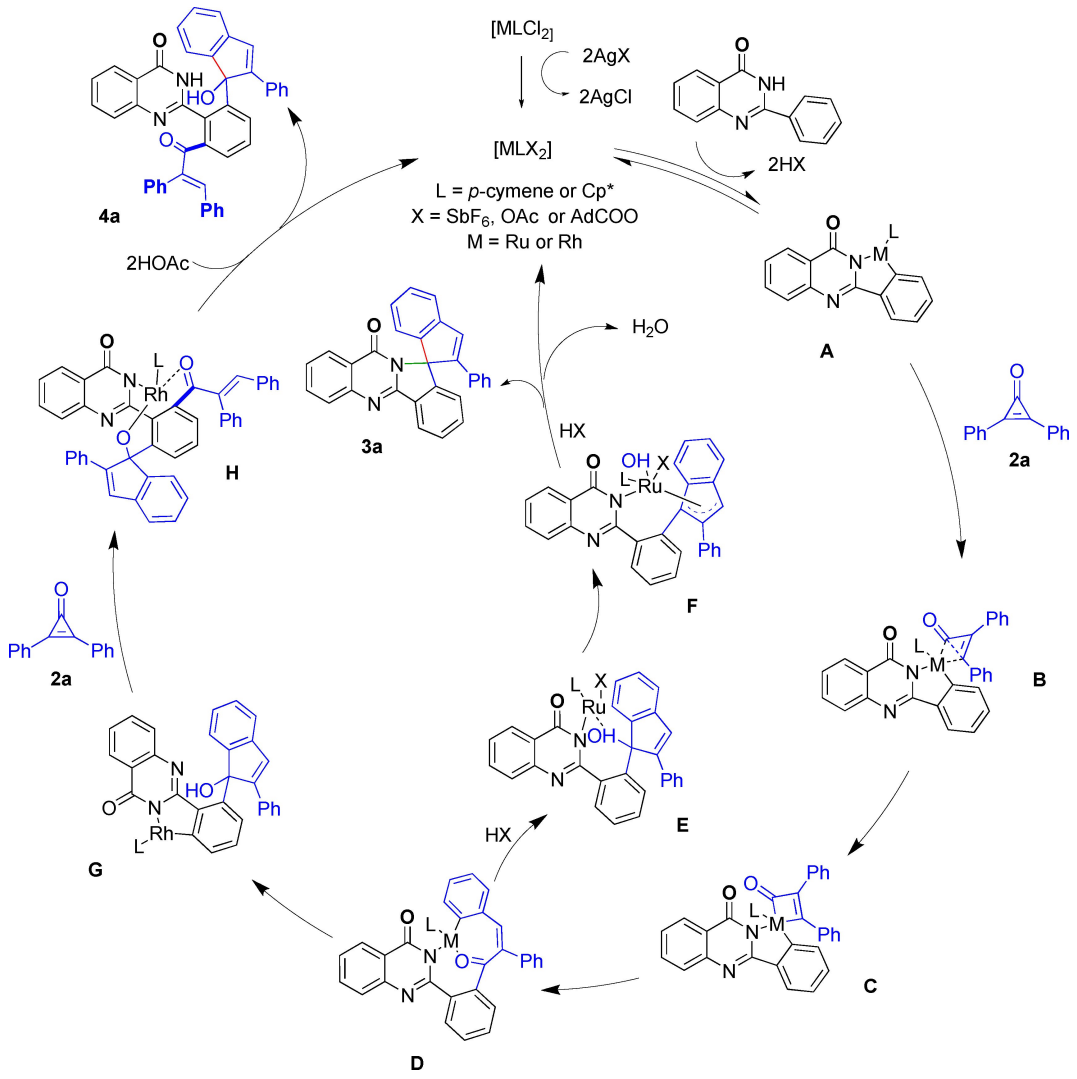



**Figure 4.** Proposed mechanism.

none. Different catalytic conditions are crucial for the outcome of the reaction. These methodologies are characterized by high chemo- and regioselectivity, good functional group tolerance, and amenability to gram-scale synthesis. We hope that these reactions can provide a reference for future derivation of new chemical scaffolds by C–H activation.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** cascade · cyclopropenone · divergent synthesis · one-pot synthesis · quinazolinone

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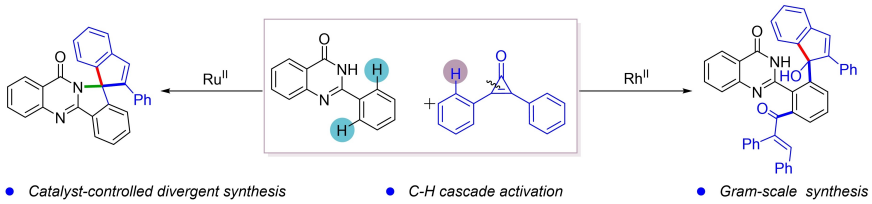
# COMMUNICATION




**Controlled cascades**: We have successfully developed attractive C–H activation cascade reactions between quinazolinones and cyclopropenones. Different structures can be selectively synthesized under the precise control of the catalysts in a one-pot manner. The high efficiency, excellent chemo-/regioselectivity, wide substrate scope, and amenability to gram-scale synthesis for both quinazolinones and cyclopropenones demonstrated the promising applicability of reactions.

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**Divergent Construction of Diverse Scaffolds through Catalyst-Controlled C–H Activation Cascades of Quinazolinones and Cyclopropenones**