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Rh(III)-Catalyzed acylation of heteroarenes with cyclobutenones *via* C–H/C–C bond activation†

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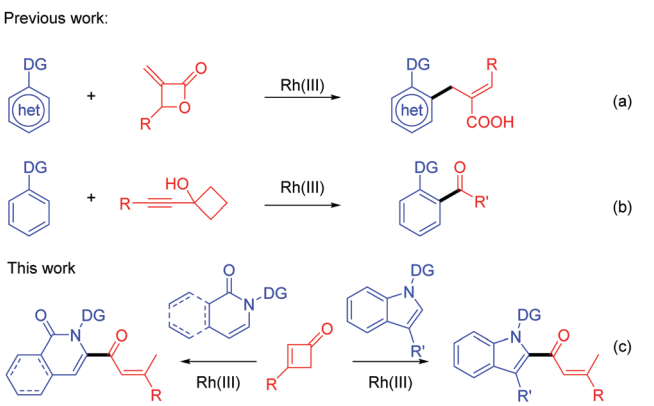
Rhodium(III)-catalyzed C–H acylation of heteroarenes has been realized using cyclobutenones as an acylating reagent. This coupling proceeded *via* integration of C–H activation of heteroarenes and C–C cleavage of cyclobutenones. The reaction features excellent regio/chemoselectivity leading to versatile chalcones with exclusive *E*-selectivity.

Metal-catalyzed C–H bond activation has emerged as a powerful strategy for the step-economical construction of a wide variety of value-added arenes.[1] In particular, high-valent Rh(III) complexes have stood out as highly efficient catalysts for the construction of C–C bonds *via* C–H activation.[2] Various unsaturated coupling partners have been applied in this system, and they can be manipulated to numerous new structural platforms.[2,3]

Among the plethora of unsaturated coupling partners, strained rings generally exhibit high activity, allowing the facile introduction of many important functional groups following C–H activation.[4–11] In this regard, three- and some reactive five-membered rings and bridged cycles such as alkylidenecyclopropane,[5] cyclopropenones,[6] vinylcyclopropanes,[7] cyclopropanols,[8] dioxazolones,[9] 7-oxa/azabenzonorbornadienes,[10] and others[11] have been successfully applied as alkylating, acylating, and amidating reagents. Despite the achievement, four-membered rings are generally less explored as coupling reagents likely due to their less strain and relatively lower reactivity compared to three-membered rings in Rh(III) catalyzed C–H bond activation. Recently, our group reported catalytic ring-opening coupling of methyleneoxetanones with arenes for the synthesis of acrylic acids, which took place *via* selective alkyl C–O cleavage (β-oxygen elimination, Scheme 1a).[12] To the best of our knowledge, 1-alkynyl cyclobutanols are the only four-membered carbocycles that have been successfully applied as coupling reagents in Rh(III)-catalyzed C–H activation (Scheme 1b).[13] Clearly, it is necessary to apply other four-membered carbocycles for diversified C–H functionalization of arenes.

As a class of important four-membered rings, cyclobutenones are readily available and they have proved to be valuable synthons in organic synthesis.[14] The ring strain and the presence of two unsaturated bonds in cyclobutenones may render them multifunctional and highly useful in metal-catalyzed C–H activation/ring-opening coupling.[15] On the other hand, indoles and isoquinolones have been identified as important skeletons in numerous natural products and biologically active compounds. Consequently, the development of efficient synthetic methods to access functionalized indoles and isoquinolones is highly attractive. We now report Rh(III)-catalyzed C–H activation of heteroarenes and coupling with cyclobutenones *via* C–C activation, leading to the facile synthesis of chalcones with exclusive *E*-selectivity (Scheme 1c).



Scheme 1 Representative Rh(III)-catalyzed ring-opening of the four-membered ring.

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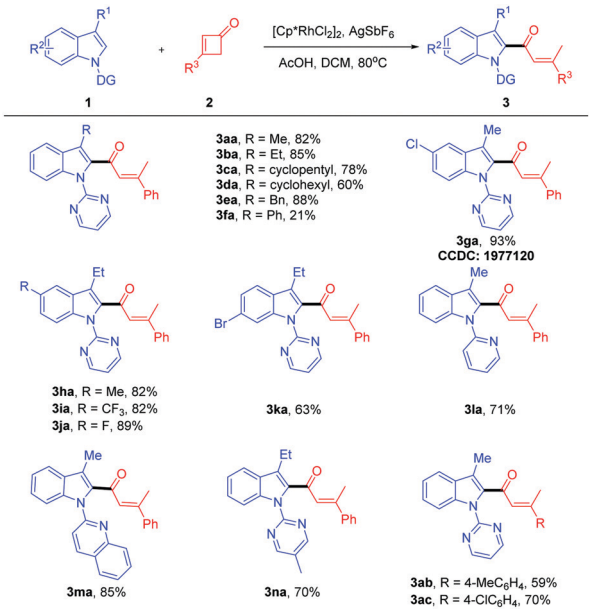
Cyclobutenones can be potentially alkylating or acylating reagents. Thus, we commenced our studies by screening the reaction parameters in the coupling of 3-methyl-*N*-(2-pyrimidinyl)-indole (**1a**) and 3-phenyl-cyclobutenone (**2a**, Table 1). With $[Cp^*RhCl_2]_2$/$AgSbF_6$ as a catalyst and AcOH as an additive, the acylation product **3aa** was isolated in 57% yield in DCE at 100 °C (Table 1, entry 1). Solvent screening indicated that dichloromethane (DCM) seemed optimal (entries 2–6). Lowering the temperature to 80 °C led to an improved isolated yield of 82% (entries 7 and 8). Switching AcOH to PivOH and $B(OH)_3$ only showed inferior results (entries 9 and 10). Employing a base additive (NaOAc or K_2CO_3) also led to a poor reaction conversion (entries 11 and 12). Further optimization using one equiv. of AcOH afforded product **3aa** in 83% yield (entries 13 and 14). Our control experiment confirmed that no desired product was observed when the rhodium catalyst or $AgSbF_6$ was omitted.

With the establishment of the optimal reaction conditions, we next explored the scope and generality of this coupling system (Scheme 2). The scope of the indole substrates was examined first. With either alkyl-(**3aa–3da**) or benzyl-(**3ea**) groups at the 3-position of the indole substrate, the reaction proceeded smoothly to afford the desired products in 60–88% yields, indicative of tolerance of the steric effect. A 3-phenylindole substrate also reacted albeit with a lower yield (**3fa**). The presence of halide, methyl, and CF_3 groups at the 5-position of the indole is tolerated, affording the corresponding product in high to excellent yields (82–93%, **3ga–3ja**). A 6-bromoindole substrate also reacted with a good yield (**3ka**). The pyrimidyl directing group (DG) was successfully extended to pyridyl, quinolinyl, and 4-Me-pyrimidyl in good to high yields (**3la–3na**, 70–85% yields). Next, the generality of cyclobutenones **2** was briefly explored. Smooth coupling was

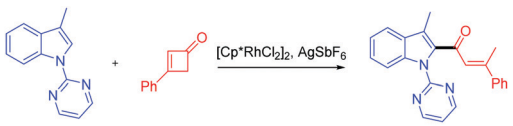


Scheme 2 Scope of *N*-pyrimidylindoles[a]. [a]Reaction conditions: indole **1** (0.2 mmol), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), and AcOH (1.0 equiv.) in DCM (2.0 mL) under argon for 20 h at 80 °C, isolated yield.

realized when the R^3 group was extended to several substituted phenyl groups (4-MeC_6H_4 and 4-ClC_6H_4), and the corresponding product was also obtained in a moderate (**3ab**, 59%) or good (**3ac**, 70%) yield.

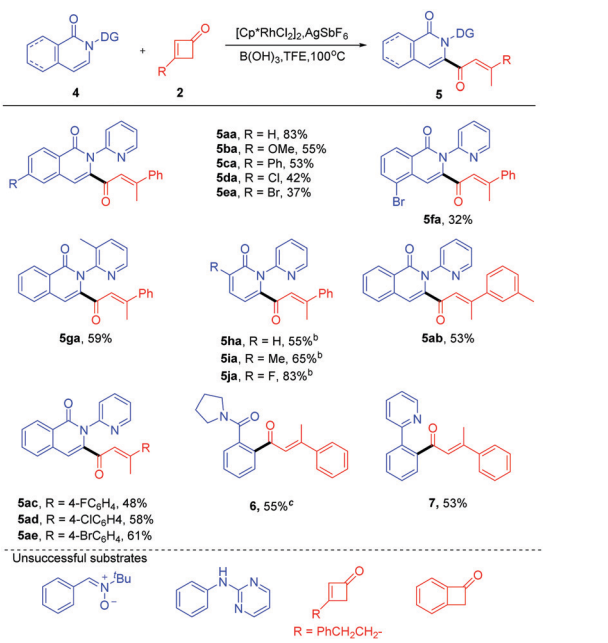
To better define the scope of the heteroarene substrate, we next extended indoles to 2-isoquinolones bearing an N-directing group (Scheme 3). The ring-opening coupling with cyclobutenone **2**

Table 1 Optimization studies[a]



Entry	Additive	Solvent	T (°C)	Yield[b] (%)
1	AcOH	DCE	100	57
2	AcOH	TFE	100	Trace
3	AcOH	THF	100	70
4	AcOH	Dioxane	100	24
5	AcOH	PhCl	100	42
6	AcOH	DCM	100	78
7	AcOH	DCM	80	82
8	AcOH	DCM	60	42
9	PivOH	DCM	80	78
10	$B(OH)_3$	DCM	80	32
11	NaOAc	DCM	80	7
12	K_2CO_3	DCM	80	Trace
13[c]	AcOH	DCM	80	82
14	—	DCM	80	68
15[c,d]	AcOH	DCM	80	NR

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), additive (0.4 mmol), solvent (2.0 mL) under argon for 20 h. [b] Isolated yield. [c] AcOH (0.2 mmol) was used. [d] No rhodium or $AgSbF_6$ was used.

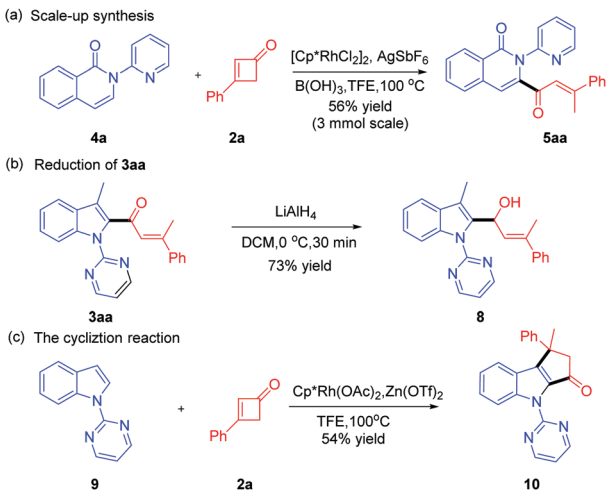


Scheme 3 Scope of isoquinolones and pyridones.[a] [a]Reaction conditions: arene (**4**, 0.2 mmol), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), $B(OH)_3$ (2.0 equiv.), TFE (2.0 mL), under argon for 20 h, isolated yield. [b]THF was used as a solvent with AcOH (2.0 equiv.). [c]DCE was used as a solvent.

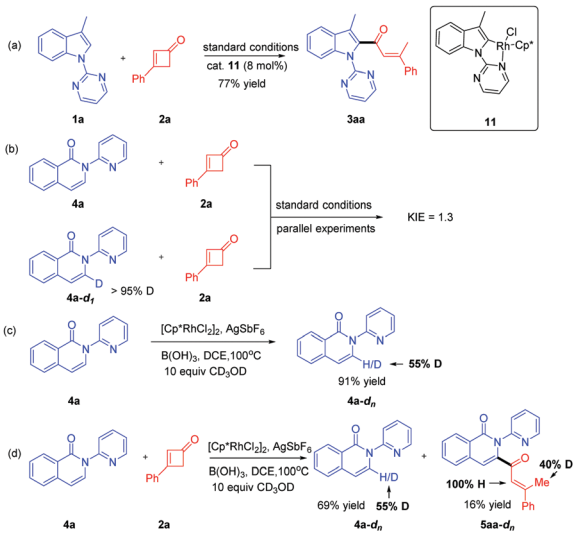
proceeded smoothly under the modified reaction conditions with boric acid additive (see the ESI† for more details). Thus, the isoquinolones bearing electron-donating and -withdrawing substituents at the 6-position of the benzene ring were all compatible (**5aa–5ea**, 37–83% yields). The introduction of a 5-bromo group was also tolerated (**5fa**, 32%). In addition, *N*-(6-methylpyridyl)isoquinone also reacted smoothly to afford the corresponding product (**5ga**, 59%). The arene substrate was further extended to 2-pyridones with *N*-pyridyl as a directing group. 2-Pyridones bearing Me- and F- groups at the 6-position all coupled efficiently with moderate to high yields (**5ha–5ja**, 55–83% yields). The reaction also proceeded well when different aryl-substituted cyclobutenones were used (**5ab–5ae**, 53–61% yields). 1-Benzoylpyrrolidine and 2-phenylpyridine could also react smoothly to afford the corresponding products in moderate yields (**6**, 55% and **7**, 53%). In contrast, arylnitrones, *N*-phenylpyrimidin-2-amine, 3-phenethyl-cyclobutenone and benzocyclobutenone failed to undergo the coupling.

To demonstrate the synthetic applicability of this protocol, a scale-up (3 mmol) synthesis of **3aa** was performed and a decent yield of 56% was isolated (Scheme 4a). Additionally, product **3aa** underwent selective 1,2-reduction by $LiAlH_4$ (**8**, 73% yield, Scheme 4b). Moreover, intramolecular cyclization occurred when 3-unsubstituted *N*-pyrimidylindole (**9**) was used in the presence of $Zn(OTf)_2$ additive, delivering a tricyclic product **10** in 54% yield (Scheme 4c).

To gain insight into the reaction mechanism, several experiments were conducted (Scheme 5). We first synthesized rhodacyclic complex **11** according to a literature report.[3] As a catalyst precursor, complex **11** successfully catalyzed the coupling of **1a** and **2a** to afford ring-opening product **3aa** in 77% yield, which indicated the relevancy of C–H bond activation in this transformation (Scheme 5a). A kinetic isotope effect (KIE) value of 1.3 was then obtained from the competitive coupling of a mixture of **4a** and **4a-d_1** with **2a** under the standard conditions (Scheme 5b), which indicated that cleavage of the C–H bond was not involved in the turnover-limiting step.[16] Moreover, H/D exchange between



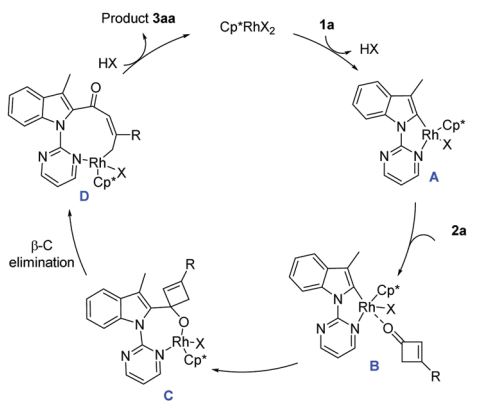
Scheme 4 Derivatization reactions.



Scheme 5 Mechanistic studies.

isoquinolone **1a** and CD_3OD was performed, and the starting material was recovered with 55% deuteration at the *ortho* positions, indicating the reversibility of C–H activation in the absence of cyclobutenones (Scheme 5c). When CD_3OD was added into the reaction of **4a** with **2a**, still 55% deuteration was observed at the *ortho* position of the recovered starting material **4a-d_n**. In addition, H/D exchange was observed at the methyl position of the product **5aa**, with no H/D exchange at the alkenyl position, indicating that ring-opening proceeded possibly through a β-C elimination–protonolysis process (Scheme 5d).

On the basis of our preliminary experiments and previous reports, a plausible mechanism of this ring-opening coupling is proposed in Scheme 6. An active catalyst $[Cp^*RhX_2]$ (X = SbF_6) is generated *via* halide abstraction, which subsequently reacts with arene **1a** *via* C–H activation to afford a rhodacyclic intermediate **A**. Coordination of cyclobutenone **2a** provides an intermediate **B**, which undergoes migratory insertion of the aryl group (Ar–Rh) into the carbonyl group of cyclobutenone (intermediate **C**), and subsequent β-carbon elimination leads to a ring-opening intermediate to provide a Rh(III) alkyl species **D**. Consistent with our deuteration results, protonolysis of **D**



Scheme 6 Proposed mechanism.

affords enone **3aa** and regenerates the active rhodium species for the next catalytic cycle. At this stage, we cannot explicitly rule out the possibility of the C(O)–C(sp^3) oxidative addition pathway[17] that leads to the formation of a Rh(v)acyl–allyl intermediate.

In summary, we have developed an efficient Rh(III)-catalyzed C–H acylation of heteroarenes with cyclobutenones *via* C–H bond activation and C–C cleavage. The coupling system features good efficiency, a broad substrate scope, and excellent functional group tolerance. Mechanistic studies including KIE and H/D exchange experiments have been performed. Considering the importance of chalcones in synthetic chemistry, this protocol may find applications in the synthesis of complex structures.

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Conflicts of interest

There are no conflicts to declare.

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