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Rhodium(III)-catalyzed synthesis of indanones *via* C–H activation of phenacyl phosphoniums and coupling with olefins†

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Phosphonium ylide acts as an efficient bifunctional directing group in Rh(III)-catalyzed C–H activation of arenes and oxidative coupling with activated olefins, leading to facile construction of indanones *via* a sequence of oxidative olefination and carboannulation. The phosphonium moiety functions as an oxophilic group, and dephosphination triggers a nucleophilic cyclization.

Indanone derivatives represent key structural motifs in various natural products and pharmaceuticals exhibiting important biological activities (Fig. 1).[1] In particular, 3-substituted 1-indanones are not only particularly important structural components of many pharmaceutical agents but also versatile intermediates in organic synthesis and medicinal chemistry. Numerous approaches have been developed for the construction of such important skeletons over the past few decades, such as Friedel–Crafts acylation of arenes,[2] Nazarov-type cyclizations,[3] hydroacylation of 2-formyl styrenes,[4] and palladium-catalyzed couplings of aryl (pseudo)halides.[5] However, existing methods generally require harsh reaction conditions, multi-step synthesis, and highly functionalized starting materials. Thus, the development of novel and efficient protocols to access useful indanone scaffolds remains highly desirable.

Transition-metal catalysts proved highly efficient in C–H activation of arenes, and this strategy has been well established as a powerful alternative in organic synthesis.[6] As a continuation of our interest in Rh(III)-catalyzed C–H activation chemistry,[7] we considered the employment of rhodium catalysts for indanone synthesis. However, Rh(III)-catalyzed C–H activation generally calls for chelation assistance of a heteroatom to ensure activity and selectivity of *ortho* C–H bonds,[8] where the heteroatom is ultimately incorporated into the product (Scheme 1a), leading to heterocycle synthesis.[9] Thus, the synthesis of complementary carbocyclic scaffolds[10] is lagging behind.[11] In this context, we recently performed Rh-catalyzed C–H activation of phenacyl ammoniums with styrenes assisted by an oxidizing C–N bond, in which a tertiary amine was extruded (Scheme 1b).[11c] In this coupling system, only *ortho* alkenylation products were obtained. We reasoned that the congeneous phenacyl phosphoniums[12] can be more

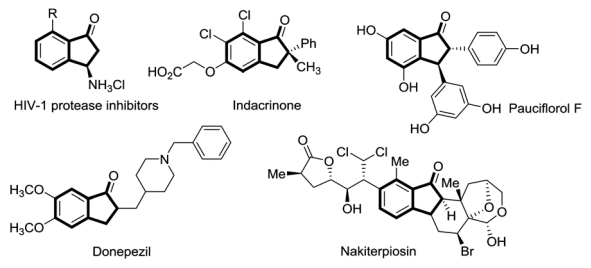
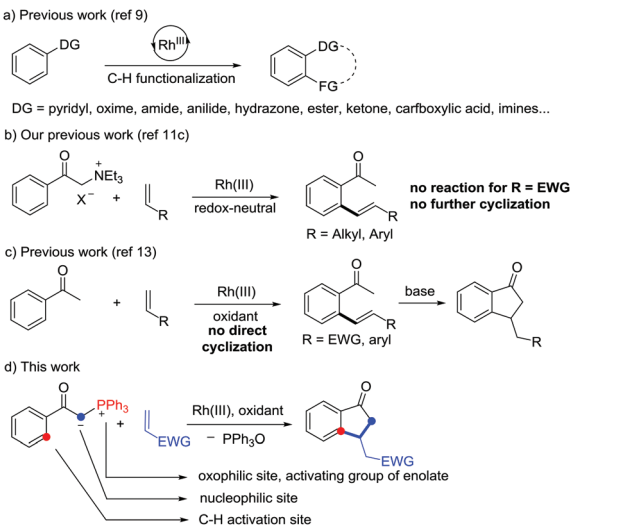


Fig. 1 Representative biologically active indanones.



Scheme 1 Rh(III)-Catalyzed C–H activation assisted by different DGs.

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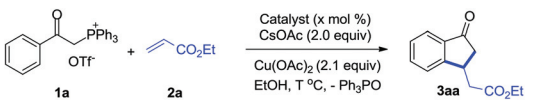
reactive compared with phenacyl ammoniums because *in situ* generation of a bifunctional ylidic DG should be more facile so that 3-substituted indanones might be constructed with alkenes *via* a cascade of C–H alkenylation and carboannulation. However, challenges remain because elimination of a phosphine seems unlikely due to its inhibitory effect. Nevertheless, we may resort to elimination of a phosphine oxide. In addition, although oxidative olefination of acetophenones has been reported, the product failed to undergo further cyclization in one step and a strong base is needed to induce cyclization (Scheme 1c).[13] We now report an efficient and step-economical protocol to access indanones *via* a Rh(III)-catalyzed C–H alkenylation and carbocyclization pathway (Scheme 1d).

We initiated our investigations by screening the reaction parameters of the coupling of phenacyl phosphonium **1a** with ethyl acrylate **2a** in the presence of CsOAc (Table 1). To our delight, indanone **3aa** was isolated in 29% yield in the presence of $Cu(OAc)_2$ (entry 2). Increasing the reaction temperature greatly improved the reaction efficiency (entries 3–5). The yield remained essentially unaffected when the catalyst was switched to $[RhCp^*Cl_2]_2$ (4 mol%)/$AgSbF_6$ (20 mol%) (entry 6). However, a diminished yield was afforded when other silver additives such as $AgNTf_2$ and AgOTf were used (entries 7 and 8). Lowering the catalyst loading led to a reduced yield (entries 9 and 10). Gratifyingly, the optimal yield was obtained at a higher reaction temperature even with a lower catalyst loading (entry 11). Our screening studies also revealed that the triflate anion was superior to other common anions including bromide, hexafluoroantimonate, and tetrafluoroborate. Thus, the following reaction conditions were adopted for further studies: $[RhCp^*Cl_2]_2$ (2 mol%)/$AgSbF_6$ (10 mol%), CsOAc (2.0 equiv.), and $Cu(OAc)_2$ (2.1 equiv.) in ethanol at 120 °C for 18 h. Under these conditions, $OPPh_3$ was also obtained in 87% GC yield. Our extensive screening studies also revealed that essentially no reaction occurred when α-bromoacetophenone was used, indicative of the unique reactivity of the phosphonium salt.

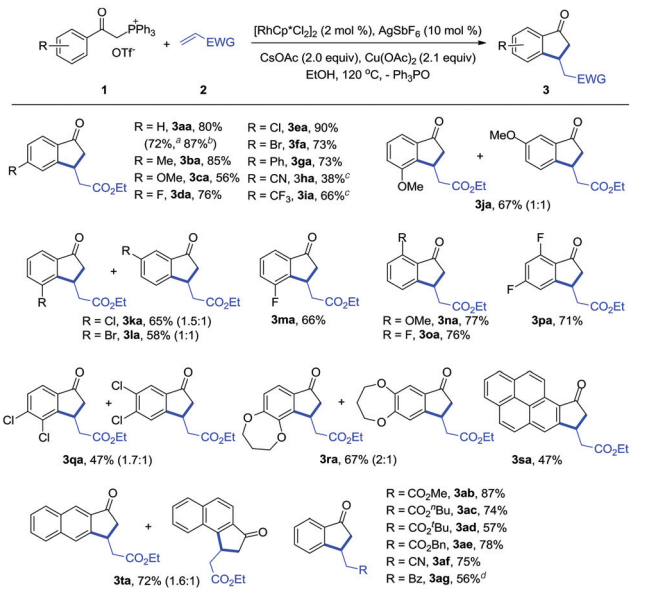
With the establishment of the optimal reaction conditions, we next investigated the scope and generality of this coupling system (Scheme 2). The scope with respect to the phenacyl phosphonium salts was then explored in the coupling with **2a**. It was found that the coupling took place smoothly over a wide range of phenacyl phosphonium salts bearing various electron-donating, -withdrawing, and halogen groups at the *para* position of the benzene ring, furnishing the corresponding indanone products in 38–90% yields (**3aa–3ia**). The carbocyclization also occurred smoothly when various *meta* substituents were attached to the phenyl ring of the phosphonium salts, although the C–H functionalization occurred at both *ortho* positions with low site selectivity (**3ja–3la**). Of note, an exception in selectivity was found for a *meta*-fluoro-substituted substrate, where C–H functionalization occurred exclusively at the more hindered position (**3ma**). In addition, substrates bearing an *ortho* OMe or F group (**3na**, **3oa**) were also applicable, indicative of tolerance of steric hindrance. Notably, disubstituted phosphonium salts have also been investigated, affording indanones in moderate to good yields (**3pa–3ra**, 47–71%). Moreover, the C–H activation system was smoothly extended to condensed rings, furnishing the desired products (**3sa**, **3ta**) in moderate to good yields. The scope of the activated olefin was then examined. The annulation reaction proceeded well with various acrylates, delivering the corres-

Table 1 Optimization studies[a]



Entry	Catalyst (mol%)	Temp (°C)	Yield[b] (%)
1[c]	$[RhCp^*(MeCN)_3](SbF_6)_2$ (8)	80	<5
2	$[RhCp^*(MeCN)_3](SbF_6)_2$ (8)	80	29
3	$[RhCp^*(MeCN)_3](SbF_6)_2$ (8)	100	57
4	$[RhCp^*(MeCN)_3](SbF_6)_2$ (8)	110	69
5	$[RhCp^*(MeCN)_3](SbF_6)_2$ (8)	120	73
6	$[RhCp^*Cl_2]_2$ (4)/$AgSbF_6$ (20)	100	76
7	$[RhCp^*Cl_2]_2$ (4)/$AgNTf_2$ (20)	100	42
8	$[RhCp^*Cl_2]_2$ (4)/AgOTf (20)	100	44
9	$[RhCp^*Cl_2]_2$ (2)/$AgSbF_6$ (10)	100	60
10	$[RhCp^*Cl_2]_2$ (1)/$AgSbF_6$ (5)	120	64
11	**$[RhCp^*Cl_2]_2$ (2)/$AgSbF_6$ (10)**	**120**	**80**

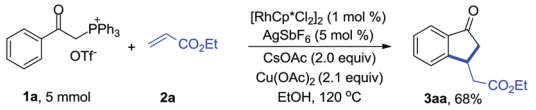
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst, and CsOAc (2.0 equiv.), $Cu(OAc)_2$ (2.1 equiv.) in ethanol (2 mL) at *T* °C for 18 h. [b] Yields of isolated products. [c] Without $Cu(OAc)_2$.



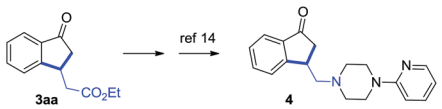
Scheme 2 Substrate scope of the synthesis of indanones. Reaction conditions: Phosphonium (0.2 mmol), olefin (0.4 mmol), $[RhCp^*Cl_2]_2$ (2 mol%), $AgSbF_6$ (10 mol%), CsOAc (2.0 equiv.), and $Cu(OAc)_2$ (2.1 equiv.) in ethanol (2 mL) at 120 °C for 18 h. [a]Yield using the isolated ylide as an arene substrate. [b]GC yield of $OPPh_3$ given in parentheses. [c]$[RhCp^*Cl_2]_2$ (4 mol%)/$AgSbF_6$ (20 mol%) were used. [d]$[RhCp^*(MeCN)_3](SbF_6)_2$ (8 mol%), CsOAc (4.0 equiv.) at 100 °C.

ponding indanones in good yields (**3ab–3ae**, 57–87%). Acrylonitrile also participated in the reaction and delivered the target product in good yield (**3af**, 75%). In addition, 3-chloropropiophenone also coupled smoothly as an enone surrogate under modified conditions (**3ag**, 56%).

To demonstrate the synthetic applicability of this protocol, a gram-scale synthesis of **3aa** was conducted, and product **3aa** was obtained in 68% yield under a reduced catalyst loading (1 mol%), illustrating that the reaction is scalable (eqn (1)). In addition, **3aa** is a direct precursor to a heterocycle that is known to exhibit biological activities (eqn (2)).[14]



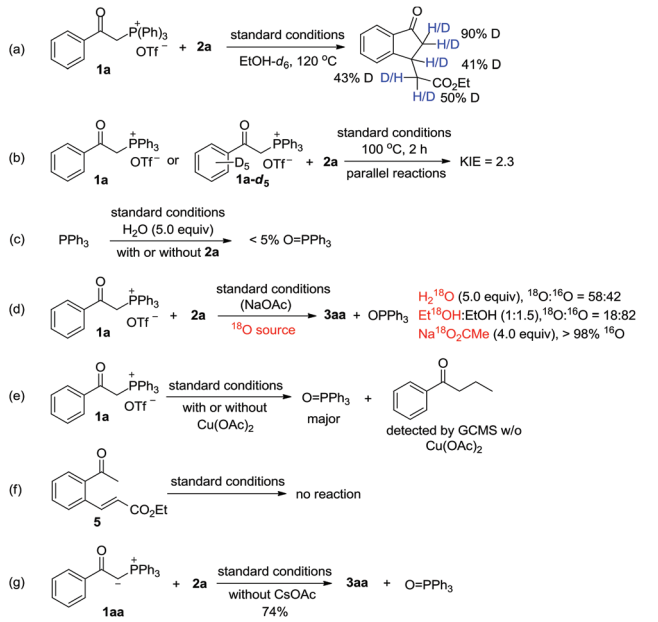
(1)



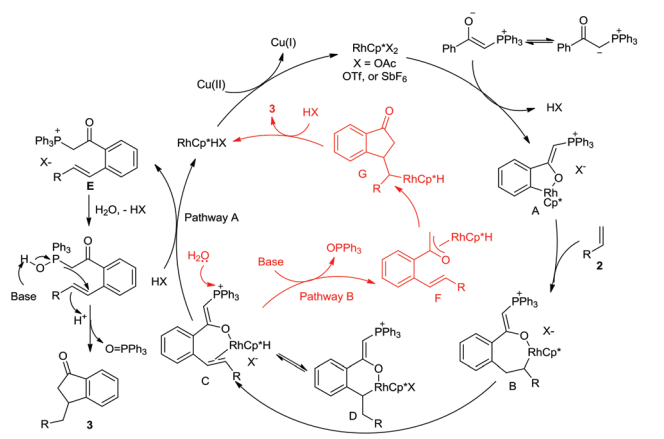
(2)

To shed light on the mechanism of indanone formation, a series of investigations have been carried out (Scheme 3). Catalysis in ethanol-d_6 afforded indanone with deuteration only at two methylene and the methine positions (Scheme 3a). Thus, the C(aryl)–H activation became irreversible in this coupling system. Control experiments also confirmed that the deuteration did not originate from post-coupling H/D exchange except for the more acidic ketone methylene. The scenario of C–H activation being a turnover-liming step was concluded from parallel KIE experiments (k_H/k_D = 2.3, Scheme 3b). To probe the likelihood of elimination and oxidation of PPh_3, another control experiment was performed (Scheme 3c). It turned out that PPh_3 failed to undergo oxidation under the standard conditions with or without **2a** or water, which suggests that O=PPh_3 instead of PPh_3 was eliminated. Moreover, labeling studies using ^{18}O-labeled water and ethanol all pointed to incorporation of ^{18}O into the O=PPh_3 (Scheme 3d). Reaction in the presence of EtOH/EtOH-^{18}O also led to ^{18}O incorporation,[15] but the extent of ^{18}O labeling is in discrepancy with the EtOH-^{18}O/EtOH ratio. This is accountable by the preferential attack by the adventitious water. In addition, subjection of substrate **1a** to reaction conditions without $Cu(OAc)_2$ led to the formation of O=PPh_3 as a major product (GC-MS and ^{31}P NMR) together with a homologated acetophenone (Scheme 3e), which is likely generated from simple acetophenone and ethanol by ethylation *via* a hydrogen-borrowing mechanism. In fact, dephosphination was observed even in the absence of the Rh catalyst. It was found that a sequence of complete dephosphination and cyclization is unlikely because no conversion was observed for acetophenone **5** under the standard conditions (Scheme 3f). Further control experiment disclosed that **1aa** demonstrated comparative yield (74%) without any base (Scheme 3g).

These mechanistic datas were extracted to construct plausible catalytic cycles for indanone synthesis (Scheme 4). O-Coordination of ylide of **1a** and cyclometalation affords a rhodacyclic intermediate **A**. Olefin coordination and migratory insertion into the Rh–Ar bond gives a Rh(III) alkyl **B**. Subsequent reversible *beta*-H elimination and reinsertion gives a hydride **C** (a direct precursor to a Rh(I) species) and an alkyl **D**, respectively. The reversibility accounts for the observed partial deuteration at the methylene and methine positions of the product. In pathway A (black), protonolysis of **E** is followed by nucleophilic attack by water (or also possibly by ethanol) to the phosphonium,[16] and subsequent Michael-cyclization produces the final annulated product together with $OPPh_3$, and this cyclization process might also be Rh-promoted. In an alternative pathway B (red), nucleophilic attack of water at the phosphonium affords an enolate **F**, and migratory insertion of the hydride or the alkyl group into the C=C bond generates an intermediate **G** (shown for alkyl insertion). Protonolysis of



Scheme 3 Mechanistic studies.



Scheme 4 Proposed mechanism for the formation of indanones.

intermediate **G** by HX or reductive elimination furnishes the final product with the regeneration of the catalyst upon oxidation. We have extensively attempted but failed in the synthesis of olefin **E**, so both pathways are possible.

Conclusions

In summary, we have developed an efficient protocol for the oxidative synthesis of indanones *via* a cascade of C–H alkenylation and carboannulation. The reaction proceeded with initial C–H activation assisted by an ylidic directing group, where the phosphonium moiety acted as a removable auxilary to activate the enolate. This arene substrate may provide a new avenue for the construction of carbocyclic scaffolds, which are currently underdeveloped. Further designs of other multifunctional DGs for activation of sp^2 and sp^3 C–H bonds are underway in our laboratories.

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