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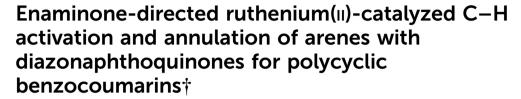


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Sudeshna Mondal, Chandan Kumar Giri D and Mahiuddin Baidya D*

The weakly coordinating enaminone functionality has been leveraged for a C-H bond activation strategy under ruthenium catalysis and employed in the regioselective annulative coupling of arenes with diazonaphthoquinones, offering polycyclic benzocoumarins in very high yields. The enaminone motif plays a dual role and the protocol operates through a Ru(II)/Ru(IV) catalytic pathway which is amenable to the diversification of various pharmacophore-coupled substrates.

Over the past two decades, transition-metal-catalyzed siteselective inert C-H bond activation and annulation strategies have revolutionized the field of synthetic chemistry, offering powerful tools for the construction of high-value carbocycles and heterocycles from simple molecular building blocks. In this context, Ru(II)-catalysis has emerged as a particularly compelling choice, garnering widespread attention for its operational simplicity, cost-effectiveness, and impressive efficiency facilitated by weak coordination.² However, the major advancements in the C-H bond activation guided annulation reactions of Ru(II)-catalysts have been accomplished with alkynes and alkenes with key applications in the synthesis of bioactive compounds.^{2,3} In contrast, the progress of such annulation reactions engaging carbene species that require the involvement of high-valent ruthenium(IV) intermediates is very limited.⁴ This is especially true when a weakly coordinating directing group is considered. An early example was disclosed by the Ackermann group wherein aromatic acids were coupled with sulfoxonium ylides, leading to the formation of functionalized isocoumarins in high yields (Scheme 1a).5 More recently, Samanta et al. demonstrated an amide-directed annulative coupling of azaheterocycles, such as indoles, with diazonaphthoquinones to afford diverse azacoumestans (Scheme 1b).⁶ However, in the latter case, the lactonization event was performed in a subsequent step in the presence of

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, Tamil Nadu, India. E-mail: mbaidya@iitm.ac.in

AcOH at 130 °C. To the best of our knowledge, these two examples represent the sole instances of Ru(II)-catalyzed annulation reactions of carbenes operating under the guidance of weakly coordinating directing groups.

Polycyclic benzocoumarins and derivatives thereof hold immense synthetic importance in light of their existence in natural products and pharmaceuticals.^{7,8} Consequently, the development of efficient synthetic protocols en route to these scaffolds is highly desirable.8 Herein, we report an annulative coupling of readily prepared aryl enaminones with diazonaphthoguinones as a concise route towards high-value polycyclic benzocoumarin motifs (Scheme 1c). Notably, the present work represents the first

(a) Ru(II)-catalyzed annulative coupling of aromatic acids with sulfoxonium ylides

(b) Ru(II)-catalyzed annulative coupling of heteroaromaic amides with diazonaphthoquinones

rk: Ru(II)-catalyzed annulative coupling of aryl enaminone with diazonaphthoguinone

$$\begin{array}{c} O \\ AI \\ \end{array}$$

OH Chryosomycin B Graphislactone A Alternario Defucogilvocarcin M

(d) Rh(III)-catalyzed annulative coupling of aryl enaminone with diazocarbony.

Scheme 1 The C-H activation and annulative coupling reactions with carbene species assisted by weak coordination

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application of the enaminone functionality as a directing group in ruthenium-catalyzed C-H activation strategies and the enaminone group serves as an intriguing one-carbon synthon to effect the desired annulation event in one pot. Of note, Zhu et al. first introduced the enaminone motif as a directing group under Rhcatalysis to access functionalized naphthalenes and the major developments towards C-H activation reactions involving the enaminone directing group have been confined to require expensive Rhcatalysis (Scheme 1d).9 Also, our work showcased the reactivity of enaminone-bearing metallacycles in combination with quinoid carbene species, which has not been previously studied.^{9,10}

We commenced our investigation following the model reaction between (E)-3-(dimethylamino)-1-(p-tolyl)prop-2-en-1-one (1a) with diazonaphthoquinone 2a (Table 1). When the mixture of 1a and 2a was treated with a catalytic amount of [Ru(p-cymene)Cl₂]₂ in the presence of AgSbF₆ (20 mol%), K₂CO₃ (0.5 equiv.) and 1-adamentanecarboxylic acid (1-AdCO₂H, 0.2 equiv.) in MeOH at 100 °C, we did not detect any product formation with the recovery of 1a (entry 1). However, a substantial amount of tetracyclic benzocoumarin 3a was formed in CF₃CH₂OH solvent (entry 1)

Optimization of the annulative coupling reactions^a Table 1

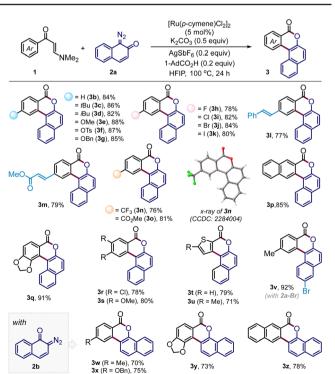
Entry	Deviation from standard conditions	$Yield^{b}$ (%)
1	MeOH/CF ₃ CH ₂ OH instead of HFIP	NR/72
2	None	94
3	Toluene/DCE/THF instead of HFIP	NR
4	Na ₂ CO ₃ /KOAc/K ₃ PO ₄ instead of K ₂ CO ₃	40/65/NR
5	AcOH/MesCO ₂ H instead of 1-AdCO ₂ H	47/56
6	At 80 °C	68
7	K_2CO_3 (1 equiv.)	60
8	Without K ₂ CO ₃	41
9	Without 1-AdCO ₂ H	43
10	Without AgSbF ₆	NR
11	Without Ru(π)-catalyst	NR
12	$Cp*Co(CO)I_2/[Cp*RhCl_2]_2$	NR/59
unsucce substra	too: (R = We	2a onditions (entry 2) 3a (6% yield)

^a Reaction conditions: 1a (0.20 mmol), 2a (1.5 equiv.), solvent (1 mL) for 24 h. b Isolated yields. NR: no reaction with the recovery of 1a.

and the reaction yield improved significantly in hexafluoroisopropanol (HFIP) medium, furnishing the desired product 3a in 94% isolated yield (entry 2). On the contrary, the reaction was unsuccessful in aprotic solvents such as toluene, DCE, and THF (entry 3). Further screening of other bases gave inferior results (entry 4). The change of acid additive from 1-AdCO₂H to AcOH or 2,4,6-trimethylbenzoic acid (MesCO₂H) also reduced the productivity (entry 5). The reaction at a lower temperature (80 °C) delivered 3a only in 68% yield (entry 6). The amount of K₂CO₃ turned out to be critical as the reaction with a higher loading of K_2CO_3 (1 equiv.) resulted in poor conversion (entry 7). Nonetheless, control experiments suggested that both K2CO3 and 1-AdCO₂H were crucial to achieving the high yield (entries 8 and 9) and the reaction completely shut down in the absence of AgSbF₆ and ruthenium(II) catalyst (entries 10 and 11). Interestingly, the reaction was unproductive with Cp*Co(III)-catalyst, while we have found moderate reactivity with the Rh(III)catalyst leading to 3a in 59% yield (entry 12). Furthermore, the enaminone motif is highly important for this C-H bond activation/annulation reaction, and our attempts to induce the coupling of 2a with other carbonyl compounds, which include aromatic ester, ketone, and chalcone derivatives, were so far unsuccessful, while the reaction with the aromatic acid gave the desired product 3a only in 6% yield (Table 1).6,9i

Having acquired the optimized conditions (Table 1, entry 2), we next investigated the substrate scope (Table 2). The protocol is quite general accommodating a wide range of arene-substituted enaminones. The reactions proceeded smoothly with substrates bearing electron-donating substituents such as alkyl (3b-d), methoxy (3e), tosyl (3f) and benzyloxy (3g) in the aryl ring to deliver the

Table 2 Exploration of substrate scope



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desired polycyclic benzocoumarins in very high yields (82-88%). The halogen functionalities such as fluoro (3h), chloro (3i), bromo (3i), and iodo (3k) were undisturbed under the reaction conditions and these halogen functionalities are useful synthetic handles for further functionalization. The presence of sensitive olefin functionalities also did not interfere with the annulation reaction, offering 31 and 3m in 77% and 79% yields, respectively. Satisfyingly, substrates with electron-withdrawing groups, which include trifluoromethyl and carboxylate ester, also effectively participated in this reaction, dispensing 3n and 3o in very high yields. The product 3n was crystalized and the presence of a polycyclic benzocoumarin framework was unambiguously confirmed through single crystal X-ray analysis. 2-Naphthyl-derived enaminone produced pentacyclic compound 3p in 85% yield where the reaction took place at the sterically less hindered site. On the other hand, annulation occurred at the more hindered site for the piperonyl-substituted enaminone to give 3q in 91% yield. This change in the regioselectivity can be attributed to the anchimeric assistance through the bridge oxygen. 11 For other enaminones having dichloro or dimethoxy substituents, the reactions proceeded at the less hindered site, forging 3r-3s with high efficiency. Heterocyclic substrates such as thiophene enaminones were also compatible to afford 3t and 3u in 79% and 71% yields, respectively. Variation in the diazonaphthoquinone coupling partner was also considered. The reaction with 6-bromo-1-diazonaphthalen-2(1H)-one (2a-Br) furnished the desired coumarin 3v in excellent yield. Gratifyingly, under the standard reaction conditions, the annulation reaction was also fruitful with diazonaphthoguinone 2b, a regioisomer of 2a, and we have successfully prepared polycyclic benzocoumarins 3w-3z in high yields (Table 2).

To expand the reaction scope further, enaminone embedded with various biologically relevant scaffolds was examined (Table 3). To our delight, enaminones coupled with commercial drugs, for instance, ibuprofen, gemfibrozil, clofibric acid, and naproxen, effortlessly afforded the desired products 4a-4d, in good to high yields. The standard conditions were also well suited for the enaminones derived from biorelevant motifs like menthol (4e), cholesterol (4f), and citronellol (4g). The strategy was equally productive with enaminone connected to valine amino acid where the polycyclic benzocoumarin 4h was obtained in 79% yield. Similarly, the pharmacophore-tethered annulated products 4i-4j were prepared in good yields by coupling diazonaphthoquione 2b (Table 3).

The synthetic utility was further showcased through postsynthetic manipulations (Scheme 2a). Satisfyingly, treatment of polycyclic benzocoumarins 3a-b with Lawesson's reagent furnished thiocoumarin analogs 5a-b in excellent yields. Product 3a was also transformed into polycyclic benzochromene 6 in 95% yield through NaBH₄ reduction (Scheme 2a, right).

To understand the nature of the C-H metallation step, deuterium incorporation experiments were performed. The reaction of enaminone 1a with 2a under standard reaction conditions for 12 h in the presence of deuterated acetic acid (10.0 equiv.) resulted in a significant amount of deuterium incorporation, indicating that the C-H ruthenation process is reversible (Scheme 2b). The competitive experiment with electron-rich and

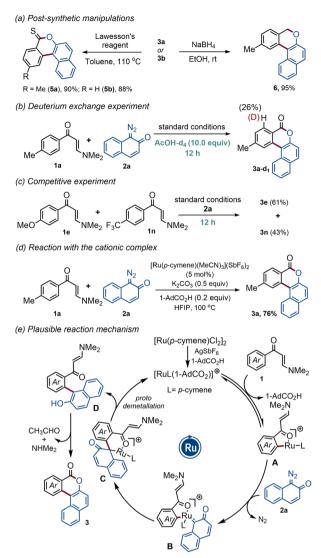
3 Synthesis pharmacophore tethered Table polycyclic benzocoumarins⁶

^a Reaction conditions: 5 (0.2 mmol), 2a or 2b (1.5 equiv.), [Ru(pcymene)Cl₂]₂ (5 mol%), 1-AdCO₂H (0.2 equiv.), AgSbF₆ (0.2 equiv.), K₂CO₃ (0.5 equiv.) and HFIP (1 mL) at 100 °C for 24 h.

electron-deficient enaminones gave a 1.4:1 mixture of benzocoumarins 3e and 3n, signifying that the C-H metallation step most likely follows a concerted metallation deprotonation (CMD) pathway (Scheme 2c). Employing the Ru(II)-cationic complex {[Ru(pcymene)(MeCN)3 (SbF6)2 instead of a combination of [Ru(pcymene)Cl₂|₂ dimer and AgSbF₆, we have isolated the annulated product 3a in 76% yield, suggesting the indispensable role of the cationic Ru(II)-complex in this transformation (Scheme 2d). Based on these results and literature precedents, a plausible reaction mechanism has been proposed in Scheme 2e. First, a cationic ruthenium complex is formed through the ligand exchange event and it then initiates the C-H activation reaction with enaminone 1 to give five-membered ruthenacycle A. Next, intermediate A reacts with diazonaphthoquinone 2a to generate the carbenoid intermediate B and the subsequent migratory insertion provides sixmembered intermediate C. Finally, protodemetallation followed by aromatization delivers D which cyclizes under the reaction conditions to produce the desired product 3.

In summary, we have exploited the versatile enaminone functionality as a directing group for C-H bond activation the reaction under ruthenium catalysis and successfully devised an annulation reaction with diazonaphthoguinones, offering biologically relevant polycyclic benzocoumarins in very high to excellent yields. The protocol is operationally simple, displays a broad substrate generality and functional group compatibility,

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Scheme 2 Post-synthetic manipulations, mechanistic study, and reaction mechanism.

and is also effective in the diversification of substrates bearing bioactive scaffolds and natural product motifs. The protocol leverages the dual role of the enaminone functionality and involves a ruthenium(II)/(IV) catalytic pathway involving quinoid carbene species.

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Conflicts of interest

There are no conflicts to declare.

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