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Letter

Rhodium(III)-Catalyzed Triple Aryl/Alkenyl C−H Bond Activation of Aryl Enaminones to Access Naphtho[1,8-*bc*]pyrans

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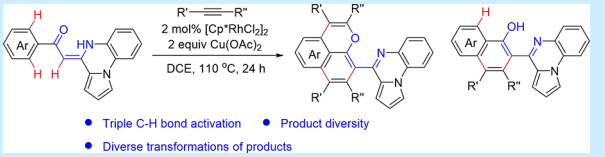
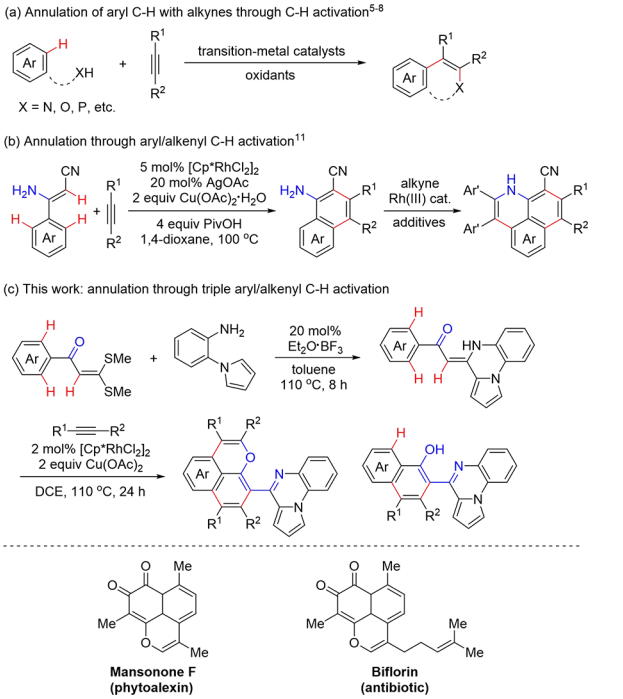
ABSTRACT: Rhodium(III)-catalyzed triple C−H bond activation of aryl enaminones was achieved to access naphtho[1,8-*bc*]pyrans by oxidative annulation to internal alkynes. 1-Naphthols might be formed as the only products, depending on the steric and/or electronic environment around the aroyl moiety of the aryl enaminones or the electronic impact from the alkynes. With propargyl alcohols as the masked terminal alkynes, aryl enaminones underwent rhodium(III)- or rhodium(I)-catalyzed internal alkenyl C−H bond activation to afford functionalized but-2-ene-1,4-diones. The resultant naphtho[1,8-*bc*]pyrans are highly fluorescent and can be further transformed by chlorination, bromination, and difluoromethylation, demonstrating potential practicability of the synthetic protocol.



Naphtho[1,8-*bc*]pyran is an important structural motif in some natural and synthetic functional molecules with biological[1] and optoelectronic properties,[2] such as Mansonone F and Biflorin.[1] Its construction has been seldom reported because such a process usually requires multistep prefunctionalization and deprotection, and inaccessible reactants.[3] C−H bond activation of arenes followed by annulation with alkynes has been considered as a useful route to arene-based complex organic compounds.[4,5] For example, Jiao et al. documented synthesis of *N*-heterocycles[6] through C−H functionalization of arenes with alkynes under transition-metal complex catalysis. Wang et al. reported the construction of *N*-alkylindoles[7a] and phosphindolium salts[7b] by means of rhodium(III) and copper(II) catalysis, and the Glorius group developed manganese(I)- and rhodium(III)-catalyzed annulation processes of arenes with functionalized alkynes[8a,b] (Scheme 1a). Miura, and Ackermann et al. developed a strategy to form naphtho[1,8-*bc*]pyrans by using 1-naphthols as the building blocks, and rhodium(III)[8c] and ruthenium(II)[8d] complexes as the catalysts. Double C−H activation was realized in palladium(II)-catalyzed oxidative cycloaromatization of biaryls with alkynes.[9] The Choudhury lab achieved rhodium(III)-catalyzed, NHC-driven cascade annulation of arenes with alkynes to access benzo[*ij*]imidazo[2,1,5-*de*]quinolizinium architectures *via* sequential double aryl C−H activation.[10] Wang and coauthors built 1-naphthylamines through rhodium(III)-catalyzed annulation of *β*-enaminonitriles with alkynes *via* double aryl/alkenyl C−H activation, and also furnished naphtho[1,8-*bc*]pyridines by modification of the reaction conditions (Scheme 1b).[11] By means of a similar catalytic system, Wang et al. also achieved cyanoacetyl-directed, Rh(III)-catalyzed cascade oxidative annulation of benzoylacetonitriles with internal alkynes, offering naphtho[1,8-*bc*]pyrans through a stepwise annulation *via* 1-naphthol intermediates.[12]

Scheme 1. Transition-Metal-Catalyzed Annulation of Arenes with Alkynes through C−H Activation



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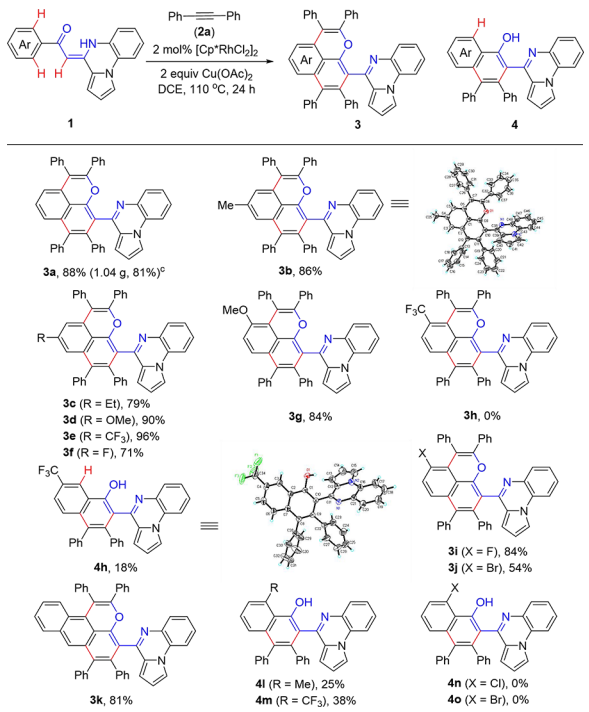
In a similar fashion, Tang et al. accomplished polyannulation of benzoylacetonitrile with internal diynes.[13]

During the ongoing investigation of transition-metal-catalyzed C−H functionalization of internal alkenes,[14] we found that a push−pull electronic effect of the substituents at two termini of an alkenyl C=C bond facilitates polarization of the alkenyl C=C moiety, and thus enhances the reactivity of an internal alkenyl C−H bond which is usually stubborn for direct C−C bond formation. We recently achieved rhodium(III)-catalyzed intermolecular cross-couplings of arenes with alkenes or allenes through aryl C−H activation.[15] Li[16a] and Lou[16b] et al. documented rhodium(III)-catalyzed annulations of α-benzoyl ketene dithioacetals to diazo compounds for the synthesis of naphthalenones and indanones, respectively, in which double aryl C−H/internal alkenyl C−H bond activation was involved. We thus reasonably envisioned that triple aryl C−H/internal alkenyl C−H bonds in polarized internal alkenes, that is, aryl enaminones, might be concurrently involved in a cascade annulation reaction with alkynes. Herein, we disclose a rhodium(III)-catalyzed cascade annulation strategy of aryl enaminones with internal alkynes through triple aryl C−H/internal alkenyl C−H bond activation to access multisubstituted naphtho[1,8-*bc*]pyrans (Scheme 1c).

Initially, the reaction of (*Z*)-1-phenyl-2-(pyrrolo[1,2-*a*]-quinoxalin-4(5*H*)-ylidene)ethan-1-one (**1a**), with 1,2-diphenylethyne (**2a**), was conducted to optimize the reaction conditions (see the Supporting Information (SI) for details). With 2 mol % $[Cp^*RhCl_2]_2$ as the catalyst and 2 equiv of $Cu(OAc)_2$ as the oxidant, the 1:2.5 molar ratio reaction of **1a** and **2a** in 1,2-dichloroethane (DCE) proceeded at 110 °C for 24 h under a nitrogen atmosphere to give the target double annulation product, i.e., naphtho[1,8-*bc*]pyran **3a**, in 88% isolated yield.

Under the optimal conditions, the scope of aryl enaminones **1** was explored (Table 1). Substituents such as methyl, ethyl, methoxy, trifluomethyl, and fluoro were tolerated at the 4-position of the α-aroyl moiety in **1**. In the same manner to access **3a**, the target products **3b**−**3f** were obtained in 71−96% yields. In the case of using 4-CF_3-functionalizd aryl enaminone **1e**, the highest yield (96%) was reached for **3e**, while the 4-F group diminished the yield of **3f** to 71%. 3-Methoxy-substituted aryl enaminone **1g** also efficiently reacted with **1a** to afford **3g** (84%). Unexpectedly, 3-CF_3-functionalizd aryl enaminone **1h** could not undergo double annulation with **2a** to form **3h** (0%), and only a monoannulation occurred to give 1-naphthol **4h** (18%) as the detectable product, which is presumably attributed to both the strong electron-withdrawing capability and steric effect of the 3-CF_3 group obviously diminished the reactivity of **1h**. However, 3-F- and 3-Br-functionalized aryl enaminones **1i** and **1j** reacted well with **2a**, affording **3i** (84%) and **3j** (54%), respectively. 2-Naphthyl enaminone **1k** reacted efficiently to produce **3k** (81%) under the same conditions. When a 2-methyl or 2-trifluoromethyl group is installed in the aryol moiety of **1**, the reaction could only give the monoannulation products **4** in low to moderate yields. Thus, 1-naphthol **4l** (R = 2-Me) and **4m** (R = 2-CF_3) were obtained in 25−38% yields without generation of compounds **3l** and **3m**. 2-Halogen-functionalized aryl enaminones **1n** (2-Cl) and **1o** (2-Br) did not react with **2a** to form a detectable amount of both the monoannulation products **4n** (0%) and **4o** (0%). It is noted that the molecular structures of **3** and **4** were further confirmed by the X-ray single crystallographic structural analysis of **3b** and **4h**, respectively (see the SI for details).

Table 1. Scope of Aryl Enaminones (1)[a,b]



[a]Conditions: **1** (0.3 mmol), **2a** (0.75 mmol), $[Cp^*RhCl_2]_2$ (0.006 mmol), $Cu(OAc)_2$ (0.6 mmol), DCE (3 mL), 110 °C, N_2, 24 h. [b]Isolated yields. [c]Yield for the gram-scale preparation.

Next, the protocol generality was investigated by carrying out the reaction of **1a** with diverse internal alkynes **2** (Table 2). Diarylalkynes bearing 4-methyl (**2b**), 4-fluoro (**2d**), or 4-chloro (**2e**) groups efficiently underwent the reaction to afford the target *O*-heterocycles **3p** (85%), **3r** (82%), and **3s** (83%), whereas 4-trifluoromethyl groups in alkyne **2c** led to a 57% yield of **3q**. 3-Methyl in 1,2-di(*m*-tolyl)ethyne (**2f**) also facilitated the formation of **3t** (87%), while both 3-Cl and 3-Br-functionalized diaryl alkynes (**2g** and **2h**) reacted with **1a** less efficiently to give **3u** (75%) and **3v** (73%), respectively. Notably, the 1:1 molar ratio reaction of **1a** and **2f** afforded **3t** (42%) as the only product, and no detectable amount of 1-naphthol **4t** was obtained, suggesting that the product diversity is independent of the reactant ratios. *ortho*-Substituents such as 2-methyl and 2-chloro exhibited a remarkable negative steric effect such that both 1,2-di(*o*-tolyl)ethyne (**2i**) and 1,2-di(*o*-chlorophenyl)ethyne (**2j**) exhibited no reactivity to **1a**. To our delight, 1,2-di(α-thienyl)ethyne (**2k**) reacted with **1a** to produce naphtho[1,8-*bc*]pyran **3w** (81%), establishing an *O*-, *N*-, and *S*-heterocyclic system. Unsymmetric alkyl aryl alkynes 1-phenylpropyne (**2l**) and 1-phenylbutyne (**2m**) could also be applied in the reaction, resulting in **3x** (87%) and **3y** (77%), respectively. $(CH_2)_3$-skipped 1,7-diarylhepta-1,6-diynes only behaved as monoalkynes, and their reactions with **1a** formed **3z** (31%) from diyne **2o** (Ar = Ph), **3z1** (30%) from diyne **2p** (Ar = 4-MeC_6H_4), and **3z2** (26%) from diyne **2q** (Ar = 4-ClC_6H_4), respectively. However, 1,4-diphenylbuta-1,3-diyne (**2r**) exhibited no reactivity to **1a** due to the possible steric effect. Internal dialkyl alkyne oct-4-yne (**2s**) showed a reactivity much lower than its diaryl alkyne analogs, giving **3z3** in 37% yield, and dimethyl acetylenedicarboxylate (**2t**)

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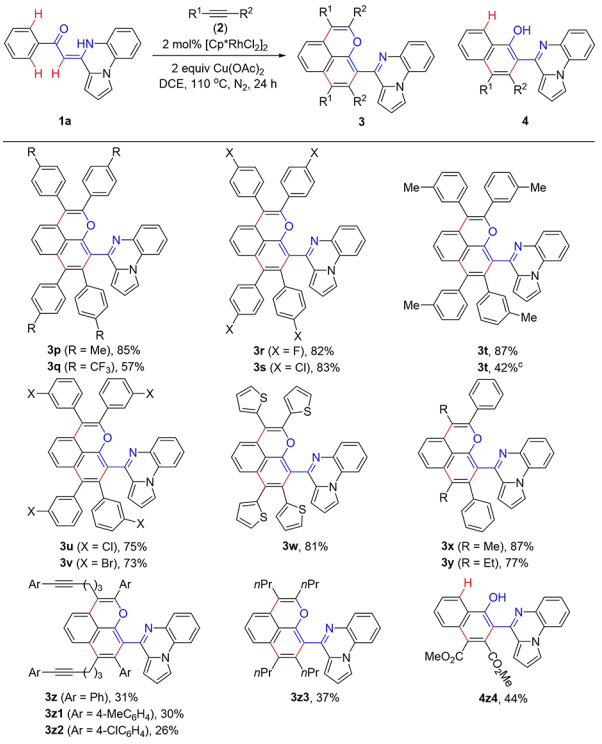
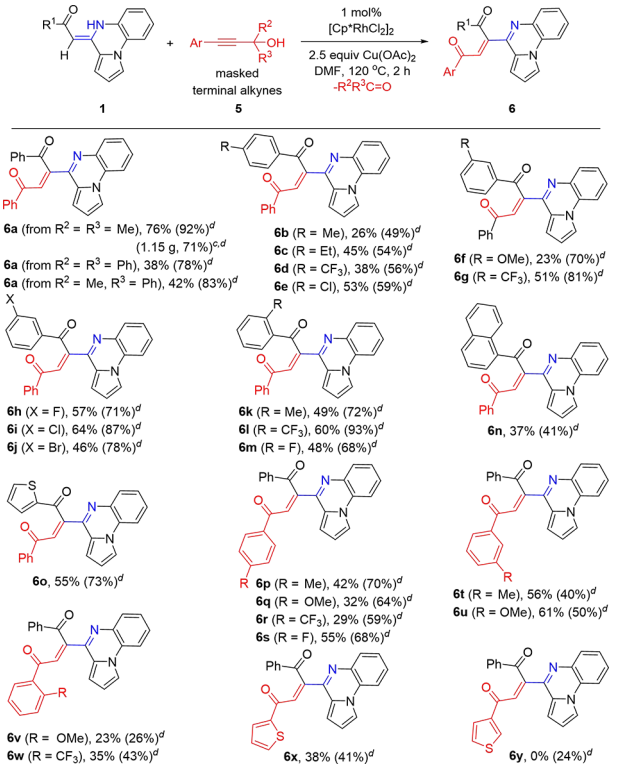
Table 2. Scope of Internal Alkynes (2)[a,b]



[a]Conditions: **1a** (0.3 mmol), **2** (0.75 mmol), $[Cp^*RhCl_2]_2$ (0.006 mmol), $Cu(OAc)_2$ (0.6 mmol), DCE (3 mL), 110 °C, N_2, 24 h. [b]Isolated yields. [c]Using **2f** (0.3 mmol).

Table 3. Reaction of Enaminones (1) with Masked Terminal Alkynes (5)[a,b]



[a]Conditions: **1** (0.3 mmol), **5** (0.9 mmol), $[Cp^*RhCl_2]_2$ (0.003 mmol), $Cu(OAc)_2$ (0.75 mmol), DMF (3 mL), 120 °C, N_2, 2 h. [b]Isolated yields. [c]Yield for the gram-scale preparation. [d]Using 1 mol % $[Rh(COD)Cl]_2$ as the catalyst.

afforded 1-naphthol **4z4** (44%) as the only product. It should be noted that terminal alkynes and 1-trimethylsilyl-based internal alkynes did not react with aryl enaminones **1** to form the target products **3** and **4** under the stated conditions.

As noted above, terminal alkynes are not suitable for the Rh(III)-catalyzed double annulation process, but internal alkyl aryl and diaryl alkynes behave efficiently for the desired annulation reaction, which encouraged us to further explore the surrogates of terminal alkynes to extend the present synthetic protocol generality. Unfortunately, a hydroxyl-functionalized terminal alkyne, that is, propargyl alcohol, could not interact with **1a** to undergo a similar multiple C−H functionalization process. Propargyl alcohols have usually been applied for alkyne formation and cyclization,[17] in which they act as terminal alkyne precursors.[18] It was found that functionalized propargyl alcohols of type **5**, a class of masked terminal alkynes, could be enabled to react with aryl enaminones **1** under the modified conditions by using DMF solvent (Table 3; see the SI for details). In the presence of 1 mol % $[Cp^*RhCl_2]_2$ catalyst at 120 °C, **5a** reacted with **1a** to give alkenyl C−H functionalization product **6a** in 76% yield, instead of the desired double annulation product of type **3**. In a similar fashion, 1,1,3-triphenylprop-2-yn-1-ol (**5a′**) and 2,4-diphenylbut-3-yn-2-ol (**5a″**) were treated with **1a** to afford the same target product **6a** (38−42%), revealing a negative steric effect from the $C(sp^3)$-phenyl group(s) (Table 3). Substituted phenyl-, 1-naphthyl-, and 1-thienyl-functionalized enaminones reacted with **5a** to form the desired products **6b−6x** in 23−64% yields. Substituents at the 2- or 4-position of the aryl moiety in 2-methyl-4-arylbut-3-yn-2-ols (**5**) affected the reaction efficiency of compounds **5** and **1a**, leading to products **6b−6s**, **6v**, and **6w** in 23−55% yields. 3-Methyl and 3-methoxy groups facilitated the reaction to give **6t** (56%) and **6u** (61%), respectively. *α*-Thienyl-based propargyl alcohol reacted with **1a** to afford **6x** (38%), but *β*-thienyl-propargyl alcohol exhibited no reactivity. It is noteworthy that $[Rh(COD)Cl]_2$ exhibited a much better catalytic activity than the $[Cp^*RhCl_2]_2$ catalyst for this type of transformations (see the SI for details). Notably, 1 mol % $[Rh(COD)Cl]_2$ promoted the reaction of **5a** and **1a** to form **6a** in an excellent yield (92%). The Rh(I) catalyst also facilitated the reactions of **5a′** and **5a″** with **1a**, leading to **6a** (78−83%). In other cases of using the $[Rh(COD)Cl]_2$ catalyst, 4-positioned methyl, ethyl, trifluoromethyl, and chloro in the aroyl moieties of **1** exhibited a negative impact on the formation of products **6b−6e** (49−59%). 3-Methoxy, trifluoromethyl, and halogens (F, Cl, and Br) showed a diminished substituent effect on the yields of **6f−6j** (70−87%). The reaction of 2-methyl and 2-fluoro-aryl enaminones **1** with **5a** also proceeded smoothly to give the target products **6k** (72%) and **6m** (68%), respectively. Moreover, 2-trifluoromethyl facilitated the reaction to generate **6l** in an excellent yield (93%). 1-Naphthyl exhibited a negative steric effect on the yield of **6n** (41%). *α*-Thienyl enaminone efficiently reacted with **5a** to form **6o** (73%). However, alkyl enaminones could not undergo the desired reaction to afford the same type of products. Substituted 2-methyl-4-arylbut-3-yn-2-ols showed various reactivities to **1a**, and their reactions resulted in **6p−6w** (26−70%) with the negative *ortho-* > *meta-* > *para*-substituent effect. Notably, 2-methyl-4-(2-thienyl)but-3-yn-2-ol and 2-methyl-4-(3-thienyl)but-3-yn-2-ol reacted with **1a** less efficiently, affording the target products **6x** (41%) and

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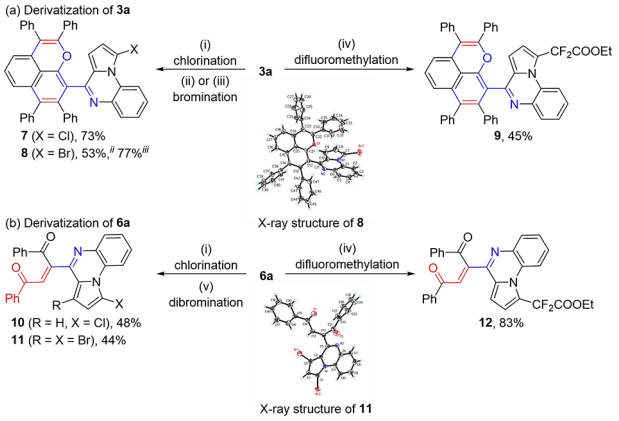
6y (24%), respectively. The molecular structures of compounds **6** were further confirmed by the X-ray crystal single structural analysis of the corresponding brominated derivative of **6a** (Scheme 2).

Scheme 2. Derivatization of Compounds 3a and 6a

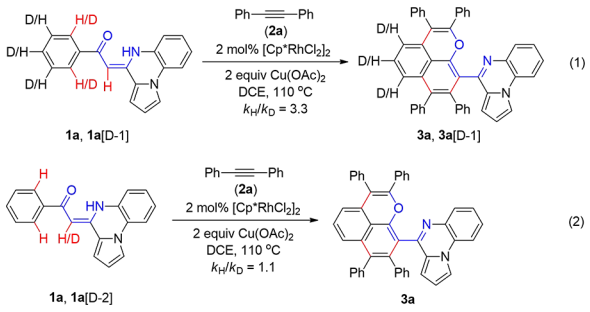


It is noted that, with replacement of the tricyclic *N*-heterocyclic functionality at one terminus of the alkenyl C=C bond in aryl enaminones **1** with NHPh/SMe or NHPh/Me groups, the resultant aryl enaminones could not interact with **2** or **5** to form the corresponding naphtho[1,8-*bc*]pyrans, 1-naphthols, or products of type **6** (see the SI for details). 1-Naphthol **4h** was treated with 1,2-diphenylethyne (**2a**) under the optimal conditions as shown in Table 1, but the reaction gave no detectable amount of the desired **3h**, which suggests that free 1-naphthols of type **4** may not be the necessary intermediates to enable the studied double annulation process.

The scale-up preparation of naphtho[1,8-*bc*]pyran and butenyl diketone derivatives was exemplified by the gram-scale synthesis of **3a** (81%) and **6a** (71%) (Tables 1 and 3). Naphtho[1,8-*bc*]pyran **3a** was subject to the chlorination,[19] bromination,[19,20] and difluoromethylation[21] conditions to form compounds **7** (73%), **8** (53−77%), and **9** (45%), respectively (Scheme 2a). In a similar fashion, compound **6a** was transformed to chlorinated **10** (48%), dibrominated **11** (44%), and difluoromethylated **12** (83%) (Scheme 2b). These results have demonstrated the potential applicability of the present synthetic protocol. The mono- and dibromination products **8** and **11** were structurally identified by the X-ray single crystal structural analysis. It is noteworthy that compounds **3** are structurally featured with two *O*- and *N*-tricycle functionalities, which are bestowed with specific fluorescence (see the SI).

In order to probe into the C−H activation mechanism, kinetic isotope effect (KIE) experiments were performed by means of the reactions of **1a** as well as its deuterated forms **1a**[D-1] and **1a**[D-2][14b] with **2a** under the standard conditions, respectively (see the SI). Primary (k_H/k_D = 3.3) and a secondary (k_H/k_D = 1.1) hydrogen isotope effects were observed, suggesting that cleavage of the aryl C−H bonds instead of the alkenyl C−H bond in the aryl enaminones **1** might be involved in the rate-limiting step of the overall catalytic cycle (eqs 1 and 2). Plausible mechanisms are proposed for the Rh(III)- and Rh(I)-catalyzed processes in the SI file.

In summary, Rh(III)-catalyzed triple C−H activation of aryl enaminones was efficiently achieved to access naphtho[1,8-*bc*]pyrans by oxidative annulation with internal alkynes. The target products can be diversely transformed, and some of them have exhibited promising fluorescence properties. The present protocol provides a concise route to multisubstituted naphtho[1,8-*bc*]pyran derivatives.



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02758.

Experimental materials and procedures, analytical data and NMR spectra of compounds, X-ray crystallographic analysis for compounds **3b**, **4h**, **8**, and **11** (PDF)

Accession Codes

CCDC 2094870, 2107834, and 2154087−2154088 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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