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(5) Supporting Information

ABSTRACT: Active pyrylium intermediates are in situ generated by a Rh-catalyzed vinylic C–H annulation reaction between exocyclic α , β -enones and alkynes, which undergo a base-promoted rearrangement via 1,5-H shift to form 1*H*-benzo[*f*]chromene derivatives.

(Benzo)pyrylium salts, a unique class of cationic aromatic compounds with nonuniform electron density distribution property, have drawn much attention since the 1950s due to their high reactivity toward various nucleophiles.¹ Their recent renaissance focuses on the chemistry of zwitterionic metalpyrylium intermediates, which are mostly in situ generated by transition-metal-catalyzed intramolecular cyclizations of enynals and undergo successive Diels–Alder, nucleophilic addition and hydrogenation reactions for the construction of synthetically useful compounds.² New methods to more easily generate active pyrylium species from simple, readily available reagents, as well as new transformations, are still in high demand.

Over the past decades, transition-metal-catalyzed chelationdirected C-H activation/annulation reactions have emerged as a straightforward and efficient strategy to construct carbocycles and N-heterocycles.^{3,4} In this context, pyridine and pyridinium derivatives are synthesized by the one-step [4 + 2] vinylic C–H *N*-annulation of $\alpha_{\beta}\beta$ -unsaturated imines or oximes with alkynes under the catalysis of [Rh] and [Ru].⁵ Nevertheless, the corresponding $\alpha_{,\beta}$ -unsaturated ketones ($\alpha_{,\beta}$ -enones) could not be annulated with alkynes in a similar manner to give the corresponding O-heterocycles, i.e. pyrylium salts, but mostly underwent vinylic C-H additions to alkynes.⁶ Recently, we showcased the first example of an intermolecular [4 + 2] vinylic C-H O-annulation of acyclic α -aryl enones with alkynes to synthesize multisubstituted furans (Scheme 1, eq 1).⁷ We recognized that this is a very convenient method to generate pyrylium salts and were interested in harnessing this highly active species for novel transformation into other useful organic skeletons. Our attention then turned to possible vinylic C-H activation/annulation of more challenging exocyclic $\alpha_{\mu}\beta$ -enones 1 with alkynes. Besides easy side reactions such as polymerization⁸ and conjugate additions⁹ under oxidative conditions, exocyclic α_{β} -enones might also suffer from weak and instable cyclometalation for effective C-H bond activation due to the twisted conformation caused by the steric hindrance of the substituents at both the α_{β} -positions.^{4b,6} We report herein a tandem rhodium and copper mediated reaction of exocyclic α,β -enones with alkynes to deliver 1*H*-benzo[*f*]chromene derivatives (Scheme 1, eq 2). The mechanism study verified



Base

1.5-H shift

Rh(III)

[4+2]

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that the reaction combines the expected Rh-catalyzed [4 + 2]*O*-annulation to generate the active pyrylium intermediates and an unprecedented rearrangement via a 1,5-H shift.

The model reaction of (E)-1-(p-methylbenzylidene)-3,4dihydronaphthalen-2(1H)-one 1a and diphenylacetylene 2a under the optimal reaction conditions for acyclic α_{β} -enones⁷ gave 1H-benzo[f]chromene **3a** in less than 5% yield (Table 1, entry 1). The structure of 3a was unambiguously confirmed by NMR spectra, HRMS spectrometry, and X-ray diffraction analysis. The reaction is characteristic of aromatization of the tetrahydronaphthalene ring and conversion of the vinylic sp² carbon into a benzylic sp³ carbon. 1H-Benzo[f]chromene derivatives represent an important class of polyheterocyclic compounds that are frequently found in many pharmaceutical and natural products.¹⁰ Systematic optimization of the reaction conditions was then conducted, and 3a was obtained in a highest yield of 75% in the presence of $[Cp*Rh(CH_3CN)_3]$ -(SbF₆)₂ (10 mol %), Cu(OAc)₂·H₂O (2.0 equiv), and Cu₂O (0.5 equiv) in DCM (1 mL) at 100 °C for 24 h in air (Table 1, entry 2).¹¹ Control experiments showed that the reaction did not occur without the rhodium catalyst, yet gave a trace amount of **3a** in the absence of $Cu(OAc)_2 \cdot H_2O$ (Table 1, entries 3–4). The combination of [Cp*RhCl₂]₂ and AgSbF₆ only gave a

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Table 1. Optimization of the Reaction Conditions^a

p-tol H 1a	$\begin{array}{c} \begin{array}{c} Ph \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	(CCDC: 1510670)
entry	variation from optimal conditions	yield (%) ^b
1 ^c	[Cp*RhCl ₂] ₂ /AgSbF ₆	<5%
2	none	75
3	without [Rh]	n.d.
4	no Cu(OAc) ₂ ·H ₂ O	trace
5 ^d	[Cp*RhCl ₂] ₂ /AgSbF ₆	55
6 ^e	$[(p-cymene)Ru(CH_3CN)_3](SbF_6)_2$	45
7^d	[Cp*Ir] or [Cp*Co]/AgSbF ₆	n.d.
8	without Cu ₂ O	57
9	CuO ^f instead of Cu ₂ O	59
10	NaOAc ^f instead of Cu ₂ O	48
11	Et ₃ N ^f instead of Cu ₂ O	n.d.
12	extra NaOAc ^f	30
13	DCE as solvent	49
14	PhCl as solvent	13

"Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), $[Cp*Rh-(CH_3CN)_3](SbF_6)_2$ (10 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.4 mmol), and Cu_2O (0.1 mmol) in DCM (1 mL) in air at 100 °C for 24 h. ^bIsolated yield. ^c $[Cp*RhCl_2]_2/AgSbF_6$ (5/20 mol %), without Cu_2O , DME as the solvent at 90 °C for 24 h (see ref 7). ^d[M]/[Ag]: $[Cp*RhCl_2]_2$ (5 mol %), $[Cp*IrCl_2]_2$ (5 mol %) or $[Cp*Co(CO)I_2]$ (10 mol %)/AgSbF₆ (20 mol %). ^e[Ru] complex (10 mol %). ^f0.2 mmol. n.d. = no detected. *p*-tol = *p*-methylphenyl.

moderate yield (Table 1, entry 5). For other catalysts, [Ru] gave a lower yield, while [Ir] and [Co] were ineffective (Table 1, entries 6–7). Cu₂O played a crucial role to achieve a high yield, while both CuO and NaOAc gave lowered yields and Et₃N ceased the reaction (Table 1, entries 8–11). The addition of an extra equivalent of NaOAc resulted in a complicated mixture, and **3a** was isolated in 30% yield (Table 1, entry 12). It is also interesting that other halogenated solvents such as DCE and PhCl were significantly inferior to DCM (Table 1, entries 13–14).

With the optimal conditions in hand, the generality of this reaction was investigated (Scheme 2). A variety of (E)-1-(arylmethylene)-3,4-dihydronaphthalen-2(1H)-ones containing both electron-donating groups, such as methoxyl, phenyl, and vinyl, and electron-withdrawing groups, including choloro, bromo, iodo, and trifluoromethyl, on different positions of the phenyl ring could smoothly react with 2a to yield the desired multisubstituted 1*H*-benzo[f]chromenes 3b-3m in moderate to good yields. The strong steric hindrance effect of the 3,4,5trimethoxyphenyl group (TMP) in 11 rendered the reaction sluggish. 31 was obtained in 57% yield after 48 h with a small amount of 11 recovered. The aryl group in 1 could be extended to bulky naphthalen-2-yl 1n and heteroaryls including 2-furyl, 2-thienyl, and 3-thienyl 10-1q, affording the corresponding (naphthalen-2-yl)- and heroaryl-containing 1H-benzo[f]chromene derivatives 3n-3q in moderate yields. In addition, enones 1r and 1s bearing functional groups such as methoxyl and bromo on the 3,4-dihydronaphthalen-2(1H)-one core worked well with 2a to yield 3r and 3s in good yields. The scope of alkynes was also examined. A series of symmetrical alkynes bearing common functional groups were successfully annulated with 1b to provide the corresponding 3t-3v in satisfactory yields. It is noteworthy that complete regioselectiv-





^{*a*}Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), [Cp*Rh-(CH₃CN)₃](SbF₆)₂ (10 mol %), Cu(OAc)₂·H₂O (0.4 mmol), and Cu₂O (0.1 mmol) in DCM (1 mL) in air at 100 °C for the indicated time. ^{*b*}Isolated yield. ^{*c*}1 mmol scale. TMP = 3,4,5-trimethoxyphenyl.

ities were achieved when unsymmetrical phenyl alkyl alkynes such as 1-phenylpropyne and 4-phenylbut-3-yn-1-yl pivalate were employed, exclusively giving 3w-3y with the phenyl ring installed adjacent to the oxygen atom of the 1H-benzo[f]-chromene core.

To gain insight into the reaction mechanism, the reaction of D_{6} -1b with 2a was conducted under the standard conditions (Scheme 3, eq 1). The ¹H NMR analysis of the product 3b

Scheme 3. Experiments to Verify Pyrylium Intermediate via Vinylic C–H Bond Cleavage



"Reaction conditions: 4 (0.2 mmol), $[Cp*Rh(CH_3CN)_3](SbF_6)_2$ (10 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.4 mmol), and Cu_2O (0.1 mmol) in DCM.

showed no benzylic deuterium, indicating that this reaction underwent a vinylic $C(sp^2)$ -H bond cleavage. The H/D exchange experiment between **1b** and D₂O showed that the initial vinylic C-H bond cleavage was irreversible. The kinetic isotope effect (KIE) was calculated to be 1.5 from the reaction of a mixture of **1b** and D₆-**1b** with **2a** (see the Supporting Information, SI), suggesting that the vinylic C-H bond cleavage was not involved in the turnover-limiting step. An analogue of the pyrylium intermediate **4** was then synthesized by a traditional method. **4** successfully converted into **5** in 32% yield under the optimal conditions (Scheme 3, eq 2), confirming the pyrylium species generated by the Rh-catalyzed direct [4 + 2] *O*-annulation of exocyclic α,β -enones with alkynes as the key intermediate.

By using 0.5 equiv of Cu₂O alone, **5** was obtained in 30% yield.¹² Surprisingly, Cu(OAc)₂·H₂O was ineffective. NaOAc and Et₃N were more beneficial for this transformation to offer **5** in high yields than Cu₂O (Scheme 3, eq 2). These control experiments for the conversion of **4** to **5** suggested that this process is probably promoted by a base. However, it is worth noting that the overall performances of NaOAc and Et₃N for the tandem reaction of exocyclic α,β -enones with alkynes were inferior (Table 1, entries 10–11), implying that the [4 + 2] annulation process is less tolerant of a basic environment. Therefore, the role of Cu₂O could possibly be to provide a compatible environment for the two inconsistent processes.

To clarify the subsequent process, it is critical to know the source of the benzylic hydrogen in **3b**. H/D exchange was not observed in the reaction of either **1b** with **2a** or product **3b** itself in the presence of 10 equiv of D_2O (see SI), suggesting the benzylic hydrogen was transferred intramolecularly. The reaction between C3- D_2 -**1b** and **2a** yielded **3b** without any benzylic deuterium (Scheme 4, eq 1), which indicated that it



was the C4–H in **1b** that was transferred to the benzylic position in **3b**. To confirm this result, C3,4- D_4 -**1b** (containing 60% C4-D) was reacted with **2a** under the standard conditions. As expected, 46% of benzyl-D was detected in **3b** (Scheme 4, eq 2).

On the basis of the preliminary experimental results and our previous research,^{3,5,7} a plausible mechanism was depicted in Scheme 5. The reaction started with an irreversible vinylic C– H bond activation of 1 by [Rh(III)] to give the five-membered rhodacycle **A**, followed by the alkyne insertion to generate the seven-membered rhodacycle **B**. Direct reductive elimination delivered the key pyrylium intermediate **C** and released the [Rh(II)] species, which was oxidized by [Cu(II)] to regenerate the [Rh(III)] catalyst. The highly active **C** was then deprotonated at the benzylic position of the pyrylium ring by a base (not identified), giving a conjugated triene **D**, which was further aromatized into the more stable 1*H*-benzo[*f*]chromene **3** through 1,5-H shift.

The 1*H*-benzo[*f*]chromene products **3** could be easily oxidized into naphthoflavylium salts **6** by bromine (Scheme 6). Further site selective photooxidation reaction in air at room temperature provided π -extended phenanthro[9,10,1-*def*]-





Scheme 6. Conversion of 1H-Benzo[f]chromene 3 into Cationic O-Containing PHAs



^{*a*}Reaction conditions: 3 (0.2 mmol), Br_2 (0.22 mmol) in AcOH at 100 °C for 1 h. ^{*b*}Reaction conditions: 6 (0.05 mmol) and HBF₄ (0.05 mmol) in AcOH under irradiation (254 nm) at rt in air for 24 h.

chromen-3-iums salts 7 in almost quantitative yields. These cationic O-containing polycyclic heteroaromatics (PHAs) may find applications in photochemistry, spintronics, and materials science.¹³

In summary, we have developed a Rh-catalyzed C–H annulation reaction between exocyclic α , β -enones and alkynes to provide 1*H*-benzo[*f*]chromene derivatives. The preliminary mechanism studies confirmed the active pyrylium salts as the key intermediates, which underwent the subsequent rearrangement via a 1,5-hydrogen shift. The 1*H*-benzo[*f*]chromene products could be easily converted into *O*-containing PHAs for further investigation as functional materials.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b04042.

Experimental procedures, characterization data, and ¹H, ¹³C, and ¹⁹F NMR spectra of products (PDF)

Accession Codes

CCDC 1510670 and 1558651 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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