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Rhodium(III)-Catalyzed, C–H Activated Annulation to Form Isocoumarins and α-Pyrones using the O–N Bond as an Internal Oxidant

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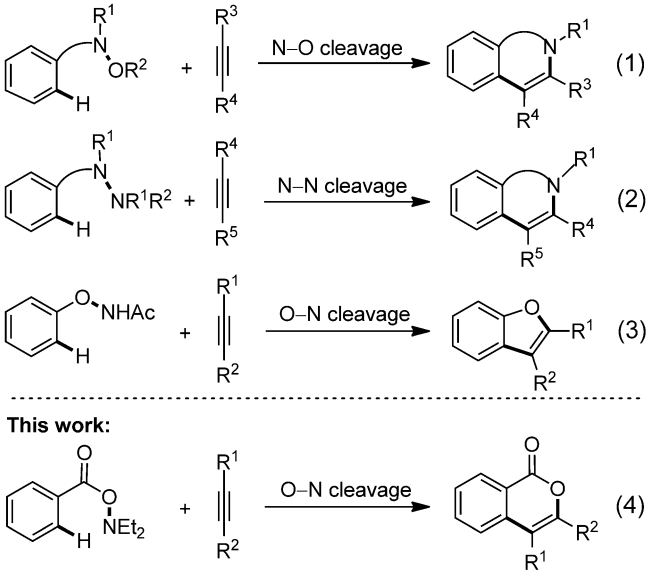
Abstract: A mild, efficient and regioselective C–H activation-based intermolecular redox-neutral annulation of *O*-benzoylhydroxylamines and internal alkynes has been achieved. The protocol employs an O–N bond as the internal oxidant and leads to isocoumarins and α-pyrones.

Keywords: annulation; C–H activation; O-heterocycles; O–N bond cleavage; redox neutral reaction; rhodium

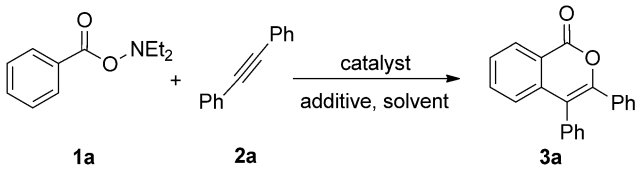
In recent years, transition metal-catalyzed chelation-assisted annulative coupling reactions between aromatic or alkenyl C–H bonds and C≡C or C=X (X = C or N) bonds have attracted great interest as methods to construct cyclic compounds.[1] Such transformations generally require transition metal catalysts, stoichiometric oxidants and severe conditions above 100 °C. More recently, the redox-neutral C–H activation annulations[2] catalyzed by Pd,[3] Rh,[4] and Ru[5] have emerged as a new strategy, which generally employed an N–O bond as the internal oxidant to construct N-heterocycles [Scheme 1, Eq. (1)]. In 2013, the usage of N–N bond cleavage for redox process was reported to construct N-heterocycles such as indoles[6] and quinolones[7] [Scheme 1, Eq. (2)]. Nevertheless, the O–N bond as the internal oxidant was reported to form benzofurans [Scheme 1, Eq. (3)].[8] As the facial route to construct very useful O-heterocycles, new reactions using the O–N bond as the internal oxidant to realize the redox-neutral annulation are in high demand.

Isocoumarin and α-pyrone are important structural motifs of various bioactive natural products.[9] Because of their diverse biological activities including antitumor, anti-inflammatory, antiallergic, antimicrobial, antidiabetic and immunomodulatory activities,[10] isocoumarin and α-pyrone motifs have been widely used as the scaffolds to construct pharmaceutical drugs.[11] However, their synthesis frequently requires specific pre-activated C–X or C–M reagents as the substrates.[12] Recently, Rh,[13] Ru[14] and Ir[15] catalyzed oxidative annulations of arylcarboxylic acids and alkynes have been developed, which require stoichiometric external oxidants and high temperatures above 100 °C. Herein, we report a mild and efficient rhodium(III)-catalyzed redox-neutral C–H activation annulation for the synthesis of isocoumarins and α-pyrones by employing an O–N bond as the internal oxidant [Scheme 1, Eq. (4)].[16]



Scheme 1. Redox-neutral C–H activation annulations with different internal oxidants.

Table 1. Optimization of the conditions for the reaction of **1a** and **2a**.[a]



1a **2a** **3a**

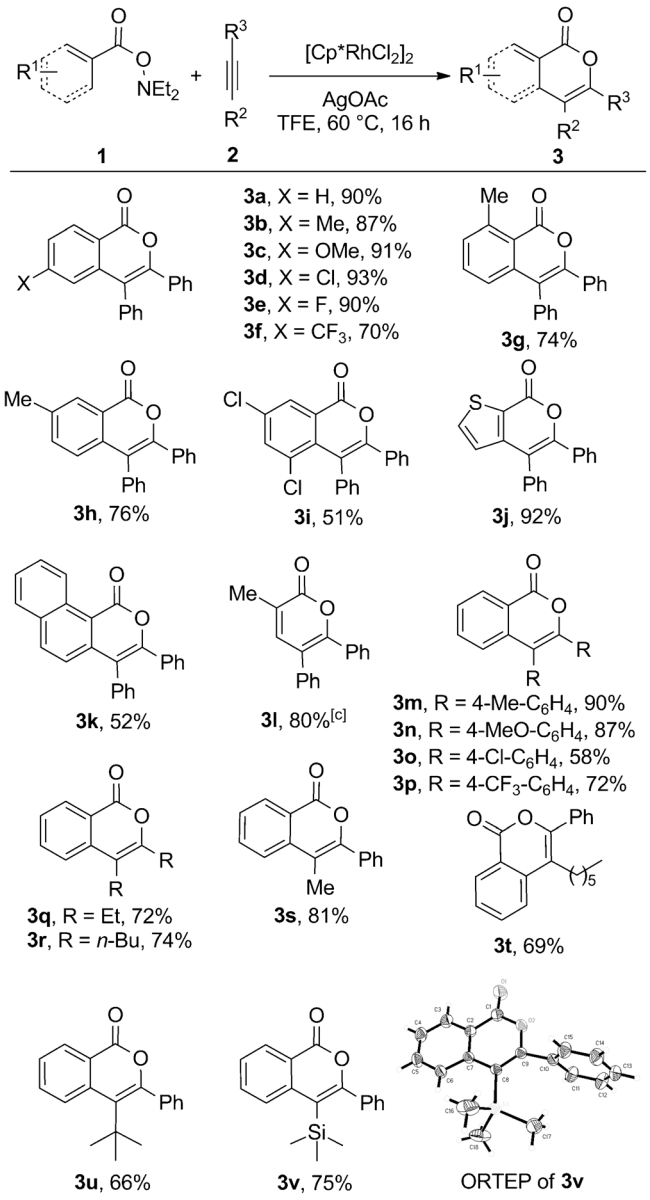
Entry	Catalyst	Additive	Solvent	Yield [%][b]
1[c]	Cp*Rh(OAc)$_2$	CsOAc	MeOH	10
2[c]	Pd(OAc)$_2$	CsOAc	MeOH	0
3[d]	[RuCl$_2$(*p*-cymene)]$_2$	CsOAc	MeOH	trace
4	[Cp*RhCl$_2$]$_2$	CsOAc	MeOH	15
5	[Cp*RhCl$_2$]$_2$	NaOAc	MeOH	13
6	[Cp*RhCl$_2$]$_2$	KOAc	MeOH	13
7	[Cp*RhCl$_2$]$_2$	AgOAc	MeOH	26
8	[Cp*RhCl$_2$]$_2$	AgOAc	dioxane	0
9	[Cp*RhCl$_2$]$_2$	AgOAc	THF	0
10	[Cp*RhCl$_2$]$_2$	AgOAc	DME	9
11	[Cp*RhCl$_2$]$_2$	AgOAc	EtOH	9
12	[Cp*RhCl$_2$]$_2$	AgOAc	CH_3CN	38
13	[Cp*RhCl$_2$]$_2$	AgOAc	TFE	61
14[e]	**[Cp*RhCl$_2$]$_2$**	**AgOAc**	**TFE**	**94**
15[e,f]	[Cp*RhCl$_2$]$_2$	AgOAc	TFE	50
16[e,g]	[Cp*RhCl$_2$]$_2$	AgOAc	TFE	60
17[e,g,h]	[Cp*RhCl$_2$]$_2$	AgOAc	TFE	82
18[e,h,i]	[Cp*RhCl$_2$]$_2$	AgOAc	TFE	56
19[g,h,j]	[Cp*RhCl$_2$]$_2$	AgOAc	TFE	72
20[k]	[Cp*RhCl$_2$]$_2$	AgOAc	TFE	85 (81)
21[l]	[Cp*RhCl$_2$]$_2$	AgOAc	TFE	68 (66)

[a] *Reaction conditions:* **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.01 mmol), additive (0.06 mmol), solvent (2 mL), at 60 °C, 16 h, under N_2.
[b] Determined by ^{1}H NMR analysis using phenyltrimethylsilane as the internal standard; yields in the parentheses are the isolated yields.
[c] 20 h.
[d] 12 h.
[e] **1a** (0.4 mmol) and **2a** (0.2 mmol) were used.
[f] At 40 °C.
[g] 0.005 mmol catalyst and 0.03 mmol additive were used.
[h] 24 h.
[i] 0.002 mmol catalyst and 0.012 mmol additive were used.
[j] **1a** (0.3 mmol) and **2a** (0.2 mmol) were used.
[k] **1a** (20 mmol), **2a** (10 mmol), catalyst (0.5 mmol) and additive (3 mmol) were used, 24 h.
[l] **1a** (15 mmol), **2a** (10 mmol), catalyst (0.25 mmol) and additive (1.5 mmol) were used, 24 h.

Initially, the cyclization of *N*,*N*-diethyl-*O*-benzoylhydroxylamine (**1a**) and 1,2-diphenylacetylene (**2a**) was carried out as a model reaction to optimize the reaction conditions (Table 1). Gratifyingly, the isocoumarin product **3a** (10% yield) was obtained in MeOH after 20 h at 60 °C with 5 mol% Cp*Rh(OAc)$_2$ as the catalyst and 30 mol% CsOAc as the additive (entry 1). When [RuCl$_2$(*p*-cymene)]$_2$ and Pd(OAc)$_2$ were applied as the catalysts, the reaction of **1a** and **2a** could not proceed to afford **3a** (entries 2 and 3). The attempt with [Cp*RhCl$_2$]$_2$ as the catalyst gave increased 15% yield (entry 4), and the change of the additive to AgOAc afforded a further enhanced 26% yield, although NaOAc, KOAc affected the reaction negatively (entries 5–7). The investigation of the solvent effect showed that CH_3CN could promote the reaction of **1a** and **2a** to 36% yield, while other solvents such as dioxane, THF, DME, ethanol were ineffective for the annulation (entries 8–12). When TFE was used as the solvent, a remarkably improved 61% yield was obtained, which illustrates that the solvent effect is crucial (entry 13). Moreover, the change of the ratio of **1a** to **2a** from 1:2 to 2:1 produced **3a** in an excellent 94% yield (entry 14). If the temperature was lowered to 40 °C, only a 50% yield was observed in the reaction of **1a** and **2a** (entry 15). Moreover, decreasing the catalyst loading or the ratio of **1a** to **2a** could lead to the decreased yields (entries 16–19). Finally, we were pleased to find that good yields could also be obtained in the scaled-up experiments (entries 20 and 21).

Under the optimized conditions, the reactions of a series of *O*-benzoylhydroxylamine **1** with various internal alkynes **2** (**1**:**2** = 2:1) were carried out at 60 °C in TFE with 5 mol% [Cp*RhCl$_2$]$_2$ as the catalyst and 30 mol% AgOAc as the additive (Table 2). For various *N*,*N*-diethyl-*O*-benzoylhydroxylamines **1** substituted with electron-donating or electron-withdrawing substitutes on the aromatic ring, the reactions proceeded smoothly to afford the desired products **3b**–**3e** in excellent yields, while the CF_3 substituted *N*,*N*-diethyl-*O*-benzoylhydroxylamine gave the product **3f** in 70% yield under the same conditions. The results demonstrated that the electronic effect of the substituents on the benzene ring seems not to be remarkable. The reaction of **2a** with substrates **1** bearing the methyl group on *ortho* or *meta* position of the phenyl ring afforded the products **3g** and **3h** in 74% and 76% yields, respectively. It is worthy of note that the reaction of *meta*-methyl substituted **1** with **2a** gave **3h** as the only product and no product of annulation adjacent to the methyl group was detected. Moreover, for the substrate **1** substituted with two *meta*-chloro groups, its reaction with **2a** generated the product **3i** in remarkably decreased 51% yield. The decreased yields of **3g** and **3h** compared with **3b**, the high regioselectivity of **3h** and the low reactivity to form **3i** revealed that the steric effect on the benzene ring in substrate **1** is distinct for the annulation of **1** and **2**. If the benzene ring of **1a** was changed to thiophene, the annulation product **3j** was also obtained in excellent 92% yield. However, the substrate **1** incorporating naphthalene only gave a 52% yield for **3k**. In addition, the annulation reaction could be expanded to alkenyl substrate **1l** and the reaction with **2a** produced α-pyrone **3l** successfully in 80% yield.

Table 2. Reactions of substrates **1** and **2** to afford the products **3**.[a,b]

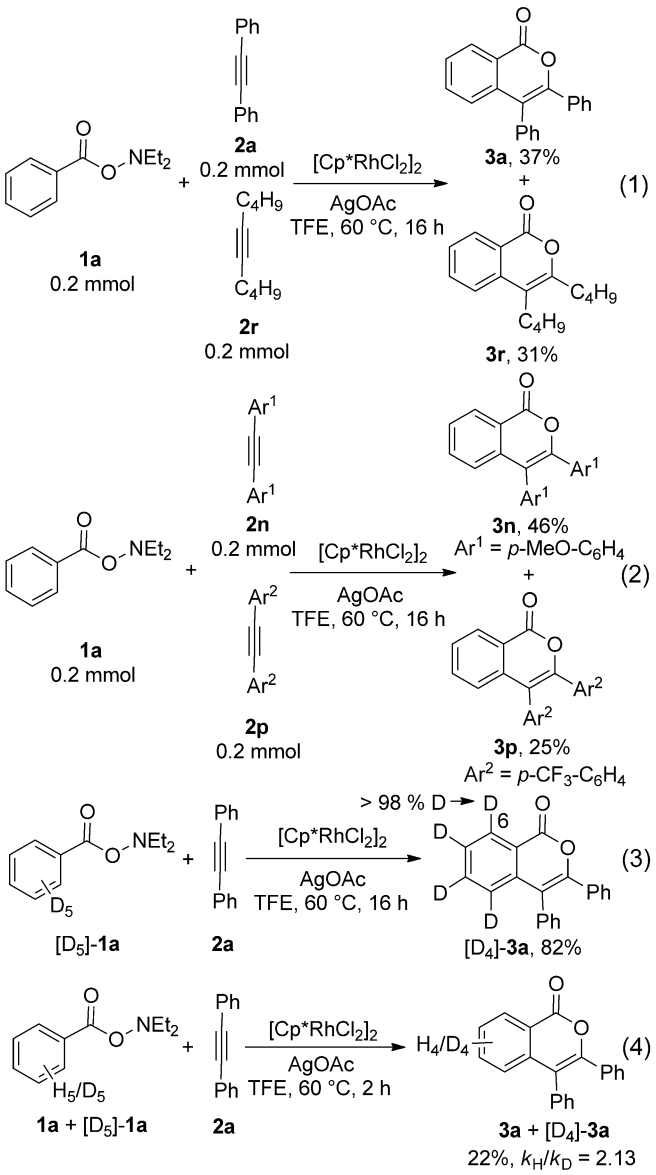


[a] *Reaction conditions:* **1** (0.4 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), AgOAc (30 mol%), TFE (2 mL), at 60 °C, 16 h, N_2, unless otherwise noted.
[b] Isolated yield.
[c] 80 °C, 24 h, and 1.0 mmol of **1** was used.

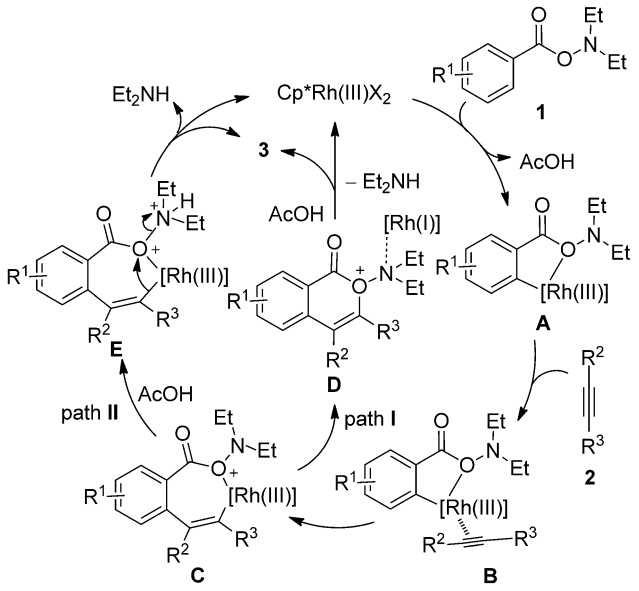
Subsequently, the scope of internal alkynes was also examined in the redox-neutral C–H activation annulation. Internal diarylalkynes bearing electron-donating Me and OMe substituents on the *para* position of the phenyl ring showed good reactivity in the reaction with **1a**, and the products **3m** and **3n** were generated in 90% and 87% yields, respectively. However, when diarylalkynes bearing electron-withdrawing Cl or CF_3 groups were used as the substrates to react with **1a**, obviously decreased 58% and 72% yields were obtained, which indicated that the electron-withdrawing substituents might affect the annulation negatively. For symmetrical aliphatic alkynes bearing two ethyl or butyl groups, the reactions with **1a** also proceeded smoothly to afford the products **3q** and **3r** in 72–74% yields. Finally, the reactivity and regioselectivity of asymmetrical internal alkynes were examined in the annulation reaction. Internal phenylacetylenes substituted with methyl group, *n*-hexyl group, *tert*-butyl group or trimethylsilyl group all reacted with **1a** smoothly to give the corresponding products **3s**–**3v** in 66–81% yields with perfect regioselectivity, and the structure of product **3v** was unambiguously confirmed by single-crystal X-ray diffraction analysis.[17] However, terminal alkynes such as phenylacetylene, 1-octyne and trimethylsilylacetylene showed no reactivity towards **1a** under the current conditions.

To investigate the reaction mechanism further, competition experiments between different alkynes were performed under the optimal conditions (Scheme 2). *N*,*N*-Diethyl-*O*-benzoylhydroxylamine (**1a**) was treated with 1,2-diphenylacetylene (**2a**) and 1,2-dibutylacetylene (**2r**), and 37% yield of product **3a** and 31% yield of product **3r** were obtained, which suggested that the difference of the reactivity between diarylalkyne and dialkylalkyne is not remarkable in this annulation reaction [Scheme 2, Eq. (1)]. For the diarylalkyne substituted with an electron-donating OMe group, its reaction with **1a** gave a 46% yield, which was much higher than the 25% yield obtained from the reaction of **1a** with the diarylalkyne substituted with an electron-withdrawing CF_3 group [Scheme 2, Eq. (2)]. The result demonstrated that the electron-donating substituent of the internal alkyne is beneficial for the reactivity of the annulation. Moreover, the reaction of isotopically-labeled $[D_5]$-**1a** with **2a** was carried out and more than 98% deuterium on the C-6 site in $[D_4]$-**3a** remained [Scheme 2, Eq. (3)], which revealed the irreversible C–H metalation in the catalytic cycle. Finally, the kinetic isotope effect (KIE) experiment was performed and a significant KIE was observed ($k_H/k_D = 2.13$), indicating that the C–H bond cleavage at the *ortho* position of **1a** is most likely involved in the rate-limiting step.

As depicted in Scheme 3, a plausible mechanism for this annulation reaction is proposed.[3–8] Firstly, substrate **1** coordinates to $Cp^*Rh(III)X_2$, and a rhodacycle intermediate **A** is formed *via* the C–H activation of the C-2 site of **1**.[18] Regioselective coordination and insertion take place to produce a seven-membered rhodacycle intermediate **C**. Complex **C** might go through a reductive elimination step to give cation **D** and Rh(I) species (path **I**).[4b,6b,7] With the aid of the Rh(I) species, intermediate **D** might be reduced to form the product **3** and regenerate the Rh(III) catalyst. As an alternative to path **I**, complex



Scheme 2. Competition and isotope experiments.



Scheme 3. Proposed reaction mechanism.

C might also undergo an intramolecular nucleophilic substitution, which leads to the breakage of the O–N bond and gives the desired product (path **II**).

In summary, we have developed a mild, efficient and regioselective redox-neutral C–H activation annulation protocol for the synthesis of isocoumarins and α-pyrones. The O–N bond was employed as the internal oxidant in the Rh(III)-catalyzed annulation and the coupling of benzoates and alkynes was achieved to construct oxygen-containing heterocycles. The results might support the development of new strategies for constructing useful oxygen-heterocycles with biological activity and medicinal value.

Experimental Section

Typical Experimental Procedure for Product 3a

To an oven-dried sealed tube charged with $[Cp^*RhCl_2]_2$ (6.2 mg, 0.01 mmol, 5 mol%), and AgOAc (10.0 mg, 0.06 mmol, 30 mol%) in TFE (2 mL) were added 1,2-diphenylacetylene (**2a**) (35.6 mg, 0.2 mmol, 1 equiv.) and *N*,*N*-diethyl-*O*-benzoylhydroxylamine (**1a**) (38.6 mg, 0.4 mmol, 2 equiv.). The reaction mixture was allowed to stir for 16 h at 60 °C. The reaction mixture was diluted with EtOAc (10 mL) and washed with water. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 25:1) to afford isocoumarin **3a**; yield: 53.5 mg (90%).

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