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Rh-Catalyzed Construction of Quinolin-2(1*H*)-ones via C−H Bond Activation of Simple Anilines with CO and Alkynes

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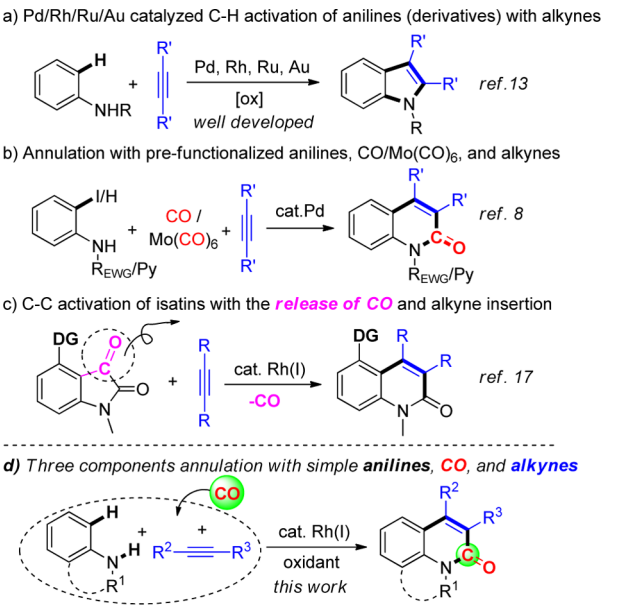
Supporting Information

ABSTRACT: A novel and efficient Rh-catalyzed carbonylation and annulation of simple anilines with CO and alkynes through N−H and C−H bond activation for the direct synthesis of quinolin-2(1*H*)-ones has been developed. Simple anilines without preactivation, broad substrate scope with hetero/polycycles, and high-value products make this protocol very practical and attractive. A key rhodacycle complex was isolated and well-characterized.

Quinolin-2(1*H*)-ones are ubiquitous fused heterocyclic motifs found in many natural products and pharmaceutically active compounds.[1] Members of the quinolin-2(1*H*)-one family have wide applications in medicinal chemistry because of their broad and remarkable biological activities, such as anticancer,[2] antibiotic,[3] antiviral,[4] antihypertensive,[4] antibacterial,[5] and other activities.[6] Moreover, quinolin-2(1*H*)-ones have been used as valuable synthetic intermediates in organic synthesis.[7] In view of their importance, many approaches to quinolin-2(1*H*)-ones, including the annulation of prefunctionalized anilines with alkynes,[8] reaction of anilines with acrylates,[9] and others,[9] have been developed. Despite their significance, most of them suffer from the need for preactivated reactants, limited substrate scope, and low efficiency. Therefore, direct and economical strategies for the efficient synthesis of quinolin-2(1*H*)-ones are still highly desired.

Transition-metal-catalyzed C−H bond functionalization has proven to be a versatile and powerful synthetic strategy.[10] Among such reactions, the direct dehydrogenative annulation of simple substrates with alkynes to construct polycyclic aromatic[11] and heteroaromatic compounds[12,13] has been significantly developed. The two-component annulation strategy to synthesize monosubstituted quinolin-2(1*H*)-ones[9] and highly related coumarins[14] from simple anilines or phenols via transition-metal-catalyzed functionalization of the ortho C−H bonds has also been significantly studied. In the past decades, transition-metal-catalyzed carbonylation with CO has been widely applied as a powerful protocol in both industry and the laboratory.[15,16] However, in contrast to the well-known transition-metal-catalyzed synthesis of indoles from anilines or their derivatives and alkynes (Scheme 1a),[13] straightforward methodology to construct six-membered N-heterocycles through dehydrogenative annulation of functionalized anilines with alkynes and CO has been barely achieved. Kadnikov and Larock[8a] developed the Pd-catalyzed carbonylative annulation of 2-iodoanilines with

Scheme 1. Transition-Metal-Catalyzed Oxidative Annulation



alkynes and CO. Beller and Wu[8b] reported this transformation via Pd-catalyzed C−H activation of *N*-pyridylanilines (the pyridyl is required as a directing group) with $Mo(CO)_6$ (Scheme 1b). Recently, Zeng and Dong[17] reported a significant directed Rh-catalyzed decarbonylative coupling of alkynes and isatins (Scheme 1c), which represents a distinct method for the synthesis of quinolin-2(1*H*)-ones with the release of CO. However, the annulation of amines and alkynes with incorporation of CO for the construction of six-membered N-heterocycles still encounters challenges.[18]

Herein we report a novel and efficient Rh-catalyzed three-component carbonylation and annulation strategy to construct 3,4-disubstituted quinolin-2(1*H*)-ones from very simple anilines, CO, and alkynes through C−H activation (Scheme 1d). Although Pd-catalyzed carbonylation of C−H bonds of anilines for the synthesis of isatoic anhydrides, isatins, and *β*-lactams has been significantly realized by the groups of Guan[19a] and Lei,[19b,c] respectively, to the best of our knowledge, carbonylation and annulation with CO incorporation through C−H activation,

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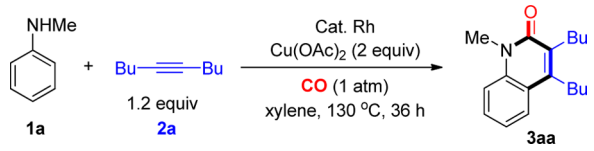
particularly from readily available substrates to give high-value products, has remained undeveloped.[20]

Initially, the carbonylation and annulation reaction between *N*-methylaniline (**1a**) and dec-5-yne (**2a**) in xylene under 1 atm CO was chosen as the model reaction (Table 1). The reaction

Table 1. Optimization of the Reaction Conditions[a]



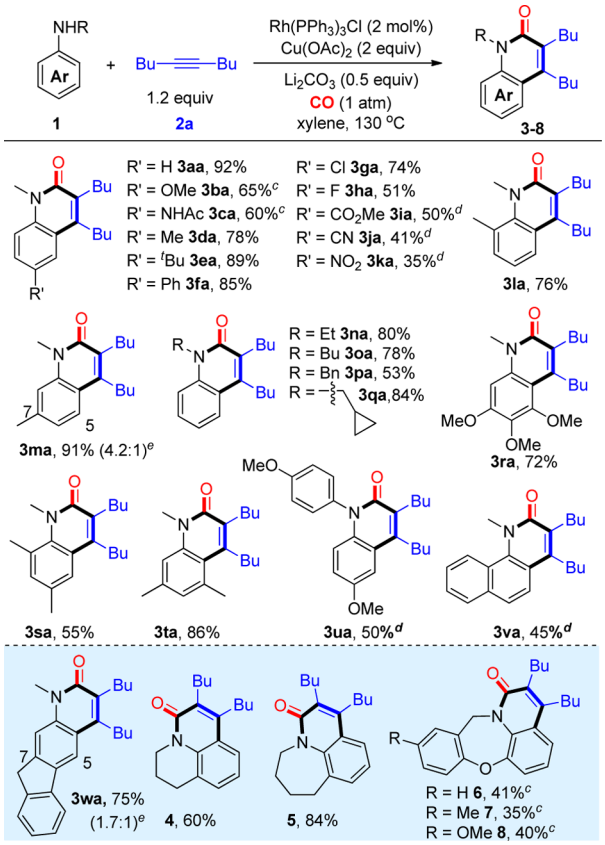
entry	cat. (mol %)	additive (mol %)	yield (%)[b]
1	$Pd(PPh_3)_2Cl_2$ (10)		trace
2	$Pd(OAc)_2$ (10)		trace
3	$[Cp^*RhCl_2]_2$ (2.5)		32
4	$[Rh(CO)_2Cl]_2$ (2.5)		34
5	$[Rh(cod)Cl]_2$ (2.5)		52
6	$Rh(PPh_3)_3Cl$ (5)		80
7	$Rh(PPh_3)_3Cl$ (5)	$AgSbF_6$ (10)	39
8	$Rh(PPh_3)_3Cl$ (5)	Li_2CO_3 (50)	95
9	$Rh(PPh_3)_3Cl$ (5)	Na_2CO_3 (50)	64
10	$Rh(PPh_3)_3Cl$ (5)	K_2CO_3 (50)	41
11	***$Rh(PPh_3)_3Cl$ (2)***	***Li_2CO_3 (50)***	***94 (92)***[c]
12	$Rh(PPh_3)_3Cl$(1)	Li_2CO_3 (50)	65

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), catalyst (as indicated), $Cu(OAc)_2$ (0.6 mmol), and additive (as indicated) in xylene (1 mL) under 1 atm CO at 130 °C for 36 h. [b]Determined by GC. [c]Isolated yields.

was totally ineffective when Pd catalysts that are efficient in C−H activation and carbonylation of anilines[19] were employed (entries 1 and 2). To our delight, the reaction catalyzed by $[Cp^*RhCl_2]_2$ afforded the designed quinolin-2(1*H*)-one **3aa** in 32% yield (entry 3). Screening of other Rh(I) catalysts indicated that readily available Wilkinson's catalyst $Rh(PPh_3)_3Cl$ exhibited efficient catalytic activity (80% yield; entry 6). Other Cu salt oxidants gave low yields (see the Supporting Information (SI)). After screening of different parameters with a Ag salt as an additive and in the presence of a base (entries 7−10; also see the SI), it was noted that the reaction in the presence of 0.5 equiv of Li_2CO_3 produced **3aa** in 95% yield (entry 8). Even when the loading of Wilkinson's catalyst was reduced to 2 mol %, the efficiency did not decrease (92% isolated yield; entry 11).

With the optimum conditions in hand, we next explored the scope of anilines **1** with **2a** (Scheme 2). A series of *N*-methylanilines bearing electron-donating groups (R = OMe, NHAc, Me, ^{t}Bu) underwent the annulation successfully to produce quinolin-2(1*H*)-ones in high efficiencies (**3ba**−**ea**). Substrates with weak electron-withdrawing groups such as Ph and Cl also performed well, giving the corresponding products (**3fa**, **3ga**) in good yields, while strong electron-withdrawing groups (R = F, CO_2Me, CN, NO_2) were relatively sluggish and provided moderate yields (**3ha**−**ka**). Also, *o*- and *m*-methyl substituents on the phenyl ring were well tolerated (**3la**, **3ma**). *N*-Alkyl-substituted anilines, even with cyclopropyl, were fully compatible (**3na**−**qa**). Several multisubstituted anilines smoothly led to the desired products in 55−86% yield (**3ra**−**ta**). In addition, an *N*-aryl-substituted aniline reacted successfully to deliver **3ua** in 50% yield. Furthermore, *N*-methylnaphthalen-1-amine and the polycyclic aniline 9*H*-fluoren-2-amine were

Scheme 2. Substrate Scope of Anilines[a,b]



[a]Reaction conditions: see Table 1, entry 11. [b]Isolated yields are shown. [c]Without Li_2CO_3. [d]$Rh(PPh_3)_3Cl$ (4 mol %) was used. [e]Regioselectivity ratio (the major isomer is substituted at the 7-position as drawn).

smoothly converted into the polycyclic heteroaromatic compounds **3va** and **3wa**, respectively.

It is noteworthy that tetrahydroquinoline, tetrahydro-1*H*-benzo[*b*]azepine, and dihydrodibenzooxazepines performed well to give moderate to good yields of the corresponding complex polycyclic heteroaromatic compounds **4**−**8** (Scheme 2), which are the core structural motifs in some natural products and bioactive compounds.

To explore the effect of substituents on the alkyne, a variety of internal alkynes were employed. Various aliphatic and aromatic internal alkynes were compatible with these reaction conditions, giving the expected products in moderate to good yields (Scheme 3). Oct-4-yne and bis(benzyloxy)but-2-yne participated in the present annulation to afford quinolin-2(1*H*)-ones **3ab** and **3ac** in 80% and 50% yield, respectively. Diarylalkynes containing electron-rich/deficient functional groups reacted smoothly to give the corresponding products in moderate to good yields (**3ad**−**ag**). In addition, the heteroaromatic alkyne bis(thiophen-2-yl)ethyne was also compatible, giving the expected product **3ah** in 54% yield. Unsymmetrical aryl alkyl alkynes such as **2i** and **2j** were also suitable for this reaction, affording the corresponding products **3ai** and **3aj** in high yields with moderate regioselectivity. Notably, macrocyclic alkyne **2k** was still tolerated, leading to the polymacrocyclic product **3ak** in 55% yield.

To gain insight into the mechanism, several isotope-labeling experiments were conducted. In the model reaction of **1a** and **2a**

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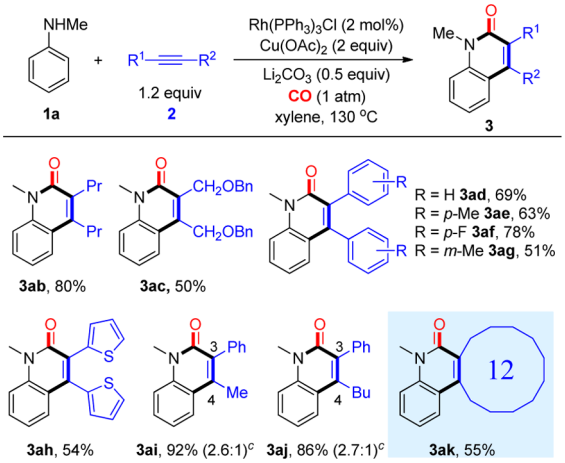
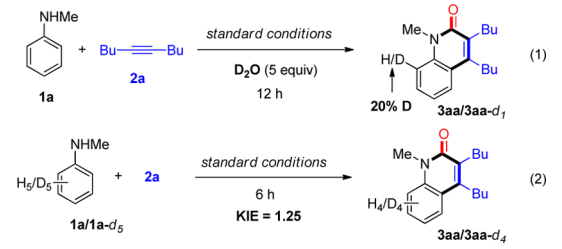
Scheme 3. Substrate Scope of Alkynes[a,b]



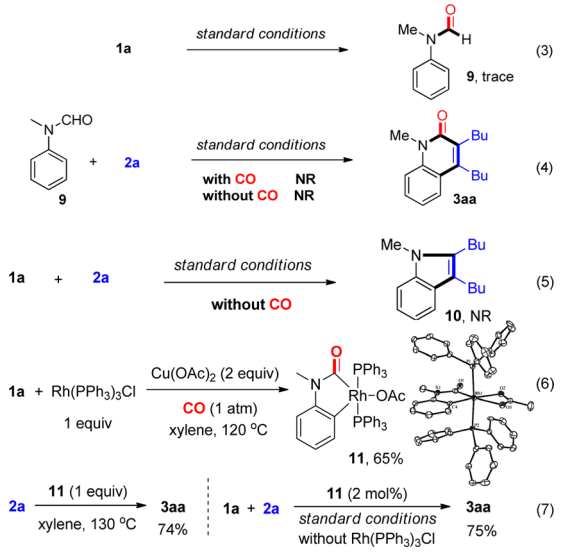
[a]Reaction conditions: see Table 1, entry 11. [b]Isolated yields are shown. [c]Regioselectivity ratio (the major isomer has the phenyl substituent at the 3-position as drawn).

under the standard conditions, a remarkable H/D exchange of 20% in product **3aa** was found upon the addition of deuterated water (eq 1), thereby implicating a reversible cyclometalation



mode. In addition, an intermolecular kinetic isotope effect (KIE) of k_H/k_D = 1.25 was determined for the annulation reaction (eq 2), indicating that C(sp^2)−H bond cleavage is not involved in the rate-determining step of the catalytic cycle.

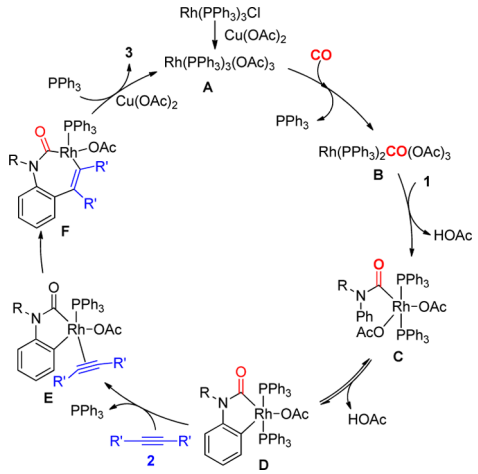
Control experiments showed that substrates were retained in the absence of alkyne **2a**, with the formation of trace amount of *N*-methyl-*N*-phenylformamide (**9**) (eq 3). Furthermore, no



desired product was observed in the absence or presence of CO when **9** was treated with **2a** (eq 4). These results indicate that the formation of formylated aniline is not involved in this process. In addition, no indole product **10** was detected in the absence of CO (eq 5), which means that the hydroamination might not be the initial step in this transformation.[13] Notably, when a stoichiometric reaction between $Rh(PPh_3)_3Cl$ and **1a** was carried out with $Cu(OAc)_2$ under CO, the metallacyclic Rh(III) complex **11** was isolated in 65% yield (eq 6), and its structure was confirmed by X-ray diffraction. Rhodacycle **11** provided **3aa** both catalytically and in a stoichiometric reaction with **2a** in good yields (eq 7).

On the basis of the above results and literature precedents, a plausible mechanism is proposed in Scheme 4. Upon the

Scheme 4. Proposed Mechanism



formation of Rh(III) complex **A** from Rh(I) via oxidation by $Cu(OAc)_2$, ligand exchange with CO affords Rh(III)−CO species **B**. Subsequently, aniline **1** coordinates to **B**, after which CO insertion forms Rh(III) complex **C**. Then **C** undergoes a concerted metalation−deprotonation process to give key rhodacycle complex **D**. Subsequent ligand exchange of **D** with alkyne **2** provides Rh(III)−alkyne complex **E**, after which alkyne insertion generates the seven-membered cyclic Rh(III) complex **F**. Finally, reductive elimination of **F** delivers product **3**, while the Rh(I) species is reoxidized to Rh(III) complex **A** in the presence of $Cu(OAc)_2$.

In conclusion, we have developed a novel and efficient Rh-catalyzed carbonylation and annulation of simple anilines with CO and alkynes for the direct synthesis of quinolin-2(1*H*)-ones through N−H and C−H bond activation. Readily available anilines without preactivation, broad substrate scope (including hetero/polycyclic rings), and high-value products make this protocol very practical and attractive. A rhodacycle species that is likely to be a key intermediate in the catalytic reaction was isolated and well-characterized. Experimental and computational mechanistic studies of this transformation and further applications are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05843.

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Notes

The authors declare no competing financial interest.

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