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

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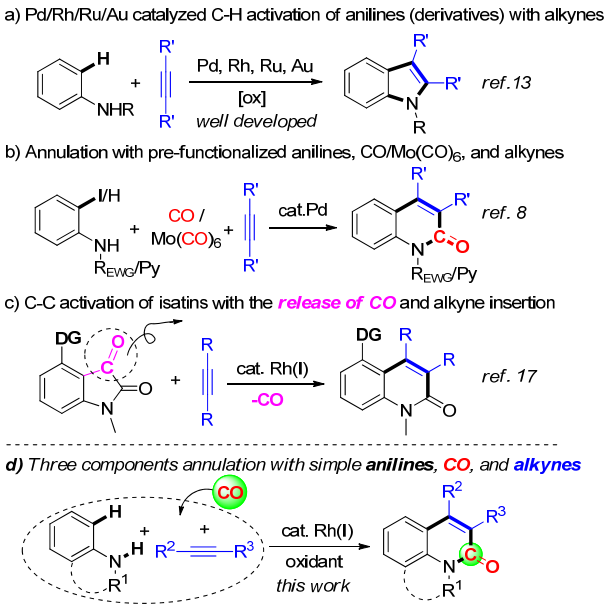
Supporting Information Placeholder

ABSTRACT: A novel and efficient Rh-catalyzed carbonylation and annulation of simple anilines with CO and alkynes through N-H and C-H bonds activation for the direct synthesis of quinolin-2(1*H*)-ones has been developed. Simple anilines without pre-activation, broad substrate scope with hetero/polycycles, as well as 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 quinolin-2(1*H*)-one family have wide applications in the medicinal chemistry regarding their broad and remarkable biological activities such as anticancer,[2] antibiotic,[3] antiviral,[4] antihypertensive,[4a] antibacterial,[5] and other activities.[6] Moreover, quinolin-2(1*H*)-ones have been used as valuable synthetic intermediates in organic synthesis.[7] Given its importance, many approaches to quinolin-2(1*H*)-ones including the annulation of pre-functionalized anilines with alkynes,[8] anilines with acrylates,[9] and others[9] have been developed. Despite the significances, most of them suffer from the pre-activated reactants, limited substrate scope, and low efficiency. Therefore, the direct and economic 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 them, 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 have 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 laboratory.[15,16] However, in contrast to the well-known transition-metal catalyzed indoles synthesis from anilines or their derivatives with alkynes (a, Scheme 1),[13] straightforward methodology to construct six-membered *N*-heterocycles through the dehydrogenative annulation of functionalized anilines with alkynes and CO has been barely achieved. Larock et al.[8a] developed the Pd-catalyzed carbonylative annulation of 2-iodoanilines with alkynes and CO. Beller and Wu[8b] reported this transformation via Pd-catalyzed C-H activation of *N*-pyridylanilines (the pyridyl is required as directing group) with $Mo(CO)_6$ (b, Scheme 1). Recently, Dong and coworkers reported a significant directed Rh-catalyzed decarbonylative coupling of alkynes and isatins (c,

Scheme 1. Transition-metal-catalyzed Oxidative Annulation



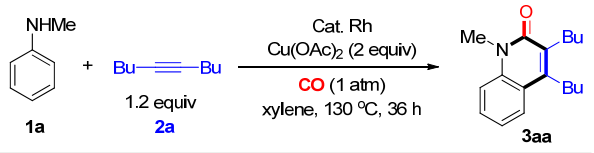
Scheme 1),[17] which represents an distinct method for quinolin-2(1*H*)-ones synthesis with the release of CO from isatins (c, Scheme 1). However, the annulation of amines and alkynes with CO incorporation for the construction of six-membered *N*-heterocycles still encounters chellanges.[18]

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 (d, Scheme 1). Although the Pd-catalyzed carbonylation of C-H bond 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, the carbonylation and annulation with CO incorporation through C−H activation, particularly from readily available substrates to 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 reactions were totally ineffective when Pd-catalysts that are efficient in C-H activation and carbonylation of anilines,[19] were employed as the catalyst (entries 1-2). 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). The screening of other Rh(I) catalysts indicated that the readily available Wilkinson's catalyst Rh(PPh$_3$)$_3$Cl performed efficient catalytic activity (80% yield, entry 6). Other Cu salt oxidants gave low yields (see SI). After the screening on different parameters with Ag salt as an additive and in the presence of a base (entries 7-10, and SI), it is noted that the reaction in the presence of 0.5 equiv Li_2CO_3 produced **3aa** in 95% yield (entry 8). Even the loading of Wilkinson's catalyst was reduced to 2 mol%, the efficiency did not decrease (92% isolated yield, entry 11).

Table 1. Optimization of the Conditions[a]



1a 2a 3aa

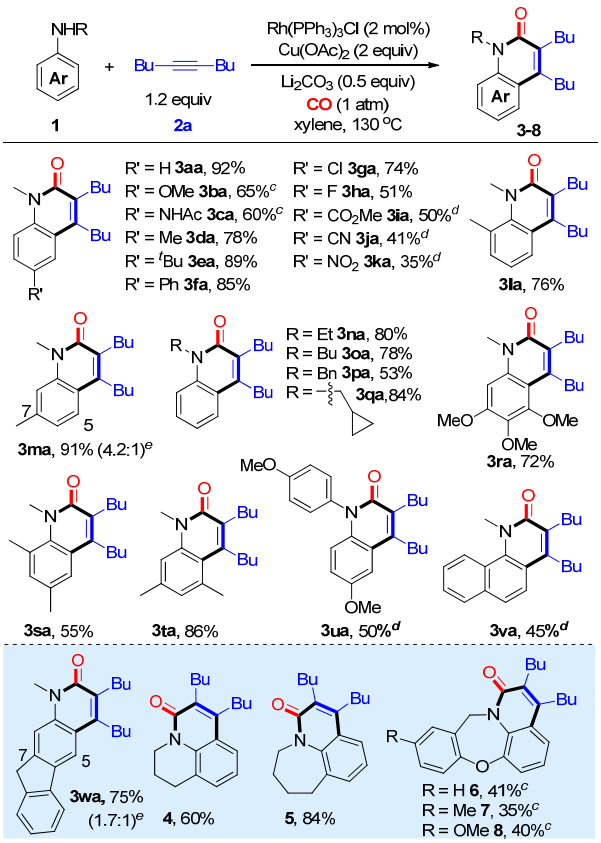
entry	Cat. (x mol%)	Additive (y mol%)	yield[b] (%)
1	$Pd(PPh_3)_2Cl_2$ (10)		trace
2	$Pd(OAc)_2$ (10)		trace
3	$[Cp^*RhCl_2]_2$ (2.5)		32
4	$[Rh(CO)_2Cl]_2$ (2.5)		34
5	[Rh(cod)Cl]$_2$ (2.5)		52
6	$Rh(PPh_3)_3Cl$ (5)		80
7	$Rh(PPh_3)_3Cl$ (5)	$AgSbF_6$ (10)	39
8	$Rh(PPh_3)_3Cl$ (5)	Li_2CO_3 (50)	95
9	$Rh(PPh_3)_3Cl$ (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 (x mol%), $Cu(OAc)_2$ (0.6 mmol), additive (y mol%) in xylene (1 mL) under 1 atm CO at 130 °C for 36 h. [b] Determined by GC. [c] Isolated yields.

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) furnished 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 in good yields (**3fa**, **3ga**). While strong electron-withdrawing groups (R = F, CO2Me, CN, NO_2) were relatively sluggish and provided the moderate yields (**3ha-ka**). *o*-, *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% yields (**3ra-ta**). In addition, *N*-aryl substituted aniline proceeded successfully to deliver the quinolin-2(1*H*)-one **3ua** in 50% yield. Furthermore, *N*-methylnaphthalen-1-amine and polycyclic anilines such as 9*H*-fluoren-2-amine, was smoothly converted into the polycyclic heteroaromatic compound **3va** and **3wa**, respectively.

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

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

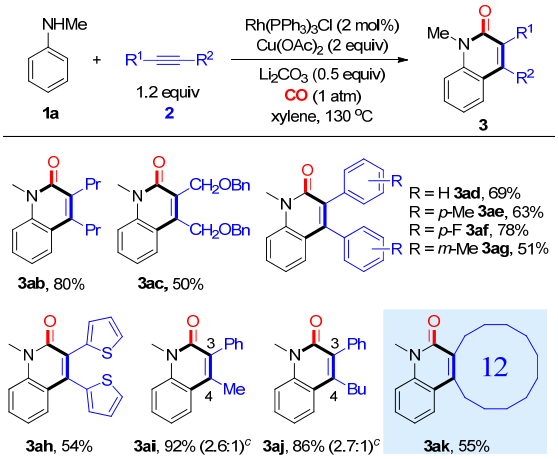


[a] Reaction conditions: see entry 11, Table 1. [b] Isolated yields. [c] Without Li_2CO_3. [d] $Rh(PPh_3)_3Cl$ (4 mol%) was used. [e] Regioselectivity ratio (the major isomer is substituted at 7-position as drawn).

To explore the effect of substituents on alkyne, a variety of internal alkynes were employed. Various aliphatic and aromatic internal alkynes were compatible under these reaction conditions, giving the expected products in moderate to good yields (Scheme 3). Dipropylalkyne 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% yields, respectively. Diarylalkynes containing electron-rich/deficient functional groups reacted smoothly to give the corresponding products in moderate to good yields (**3ad**−**ag**). In addition, di(thiophen-2-yl)ethyne as heteroaromatic alkyne was also compatible, giving the expected product **3ah** in 54% yield. The 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.

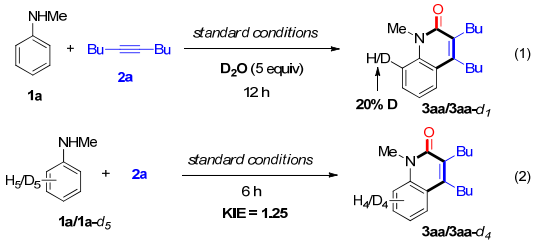
To gain insight into the mechanism, several experiments were conducted. Upon treatment of the model reaction of **1a** and **2a** under standard condition with isotopically labeled

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



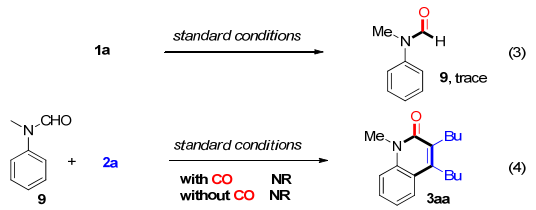
[a] Reaction conditions: see entry 11, Table 1. [b] Isolated yields. [c] Regioselectivity ratio (the major isomer: phenyl substituent at 3-position as drawn).

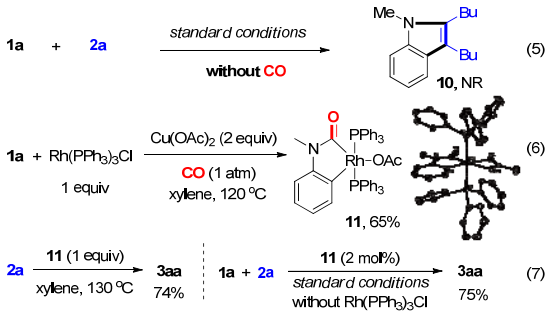
experiment, a remarkable H/D exchange of 20% in product **3aa** was found with the addition of deuterated water, thereby implicating a reversible cyclometalation mode (eq 1). In addition, an intermolecular KIE for the annulation reaction was determined to be k_H/k_D = 1.25, indicating that the C(sp^2)–H bond cleavage should not be involved in the rate-determining step of the catalytic cycle (eq 2).



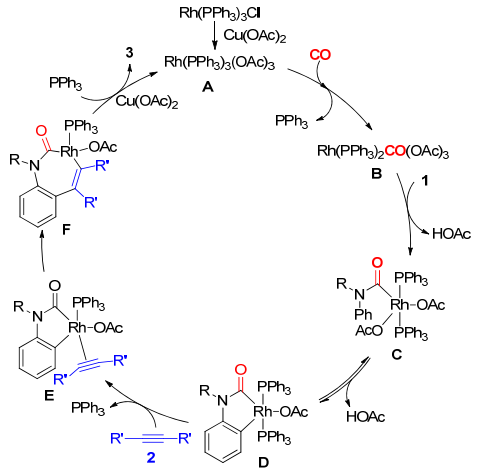
Control experiments showed that substrates keep retained in the absence of alkyne **2a** with the formation of trace amount of *N*-methyl-*N*-phenylformamide **9** (eq 3). Furthermore, there was no desired product observed in the absence or presence of CO, when **9** was treated with **2a** (eq 4). These 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 stoichiometric reaction between $Rh(PPh_3)_3Cl$ and **1a** was carried out with $Cu(OAc)_2$ under CO, Rh(III) metallacyclic complex **11** was isolated in 65% yield, and confirmed by X-ray diffraction (eq 6). Rhodacycle **11** provides **3aa** both catalytically and in a stoichiometric reaction with **2a** in good yields (eq 7).

On the basis of the above results and precedent reports, a plausible mechanism is proposed (Scheme 4). Upon the formation of Rh(III) **A** from Rh(I) oxidized by $Cu(OAc)_2$, the ligand exchange with CO affords Rh(III)-CO species **B**. Subsequently, aniline **1** coordinates to **B**, followed by CO





Scheme 4. Proposed Mechanism



insertion forms Rh(III) complex **C**. Then **C** undergoes concerted metalation-deprotonation (CMD) process to give key rhodacycle complex **D**. The subsequent ligand exchange of **D** with alkyne **2** provides Rh(III)-alkyne complex **E**, which proceeds insertion to generate 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) **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 bonds activation. Readily available anilines without pre-activation, broad substrate scope with hetero/polycyclic rings, as well as the high-value products, make this protocol very practical and attractive. A rhodacycle species was isolated and well characterized, which is likely to be a key intermediate in the catalytic reaction. Experimental and calculational mechanistic studies of this transformation and further applications are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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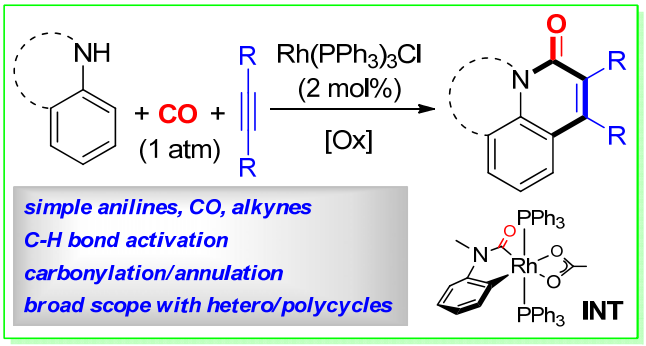
NH
+ CO +
(1 atm)
R
R
Rh(PPh3)3Cl
(2 mol%)
[Ox]
O
N
R
R
simple anilines, CO, alkynes
C-H bond activation
carbonylation/annulation
broad scope with hetero/polycycles
PPh3
N
O
Rh
O
O
PPh3
INT