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Access to Indenones by Rhodium(III)-Catalyzed C−H Annulation of Arylnitrones with Internal Alkynes

Zisong Qi,[†,‡] Mei Wang,[‡] and Xingwei Li*[,†]

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China, and State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116024, China

xwli@dicp.ac.cn

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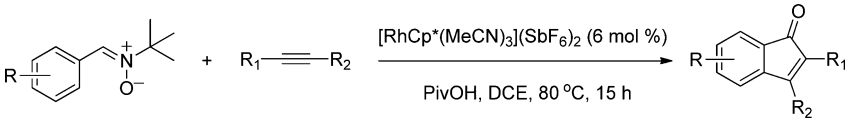
ABSTRACT



Under redox-neutral conditions, rhodium(III)-catalyzed C−H annulation of *N-tert*-butyl-α-arylnitrones with internal alkynes has been realized for the synthesis of indenones under mild conditions. This reaction proceeded in moderate to high yields and with good functional group tolerance.

Indenones are important carbocycles that are useful skeletons in synthetic chemistry, biology, and material science.[1] Consequently, different metal-catalyzed routes for efficient preparation of indenones have been developed in the past decades.[2] A well-studied strategy of catalytic synthesis of indenones utilized *ortho*-functionalized esters,[3] amides,[3] aldehydes,[4] nitriles,[5] or halides[6] as the starting material. Wender and co-workers took advantage of the strained cyclopropenones and achieved a coupling with in situ generated benzyne to give this type of product.[7] On the other hand, metal-catalyzed C−H bond activation has proven to be a powerful strategy for the construction of C−C bonds and has received increasing attention in the past decade.[8] Thus under rhodium(I) catalysis, the coupling of aroyl chlorides with internal alkynes gave

[†] Chinese Academy of Sciences.
[‡] Dalian University of Technology.

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indenones (Scheme 1a).[9] Takai and co-workers reported indenone synthesis via rhenium- and amide-catalyzed three-component cycloaddition with C−H bond activation to produce indinones.[10]

Recently, we reported indenamine synthesis via ruthenium and sulfonamide-cocatalyzed cyclization between *N*-sulfonyl imines and alkynes, and subsequent aerobic oxidation gave indenones.[11] Rhodium(III)-catalyzed addition of C−H bonds to alkyne derivatives has been extensively investigated[12] along with alkenes,[13] imines,[14] aldehydes,[15] isocyanates,[16] allenes,[17] carbenes,[18] azides,[19] aziridines,[20] and other strained rings,[21] where a wide variety of directing groups have also been extensively explored.[12f,j,13b,15b,22] Very recently, Shi and co-workers developed a rhodium-(III)-catalyzed C−H activation and annulation of benzimides, in which a catalytic amount of copper acetate additive is necessary (Scheme 1b).[23] However, these routes of indenone synthesis suffer from multiple steps, high temperature, or prior activation of substrates. We recently reported rhodium-catalyzed C−H activation of azomethines and subsequent oxidative olefination[13c] and redox-neutral annulation with alkynes (Scheme 1c),[24] whereas the azomethine acts as an efficient directing group. We reason that a ylidic nitrone could also function as a directing group, although it is a relatively weaker ligating group. Indeed, stoichiometric C−H activation of nitrone has been recently reported by Yao and us.[25] However, no catalytic C−H activation of nitrone has been reported. We now report a relatively mild approach to access indenones via rhodium(III)-catalyzed annulation of *N*-*tert*-butyl-α-arylnitrones with internal alkynes.

Scheme 1. Rhodium-Catalyzed Synthesis of Indenones via C−H Activation

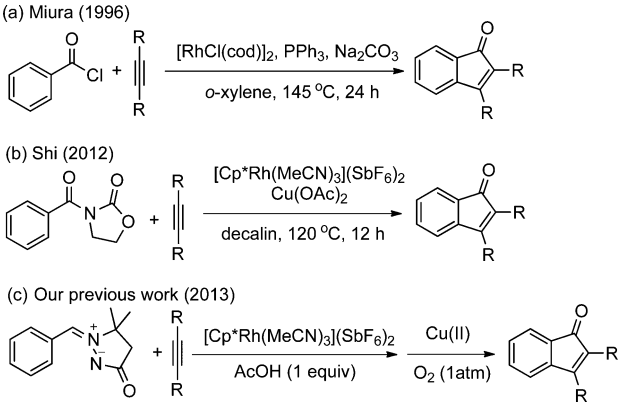
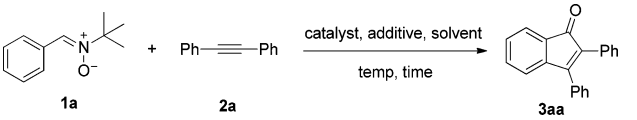


Table 1. Optimization Studies[a]



entry	catalyst	additive (equiv)	solvent	yield[b] (%)
1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$ (2.1)	DCE	nd
2	$[RhCp^*Cl_2]_2$	AgOAc (2.1)	DCE	nd
3	$[RhCp^*Cl_2]_2/AgSbF_6$		DCE	39
4	$[RhCp^*Cl_2]_2/AgSbF_6$	PivOH (1.0)	DCE	62
5	$[RhCp^*Cl_2]_2/AgSbF_6$	AcOH (1.0)	DCE	46
6	$[RhCp^*(MeCN)_3](SbF_6)_2$	PivOH (1.0)	DCE	70
7	$[RhCp^*(MeCN)_3](SbF_6)_2$	PivOH (1.0)	dioxane	trace
8	$[RhCp^*(MeCN)_3](SbF_6)_2$	PivOH (1.0)	*t*-AmOH	trace
9	$[RhCp^*(MeCN)_3](SbF_6)_2$	PivOH (1.0)	DCM	43
10[c]	$[RhCp^*(MeCN)_3](SbF_6)_2$	PivOH (1.0)	DCE	58

[a] Reaction conditions: $[RhCp^*Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %) or $[RhCp^*(MeCN)_3](SbF_6)_2$ (6 mol %), additive, **1a** (0.36 mmol), and **2a** (0.25 mmol) in solvent (2 mL) at 80 °C for 15 h. [b] Yield of isolated product. [c] The reaction was carried out at 50 °C.

We initiated our studies with the screening of the reaction conditions for the coupling of *N*-*tert*-butyl-α-phenylnitrone (PBN, **1a**) with diphenylacetylene (**2a**) using a rhodium(III) catalyst (Table 1). While no product was detected with $Cu(OAc)_2$ or AgOAc being an additive when $[RhCp^*Cl_2]_2$ was used as a catalyst (Table 1, entries 1 and 2), addition of $AgSbF_6$ (16 mol %) improved the efficiency and the desired indenone **3aa** was isolated in 39% yield (entry 3). Further addition of pivalic acid (PivOH) boosted the yield to 62% (entry 4). In contrast, a lower yield was isolated when AcOH was used as an additive (entry 5). To our delight, **3aa** was isolated in 70% yield when a cationic rhodium catalyst was employed (entry 6). Under these conditions, changing the solvent or lowering the reaction temperature all gave inferior results (Table 1, entries 7−10). In contrast to the good

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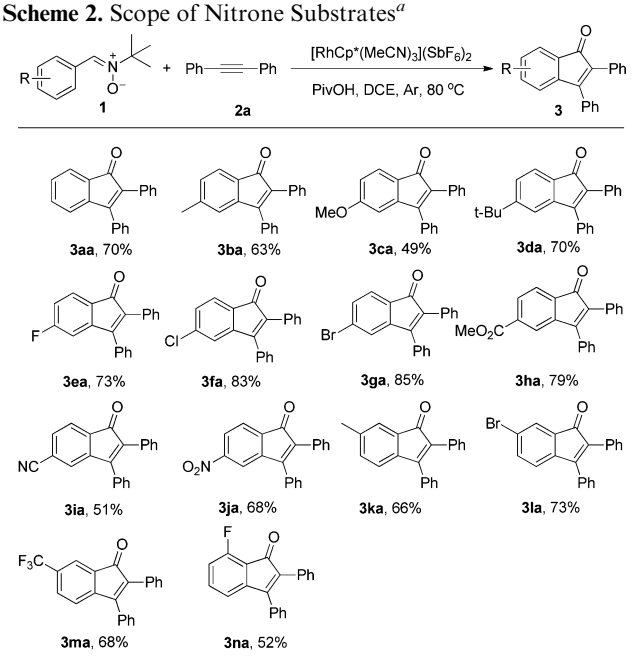
efficiency of **1a**, coupling using an *N*-methyl analogue of this notrone only afforded **3aa** in 40% isolated yield. Thus the following conditions were eventually chosen for subsequent studies: $[RhCp^*(MeCN)_3](SbF_6)_2$ (6 mol %) and PivOH (1.0 equiv) in DCE under argon at 80 °C.

Scheme 2. Scope of Nitrone Substrates[a]

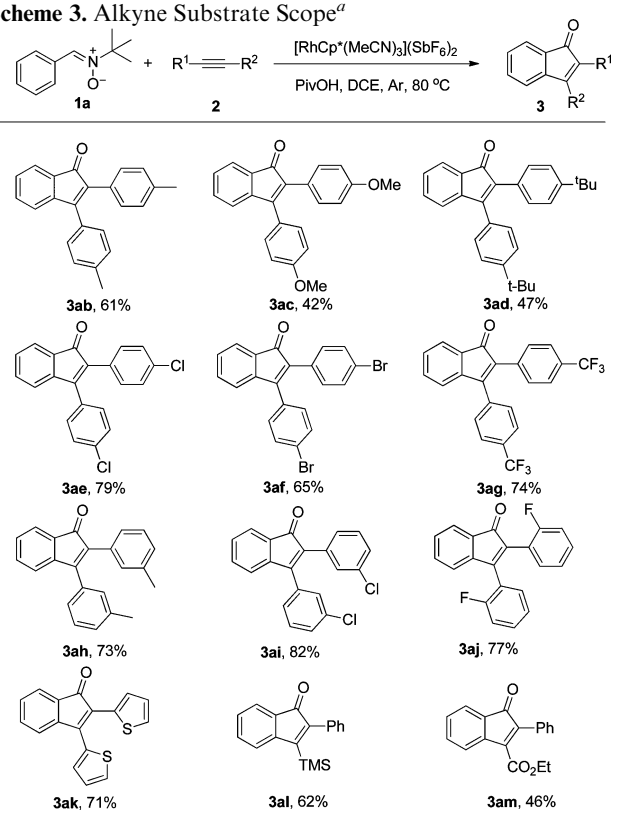


[a] Reaction conditions: $[RhCp^*(MeCN)_3](SbF_6)_2$ (6 mol %), PivOH (1.0 equiv), nitrone (0.36 mmol), and alkyne (0.25 mmol) in DCE (2 mL) at 80 °C for 15 h.

With the optimized conditions in hand, we first examined the reaction scope of the *N*-*tert*-butyl-α-substrate (Scheme 2). Nitrones bearing electron-donating and -withdrawing substituents all underwent smooth coupling with diphenylacetylene (**2a**) to afford the indenones in moderate to good yields (**3aa**−**3ga**). The reaction efficiency is related to the electronic effect of the *para* substituent. Thus a relatively lower yield was obtained for electron-donating groups (**3ba**, **3ca**). In particular, functionalizable electron-withdrawing groups such as ester, cyano, and nitro groups are also well-tolerated, and the corresponding indenones were isolated in 51−79% yields (**3ha**−**3ja**). In contrast, electronic effect seems less obvious for *meta* substituents (**3ka**−**3ma**). Halogen groups are also well-tolerated, although introduction of a fluoro group at the *ortho* position tends to lower the yield of the desired product (**3na**).

The scope of the internal alkynes was next investigated (Scheme 3). Symmetric diarylacetylenes bearing various substituents such as methyl, methoxy, *tert*-butyl, halo, and trifluoromethyl at different positions coupled with **1a** to afford the corresponding products in 42−82% yields (**3ab**−**3ai**). It is interesting to note that *ortho*-fluoro-substituted diarylacetylene is also tolerated (**3aj**). In addition, the aryl group of the alkyne is not limited to the benzene ring. When di(2-thiophenyl)acetylene was applied, product **3ak** was isolated in 71% yield. More importantly,

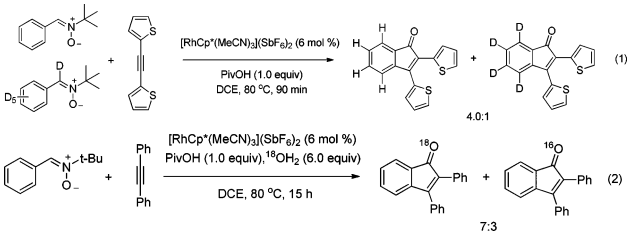
Scheme 3. Alkyne Substrate Scope[a]



[a] Reaction conditions: $[RhCp^*(MeCN)_3](SbF_6)_2$ (6 mol %), PivOH (1.0 equiv), **1a** (0.36 mmol), and alkyne (0.25 mmol) in DCE (2 mL) at 80 °C for 15 h.

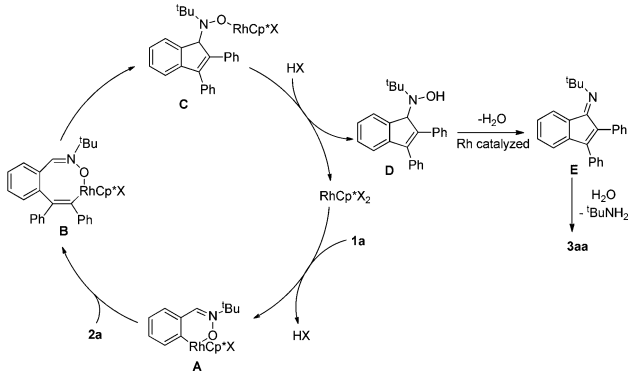
TMS-substituted phenylacetylene and ethyl phenylpropiolate are also viable substrates, and the indenone products (**3al** and **3am**) were isolated in moderate yield, which could be further readily derivatized to other useful structures. In contrast, alkyl-substituted internal alkynes failed to react under the standard conditions.

We further performed several experiments to gain insight into the reaction mechanism. A kinetic isotope effect (KIE) value of 4.0 was obtained using an equimolar mixture of **1a** and **1a**-d_6 in the coupling with di-(2-thiophenyl)acetylene at a low conversion under the standard conditions (eq 1). This result indicated that cleavage of the C−H bond activation is involved in the rate-limiting step. Moreover, both ^{18}O-labeled indenone **3aa** and regular **3aa** were obtained when ^{18}O-labeled water was introduced into the catalytic system, indicating that the oxygen atom in indenone could originate from water (eq 2).



On the basis of these experimental results, a proposed reaction mechanism is given in Scheme 4.[24] Coordination

Scheme 4. Proposed Reaction Mechanism



of **1a** to the cationic rhodium and subsequent C−H activation generates rhodacycle **A**. Alkyne coordination and subsequent insertion give an eight-membered rhodacyclic intermediate **B**, which is believed to undergo migratory insertion of the Rh−vinyl bond into the azomethine imine group to form a rhodium(III) amino oxide **C**. Protonolysis of **C** releases the hydroxyl amine intermediate **D**, which is proposed to undergo dehydration to give an imine **E**. This dehydration could be metal-catalyzed since **D** can be a stable compound. Hydrolysis of this imine eventually furnished the indenone product.

In summary, we have developed a mild approach to access indenones[26] through cationic rhodium(III)-catalyzed C−H activation and annulation of *N*-*tert*-butyl-α-arylnitrones with internal alkynes, where nitrone functions as both a directing group and an electrophile. The scope of the arylnitrone and internal alkyne substrates has been defined, and good functional group tolerance has been achieved. This work established nitrone as an efficient directing group for C−H bond activation and may find applications in the synthesis of useful structures.

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Supporting Information Available. Standard experimental procedure and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(26) After the submission of this paper, Cheng and co-workers reported an oxidative synthesis of indenones from benzaldehydes under Rh(III) catalysis. See: Chen, S.; Yu, J.; Jiang, Y.; Chen, F.; Cheng, J. *Org. Lett.* **2013**, *15*, 4754.