Organic LETTERS

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Rh(III)-Catalyzed [4 + 1]-Annulation of Azoxy Compounds with Alkynes: A Regioselective Approach to 2*H*-Indazoles

Zhen Long, Yudong Yang, and Jingsong You*

Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, Sichuan University, 29 Wangjiang Road, Chengdu 610064, P.R. China

Supporting Information

ABSTRACT: A rhodium-catalyzed regioselective C−H activation/cyclization of azoxy compounds with alkynes has been disclosed to construct a variety of 2*H*-indazoles. A [4 + 1]-cycloaddition rather than a normal [4 + 2] mode is observed in the process of cyclative capture along with an oxygen-atom transfer and a C≡C triple bond cleavage. This protocol features a broad substrate scope, a good functional group tolerance, and an exclusive regioselectivity.

The indazole scaffold is a class of important structural core frequently found in natural products, pharmaceuticals, agrochemicals, and bioactive compounds.[1] In particular, the 2*H*-indazole backbone is often recognized as an effective pharmacophore and thus has attracted increased interest (Figure 1).[2] However, the existing approaches to *N*-substituted indazoles often preferentially lead to a thermodynamically more stable 1*H*-indazole or give a mixture of 1*H*- and 2*H*-indazoles.[1b,3] Only a limited number of methods to prepare 2*H*-indazoles have been developed, including cyclization of 2-azidoimines,[4] reductive cyclization of *N*-(2-nitroarylidene)amines, 2-nitroiminobenzenes, or 2-nitrobenzylamines,[5] aryne [3 + 2]-cycloaddition,[6] and alkylation of 1*H*-indazoles.[7] Nevertheless, these routes often suffer from narrow substrate scope, harsh reaction conditions, and uneasily available starting materials.

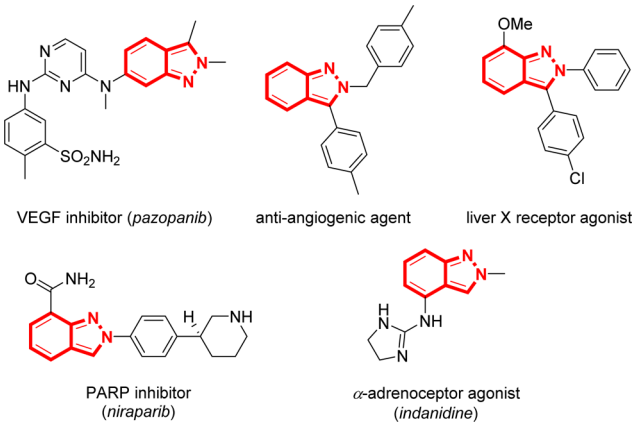
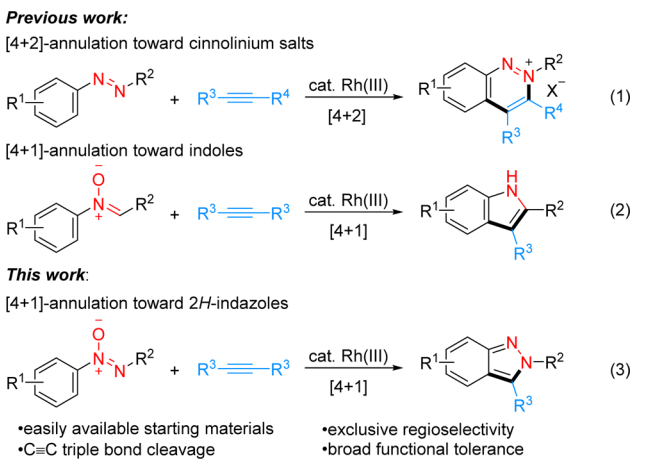


Figure 1. Selected bioactive 2*H*-indazoles.

Over the past few years, transition-metal-catalyzed directing group-assisted C−H bond activation/cyclization has proven to be a concise and efficient strategy for the synthesis of heterocycles.[8]

In this context, a few examples on the synthesis of 2*H*-indazoles through chelation-assisted transition-metal-catalyzed annulation of azobenzenes with aldehydes have been reported.[9] However, the regioselective control of C−H bond activation in unsymmetrical azobenzenes has not been solved effectively because the two electronically similar nitrogen atoms in the azo group could competitively coordinate to the metal center. We envisioned the utility of azoxy as the directing group could solve this issue and further provide a novel approach to 2*H*-indazoles because the different coordination capabilities of nitrogen and oxygen atoms to the metal center would enable site-selective C−H bond activation.[10,11] Previously, our group and Cheng independently described an efficient rhodium-catalyzed C−H activation/[4 + 2]-cyclization of azo compounds with alkynes to provide six-membered cinnolinium salts (Scheme 1, eq 1).[12] Recently, Wan and Wang disclosed a Rh(III)-catalyzed

Scheme 1. Directed C−H Annulation of Azo-, Azoxy- and Nitrone Compounds with Internal Alkynes



Received: April 1, 2017

DOI: 10.1021/acs.orglett.7b00982
Org. Lett. XXXX, XXX, XXX−XXX

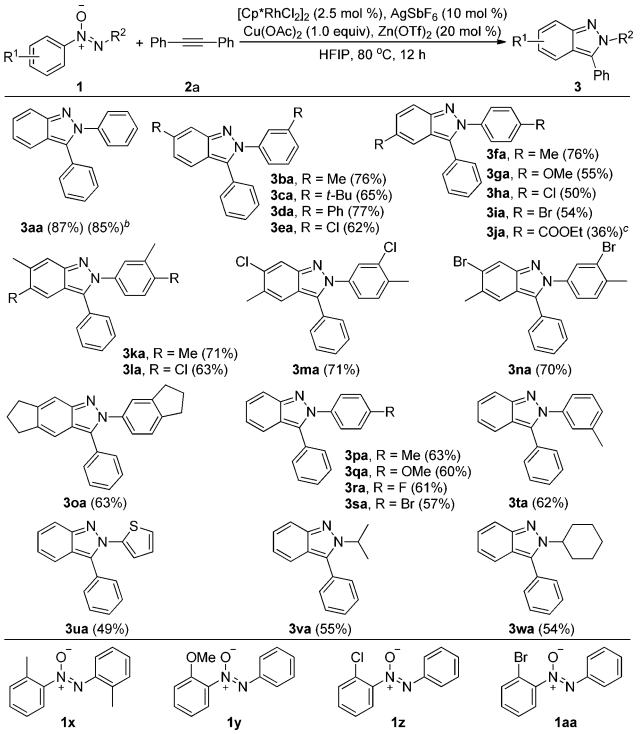
regioselective cyclization of nitrones with symmetrical diaryl alkynes for the synthesis of 2,3-diaryl-substituted indoles along with the cleavage of C≡C triple bond of alkynes (Scheme 1, eq 2).[13] Inspired by these reports, we proposed that a convergent approach to 2*H*-indazoles would be possible by rhodium(III)-catalyzed [4 + 1]-annulation of an azoxy compound and an alkyne (Scheme 1, eq 3). In addition, the regioselectivity relative to the final products could be predicted easily, and thus, a set of 2,3-disubstituted 2*H*-indazoles could be constructed in a highly regioselective manner.

We started our study with the reaction of azoxybenzene **1a** (1.0 equiv) and diphenylacetylene **2a** (1.2 equiv) in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2$ (1.0 equiv) in DCE at 100 °C for 12 h. However, no desired product **3aa** was detected (Table S1, entry 1). Further screening of solvents indicated that fluoro alcohols such as 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) could promote this transformation, and other solvents including dioxane, CH_3CN, THF, and MeOH were ineffective (Table S1, entry 2−7). It should be noted that $Cu(OAc)_2$ was essential for this reaction (Table S1, entries 8−10). Other inorganic salts including CuF_2, $Cu(OTf)_2$, $Ni(OAc)_2$, $Mn(OAc)_2$, AgOAc, and $K_2S_2O_8$ and organic oxidants such as PIDA and NMO gave only trace or diminished yields (Table S1, entries 11−18). To our delight, the combination of $Zn(OTf)_2$ (20 mol %) and $Cu(OAc)_2$ (1.0 equiv) furnished **3aa** in a 72% yield (Table S1, entry 19).[14] Other additives such as LiOTf and AgOTf were demonstrated less effective and protic acid PivOH showed no obvious effect on the efficiency (Table S1, entries 20−22). A slightly lower reaction temperature (80 °C) could improve the yield to 87% (Table S1, entry 27). Finally, the optimized reaction condition is composed of $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2$ (1.0 equiv), and $Zn(OTf)_2$ (20 mol %) in HFIP at 80 °C for 12 h.[15]

With the optimized conditions in hand, we next explored the substrate scope with respect to the azoxy compounds. The reactivity of various symmetrically substituted diaryldiazene oxides was first examined (**3aa**−**oa**) (Scheme 2). Azoxybenzenes substituted with both the electron-donating groups, such as Me, *t*-Bu, and OMe, and the electron-withdrawing groups, including F, Cl, Br, and COOEt, were all compatible under the standard conditions, giving the corresponding desired products in moderate to high yields. Notably, *meta*-substituted azoxybenzenes smoothly underwent the [4 + 1]-cycloaddition at the less sterically hindered position to afford a single regioisomer (**3ba**−**ea** and **3ka**−**oa**) (Scheme 2). Unsymmetrically substituted diaryldiazene oxides were also suitable substrates to deliver a series of 2*H*-indazole derivatives (**3pa**−**ua**) (Scheme 2). It should be noted that the unsymmetrical azoxybenzenes with the two electronically highly similar phenyl moieties could even give the products with complete regioselectivity (**3pa** and **3ta**). Furthermore, monoaryldiazene oxides, exemplified by **1v** and **1w**, smoothly reacted with **2a** to deliver 2-alkyl-3-aryl-2*H*-indazoles in synthetically useful yields (**3va** and **3wa**) (Scheme 2). Unfortunately, azoxybenzenes bearing functional groups such as Me (**1x**), OMe (**1y**), Cl (**1z**), and Br (**1aa**) at the *ortho*-position of the *NO*-phenyl ring failed to undergo this annulation possibly due to steric congestion.

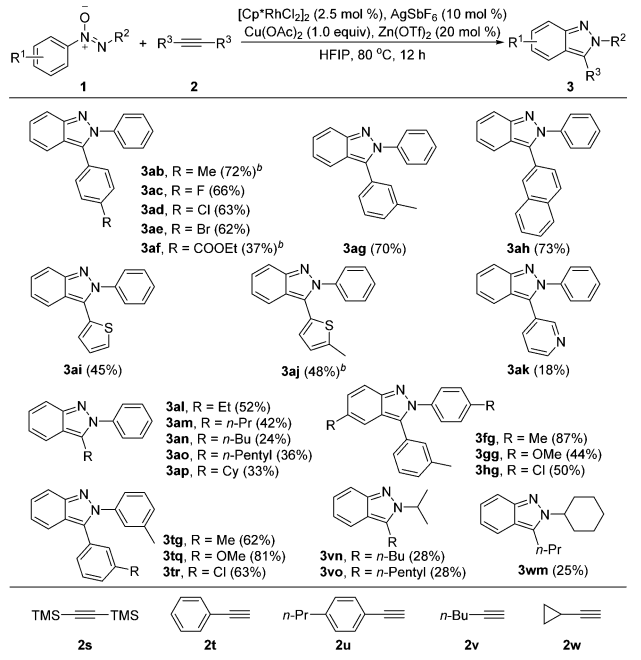
Subsequently, we investigated the generality of alkynes (Scheme 3). Gratifyingly, various symmetrical diarylalkynes bearing both electron-donating and electron-withdrawing groups worked well under the standard conditions. Diarylacetylenes containing naphthalenyl, thienyl, or pyridyl moieties were also

Scheme 2. Scope of Azoxy Compounds[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2$ (1.0 equiv), $Zn(OTf)_2$ (20 mol %) and HFIP (1.0 mL) under N_2 at 80 °C for 12 h. [b]1.0 mmol scale. [c]**2a** (2.0 equiv) was used.

Scheme 3. Scope of Alkynes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (1.2 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2$ (1.0 equiv), $Zn(OTf)_2$ (20 mol %) and HFIP (1.0 mL) under N_2 at 80 °C for 12 h. [b]For 24 h.

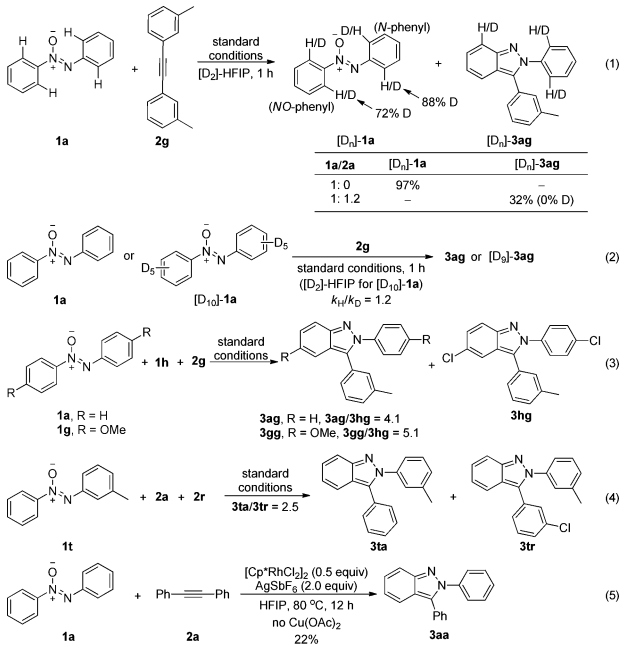
compatible in this reaction (**3ah**−**ak**) (Scheme 3). In addition, dialkylalkynes could undergo this type of [4 + 1]-cycloaddition to afford the 3-alkyl-2*H*-indazole products (**3al**−**ap**, **3vn**, **3vo**,

DOI: 10.1021/acs.orglett.7b00982
Org. Lett. XXXX, XXX, XXX−XXX

and **3wm**) (Scheme 3). Notably, annulation of monoaryldiazene oxides with aliphatic alkynes was also achieved, albeit in low yields (**3vn**, **3vo**, and **3wm**). However, the reactions of azoxybenzene with bis(trimethylsilyl)acetylene (**2s**) or monosubstituted alkynes such as phenylacetylene, (**2t**), 1-ethynyl-4-propylbenzene (**2u**), 1-hexyne (**2v**), and ethynylcyclopropane (**2w**) did not provide the desired annulation products.

To gain mechanistic insight into this transformation, a series of experiments were carried out. First, treatment of azoxybenzene **1a** alone with [D_2]-HFIP under standard conditions for 1 h gave rise to a significant amount of deuterated **1a**, indicating that the C−H bond cleavage was a reversible process (Scheme 4, eq 1).

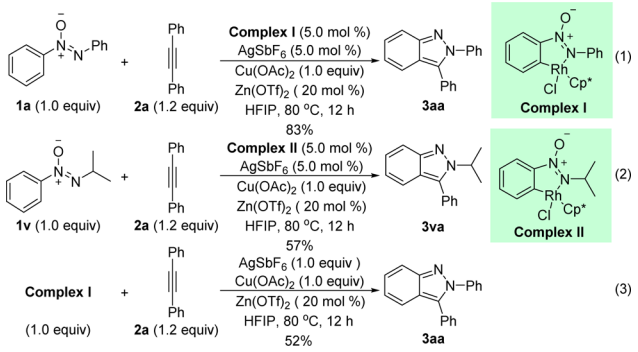
Scheme 4. Mechanistic Studies



However, when the same reaction was performed in the presence of diphenylacetylene **2g**, no significant H/D exchange was observed in the product **3ag**. These results imply that the alkyne insertion step in this reaction was most likely irreversible.[16] A kinetic isotope effect (k_H/k_D = 1.2) was observed in the parallel competitive reactions between **1a** and [D_{10}]-**1a** with diphenylacetylene **2a**, indicating that the arene C−H bond cleavage might not be involved in the rate-determining step (Scheme 4, eq 2).[17,18] In addition, two competition experiments between electronically differentiated azoxybenzene **1a** and **1g** were conducted, and the molar ratios of **3ag**/**3hg** and **3gg**/**3hg** were determined to be 4.1 and 5.1, respectively (Scheme 4, eq 3). These observations revealed that an electrophilic aromatic substitution process was likely involved in the catalytic cycle.[13,19] The competition reaction between alkynes was also performed, and the relatively electron-rich alkyne **2a** displayed a higher reactivity in this transformation (Scheme 4, eq 4). Furthermore, a control experiment with 0.5 equiv of rhodium catalyst in the absence of $Cu(OAc)_2$ was carried out, delivering **3aa** in a 22% yield, which demonstrates the function of $Cu(OAc)_2$ as the oxidant in the catalytic cycle(Scheme 4, eq 5).

In addition, two five-membered rhodacycle complexes **I** and **II** were obtained, and their structures were determined by X-ray crystallographic analysis (see the SI).[20] The complexes **I** and **II** were found to be efficient catalysts to promote the annulation of **1a** and **1v** with **2a**, giving the corresponding products **3aa** and **3va** in 83% and 57% yields, respectively (Scheme 5). A

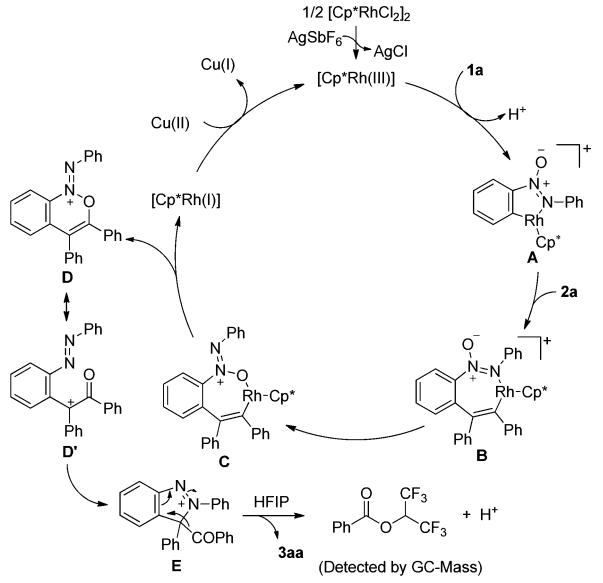
Scheme 5. Reactions of Rhodium(III) Complexes



stoichiometric amount of complex **I** could also react with diphenylacetylene **2a** to give **3aa** in a 52% yield. These results suggested that the five-membered rhodacycle complex was probably the intermediate in the catalytic cycle.

On the basis of the above investigations and the previous report,[13] a plausible mechanism is described in Scheme 6.

Scheme 6. Plausible Mechanism



Initially, the coordination of the azoxy nitrogen atom to an electrophilic Rh(III) species gives a five-membered rhodacycle **A** through a selective C2−H bond cleavage. Subsequently, a seven-membered rhodacyclic intermediate **B** is formed via an alkyne insertion. At this moment, the alteration of coordination atom from nitrogen to oxygen may take place to give a seven-membered rhodacycle **C**, which subsequently undergoes a C−O reductive elimination to afford the intermediate **D** and Rh(I) species. The tautomerization of **D** to **D′** and subsequent intramolecular nucleophilic addition at the cationic carbon center of **D′** delivers a cationic heterocyclic intermediate **E**.[21] Finally, with the help of HFIP, the desired product **3aa** is generated together with 1,1,1,3,3,3-hexafluoropropan-2-yl benzoate (detected by GC−MS). The released Rh(I) species is oxidized by copper salt to regenerate the Rh(III) species to fulfill the catalytic cycle. Although the C−H activation could also occur

DOI: 10.1021/acs.orglett.7b00982
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at the *N*-phenyl ring of azoxybenzenes (Scheme 4, eq 1), the formed rhodacyle species could not lead to the desired product.

In conclusion, we have developed a concise and efficient approach to construct a set of 2*H*-indazoles through a rhodium-catalyzed regioselective C−H activation/cyclization of the azoxy compounds with alkynes. A [4 + 1]-cycloaddition rather than a normal [4 + 2] mode is observed in the process of cyclative capture along with an oxygen-atom transfer and a C≡C triple bond cleavage. The features of this reaction include exclusive regioselectivity and broad functional group tolerance. Further studies on other valuable synthetic reactions starting from the azoxy compounds are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00982.

Detailed experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of key intermediates and final products (PDF)

X-ray crystallographic data for complex **I** (CIF)

X-ray crystallographic data for complex **II** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jsyou@scu.edu.cn.

ORCID

Jingsong You: 0000-0002-0493-2388

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by grants from the National NSF of China (No. 21432005).

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(15) In this work, all the Rh-catalyzed cyclizations of the azoxy compounds with alkynes were assembled in the glovebox. However, a benchtop-assembled reaction of azoxybenzene **1a** with alkyne **2a** was performed, giving the desired product in an 86% yield.

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(18) The parallel competitive reactions were repeated twice, and similar kinetic isotope effect values were observed.

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(20) CCDC 1495382 (**I**) and 1534198 (**II**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

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DOI: 10.1021/acs.orglett.7b00982
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