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Propargyl Alcohols as One-Carbon Synthons: Redox-Neutral Rhodium(III)-Catalyzed C−H Bond Activation for the Synthesis of Isoindolinones Bearing a Quaternary Carbon

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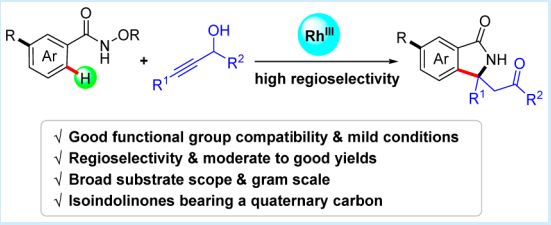
Supporting Information

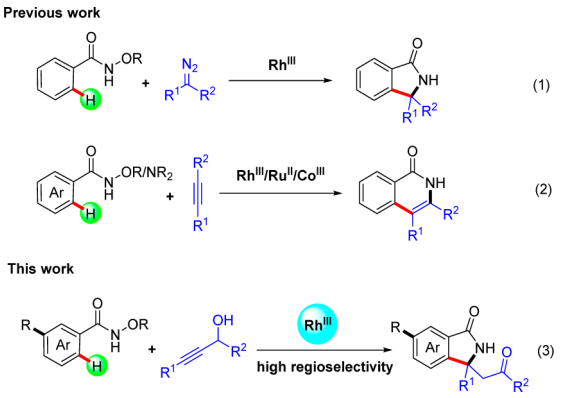
ABSTRACT: Herein, rhodium(III)-catalyzed C−H activation/subsequent [4 + 1] cyclization reactions between benzamides and propargyl alcohols are reported in which propargyl alcohols serve as unusual one-carbon units. This title transformation led to a series of isoindolinones bearing a quaternary carbon with moderate to good yields without the requirement for external metal oxidants. Due to the mild and simple reaction conditions, this reaction is compatible with various functional groups.



Isoindolinones are ubiquitous in pharmaceuticals and complex natural products.[1] Efficient methods for their preparation are an important topic of research because of their varied biological activities.[2,3] In the past decade, transition-metal-catalyzed cycloaddition reactions have emerged as an efficient method to synthesize heterocycles;[4] however, stoichiometric amounts of external oxidants are usually required in annulations involving C−H activation steps. Therefore, an oxidizing directing group that acts as an internal oxidant becomes an elegant and environmentally friendly strategy for transition-metal-catalyzed annulations.[5] Accumulating studies have demonstrated that oxidizing directing groups are effective internal oxidants.[5a] For instance, Rovis et al. pioneered the development of rhodium(III)-catalyzed C−H activation/cyclization of benzamides and diazo compounds for isoindolinone synthesis (Scheme 1, eq 1).[6a] In this case, benzamides with a N−O group serve as an internal oxidant and α-diazo carbonyl compounds can serve as one-carbon units in a [4 + 1] cyclization reaction that provides interesting isoindolinones bearing a quaternary carbon.

In recent years, transition-metal-catalyzed redox-neutral annulation reactions of benzamides with internal alkynes have been well established (eq 2). Among these reactions, internal alkynes generally serve as two-carbon reaction partners[5a,7−9] and are seldom considered as one-carbon components.[10] To the best of our knowledge, there have been few examples of Rh(III)-catalyzed [4 + 1] cyclizations[10a,11] of arenes with internal alkynes under external oxidant-free conditions. Rh(III)-catalyzed [4 + 1] annulation reactions of aromatic compounds with one-carbon partners represent a powerful approach for the synthesis of isoindolinones; therefore, we are interested in developing Rh(III)-catalyzed [4 + 1] annulation reactions with internal alkynes. Thus, in the present study, we report a Rh(III)-catalyzed [4 + 1] cyclization reaction of benzamides with propargyl alcohols to produce isoindolinones bearing a quaternary carbon under external oxidant-free conditions (eq 3) in which internal alkynes serve as unusual one-carbon units rather than normal two-carbon components.

Scheme 1. Rh(III)-Catalyzed C−H Activation Assisted by Oxidizing Directing Groups



We initiated our investigations with the reaction of *N*-*tert*-butoxybenzamide **1a**-**1** and propargyl alcohol **2a** catalyzed by rhodium complexes in the presence of CsOAc at 80 °C for 12 h. First, after a screen of solvents (see Table S1), we found that no reaction took place in MeOH, CH_3CN, and DMF. When we use THF or DCE as the solvent, the reaction gave the desired

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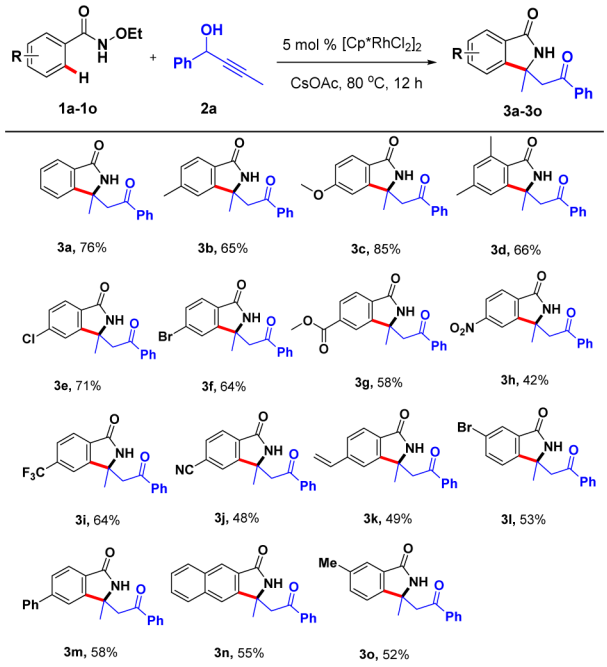
product **3a** in 26% yield and 40% yield, respectively. The reaction did not take place while using Na_2CO_3 as the base; when $[Cp^*Rh(CH_3CN)_3SbF_6]_2$ was used as the catalyst, an unsatisfactory result was obtained. The ^1H NMR yield was improved to 77%, and the ratio of **3a**/**4a** was also improved to 90/10 when substrate **1a** was used. In addition, it failed to give the desired product **3a** when pivaloyl instead of a methyl group was used. When 3.0 equiv of propargyl alcohol **2a** was used, the ^1H NMR yield increased to 89%. Moreover, the reaction did not take place in the absence of CsOAc or the catalyst $[Cp^*RhCl_2]_2$.

With the optimized reaction conditions in hand, we first explored the substrate scope of benzamides **1** with propargyl alcohol **2a** (Scheme 2). Generally, the benzamides with various

Scheme 2. Scope of Benzhydroxamic Acids[a,b]

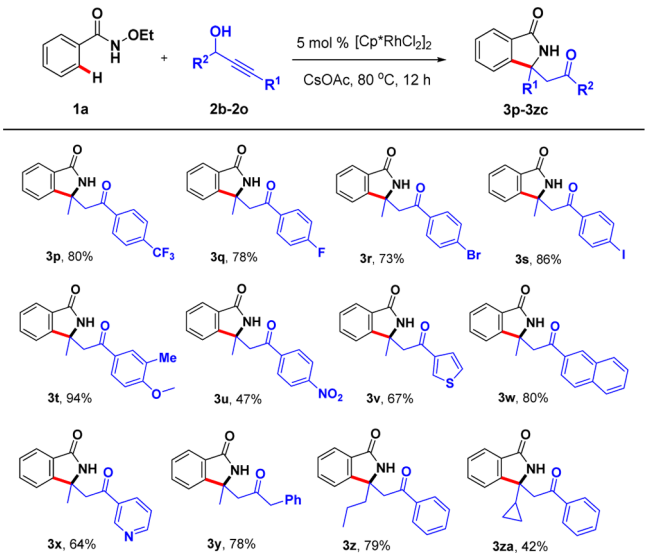


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), CsOAc (1 equiv) in anhydrous DCE (4 mL) at 80 °C for 12 h, Ar atmosphere. [b]Isolated yields are reported.

electron-withdrawing groups, electron-donating groups, and neutral groups all underwent smooth coupling with propargyl alcohol **2a**, and the desired products were obtained in moderate to good yields (42−85%). We found that the electron density of benzamides **1** played an important role in this reaction. Introduction of electron-donating groups (−Me and −OMe) could give good yields (**1b**−**d**,**o**). In contrast, substrates bearing strong electron-withdrawing groups such as COOMe, NO_2, and CN (**1g**, **1h**, and **1j**) resulted in decreased yields of the desired products. In addition, the desired products were obtained in good yields when halogen groups such as chlorine (**1e**) and bromine (**1f**) were introduced at the *para* position of the benzene ring. When a bromine group (**1l**) was placed at the *meta* position of the benzene ring, a single isomer was obtained in 53% yield; a similar effect was also observed with naphthylamides (**1n**) and substrate **1o**. It is worth mentioning that a *p*-vinyl group (**1k**) is well tolerated in this reaction. Because of the mild conditions, various functional groups (such as vinyl, cyano, nitro, methyl carboxylate, halides, etc.) were compatible with the standard reaction conditions, which guaranteed further transformation. These results showed good reactivity and regioselectivity in this reaction.

Furthermore, the scope of propargyl alcohols was explored (Scheme 3). We found the propargyl alcohols bearing electron-

Scheme 3. Scope of Propargyl Alcohols[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), CsOAc (1 equiv) in anhydrous DCE (4 mL) at 80 °C for 12 h, Ar atmosphere. [b]Isolated yields are reported.

poor substituents showed good reactivity and afforded the desired products (**3p**−**s**) in good yields. A nitro group on the phenyl moiety of the propargyl alcohols (**2g**) gave a decreased yield. In addition, the structure of **3s** was confirmed by X-ray crystallographic analysis (see the Supporting Information for details).[12] Coupling with an electron-rich group propargyl alcohol provided the desired product (**3t**) in excellent yield. Furthermore, other aryl groups, including thiophene **2h**, naphthalene **2i**, and pyridine **2j**, also reacted with **1a** to generate the desired product in good yields. When we used a benzyl group to replace the phenyl moiety of the propargyl alcohol, it also gave a satisfactory result (**3y**). Notably, the introduction of bulkier groups (such as propyl and cyclopropyl) in the R^1 moiety of substrates also provided the corresponding products in moderate to good yields (**3z** and **3za**). Unfortunately, the reaction did not yield the desired products **3zb** and **3zc** when 1,3-diphenylprop-2-yn-1-ol **2n** and 1-phenylprop-2-yn-1-ol **2o** were used as substrates, respectively. In general, substrates bearing electron-withdrawing groups (such as trifluoromethyl, nitro, and halides), electron-donating groups, and heteroaryl groups were well tolerated under the standard reaction conditions.

To assess the efficiency and potential for applications of this method, we carried out a scale-up experiment and explored the transformation of the product **3zd** to construct isoindolo[2,1-*a*]quinoline derivative **3zd-1** (Scheme 4).

To probe the reaction mechanism, a series of deuterium-labeling experiments were performed. First, we carried out the reaction without the propargyl alcohol in the presence of methanol-d_4 to determine the reversibility of the C−H activation (Scheme 5). We found that about 30% of the deuterium was incorporated at the *ortho* position of the

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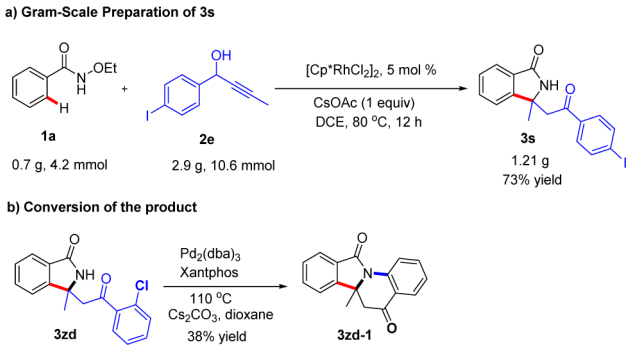
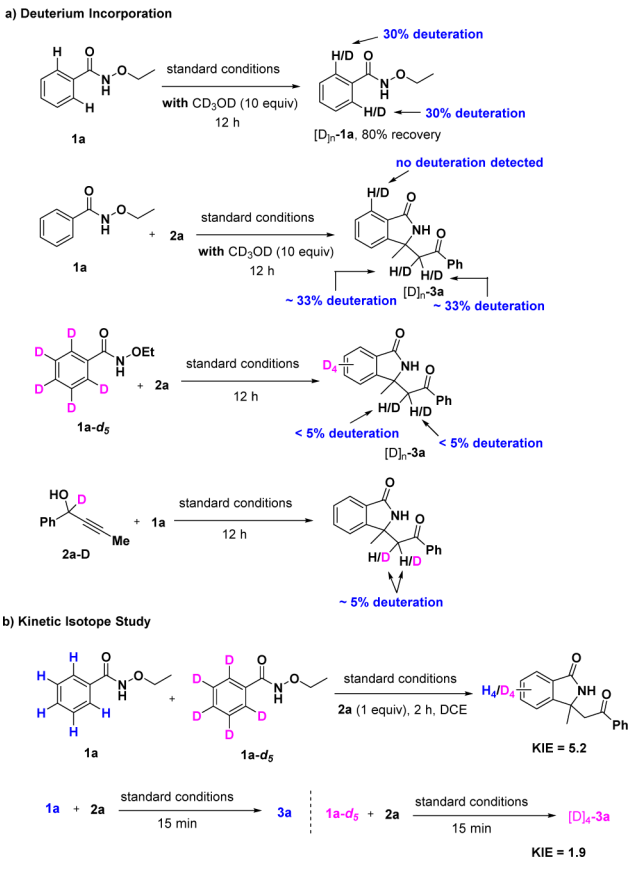
Scheme 4. Gram-Scale Preparation of 3s and Conversion of the Product



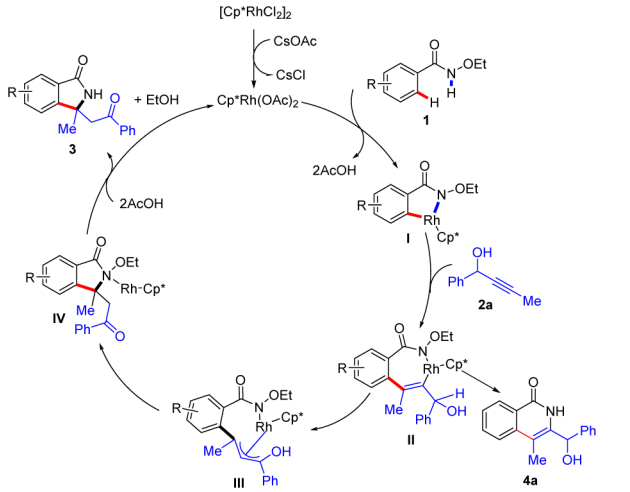
Scheme 5. Preliminary Mechanism Studies



benzamides based on ^{1}H NMR analysis (see the SI for details). Performing the same reaction in the presence of methanol-d_4 and propargyl alcohol **2a** led to no deuterium being incorporated at the *ortho* position of γ-lactam **3a**. These results suggested that the step of C−H activation might be irreversible under the reaction conditions. In addition, both protons at the α-methylene group of **3a** were partially deuterated (33% D). Compound **1a**-d_5 was subjected to the reaction with propargyl alcohol **2a** under the standard conditions and produced the product $[D]_n$-**3a** smoothly and less than 5% deuterium incorporation at the α-methylene group. In addition, we carried out the reaction using a deuterium-labeled propargyl alcohol **2a**-D; about 5% deuteration was observed at the α-methylene group. To probe the C−H activation process further, treatment of an equimolar mixture of **1a** and **1a**-d_5 with propargyl alcohol **2a** under the standard reaction conditions gave a relatively large kinetic isotope effect (KIE) value (k_H/k_D = 5.2). Besides, two independent reactions using **1a** and **1a**-d_5 gave a KIE value of 1.9. These results indicated that C−H bond cleavage was likely involved in the rate-limiting step. In addition, to determine whether the first step comprises propargyl alcohol isomerizing to an α,β-unsaturated ketone under Rh(III) catalysis, we performed two control experiments (see the SI for details). The reaction did not provide the desired product when an α,β-unsaturated ketone was used as the substrate. The control experiments confirmed that the first step of the reaction was not propargyl alcohol isomerizing to an α,β-unsaturated ketone.

Based on the preliminary mechanistic experiments and previous studies,[7b,13] we proposed a plausible catalytic cycle (Scheme 6). The first step is the formation of an active catalyst

Scheme 6. Proposed Mechanism



through anion exchange with cesium acetate. Next, the coordination of benzamide **1** via the amide nitrogen to Rh(III) and subsequent irreversible C−H bond cleavage of **1** occurs to produce a five-membered rhodacycle **I**, which is coordinated and inserted with propargyl alcohol **2a** to form a seven-membered rhodacycle intermediate **II**. One pathway is followed by the reductive elimination of intermediate **II** to provide the minor product **4a**. The other pathway presumably follows the abstraction of the allylic proton by the rhodium complex to form a π-allylic rhodacycle intermediate **III**. Subsequently, reductive elimination and enol−keto tautomerism of intermediate **III** leads to intermediate **IV**. Finally, Rh(I) complexes in intermediate **IV** could be oxidized by the intramolecular N−O bond, providing the desired product **3**, EtOH, and the active Rh(III) catalyst to furnish the catalytic cycle.

In summary, by use of an oxidizing directing group, a mild and efficient Rh(III)-catalyzed [4 + 1] cyclization reaction between benzamides and propargyl alcohols was developed. This reaction provides a straightforward method for accessing potentially bioactive isoindolinones bearing a quaternary carbon with moderate to good yields. The biggest characteristic of this method is that a novel synthetic utility of propargyl alcohols has been found in Rh(III)-catalyzed cyclizations with benzamides, which can lead to an unusual [4 + 1] transformation. In view of the mild reaction conditions and good functional group tolerance, this reaction might have potential for practical applications.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00089.

Experimental procedure, characterization of the products, and ^{1}H, ^{19}F, and ^{13}C NMR spectra of products (PDF)
Crystallographic data of **3s** (CIF)

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Notes

The authors declare no competing financial interest.

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