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Rh^{III}-Catalyzed Redox-Neutral C−H Activation of Pyrazolones: An Economical Approach for the Synthesis of N-Substituted Indoles

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Supporting Information

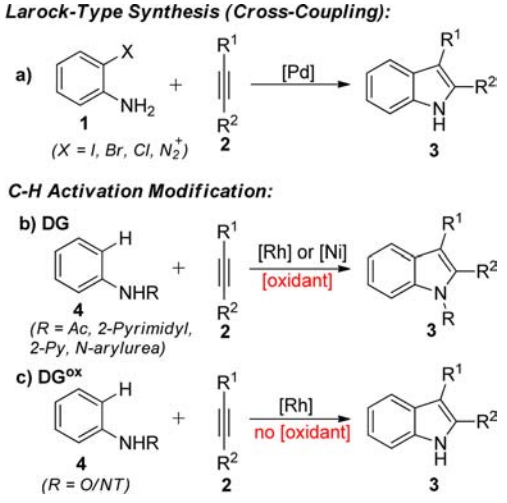
ABSTRACT: A new strategy is reported for the economical synthesis of indoles bearing an *N*-(3-aminobut-2-enoyl) substituent through Rh^{III}-catalyzed redox-neutral C−H activation of pyrazolones and alkynes. This approach utilizes cheap substrates and mild reaction conditions to access a unique class of indoles via a N−N bond oxidative cleavage without loss of the N-terminus, therefore meeting all the atom/step/redox economy principles.

The indole backbone is commonly embedded in various natural products and synthetic congeners[1] possessing a wide spectrum of biological properties, including anticancer, antiviral, and antidiabetic.[2] In the past decades, preparation of indoles **3** mainly depended on three synthetic strategies: [3,3]-sigmatropic rearrangements (Fischer and Bartoli synthesis),[3i,j] nucleophilic cyclization (Madelung and Smith reactions),[3a] and transition-metal-catalyzed cross-coupling (Larock and Mori-Ban synthesis).[3d,f,g] However, drawbacks such as the instability of Grignard reagents, the utilization of strong bases, and additional procedures for preactivating reagents restricted the practicality of these reactions. Therefore, development of new methods to assemble indoles readily, especially polycyclic or multisubstituted variants, is rather daunting.

Recently, directing group (DG)-assisted C−H activation has revolutionized the traditional design concept to the synthesis of many complex molecules.[4] Based on Larock-type Pd-catalyzed cross-coupling indole synthesis (Scheme 1a),[5] many DG-assisted oxidative couplings toward substituted indoles have been reported by Fagnou,[6a,b] Ackermann,[6c] and others[6] (Scheme 1b). More recently, the redox-neutral coupling with an oxidizing directing group (DG^{ox}) as an internal oxidant has emerged as an attractive strategy in C−H activation (Scheme 1c).[7] In such external oxidant-free protocols, a DG^{ox} bearing a N−O bond is generally used and the catalytic process is reinitiated by the cleavage of the N−O bond.[8] Compared to the N−O DG^{ox} protocols, nevertheless, C−H activations utilizing a DG^{ox} containing a N−N bond have been scarcely described.[9]

In 2013, Huang[9b] reported a synthesis of indoles through a Rh-catalyzed alkyne annulation using a triazene as the DG. In this reaction, the N=N double bond was successfully cleaved to release the catalyst. However, an external oxidant was needed. Using a nitroso as the N-terminus (NT) of the N−N bond in the DG^{ox} was reported by Zhu[9d] and Huang.[9e] In this approach, the reaction proceeded with assistance of the DG^{ox} via a redox-neutral C−H activation. In addition, Glorius,[9c] Hua,[9h] and Cheng[9j] also reported additional examples to access indoles using acetamido or imino as the NT (Scheme 2). Despite the progress, however, judging by the three economy principles, atom/step/redox,[7,10] these reactions only fulfilled the redox economy and lacked atom/step economy. All of these approaches suffered from two major defects: (1) the DG^{ox}-containing substrates need to be prepared in advance; (2) the N−N bond cleavage led to loss of the N-terminus in the products.

Scheme 1. Representative Strategies of Indole Synthesis



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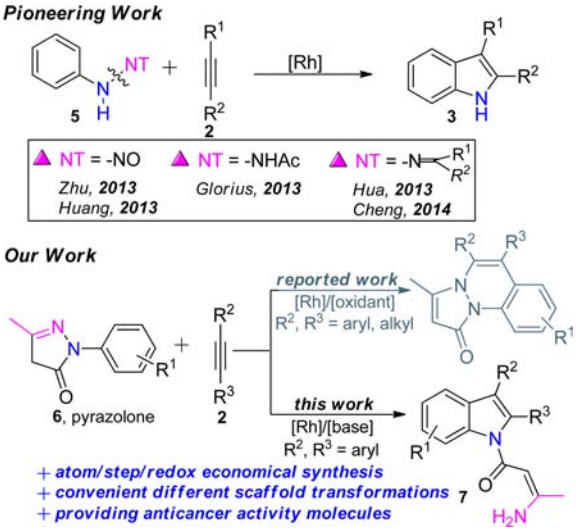
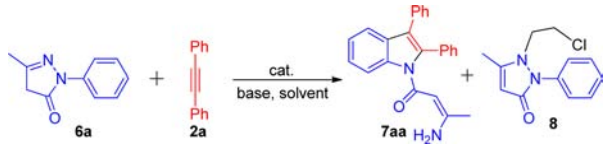
Scheme 2. Rh^{III}-Catalyzed Redox-Neutral Coupling through N−N Bond Cleavage (NT = N-Terminus)



We recently reported a rhodium-catalyzed oxidative coupling of *N*-aryl-1*H*-pyrazol-5(4*H*)-one **6** with internal alkynes **2**[11b] using the pyrazolone function as an intrinsic directing group.[11] As a continuation of this work, we envisaged that the N−N bond in the pyrazolone substrate might also be used as a DG^{ox} and undergo a redox-neutral C−H activation that would lead to products with a different structural scaffold. While our paper was in preparation, the Huang group reported a ruthenium-catalyzed redox-neutral C−H activation reaction of 1-phenylpyrazolidin-3-one (phenidone) with alkynes, leading to the synthesis of N-substituted indoles.[12] Herein, we report that the Rh^{III}-catalyzed redox-neutral C−H activation of pyrazolones **6** with alkynes **2** occurred smoothly, yielding a unique class of indoles **7** bearing a 3-aminobut-2-enoyl substituent, which cannot be conveniently prepared through the above-mentioned methods. In addition, this reaction represents a novel Rh-catalyzed redox-neutral C−H activation via N−N cleavage, satisfying all the atom/step/redox economy principles.

Our initial investigation was carried out by treating pyrazolone **6a** with diphenylacetylene **2a** using $[RhCp^*Cl_2]_2$ (2.5 mol %) and CsOAc (2 equiv) in $ClCH_2CH_2Cl$ at 100 °C for 6 h,[9c] but the desired product **7aa** was not obtained (Table 1, entry 1). We then investigated a variety of bases instead of CsOAc in this reaction (Table 1, entries 2−5). It was found that product **7aa** was obtained in 6% yield using NaOAc as the base, and the structure was confirmed by the X-ray crystallography (see the Supporting Information). Compound **8** was obtained as a side product that was formed by alkylation of **6a** with the solvent $ClCH_2CH_2Cl$ in the presence of CsF as the base (Table 1, entry 4). This reminded us that changing the solvent was urgent. Among the solvents we tested (entries 6−11 of Table 1), chlorobenzene led to an improved yield of 44%. Screening the reaction temperature from 80 to 130 °C (Table 1, entries 12−14), we found that the yield of **7aa** was slightly improved (57%) at 130 °C. In addition, other halogenated arenes were investigated as the solvent, and we were surprised to find that bromobenzene gave a high yield of 75% (Table 1, entry 15). The exact reason why bromobenzene is superior to chlorobenzene as the solvent is unclear at this moment. Therefore, the best reaction condition was concluded as follows: pyrazolones **6**, alkynes **2**, $[RhCp^*Cl_2]_2$ (catalyst), NaOAc (base) in PhBr (solvent) at 130 °C in a sealed tube.

Table 1. Reaction Optimization for the Synthesis of 7aa[a]



entry	base	solvent	temp (°C)	yield (%)[b]
1	CsOAc	$ClCH_2CH_2Cl$	100	0
2	NaOAc	$ClCH_2CH_2Cl$	100	6
3	Li_2CO_3	$ClCH_2CH_2Cl$	100	0
4[c]	CsF	$ClCH_2CH_2Cl$	100	0
5	NaH_2PO_4	$ClCH_2CH_2Cl$	100	0
6[d]	NaOAc	dioxane	100	14
7[d]	NaOAc	*m*-xylene	100	20
8[d]	NaOAc	mesitylene	100	28
9[d]	NaOAc	DME	100	21
10[e]	NaOAc	PhCl	100	44
11[d]	NaOAc	toluene	100	26
12[e]	NaOAc	PhCl	80	30
13	NaOAc	PhCl	120	50
14	NaOAc	PhCl	130	57
15	NaOAc	PhBr	130	75
16	NaOAc	PhI	130	45
17	NaOAc	PhF	100	43

[a]Reaction conditions: **6a** (0.1 mmol), **2a** (0.1 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), base (0.2 mmol), solvent (1 mL), 2 h. [b]Yields determined by ^1H NMR analysis using 1,2-dibromoethane as internal standard. [c]Compound **8** as the only product. [d]6 h. [e]4 h.

With the optimized reaction conditions in hand, the scope and limitations were assessed with different pyrazolones and various internal alkynes (Scheme 3). Except for the *ortho*-substituted phenyl substrates, all monosubstituted, disubstituted, or fused phenyl pyrazolones went through the reaction smoothly and afforded the corresponding products in moderate to excellent yields. For the *para*-substituted phenyl pyrazolones, both electron-withdrawing and electron-donating groups, such as chloro, methyl, and methoxyl, were tolerant under the reaction conditions, and the corresponding products **7ca**, **7ba**, and **7da** were obtained in 76, 81, and 65% yields, respectively. The *meta*-substituted phenyl substrates gave varying yields ranging between 61 and 85% (**7ea**−**7ha**). Substrates with electron-withdrawing and strong electron-donating groups afforded slightly lower yields (61−68%). The ring-fused pyrazolone **6n** also participated in this reaction and afforded product **7na** in 62% yield. In the case of 1-(3-fluorophenyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one, a mixture of regioisomers **7ia** and **7ia′** was observed. A low yield of 36% was obtained for indole derivative **7ma**, likely due to the steric hindrance of the isopropyl group. Symmetric diaryl acetylenes were also efficiently converted to the desired indole derivatives (**7ab**−**7ah**) in 48−74% yields. However, alkyl−alkyl (**2i**) and aryl−alkyl (**2j**) disubstituted alkynes underwent a cyclization process[11b] and generated pyrazolo[1,2-*a*]cinnolines (**7ai** and **7aj**) and the tautomers (**7ai′** and **7aj′**), with the former products in slightly higher yields. In addition, we also investigated diheteroaryl alkynes, including 1,2-di(thiophen-2-yl)ethyne and 1,2-di(pyridin-4-yl)ethyne, as well as phenyl acetylene; unfortunately, no products were obtained.

A plausible mechanism is presented in Scheme 4 (based on the model reaction of **6a** and **2a**). The active catalyst [RhCp*-

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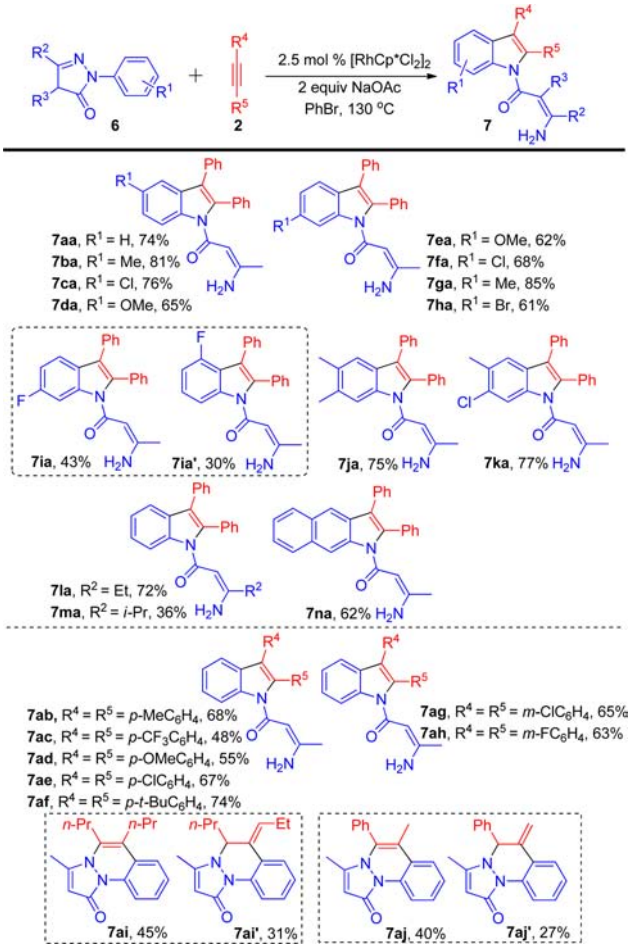
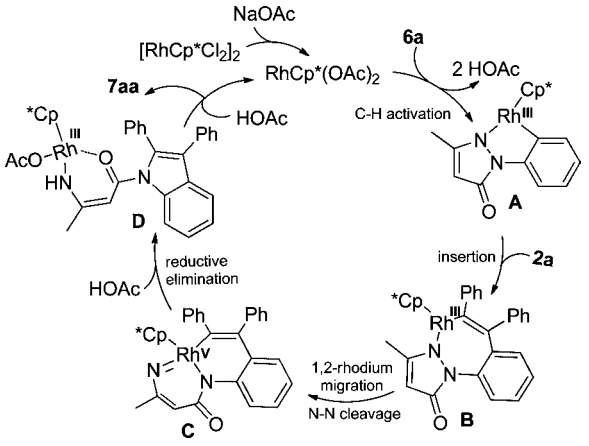
Scheme 3. Reaction Scope for the Synthesis of N-Substituted Indoles 7[a]



[a]Reaction conditions: $[RhCp^*Cl_2]_2$ (2.5 mol %), NaOAc (1 mmol), pyrazolones **6** (0.5 mmol), and alkynes **2** (0.5 mmol) in PhBr (2.5 mL) for 2−3 h under 130 °C. Isolated yields are given.

Scheme 4. Proposed Mechanism



$(OAc)_2]_2$ was first formed from $[RhCp^*Cl_2]_2$ and NaOAc.[9h,13] A directed C−H bond cleavage process then occurred to form a rhodacycle **A**,[11b,c] which was followed by insertion of alkyne **2a**, affording the seven-membered intermediate **B**. The [5,7]-bicyclic Rh complex **B** (Rh^{III}) was then converted to a more stable [6,6]-bicyclic metallacycle **C** (Rh^{V}) via a 1,2-rhodium migration, accompanied by the N−N bond cleavage.[9c,14] The intermediate **C** then underwent a reductive elimination and protonation to form the complex **D**, which was subsequently protonated by acetic acid to afford the target product **7aa** and regenerate the Rh^{III} catalyst.

Since the unique structure of the *N*-(3-aminobut-2-enoyl)-substituted indoles in the current protocol is distinctly different from the ones in other methods, we evaluated the inhibitory effects of these compounds against the proliferation of several cancer cells, including squamous carcinoma KB cells and vincristine (VCR)-resistant KB/VCR cells. Tanshinone-1, which is equally potent against KB and KB/VCR cells, and VCR, which is highly potent and selective against KB cells, were used as positive controls. The results are summarized in Table 2.

Table 2. Cytotoxicity of Selected Compounds Against Cancer Cells

	IC_{50} (μM)	
compound	KB	KB/VCR
7ba	16.7	2.59
7ka	15.8	17.9
7na	17.6	>20
7ac	>20	15.0
9	>20	>20
VCR	0.83	>20
Tanshinone-1	2.75	2.47

Compared to Tanshinone-1 and VCR, most of our selected compounds showed much less potency against the two cancer cell lines. However, compound **7ba** exhibited good potency against KB/VCR with an IC_{50} value of 2.59 μM, which is equally potent as that of Tanshinone-1. Meanwhile, **7ba** is nearly inactive against KB cells (16.7 μM), indicating that this compound might have potential use to overcome tumor resistance to vincristine selectively upon further structure optimization. Further, removal of the indole N-substituent by treating **7aa** with aqueous NaOH (20%) provided 2,3-diphenyl-1*H*-indole (**9**) in 85% yield (see the Supporting Information). Compound **9** was inactive in our biological assay, indicating the importance of the *N*-(3-aminobut-2-enoyl) side chain in our compounds.

In summary, we have established an economical synthesis of a unique class of indoles bearing an *N*-(3-aminobut-2-enoyl) substituent from pyrazolones and alkynes through Rh^{III}-catalyzed redox-neutral C−H activation. This reaction is proposed to undergo a 1,2-rhodium shift/oxidation via N−N bond cleavage without loss of the N-terminus in one step. Biological assay showed that compound **7ba** was potent and selective against vincristine-resistant KB/VCR cell lines and may be used as a hit/lead for further structure optimization.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data of all compounds, and CIF file for compound **7aa** (CCDC 1033339). This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

[‖]Z.F., S.S., and W.L. contributed equally.

Notes

The authors declare no competing financial interest.

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