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Synthesis of Spiropentadiene Pyrazolones by Rh(III)-Catalyzed Formal sp^3 C−H Activation/Annulation

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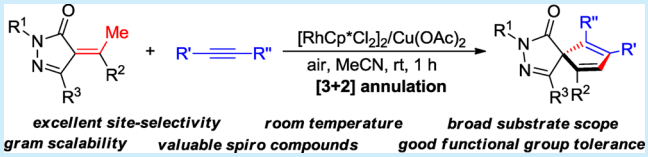
Supporting Information

ABSTRACT: A Rh-catalyzed enol-directed formal sp^3 C−H activation/annulation of α-arylidene pyrazolones with alkynes has been developed. This reaction provides a convenient route to synthesize spiropentadiene pyrazolones in good to excellent yields at room temperature, exhibiting good functional group tolerance, gram scalability, and high regioselectivity. Of note, the α-arylidene pyrazolone was introduced as a novel C3 synthon in C−H activation/annulation.



Spiropyrazolones are important structural motifs that are widely found in pharmaceuticals and biologically active molecules,[1] such as antitumor and antibacterial agents, and type 4 phosphodiesterase inhibitors.[2] Therefore, the exploration of efficient methods to build such core frameworks has attracted much attention in the synthetic community. In the past few decades, significant effort has focused on the synthesis of 4-spiro-5-pyrazolones with a six-membered ring.[3] However, the methods to prepare five-membered-ring 4-spiro-5-pyrazolones were rarely explored. Recently, Lu[4] and Enders[5] independently reported a [1 + 4] annulation reaction to achieve spirocyclopentane pyrazolones employing pyrazolones as the C1 synthon (Scheme 1a). Du and co-workers developed a phosphine-mediated [2 + 3] annulation reaction to offer spirocyclopentanone pyrazolones with unsaturated pyrazolones as the C2 synthon (Scheme 1b).[6] Shortly after, Enders further disclosed an efficient three-component, one-pot method to deliver spiro-pyrazolones relying on the in situ formed unsaturated pyrazolones as the C2 synthon (Scheme 1b).[7] Despite these elegant advances in realizing five-membered-ring 4-spiro-5-pyrazolones, the substrate scope was still limited to pyrazolones or unsaturated pyrazolones as the C1 or C2 synthon.[8]

Recently, transition-metal-catalyzed C−H functionalization as an efficient tool was applied to construct spirocyclic compounds.[9] Luan,[10] You,[11] and Gulías[12] reported Ru- or Rh-catalyzed phenol-directed sp^2 C−H activation/annulation of naphthols or 2-alkenylphenols to offer spirocyclic enones. Lam and co-workers[13] demonstrated enol-directed sp^2 C−H activation/annulation of 2-aryl cyclic-1,3-dicarbonyl compounds to synthesize spiroindenes. To the best of our knowledge, the

Scheme 1. Methods To Construct Five-Membered-Ring 4-Spiro-5-pyrazolones

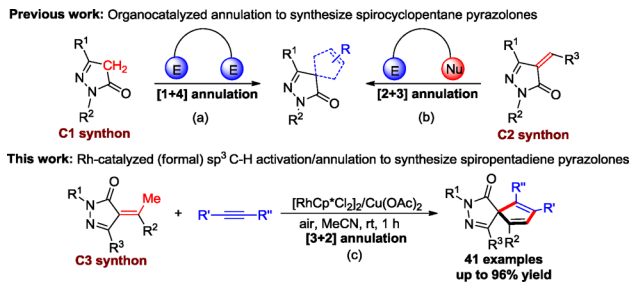
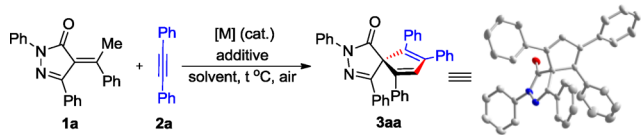


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	additive	solvent	yield[b] (%)
1	$[Ru(p\text{-cymene})Cl_2]_2$	$Cu(OAc)_2$	DMF	42
2[d]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	0
3	$[IrCp^*Cl_2]_2$	$Cu(OAc)_2$	DMF	14
4	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	DMF	69
5[d]	$Rh(OAc)_2$	$Cu(OAc)_2$	DMF	trace
6	$[Rh(COD)Cl]_2$	$Cu(OAc)_2$	DMF	trace
7	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	1,4-dioxane	40
8	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	toluene	39
9	**$[RhCp^*Cl_2]_2$**	**$Cu(OAc)_2$**	**MeCN**	**92**
10	$[RhCp^*Cl_2]_2$	AgOAc	MeCN	81
11	$[RhCp^*Cl_2]_2$	Ag_2CO_3	MeCN	30
12	$[RhCp^*Cl_2]_2$	$K_2S_2O_8$	MeCN	0
13[e]	**$[RhCp^*Cl_2]_2$**	**$Cu(OAc)_2$**	**MeCN**	**89**
14[f]		$Cu(OAc)_2$	MeCN	nr[c]
15[g]	$[RhCp^*Cl_2]_2$		MeCN	nr[c]

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), catalyst (2.5 mol %), additive (1.0 equiv), solvent (1.0 mL) at 85 °C for 1 h under air atmosphere. [b]Isolated yields. [c]No reaction. [d]Catalyst (5.0 mol %). [e]The reaction was conducted at room temperature. [f]Without $[RhCp^*Cl_2]_2$. [g]Without $Cu(OAc)_2$.

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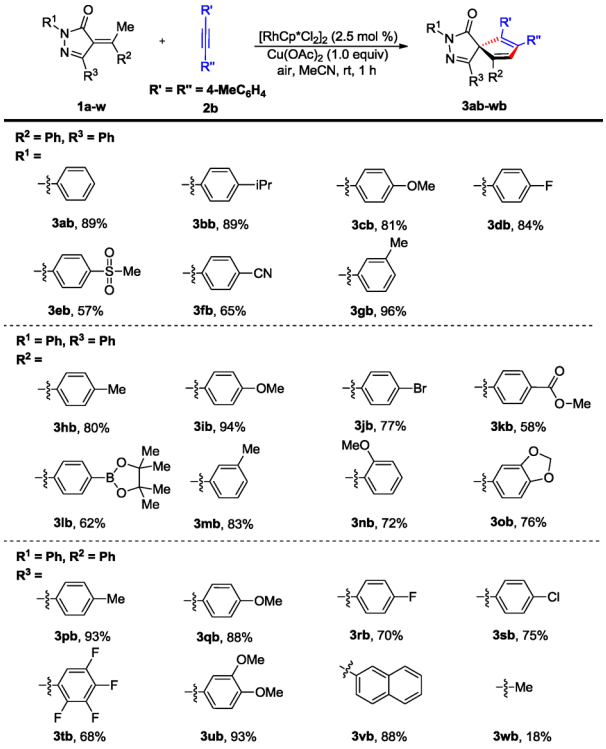
Scheme 2. Substrate Scope of α-Arylidene Pyrazolones[a,b]



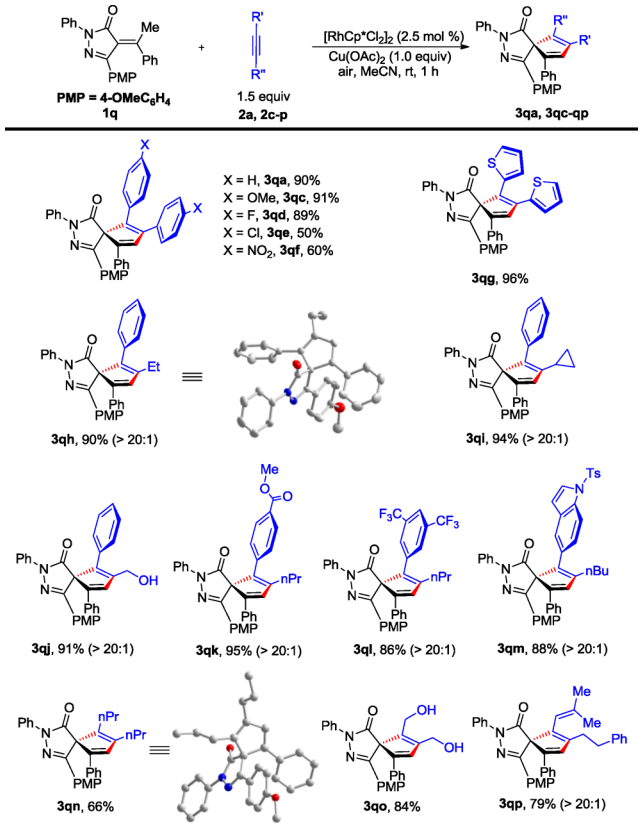
[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2b** (0.3 mmol, 1.5 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (1.0 equiv), MeCN (1.0 mL) at room temperature for 1 h under air atmosphere. [b]Isolated yields.

employment of α-arylidene pyrazolones[3f] as the C3 synthon to construct five-membered-ring 4-spiro-5-pyrazolones has not been reported. In view of our continuous interest in preparing spirocyclic scaffolds,[14] herein, we describe a Rh-catalyzed enol-directed formal sp^3 C−H activation/annulation of α-arylidene pyrazolones with internal alkynes to synthesize spiropentadiene pyrazolones at room temperature (Scheme 1c).

We commenced our research by examining (*E*)-1,3-diphenyl-4-(1-phenylethylidene)-1*H*-pyrazol-5(4*H*)-one **1a** and diphenylethyne **2a** as the model substrates (Table 1). Screening of catalysts found that $[RhCp^*Cl_2]_2$ with stoichiometric $Cu(OAc)_2$ as the additive in DMF at 85 °C offered the desired spiropentadiene pyrazolone **3aa** in 69% yield (Table 1, entry 4), whereas other catalysts such as $[Ru(p\text{-cymene})Cl_2]_2$, $Pd(OAc)_2$, $[IrCp^*Cl_2]_2$, $Rh(OAc)_2$, and $[Rh(COD)Cl]_2$ revealed inferior capacities (Table 1, entries 1−6). The structure of **3aa** was assigned by an X-ray crystallographic analysis (see the Supporting Information (SI) for details).[15] The yield of **3aa** could be further increased to 92% when MeCN was chosen as a solvent (Table 1, entries 4 and 7−9). Employment of other additives instead of $Cu(OAc)_2$ failed to promote the efficiency of the reaction (Table 1, entries 10−12). Gratifyingly, the reaction could also proceed at room temperature without significant loss of the yield, and **3aa** could be isolated in 89% yield (Table 1, entry 13). Control experiments showed that $[RhCp^*Cl_2]_2$ and $Cu(OAc)_2$ played a pivotal role in the transformation of the reaction (Table 1, entries 14 and 15).

Having optimized the reaction conditions, we then examined the substrate scope of α-arylidene pyrazolones, and the results are shown in Scheme 2. The reaction worked well with electron-donating groups (EDGs) on the N-aryl moiety (R^1), providing

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



[a]Reaction conditions: **1q** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (1.0 equiv), MeCN (1.0 mL) at room temperature for 1 h under air atmosphere. [b]Isolated yields.

3ab−**cb** in 81−89% yields, whereas electron-withdrawing groups (EWGs) underwent moderate conversion into the products. Substrates with methyl and methoxy groups on the arylidene moiety (R^2) offered **3hb** and **3ib** in 80 and 94% yields. Functional groups, such as bromide, ester, and boronate groups gave **3jb**−**lb** in 58−77% yields, which presented an opportunity for further transformation. Steric hindrance of the aromatic ring did not obviously affect the reaction performance, offering **3mb** and **3nb** in 83 and 72% yield, respectively. As expected, the presence of EDGs and EWGs at R^3 yielded **3pb**−**sb** in 70−93% yields. Polyfluorinated phenyl and naphthyl groups took place smoothly to deliver **3tb** and **3vb** in 68 and 88% yield, respectively. When the aryl group was replaced by methyl group, **3wb** was obtained in 18% yield.

Next, the substrate scope of alkynes was investigated using **1q** as a representative α-arylidene pyrazolone. As shown in Scheme 3, symmetrical alkynes with various aryl substituents were all found to be suitable for the reaction and gave **3qa** and **3qc**−**qf** in moderate to good yields. 2-Thienyl-substituted alkyne could deliver **3qg** in 96% yield. With nonsymmetrical alkynes, the C−C bond formation in alkyne insertion step preferentially occurred at the alkyne carbon with the alkyl group, exhibiting excellent regioselectivity. 1-Phenyl-1-butyne **2h** delivered **3qh** in 90% yield. Similarly, 94% yield of **3qi** was obtained from (cyclopropylethynyl)benzene **2i**. 3-Phenylprop-2-yn-1-ol **2j** with a hydroxyl group produced **3qj** in 91% yield. Other unsymmetrical alkynes with ester group (**2k**) or trifluoromethyl group (**2l**) on the benzene ring were both adaptable. More

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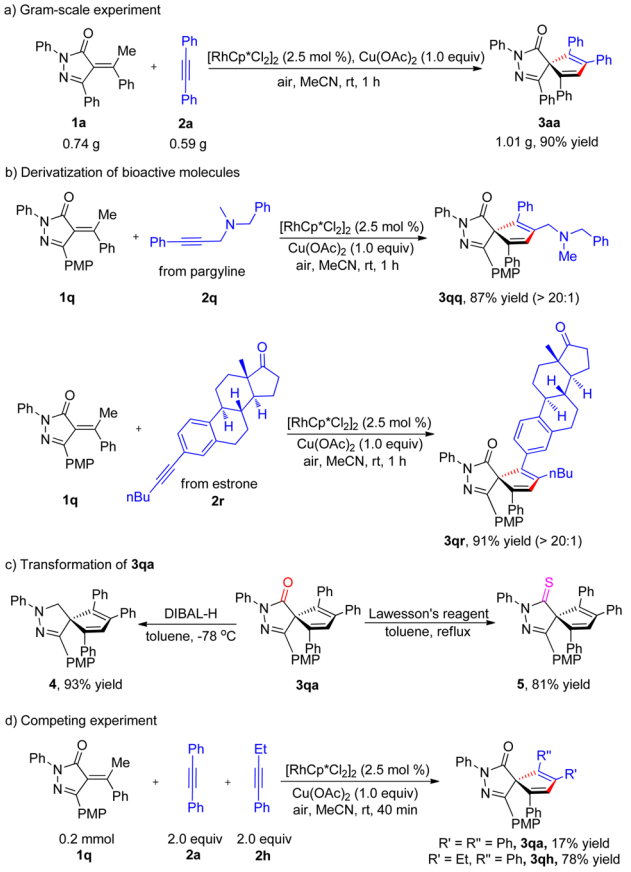
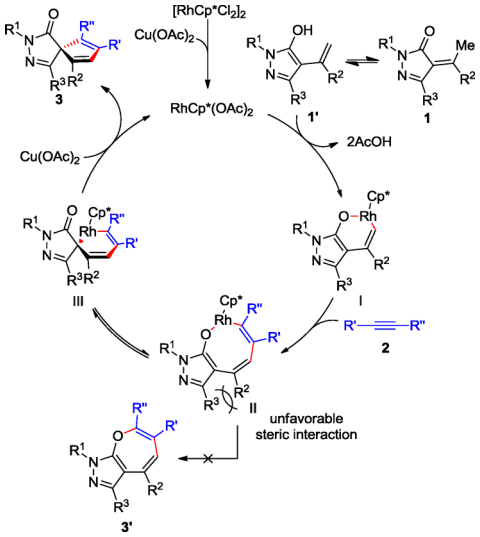
Scheme 4. Further Study of Rh-Catalyzed C−H Activation/Annulation of α-Arylidene Pyrazolones with Alkynes



Scheme 5. Proposed Mechanism



importantly, this reaction could be further amplified by replacement of the aromatic ring with indolyl group (**3qm**). Alkynes bearing symmetrical alkyl groups underwent prosperously. 4-Octyne **2n** provided **3qn** in 66% yield. 2-Butyne-1,4-diol **2o** with two hydroxyl groups gave **3qo** in 84% yield. The reaction could also proceed with conjugated enynes like **2p**, leading to **3qp** in 79% yield. The structures of **3qh** and **3qn** were both confirmed by X-ray crystallographic analysis (see the SI for details).[15]

To evaluate the efficiency and practicality of this reaction, a gram-scale experiment was examined. As shown in Scheme 4a, the preliminary test of **1a** with **2a** led to 1.01 g of **3aa** in 90% yield. This efficient and facile protocol could also find applications in some pharmacologically active molecules (Scheme 4b). The alkyne **2q** derived from pargyline, which was mainly used for clinical severe hypertension, afforded **3qq** in 87% yield. Spiropentadiene pyrazolones could be conveniently installed on estrone to construct **3qr** in 91% yield, albeit with a large steric hindrance. The synthetic utility of the products was further demonstrated by their ability to undergo several transformations (Scheme 4c). The reduction of the amide group in **3qa** with DIBAL-H at −78 °C provided pyrazoline derivative **4** in 93% yield. Treatment of **3qa** with Lawesson's reagent in toluene afforded spiropyrazole-5-thione **5** in 81% yield. To compare the activity of alkynes, the treatment of **1q** with 1-phenyl-1-butyne **2h** and diphenylacetylene **2a** was tested, affording **3qh** as the preferential product in 78% yield and **3qa** in 17% yield (Scheme 4d). This result suggested that the steric hindrance of alkyne may influence the reactivity.

On the basis of previous reports,[10−13] a putative mechanism was proposed as shown in Scheme 5. Mixture of $[RhCp^*Cl_2]_2$ with $Cu(OAc)_2$ forms the activated Rh catalyst. Deprotonation of substrate **1** generates a dienolate **1′**. The in situ formed enol group bonds to the Rh catalyst through ligand-to-ligand exchange, which then cleaves the adjacent C−H bond to generate a six-membered rhodacycle intermediate **I**. Coordination and regioselective migratory insertion of alkyne **2** generates an eight-membered rhodacycle intermediate **II**.[16] To relieve the unfavorable steric interaction between R^2 and R^3,[12,17] the key six-membered intermediate **III** is formed after isomerization, whereas the [5 + 2] annulation product **3′** could not be formed under the standard reaction conditions. Finally, C−C bond reductive elimination takes place to offer the spirocyclic product **3**, and the activated Rh catalyst is regenerated after oxidation by $Cu(OAc)_2$.

In summary, we have developed an unprecedented Rh-catalyzed enol-directed formal sp^3 C−H activation/oxidative annulation of α-arylidene pyrazolones with alkynes, providing spiropentadiene pyrazolones in good to excellent yields at room temperature. The α-arylidene pyrazolone was first introduced as a novel C3 synthon in C−H activation/annulation. Further applications of α-arylidene pyrazolones in transition-metal-catalyzed C−H functionalization to synthesize spiropyrazolones are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00930.

^1H and ^{13}C NMR spectra for all new compounds (PDF)
X-ray data for **3aa** (CIF)
X-ray data for **3qh** (CIF)
X-ray data for **3qn** (CIF)

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Notes

The authors declare no competing financial interest.

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(8) During and after the submission of our paper, a Rh-catalyzed C−H functionalization/annulation to synthesize five-membered-ring 4-spiro-5-pyrazolones using 4-aryl-5-pyrazolone as C3 synthon was disclosed: Zheng, J.; Wang, S.-B.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2017**, *56*, 4540.

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(15) Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition numbers CCDC 1525039 (**3aa**), 1525058 (**3qh**), and 1525049 (**3qn**). Detailed information can be found in the Supporting Information.

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