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Rhodium(III)-Catalyzed Oxidative Annulation of 7-Azaindoles and Alkynes via Double C−H Activation

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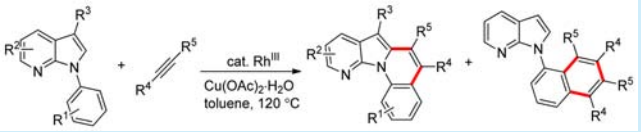
S *Supporting Information*

ABSTRACT: Rhodium(III)-catalyzed double C−H activation involving *N*-directed *ortho* C−H activation and subsequent *roll-over* C−H activation of the heterocycle ring has been developed to form complex 7-azaindole derivatives in moderate to excellent yields. A broad scope of 7-azaindoles and internal alkynes has been demonstrated in this oxidative annulation reaction.

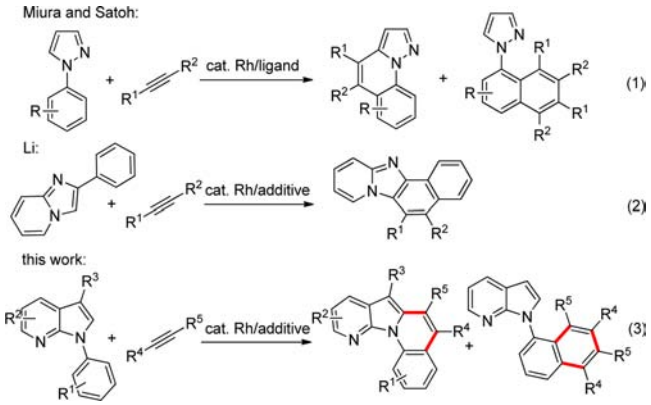


The azaindole skeleton is a valuable structural unit in numerous potential bioactive compounds and pharmaceutical molecules.[1] In particular, the functional 7-azaindole structures have been successfully used in many agents, including anticancer drug Vemurafenib (PLX-4032),[2] hNK1 receptor,[3] and PLX4720.[4] These facts led to an increased interest in developing new methods for efficient functional group modifications of this motif.

Transition-metal-catalyzed direct C−H bond functionalization has been widely exploited in the synthesis of various heterocyclic compounds due to its high efficiency and environmentally benign features.[5] Therefore, several approaches have been developed to modify the structure of 7-azaindole. For example, palladium-catalyzed direct arylations of 7-azaindole have been described.[6] Recently, Xu and co-workers reported an unexpected rhodium-catalyzed regioselective C−H chlorination of 7-azaindoles.[7] However, C−H activation and cyclization with alkynes using 7-azaindole as the directing group has not been studied yet.

The heteroatom-assisted chelation is broadly employed in rhodium- or ruthenium-catalyzed C−H activation.[8] To the best of our knowledge, there are only two examples that reported rhodium-catalyzed cyclization reactions between *N*-phenylpyrazoles or 2-phenylimidazo[1,2-α]pyridines and alkynes via *N*-directed *ortho* C−H activation and subsequent *roll-over* C−H activation (Scheme 1, eqs 1 and 2).[9] However, most nitrogen heterocycles, such as 2-phenylpyridines, have no such reactivity to provide oxidative annulation products, indicating that dechelation of nitrogen and *roll-over* C−H activation probably have a high kinetic barrier.[10] Therefore, we hoped to use *N*-arylazaindoles as substrates to synthesize aza-fused scaffolds through double C−H activation resulting in oxidative annulation due to the high reactivity of the 2-position of the pyrrole ring. Herein, we describe an efficient condition-controlled protocol to access complex 7-azaindole derivatives via rhodium(III)-catalyzed *N*-directed *ortho* C−H activation followed by subsequent *roll-over* C−H activation, and *N*-naphthylazole derivatives where 2 equiv of alkynes are incorporated (Scheme 1, eq 3).

Scheme 1. *N*-Directed *Ortho* C−H Activation and Subsequent *Roll-Over* C−H Activation



At the outset of our study, we investigated the rhodium(III)-catalyzed coupling reaction of 7-azaindole **1a** with diphenylacetylene **2a** (Table 1). With the exception of $Cu(OAc)_2·H_2O$, the presence or absence of additives afforded no annulation reaction (entries 1−6). During the survey of the reaction conditions, several solvents such as DMF, *t*-AmOH, 1,4-dioxane, and CH_3CN were screened. It is worth mentioning that most of the solvents were compatible with this reaction (entries 7−10).

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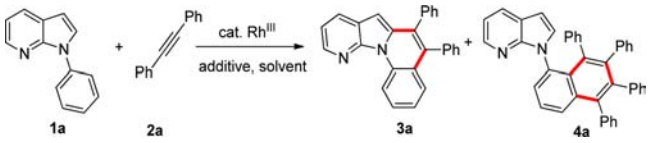
Table 1. Optimization of the Reaction Conditions[a]



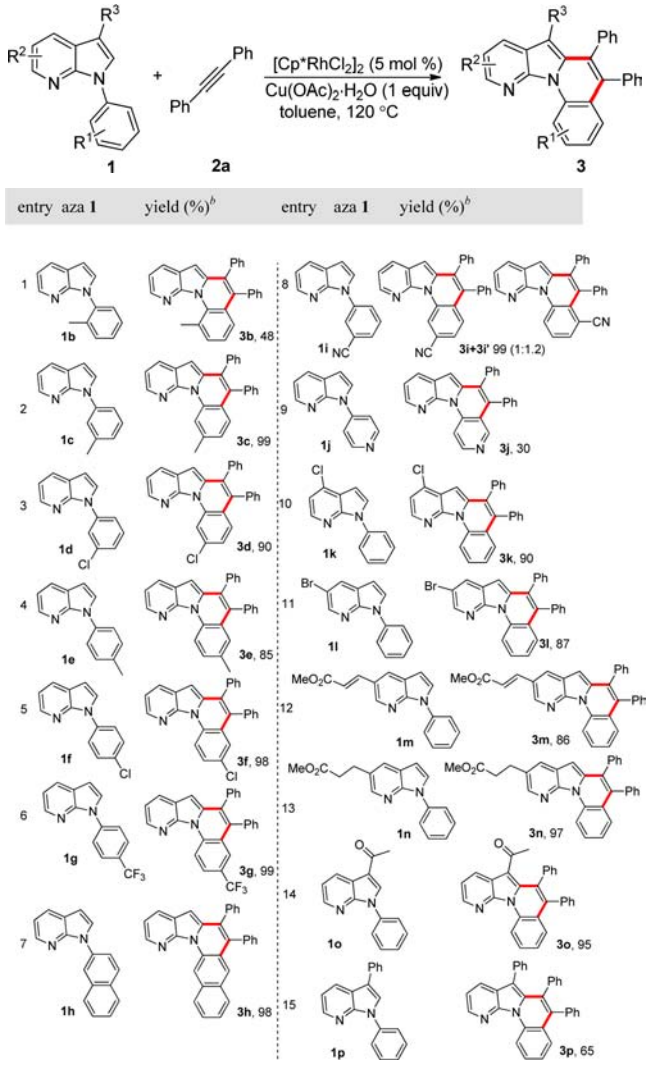
entry	catalyst	additive	solvent	yield (%)[b] 3a/4a
1	$[Cp^*RhCl_2]_2$	--	toluene	N.R
2	$[Cp^*RhCl_2]_2$	Ag_2O	toluene	N.R.
3	$[Cp^*RhCl_2]_2$	Ag_2CO_3	toluene	N.R.
4	$[Cp^*RhCl_2]_2$	$Cu(OTf)_2$	toluene	N.R.
5	$[Cp^*RhCl_2]_2$	CuI	toluene	N.R.
6	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	toluene	97/0
7	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	DMF	82/0
8	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	*t*-AmOH	85/0
9	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	1,4-dioxane	90/0
10	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	95/0
11[c]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	toluene	33/0
12[d]	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	$Cu(OAc)_2{\cdot}H_2O$	toluene	71/22
13[d]	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	30/53
14[e]	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	28/65
15[f]	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	10/75

[a]Reaction conditions unless otherwise specified: 0.04 mmol of **1a**, 0.048 mmol of **2a**, 5 mol % of catalyst, 1.0 equiv of additive, 0.6 mL of solvent, 120 °C, 24 h, Ar atmosphere. [b]Isolated yield. [c]100 °C, 48 h. [d]1.5 equiv, 0.06 mmol of **2a**. [e]2.5 equiv, 0.10 mmol of **2a**. [f]3.5 equiv, 0.14 mmol of **2a**.

Lower temperatures, even with extended reaction times, resulted in lower isolated yields (entry 11). Furthermore, a *N*-naphthoxazole derivative was isolated when $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ was used as a catalyst (entry 12). An opposite ratio of annulated products was observed when switching solvents from toluene to acetonitrile (entry 13). The ratio of *N*-naphthoxazole can be improved by increasing the number of equivalents of diphenylacetylene **2a** (entries 14 and 15).

With the optimized reaction conditions in hand, the scope of 7-azaindole derivatives was examined in Table 2. Electron-donating and -withdrawing substituents on different positions of 7-azaindole were employed in the reaction affording the corresponding products in good to excellent yields. As we imagined, the methyl group at the *ortho*-position of the benzene ring would block the *roll-over* process to give **3b** in only 48% yield. To our delight, *meta*-substituted aryl substrates **1c** and **1d** showed excellent regioselectivity and the corresponding products were produced in excellent yields, probably due to strong steric effects. The electronic effects of various *para*-substituted groups slightly impacted the reaction efficiency. Compounds **3f** and **3g** were obtained in 98% and 99% yields, respectively, while **3e** was obtained in 85% yield. Interestingly, the reaction using β-naphthalene-substituted **1h** proceeded smoothly through the activation of the less hindered C−H bond rather than the active α-H of naphthalene, providing the single product **3h** in 98% yield. In contrast, the observation of two regeoisomers in the case of **3i** and **3i′** may be due to the ability of the nitrile group to coordinate to rhodium. In addition, 7-azaindole bearing a *N*-heteroaryl group was less productive, furnishing **3j** in only 30% yield. Moreover, substrates with a halogen on pyridine ring were well tolerated, and the products **3k** and **3l** were prepared in 90% and 87% yields, respectively. The cyclization products provided an ideal platform for iterative cross-coupling and further functionalization. Moreover, the functionalized alkene substituted substrate **1m** and alkyl substituted substrate **1n** were suitable for this coupling process giving

Table 2. Substrate Scope of 7-Azaindoles[a]



[a]Reactions were carried out by using 0.10 mmol of **1**, 0.12 mmol of **2a**, 5 mol % of $[Cp^*RhCl_2]_2$, 1.0 equiv of $Cu(OAc)_2{\cdot}H_2O$, 1.5 mL of toluene, 120 °C, 24−32 h, Ar atmosphere. [b]Yields refer to isolated yields.

corresponding products in 86% and 97% yields, respectively. To our delight, substituents in the 3-position of the pyrrole ring were also suitable coupling partners for diphenylacetylene insertion. The substrate **1o** could also react smoothly with **2a** to give the desired product **3o** in 95% yield. In contrast, the bulky phenyl substrate **1p** afforded the corresponding product **3p** in only 65% yield.

Table 3 summarized the scope of diverse alkynes that led to successful reactions using this method. A wide variety of internal alkynes afforded the annulation products in moderate to excellent yields. First, we employed symmetrical diarylacetylene as a coupling partner to examine the reaction. The diarylacetylene with different electronic properties at the various positions of the benzene ring were well tolerated in the reaction with **1a**, and the corresponding products (**3q**−**3u**) were afforded in high yields. In contrast, the alkyl-disubstituted alkyne **2v** gave a slightly lower yield. Unsymmetrical alkynes **2w** and **2x** were employed to give the isomers in moderate yields with poor regioselectivity; in addition, **2y** participated in this coupling reaction smoothly affording the corresponding product **3y** in

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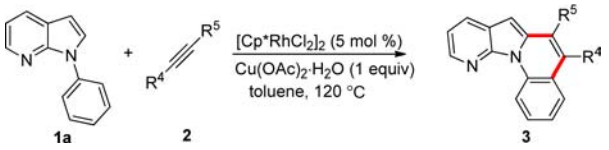
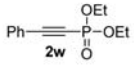
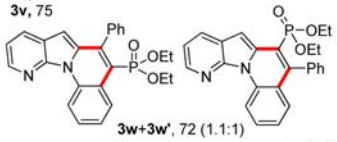
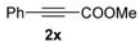
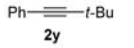
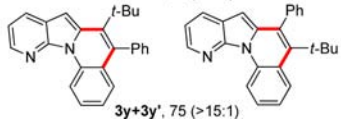
Table 3. Substrate Scope of Alkynes[a]



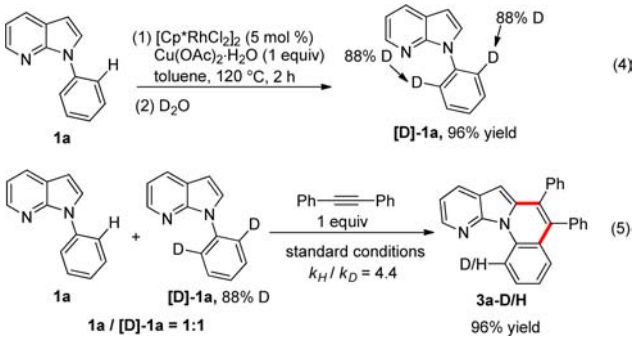
entry	alkynes **2**	yield (%)[b]
1	**2q** ($R^4 = R^5 = o$-MeC_6H_4)	**3q**, 89
2	**2r** ($R^4 = R^5 = m$-ClC_6H_4)	**3r**, 91
3	**2s** ($R^4 = R^5 = p$-ClC_6H_4)	**3s**, 96
4	**2t** ($R^4 = R^5 = p$-FC_6H_4)	**3t**, 96
5	**2u** ($R^4 = R^5 = p$-MeC_6H_4)	**3u**, 95
6	**2v** ($R^4 = R^5 = n$Bu)	**3v**, 75
7	 **2w**	 **3w+3w'**, 72 (1.1:1)
8	 **2x**	 **3x+3x'**, 50 (1.5:1)
9	 **2y**	 **3y+3y'**, 75 (>15:1)

[a]Reaction were carried out by using 0.10 mmol of **1a**, 0.12 mmol of **2**, 5 mol % of $[Cp^*RhCl_2]_2$, 1.0 equiv of $Cu(OAc)_2 \cdot H_2O$, 1.5 mL of toluene, 120 °C, 24−40 h, Ar atmosphere. [b]Yields refer to isolated yields. Ratios of regioisomers are given within parentheses and were determined by ^1H NMR analysis.

75% yield with high regioselectivity, likely due to the electronic effect during formation of the rhodacyclic intermediate. Terminal alkynes failed to react under the conditions described.

To investigate the mechanism of this reaction, deuterium-labeling experiments were conducted (Scheme 2). When **1a** was quenched by D_2O in the absence of alkynes, deuterium was observed at both *ortho*-positions (eq 4). A deuterium kinetic isotope effect (DKIE) of 4.4 was observed, which indicates that the first *ortho* C−H bond cleavage might be involved in the rate-determining step (eq 5).

Scheme 2. Deuterium-Labeling Experiments



In summary, we have successfully developed a rhodium(III)-catalyzed oxidative annulation of 7-azaindoles with internal alkynes to form diverse complex 7-azaindole derivatives. The expected double C−H activation process might involve *N*-directed *ortho* C−H activation and subsequent *roll-over* C−H activation of the heterocycle ring. A broad scope of 7-azaindoles and internal alkynes has been demonstrated, and most of the examples gave moderate to excellent yields. Further applications of the approach to build biologically active molecules are being conducted in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, structural proofs, and NMR spectra of the products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01228.

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Notes

The authors declare no competing financial interest.

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