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Rhodium-catalyzed Synthesis of 1-(Acylamino)isoquinolines through Direct Annulative Coupling of 3-Aryl-1,2,4-oxadiazoles with Alkynes

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A Rh(III)-catalyzed direct annulative coupling of 3-aryl-1,2,4-oxadiazoles with alkynes through coordination-assisted C–H activation is developed, providing a facile route to 1-(acylamino)isoquinolines. The oxadiazole ring acts as directing group as well as internal oxidant.

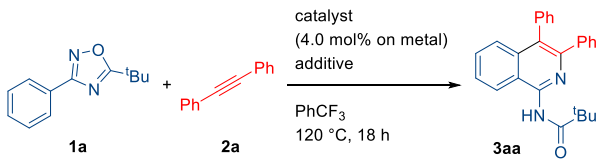
Keywords: C-H activation, Rhodium, Isoquinoline

Isoquinolines are ubiquitous in nature and important structural motifs for many biologically active compounds.[1] In addition, isoquinoline derivatives have been of frequent use as chiral ligands in asymmetric synthesis.[2] Recently, transition metal-catalyzed C–H activation and subsequent cyclization using imines[3] or oxime derivatives[4,5] as directing groups have been a versatile synthetic tool for the construction of isoquinoline frameworks. It is noteworthy that, in the latter cases, the N–O bond in the directing group serves as internal oxidant, achieving the formal oxidative coupling reaction without any additional oxidant.[6] Similar phenomena merged in the Rh-catalyzed isoquinoline synthesis using hydrazones or vinyl azides, where the N–N bond acts as internal oxidant.[7]

For extension of our research interest in catalytic isoquinoline synthesis,[3b,3c,8] we envisaged that the use of 3-aryl-1,2,4-oxadiazoles, which bear an N–O linkage in the heterocyclic ring as directing group, would be beneficial to achieve an efficient synthesis of 1-aminoisoquinolines.[9,10] The 1,2,4-oxadiazole core is rather stable owing to its aromatic nature, and various substituted derivatives are available, since Grignard reagents[11] or boronic acids[12] can be a source of C3-aryl group. We herein report a Rh(III)-catalyzed direct annulative coupling of 3-aryl-1,2,4-oxadiazoles **1** and alkynes **2** to furnish 1-(acylamino)isoquinolines, where the cleavage of labile N–O bond plays a crucial role to achieve an external-oxidant free protocol.[13]

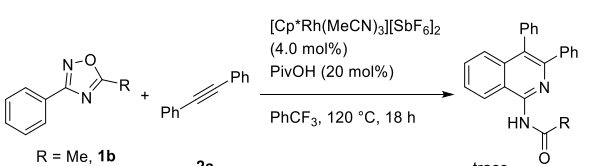
We began our investigation into the annulative coupling reaction using 5-(tert-butyl)-3-phenyl-1,2,4-oxadiazole (**1a**) with diphenylacetylene (**2a**) as model substrates (Table 1). The corresponding 1-aminoisoquinoline **3aa** was obtained in 28% yield in the presence of $[Cp^*RhCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) and $AgSbF_6$ (entry 2). Exclusion of $AgSbF_6$ resulted in the negligible outcome (entry 1). Consequently, a cationic complex $[Cp^*Rh(MeCN)_3][SbF_6]_2$ was used as catalyst and a significant increase of the yield was observed; however, the duplicability of the reaction runs was insufficient (entry 3). This might be due to the fact that oxadiazole **1a** contained a trace amount of pivalic acid, the amount of which would be varied upon the purification processes. We thereby tested several carboxylic acids to the present reaction as additives, and found that the addition of 20 mol% of pivalic acid considerably improved both the reaction efficiency and reproducibility (entries 4 and 5). Acetic acid and benzoic acid were less effective (entries 6 and 7). No desired product was obtained with $CpCoI_2(CO)$ or $[RuCl_2(p\text{-cymene})]_2$ as catalyst (entries 8 and 9). We also evaluated the effect of C5-substituent on the oxadiazole ring: methylated **1b** and phenylated **1c** substrates were found to be inadequate, giving only trace amounts of annulation products (eq. 1).

Table 1. Optimization study



entry	catalyst	additive	yield [a]
1	$[Cp^*RhCl_2]_2$	--	n.d.
2	$[Cp^*RhCl_2]_2$	$AgSbF_6$ (8.0 mol%)	28%
3	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	--	10-91% [b]
4	**$[Cp^*Rh(MeCN)_3][SbF_6]_2$**	**PivOH (20 mol%)**	**81%** [b,c]
5	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	PivOH (100 mol%)	59% [b]
6	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	AcOH (20 mol%)	50%
7	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	$PhCO_2H$ (20 mol%)	17%
8	$CpCoI_2(CO)$ (10 mol%)	$AgSbF_6$ (20 mol%)	n.d.
9	$[RuCl_2(p\text{-cymene})]_2$	KPF_6 (30 mol%)	n.d.

Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), catalyst (4.0 mol% on metal), and $PhCF_3$ (1.0 mL). [a]Determined by NMR analysis. [b]Isolated yield. [c]Average of three runs. n.d. = not detected

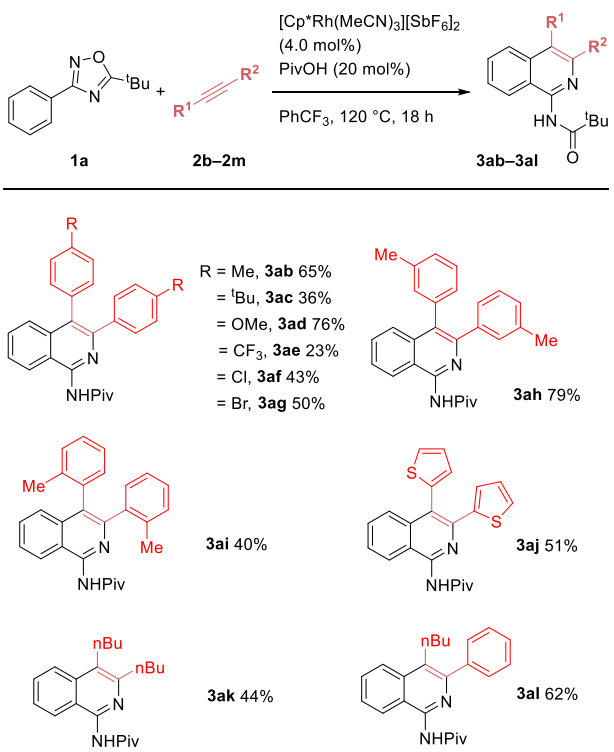


(1)

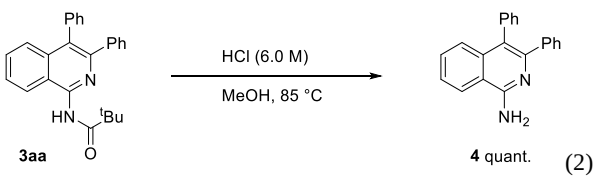
Under the optimized reaction conditions in hand, substrate scope for alkynes was investigated (Table 2). 4,4'-Disubstituted diphenylacetylenes bearing electron-donating

2b–**2d** and -withdrawing **2e**–**2g** groups were all converted into the corresponding 1-aminoquinolines **3ab**-**3ag**, albeit a diminished yield was obtained for the electron deficient alkyne **2e**. The *ortho* substituents on **2i** considerably retarded the reaction as compared to **2b** and **2h** probably due to its steric bulk around the alkyne moiety. Di(2-thienyl)acetylene (**2j**) and 5-decyne (**2k**) also underwent the reaction. Noteworthy, an unsymmetrically substituted alkyne **2l** furnished the annulated product as a single regioisomer, where the phenyl group was installed to the nitrogen side. Use of a terminal alkyne such as phenylacetylene, however, did not give any coupling product. The pivaloyl group on **3aa** could be easily removed by acidic treatment and aminoquinoline **4** was obtained quantitatively (eq. 2).

Table 2. Substrate scope for alkynes



Reaction conditions: **1a** (0.2 mmol), **2** (0.22 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4.0 mol%), PivOH (20 mol%), and $PhCF_3$ (2.0 mL). Isolated yields are shown.

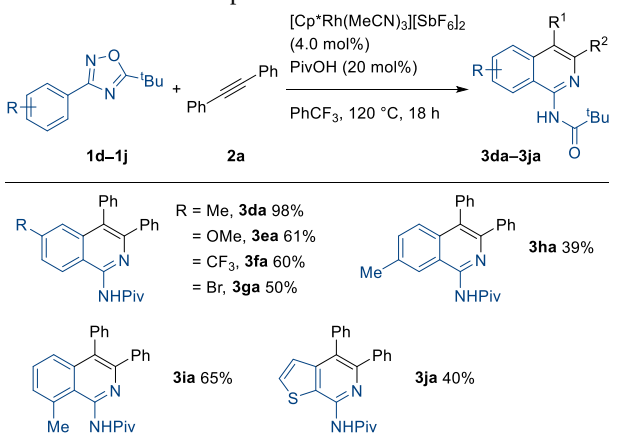


(2)

Next, we examined the reaction of a number of 3-aryl-1,2,4-oxadiazoles with diphenylacetylene (**2a**) (Table 3). The *para*-substituted oxadiazoles **1d**–**1g** reacted successfully to give the corresponding isoquinolines in good to high yields. The reaction proceeded predominantly at the sterically uncongested position for **1h**, and **3ha** was obtained as a sole product. The *ortho*-substituted oxadiazole **1i** was also compatible. Construction of a thieno-fused pyridine framework was achieved via the annulative coupling of **1j**.

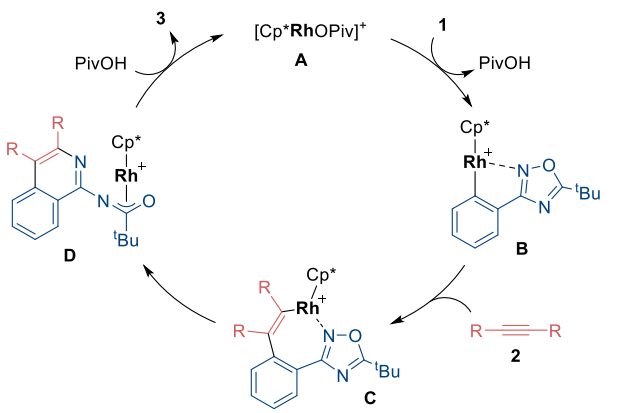
A plausible mechanism for the present reaction is illustrated in Scheme 2. The catalytically active specie is assumed to be $[Cp^*RhOPiv]^+$ **A** which may arise from the Rh precatalyst and pivalic acid. The 2-N atom of oxadiazole **1** coordinates to the metal and thereby C–H bond cleavage occurs to give 5-membered rhodacycle **B**. This step should be reversible according to the preliminary deuterium labeling experiment: 11% hydrogen incorporation was observed in the recovered starting material for the reaction of **1a**-d_5 with **2a**.[14] Subsequently, alkyne **2** inserts into the Rh–C bond to generate intermediate **C**. At this stage, stepwise[6g] or concerted[15] C–N bond formation/N–O bond scission takes place to form the isoquinoline ring. Protonation of complex **D** liberates the product **3** and regenerates the catalyst.

Table 3. Substrate scope for oxadiazoles



Reaction conditions: **1** (0.2 mmol), **2a** (0.22 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4.0 mol%), PivOH (20 mol%), and $PhCF_3$ (2.0 mL). Isolated yields are shown.

Scheme 2. Proposed reaction mechanism for the coupling reaction of oxadiazole **1** with alkyne **2**



In summary, we have developed a Rh(III)-catalyzed direct coupling reaction of 3-aryl-1,2,4-oxadiazoles and alkynes. The oxadiazole ring works as directing group as well as formal oxidizing reagent to ensure the catalytic turnover. This protocol appears to be an effective method for the synthesis of 1-aminoisoquinoline derivatives of interest in pharmaceutical chemistry.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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14 For details, see the Supporting Information.

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