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COMMUNICATION

Rh(III)-catalyzed Cyclization Reaction of Azoles with Alkynes: Efficient Synthesis of Azole-fused-Pyridines

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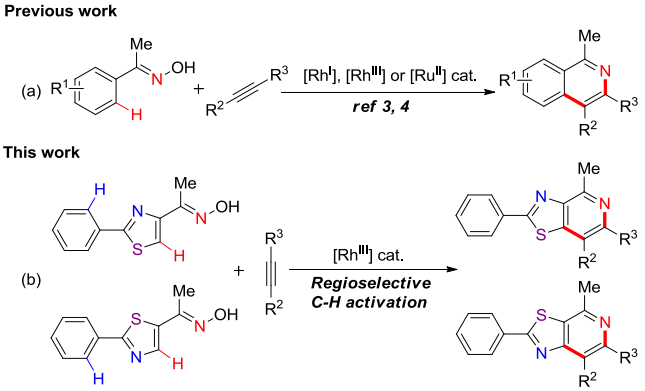
Rh(III)-catalyzed cyclization of azoles with alkynes has been developed. A variety of azole-fused-pyridines were accomplished in good to excellent yields and regioselectivity. Both the C5 position and the C4 position of azoles were suitable in the reaction.

In the past few years, chelation-assisted electrophilic metalation of an ortho sp2 C-H bond directed by the nitrogenous groups offering an advanced route for the construction of azacyclic compounds.[1] Among of these nitrogenous directing groups, oximido was frequently reported in recent years.[2] Cheng and Chiba's groups reported the Rh(I) or Rh(III)-catalyzed tandem C-C/C-N bond formation reaction between oximes and alkynes respectively.[3] In 2012, Ackermann and Jeganmohan completed the same reaction employing Ru(II) as the catalyst.[4] These examples provided concise ways to the synthesis of isoquinolines and their derivatives (**Scheme 1,** a).[5] However, to our knowledge, the heterocycle-fused-pyridines, which possess extensive bioactivities, were not studied specifically up to now.[6] When come to heterocycles in directed C-H activation reactions, two problems maybe meet: (1) Heteroatoms such as nitrogen or sulphur atoms in substrates often outcompete the directing groups for catalyst binding, thus making the catalyst poisoned or preventing the C-H activation progress.[7] (2) Some nitrogen-containing heterocyclic rings such as azoles themselves could play as directing groups,[8] which could make the C-H functionalization at an undesired position.



Scheme 1. Transition metal catalyzed reaction of oximes with alkynes

Azole-fused-pyridines are common structural skeleton in bioactive molecules.[9] The existing methods to prepare azole-fused-pyridines mostly start from substituted pyridines to synthesize the azole rings.[10] Recently, our group focused on the direct functionalization of azoles via C-H activation.[11] As we know, the C-H activation of the C4 position of azoles was more challenging compared to the C5 position, and few examples on the C-H functionalization of the C4 position of azoles with non-preactivated reagents have been reported.[12] Continuing our interest in the transition metal catalyzed C-H functionlization of azoles, in this paper, we will report a Rh(III)-catalyzed cyclization reaction of thiazoles/oxazoles with alkynes to construct thiazole/oxazole-fused-pyridines (**Scheme 1**, b), both the C5 and the C4 position of azoles are suitable in this reaction.

Initially, we examined the reaction of 1-(2-phenylthiazol-4-yl)ethanone oxime (**1a**) with 1,2-diphenylethyne (**2a**) as the model reaction to optimize the reaction conditions. When the two substrates were treated with 2.5 mol % $[RhCp^*Cl_2]_2$ as a catalyst, 2 equivalent of NaOAc as an additive in MeOH at 60 ^oC for 24 h, we were delighted to get the corresponding product **3a** in 91% isolated yield (**Table 1**, entry 1). Screening of the base additives revealed that CsOAc was an alternative base of NaOAc, while K_2CO_3 decreased the yield to 67% (**Table 1**, entries 2-3). Decreasing the equivalent of **2a** to 1.2 led to 95%

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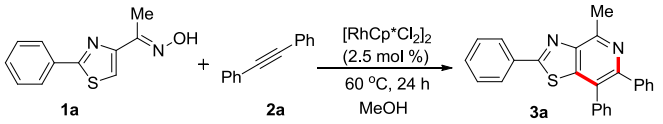
yield (**Table 1**, entry 4). The similar yields were achieved when the equivalent of NaOAc was decreased to 1 or 0.3 (**Table 1**, entries 5-6). Decreasing the amount of catalyst $[RhCp^*Cl_2]_2$ to 1 mol % reduced the yield to 76% (**Table 1**, entry 7). Finally, when $[RuCl_2(p\text{-Cymene})]_2$ was also employed as the catalyst, no product was observed (**Table 1**, entry 8).

Table1. Optimization of the reaction conditions [a]



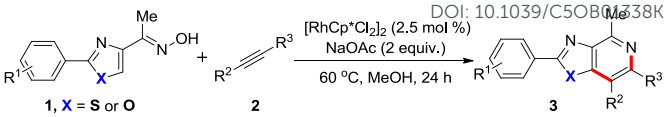
1a 2a 3a

Entry	Additive (2 equiv.)	Equiv. of **2a**	Yield (%)[b]
1	NaOAc	2	91
2	CsOAc	2	88
3	K_2CO_3	2	67
4	**NaOAc**	**1.2**	**95**
5	NaOAc (1 eq.)	1.2	94
6	NaOAc (0.3 eq.)	1.2	90
7[c]	NaOAc	1.2	76
8[d]	NaOAc	1.2	NR

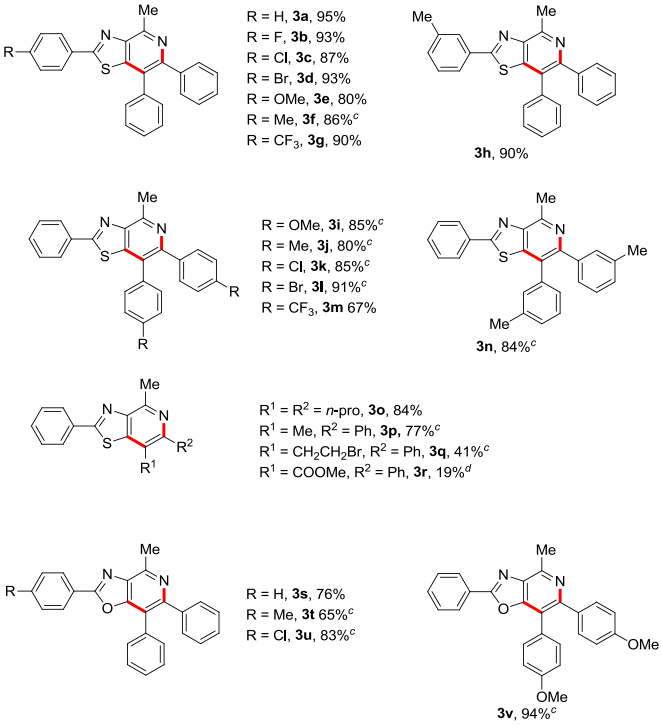
[a] Reaction conditions: **1a** (0.2 mmol, 1 equiv.) **2a** (0.4 mmol , 2 equiv.), $[RhCp^*Cl_2]_2$ (2.5 mol %), additive (0.4 mmol, 2 equiv.) in 2 mL MeOH at 60 °C for 24 h under air atmosphere. [b] Isolated yield. [c] 1 mol % $[RhCp^*Cl_2]_2$ was used. [d] 2.5 mol % $[RuCl_2(p\text{-Cymene})]_2$ was used.

With the optimal reaction conditions in hand, the scope and generality were investigated for this Rh(III)-catalyzed cyclization reaction of azoles with alkynes. The results are shown in **Table 2**. We firstly examined the scope of the thiazoles, electron-donating groups such as methoxy and methyl as well as halogen groups (F, Cl, Br), and trifluoromethyl on the para-position of phenyl rings were tolerated well and afforded the corresponding products in good to excellent yields (**Table 2, 3a-3g**). When the thiazole-substituted benzene carried a methyl at the meta-position, the corresponding product **3h** could also be obtained in 90% yield. Moreover, the scope of internal alkynes was also examined in this cyclization reaction. Internal diarylalkynes bearing methoxy, methyl and halogen groups (Cl, Br) at the para-position of the phenyl ring offered **3i-3l** in 80-91% yields. Strong electron-withdrawing group trifluoromethyl offered the desired product **3m** in 67% yield. 1,2-di-m-tolylethyne gave **3n** in 84% yield. In addition, the scope of the alkyne could be extended to dialkyl-substituted alkyne (oct-4-yne) and **3o** was obtained in 84% yield. Unsymmetrical alkynes were also compatible in our reaction, **3p** and **3q** could be finished in 77% and 41% yield respectively. When methyl 3-phenylpropiolate was tested, the corresponding **3r** was only observed in 19% yield even with increased catalyst loading maybe due to the electron deficiency property. Finally, we tried the cyclization of 1,2-diphenylethynes with 1-(2-phenyloxazol-4-yl)ethanone oximes

Table 2. Scope of thiazoles/oxazoles and alkynes [a, b]

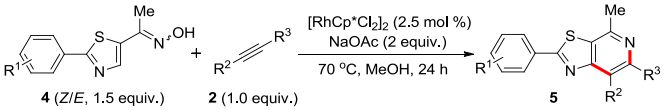


1, X = **S** or **O** 2 3

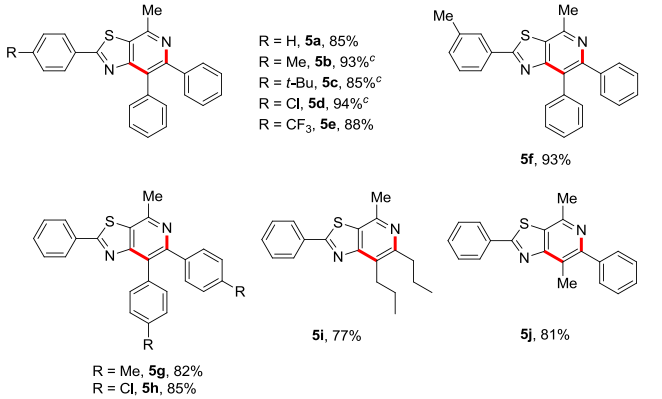


[a] Reaction conditions: **1** (0.2 mmol, 1 equiv.), **2** (0.24 mmol, 1.2 equiv.), $[RhCp^*Cl_2]_2$ (2.5 mol %), additive (0.4 mmol, 2 equiv.) in 2 mL MeOH at 60 °C for 24 h under an air atmosphere. [b] Isolated yield. [c] 70 °C. [d] 5 mol % $[RhCp^*Cl_2]_2$ was used.

Table 3. Scope of thiazoles and alkynes [a, b]



4 (*Z*/*E*, 1.5 equiv.) 2 (1.0 equiv.) 5

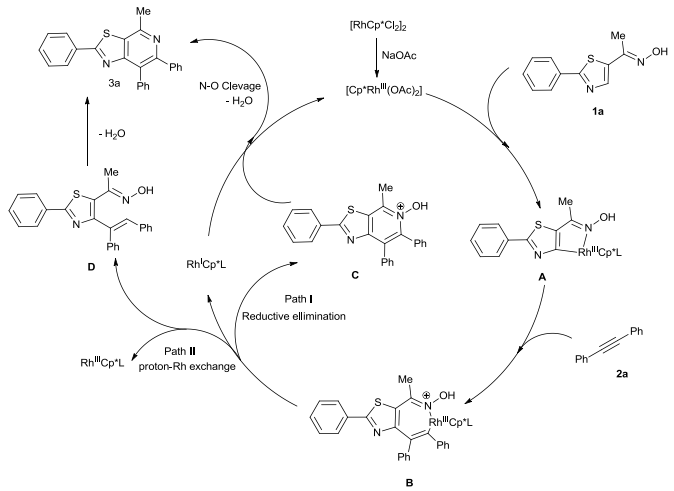


[a] Reaction conditions: **4** (0.3 mmol, 1.5 equiv.), **2** (0.2 mmol, 1 equiv.), $[RhCp^*Cl_2]_2$ (2.5 mol %), additive (0.4 mmol, 2 equiv.) in 2 mL MeOH at 70 °C for 24 h under an air atmosphere. [b] Isolated yield. [c] 2.0 equiv. of **4** was used.

and found that oxazoles could also afford the desired products **3s-3v** in 65%-94% yields.

After the achievement of alkynes coupled with C5 position of thiazoles/oxazoles, we tried the reaction of alkynes with the C4 position of thiazoles, which has lower reactivity compared to C5 position. In contrast to 4-substituented thiazoles, the 5-substituented thiazole substrate 1-(2-phenylthiazol-5-yl)ethanone oxime (**4a**) have two Z/E isomers with the ratio of 2:3, which are inseparable via slica column chromatography. We noticed that the Z-isomer was difficult to activate because it's difficult to accomplish the five-membered rhodacycle intermmediate.[3] To realize our target, we set the equivalent of **2a** as 1.0 equivalent while increased **4a** (Z/E mixtures) to 1.5 equivalent at 70 °C in MeOH with $[RhCp^*Cl_2]_2$ (2.5 mol %) as a catalyst and NaOAc (2.0 equiv.) as an additive. Fortunately, we found that the corresponding product **5a** was obtained in 85% isolated yield. Subsequently, the scope of thiazoles and internal alkynes was investigated. As shown in **Table 3**, all the substrates including thiazoles bearing different substituents, symmetrical or unsymmetrical alkynes could offer the desired products **5a-5j** in 77%-94% yields.

Based on the previous studies,[2-5,13] we proposed a reaction mechanism as illustrated in **Scheme 2**. The $[RhCp^*Cl_2]_2$ presumably dissociates into the monomer form followed by ligand exchange with NaOAc, which gives a rhodium acetate species to initiate the catalytic cycle. The first step involves coordination of the oximido nitrogen atom to the active rhodium catalyst followed by ortho C-H bond activation to form the five-membered rhodacycle **A**. Insertion of the alkyne **2a** into the rhodium-carbon bond of intermediate **A** gives a seven-membered rhodacyclic intermediate **B**. Then two pathways with this common intermediate can be envisioned as given. In pathway **I**, the reductive elimination of **B** gives a Rh(I) intermediate and a hydroxyisoquinolinium species **C**. Subsequent N-O bond cleavage regenerates Rh(III) catalyst and furnishes the product **3a**. In pathway **II**, proton-Rh exchange is proposed to yield intermediate **D** and regenerate Rh(III) catalyst to next catalytic cycle. Finally, the desired product is afforded via 6π-electrocyclization with elimination of water.



Scheme 2. Proposed mechanism

In summary, we have developed a Rh(III)-catalyzed cyclization reaction of azoles with alkynes via selective C-H activation. A variety of azole-fused-pyridines were accomplished in good to excellent yields and regioselectivity. Furthermore, the reaction of alkynes with C4 position of thiazoles through C-H activation was achieved for the first time. More direct functionlization of azoles are in progress in our laboratory.

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