Rhodium(III)-catalyzed annulation of 2-arylimidazo[1,2-a]pyridines and alkynes via direct double C−H activation

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ABSTRACT

A series of naphtho[1′,2′:4,5]imidazo[1,2-a]pyridines were synthesized smoothly from 2-arylimidazo[1,2-a]pyridines and alkynes involving rhodium(III)-catalyzed C−H bond functionalization. The process selected Co(OAc)$_2$·4H$_2$O as the co-catalyst for the first time and minimized the reaction time to 2 h under air atmosphere. Some products exhibited deep blue luminescence properties.

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1. Introduction

Direct construction of complex organic molecules by utilizing simple starting materials and process is the primary aspiration of many chemists. The transition metal-catalyzed C−H bond activation provides a shortcut route for chemical synthesis and meets the requirements of green and sustainable chemistry. During the past decades, drastic achievements have been made in this field.[1] In particular, Rh(III) catalysts exhibited some merits, such as stability, multiple valents and excellent application in C−H functionalization.[2] In the past few years, rhodium(III)-catalyzed annulation of aromatic substrates with alkynes has been extensively studied.[3] The rhodium(III)-catalyzed coupling reaction between benzoic acid and internal alkynes using Cu(OAc)$_2$·H$_2$O as the oxidant was reported in 2007.[4] Many other acids such as heteroaromatic and acrylic acids could also undergo the rhodium(III)-catalyzed intermolecular cyclization with alkynes.[5] Henceforth, phenols,[6] alcohols,[7] imines,[8] amides,[9] phenylazoles,[10] and phenylpyridines[11] have been reported in coupling with internal alkynes via rhodium(III)-catalyzed oxidative annulation. Recently, aza-fused polycyclic quinolines,[12] pyrrolo[1,2-a]quinoline,[13] multisubstituted 2-aminoquinolines,[14] substituted naphtho[1,8-bc]pyrans,[15] and phenanthroimidazoles[16] have been established successfully through the rhodium(III)-catalyzed C−H bond activation and alkyne annulation. All these reports demonstrate that rhodium(III)-

catalyzed annulation between arenes and alkynes is an important strategy to construct polycyclic aromatic frameworks.

Imidazo[1,2-a]pyridine derivant is an important fragment that exists in many anxyolytic drugs, such as alpidem, necopidem, saripidem et al. (Fig. 1).[17] The majority of reports focused on the decoration of imidazo[1,2-a]pyridine.[18] The strategy of cross-coupling and C−H activation was usually applied to functionalization of imidazo[1,2-a]pyridine.[19] However, there were few reports on the annulation of 2-phenylimidazo[1,2-a]pyridines via rhodium(III)-catalyzed double C−H activation. Inspired by the above reports, we speculated that 2-phenylimidazo[1,2-a]pyridine could participate in the annulation reaction with internal alkynes via double C−H bond activation.

2. Results and discussion

The oxidative annulation of heterocyclic frameworks was performed using 2-phenylimidazo[1,2-a]pyridine **1a** and diphenylacetylene **2a** as the model substrates. [RhCp*Cl$_2$]$_2$ (5 mol %) was selected as the catalyst in the initial test. Without any additives attendance, the results showed that no reaction occurred (Entry 1, Table 1). Cu(NO$_3$)$_2$·3H$_2$O, CuCl$_2$·2H$_2$O and K$_2$S$_2$O$_8$ as the additives do not fit the catalytic system (Entries 2—4, Table 1). The addition of Cu(OTf)$_2$ could generate the desired product **3aa**, but only 10% yield was obtained (Entry 5, Table 1). When Cu(OAc)$_2$·H$_2$O was introduced as an additive, the yield increased remarkably (81%) (Entry 6, Table 1). Nevertheless, in the absence of the catalyst, Cu(OAc)$_2$·H$_2$O could not promote the reaction (Entry 7, Table 1). Subsequently, we tested other transition metal catalysts, such as

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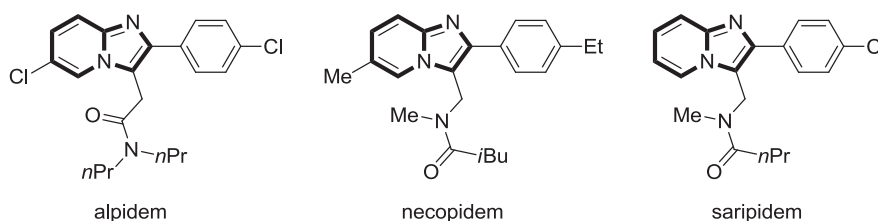
Fig. 1. Drugs with imidazo[1,2-a]pyridine framework.

Table 1
Screening of the reaction conditions

Entry[a]	Catalyst	Additive	Solvent	t (h)	Yield[b] (%)
1	[RhCp*Cl₂]₂	—	Toluene	12	—
2	[RhCp*Cl₂]₂	Cu(NO₃)₂·3H₂O	Toluene	16	—
3	[RhCp*Cl₂]₂	CuCl₂·2H₂O	Toluene	16	—
4	[RhCp*Cl₂]₂	K₂S₂O₈	Toluene	16	—
5	[RhCp*Cl₂]₂	Cu(OTf)₂	Toluene	16	10
6	[RhCp*Cl₂]₂	Cu(OAc)₂·H₂O	Toluene	16	81
7	—	Cu(OAc)₂·H₂O	Toluene	16	—
8[c]	Pd(OAc)₂	Cu(OAc)₂·H₂O	Toluene	8	17
9[c]	[RuCl₂(p-cymene)]₂	Cu(OAc)₂·H₂O	Toluene	8	4
10	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	Toluene	16	87
11	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	DMF	2	92
12	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	Xylene	2	41
13	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	AcOH	2	12
14	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	Dioxane	2	77
15	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	2-Methyl-2-butanol	2	81
16	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	DCE	2	26
17	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	o-Xylene	2	28
18[d]	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	DMF	2	88
19[e]	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	DMF	2	76
20	[RhCp*Cl₂]₂	Co(OAc)₂	DMF	2	92
21[f]	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	DMF	2	64
22[g]	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	DMF	2	14
23[h]	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	DMF	2	64
24[i]	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	DMF	2	76
25[c]	[RhCp*Cl₂]₂	Co(OAc)₂·4H₂O	DMF	2	87
26	—	Co(OAc)₂·4H₂O	DMF	2	—

[a] Reaction conditions unless otherwise specified: **1a** (0.10 mmol), **2a** (0.20 mmol), Cat. (5 mol %), additive (0.12 mmol), solvent (1 mL), 110 °C, air atmosphere.
[b] Isolated yield.
[c] Under Ar.
[d] 90 °C.
[e] 70 °C.
[f] [RhCp*Cl₂]₂ (2.5 mol %).
[g] Co(OAc)₂·4H₂O (5 mol %).
[h] Co(OAc)₂·4H₂O (25 mol %).
[i] Co(OAc)₂·4H₂O (50 mol %).

Pd(OAc)₂ and [RuCl₂(p-cymene)]₂, and poor yields were observed (Entries 8–9, Table 1). In the previous studies, Cu and Ag salts were often used as the additives to accelerate the pace of the reaction.[3–16] Inspired by Yoshikai's work,[20] we wondered whether Co salts could take place of them and promote the reaction successfully. It was exciting that the desired product **3aa** was obtained in 87% yield when Co(OAc)₂·4H₂O was introduced to our catalytic system (Entry 10, Table 1).

With [RhCp*Cl₂]₂ and Co(OAc)₂·4H₂O chosen as catalyst and additive, the solvent of the reaction was then screened. DMF was chosen as the initial solvent, and the substrates have been completely consumed after 8 h in good yield (92%). After the initial test,

the reaction time was monitored and minimized to 2 h. To our delight, the reaction was still finished completely. With 2 h as the standard reaction time (Entry 11, Table 1), other solvents were also attempted. Low yields were obtained in AcOH, DCE and o-xylene (Entry 13, and Entries 16–17, Table 1). Additionally, 77% yield was achieved in dioxane as well as 81% yield in 2-methyl-2-butanol (Entries 14–15, Table 1). A moderate yield could be acquired in xylene (Entry 12, Table 1). The yield was decreased to 88% and 76% when lowering the temperature at 90 °C and 70 °C, respectively (Entries 18–19, Table 1). When Co(OAc)₂ was applied to the reaction as the additive, it did not affect the catalytic activity, and still generate 92% yield (Entry 20, Table 1). To further investigate the effects of catalyst and additive loading on the catalytic system, more experiments were carried out. Decreasing the loading of [RhCp*Cl₂]₂—2.5 mol % in the presence of 1.2 equiv Co(OAc)₂·4H₂O, an unsatisfactory result (64%) was observed after 2 h (Entry 21, Table 1). Using 5.0 mol % [RhCp*Cl₂]₂ as the catalyst, the decrease in the dosage of Co(OAc)₂·4H₂O led to the lower yields (Entry 22–24, Table 1). It is very interesting to notice that relatively high yield (87%) could still be obtained even under Ar atmosphere (Entry 25, Table 1). Under the optimal conditions, the reaction couldn't take place in the absence of [RhCp*Cl₂]₂ (Entry 26, Table 1). It implies that [RhCp*Cl₂]₂ plays as the catalyst in the catalytic cycle.

With the optimized conditions established, we explored the reaction of various internal alkynes. As can be seen from Scheme 1, 2-phenylimidazo[1,2-a]pyridine could react smoothly with symmetrical diaryl alkynes in high yields (**3aa**–**3ae**, Scheme 1). The symmetrical diaryl alkynes with electron-withdrawing groups at the para position of the phenyl ring seemed more reactive than those bearing electron-donating groups, affording slightly higher yield (**3ab**, 88% vs **3ad**, 80%; and **3ac**, 97% vs **3ae**, 84%). A few unsymmetrical diaryl alkynes were also employed to the reaction, and a moderate to high yields were observed (**3af/3af'** 79%, **3ag/3ag'** 80%, **3ah/3ah'** 90%). The ratio of two regioisomeric products was 1:1 from the ¹H NMR spectroscopic analysis. It indicates that different substituents on the unsymmetrical diaryl alkynes did not influence on the regioselectivity of the products (**3af**–**3ah**, Scheme 1). Unfortunately, alkyl-substituted alkynes could not work well in the system and poor yields were achieved (data not shown).

Subsequently, we paid our attention to using diverse substituted 2-phenylimidazo[1,2-a]pyridines in the annulation with diaryl alkynes. The results were exhibited in Scheme 2. Imidazo[1,2-a]pyridines rings bearing electron-donating groups could react with diphenylacetylene very well (**3ba** 92%, **3ea** 96%, and **3ha** 94%, Scheme 2). The yields of target products were decreased from 79% to 28% when electron-withdrawing groups such as F, Cl were introduced to imidazo[1,2-a]pyridine rings (**3ca** 79% and **3da** 28%, Scheme 2). On the other hand, when electron-donating groups such as Me, and MeO were incorporated into phenyl ring, increased yields were observed for most substrates (**3ea**, 96% vs **3ba**, 92%; **3fa**, 91% vs **3ca**, 79%; **3ga**, 32% vs **3da**, 28%; and **3ea**, 94% vs **3ba**, 92%, Scheme 2).

With previous results in hand, the coupling reaction of 2-arylimidazo[1,2-a]pyridine bearing electron-donating groups with