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Synthesis of Aza-Fused Polycyclic Quinolines via Double C–H Bond Activation

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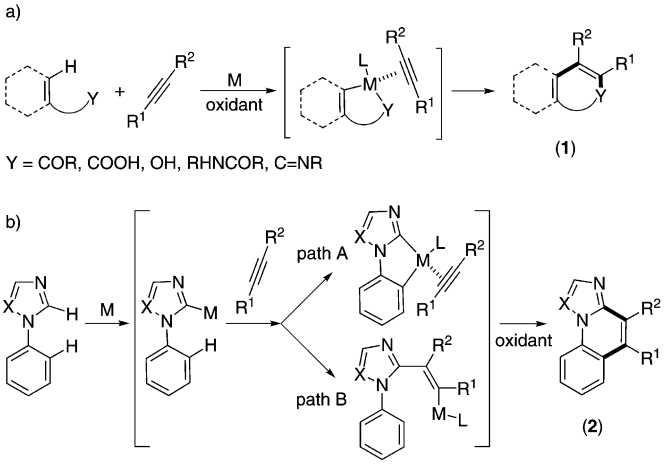
Heterocyclic frameworks are embedded in a large number of compounds that exhibit diverse physical, chemical and biological properties.[1] In this respect, substituted quinolines and related derivatives represent an important class of subunits that are widely implicated in fluorescent optical whiteners, dispersed dyes, natural products, and biologically active compounds.[2–6] However, aza-fused quinolines, such as imidazo[1,2-*a*]quinolines and benzimidazo[1,2-*a*]quinolines, have remained relatively unexplored, although some analogues have been identified as promising antitumor agents,[7] probably because of the lack of general and efficient methods for the synthesis of these compounds. The commonly used protocols for their synthesis involve cyclization or photochemical dehydrocyclization conditions; however, these methods usually require several transformations and suffer from low yields or limited substrate scope.[7,8] Therefore, the development of new protocols for efficient access to aza-fused quinolines is highly desirable.

Recently, the transition-metal-catalyzed directed functionalization of a variety of less active C–H bonds has triggered increasing interest in the synthesis of heterocyclic scaffolds.[9] In particular, a number of methodologies were established to generate diverse heterocyclic compounds via rhodium- or ruthenium-catalyzed C–H activation and subsequent intermolecular cyclization with alkynes, eliminating the heteroatom-assisted chelation that was often required in the early reaction stage (Scheme 1 a).[10–13] Encouraged by such results, we hoped to use *N*-aryl-substituted azole substrates that could be engaged in a cyclization process with alkynes to deliver complex aza-fused quinolines via direct double C–H activation without the chelation assistance from an adjacent functional group, as outlined in Scheme 1 b.[14,15]



Scheme 1. Transition-metal-catalyzed C–H activation and subsequent cyclization with alkynes. a) Previous work: C–H activation via heteroatom-assisted chelation. b) This work: direct double C–H activation without heteroatom chelation assistance.

The study began by investigating the potential reaction of *N*-phenyl benzimidazole **1a** and diphenyl acetylene **2a** to form benzimidazo[1,2-*a*]quinoline **3a**. $[RhCl(PPh_3)_3]$ or $[\{Cp^*RhCl_2\}_2]$ were initially tested as catalysts without using any additives, however, only a trace amount of product **3a** could be detected under these conditions, either in the presence or absence of O_2 (entries 1–3, Table 1). The use of $Cu(OTf)_2$ as an additive was not successful (entry 4, Table 1); however, the addition of AgOAc or $Cu(acac)_2$ (where acac is acetylacetonate) delivered desired product **3a** albeit in low yields (entries 5 and 6, Table 1). No reaction occurred in the presence of NaOAc and organic benzoquinone (BQ) (entry 7, Table 1). Fortunately, the yield increased significantly (to 94%) when $Cu(OAc)_2$ was applied as an additive, although no reaction was observed when it was used alone in the absence of catalyst (entries 8 and 9, Table 1). It is possible that $Cu(OAc)_2$ might be acting not only as an oxidant but also as a co-catalyst, especially in the initial C–H activation of the benzimidazole motif.[15–17]

Subsequently, further metal catalysts, such as $[\{Rh(cod)Cl\}_2]$ (cod = 1,5-cyclooctadiene) and $[\{RuCl_2(p$-

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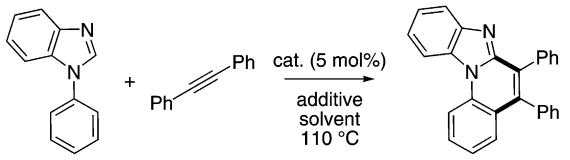
Table 1. Optimization of reaction conditions.[a]



1a 2a 3a

Entry	Catalyst	Additive	Solvent	t [h]	Yield[b] [%]	Entry	Catalyst	Additive	Solvent	t [h]	Yield[b] [%]
1	$[RhCl(PPh_3)_3]$	–	toluene	7	trace	10	$[\{Rh(cod)Cl\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	toluene	7	trace
2	$[\{Cp^*RhCl_2\}_2]$	–	toluene	4	trace	11	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	toluene	14	18
3[c]	$[\{Cp^*RhCl_2\}_2]$	–	toluene	4	trace	12	$[\{Cp^*RhCl_2\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	xylene	4	88
4	$[\{Cp^*RhCl_2\}_2]$	$Cu(OTf)_2$	toluene	4	ND[d]	13	$[\{Cp^*RhCl_2\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	2-methyl-2-butanol	4	76
5	$[\{Cp^*RhCl_2\}_2]$	AgOAc	toluene	4	43	14	$[\{Cp^*RhCl_2\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	AcOH	7	58
6	$[\{Cp^*RhCl_2\}_2]$	$Cu(acac)_2$	toluene	4	38	15[e]	$[\{Cp^*RhCl_2\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	toluene	4	81
7	$[\{Cp^*RhCl_2\}_2]$	NaOAc+BQ	toluene	4	ND[d]	16[f]	$[\{Cp^*RhCl_2\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	toluene	8	84
8	$[\{Cp^*RhCl_2\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	toluene	4	94	17[g]	$[\{Cp^*RhCl_2\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	toluene	4	98
9	–	$Cu(OAc)_2{\cdot}H_2O$	toluene	4	ND[d]						

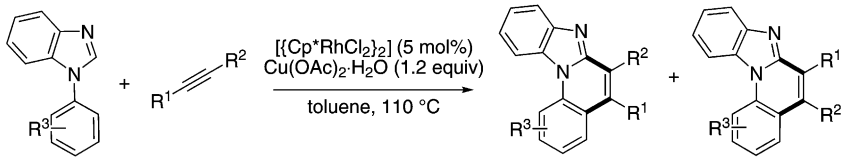
[a] Reaction conditions unless otherwise specified: **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (5 mol%), additive (0.12 mmol), solvent (1 mL), 110°C, Ar atmosphere. [b] Isolated yield. [c] Under air. [d] Not detected. [e] K_2CO_3 (0.2 mmol) was added. [f] Catalyst (2 mol%) was used. [g] **1a** (1 mmol) and **2a** (2 mmol) were used.

cymene)}$_2$], were further tested in the presence of $Cu(OAc)_2$ but found to be less effective (entries 10 and 11, Table 1). These results indicate the importance of $[\{Cp^*RhCl_2\}_2]$.

The choice of solvent was also vital to the efficiency of the catalytic reaction. Good results were attained when the reaction was performed in xylene (entry 12, Table 1), but much lower yields were observed in 2-methyl-2-butanol, AcOH (entries 13 and 14, Table 1) or *N*,*N*-dimethylformamide (18% yield). In addition, lower yield was observed when K_2CO_3 was added (entry 15, Table 1). The reaction rate was significantly diminished when less catalyst was used in the reaction, while a good yield was obtained by extending the reaction time (entry 16, Table 1). To our delight, **3a** was obtained in 98% yield when the reaction was scaled up by a factor of ten (1 mmol **1a**, 2 mmol **2a**; entry 17, Table 1).

With the optimized reaction conditions established, we examined the reactions of a variety of *N*-aryl benzimidazoles (**1a–o**) with internal alkynes (**2a–k**). The results are summarized in Table 2. The process showed wide substrate tolerance with internal alkynes. *N*-Phenyl benzimidazole **1a** reacted with diverse acetylenes (**2a–d**), with either electron-rich or electron-poor diaryl groups, to give products **3a–d** in good

Table 2. Reaction of *N*-aryl benzimidazoles **1** with alkynes **2**.[a]



1 2 3

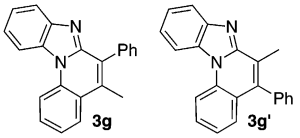
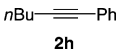
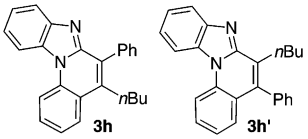
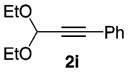
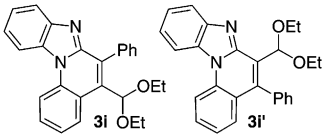
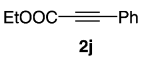
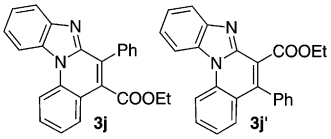
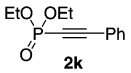
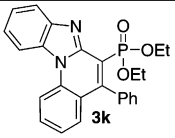
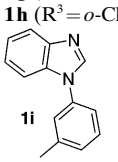
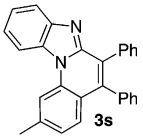
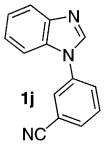
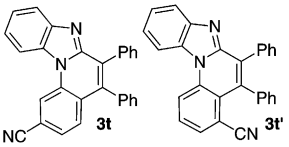
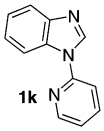
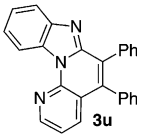
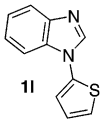
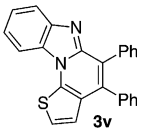
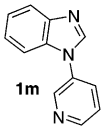
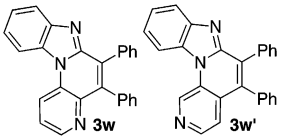
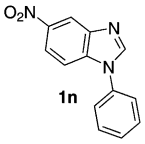
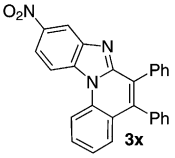
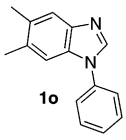
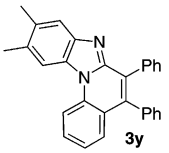
Entry	Benzimidazoles **1**	Alkynes **2**	Product	Yield[b] [%]
1	**1a**	**2a** ($R^1=R^2=$Ph)	**3a**	94
2	**1a**	**2b** ($R^1=R^2=p$-MePh)	**3b**	93[c]
3	**1a**	**2c** ($R^1=R^2=p$-MeOPh)	**3c**	77[c]
4	**1a**	**2d** ($R^1=R^2=p$-ClPh)	**3d**	75
5	**1a**	**2e** ($R^1=R^2=$3-Py)	**3e**	83
6	**1a**	**2f** ($R^1=R^2=n$Bu)	**3f**	76
7	**1a**	 **2g**	 **3g** **3g'**	68/15
8	**1a**	 **2h**	 **3h** **3h'**	68/20
9	**1a**	 **2i**	 **3i** **3i'**	81 (5.6:1)
10	**1a**	 **2j**	 **3j** **3j'**	74 (1:5)[d,e]

Table 2. (Continued)

Entry	Benzimidazoles **1**	Alkynes **2**	Product	Yield[b] [%]
11	**1a**	 **2k**	 **3k**	84
12	**1b** (R^3 = *p*-MeO)	**2a**	**3l**	99
13	**1c** (R^3 = *p*-NH_2)	**2a**	**3m**	51
14	**1d** (R^3 = *p*-Cl)	**2a**	**3n**	90
15	**1e** (R^3 = *p*-COOEt)	**2a**	**3o**	99
16	**1f** (R^3 = *p*-NO_2)	**2a**	**3p**	39
17	**1g** (R^3 = *o*-MeO)	**2a**	**3q**	81
18	**1h** (R^3 = *o*-Cl)	**2a**	**3r**	84
19	 **1i**	**2a**	 **3s**	76
20	 **1j**	**2a**	 **3t** **3t'**	99 (4:1)[d]
21	 **1k**	**2a**	 **3u**	92
22	 **1l**	**2a**	 **3v**	53
23	 **1m**	**2a**	 **3w** **3w'**	99 (5:2)
24	 **1n**	**2a**	 **3x**	48
25	 **1o**	**2a**	 **3y**	99

[a] Reaction conditions unless otherwise specified: **1** (0.1 mmol), **2** (0.2 mmol), [{Cp*$RhCl_2$}$_2$] (5 mol%), Cu(OAc)$_2$·H_2O (0.12 mmol), toluene (1 mL), 110 °C, Ar atmosphere, 4–6 h. [b] Isolated yield. [c] Benzimidaole **1** (0.2 mmol) and alkyne **2** (0.1 mmol) were used. [d] Isolated yield of a mixture of regioisomers; regioselectivity was determined by ^{1}H NMR analysis. [e] Compound **2j** (4 equiv) was partially added to the reaction mixture.

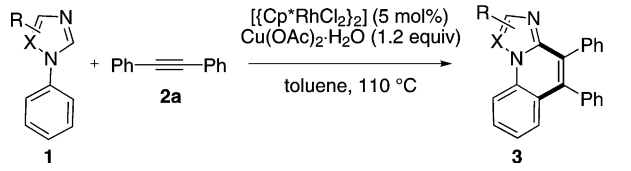
yields (entries 1–4, Table 2). The catalytic reaction was successfully expanded to heteroaryl and alkyl-substituted alkynes (entries 5 and 6, Table 2).

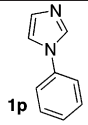
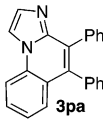
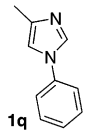
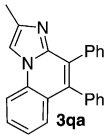
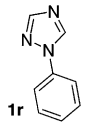
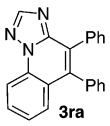
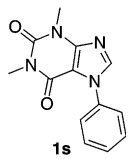
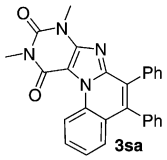
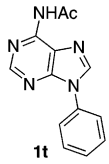
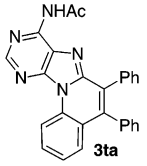
To study the regioselectivity of this reaction, a few unsymmetrically disubstituted alkynes were employed. High reactivity was observed for alkynes **2g–i**, generating the expected products in high yield albeit with modest regioselectivity (entries 7–9, Table 2). Fortunately, electron-deficient alkyne **2j** could be easily applied (entry 10, Table 2). Surprisingly, a single isomer **3k** was produced by using phosphonate alkyne **2k** (entry 11, Table 2). It was found that terminal alkynes are not tolerated in this system.

Subsequently, a range of benzimidazoles with diverse *N*-aryl groups were explored. High yields were generally obtained for *para*- or *ortho*-substituted aryl substrates (entries 12–18, Table 2), except for **1c** and **1f** that have *para*-amino and nitro groups, respectively (entries 13 and 16, Table 2). Excellent regioselectivity was observed for reactions with benzimidazole **1i**, probably owing to the steric effects of the *meta*-methyl group (entry 19, Table 2). In contrast, a mixture of regioisomers was generated by the reaction of benzimidazole with a *meta*-cyanophenyl group **1j** (entry 20, Table 2). Meanwhile, benzimidazoles bearing an *N*-heteroaryl group were also compatible (entries 21 and 22, Table 2). The regioisomers were also formed by the reaction with 3-pyridyl-substituted benzimidazole **1m** (entry 23, Table 2). While a dramatic decrease in yield was noted when using 5-nitro-substituted benzimidazole **1n**, excellent results were obtained for benzimidazole **1o** containing electron-donating groups (entries 24 and 25, Table 2).

The catalytic system was also found to be effective for an array of substituted imidazoles and other azoles. *N*-Phenyl imidazoles **1p** and **1q** reacted with diphenyl acetylene **2a** in moderate yields (entries 1 and 2, Table 3), while *N*-phenyl 1-2,4-triazole **1r** reacted with an even higher yield (entry 3, Table 3). Importantly, purine derivatives **1s** and **1t** were also tolerated under the standard conditions, furnishing the fused heterocycles **3sa** and **3ta** in 81% and 52% yield, respectively (entries 4 and 5, Table 3).

Table 3. Reaction of azoles **1** with diphenyl acetylene.[a]



Entry	Azole **1**	Product	Yield[b] [%]
1	 **1p**	 **3pa**	56
2	 **1q**	 **3qa**	75
3	 **1r**	 **3ra**	84
4	 **1s**	 **3sa**	81
5	 **1t**	 **3ta**	52[c]

[a] Reaction conditions unless otherwise specified: **1** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol%), $Cu(OAc)_2{\cdot}H_2O$ (0.12 mmol), toluene (1 mL), 110 °C, Ar atmosphere, 4–10 h. [b] Isolated yield. [c] **1t** (0.2 mmol) and alkyne **2a** (0.1 mmol) were used.

In conclusion, we have developed a new simplified method for efficient construction of complex aza-fused polycyclic quinolines from *N*-aryl azoles and disubstituted alkynes. The process is based on the rhodium(III)-catalyzed double C–H bond activation of *N*-aryl azoles without heteroatom-assisted chelation, followed by two C–C bond formation reactions with alkynes. In addition to acting as an oxidant, copper(II) acetate might also play an important role in the C–H activation process.[16] Currently, studies on the catalytic mechanism and the additional roles of rhodium catalysts in other C–H functionalization reactions are being conducted, and the results will be reported in due course.

Experimental Section

General procedure:A solution of *N*-aryl benzimidazole **1** (0.1 mmol), internal alkyne **2** (0.2 mmol), $[\{Cp^*RhCl_2\}_2]$ (5 mol%, 3.1 mg) and $Cu(OAc)_2{\cdot}H_2O$ (0.12 mmol, 24 mg) in toluene (1.0 mL) was stirred under Ar at 110 °C for 4–10 h. Thin layer chromatography (TLC) of the reaction mixture confirmed formation of **3**. The product was isolated by chromatography on silica gel using petroleum ether/EtOAc or CH_2Cl_2/MeOH.

Characterization data for the products are summarized in the Supporting Information.

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Keywords: alkynes · annulation · aza-fused polycyclic quinolines · C–H activation · heterocycles · rhodium

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[15] A plausible catalytic mechanism is presented in the Supporting Information. The reaction can afford the five-membered rhodacycle intermediate (path A), and it was also speculated that the formation of a vinyl intermediate (path B) is also possible. However, the reaction did not proceed under these conditions, and only starting material was recovered when *N*-methyl benzimidazole was used as a substrate. For more details, see the Supporting Information.

[16] For selected examples of copper-catalyzed C(2)−H activation of azoles, see: a) H. Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404; b) T. Kawano, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2010**, *132*, 6900; c) D.-B. Zhao, W.-H. Wang, F. Yang, J.-B. Lan, L. Yang, G. Gao, J.-S. You, *Angew. Chem.* **2009**, *121*, 3346; *Angew. Chem. Int. Ed.* **2009**, *48*, 3296; d) F. Besselièvre, S. Piguel, *Angew. Chem.* **2009**, *121*, 9717; *Angew. Chem. Int. Ed.* **2009**, *48*, 9553; e) M. Miyasaka, K. Hirano, T. Satoh, R. Kowalczyk, C. Bolm, M. Miura, *Org. Lett.* **2011**, *13*, 359; f) P.-H. Xi, F. Yang, S. Qin, D.-B. Zhao, J. B. Lan, G. Gao, C.-W. Hu, J.-S. You, *J. Am. Chem. Soc.* **2010**, *132*, 1822.

[17] Deuterium kinetic isotope effect (DKIE) measurements were conducted by comparing the initial rates between **1a** and **[D_5]-1a**, as well as between **1a** and **[D_6]-1a**. For more details, see the Supporting Information.

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Heterocycles

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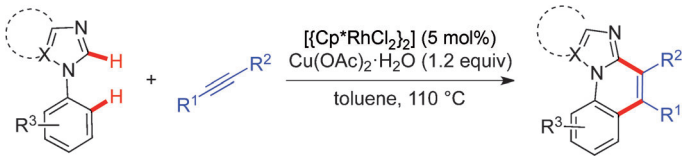
Synthesis of Aza-Fused Polycyclic Quinolines via Double C–H Bond Activation



Simple but efficient: Aza-fused polycyclic quinolines were efficiently assembled via rhodium(III)-based direct double C–H activation of *N*-aryl azoles followed by cyclization with alkynes without heteroatom-assisted chelation. Copper(II) acetate, aside from acting as an oxidant, could also play an important role in the C–H activation process.

