ORGANIC LETTERS

2013
Vol. 15, No. 8
1878–1881

Rhodium(III)-Catalyzed Direct Selective C(5)−H Oxidative Annulations of 2-Substituted Imidazoles and Alkynes by Double C−H Activation

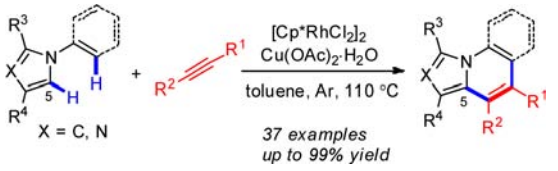
Ji-Rong Huang, Qian-Ru Zhang, Chuan-Hua Qu, Xun-Hao Sun, Lin Dong,* and Ying-Chun Chen*

Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry, Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

dongl@scu.edu.cn; ycchenhuaxi@yahoo.com.cn

Received February 26, 2013

ABSTRACT



Double C−H activations of C(5)−H and Csp^2−H of 2-substituted *N*-vinyl- or arylimidazoles were realized without heteroatom-directing assistance by rhodium(III) catalyst. A subsequent oxidative annulation reaction with alkynes efficiently produced aza-fused heterocycles with high molecular complexity in low to excellent yields.

The transition-metal-catalyzed functionalization of C−H bonds has been a highly intriguing research topic in the past decade.[1] Recently, direct C−H alkenylation and alkylation of nitrogen heterocycles have been significantly developed, which could be broadly grouped into different subfields.[2−4] The most popular strategy was to introduce a directing group into the substrate, assisting *ortho* C−H activation or *roll-over* C−H activation to form the active metallacyclic complex.[2] Another well-developed tool is that sp^2-hybridized nitrogen initially associates with Rh catalyst and then affords an Rh−NHC complex at the *ortho* position.[3] Nickel could also catalyze the alkenylation of nitrogen heterocycles via the formation of alkyne-coordinated Ni species.[4] Very recently, Jiao and co-workers reported the Pd-catalyzed oxidative cycloaromatization of biaryls with alkynes through dual activation of C−H bonds without directing groups (Scheme 1, eq 1).[5,6]

(1) For selected recent reviews about C−H bond functionalizations, see: (a) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (b) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (c) Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637. (d) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (e) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (f) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (g) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236.

(2) For selected examples of C−H alkenylation and alkylation of nitrogen heterocycles using directing groups, see: (a) Wang, L.; Huang, J.; Peng, S.; Liu, H.; Jiang, X.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1768. (b) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Shibata, T.; Takayasu, S.; Yuzawa, S.; Otani, T. *Org. Lett.* **2012**, *14*, 5106. (e) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2010**, *132*, 9602. (f) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788.

(3) For selected examples containing Rh−NHC complex, see: (a) Ryu, J.; Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3677. (b) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (c) Wiedemann, S. H.; Lewis, J. C.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2006**, *128*, 2452. (d) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202. (e) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2010**, *12*, 2978.

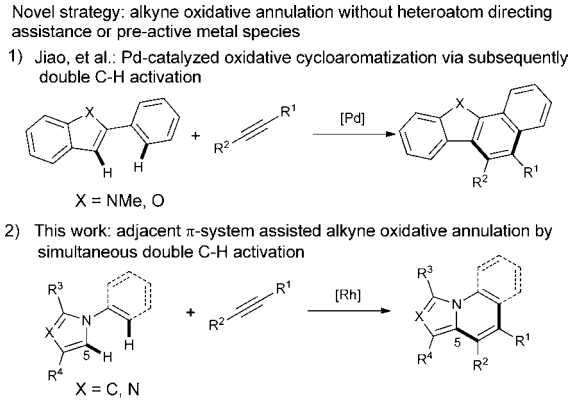
(4) (a) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146. (b) Kanyiva, K. S.; Löbermann, F.; Nakao, Y.; Hiyama, T. *Tetrahedron Lett.* **2009**, *50*, 3463.

(5) Shi, Z.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7895.

(6) For selected examples of oxidative annulations of alkynes without directing groups, see: (a) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Nagase, Y.; Miyamura, T.; Shirakawa, E. *J. Am. Chem. Soc.* **2008**, *130*, 15823. (b) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E.; Kawakami, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 1336.

10.1021/ol400537b
Published on Web 03/28/2013

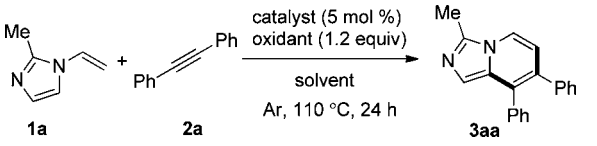
Scheme 1. Transition-Metal-Catalyzed C−H Alkenylation and Alkylation of Nitrogen Heterocycles



Nevertheless, Rh-catalyzed direct C−H activation of nitrogen heterocycles without directing groups still remains a huge challenge.[7] Previously, we have demonstrated that C(2)−H of *N*-arylazoles could be utilized to synthesize complex aza-fused quinolines via double C−H activation.[8,9] However, oxidative annulation reaction via regioselective activation of the C(5)−H bond of imidazoles was still unrealized, for there was no extra directing group or sp^2-hybridized nitrogen to assist such a C−H activation.[4b,7a] Herein, we described an efficient protocol to access complex aza-fused scaffolds by direct Rh(III)-catalyzed double C−H activations of Csp^2−H (vinylic sp^2 C−H or aryl Csp^2−H) and C(5)−H of 2-substituted imidazoles and then coupling with alkynes (Scheme 1, eq 2).[10]

The assistance of adjacent π system might provide the driving force to induce the activation of less reactive C(5)−H to give the five-membered metallacycle.[11,12]

Table 1. Optimization of the Reaction Conditions for Synthesis of **3aa**[a]



entry	catalyst	oxidant	solvent	yield[b] (%)
1	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	toluene	75
2	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2\cdot H_2O$	toluene	12
3	$(PPh_3)_3RhCl$		toluene	N.R.
4	$Pd(OAc)_2$	$Cu(OAc)_2\cdot H_2O$	toluene	N.R.
5	$[Cp^*RhCl_2]_2$	AgOAc	toluene	65
6	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	DMF	18
7	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	dioxane	65
8[c]	**$[Cp^*RhCl_2]_2$**	**$Cu(OAc)_2\cdot H_2O$**	**toluene**	**99**

[a] Unless noted otherwise, reaction conditions were conducted with 0.1 mmol of **1a**, 0.2 mmol of **2a**, 5 mol % of catalyst, 0.12 mmol of oxidant, 1 mL of solvent, 110 °C, under Ar atmosphere. [b] Isolated products. [c] **1a**:**2a** = 2.

We began our studies with the oxidative annulation of 2-methyl-*N*-vinylimidazole (**1a**) and diphenylacetylene (**2a**). Gratifyingly, the desired product **3aa** was formed in 75% yield by using $[Cp^*RhCl_2]_2$ as a catalyst and $Cu(OAc)_2\cdot H_2O$ as an oxidant (Table 1, entry 1). However, other transition metals such as $[RuCl_2(p\text{-cymene})]_2$, $(PPh_3)_3$-RhCl and $Pd(OAc)_2$[5,13] showed much less or negative catalytic activity (Table 1, entries 2−4). The yield was reduced to 65% when AgOAc was used as an oxidant (Table 1, entry 5). Inferior results were also obtained in DMF or 1,4-dioxane (Table 1, entries 6 and 7). Pleasingly, a quantitative yield was produced when excess imidazole **1a** was used (Table 1, entry 8).[13]

With the established conditions in hand, we first examined various internal alkynes in place of **2a** in the reactions with imidazole **1a** (Scheme 2). An array of diversely substituted diarylacetylenes underwent the annulations to afford the corresponding imidazo[1,5-α]pyridines (**3ab**−**ad**) in moderate to excellent yields, even for heteroaryl- (**2e**) or alkyl-disubstituted (**2f**) alkynes. The present catalytic system was also extended to unsymmetrically disubstituted alkynes, could be utilized in the annulation reaction, though the desired product **3aj** was formed in low regioselectivity. It was found that terminal alkynes were not tolerated in this system.

Next we investigated the scope of *N*-substituted imidazoles (Scheme 3). Various substituents such as alkyl, aryl,

(7) For selected examples of Rh-catalyzed oxidative annulations of alkynes, see: (a) Umeda, N.; Hirano, K.; Satoh, T.; Shibata, N.; Sato, H.; Miura, M. *J. Org. Chem.* **2011**, *76*, 13. (b) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212.

(8) Huang, J.-R.; Dong, L.; Han, B.; Peng, C.; Chen, Y.-C. *Chem.—Eur. J.* **2012**, *18*, 8896.

(9) For selected examples on transition-metal-catalyzed C(2)−H activation of azoles, see: (a) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169. (b) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 6993. (c) Yamashita, M.; Horiguchi, H.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7481. (d) Lu, W.-J.; Jia, C.-G.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **2000**, *2*, 2927. (e) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4698. (f) Kandukuri, S. R.; Schiffner, J. A.; Oestreich, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 12047. (g) Dong, J.; Huang, Y.; Qin, X.; Cheng, Y.; Hao, J.; Wan, D.; Li, W.; Liu, X.; You, J. *Chem.—Eur. J.* **2012**, *18*, 6158.

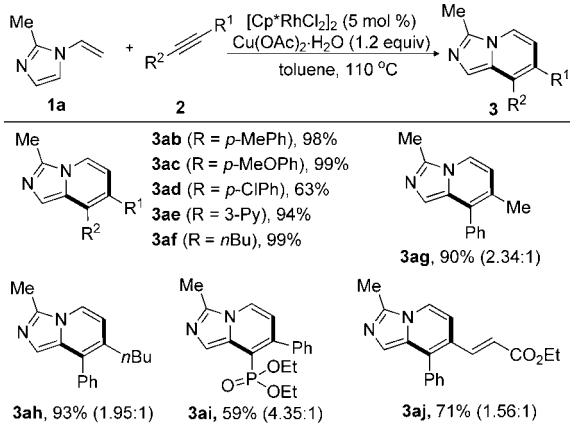
(10) For selected recent examples on Rh(III)-catalyzed vinylic sp^2 C−H activation, see: (a) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (b) Hyster, T. K.; Rovis, T. *Chem. Sci* **2011**, *2*, 1606. (c) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338. (d) Lian, Y. J.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 629. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645.

(11) For selected examples of five-membered metallacycles, see: (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) Davies, D. L.; Al-Duaij, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, D. R. *Dalton Trans.* **2003**, 4132. (c) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Macgregor, S. A.; Pölleth, M. *J. Am. Chem. Soc.* **2006**, *128*, 4210. (d) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. (e) Boutadla, Y.; Al-Duaij, O.; Davies, D. L.; Griffith, G. A.; Singh, K. *Organometallics* **2009**, *28*, 433. (f) Han, Y.-F.; Li, H.; Hu, P.; Jin, G.-X. *Organometallics* **2011**, *30*, 905. (g) Boutadla, Y.; Davies, D. L.; Jones, R. C.; Singh, K. *Chem.—Eur. J.* **2011**, *17*, 3438. (h) Kisenyi, J. M.; Sunley, G. J.; Cabeza, J. A.; Smith, A. J.; Adams, H.; Salt, N. J.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1987**, 2459.

(12) The reaction did not give the desired product when 2-methyl-*N*-CH_3-imidazole was used as a substrate. Almost all starting materials were recycled, which might support the assistance of adjacent π system to induce the C(5)−H activation to give the five-membered metallacycle.

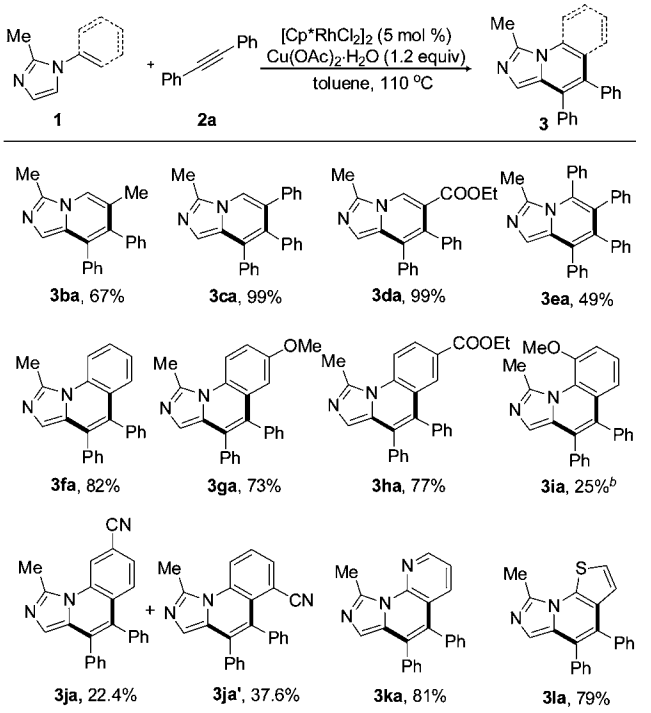
(13) For more details of condition screenings, see the Supporting Imformation.

Scheme 2. Substrate Scope of Alkynes[a]



[a] Unless noted otherwise, reaction conditions were conducted with 0.2 mmol of **1a**, 0.1 mmol of **2**, 5 mol % of $[Cp^*RhCl_2]_2$, 0.12 mmol of $Cu(OAc)_2 \cdot H_2O$, 1 mL of toluene, 110 °C, under Ar atmosphere. Yields are reported for the isolated products. Ratios of regioisomers are given in parentheses and were determined by ^1H NMR analysis. Major isomers are shown.

Scheme 3. Scope and Limitations of *N*-Substituted Imidazoles[a]



[a] Unless noted otherwise, reaction conditions were conducted with 0.2 mmol of **1**, 0.1 mmol of **2a**, 5 mol % of $[Cp^*RhCl_2]_2$, 0.12 mmol of $Cu(OAc)_2 \cdot H_2O$, 1 mL of toluene, 110 °C, under Ar atmosphere. Yields are reported for the isolated products. [b] 0.1 mmol of **1i** and 0.2 mmol of **2a** were used.

and ester groups on *N*-alkenyl moiety were well tolerated, and the corresponding imidazo[1,5-α]pyridines (**3ba**−**da**) were constructed effectively. An imidazole with a disubstituted alkenyl group also proceeded smoothly leading to the highly substituted pyridine derivative **3ea** albeit in a fair yield. To our delight, an *N*-phenylimidazole exhibited the similar C−H activation pattern toward this catalyst system and the corresponding imidazo[1,5-α]quinoline product (**3fa**) was obtained in 82% yield. In addition, imidazoles bearing either electron-donating or -withdrawing groups at the *para*-position of the *N*-aryl ring showed good reactivity to give products **3ga** and **3ha** in 73% and 77% yield, respectively. However, an *ortho*-substituted aryl substrate only produced the corresponding tricycle **3ia** in 25% yield, probably because of steric hindrance. A mixture of regioisomers (**3ja** and **3ja′**) was generated by employing an imidazole with a *meta*-cyanophenyl group. Fortunately, imidazoles bearing *N*-heteroaryl group were also compatible, producing **3ka** and **3la** in good isolated yields.

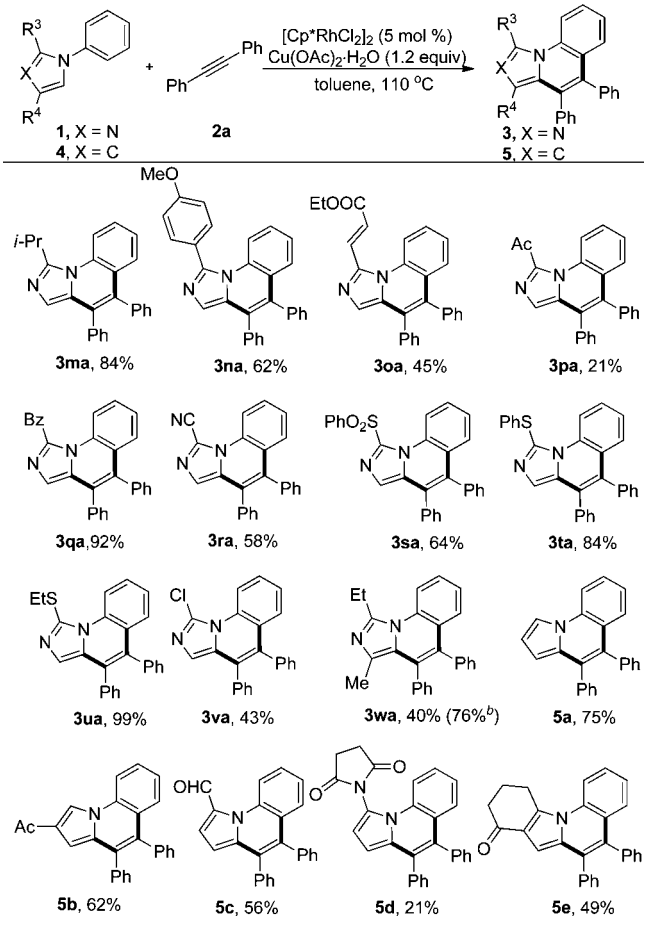
Encouraged by the good tolerance toward various functional groups, the scope of various C2-substituted imidazoles was further examined. The results are summarized in Scheme 4. An imidazole with a bulky isopropyl group provided the desired **3ma** in a high yield. Aryl and vinyl moieties on C2 position were compatible with the reaction system and the corresponding imidazo[1,5-α]quinolines **3na** and **3oa** were produced exclusively, albeit with moderate yields. Interestingly, an imidazole with an acetyl group could react with **2a** to afford **3pa** albeit in low yield due to some side reactions, while excellent yield was obtained for **3qa** with a benzoyl group. In addition, imidazoles bearing a cyano or sulfonyl group exhibited the similar reactivity, giving **3ra** or **3sa**, respectively, in moderate yields. Notably, the thioether functional group did not affect the catalytic activity, and high yields were achieved for products **3ta** and **3ua**. Moreover, even an imidazole with a 2-Cl group could be applied, though the product **3va** was obtained in a fair yield. 2,4-disubstituted imidazole also proceeded well in the reaction with **2a** to produce **3wa** in 40% yield, and the yield could be improved to 76% yield by changing the ratio of the starting materials. On the other hand, it was pleasing that α-C−H bond of *N*-aryl pyrroles **4** could also be activated under the same catalytic system, an array of pyrrolo[1,2-α]quinoline derivatives (**5a**−**e**) were smoothly produced in low to good yields.[14]

We further carried out some deuterium experiments to gain some insights into the catalytic mechanism. The C(5)−H kinetic isotopic effects were determined to be 1.5, however, DKIE in Csp^2−H of 1.0 was obtained, thus indicating that cleavage of C(5)−H bond in imidazole might be involved in the rate-determining step (Scheme 5, eqs 3 and 4).[15]

(14) For selected examples of α-C−H activation of pyrroles, see: (a) Ref. (9i). (b) Tsuchimoto, T.; Hatanaka, K.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2003**, 2454. (c) Blaszykowski, C.; Aktoudianakis, E.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 2043. (d) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (e) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981.

(15) We conducted deuterium exchange and competition reactions to gain some insights into the mechanism. For more details, see the Supporting Information.

Scheme 4. Annulation Reactions of Diverse Imidazoles and Pyrroles[a]

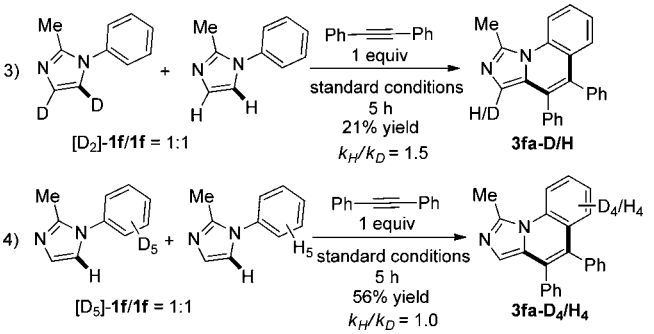


[a] Unless noted otherwise, reaction conditions were conducted with 0.2 mmol of **1** or **4**, 0.1 mmol of **2a**, 5 mol % of $[Cp^*RhCl_2]_2$, 0.12 mmol of $Cu(OAc)_2 \cdot H_2O$, 1 mL of toluene, 110 °C, under Ar atmosphere. Yields are reported for the isolated products. [b] 0.1 mmol of **1**, 0.2 mmol of **2a**.

A plausible mechanism for the oxidative annulation was proposed (Scheme 6). C(5)−H first undergoes insertion by Rh(III) catalyst to give intermediate **I**, presumably facilitated by the assistance of adjacent π system.[12] Then the following vinylic sp^2 C−H activation event occurs to afford the five-membered rhodacycle intermediate **II**. Subsequently, alkyne coordinates to Rh(III) to yield intermediate **III**. Regioselective insertion of the alkyne into the Rh−C bond gives an alkyne-coordinating seven-membered ring intermediate **IV**, which would subsequent reductive elimination to give product **3aa**.

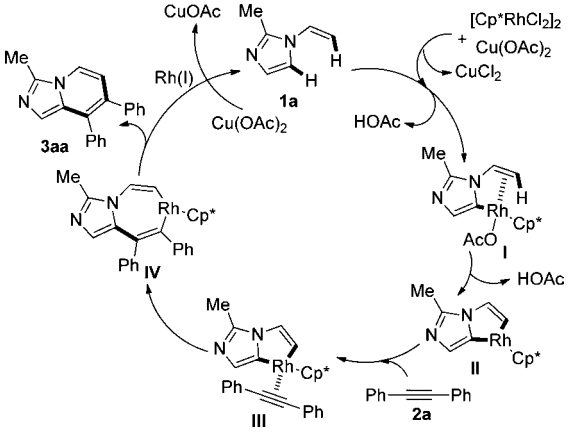
In conclusion, we have successfully developed a Rh(III)-catalyzed double C−H activation of C(5)−H of 2-substituted imidazole substrates and Csp^2−H without heteroatom directing assistance, followed by an annulation reaction with alkynes to give diverse aza-fused quinolines

Scheme 5. Kinetic Isotopic Effects



and pyridines with high molecular complexity. This catalytic strategy was also applicable to the double C−H activation of *N*-arylpyrrole substrates to access pyrrolo-[1,2-α]quinoline scaffolds. Further investigation of the catalytic mechanism and synthetic application of this reaction is underway in this laboratory.

Scheme 6. Plausible Mechanism



Acknowledgment. We are grateful for financial support from the NSFC (21202106), Sichuan University Scientific Research Foundation, Sichuan University "985 project-Science and technology innovation platform for novel drug development", and the Open Research Fund from State Key Laboratory of Breeding Base of Systematic Research, Development and Utilization of Chinese Medicine Resources.

Supporting Information Available. Experimental procedures, structural proofs, and NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.