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Editor's Choice

Rhodium(III)-catalyzed C(sp^3)–H Amidation of 8-Methylquinolines with Amides at Room Temperature

Xiaolei Huang and Jingsong You*

Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, Sichuan University, 29 Wangjiang Road, Chengdu 610064, P. R. China

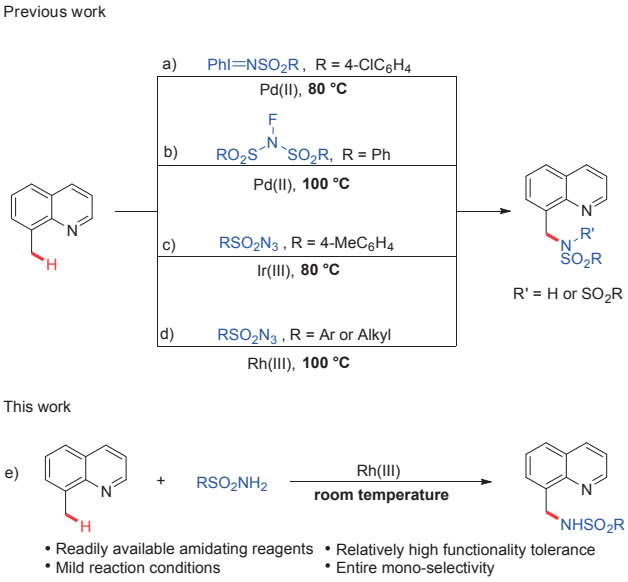
(E-mail: jsyou@scu.edu.cn)

Here we disclose a Rh(III)-catalyzed chelation-assisted C(sp^3)–H activation of 8-methylquinolines, which can enable intermolecular amidation using commercially available, reliable amides as the amidating reagent to provide an efficient route to quinolin-8-ylmethanamine derivatives. This amidation proceeds at room temperature in moderate to excellent yields, and features good functional group tolerance and complete mono-selectivity.

Nitrogen-containing compounds are very important skeletons that widely exist in natural products, pharmaceuticals, biologically active substances, and diverse material molecules.[1] Thus, the formation of C–N bonds is a lasting hot topic, and has been attracting significant attention in the synthetic organic community.[2] In recent years, transition-metal-catalyzed C–H bond activation and subsequent amination or amidation has been one of the most important strategies for the construction of C–N bonds.[3,4] Although transition-metal-catalyzed C(sp^2)–N formation[4c] has been well established, reports on C(sp^3)–N formation reactions via C–H activation,[4a,4b] especially intermolecular amination or amidation still remain underrepresented.[5,6] In the existing C–H amidation reactions, a variety of amidating reagents, such as amides,[7] azides,[8] nitrene precursors,[6a] *N*-fluorobis(phenylsulfonyl)imide (NFSI),[6b] *N*-substituted hydroxylamines,[9] and 1,4,2-dioxazol-5-ones[10] have been investigated. For safety and availability reasons, commercially available, reliable amides could be an ideal amino source.

Quinolin-8-ylmethanamine derivatives are fundamental building blocks in medicinal chemistry and synthetic chemistry.[11] In the past years, 8-methylquinolines have been used as the preferential substrates to afford quinolin-8-ylmethanamines through transition-metal-catalyzed C(sp^3)–H activation/intermolecular amidation due to the conformational bias in favor of the construction of the metallacycle.[12] In 2006, Che and Yu reported the palladium-catalyzed C(sp^3)–H activation and subsequent nitrene insertion of 8-methylquinoline using a nitrene precursor as amidating reagent (Scheme 1a).[6a] After that, palladium-catalyzed chelation-assisted C(sp^3)–H amidation of 8-methylquinolines with NFSI was developed by Muñiz and co-workers (Scheme 1b).[6b] Recently, iridium (Scheme 1c)[6d] and rhodium (Scheme 1d)[13] demonstrated catalysis in the amidation of 8-methylquinolines using azides as the nitrogen atom source. Although the precedent examples feature high chemoselectivity and efficiency, elevated temperatures are necessary for the reaction to proceed. Undoubtedly, the development of an efficient catalytic system for C(sp^3)–H bond activation of 8-methylquinolines and subsequent amidation under mild reaction conditions, especially room temperature, would be highly valuable and desirable.

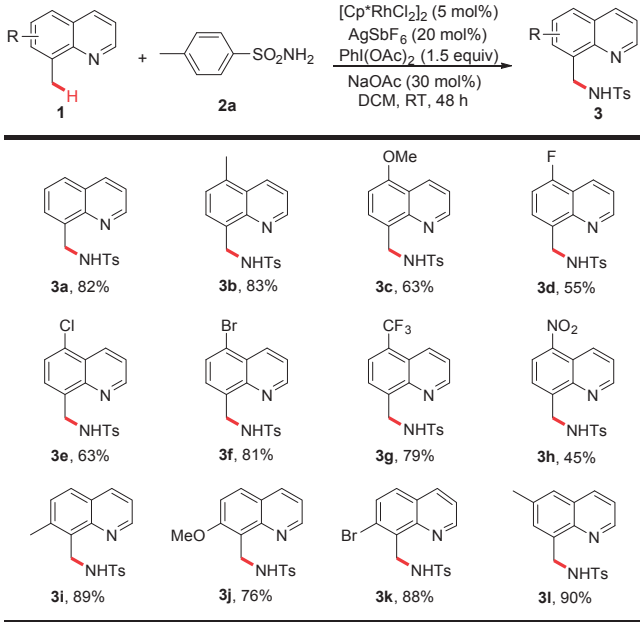
Our group remains committed to rhodium(III)-catalyzed C–H activation.[14] Very recently, we reported rhodium(III)-catalyzed chelation-assisted unreactive, aliphatic C–H bond amidation under mild reaction conditions.[15] In this work, the rhodium(III)-catalyzed C(sp^3)–H activation is successfully extended to the amidation of 8-methylquinolines at room temperature for the synthesis of quinolin-8-ylmethanamine derivatives (Scheme 1e).



Scheme 1. Transition-metal-catalyzed C(sp^3)–H activation/intermolecular amidation of 8-methylquinolines.

Our investigation was initiated with the reaction of 8-methylquinoline (**1a**) and 4-methylbenzenesulfonamide (**2a**) as the model reaction (Table S1 in Supporting Information). Initially, **3a** was obtained in 59% yield in the presence of 5 mol % of $[Cp^*RhCl_2]_2$ and 20 mol % of $AgSbF_6$, using 1.5 equiv of $PhI(OAc)_2$ as the oxidant in dichloromethane (DCM) at 90 °C for 24 h (Table S1, Entry 1). In the absence of $[Cp^*RhCl_2]_2$ or $AgSbF_6$, no product was observed (Table S1, Entry 2). Decreasing the catalyst loading gave a lower yield (Table S1, Entry 3). When an excess of **2a** was added, the yield of **3a** was decreased to 26%, and no bisamidated and triamidated products were observed (Table S1, Entry 4). Among the various solvents examined, DCM proved to be superior to 1,2-dichloroethane (DCE), toluene, methanol, and *N*,*N*-dimethylformamide (DMF) (Table S1, Entries 1 and 5–8). Other oxidants such as $Cu(OAc)_2$, Ag_2CO_3, and AgOAc were ineffective for the process (Table S1, Entries 9–11). To our delight, this amidation could occur at room temperature, and **3a** was obtained in 60% yield (Table S1, Entries 12 and 13). Furthermore, the addition of NaOAc as the additive turned out to benefit amidation, and the desired product was obtained in 82% yield for 48 h (Table S1, Entries 14–17). Thus, the optimal conditions were obtained by using $PhI(OAc)_2$ (1.5 equiv) as the oxidant and NaOAc

Table 1. The scope of 8-methylquinolines[a,b]



[a]Reactions were performed with **1** (0.50 mmol) and **2a** (0.25 mmol) in 1.0 mL of DCM. [b]Yields of isolated products.

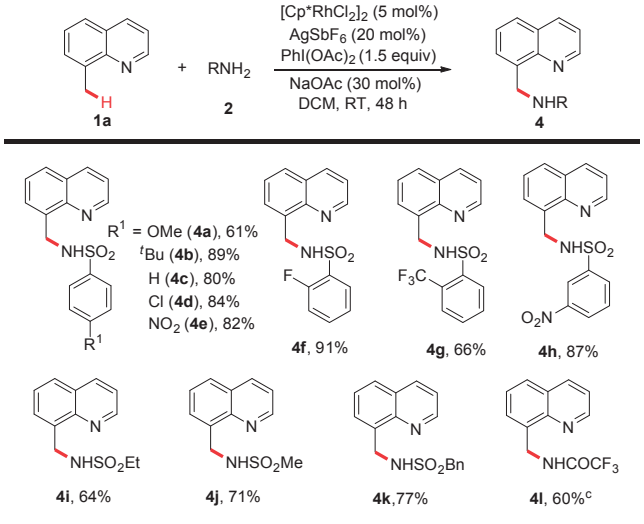
(30 mol %) as the additive in the presence of $[Cp^*RhCl_2]_2$ (5.0 mol %) and $AgSbF_6$ (20 mol %) in DCM at room temperature for 48 h.

With the optimal conditions in hand, we examined the reaction of 8-methylquinolines (**1**) with 4-methylbenzenesulfonamide (**2a**) (Table 1). Substrates with various commonly encountered functional groups, such as Me, MeO, X (X = F, Cl, Br), CF_3, and NO_2, were compatible with this amidation reaction to afford quinolin-8-ylmethanamine derivatives in moderate to good yields (Table 1, **3b**–**3h**). It is worth noting that 8-methylquinolines bearing an electron-donating group on the C-5 position could well undergo the amidation (Table 1, **3b** and **3c**), while the same substrates gave lower yields in the work of Wang.[13] The C-6- or C-7-substituted 8-methylquinolines exhibited higher reactivity, and the C(sp^3)-amidated products were obtained in good to excellent yields (Table 1, **3i**–**3l**). Furthermore, no product was detected when 8-ethylquinoline served as the coupling partner. This observation indicated that steric hindrance could restrain the formation of a five-membered rhodacycle that could offer favorable driving force to promote the desired C–H activation.

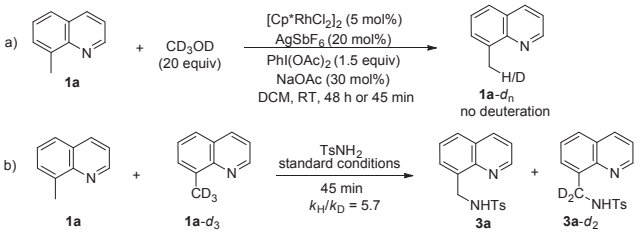
Subsequently, the scope of amides was investigated. As summarized in Table 2, a variety of aryl sulfonamides containing electron-donating, electron-neutral, and electron-withdrawing groups could undergo the amidation process, and the desired products were obtained in satisfactory yields (**4a**–**4h**). Alkyl sulfonamides could also be used as the amidating reagent in the coupling reaction (**4i**–**4k**). When an excess of 2,2,2-trifluoroacetamide served as the substrate, 2,2,2-trifluoro-*N*-(quinolin-8-ylmethyl)acetamide was produced in 60% yield (**4l**).

Deuterium-labeling experiments were conducted to explore some preliminary insight into the mechanism of the C–H amidation reaction. The H/D exchange experiments revealed that the C(sp^3)–H bond cleavage is irreversible (Scheme 2a). Then, the intermolecular competition reaction was carried out. **1a** and **1a**-d_3

Table 2. The scope of amides[a,b]



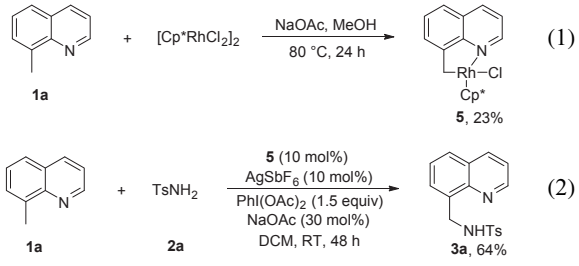
[a]Reactions were performed with **1a** (0.50 mmol) and **2** (0.25 mmol) in 1.0 mL of DCM. [b]Yields of isolated products. [c]**1a** (0.25 mmol) and 2,2,2-trifluoroacetamide (0.50 mmol).

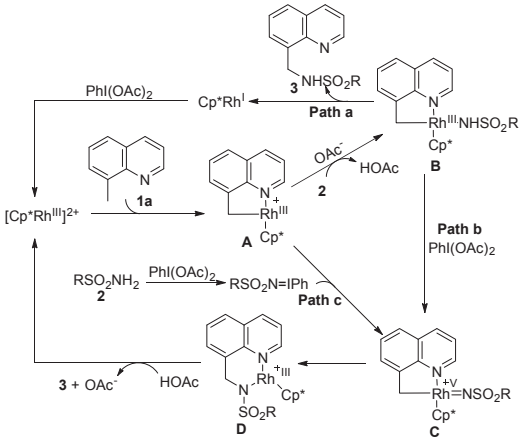


Scheme 2. Deuterium-labeling experiments.

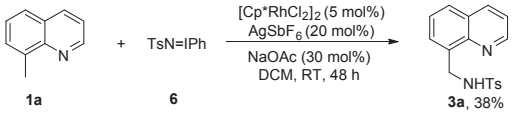
reacted with 4-methylbenzenesulfonamide in one vessel to afford a notable primary kinetic isotopic effect ($k_H/k_D = 5.7$) (Scheme 2b), indicating that C–H bond activation is likely related with the rate-determining step.[16]

Treatment of 8-methylquinoline with $[Cp^*RhCl_2]_2$ afforded the neutral rhodium species **5** (eq 1),[12d] which could catalyze the amidation of 8-methylquinoline in 64% yield in the presence of $AgSbF_6$ (eq 2). This result revealed the plausible intermediacy of a cyclometalated Rh(III) complex in the catalytic cycle. In addition, the reaction of 8-methylquinoline (**1a**) with *N*-tosyliminophenyliodinane (**6**)[17] was conducted in the absence of $PhI(OAc)_2$ under standard conditions to identify whether a nitrene precursor was involved in the amidation. As a result, **3a** was obtained in 38% yield (eq 3), implying that a nitrene intermediate generated in situ in the reaction of $PhI(OAc)_2$ and sulfonamide might be related to the amidation process.





Scheme 3. Proposed mechanism.



1a 6 (3)

According to the experimental investigations and the previous work on Rh(III)-catalyzed C–H bond amidation,[7b,15] a plausible mechanism is proposed (Scheme 3). First, N-chelator-assisted C(sp^3)–H activation affords the five-membered rhodacycle intermediate **A**. Subsequently, intermediate **A** might undergo reaction via three possible paths. In *path a*, treatment of **A** with a sulfamide produces intermediate **B**, which could go through reductive elimination to give the desired product **3**. Meanwhile, the generated Cp*Rh(I) species is reoxidized to the Cp*Rh(III) species. In *path b* and *c*, a Rh(V)–nitrenoid intermediate **C** could be obtained from either the oxidation of intermediate **B** or the reaction of **A** with a nitrene intermediate generated from $PhI(OAc)_2$ and sulfonamide **2**. Then, **C** is transformed into intermediate **D**, and further releases product **3** in the presence of HOAc.

In summary, we have addressed a Rh(III)-catalyzed chelation-assisted C(sp^3)–H bond amidation of 8-methylquinolines using commercially available amides as the amidating reagent at room temperature in moderate to excellent yields. This protocol has good functional group tolerance and complete mono-selectivity. This strategy would represent a powerful route to quinolin-8-ylmethanamine derivatives.

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Supporting Information is available electronically on J-STAGE.

References and Notes

1 a) P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Álvarez, *Chem.—Eur. J.* **2011**, *17*, 1388. b) M. Liang, J. Chen, *Chem. Soc. Rev.* **2013**, *42*, 3453. c) *The Practice of Medicinal Chemistry*, 3rd ed., ed. by C. G. Wermuth, Academic Press, London, **2008**. d) M. Waser, in *Progress in the Chemistry of Organic Natural Products*, ed. by A. D. Kinghorn, H. Falk, S. Gibbons, J. Kobayashi, Springer-Verlag, New York, **2012**, Vol. 96. doi:10.1007/978-3-7091-1163-5. e) *Amino Group Chemistry: From Synthesis to the Life Sciences*, ed. by A. Ricci, Wiley-VCH, Weinheim, Germany, **2008**. doi:10.1002/9783527621262.

2 For selected reviews, see: a) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805. b) P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905. c) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534. d) J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911.

3 For selected reviews on C–H activation, see: a) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068. b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315. c) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740. d) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788.

4 For reviews on C–H activation/C–N formation, see: a) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061. b) J. L. Jeffrey, R. Sarpong, *Chem. Sci.* **2013**, *4*, 4092. c) M.-L. Louillat, F. W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901.

5 For selected examples on intramolecular C(sp^3)–H amination, see: a) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3. b) Q. Zhang, K. Chen, W. Rao, Y. Zhang, F.-J. Chen, B.-F. Shi, *Angew. Chem., Int. Ed.* **2013**, *52*, 13588. c) M. Yang, B. Su, Y. Wang, K. Chen, X. Jiang, Y.-F. Zhang, X.-S. Zhang, G. Chen, Y. Cheng, Z. Cao, Q.-Y. Guo, L. Wang, Z.-J. Shi, *Nat. Commun.* **2014**, *5*, 4707. d) Z. Wang, J. Ni, Y. Kuninobu, M. Kanai, *Angew. Chem., Int. Ed.* **2014**, *53*, 3496. e) X. Wu, K. Yang, Y. Zhao, H. Sun, G. Li, H. Ge, *Nat. Commun.* **2015**, *6*, 6462.

6 For examples on intermolecular C(sp^3)–H amination, see: a) H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048. b) Á. Iglesias, R. Álvarez, Á. R. de Lera, K. Muñiz, *Angew. Chem., Int. Ed.* **2012**, *51*, 2225. c) T. Kang, H. Kim, J. G. Kim, S. Chang, *Chem. Commun.* **2014**, *50*, 12073. d) T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 4141.

7 a) B. Xiao, T.-J. Gong, J. Xu, Z.-J. Liu, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 1466. b) H. Zhao, Y. Shang, W. Su, *Org. Lett.* **2013**, *15*, 5106.

8 K. Shin, H. Kim, S. Chang, *Acc. Chem. Res.* **2015**, *48*, 1040.

9 a) S. Yu, B. Wan, X. Li, *Org. Lett.* **2013**, *15*, 3706. b) B. Zhou, J. Du, Y. Yang, H. Feng, Y. Li, *Org. Lett.* **2014**, *16*, 592. c) M. A. Ali, X. Yao, H. Sun, H. Lu, *Org. Lett.* **2015**, *17*, 1513.

10 Y. Park, K. T. Park, J. G. Kim, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 4534.

11 a) J.-A. Ma, L.-X. Wang, W. Zhang, Q.-L. Zhou, *Tetrahedron: Asymmetry* **2001**, *12*, 2801. b) J. Chiron, J.-P. Galy, *Heterocycles* **2003**, *60*, 1653. c) N. C. Warshakoon, J. Sheville, R. T. Bhatt, W. Ji, J. L. Mendez-Andino, K. M. Meyers, N. Kim, J. A. Wos, C. Mitchell, J. L. Paris, B. B. Pinney, O. Reizes, X. E. Hu, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5207.

12 a) J. Zhang, E. Khaskin, N. P. Anderson, P. Y. Zavalij, A. N. Vedernikov, *Chem. Commun.* **2008**, 3625. b) S. Zhang, F. Luo, W. Wang, X. Jia, M. Hu, J. Cheng, *Tetrahedron Lett.* **2010**, *51*, 3317. c) K. B. McMurtrey, J. M. Racowski, M. S. Sanford, *Org. Lett.* **2012**, *14*, 4094. d) B. Liu, T. Zhou, B. Li, S. Xu, H. Song, B. Wang, *Angew. Chem., Int. Ed.* **2014**, *53*, 4191. e) W. Zhang, S. Ren, J. Zhang, Y. Liu, *J. Org. Chem.* **2015**, *80*, 5973.

13 N. Wang, R. Li, L. Li, S. Xu, H. Song, B. Wang, *J. Org. Chem.* **2014**, *79*, 5379.

14 a) J. Dong, Z. Long, F. Song, N. Wu, Q. Guo, J. Lan, J. You, *Angew. Chem., Int. Ed.* **2013**, *52*, 580. b) X. Qin, H. Liu, D. Qin, Q. Wu, J. You, D. Zhao, Q. Guo, X. Huang, J. Lan, *Chem. Sci.* **2013**, *4*, 1964. c) X. Huang, J. Huang, C. Du, X. Zhang, F. Song, J. You, *Angew. Chem., Int. Ed.* **2013**, *52*, 12970. d) X. Liu, G. Li, F. Song, J. You, *Nat. Commun.* **2014**, *5*, 5030.

15 X. Huang, Y. Wang, J. Lan, J. You, *Angew. Chem., Int. Ed.* **2015**, *54*, 9404.

16 E. M. Simmons, J. F. Hartwig, *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.

17 Y. Yamada, T. Yamamoto, M. Okawara, *Chem. Lett.* **1975**, 361.

