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ARTICLE TYPE

Copper-Catalyzed C-H Alkylation of 8-Aminoquinolines via 8-Amide Chelation Assistance

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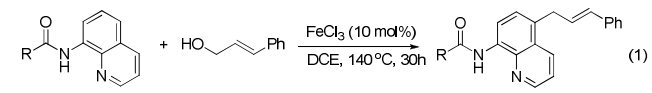
A copper-catalyzed 8-amide chelation-assistance C-H alkylation of 8-aminoquinolines was described. The secondary and tertiary alkyl carboxylic acids can be used as alkylating agent. This reaction allows for the highly regioselective preparation of C2-adamantyl 8-aminoquinoline scaffolds by the decarboxylative alkylation catalytic system.

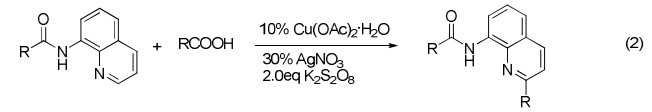
The quinoline was one of the important scaffolds in bioactive molecules and natural products, which has inspired considerable efforts toward the development of efficient strategies for the functionalization of these interesting structural motifs.[1] As early as 1968, F. Minisci discovered that heteroaromatic compouds can be substituted by nucleophilic carbon-centered radicals to get functionalized heteroaromatic compouds.[2] After that, many successful examples in this field were reported which typically focus on the transformation of C−H bonds at the C2, C4 and C8 positions of quinolines.[3] Although great progress has been made in these transformations, including alkylation,[3g] arylation,[3j] ammoniation[3k] and so on, new transformations are still needed in modern organic synthesis.

Substituted 8-aminoquinolines are significant synthetic intermediates which are widely used in dye, medicine and material chemisty.[4] Since the pioneering works by Daugulis, [5] 8-aminoquinolines as auxiliary chelating directing-groups have been used to assist C−H functionalization, which provides a powerful tool toward diverse molecule synthesis. Current researches in this field typically focus on the C−H functionalization on the carboxamide scaffolds.[6] Few studies were reported on C−H transformations of the 8-aminoquinoline frameworks. At same time, duing to the difficulty in the control of the regioselectivity, the C−H functionalization of 8-aminoquinolines meet a significant challenge.[7] Recently, the Zeng group successfully realized C5- or the C4-allylation of 8-aminoquinoline (Scheme 1-1).[8] However, C2 functionalization of 8-aminoquinoline was rarely reported. Alkyl carboxylic acids can easily undergo decarbonylation to generate alkyl radicals which can be used in many synthetic transformations.[9] Herein, we successfully realized a copper-catalyzed C2-alkylation of 8-aminoquinolines via 8-amide chelation assistance using alkyl carboxylic acids as alkylating agent (Scheme 1-2). In our opinion, firstly, the copper catalyst coordinates with the substrate **1** and **2** to form the chelation complex **B**. The amido group in complex **B** can adjust the distribution of electron density on the quinoline. Then the complex **B** was oxidized to give the radical-cation amidoquinoline **C** via an SET mechanism. Last, the carbon at the 2-position went through nucleophilic attack of alkyl radicals to give the C2-alkyl 8-aminoquinoline through an oxidative decarboxylation, deprotonation and aromatization processes (**Scheme 2**).

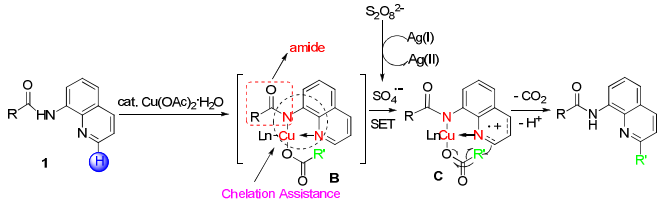
Zeng's work:



Our work:



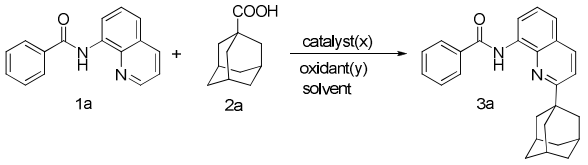
Scheme 1. Functionalization of 8-aminoquinolines



Scheme 2. Our design

Our investigation began with the reaction of **1a** with adamantanecarboxylic acid **2a** using $Cu(OAc)_2·H_2O$ as catalyst and Ag_2CO_3 as oxidant. To our delight, a decarboxylative coupling product **3a** was obtained (Table 1, entry 1). With $AgNO_3$ as an oxidant, a 20% yield was obtained (entry 2). When $K_2S_2O_8$ was used as oxidant and $AgNO_3$ as co-catalyst, a 40% product was separated. In order to further improve the yield, water was added as co-solvent according to previous report,[9g] and the yield can increase to 64% (entry 5). The loading of the catalysts were also screened (entries 6-8), and 30% $AgNO_3$ gave a better result. When $(NH_4)_2S_2O_8$ was instead of $K_2S_2O_8$, a lower yield was got. When 10% $Pd(OAc)_2$ was employed as catalyst, no target product was achieved. The oxidant was proved to be crucial for the reaction because no product was obtained in the absence of $K_2S_2O_8$. Meanwhile, when the catalyst was omitted, no reaction occurred (entry 12).

Table 1. Optimization of Reaction Conditions [a]

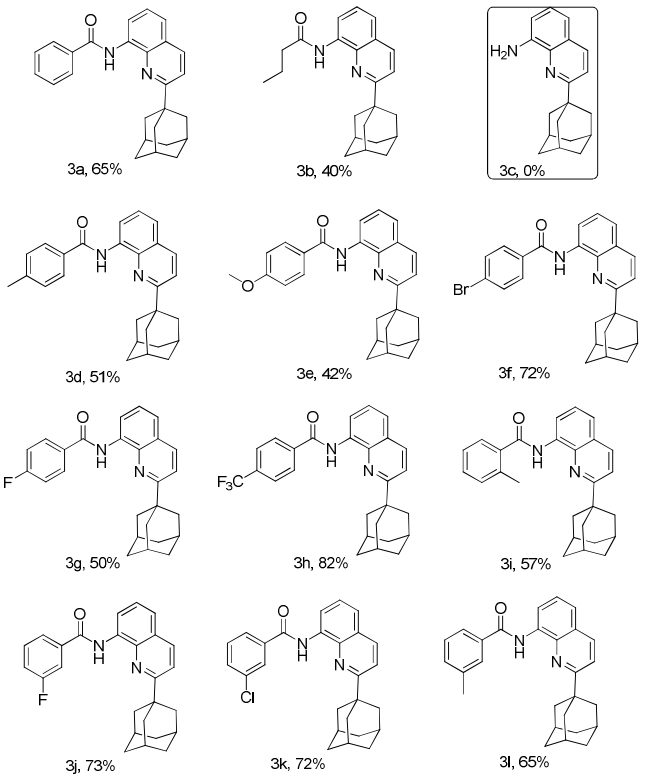


Entry	Catalyst (x% mmol)	Oxidant (y eq.)	Solvent	Yield[b]
1	$Cu(OAc)_2H_2O$(20)	Ag_2CO_3(2)	CH_3CN	15%
2	$Cu(OAc)_2H_2O$(20)	$AgNO_3$(2)	CH_3CN	20%
3	$Cu(OAc)_2H_2O$(20) +$AgNO_3$(30)	$K_2S_2O_8$(2)	CH_3CN	40%
4	$Cu(OAc)_2H_2O$(20) +$AgNO_3$(30)	$K_2S_2O_8$(2)	CH_3CN/H_2O (9:1)	50%
5	$Cu(OAc)_2H_2O$(20) +$AgNO_3$(30)	$K_2S_2O_8$(2)	CH_3CN/H_2O (1:1)	64%
6	***$Cu(OAc)_2H_2O$(10) +$AgNO_3$(30)***	***$K_2S_2O_8$(2)***	***CH_3CN/H_2O (1:1)***	***65%***
7	$Cu(OAc)_2H_2O$(10) +$AgNO_3$(20)	$K_2S_2O_8$(2)	CH_3CN/H_2O (1:1)	60%
8	$Cu(OAc)_2H_2O$(10) +$AgNO_3$(10)	$K_2S_2O_8$(2)	CH_3CN/H_2O (1:1)	58%
9	$Cu(OAc)_2H_2O$(10) +$AgNO_3$(30)	$(NH_4)_2S_2O_8$(2)	CH_3CN/H_2O (1:1)	55%
10	$Pd(OAc)_2$ (10) + $AgNO_3$(30)	$K_2S_2O_8$(2)	CH_3CN/H_2O (1:1)	<5%
11	$Cu(OAc)_2H_2O$(10) +$AgNO_3$(30)	—	CH_3CN/H_2O (1:1)	0
12	—	$K_2S_2O_8$(2)	CH_3CN/H_2O (1:1)	0

[a] Reaction conditions: **1a** (0.30 mmol), **2a** (2.0 equiv), 80 °C, 12h. [b] Isolated yields.

Under the optimized reaction conditions (Table 1, entry 6), firstly, the influence of 8-amide scaffolds on the C−H alkylation of quinolines was probed (Scheme 3). Benzoyl protected 8-aminoquinoline can deliver a 65% yield of the product. An alkyl-substituted acyl-quinoline gave a lower yield (**3b**). When 8-aminoquinoline without any protection was subjected to the standard reaction conditions, no product was detected. According to these phenomenons, the acyl protecting group was significant to the reaction, which is in accordance with the proposed mechanism. Then, a series of functional groups were screened in different positions of benzoyl groups in this reaction, including chloro, bromo, fluoro, trifluoromethyl and ether substituents. An electron-withdrawing substituent favored product formation (**3f**, **3h**, **3j**, **3k**), whereas an electron-donating group slightly hindered the reaction (**3d**, **3e**). Trifluoromethyl substituted substrate gave the best result (**3h**). When a sterically demanding ortho substituent was used, a low yield was obtained (**3i**). To confirm further the structural assignment of products in the present decarboxylative alkylation, the structure of the product **3f** was unambiguously assigned by X-ray crystallography (see Figure 1).[10]

Next, we tune our attention on the alkyl carboxylic acids, the adamantinecarboxylic acids with carbonyl and hydroxyl can be well-tolerated to give the corresponding products in moderate yields (Scheme 4, **3m** and **3n**). Substituted methoxy 8-aminoquinoline can deliver the products **3o** and **3p** in moderate yields. 3-Noradamantanecarboxylic acid can be also used in the decarboxylative coupling reaction to give the product **3q** in 35% yield. Substituted pyridine-2-ylmethanamine can participate in the reaction to give the alkylation product **3r** in moderate yield. To our disappointment, other non-cyclic tertiary acids such as pivalic acid and 3-hydroxy-2,2-dimethylpropanolic acid did not give any products in the reaction conditions, and the starting materials can be quantitatively recovered. When secondary aliphatic carboxylic acids such as cyclohexanecarboxylic acid and cyclopentanecarboxylic acid were subjected to the standard conditions, mixed isomers were obtained in moderate to good yields (**3s, r.r. = 3:5; 3t, r.r.= 5:3**). 2,3-Dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid was also tolerated in this reaction to give a mixed isomer **3u** (78%, **r.r.= 5:3**). Unfortunately, when primary aliphatic carboxylic acid such as 2-(*p*-tolyloxy)-acetic acid was employed, no reaction occurred duing to the poor reactivity.



Scheme 3. Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), $Cu(OAc)_2.H_2O$ (10% mmol), $AgNO_3$(30% mmol), $K_2S_2O_8$ (0.6 mmol), CH_3CN/H_2O (1:1, 2.0 mL), 80 °C, 12h.

To gain insight into the mechanism, 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) as a radical quencher was added into the reaction system, and the reaction was completely inhibited, suggesting that the reaction involved a radical pathway, which is in accordance with classical Minisci reaction (Scheme 5).

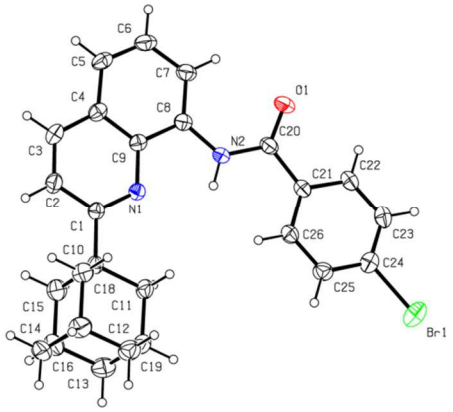
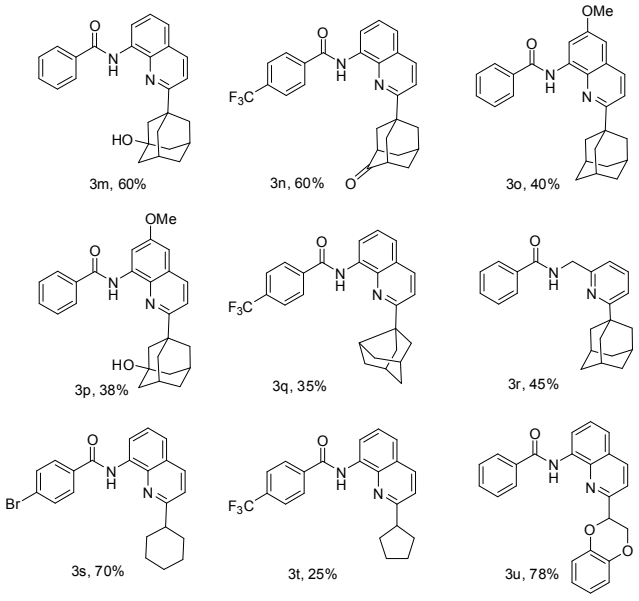
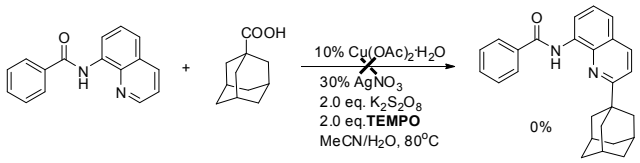


Figure 1. The structure of **3f**.

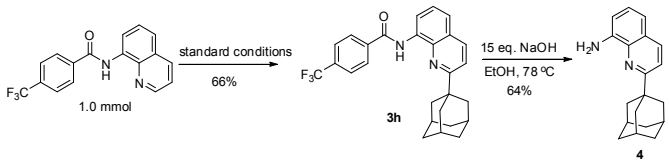


Scheme 4. Reaction conditions: **1** (0.3 mmol), alkyl carboxylic acids (0.6 mmol), $Cu(OAc)_2{\cdot}H_2O$ (10% mmol), $AgNO_3$(30% mmol), $K_2S_2O_8$ (0.6 mmol), CH_3CN/H_2O (1:1, 2.0 mL), 80 °C, 12h. [a]. Regiomeric ratio (r.r.) determined by ^1H NMR spectroscopy (C2/C4). **3q**, r.r.= 2:3, **3s**, r.r.= 3:5. **3t**, r.r.= 5:3. **3u**, r.r.= 5:3.

The benzoyl protecting group can be easily removed by base hydrolysis. For example, treatment of **3h** with 15 equivalent of NaOH in EtOH at 80°C for 8 h affords 2-adamantyl-8-aminoquinoline **4** in moderate yield (64%), which meant that the synthetic method was useable (Scheme 6).[11]



Scheme 5. Mechanism experiment



Scheme 6. Removal of the protecting group.

Conclusions

In summary, we have developed a copper-catalyzed 8-amide chelation-assistance C-H alkylation of 8-aminoquinolines via an SET mechanism. This new-fashioned strategy is operationally simple providing a convenient synthetic route to substituted 2-alkyl-8-aminoquinoline from the secondary and tertiary alkyl carboxylic acids. It allows for the highly regioselective preparation of C2-adamantyl 8-aminoquinolines, but moderate regioselectivity for secondary alkylcarboxylic acids. Non-cyclic tertiary alkylcarboxylic acids and primary aliphatic carboxylic acids failed in the reaction system duing to poor reactivity.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1. (a) T. J. Egan, D. C. Ross, and P. A. Adams, *FEBS Lett.* 1994, **352**, 54;
(b) M. Foley, and L. Tilley, *Pharmacol. Ther.* 1998, **79**, 55; (c) T. Eicher, and S. Hauptmann, *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2003; (d) J. P. Michael, *Nat. Prod. Rep.* 2008, **25**, 166; (e) V. R. Solomon, and H. Lee, *Curr. Med. Chem.* 2011, **18**, 1488; (f) *Chemistry of Heterocyclic Compounds: Quinolines*; G. Jones, Ed.; Wiley: Chichester, U.K., 1977 (Part I), 1982 (Part II), 1990 (Part III); Vol. 32.
2. (a) F. Minisci, E. Vismara, and F. Fontana, *Heterocycles* 1989, **28**, 489; (b) K. S. K. Murthy, and E. E. Knaus, *Drug Dev. Res.* 1999, **46**, 155; (c) W. R. Bowman, and J. M. D. Storey, *Chem. Soc. Rev.* 2007, **36**, 1803; (d) F. Minisci and A. Citterio, *Acc. Chem. Res.* 1983, **16**, 27.
3. For selected examples, see: (a) J. Kwak, M. Kim, and S. Chang, *J. Am. Chem. Soc.* 2011, **133**, 3780; (b) M. Tobisu, I. Hyodo, and N. Chatani, *J. Am. Chem. Soc.* 2009, **131**, 12070; (c) I. B. Seiple, S. Su,

R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, and P. S. Baran, *J. Am. Chem. Soc.* 2010, **132**, 13194; (d) A. M. Berman, J. C. Lewis, R. G. Bergman, and J. A. Ellman, *J. Am. Chem. Soc.* 2008, **130**, 14926; (e) X. Ren, P. Wen, X. Shi, Y. Wang, J. Li, S. Yang, H. Yan, and G. .Huang, *Org. Lett.* 2013, **15**, 5194; (f) G. Deng, and C.-J. Li, *Org. Lett.* 2009, **11**, 1171; (g) U. Sharma, Y. Park, and S. Chang, *J. Org. Chem.* 2014, **79**, 9899; (h) J. Jeong, P. Patel, H. Hwang,and S. Chang, *Org. Lett.* 2014, **16**, 4598; (i) H. Hwang, J. Kim, J. Jeong, and S. Chang , *J. Am. Chem. Soc.* 2014, **136**, 10770; (j) D. E. Stephens, J. Lakey-Beitia, A. C. Atesin, T. A. Atesin, G. Chavez, H. D. Arman, and O. V. Larionov, *ACS Catal.* 2015, **5**, 167; (k) C. Zhu, M. Yi, D. Wei, X. Chen, Y. Wu, and X. Cui , *Org. Lett.* 2014, **16**, 1840.

4. For selected examples, see: (a) F. I. Carroll, J. T. Blackwell, A. Philip, and C. E. Twine. *J. Med. Chem.* 1976, **19** 1111; (b) H. Shiraki, M. P. Kozar, V. Melendez, T. H. Hudson, C. Ohrt, A. J. Magill, and A. J. Lin. *J. Med. Chem.*, 2011, **54**, 131; (c) P. Pal, S. K. Rastogi, C. M. Gibson, D. Eric Aston, A. Larry Branen, and T. E. Bitterwolf. *ACS Appl. Mater. Interfaces*, 2011, **3**, 279; (d) M. J. Araújo, J. Bom, R. Capela, C. Casimiro, P. Chambel, P. Gomes, J. Iley, F. Lopes, J. Morais, R. Moreira, E. de Oliveira, V. do Rosário, and N. Vale. *J. Med. Chem.*, 2005, **48**, 888.
5. V.G. Zaitsev, D. Shabashov, and O. Daugulis, *J. Am. Chem. Soc.* 2005, **127**, 13154.
6. For selected reviews, see: (a) G. Rouquet, and N. Chatani, *Angew. Chem., Int. Ed.* 2013, **52**, 11726. (b) M. Corbet, and F. De Campo, *Angew.Chem., Int. Ed.* 2013, **52**, 9896.
7. A. M. Suess, M. Z. Ertem, C. J. Cramer, and S. S. Stahl, *J. Am. Chem. Soc.* 2013, **135**, 9797.
8. X. Cong, and X. Zeng. *Org. Lett.*, 2014, **16**, 3716.
9. For selected examples, see: (a) R. Shang, Z.-W. Yang, Y. Wang, S.-L. Zhang, and L. Liu, *J. Am.Chem. Soc.* 2010, **132**, 14391; (b) R. Shang, D.-S. Ji, L. Chu, Y. Fu,. and L. Liu, *Angew. Chem., Int. Ed.* 2011, **50**, 4470; (c) R. Shang, Z. Huang, L. Chu, Y. Fu, and L. Liu, *Org. Lett.* 2011, **13**, 4240; (d) R. Shang, Z. Huang, X. Xiao, X. Lu, Y. Fu, and L. Liu, *Adv. Synth. Catal.* 2012, **354**, 2465; (e) H.-P. Bi, L. Zhao, Y.-M. Liang, C.-J. Li, *Angew. Chem., Int. Ed.* 2009, **48**, 792; (f) C. Zhang, and D. Seidel, *J. Am. Chem. Soc.* 2010, **132**, 1798; (g) P.-F.Wang, X.-Q. Wang, J.-J. Dai, Y.-S. Feng, and H.-J. Xu. *Org. Lett.* 2014, **16**, 4586; (h) R. Xia, M.-S. Xie, H.-Y. Niu, G.-R. Qu, and H.-M. Guo, *Org. Lett.* 2014, **16**, 444; (i) F. Hu, X. Shao, D. Zhu, L. Lu, and Q. Shen, *Angew. Chem., Int. Ed.* 2014, **53**, 6105; (j) Z. Wang, L. Zhu, F. Yin, Z. Su, Z. Li, and C. Li, *J. Am. Chem. Soc.* 2012, **134**, 4258; (k) X. Liu, Z. Wang, X. Cheng, and C. Li, *J. Am. Chem. Soc.* 2012, **134**, 14330.
10. CCDC 1029795 (**3f**) contains the supplementary crystallographic data for this paper.
11. X.-Q. Hao, L.-J. Chen, B. Ren, L.-Y. Li, X.-Y. Yang, J.-F. Gong, J.-L. Niu, and M.-P. Song. *Org. Lett.* 2014, **16**, 1104.