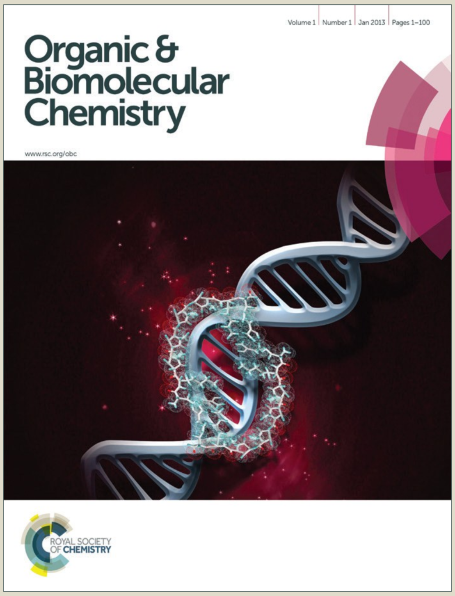
Organic & Biomolecular Chemistry

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

ARTICLE

Copper Catalysed Direct Amidation of Methyl Groups with N-H Bonds

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

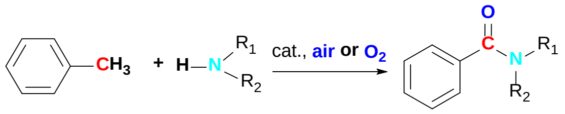
www.rsc.org/

Yao Huang,[a] Tieqiao Chen,*[a] Qiang Li,[a] Yongbo Zhou,[a] and Shuang-Feng Yin*[a]

An efficient copper catalyzed direct aerobic oxidative amidation of methyl groups of azaarylmethanes with N-H bonds producing amides is successfully developed, which can produce primary, secondary and tertiary amides, including those with functional groups. This reaction represents a straightforward method for the preparation of amides from the readily available hydrocarbon starting materials.

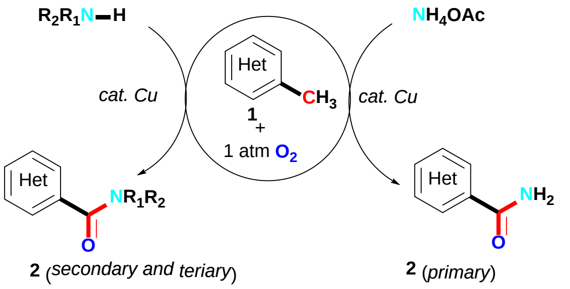
Introduction

New green synthetic reactions *via* direct transformations of inert chemical bonds play an important role in sustainable chemistry.[1-3] In this regard, the cleavage and functionalization of C-H bonds have attracted extensive interests.[2] The direct functionalization of C-H bonds can short-cut the synthetic procedures and is the most straightforward way for the generation of valuable chemicals.[2] Aromatic amides are one of the basic starting materials for industry. They are also important building blocks for the synthesis of fine chemicals such as pharmaceuticals, natural products and functional materials. Current methods[4-9] for their preparation are based on the transformations of carboxylic acids derivatives,[5] organohalides,[6] amides,[7] alcohols[8] and aldehydes[9] etc. These reactions are based on the functional group transformations and require preactivation, prefunctionalization or a strong oxidant, suffering from low atom-economic efficiency. No need to say, the direct aerobic oxidative amidation of methyl groups with N-H bonds is the most economic and clean way for the preparation of such compounds (eqn 1). However, to date, this strategy has only met with limited success.[10]



(1)

Herein, we report an efficient copper catalysed synthesis of amides **2** *via* the direct aerobic oxidative amidation of the methyl groups of azaarylmethane **1** with N-H bonds (Scheme 1). All kinds of amides (primary, secondary and tertiary) **2**, including those with functional groups, can be prepared from the readily available **1**.



Scheme 1 Copper-catalysed aerobic oxidative amidation of azaarylmethanes **1** forming amides **2**.

Results and discussion

We initiate this study by examining the reactivity of 2-methylquinoline **1a** with ammonium salts in the presence of a metal catalyst under oxygen atmosphere and the obtained results are compiled in Table 1. After an extensive screening on the conditions and catalysts, we found that copper salts and the metallic copper served as the catalysts for the direct aerobic oxidative amidation reaction to produce the corresponding amide **2a** in high yields. Thus, under an atmospheric oxygen, a mixture of **1a** (0.2 mmol) and NH_4OAc (0.8 mmol) in dioxane (1.0 mL) was heated at 130 °C overnight to produce quinoline-2-carboxamide **2a** in 88% yield (entry 1). Other copper compounds such as $CuBr_2$, $Cu(OAc)_2$, CuBr, CuI and Cu_2O also similarly catalysed this aerobic oxidative dehydrogenative amidation to give **2a** in good yields (entries 2-6). Interestingly, metallic copper also efficiently catalysed this reaction to produce **2a** in 88% yield (entry 7). Noteworthy, copper is essential for this reaction. In the absence of copper, **2a** could not be obtained at all (entry 8). $FeCl_3$ and $PdCl_2$ were also not effective for this transformation under similar reaction conditions (entries 9 and 10). In addition to dioxane, the reaction also took place readily in PhOMe, toluene and DMF, but hardly proceeded in $Cl_2CH_2CH_2Cl_2$ and DMSO (entries 11-15). As to the ammonium source, urea and ammonia only gave traces amount of the product and NH_4Br did not produce

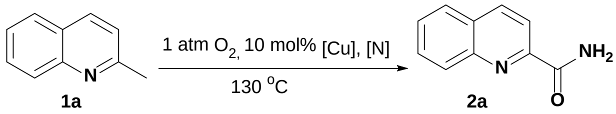
---

[a] State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China. E-mail: chentieqiao@hnu.edu.cn; sf_yin@hnu.edu.cn

Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

2a at all (entries 16-18). These results indicate that a suitable pH condition would be essential.

Table 1 Metal-catalysed aerobic oxidative amidation of 2-methylquinoline with ammoniun.[a]



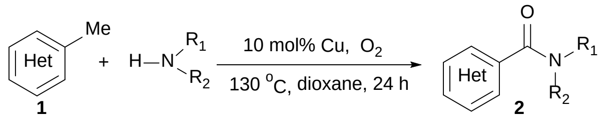
Entry	[Cu]	[N]	Solvent	Yield[b]
1	$CuCl_2$	NH_4OAc	Dioxane	88%
2	$CuBr_2$	NH_4OAc	Dioxane	66%
3	$Cu(OAc)_2$	NH_4OAc	Dioxane	67%
4	CuBr	NH_4OAc	Dioxane	86%
5	CuI	NH_4OAc	Dioxane	76%
6	Cu_2O	NH_4OAc	Dioxane	71%
7	Cu	NH_4OAc	Dioxane	88%(none)[c]
8	-	NH_4OAc	Dioxane	none
9	$FeCl_3$	NH_4OAc	Dioxane	none
10	$PdCl_2$	NH_4OAc	Dioxane	none
11	Cu	NH_4OAc	PhOMe	74%
12	Cu	NH_4OAc	Toluene	62%
13	Cu	NH_4OAc	DMF	48%
14	Cu	NH_4OAc	DMSO	10%
15	Cu	NH_4OAc	$Cl_2CHCHCl_2$	11%
16	Cu	urea	Dioxane	<1%
17	Cu	$NH_3 \cdot H_2O$	Dioxane	9%
18	Cu	NH_4Br	Dioxane	none

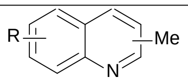
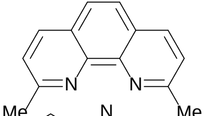
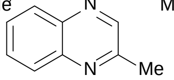
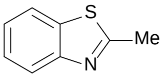
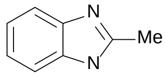
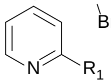
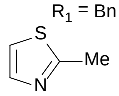
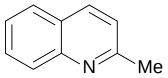
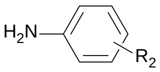
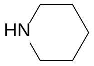
[a] Conditions: 2-methylquinoline (0.2 mmol), ammonium source (0.8 mmol based on nitrogen), 10 mol% catalyst, solvent (1 mL), 1 atm O_2, 24 h, in a 25 mL sealed tube. [b] GC yields using dodecane as an internal standard. [c] Yield in the bracket under N_2 atmosphere.

This copper catalysed direct aerobic oxidative amidation of methyl groups with N-H bonds could be readily applied to other substrates to produce the corresponding amides. As shown in Table 2, a variety of 2-methylquinoline analogues with either an electron-donating or electron-withdrawing group, all were converted readily to the corresponding amides efficiently (entries 1-12). Thus, in addition to 2-methylquinoline, the direct oxidative amidation of 4-methylquinoline was achieved (entry 2). High yields of the amides were also obtained from 2-methylquinoline analogues bearing methyl and methoxy groups (entries 3-5). Very interestingly, substrates with an amino NH_2 group (entry 6) and an amido group (entry 7) could also be used in this reaction to produce the corresponding amides.

Gratifyingly, 2-methylquinolines with fluoro (entry 8), chloro (entry 9) and bromo (entry 10) all served as good substrates to produce the corresponding amides **2h**, **2i** and **2j** in excellent yields. These compounds are versatile starting materials for the synthesis of functional materials *via* the transformations of the carbon-halogen bonds. Copper catalysed aerobic oxidative amidation of 2-methylquinoline analogues with electron-withdrawing substituents (CO_2Me and NO_2) were also successfully achieved, giving the desired products **2k** and **2l** in 61% and 46% yields, respectively (entries 11 and 12). As exemplified by neocuproine, two amido groups could be generated in one pot to produce the corresponding bisamides in good yields (entry 13).

Table 2 Cu-catalysed aerobic oxidative amidation of methyl groups with N-H bonds producing amides.[a]

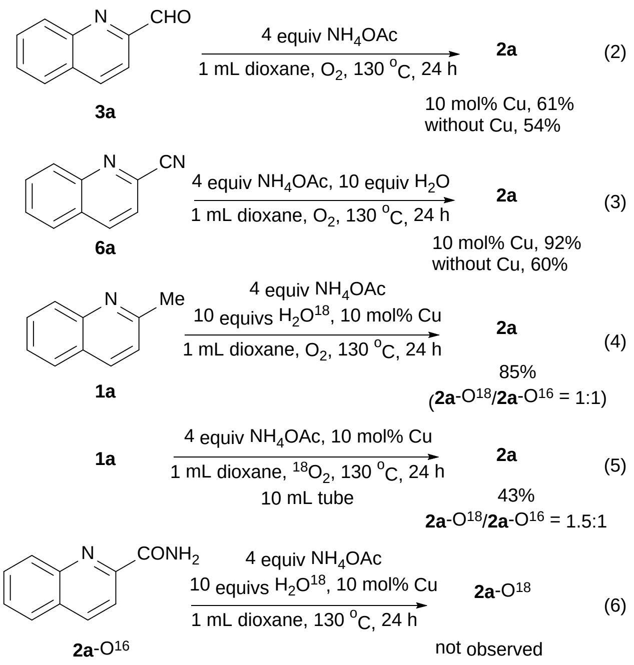


Entry	Arylmethane	N source	Product	Yield[b]
1	 2-Me, R = H	NH_4OAc	**2a**	85%
2[c,d]	4-Me, R = H		**2b**	53%
3	2-Me, R = 6-Me		**2c**	91%
4	2-Me, R = 6-OMe		**2d**	90%
5[d]	2-Me, R = 8-OMe		**2e**	80%
6[d]	2-Me, R = 4-NH_2		**2f**	49%
7	2-Me, R = 4-NHC(O)Bu-*t*		**2g**	67%
8[e]	2-Me, R = 6-F		**2h**	90%
9[e]	2-Me, R = 6-Cl		**2i**	96%
10[e]	2-Me, R = 6-Br		**2j**	94%
11[d,f]	2-Me, R = 6-COOMe		**2k**	61%
12	2-Me, R = 6-NO_2		**2l**	46%
13			**2m**	56%
14[d]			**2n**	93%
15[d]			**2o**	91%
16			**2p**	20%
17[g]	 R_1 = Me		**2q**	48%
18[h,d]	R_1 = Et		**2q**	27%
19[i]	R_1 = Bn		**2q**	none
20[g]			**2r**	51%
21		 R_2 = H	**2s**	69%
22		4-Me	**2t**	60%
23		2-OMe	**2u**	54%
24		2-Cl	**2v**	72%
25		4-Cl	**2w**	66%
26		4-NO_2	**2x**	39%
27		H_2N—Pr-*i*	**2y**	29%
28			**2z**	41%

[a] Conditions: 0.2 mmol arylmethane, 0.8 mmol NH_4OAc (for an amine: 0.4 mmol amine and 0.2 mmol Ph_2PO_2H), 10 mol% copper (for an amine, 10 mol% CuI was used), 1 mL dioxane (for an amine, PhOMe was used), 1 atm O_2, 130 °C, 24 h. [b] Isolated yield. [c] 10 mol% 1,10-phenanthroline and 0.5 mL H_2O were used. [d] 1.6 mmol NH_4OAc was added. [e] 36 h. [f] 20 mol% copper was loaded. [g] 10 mol% CuBr was used. [h] 150 °C. [i] 74% phenyl(pyridin-2-yl)methanone was produced.

Other azaarylmethanes with two heteroatoms (entries 14-15) also produced the corresponding amides in high yields under similar reaction conditions. 2-Methylpyridine served well in the current amidative system (entry 17). Interestingly, 2-ethylpyridine also reacted with NH_4OAc under similar reaction conditions to produce **2q** in 27% yield through the oxidative amidation of carbon-carbon bond (entry 18); however, when 2-benzylpyridine was employed, no **2q** was detectable, 74% yield of phenyl(pyridin-2-yl)methanone was produced instead (entry 19). In addition, 2-methylthiazole was also applicable to this reaction (entry 20). Unfortunately, when toluene, 3-methylquinoline and 2-methylthiophene were employed as the substrate, no products were detected under similar reaction conditions.

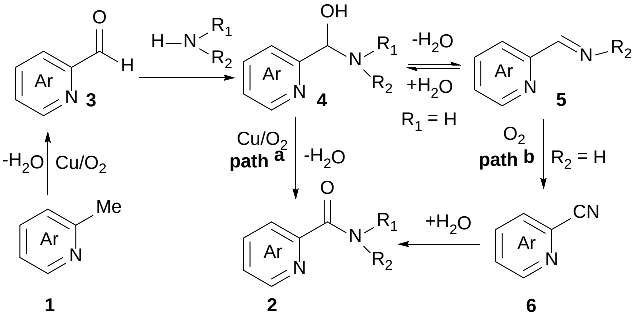
In addition to the synthesis of primary amides as described above, it was particularly noteworthy that this strategy of direct aerobic oxidative amidation of methyl groups with N-H bonds is applicable for the preparation of secondary and tertiary amides. As presented by entries 21-26, the reactions of 2-methylquinoline with a variety of anilines took place smoothly to yield the corresponding secondary amides in moderate to good yields. Similar oxidative amidation with isopropylamine took place to generate **2y** in 29% yield (entry 27). A tertiary amide **2z** was also produced in 41% yield *via* the reaction of 2-methylquinoline with piperidine under similar reaction conditions (entry 28). To the best of our knowledge, this is the first successful direct aerobic oxidative amidation of aromatic methyl groups with primary and secondary amines.[10]



Scheme 2 Control experiments.

In order to clarify the mechanism, control experiments were conducted. It was found that under the reaction conditions, quinoline-2-carbaldehyde **3a** was converted to **2a** in 61% yield. Interestingly, in the absence of copper, **2a** was also afforded in 54%,[9l,9m] indicating that an aldehyde **3** could be the possible intermediate in the copper catalysed oxidative amidation and the copper catalyst perhaps only worked in the aerobic oxidation of methyl groups (eqn 2).[11] In the presence of water, quinoline-2-carbonitrile **6a** was hydrolyzed smoothly to give **2a** in 92% yield under the standard reaction conditions (eqn 3). It is assumed that copper catalyses the aerobic oxidation of methyl groups to generate aldehydes **3** first.[12-15] Quick addition of amine to **3** can afford a carbinolamine **4** which then produces nitrile **6** *via* dehydration and oxidation. Hydrolysis of the nitrile **6** produces the amide **2** (Scheme 3, path b).[10] However, although this reaction path can well explain the formation of primary amides, it cannot explain the formation of secondary and tertiary amides. Therefore, another reaction path (Scheme 3, path a) *via* the direct oxidation of carbinolamine **4** to **2** should also operate.[11] This direct oxidation (Scheme 3, path a) perhaps also works, at least partly, for the generation of the primary amide **2a**.

^{18}O experiments showed that the oxygen atom in **2a** can come from both dioxygen and NH_4OAc. The aerobic oxidative amidation of 2-methylquinoline **1a** with NH_4OAc in the presence of a large excess of H_2O^{18} produced 85% yield of **2a** with a 1:1 ratio of **2a**-O^{18}: **2a**-O^{16} (eqn 4). Under $^{18}O_2$ atmosphere, **2a** was produced in 43% yield with a 1.5:1 ratio of **2a**-O^{18}: **2a**-O^{16}. The O^{16} clearly came from NH_4OAc (eqn 5).[16] It was noted that in the presence of a large excess of H_2O^{18}, **2a**-O^{16} could not be isomerized to **2a**-O^{18} under similar reaction conditions (eqn 6).



Scheme 3 Proposed mechanism for the copper catalysed direct aerobic oxidative amidation of methyl groups with N-H bonds.

Conclusions

In summary, we have successfully developed an efficient copper catalysed direct aerobic oxidative amidation of aromatic methyl groups with N-H bonds. Mechanistic studies indicate two reactions paths operate in this reaction. Extension of the current direct oxidative amidation to other substrates is underway.

Acknowledgements

We are grateful for the financial support from NSFC 21403062, HNNSF 2015JJ3039 and Fundamental Research Funds for the Central Universities (Hunan University).

Notes and references

‡ A typical procedure: Under an oxygen atmosphere (1 atm), **1a** (0.2 mmol), NH_4OAc (0.8 mmol), metallic Cu (0.02 mol) and dioxane (1.0 mL) were placed into a glass tube (25 mL) and sealed. The mixture was heated at 130 °C for 24 hours. After removal of the volatiles in vacuum, the residues were purified by chromatography on silica gel (particle size 37-54 μm) using ethyl acetate/petroleum ether as eluent to obtain 85% yield of **2a**.

1 (a) B. M. Trost, *Science*, 1991, **254**, 1471; (b) C.-J. Li and B. M. Trost, *Proc. Natl. Acad. Sci. USA*, 2008, **105**, 13197; (c) K. Sanderson, *Nature*, 2011, **469**, 18; (d) R. A. Sheldon, *Chem. Soc. Rev.*, 2012, **41**, 1437; (e) G. Reniers and C. A. Brebbia, Sustainable Chemistry, WIT press, 2011; (f) A. E. Marteel-Parrish and M. A. Abraham, Green Chemistry and Engineering: A Pathway to Sustainability, Wiley-AIChE, 2014.

2 (a) S. A. Girard and C.-J. Li, *Angew. Chem. Int. Ed.*, 2014, **53**, 74; (b) J. Schranck, A. Tlili and M. Beller, *Angew. Chem. Int. Ed.*, 2014, **53**, 9426; (c) Y. Segawa, T. Maekawa and K. Itami, *Angew. Chem. Int. Ed.*, 2015, **54**, 66; (d) R. A. Baillie, P. Legzdins, *Acc. Chem. Res.*, 2014, **47**, 330; (e) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (f) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **112**, 624; (g) J.-Q. Yu and Z. Shi, C-H Activation, Springer-Verlag, Berlin Heidelberg, 2010.

3 (a) G. Dong, C-C Bond Activation, Springer-Verlag, Berlin Heidelberg, 2014; (b) C.-H. Jun, *Chem. Soc. Rev.*, 2004, **33**, 610.

4 (a) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471; (b) C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405; (c) R. M. Lanigan and T. D. Sheppard, *Eur. J. Org. Chem.*, 2013, 7453; (d) R. García-álvarez, P. Crochet and V. Cadierno, *Green Chem.*, 2013, **15**, 46; (e) E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606; (f) T. J. Ahmed, S. M. M. Knapp and D. R. Tyler, *Chem. Soc. Rev.*, 2011, **255**, 949; (g) A. Brennführer, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.*, 2009, **48**, 4114.

5 (a) M. Hosseini-Sarvari and H. Sharghi, *J. Org. Chem.*, 2006, **71**, 6652; (b) C. Han, J. P. Lee, E. Lobkovsky and J. A. Porco, *J. Am. Chem. Soc.*, 2005, **127**, 10039; (c) X. Chen, T. Chen, Q. Li, Y. Zhou, L.-B. Han and S.-F. Yin, *Chem. Eur. J.*, 2014, **20**, 12234; (d) B. Xiong, L. Zhu, X. Feng, J. Lei, T. Chen, Y. Zhou, L.-B. Han, C.-T. Au and S.-F. Yin, *Eur. J. Org. Chem.*, 2014, **2014**, 4244; (e) C. Battilocchio, J. M. Hawkins and S. V. Ley, *Org. Lett.*, 2014, **16**, 1060; (f) W. Yin, C. Wang and Y. Huang, *Org. Lett.*, 2013, **15**, 1850.

6 (a) A. Schoenberg and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3327; (b) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2007, **46**, 8460; (c) Q. Huang and R. Hua, *Adv. Synth, Catal.*, 2007, **349**, 849.

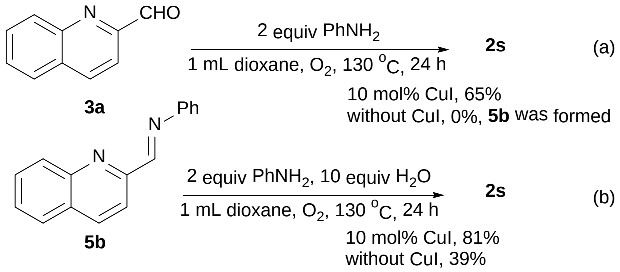
7 (a) J. D. Hicks, A. M. Hyde, A. M. Cuezva and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 16720; (b) M. C. Willis, G. N. Brace and I. P. Holmes, *Angew. Chem. Int. Ed.*, 2005, **44**, 403; (c) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2010, **1**, 13; (d) N. A. Stephenson, J. Zhu, S. H. Gellman and S. S. Stahl, *J. Am. Chem. Soc.*, 2009, **131**, 10003; (e) J. M. Hoerter, K. M. Otte, S. H. Gellman, Q. Cui and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 647; (f) J. M. Hoerter, K. M. Otte, S. H. Gellman and S. S. Stahl, *J. Am. Chem. Soc.*, 2006, **128**, 5177.

8 (a) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131**, 1766; (b) C. Gunanathan, Y. Ben-David and D. Milstein, *Science*, 2007, **317**, 790.

9 (a) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita and M. Tokuda, *J. Am. Chem. Soc.*, 2004, **126**, 14342; (b) K. Yamaguchi, M. Matsushita and N. Mizuno, *Angew. Chem. Int. Ed.*, 2004, **43**, 1576; (c) S.-I. Murahashi, T. Naota and E. Saito, *J. Am. Chem. Soc.*, 1986, **108**, 7846; (d) J. W. Kim, K. Yamaguchi and N. Mizuno, *Angew. Chem. Int. Ed.*, 2008, **47**, 9249; (e) X.-F. Wu, C. B. Bheeter, H. Neumann, P. H. Dixneuf and M. Beller, *Chem. Commun.*, 2012, **48**, 12237; (f) C. Tang and N. Jiao, *Angew. Chem. Int. Ed.*, 2014, **53**, 6528; (g) C. Qin, W. Zhou, F. Chen, Y. Ou and N. Jiao, *Angew. Chem. Int. Ed.*, 2011, **50**, 12595; (h) R. Vanjari, T. Guntreddi and K. N. Singh, *Org. Lett.*, 2013, **15**, 4908; (i) D. L. Priebbenow and C. Bolm, *Org. Lett.*, 2014, **16**, 1650; (j) M. Sharif, J.-L. Gong, P. Langer, M. Beller and X.-F. Wu, *Chem. Commun.*, 2014, **50**, 4747; (k) Q. Song, Q. Feng and K. Yang, *Org. Lett.*, 2014, **16**, 624; l) W. Wang, X.-M. Zhao, J.-L. Wang, X. Geng, J.-F. Gong, X.-Q. Hao and M.-P. Song, *Tetrahedron Lett.*, 2014, **55**, 3192; m) X.-F. Wu, M. Sharif, J.-B. Feng, H. Neumann, A. Pews-Davtyan, P. Langer and M. Beller, *Green Chem.*, 2013, **15**, 1956.

10 In 2012, Mizuno and *et al* reported that good yields of primary aromatic amides were obtained from methylarenes (as solvent) and urea in the presence of MnO_2 (4 equivs) and dioxygen (5 atm). Y. Wang, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.*, 2012, **51**, 7250.

11 We performed the reaction of **3a** with aniline under similar reaction conditions, giving **2s** in 65% yield. However, in the absence of CuI, the yield of **2s** was 0% and imine **5b** was formed instead. In the presence of water, imine **5b** could be converted to **2s** even without CuI. These results indicate that water and copper catalyst would promote the amidation via path a.

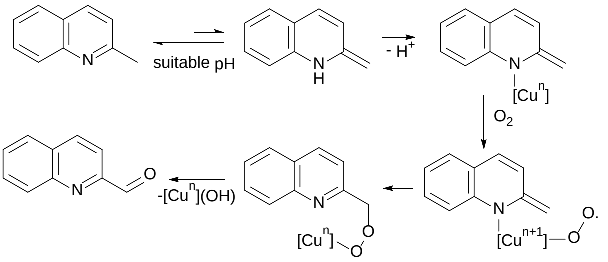


12 (a) J. Liu, X. Zhang, H. Yi, C. Liu, H. Zhang, K. Zhuo and A. Lei, *Angew. Chem. Int. Ed.*, 2015, **54**, 1261; (b) J. D. Houwer, K. A. Tehrani and B. U. W. Maes, *Angew. Chem. Int. Ed.*, 2012, **51**, 2745.

13 In the absence of NH_4OAc, **3a** could be confirmed by GC-MS when 2-methylquinoline was treated under the standard reaction conditions.

14 The aerobic oxidation of methyl groups was thought to be rate determining. When the reaction of 2-methylquinoline with NH_4OAc was conducted at 100 °C, no product could be detected, whereas quinoline-2-carbaldehyde **3a** gave **2a** in 29% yield under similar reaction conditions.

15 Considering that the reaction did not take place with toluene, 3-methylquinoline and 2-methylthiophene, the nitrogen atom in **1** would be crucial and the methyl group should be located at 2- or 4-position. Besides, suitable pH condition was required. Thus on the basis of these results and reported literatures, a plausible mechanism for the copper catalysed aerobic oxidation of azaarylmethanes was proposed below.



For related contributions, see: (a) B. Qian, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia and H. Huang, *J. Am. Chem. Soc.*, 2010, **132**, 3650; (b) Z.-J. Cai, S.-Y. Wang and S.-J. Ji, *Org. Lett.*, 2012,

14, 6068; (c) Q. Li, Y. Huang, T. Chen, Y. Zhou, Q. Xu and S.-F. Yin, *Org. Lett.*, 2014, **16**, 3672; (d) G. Zhang, J. Miao, Y. Zhao and H. Ge, *Angew. Chem. Int. Ed.*, 2012, **51**, 8318.

16 The *O* exchange exists between the acetate and water under the reaction conditions. R. L. Redlngton, *J. Phys. Chem.*, 1976, **80**, 229.