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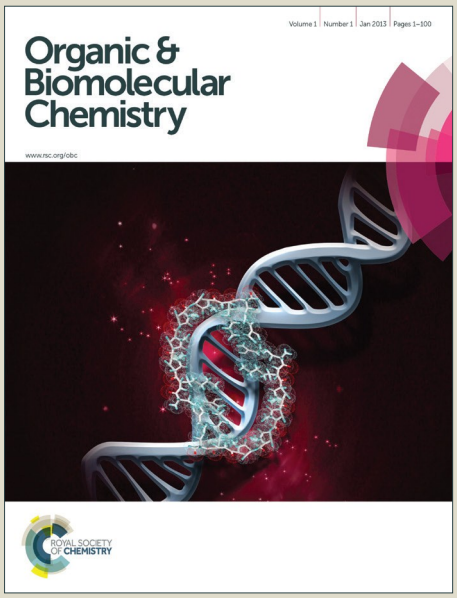

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COMMUNICATION

Copper-Catalyzed Efficient Direct Amidation of 2-Methylquinolines with Amines

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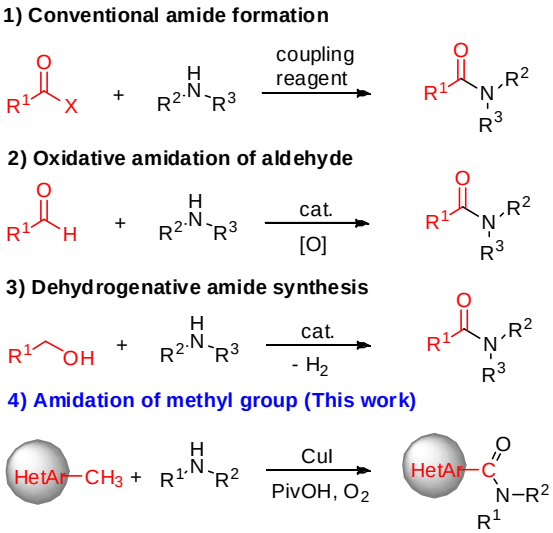
A novel Cu-catalyzed direct amidation of 2-methylquinolines with amines is described. This method afforded an efficient approach for the synthesis of biologically important aromatic amides from readily available coupling partners using molecular oxygen as the oxidant.

Amide motifs are present in many natural products, pharmaceuticals, functional materials and biological systems.[1] Amides are also of great importance as key intermediates for the preparation of various useful organic compounds.[2] Conventional amide bond formation utilizes carboxylic acids and amines as coupling partners in the presence of stoichiometric activating agents for the acid functionality.[3] Recently, great efforts have been made to explore environmentally benign processes toward amide synthesis.[4] Among the various methods developed, replacement of the carboxylic acids with other organic chemicals was proved to be very powerful for clean amide synthesis.[5]



Scheme 1 Different pathways for the amide bond formation.

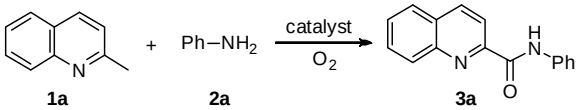
The transition-metal-catalyzed direct amidation of aldehydes with amines has been proved to be an attractive alternative to the traditional amide synthesis. Transition metals such as Cu,[6] Ru,[7] Pd,[8] Rh,[9] Au[10] and lanthanide series[11] or even organic carbene[12] were successfully exploited for this transfromation. In recent years, much efforts has been paid on using readily available alcohols as the coupling partners for amide synthesis. Murahashi and Naota reported the synthesis of lactams from an intramolecular reaction of amino alcohols.[13] In 2007, the Milstein group made a breakthrough for intermolecular amidation of alcohols with amines using ruthenium pincer as the catalyst.[14] This amide synthetic route is very environmentally benign since molecular hydrogen is the only by-product. Since that, various catalytic procedures have been developed for efficient synthesis of amides and ployamides from alcohols and amines.[15] In these processes, alcohols were oxidized into the corresponding aldehydes via dehydrogenation reaction.[16] The Milstein group also found that esters could smoothly reacted with amines with liberation of hydrogen under neutral conditions.[17] Johnston and co-workers developed an efficient procedure for amide and peptide synthesis using α-halo nitroalkanes as the coupling partners in the presence of an electrophilic iodine source.[18] In recent years, direct amidation of C-H bond with amides or other nitrogen sources provided another efficient route for amide synthesis.[19]

In general, aromatic aldehydes and benzylic alcohols are prepared from methylarenes via oxidation/reduction processes. Therefore, direct amidation of methylarenes with amines can potentially lead to a more efficient synthesis by eliminating the need for activation one of the coupling partners. However, efficient direct amidation of methyl group under mild conditions is rare.[20, 21] Herein, we wish to report a copper-catalyzed efficient direct amidation of 2-methylquinolines with amines to provide various aromatic amides containing a quinoline motif in good yields.[22] The methyl group at C2 position of quinolines was activated in situ with catalytic amount of CuI catalyst using molecular oxygen as a green oxidant.

First, we investigated the amidation of 2-methylquinoline (**1a**) and aniline (**2a**) in 1,2-dichlorobenzene at 120 °C under an oxygen atmosphere (Table 1). When the reaction was carried out in the absence of catalyst, no *N*-phenylquinoline-2-carboxamide (**3a**) was formed as determined by GC-MS and ^{1}H NMR methods (entry 1). We found that such reactions proceeded when catalytic amount of iodine or CuI was employed as the catalyst (entries 2 and 4). Halonium ion source such as *N*-iodo succinimide (NIS) was proved to be

ineffective for this kind of transformation (entry 3). Among the various copper salts investigated, CuI showed the best efficiency (entries 4-6). The choice of additives was very crucial for this reaction. Basic additive such as K_2CO_3 significantly decreased the reaction yield (entry 7). To our delight, the reaction yield could be improved to 53% and 60% when 1.5 equiv of acetic acid and pivalic acid (PivOH) were used, respectively (entries 8 and 10). The amount of acid affected the reaction yield profoundly. When the reaction was carried out in pure pivalic acid, the reaction yield could be slightly promoted to 70% (entry 11). Decreasing or increasing the reaction temperature both decreased the reaction yield (entries 14 and 15). The reaction yield could be further improved to 80% by extending the reaction time to 48 h (entry 16). Much lower yield was observed when the model reaction was performed in air (entry 17).

Table 1 Optimization of the reaction conditions[a]



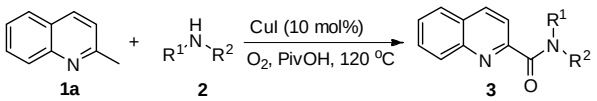
1a **2a** **3a**

Entry	Catalyst	Additive	Solvent	Yield[b] [%]
1			1,2-dichlorobenzene	0
2	I_2		1,2-dichlorobenzene	6
3	NIS		1,2-dichlorobenzene	trace
4	CuI		1,2-dichlorobenzene	11
5	CuBr		1,2-dichlorobenzene	7
6	$CuCl_2$		1,2-dichlorobenzene	trace
7	CuI	K_2CO_3	1,2-dichlorobenzene	trace
8	CuI	AcOH	1,2-dichlorobenzene	53
9	CuI	TsOH	1,2-dichlorobenzene	15
10	CuI	PivOH	1,2-dichlorobenzene	60
11	CuI		PivOH	70
12	CuI		AcOH	30
13	CuI		H_3PO_4	trace
14[c]	CuI		PivOH	51
15[d]	CuI		PivOH	48
16[e]	**CuI**		**PivOH**	**80**
17[f]	CuI		PivOH	19

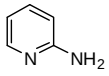
[a] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.02 mmol), additive (0.3 mmol), solvent (0.4 mL) under oxygen, 120 °C, 24 h. [b] GC yield based on **1a**. [c] 110 °C. [d] 130 °C. [e] 48 h. [f] Under air.

To demonstrate the general applicability of the CuI/PivOH system, various amines were tested in amidation reaction with 2-methylquinoline (**1a**). In general, aromatic amines with substituents at the *para* position were able to smoothly react with **1a** to afford the corresponding aromatic amide products in good yields (entries 2-9). Lower yields were obtained when electron-donating groups were presented at the phenyl ring (entries 2 and 3). Introduction of electron-withdrawing groups to the phenyl ring of anilines slightly improved the reaction yield. For example, the desired product **3d** was isolated in 89% yield when 4-(trifluoromethyl)aniline (**2d**) was used (entry 4). Functional groups such as cyano, fluoro and chloro were compatible under the optimized reaction conditions (entries 5, 7-8). When 4-bromoaniline was used as the coupling partner, the desired product was achieved in 72% yield (entry 9). The position of the substituents on the phenyl ring of anilines affected the reaction yield slightly (entries 10-14). Heterocyclic aniline 2-amino pyridine (**2o**) was also suitable amidation partner to give the hetero amide (**3o**) in 81% yield (entry 15). When aromatic secondary amine *N*-methylaniline (**2p**) was used, unexpected product **3a** was obtained by losing the methyl substituent (entry 16). It should be noted that cyclic secondary amines such as morpholine (**2q**) and piperidine (**2r**) were also able to couple with **1a** to give the desired products in moderate yields (entries 17 and 18).

Table 2 Reaction of various amines with 2-methylquinoline (**1a**)[a]



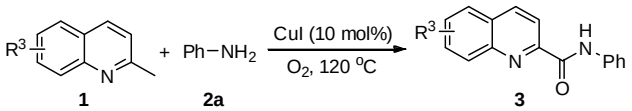
1a **2** **3**

Entry	Amines	Product	Yield[b] [%]
1	R = H	**2a** **3a**	76
2	R = 4-CH_3	**2b** **3b**	57
3	R = 4-OCH_3	**2c** **3c**	49
4	R = 4-CF_3	**2d** **3d**	89
5	R = 4-CN	**2e** **3e**	86
6	R = 4-OCF_3	**2f** **3f**	86
7	R = 4-F	**2g** **3g**	85
8	R = 4-Cl	**2h** **3h**	79
9	R = 4-Br	**2i** **3i**	72
10	R = 3-Me	**2j** **3j**	69
11	R = 3-CF_3	**2k** **3k**	88
12	R = 3-Cl	**2l** **3l**	84
13	R = 2-CH_3	**2m** **3m**	56
14	R = 2-Cl	**2n** **3n**	71
15		**2o** **3o**	81
16		**2p** **3a**	57
17[c]		**2q** **3p**	62
18[c]		**2r** **3q**	42

[a] Conditions: **1a** (0.5 mmol), **2** (1.0 mmol), CuI (0.05 mmol), PivOH (0.8 mL), 120 °C, 48 h, under oxygen. [b] Isolated yield based on **1a**. [c] CuI (0.05 mmol), PivOH (0.2 mL), 1,2-dichlorobenzene (0.6 mL).

To further explore the scope of the reaction, various 2-methylquinolines were employed to react with **2a** under the optimized conditions (Table 3). To our surprise, no product was obtained when a methoxy group was located at C4 position of the pyridine ring (entry 1). However, moderate to good yields were achieved when the substituents were presented at the phenyl ring of quinolines (entries 2-8). Functional groups such as trifluoromethoxy, trifluoromethyl and fluoro were well tolerated under the optimized reaction conditions (entries 3, 4 and 6). However, much lower yields were obtained when bromo and chloro substituents were presented (entries 5 and 7). Interestingly, the desired product **3y** was obtained in 88% when the methoxy group was situated at C8 position (entry 8). Unfortunately, 2-methylpyridine and toluene were not effective coupling partners under the current reaction conditions.

Table 3 Reaction of 2-methylquinolines with aniline (**2a**)[a]



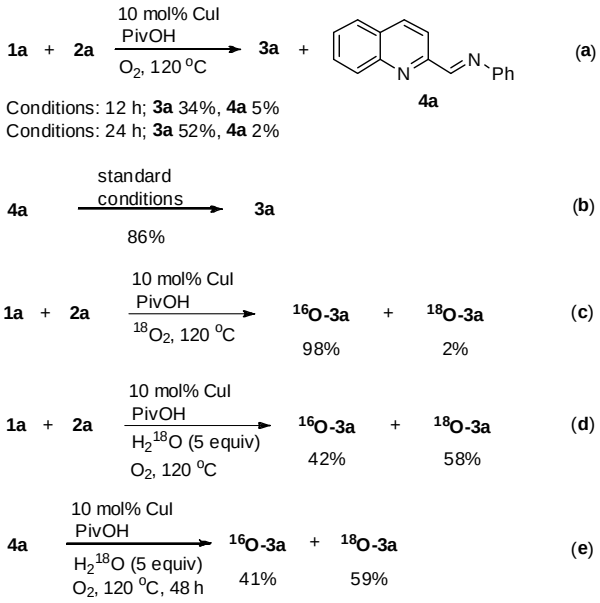
1 **2a** **3**

Entry	2-Methylquinolines		Product	Yield[b] [%]
1	R^3 = 4-MeO	**1b**	**3r**	trace
2	R^3 = 6-Me	**1c**	**3s**	78
3	R^3 = 6-OCF_3	**1d**	**3t**	86
4	R^3 = 6-CF_3	**1e**	**3u**	88
5	R^3= 6-Br	**1f**	**3v**	44
6	R^3 = 7-F	**1g**	**3w**	81
7	R^3 = 7-Cl	**1h**	**3x**	47
8	R^3 = 8-MeO	**1i**	**3y**	88

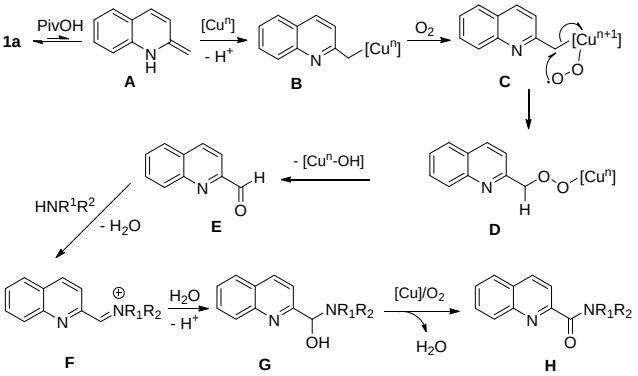
[a] Conditions: **1** (0.5 mmol), **2a** (1.0 mmol), CuI (0.05 mmol), PivOH (0.8 mL), 120 °C, 48 h, under oxygen. [b] Isolated yield based on **1**.

To gather more information, some control experiments were set up under various conditions. When the reaction was stopped in 12 h, the desired product **3a** was obtained in 34% together with 5% of **4a**. If prolonged the reaction time to 24 h, the yield of **3a** could be improved to 52% with a reduced amount of **4a** (Scheme 2a). Treatment of **4a** under the standard reaction conditions afforded the corresponding amidation product **3a** in 86% yield (Scheme 2b). When the reaction of **1a** and **2a** was conducted under $^{18}O_2$ atmosphere, the major product is the normal ^{16}O-**3a** (Scheme 2c). When 5 equiv. of $H_2{}^{18}O$ was used, both ^{16}O-**3a** (42%) and ^{18}O-**3a** (58%) were detected (Scheme 2d). The ^{16}O comes from water existed in pivalic acid solvent as well as water generated from the reaction. When the reaction of **4a** was performed in the presence of $H_2{}^{18}O$, similar result was observed (Scheme 2e). This means the oxygen atom in the product mainly comes from water (generated during the reaction or existed in the reaction mixture).

Based on these observations, a plausible reaction pathway for the direct amidation of 2-methylquinolines is proposed in Scheme 3. Isomerization of **1a** generates an enamine intermediate **A**[23] which further reacts with copper catalyst to afford intermediate **B**. Single-electron transfer from Cu to O_2 generates peroxycopper intermediate **C**. Reaction of the oxygen radical with the benzyl group yields a peroxycopper intermediate **D**. Elimination of Cu-OH releases aldehyde **E**[24], which can undergo spontaneous imidization with amine to produce intermediate **F**. Hydrolysis and oxidation of **F** provides the final product **H**.[25] The hydrolysis reaction could give a reasonable explanation why part of the oxygen atom in the product comes from water.



Scheme 2 Control experiments under various conditions.



Scheme 3 Plausible reaction pathway.

In summary, we have developed a novel direct amidation of 2-methylquinolines with amines in the presence of catalytic amount of CuI. Aromatic amides were formed in good yields using molecular oxygen as the green oxidant. Functional groups such as cyano, halogen, CF_3 and OCF_3 were well tolerated under the optimized conditions. This method afforded a novel approach for the synthesis of biologically important aromatic amides from readily available coupling partners using cheap copper catalyst. A detailed reaction mechanism and further application of this reaction are

underway in our laboratory.

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