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Copper-catalyzed intermolecular amidation of 8-methylquinolines with *N*-fluoroarylsulfonimides *via* Csp^3–H activation†

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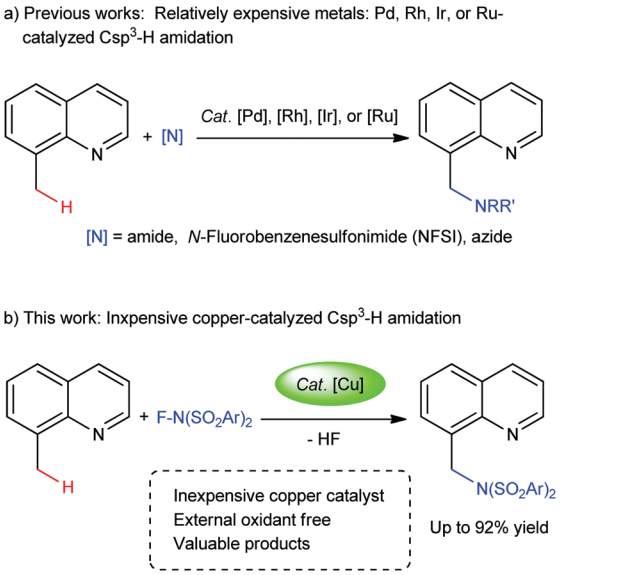
An efficient copper-catalyzed C–H amidation of 8-methylquinolines with *N*-fluoroarylsulfonimides *via* Csp^3–H activation is described. The reaction proceeds with high functional group tolerance, providing a novel approach to valuable quinolin-8-ylmethanamine derivatives in the absence of an additional oxidant.

Nitrogen-containing molecules are widely present in both natural products and synthetic compounds of high utility in pharmaceutical, agrochemical, and materials chemistry.[1] Consequently, the direct amination/amidation of C–H bonds has received increasing attention. Although synthetic tools enabling Csp^2–N bond formation have been well established,[2] facile amination/amidation of Csp^3–H bonds under mild conditions still remains a challenge in synthetic chemistry.[3] Therefore, in the past decade, only limited examples of direct amidation/amination of the Csp^3–H bonds have been reported.[4–6]

The quinolin-8-ylmethanamine derivatives are valuable compounds, which have been reported as a building block in enormous areas involved in medicinal chemistry, organic synthesis, and analytical chemistry.[7] 8-Methylquinoline is an ideal substrate that could be used for the synthesis of quinolin-8-ylmethanamine derivatives *via* Csp^3–H functionalization. In 2006, Che *et al.* reported Pd(II)-catalyzed C–H amination of 8-methylquinolines with amides employing stoichiometric $K_2S_2O_8$ as the oxidant (a, Scheme 1).[8] Recently, the Muñiz group[9] realized Pd(II)-catalyzed amidation of 8-methylquinoline by using *N*-fluorobenzenesulfonimide (NFSI) as the nitrogen source.[10] Nearly simultaneously, the groups of Wang[6h] and Chang[6g] developed the amidation reactions of



Scheme 1 Transition-metal-catalyzed Csp^3–H amidation of 8-methylquinolines *via* C–H activation.

8-methylquinolines with azides catalyzed by Rh^{III} and Ir^{III} catalysts, respectively. Very recently, Ru^{II}-catalyzed C–H amidation reaction of 8-methylquinolines with azides was also realized by Wang and co-workers (a, Scheme 1).[6f] Although this significant progress has been made in C–H amidation reactions of 8-methylquinolines, some limitations still exist, *e.g.*, the presence of a strong oxidant may limit the functional compatibility of the substrates. In addition, in some procedures which utilize azides as the nitrogen source, some toxicity and explosiveness of these reagents may limit their further applications. Meanwhile, all these reported C–H amidation reactions of 8-methylquinolines are catalyzed by relatively expensive palladium, rhodium, iridium and ruthenium, and there is no report on the use of inexpensive copper catalysts. As part of our continuing efforts for accessing N-containing biologically active molecules and the development of new synthetic methodologies for C–N bond formation *via* transition-metal-catalyzed

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†Electronic supplementary information (ESI) available. Compound **3f**: CCDC 1476725. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ob00553e
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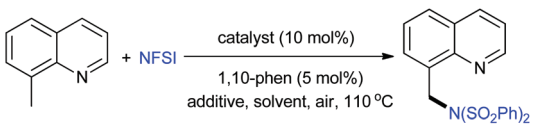
C–H activation,[11] we report herein an efficient inexpensive copper-catalyzed intermolecular C–H amidation of 8-methylquinolines *via* Csp^3–H activation utilizing *N*-fluoroarylsulfonimides as an efficient and safe nitrogen source under external oxidant free conditions (b, Scheme 1). This method potentially provides an alternative rapid approach to quinolin-8-ylmethanamine derivatives for pharmaceuticals and chiral ligands synthesis.

To explore the Cu-catalyzed amidation of Csp^3–H bonds, commercially available 8-methyl-quinoline (**1a**) was chosen as a model substrate to react with NFSI (**2a**) in air (Table 1). Initially, the effect of the Cu source on the model reaction was examined. CuBr was found to be the most efficient catalyst, although only 46% yield of **3a** was obtained (entry 2). CuCl and CuI were less effective (entries 1 and 3). A screening of solvents indicated that solvents other than 1,2-dichloroethane (DCE) afforded inferior results (entries 4–6). Among various bases screened (entries 7–10), the use of Na_2CO_3 resulted in a notable increase in the product yield to 66% in air (entry 10), whereas only 20% yield of **3a** was obtained under argon (entry 11). By changing the ratio of **1a** : **2a** and the reaction time (entries 12 and 13), we were pleased to observe that a higher yield was obtained when 1.3 equivalents of **2a** were used and the reaction time was 15 hours (entry 12). Finally, we chose the reaction conditions of entry 12 as the standard conditions. Control experiments (entries 14 and 15) revealed that the amidation reaction can proceed in the absence of 1,10-phen, albeit with much lower efficiency (entry 14). But CuBr is necessary for the amidation (entry 15).

Table 1 Optimization of reaction conditions[a,b]



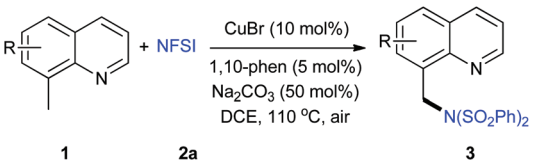
1a 2a 3a

Entry	Catalyst	Additive	Solvent	Yield (%)
1	CuCl	—	DCE	36
2	CuBr	—	DCE	46
3	CuI	—	DCE	33
4	CuBr	—	MeCN	38
5	CuBr	—	CH_3NO_2	n.r.
6	CuBr	—	Dioxane	n.r.
7	CuBr	Li_2CO_3	DCE	39
8	CuBr	Cs_2CO_3	DCE	n.r.
9	CuBr	$NaHCO_3$	DCE	33
10	CuBr	Na_2CO_3	DCE	66
11[c]	CuBr	Na_2CO_3	DCE	20
12[d,e]	**CuBr**	**Na_2CO_3**	**DCE**	**81**
13[d,f]	CuBr	Na_2CO_3	DCE	69
14[g]	CuBr	Na_2CO_3	DCE	34
15[h]		Na_2CO_3	DCE	n.r.

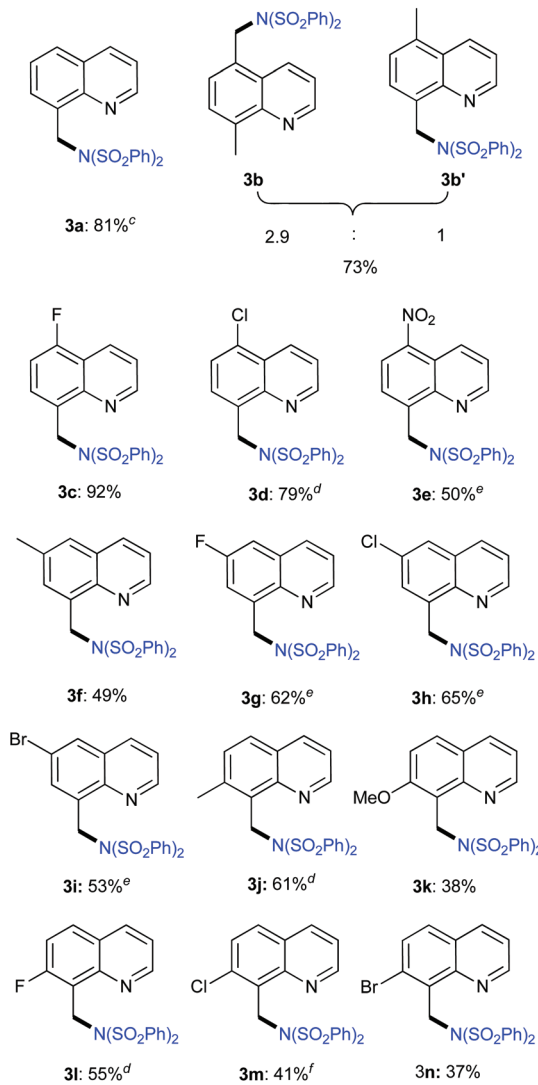
[a] Reaction conditions: **1a** (1.0 mmol), NFSI (1.1 equiv.), catalyst (10 mol%), 1,10-phen (5 mol%), additive (0.5 mmol), in 3 mL solvent in air for 12 h. [b] Isolated yields. [c] The reaction was carried out under Ar. [d] NFSI (1.3 equiv.). [e] 15 h. [f] 17 h. [g] Without 1,10-phen. [h] Without CuBr.

With an efficient protocol for the amidation in hand, the substrate scope was then investigated. The generality of the reaction is showcased by the remarkable compatibility with various functional groups at different positions of 8-methylquinolines (**1a–n**) (Table 2). The reaction of 5-, 6-, or 7-substituted 8-methylquinolines with NFSI (**2a**) proceeded smoothly

Table 2 Substrate scope of 8-methyl-quinolines[a,b]



1 2a 3

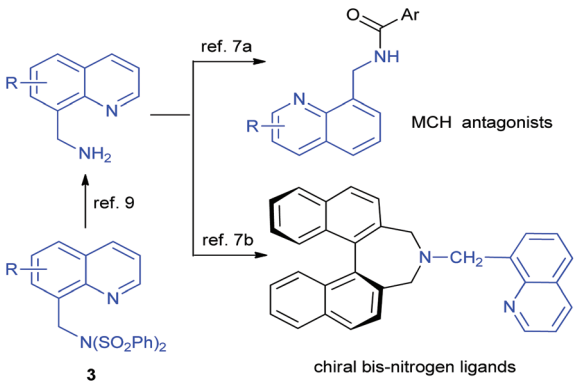


[a] Reaction conditions: **1** (0.3 mmol), **2a** (1.3 equiv.), CuBr (10 mol%), 1,10-phen (5 mol%), Na_2CO_3 (50 mol%), in 3 mL DCE at 110 °C in air for 15 h. [b] Isolated yields. [c] 1.0 mmol scale. [d] 22 h. [e] Modified reaction conditions: **1** (0.3 mmol), **2a** (2 equiv.), $Cu(OAc)_2$ (2 equiv.), Li_2CO_3 (50 mol%), in 1.5 mL solvent (DCE : CH_3CN = 1 : 1) at 110 °C for 22 h. [f] 36 h.

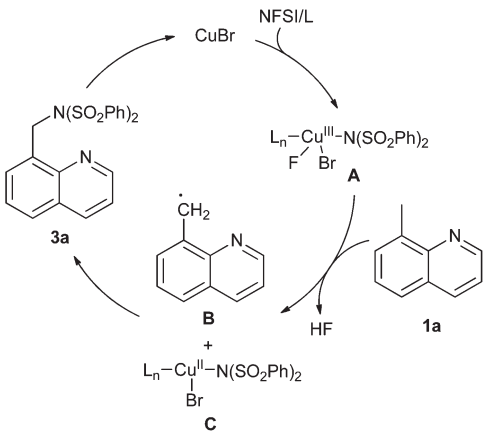
to afford Csp^3-amidated products (**3a–n**) in moderate to good yields. Meanwhile, substrates with either electron-donating groups (*e.g.*, Me, MeO) (**1b**, **1f** and **1j–k**) or electron-withdrawing groups (*e.g.*, NO_2, F) (**1c**, **1e**, **1g** and **1l**) were tolerated in this transformation. It is important to stress that chloro or bromo-substituted 8-methyl-quinoline substrates were smoothly amidated to furnish highly functionalized products (**3d**, **3h**, **3i**, **3m**, and **3n**), thus allowing the potential for further derivatization.

In addition to NFSI (**2a**), NFSI derivatives, NFR1 (*N*-fluoro-4-methyl-*N*-tosylbenzenesulfonamide) (**2b**) and NFR2 (*N*,4-difluoro-*N*-((4-nitrophenyl)sulfonyl)benzenesulfonamide) (**2c**) were also explored to extend the substrate scope and investigate the electronic effect of the aryl part of NFSI derivatives (Table 3). Gratifyingly, NFSI derivatives, bearing either electron-donating groups (*e.g.*, Me) (NFR1) or electron-withdrawing groups (*e.g.*, F, NO_2) (NFR2), performed efficiently giving the desired C–H amidation products (**3o–s**) in moderate to good yields. Noteworthy is that the amidation products with halo groups, and the nitro group on the aromatic rings could be utilized in the further organic transformations.

Quinolin-8-ylmethanamine is a very useful synthetic intermediate and building block in organic synthesis. It could undergo some significant transformations according to the literature (Scheme 2). Its derivatives have been reported as potent and selective melanin concentrating hormone (MCH) antagonists.[7a] In addition, they are also building blocks in organic synthesis such as the synthesis of chiral bis-nitrogen ligands possessing both imine and amine moieties.[7b] Our present work provides a new simple approach to synthesize this class of compounds followed by a simple deprotection process.[9]

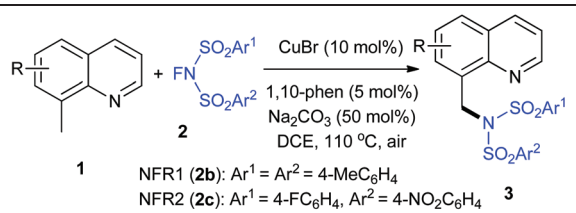


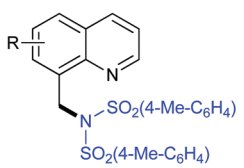
Scheme 2 Transformations of amidated products.



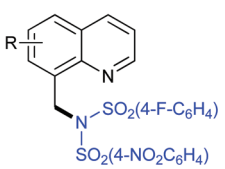
Scheme 3 Proposed reaction mechanism.

Table 3 Different *N*-fluoroarylsulfonimides NFR1–2[a,b]





R = H: **3o**, 80%[c]
R = 6-F: **3p**, 51%[c]



R = H: **3q**, 50%
R = 5-F: **3r**, 72%
R = 6-Br: **3s**, 83%[c]

[a] Reaction conditions: **1** (0.15 mmol), **2** (1.3 equiv.), CuBr (10 mol%), 1,10-phen (5 mol%), Na_2CO_3 (50 mol%), in 1.5 mL DCE at 110 °C in air for 22 h. [b] Isolated yields. [c] Modified reaction conditions: **1** (0.15 or 0.1 mmol), **2** (2 equiv.), $Cu(OAc)_2$ (2 equiv.), Li_2CO_3 (50 mol%), in 1 mL solvent (DCE : MeCN = 1 : 1) at 110 °C for 22 h.

A possible mechanistic pathway involving Cu(I), Cu(II), and Cu(III) species in this transformation is proposed in Scheme 3.[10e–g,12,13] Initially, CuBr is oxidized with NFSI in the presence of ligands affording the Cu^{III} complex **A**, which abstracts a hydrogen atom from substrate **1a** to afford the radical intermediate **B** and the Cu^{II} species **C**. Subsequently, oxidation of the radical **B** by the Cu^{II} species **C** leads to the formation of the amination product **3a** along with CuBr for the next catalytic cycle.

Conclusions

In conclusion, we have developed an efficient Cu-catalyzed directed Csp^3–H amidation of 8-methylquinolines with *N*-fluoroarylsulfonimides. A number of 8-methylquinolines were selectively amidated in moderate to excellent yields with high functional group tolerance. An additional oxidant is not required in this amidation transformation. Further studies on the reaction mechanism and synthetic applications are ongoing in our laboratory.

Acknowledgements

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13 This reaction may involve a radical process (see the ESI: the radical-trapping experiment†).