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Iron-mediated remote C–H bond benzylation of 8-aminoquinoline amides

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ABSTRACT

An efficient and convenient method for C5-benzylation of quinoline frameworks is developed with the using of inexpensive $FeCl_3$ catalyst. A range of N-bisbenzylic and N-monobenzylic sulfonamides smoothly react with aliphatic amides and aromatic amides, giving the corresponding products in moderate to excellent yields.

Introduction

Quinolines represent an important class of N-based heterocyclic compounds due to their wide spectrum of anti-malarial, antibacterial, antifungal agent and anticancer activities.[1] They can also be used as directing groups or ligands in organic reactions.[2] Thus, the development of efficient methods for synthesizing substituted amidoquinoline derivatives has attracted tremendous researches interest in organic synthesis.[3] A highly desirable synthetic method is the site-selective C–H functionalization of a preformed quinoline scaffold.[4] But, due to the electron nature of quinoline moieties, it is usually not easy to control the regio-selectivity. Several successful transformations are mainly focusing on the functionalization at the C2 position owing to the intrinsic reactivity of the C=N bonds.[5] Regio-selective functionalization at C3 and C8 positions of quinolines had also been disclosed.[6] However, much less effort had been taken to the functionalization at the C5 position of quinoline derivatives with high regio-selectivity. In 2013, the group of Stahl reported a copper-catalyzed chlorination at the C5 position of quinoline derivatives (Scheme 1a).[7] It was found that a regio-specific C5 position functionalization could be achieved by the aid of amidoquinoline derived chelation assistance with a transition metal. Furthermore, Zeng and co-workers[7c] described the regiodivergent C–H allylation of quinolines on the C5 position that was enabled by 8-amino and catalyzed by iron via remote C–H activation (Scheme 1b). Subsequently, Cu-mediated chalcogenation[7d] and sulfonylation[7e] of amidoquinoline at C5 position has also been discovered. However, the remote C5 C–H benzylation of organisation of the template quinolines has never been reported.

Inspired by recent elegant work on the site-selective C–H functionalization of quinolines, herein, we reported the first Fe-catalyzed benzylation of 8-Aminoquinoline derivatives at the C5 position. It provides an example for the combination of both C–H functionalization and Csp^3–N bond cleavage[8] and affords an easy access to the synthesis of benzyl group substituted quinoline derivatives,[9] which are the common structural moieties in pharmaceuticals and biologically active natural products.[10]

To begin our research, we chose 2,2-dimethyl-N-(quinolin-8-yl)-butanamide (**1a**), which was synthesized from 2,2-dimethylbutanoic acid and 8-aminoquinoline, as the model substrates to test the benzylation reaction (Table 1). N-benzylic sulfonamides (**2a**), which is first developed by Mall group and used as a unique alkylating regent in many catalytic transformations, was selected as the benzyl source.[11] Initially, treatment of **1a** and **2a** with a catalytic amount of $FeCl_3$ (10 mol%) at 140 °C for 2 d under Ar atmosphere in DMSO gave no desired product (entry 1). Changing DMSO to other polar solvent such as DMF also showed no improvement (entry 2). To our delight, when this reaction was conducted in THF, the benzylation product **2a** could be detected with a yield of 12% (entry 3). The starting materials remain unchangeable, and

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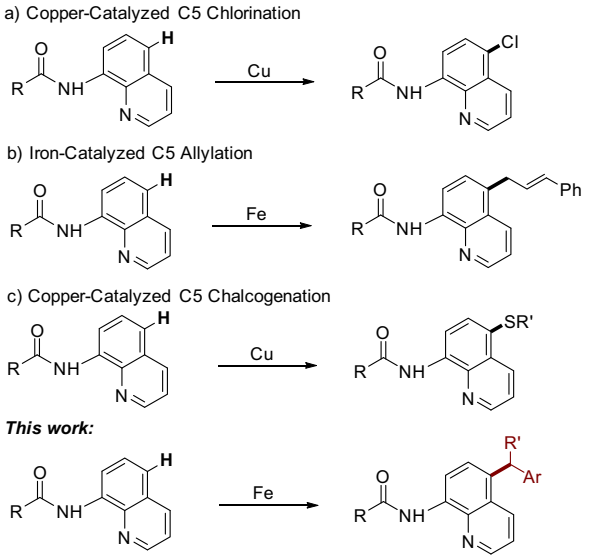


Scheme 1. Site-selective C–H functionalization of 8-aminoquinolines at the C5 position.

the C5 benzylation of the template quinolones was the only product. The yield could be dramatically improved to 40% by employing dioxane as the solvent (entry 4). After further screen of various solvents (entry 5 and 6), we found that DCE gave the optimal result (85% NMR yield and 82% isolated yield).

Further changes of catalyst loading did not improve the reaction (entry 7). Additionally, the benzylation reaction proved rather sensitive to water. A sharp decrease in reaction yield could be observed when switching the catalyst to $FeCl_3{\cdot}6H_2O$ or exposing the reaction system to air (entry 8 and 9). It is also worth noting that the reaction efficiency was significantly affected by the electron-withdrawing groups on the amine nitrogen atoms. No better yield was obtained when replacing the ptoluenesulfonyl group with other sulfonyl or acyl groups (entry 10–13). Further attempts by using other Lewis acid as catalyst failed to trigger the cross-coupling (entry 14–15). Finally, without $FeCl_3$ as catalyst, the benzylation reaction did not occur (entry 16).

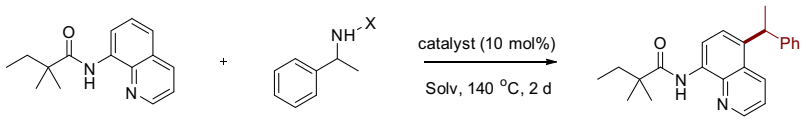
With the optimized conditions in hand, we set out to explore the scope of aminoquinoline amides. As depicted in Table 2, both linear and circinal aliphatic amides could smoothly react with **2** and provided the corresponding benzylation products in moderate to good yields (**3a**–**3q**).

Various functional groups, including methyl (**3a**), chloro (**3b**, **3k**), trifluoromethyl (**3e**), naphthyl (**3f**), ester (**3i**), fluoro (**3n**), terminal (**3g**) and internal alkenyl groups (**3h**), could be well tolerated under the present reaction condition. The tertiary α-carbon moiety of the aliphatic amides is not essential as the isobutyl amide (**3p**) also reacted well in this benzylation reaction. Besides aliphatic amides, aromatic amides were suitable reaction partners either (**3r**–**3t**). In addition, the substrates bearing Me and MeO groups on the quinoline ring could afford the desired products in 56% and 89% yields (**3u**, **3v**).

Next, we investigated the variation of virous N-benzylic sulfonamides (Table 3). Replacing the methyl group of **2** with long-chain alkyl group resulted in slightly diminished yields (**3aa**). Both N-benzylic sulfonamides with electron-donating (**3ba**, **3ha**) and -withdrawing substituents (e.g. **3da**) on the aromatic ring gave rise to the desired products in good to excellent yields. This reaction also showed good tolerance toward a variety of functional groups such as methyl (**3ba**), fluoro (**3da**), chloro (**3ea**), bromide (**3fa**), nitro (**3ga**) and methoxy groups (**3ha**). However, when alkyl sulfonamide was used under the standard reaction condition, no cross-coupling occurred (**3ia**).

To further explore the synthetic utility of this new reaction, we conducted a gram-sacle reaction and the desired product **3a** was obtained in 75% yield. The aminoquinoline amide moiety of **3a** could be easily converted to the corresponding C5 benzylated

Table 1
Reaction optimization.[a]



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

Entry	X	Catalyst	Solvent	Yield[a] (%)
1	Ts	$FeCl_3$	DMSO	Trace
2	Ts	$FeCl_3$	DMF	Trace
3	Ts	$FeCl_3$	THF	12
4	Ts	$FeCl_3$	Dioxane	40
5	Ts	$FeCl_3$	Toluene	45
6	**Ts**	**$FeCl_3$**	**DCE**	**85** (**82**[b])
7[c]	Ts	$FeCl_3$	DCE	52
8	Ts	$FeCl_3{\cdot}6H_2O$	DCE	30
9[d]	Ts	$FeCl_3$	DCE	37
10	Ms	$FeCl_3$	DCE	50
11	Tf	$FeCl_3$	DCE	Trace
12	PhCO	$FeCl_3$	DCE	18
13	Ac	$FeCl_3$	DCE	Trace
14	Ts	$ZnCl_2$	DCE	Trace
15	Ts	$Cu(OTf)_2$	DCE	Trace
16	Ts	None	DCE	Trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (0.02 mmol), in 0.5 mL solvent at 140 °C for 2 d under Ar atmosphere. Yields were determined by ^1H NMR analysis of the crude reaction mixture using dibromomethane as the internal standard.
[b] Isolated yields.
[c] 5 mol% of $FeCl_3$ was used.
[d] The reaction was run under an air atmosphere.