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# Copper-catalyzed C5-regioselective C−H sulfonylation of 8-aminoquinoline amides with aryl sulfonyl chlorides

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ABSTRACT

Copper-catalyzed C-H sulfonylation of 8-aminoquinoline scaffolds in the unusual C5 position was developed. The protocol using inexpensive CuI as the catalyst and commercially available aryl sulfonyl chlorides as the sulfonylation reagents, shows broad substrate scope, producing moderate to good yield of sulfone. The developed method was conveniently applied to synthesize a potential fluorinated PET radioligand of 5-$HT_6$ serotoninergic receptor. Moreover, mechanistic studies revealed that the reactions underwent a radical process.



The quinoline skeleton is one of the most important aromatic heterocycles[1] present in various natural products[2] and pharmaceuticals.[3] Quinolines can also be employed as ligands[4] and directing groups[5] in organic synthesis, as well as fluorescence probes in analytical chemistry.[6] Thus, considerable efforts have been directed toward the formation and modification of quinoline-based scaffolds.[7]

Quinoline rings are often constructed via annulation of anilines and carbonyl compounds by using a variety of classic named reactions (e.g., Friedländer, Combes, Skraup, Gould−Jacobs, Conrad−Limpach, Doebner−Miller, and Povarov syntheses).[8] Nevertheless, these methods usually require harsh acidic or basic conditions and prohibit adequate diversity and substitutes in the quinoline ring system. By contrast, the functionalization of preformed quinoline scaffold is more straightforward for the rapid preparation of diversely substituted quinolines. However, for the electron-deficient property of quinoline ring and the interaction of $sp^2$-hybridized nitrogen atoms with electrophiles or Lewis acids, direct functionalization of quinolines presents a significant challenge.[9]

In the past decade, significant progress has been made in transition-metal-catalyzed C−H bond functionalization.[10] In contrast to the widely studied C−H functionalization on the phenyl rings, C−H functionalization on the quinoline ring systems remains underdeveloped.[11] Most examples of site-selective C−H functionalization of quinolines focus on the transformation in the C2,[12] C4,[13] and C8[14] positions. However,
efficient approaches toward the C5-functionalization of quinolines are rarely reported.[15] Stahl et al. recently reported the first C5 chlorination of 8-aminoquinoline amides via Cu-catalyzed single-electron-transfer mechanism.[15a] Zeng,[15b] Yin,[15c] and Zhang[15d] subsequently reported the allylation, chlorination, and chacogenation of 8-aminoquinoline amides in the C5 position, respectively.

Heterocyclic aromatic sulfones are ubiquitous structural motifs found in numerous biologically active natural products, pharmaceuticals and functional materials.[16] Direct C−H bond sulfonylation has recently been obtained under transition-metal catalysis or metal-free conditions.[17] No direct method for the sulfonylation of quinolines was available in C5 position via C−H functionalization before this study was conducted. The conventional method for synthesis of quinoline sulfones requires a multi-step operation, involving the de novo synthesis of halogenated quinoline and cross-coupling of the halide with thiol, followed by oxidation to the corresponding sulfone.[16a] During our study, Wei[15e] et al. reported a CuCl-catalyzed direct C5−H bond sulfonylation of 8-aminoquinoline amides with arylsulfonyl chloride. Shortly thereafter, Wu[15f] et al. reported the similar reactions in air by using CuI as the catalyst, and the substrate scope was expanded to cyclic aliphatic sulfonic chlorides. However, the detailed mechanism of this sulfonylation remains unclear. Two different mechanisms, organometallic and radical processes were proposed in the

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