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Transition Metal-Free C5 Tosyloxylation of 8-Aminoquinolines with Phenyliodine Bistrifluoroacetate and Substituted 1, 2-Disulfonyl Hydrazides

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Abstract: A novel and efficient method for direct tosyloxylation at C5 position of 8-aminoquinolines has been accomplished by nonmetal-catalyzed C-H functionalization at mild conditions. It is the first time to discovery that the radical RSO_3· was generated by the reaction of phenyliodine bistrifluoroacetate with substituted 1, 2-disulfonyl hydrazides. This reaction reveals excellent reactivity, good functional group tolerance and moderate to good yield.

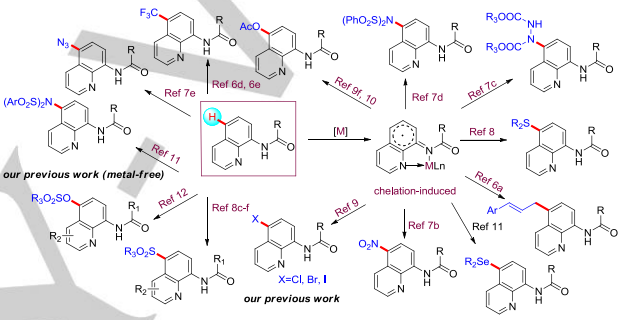
Introduction

Quinoline derivatives are important structural motifs in various natural products and bioactive molecules [1] which have inspired considerable efforts to develop efficient strategies for the synthesis of these structural motifs and have been widely applied to synthetic chemistry during the past decades.[2] Among various strategies, direct C-H bond functionalization of quinolines has become a more attractive method compared with the traditional synthetic methods which usually undergo harsh conditions such as high reaction temperature and acid condition. Until now, many successful examples in this field typically focusing on the direct functionalization of C-H bonds of quinolines at C2,[3] C3,[4] and C8 [5] positions have been reported.

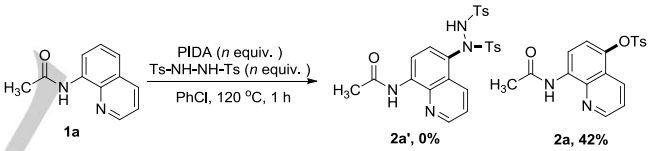
Recently, direct C-H functionalization at C5 position of quinoline has been realized including direct construction of C-C,[6] C-N,[7] C-S,[8] C-X[9], C-O[9e, 10] and C-Se [11] (Scheme 1).[12] To the best of our knowledge, few examples are known for the direct C-H functionalization of 8-aminoquinolines at C5 position under metal-free conditions. In our previous work, we developed an efficient and facile process for the remote C-H bond amidation of 8-aminoquinoline scaffolds at C-5 position without the assistance of a transition-metal catalyst.[13] Subsequently, Shen et al. demonstrated remote radical C-O cross-coupling reaction by synthesizing aryl sulfonate esters with various sulfonic acids in the absence of metal.[14]

As part of our continuing efforts in metal-free modification of quinolines, we attempted to develop a novel approach to prepare *N*-(5-hydrazinylquinolin-8-yl) amide starting with phenyliodine (III) diacetate (PIDA) and 1, 2-disulfonyl hydrazides. To our surprise, tosyloxylation of aminoquinolines at C5 position instead of *N*-(5-hydrazinylquinolin-8-yl) amide was obtained (Scheme 2).

Scheme 1. Direct modification of quinoline amides on C5 position.



Scheme 2. Direct tosyloxylation of 8-aminoquinoline.



This is an interesting transformation. For all we know, there are just several reports of direct tosyloxylation of anilide. One is previously mentioned that synthesizes aryl sulfonate esters with sulfonic acid using iodobenzene as catalyst and peroxyacetic acid as oxidant.[14] The other is direct tosyloxylation of anilide using phenyliodine (III) bistrifluoroacetate (PIFA) with *p*-toluene sulfonic acid (TsOH) to provide aryl tosylate.[14-15] Xiong et al. demonstrated oxysulfonylation of α-substituted β-keto esters through α-oxidation in the presence of *p*-toluenesulfonic acid and *m*-CPBA.[16] All of them use sulfonic acid as the source of RSO_3-. To our knowledge, using both 1, 2-disulfonyl hydrazides and PIDA as sulfonate source has never been reported before. This prompted us to further study this cross-coupling reaction. Herein, we reported an efficient method of direct tosyloxylation of 8-aminoquinoline scaffolds at C5-position in the presence of hypervalent iodine compounds and substituted 1, 2-disulfonyl hydrazides under mild conditions.

Results and Discussion

To make further study on this new reaction, we commenced our investigation with 8-acylaminoquinoline, 1, 2-disulfonyl hydrazide and PIDA as a model substrate (Table 1). It

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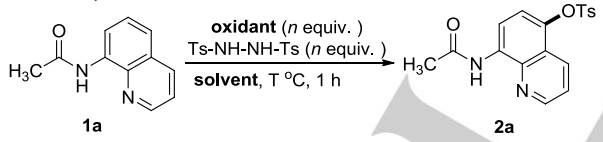
Supporting information for this article is given via a link at the end of the document.

was necessary to verify where the oxygen atom of "TsO" comes from. We speculated that the oxygen atom may come from water, oxygen or oxidant PIDA. To further verify our speculation, firstly we carried out this reaction in the presence of disulfonyl hydrazide (1.1 equiv.) and PIDA (3.3 equiv.) in chlorobenzene under nitrogen atmosphere at refluxing temperature for 1 h, with **2a** being obtained as main product with a yield of 42% (Entry 1). The result was inferred that the O_2 is not the oxygen source of the "TsO", but also not influence this reaction. Secondly, to verify whether water was the source of the oxygen, $H_2{}^{18}O$ was added under nitrogen atmosphere. There is only molecular weight of **2a** by MS analysis, which demonstrated that the oxygen atom did not come from water (Entry 2). Based on the above results, the PIDA is likely to be the source of oxygen. To further verify the essential role of PIDA in the reaction, some other oxidants such as hydrogen peroxide,[17] *m*-CPBA,[18] *t*-BuOOH,[19] Ag_2O[20] and CuO were utilized under the same reaction conditions as those in Entry 1 (Entry 3-7), failed to obtain any desired product. The results showed that replacement of PIDA with some other hypervalent iodine compounds such as phenyliodine bistrifluoroacetate (PIFA),[21] Dess Martin periodinane (DMP), only PIFA could carry the reaction well and improve the yield (Entry 8-9). So PIFA was chosen for further study. In the next study, we found that the yield is influenced by the amount of oxidant. When the amount of the oxidant was decreased from 3.3 equiv. to 1.65 equiv., the yield of tosyloxylation product was also decreased to only 35% (Entry 10). The solubility of the disulfonyl hydrazide and PIFA is not well in chlorobenzene, which may be influenced the reaction activity and yield. So several solvents such as THF, acetonitrile, 1, 4-dioxane, *N*, *N*-dimethylformamide, dichloromethane and 1, 2-dichloroethane were screened in this reaction (Entry 11-16). The results demonstrated that THF as solvent could significantly improve the yield (Entry 11) at 65 ℃, indicated that the reaction may be not influenced by temperature. To our delight, the reaction could even be performed at room temperature with good yield (Entry 17).

Table 1. Optimization of the reaction conditions. [a]



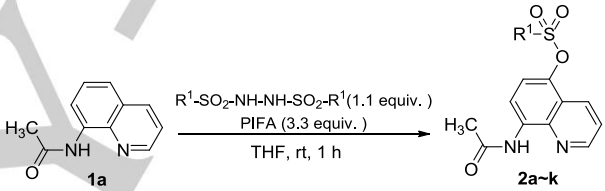
1a 2a

Entry	Oxidant	Solvent[b]	T[°C]	Yield [%][c]
1	PIDA	PhCl	120	42
2[d]	PIDA	PhCl	120	40
3	H_2O_2	PhCl	120	n.d.[e]
4	*m*-CPBA	PhCl	120	n.d.
5	*t*-BuOOH	PhCl	120	n.d.
6	Ag_2O	PhCl	120	n.d.
7	CuO	PhCl	120	n.d.
8	PIFA	PhCl	120	65
9	DMP	PhCl	120	n.d.
10[f]	PIFA	PhCl	120	35
11	PIFA	THF	65	80
12	PIFA	CH_3CN	80	n.d.
13	PIFA	Dioxane	100	70
14	PIFA	DMF	100	n.d.
15	PIFA	DCM	40	n.d.
16	PIFA	DCE	80	n.d.
17	**PIFA**	**THF**	**rt**	**74**

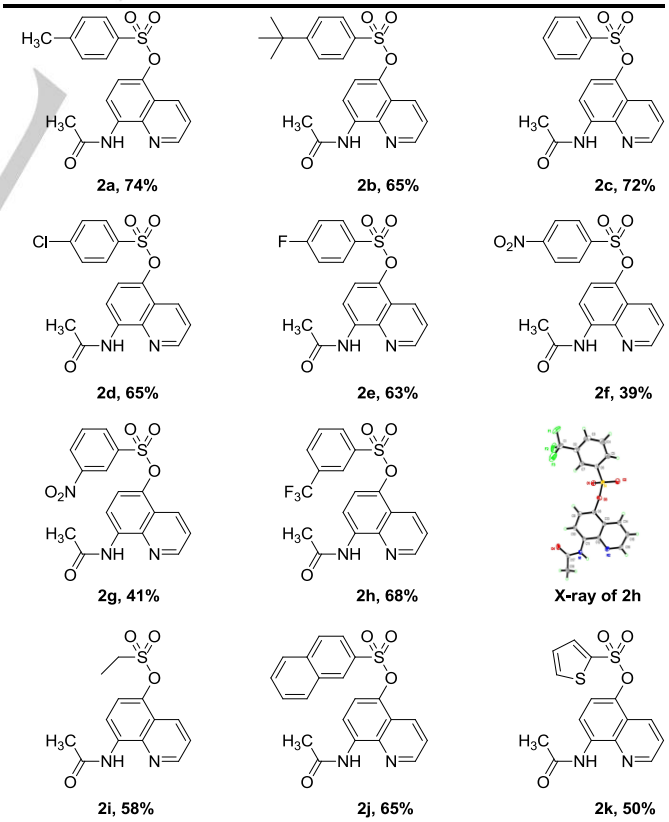
[a] Experiments were performed with **1a** (1 mmol), *N*, *N*'-disulfonyl hydrazides (1.1 mmol), PIFA (3.3 mmol) refluxed in chlorobenzene (6 mL) for 1 h. [b] Purified solvent. [c] The numbers refer to isolated yields. [d] $H_2{}^{18}O$ was added. [e] n.d. not detected. [f] Experiments were performed with **1a** (1 mmol), *N*, *N*'-disulfonyl hydrazides (0.55 mmol), PIFA (1.65 mmol).

With the optimized conditions in hand, the scope of the reaction was explored. The results indicated that the reaction was quite well for a series of diversely substituted disulfonyl hydrazides (Table 2). The 4-methyl and 4-tetra-butyl substituted dibenzenesulfonyl hydrazide furnished corresponding products **2a**-**2b** in high yield (74% for **2a** and 65% for **2b**). Substrate of unsubstituted on aryl ring was also suitable for this reaction, giving corresponding product **2c** in the yield of 72%. Replacement of methyl group with halogen groups resulted in the desired products **2d** and **2e** in 65% and 63% respectively. It was noted that the yields were reduced when electron-withdrawing group (EWG) such as nitro was introduced at the aryl ring (**2f**). Hydrazides with EWG substituted on meta-position of aryl ring went smoothly as well (**2g**-**2h**). The structure of **2h** was confirmed by single-crystal X-ray analysis (see supporting information for details). For dialkanesulfonyl hydrazides, substrate with ethyl substitute gave a moderate yield (**2i**). Same results were realized when heterocycles-substituted disulfonyl hydrazides reacted with 8-acylaminoquinolines **2j** and **2k** in moderate yield.

Table 2. Substrate scope with respect to 1, 2-disulfonyl hydrazides. [a]



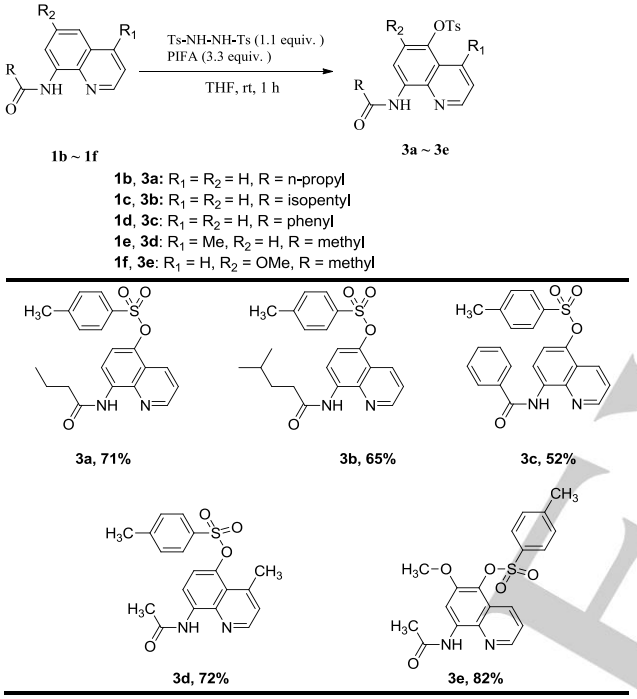
1a 2a~k



[a] Experiments were performed with **1a** (1 mmol), *N*, *N*'-disulfonyl hydrazides (1.1 mmol), PIFA (3.3 mmol) at room temperature in THF (6 mL) for 1 h. The numbers refer to isolated yields.

The reaction was not only restricted to 8-acylaminoquinolines, it also worked equally well with other substituted 8-aminoquinolines (Table 3). The carboxamides with alkyl substitutions furnished tosyloxylation smoothly as well (**3a**-**3b**). The carboxamide derived from the aromatic compound was also a suitable substrate for this reaction (**3c**). Furthermore, substitution at the quinoline scaffold was also explored. The results showed that the reaction was quite general for a series of diversely substituted 8-aminoquinolines in the presence of 1.1 equiv. of hydrazine and 3.3 equiv. of PIFA. For example, 4-Me substituted quinoline derivative could realize the tosyloxylation at C5 position, giving corresponding product in a moderate yield (**3d**). The 6-OMe substituted quinoline derivative also obtained the desired product **3e** in a high yield (82 %).

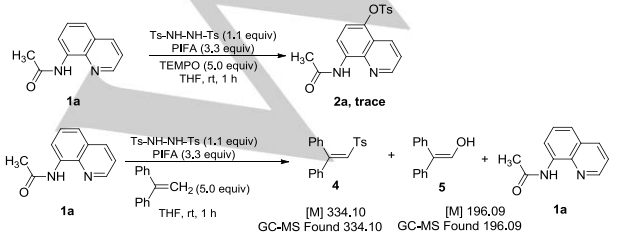
Table 3. Substrate scope with respect to 8-aminoquinoline. [a]



[a] Experiments were performed with **1b**-**1f** (1 mmol), *N*, *N*'-disulfonyl hydrazides (1.1 mmol), PIFA (3.3 mmol) at room temperature in THF (6 mL) for 1 h. The numbers refer to isolated yields.

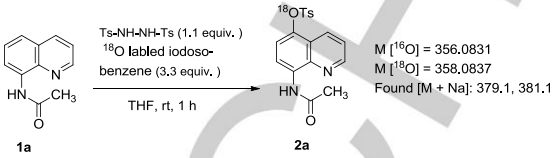
In order to explore the reaction mechanism, some preliminary studies were performed. First, no product was obtained in the presence of 2, 2, 6, 6-tetra-methylpiperidine *N*-oxide (TEMPO) (Scheme 3), implying that single-electron-transfer (SET) or a radical mechanism might be involved in the reaction process. Second, the (2-tosylethene-1, 1-diyl) dibenzene **4** and 2, 2-diphenylethen-1-ol **5** were detected by GC-MS when 1, 1-diphenylethylene was employed as a radical scavenger, indicating that tosyl radical was formed in the reaction.

Scheme 3. Radical inhibition for tosyloxylation.



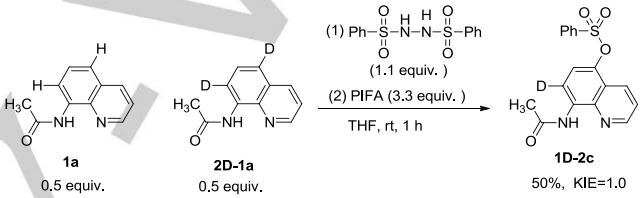
To verify our speculation that the oxygen of RSO_3- comes from the oxidant PIFA, PIFA was replaced with ^{18}O labeled iodosobenzene[22] to realize this reaction in the optimized conditions (Scheme 4). From the result of mass spectrum (see supporting information for details), it is confirmed that the oxygen comes from the PIFA.

Scheme 4. Synthesis of sulfonates by ^{18}O labeled iodosobenzene.



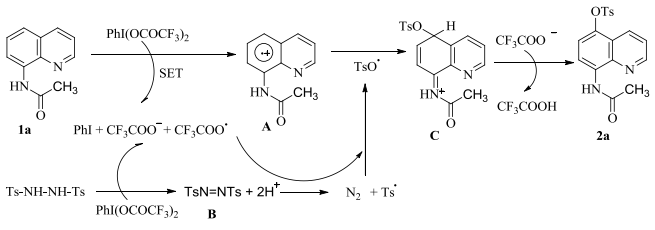
Finally, no kinetic isotope effect (KIE) was observed in an intermolecular competition experiment between **1a** and the dideuterated substrate **2D-1a** with *N*, *N*'-dibenzenesulfonyl hydrazine (Scheme 5). The result implied that the cleavage of the C-H bond was not the rate-determining step.

Scheme 5. Kinetic isotope experiment.



Based on the above experiment results and literature precedence,[8e, 15, 23] a plausible mechanism of the present sulfoxylation reaction of 8-aminoquinoline amides is outlined in Scheme 6. Initially, **1a** generates a radical cation intermediate **A** and simultaneously PIFA generates iodobenzene, acetoxy radical and acetoxy anion by SET. At the same time, 1, 2-disulfonyl hydrazide forms an intermediate **B** under the influence of PIFA. Subsequently, intermediate **B** is transformed to tosyl radical with the release of N_2. Tosyl radical seizes oxygen atom from acetoxy radical and is converted into tosyloxyl radical, tosyloxyl radical undergoes addition with intermediate **A** to produce iminium ion **C**, which is converted to the target compound **2a** via the elimination of a proton.

Scheme 6. Proposed mechanism.



Conclusions

In summary, we have developed a novel and efficient method for direct tosyloxylation of 8-aminoquinolines at C5 position under metal-free and mild conditions. This reaction demonstrates excellent reactivity, good functional group tolerance. Beyond these, it is the first discovery that phenyliodine bistrifluoroacetate and substituted 1, 2-disulfonyl hydrazides are adopted as radical RSO_3· source. Further

mechanism studies and the use of this transformation in organic synthesis are ongoing in our laboratory.

Experimental Section

General

All reactions were carried out under air. NMR spectra were recorded on a Bruker Avance 300 spectrometer operating at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) or at 400 MHz (^{1}H NMR) and 101 MHz (^{13}C NMR) in $CDCl_3$ or DMSO-d_6. All ^{1}H and ^{13}C NMR chemical shifts are reported in ppm and coupling constants J are given in Hz, the following abbreviations are used to describe peak patterns where appropriate: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad resonances (br). The thin layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm).

Chemicals

Unless noted otherwise, the materials that obtained from commercial suppliers were used without further purification. All solvents were analytically pure.

General procedure for the preparation of substituted disulfonyl hydrazides (*J. Med. Chem.* 1985, 28, 525)

4-methyl-*N*'-tosylbenzenesulfonohydrazide: white solid; m.p.208-209 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.60 (s, 2H), 7.65 (d, J = 8.3 Hz, 4H), 7.39 (d, J = 8.0 Hz, 4H), 2.40 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 143.91, 135.94, 129.91, 128.26, 21.51; MS (EI): calcd. for $C_{14}H_{16}N_2O_4S_2$ 340.1; found 363.1.

4-(tert-butyl)-*N*'-((4-(tert-butyl)phenyl)sulfonyl)benzenesulfonohydrazide: white solid; m.p.215-216 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.62 (s, 2H), 7.74 (d, J = 8.5 Hz, 4H), 7.63 (d, J = 8.5 Hz, 4H), 1.32 (s, 18H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 156.53, 136.05, 128.14, 126.37, 35.39, 31.29; MS (EI): calcd. for $C_{20}H_{28}N_2O_4S_2$ 424.2; found 447.2.

***N*'-(phenylsulfonyl)benzenesulfonohydrazide:** white solid; m.p.212-213 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.75 (s, 2H), 7.80 - 7.78 (m, 4H), 7.72 - 7.67 (m, 2H), 7.63 - 7.59 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 138.78, 133.61, 129.54, 128.20; MS (EI): calcd. for $C_{12}H_{12}N_2O_4S_2$ 312.0; found 335.0.

4-chloro-*N*'-((4-chlorophenyl)sulfonyl)benzenesulfonohydrazide: white solid; m.p.227-228 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.88 (s, 2H), 7.78 (d, J = 8.4 Hz, 4H), 7.70 (d, J = 8.4 Hz, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 138.72, 137.37, 130.19, 129.72; MS (EI): calcd. for $C_{12}H_{10}Cl_2N_2O_4S_2$ 380.0; found 403.0.

4-fluoro-*N*'-((4-fluorophenyl)sulfonyl)benzenesulfonohydrazide: white solid; m.p.212-213 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.81 (s, 2H), 7.94 - 7.77 (m, 4H), 7.55 - 7.40 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 165.18 (d, J = 252.5 Hz), 134.95 (d, J = 2.8 Hz), 131.37 (d, J = 9.8 Hz), 116.74 (d, J = 22.9 Hz) ; MS (EI): calcd. for $C_{12}H_{10}F_2N_2O_4S_2$ 348.0; found 371.0.

4-nitro-*N*'-((4-nitrophenyl)sulfonyl)benzenesulfonohydrazide: white solid; m.p.235-236 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.28 (s, 2H), 8.44 (d, J = 8.7 Hz, 4H), 8.03 (d, J = 8.7 Hz, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 150.16, 144.64, 129.72, 124.70; MS (EI): calcd. for $C_{12}H_{10}N_4O_8S_2$ 402.0; found 401.0.

3-nitro-*N*'-((3-nitrophenyl)sulfonyl)benzenesulfonohydrazide: white solid; m.p.226-227 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.24 (s, 2H), 8.57 (d, J = 8.2 Hz, 2H), 8.47 (s, 2H), 8.22 (d, J = 7.8 Hz, 2H), 7.96 (t, J = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 148.28, 139.94, 134.35, 131.88, 128.47, 122.92; MS (EI): calcd. for $C_{12}H_{10}N_4O_8S_2$ 402.0; found 401.0.

3-(trifluoromethyl)-*N*'-((3-(trifluoromethyl)phenyl)sulfonyl)benzenesulfonohydrazide: white solid; m.p.219-221 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.12 (s, 2H), 8.11 (t, J = 8.0 Hz, 4H), 8.02 (s, 2H), 7.91 (t, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 139.68, 132.21, 131.19, 130.46 (q, J = 3.3 Hz), 130.24 (q, J = 32.5Hz), 124.51 (q, J = 4.0 Hz), 123.77 (q, J = 271.1 Hz) ; MS (EI): calcd. for $C_{14}H_{10}F_6N_2O_4S_2$ 448.0; found 447.0.

***N*'-(ethylsulfonyl)ethanesulfonohydrazide:** white solid; m.p.126-128 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.53 (s, 2H), 3.21- 2.98 (m, 4H), 1.31-1.12 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 44.08, 7.76; MS (EI): calcd. for $C_4H_{12}N_2O_4S_2$ 216.0; found 239.0.

***N*'-(naphthalen-2-ylsulfonyl)naphthalene-2-sulfonohydrazide:** white solid; m.p.216-217 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.85 (s, 2H), 8.47 (s, 2H), 8.19 (d, J = 7.9 Hz, 2H), 8.11 (d, J = 8.7 Hz, 2H), 8.05 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.6 Hz, 2H), 7.75 - 7.67 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 135.76, 135.03, 132.08, 129.80, 129.59, 129.56, 129.48, 128.25, 128.00, 123.51; MS (EI): calcd. for $C_{20}H_{16}N_2O_4S_2$ 412.1; found 435.1.

***N*'-(thiophen-2-ylsulfonyl)thiophene-2-sulfonohydrazide:** brown solid; m.p.190-193 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.02 (s, 2H), 8.01 (d, J = 4.2 Hz, 2H), 7.67 - 7.55 (m, 2H), 7.29 - 7.16 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 138.41, 133.98, 133.43, 127.68; MS (EI): calcd. for $C_8H_8N_2O_4S_4$ 323.9; found 346.9.

A representative procedure for the direct tosyloxylation of 8-aminoquinolines.

To a 25 mL flask equipped with a magnetic stirring bar and condenser tube was added THF (6.0 mL), aminoquinoline derivatives (**1**) (1.0 mmol) and *N*, *N*'-ditosylhydrazine (1.1 mmol) under ambient condition, PIFA (3.3 mmol) was added in portion within 30 deg. c. The reaction mixture was stirred for 1 h, then it was filtered through a plug of celite. After removal of solvent under reduced pressure, crude product was obtained and was further purified through chromatography on silica gel with (PE/EA) as an eluent to give the desired products (**2a**, **2c**, **2d**, **2e**, **2f**, **2i**, **2k**, **3b**, **3c** was obtained by prep-TLC (PE/EA = 2:1)).

8-acetamidoquinolin-5-yl-4-methylbenzenesulfonate (2a): pale yellow solid; m.p. 166 – 167 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.74 (s, 1H), 8.89 - 8.79 (m, 1H), 8.63 (d, J = 8.2 Hz, 1H), 8.41 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 7.4 Hz, 2H), 7.58 - 7.45 (m, 1H), 7.34 (d, J = 7.5 Hz, 2H), 6.98 (d, J = 8.4 Hz, 1H), 2.47 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.83, 148.81, 145.84, 139.39, 133.81, 131.98, 131.75, 131.36, 129.97, 128.67, 122.90, 122.17, 119.85, 115.07, 25.14, 21.78; HRMS (ESI): $[M+H]^+$ calcd. for $C_{18}H_{17}N_2O_4S$ 357.0904; found 357.0907.

8-acetamidoquinolin-5-yl-4-(tert-butyl)benzenesulfonate (2b): white solid; m.p. 142 - 145 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.71 (s, 1H), 8.79 - 8.78 (m, 1H), 8.63 (d, J = 8.6 Hz, 1H), 8.30 (dd, J = 8.5, 1.5 Hz, 1H), 7.78 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.43 (dd, J = 8.5, 4.2 Hz, 1H), 7.03 (d, J = 8.6 Hz, 1H), 2.34 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.65, 158.72, 148.61, 139.35, 138.27, 133.74, 132.05, 131.21, 128.39, 126.25, 122.84, 121.92, 119.90, 115.13, 35.31, 30.94, 24.97; HRMS (ESI): $[M+H]^+$ calcd. for $C_{21}H_{23}N_2O_4S$ 399.1373; found 399.1372.

8-acetamidoquinolin-5-yl-benzenesulfonate (2c): white solid; m.p. 165 - 168 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.77 (s, 1H), 8.85 (d, J = 4.3 Hz, 1H), 8.67 (d, J = 8.6 Hz, 1H), 8.39 (d, J = 8.4 Hz, 1H), 7.92 (d, J =

7.3 Hz, 2H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.60 - 7.48 (m, 3H), 7.04 (d, *J* = 8.6 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 168.33, 148.33, 138.34, 137.61, 134.49, 134.07, 130.67, 128.86, 128.10, 122.29, 121.67, 119.40, 119.30, 114.59, 24.58; HRMS (ESI): $[M+H]^+$ calcd. for $C_{17}H_{15}N_2O_4S$ 343.0747; found 343.0747.

8-acetamidoquinolin-5-yl-4-chlorobenzenesulfonate (2d): white solid; m.p. 151 - 154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.77 (s, 1H), 8.87 (d, *J* = 4.2 Hz, 1H), 8.68 (d, *J* = 8.6 Hz, 1H), 8.38 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.54 (dd, *J* = 8.5, 4.2 Hz, 3H), 7.07 (d, *J* = 8.6 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 168.35, 148.39, 140.95, 138.64, 137.80, 133.55, 133.06, 130.65, 129.50, 129.24, 122.22, 121.78, 119.37, 114.67, 24.57; HRMS (ESI): $[M+H]^+$ calcd. for $C_{17}H_{14}ClN_2O_4S$ 377.0357; found 377.0363.

8-acetamidoquinolin-5-yl-4-fluorobenzenesulfonate (2e): white solid; m.p. 120 - 122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.76 (s, 1H), 8.85 (d, *J* = 3.5 Hz, 1H), 8.68 (d, *J* = 8.6 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 7.93 (dd, *J* = 8.4, 5.0 Hz, 2H), 7.52 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.24 (t, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 168.26, 148.37, 138.69, 133.55, 132.83, 131.06, 130.93, 130.57, 122.21, 121.70, 119.37, 116.41, 116.11, 114.62, 24.51; HRMS (ESI): $[M+H]^+$ calcd. for $C_{17}H_{14}FN_2O_4S$ 361.0653; found 361.0656.

8-acetamidoquinolin-5-yl-4-nitrobenzenesulfonate (2f): pale yellow solid; m.p. 143 - 147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.76 (s, 1H), 8.87 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.69 (d, *J* = 8.6 Hz, 1H), 8.45 - 8.38 (m, 2H), 8.34 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.17 - 8.08 (m, 2H), 7.54 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 168.35, 150.67, 148.52, 140.40, 138.32, 137.81, 133.89, 130.36, 129.48, 123.99, 122.00, 121.92, 119.30, 114.69, 24.52; HRMS (ESI): $[M+H]^+$ calcd. for $C_{17}H_{14}N_3O_6S$ 388.0598; found 388.0601.

8-acetamidoquinolin-5-yl-3-nitrobenzenesulfonate (2g): white solid. m.p. 139 - 140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.72 (s, 1H), 8.88 - 8.82 (m, 1H), 8.82 - 8.77 (m, 1H), 8.67 (d, *J* = 8.6 Hz, 1H), 8.54 (d, *J* = 8.2 Hz, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 7.78 (t, *J* = 8.0 Hz, 1H), 7.52 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 168.73, 148.99, 148.32, 138.69, 138.33, 137.35, 134.39, 133.83, 130.75, 128.82, 123.69, 122.37, 119.77, 114.98, 24.98; HRMS (ESI): $[M+H]^+$ calcd. for $C_{17}H_{14}N_3O_6S$ 388.0598; found 388.0603.

8-acetamidoquinolin-5-yl-3-(trifluoromethyl)benzenesulfonate (2h): white solid; m.p. 150 - 152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.75 (s, 1H), 8.92 - 8.79 (m, 1H), 8.69 (d, *J* = 8.6 Hz, 1H), 8.32 (d, *J* = 8.5 Hz, 1H), 8.22 (s, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 7.50 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 168.29, 148.41, 138.38, 137.81, 136.00, 133.75, 131.26, 130.60, 130.55, 130.30, 129.69, 125.09, 125.04, 122.00, 121.75, 119.41, 114.57, 24.49; HRMS (ESI): $[M+H]^+$ calcd. for $C_{18}H_{14}F_3N_2O_4S$ 411.0621; found 411.0625.

8-acetamidoquinolin-5-yl-ethanesulfonate (2i): pale brown solid; m.p. 85 - 88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.81 (s, 1H), 8.91 (d, *J* = 2.8 Hz, 1H), 8.82 (d, *J* = 8.6 Hz, 1H), 8.58 (d, *J* = 8.5 Hz, 1H), 7.63 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 3.49 (q, *J* = 7.4 Hz, 2H), 2.40 (s, 3H), 1.67 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 168.39, 148.44, 138.14, 137.96, 133.42, 130.85, 122.43, 121.93, 119.27, 114.94, 45.15, 24.61, 7.91; HRMS (ESI): $[M+H]^+$ calcd. for $C_{13}H_{15}N_2O_4S$ 295.0747; found 295.0720.

8-acetamidoquinolin-5-yl-naphthalene-2-sulfonate (2j): off-white solid; m.p. 154 - 157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.72 (s, 1H), 8.81 (d, *J* = 3.1 Hz, 1H), 8.60 (d, *J* = 8.6 Hz, 1H), 8.44 (d, *J* = 8.7 Hz, 2H), 8.05 - 7.89 (m, 4H), 7.81 - 7.64 (m, 2H), 7.46 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 168.22, 148.26, 138.88, 137.81, 135.02, 134.12, 133.37, 131.51, 131.31, 130.83, 130.76, 130.16, 129.32, 129.24, 128.97, 127.53, 122.31, 121.62, 119.32, 114.68, 24.51; HRMS (ESI): $[M+H]^+$ calcd. for $C_{21}H_{17}N_2O_4S$ 393.0904; found 393.0911.

8-acetamidoquinolin-5-yl-thiophene-2-sulfonate (2k): white solid; m.p. 184 - 187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.72 (s, 1H), 8.80 (d, *J* = 3.2 Hz, 1H), 8.66 (d, *J* = 8.6 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 4.9 Hz, 1H), 7.61 (d, *J* = 3.2 Hz, 1H), 7.47 (dd, *J* = 8.4, 4.1 Hz, 1H), 7.17 - 7.04 (m, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 168.86, 148.87, 139.27, 138.27, 135.90, 135.12, 134.14, 134.09, 130.96, 127.81, 122.72, 122.27, 119.91, 115.08, 25.14; HRMS (ESI): $[M+H]^+$ calcd. for $C_{15}H_{13}N_2O_4S_2$ 349.0311; found 349.0317.

8-butyramidoquinolin-5-yl-4-methylbenzenesulfonate (3a): off-white solid; m.p. 120 - 122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.77 (s, 1H), 8.85 (d, *J* = 2.7 Hz, 1H), 8.67 (d, *J* = 8.6 Hz, 1H), 8.48 - 8.32 (m, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.51 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 1H), 2.57 (t, *J* = 7.4 Hz, 2H), 2.49 (s, 3H), 1.94 - 1.82 (m, 2H), 1.09 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 171.40, 148.29, 145.31, 138.83, 137.93, 133.33, 131.56, 130.78, 129.45, 128.14, 127.34, 121.61, 119.36, 114.58, 39.59, 21.23, 18.57, 13.28; HRMS (ESI): $[M+H]^+$ calcd. for $C_{20}H_{21}N_2O_4S$ 385.1217; found 385.1220.

8-(4-methylpentanamido)quinolin-5-yl-4-methylbenzenesulfonate (3b): off-white solid; m.p. 98 - 101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.78 (s, 1H), 8.85 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.67 (d, *J* = 8.6 Hz, 1H), 8.43 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.52 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 1H), 2.63 - 2.56 (m, 2H), 2.49 (s, 3H), 1.79 - 1.69 (m, 3H), 1.01 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 171.62, 148.27, 145.29, 138.82, 137.91, 133.37, 131.58, 130.88, 129.45, 128.16, 122.43, 121.60, 119.38, 114.60, 35.71, 33.87, 27.30, 21.86, 21.24; HRMS (ESI): $[M+H]^+$ calcd. for $C_{22}H_{25}N_2O_4S$ 413.1540; found 413.1540.

8-benzamidoquinolin-5-yl-4-methylbenzenesulfonate (3c): off-white solid; m.p. 176 - 179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 10.68 (s, 1H), 8.98 - 8.76 (m, 2H), 8.44 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.09 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.67 - 7.48 (m, 4H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 164.96, 148.45, 145.31, 139.17, 138.41, 134.34, 133.40, 131.68, 131.53, 130.94, 129.46, 128.35, 128.18, 126.77, 122.53, 121.70, 119.43, 114.82, 21.21; HRMS (ESI): $[M+H]^+$ calcd. for $C_{23}H_{19}N_2O_4S$ 419.1060; found 419.1062.

8-acetamido-4-methylquinolin-5-yl-4-methylbenzenesulfonate (3d): off-white solid; m.p. 188 - 190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.94 (s, 1H), 8.65 (d, *J* = 4.4 Hz, 1H), 8.57 (d, *J* = 8.7 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 4.8 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 2.99 (s, 3H), 2.51 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 168.31, 147.56, 145.31, 144.30, 139.93, 138.59, 133.77, 132.33, 129.52, 128.24, 124.86, 122.52, 119.54, 114.19, 24.65, 23.12, 21.26; HRMS (ESI): $[M+H]^+$ calcd. for $C_{19}H_{19}N_2O_4S$ 371.1060; found 371.1065.

8-acetamido-6-methoxyquinolin-5-yl-4-methylbenzenesulfonate (3e): off-white solid; m.p. 160 – 163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm): 9.83 (s, 1H), 8.75 - 8.65 (m, 2H), 8.44 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.50 (dd, *J* = 8.6, 4.2 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 3.65 (s, 3H), 2.50 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* (ppm): 168.90, 149.63, 146.22, 145.05, 134.71, 133.80, 130.81, 129.94, 129.31, 128.74, 128.59, 125.80, 124.93, 124.29, 122.57, 104.20, 56.02, 25.03,

21.61; HRMS (ESI): $[M+H]^+$ calcd. for $C_{19}H_{19}N_2O_5S$ 387.1009; found 387.1002.

Radical inhibition experiments for tosyloxylation on the C5 position.

To a 25 mL flask equipped with a magnetic stirring bar and condenser tube was added THF (6.0 mL), 8-acetylaminoquinoline (**1a**) (1.0 mmol), TEMPO (5.0 mmol) and *N*, *N*'-ditosylhydrazine (1.1 mmol) under ambient conditions, PIFA (3.3 mmol) was added in portion within 30 deg. c. The reaction mixture was stirred for 1 h. TLC indicated that no product was generated.

To a 25 mL flask equipped with a magnetic stirring bar and condenser tube was added THF (6.0 mL), 8-acetylaminoquinoline (**1a**) (1.0 mmol), 1, 1-diphenylethylene (5.0 mmol) and *N*, *N*'-ditosylhydrazine (1.1 mmol) under ambient conditions, PIFA (3.3 mmol) was added in portion within 30 deg. c. The reaction mixture was stirred for 1 h, then it was filtered through a plug of celite. After removal of solvent under reduced pressure, (2-tosylethene-1, 1-diyl) dibenzene (**4**) was obtained by prep-TLC (PE/EA = 3:1); off-white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.36 (d, *J* = 8.3 Hz, 2H), 7.30 - 7.15 (m, 6H), 7.12 - 7.06 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.98 (dd, *J* = 8.2, 1.3 Hz, 2H), 6.88 (s, 1H), 2.26 (s, 3H).

Synthesis of sulfonates by ^{18}O labeled iodosobenzene.

To a 25 mL flask equipped with a magnetic stirring bar and condenser tube was added THF (6.0 mL), 8-acetylaminoquinoline (**1a**) (1.0 mmol) and *N*, *N*'-ditosylhydrazine (1.1 mmol) under ambient condition, ^{18}O labeled iodosobenzene (3.3 mmol) was added in portion within 30 deg. c. The reaction mixture was stirred for 1 h, then it was filtered through a plug of celite. After removal of solvent under reduced pressure, crude product was obtained and was further purified by chromatography on silica gel (PE/EA = 2:1) to give the desired products **2a**. The exact mass of **2a** is measured via mass spectrum.

Kinetic isotope experiment

To a 25 mL flask equipped with a magnetic stirring bar and condenser tube was added THF (6.0 mL), 8-acetylaminoquinoline (**1a**) (0.5 mmol), the dideuterated 8-acetylaminoquinoline (**2D-1a**) (0.5 mmol) and *N*, *N*'-dibenzenesulfonyl hydrazine (1.1 mmol) under ambient conditions, PIFA (3.3 mmol) was added in portion within 30 deg. c. After stirring 1 h, the reaction mixture was filtered through a plug of celite. After removal of solvent under reduced pressure, crude product was obtained and was further purified by prep-TLC (PE/EA = 2:1) to give the desired product **1D-2c**: pale brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.75 (s, 1H), 8.84 (d, *J* = 3.0 Hz, 1H), 8.66 (d, *J* = 8.7 Hz, 1/2H), 8.38 (d, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.61 - 7.46 (m, 3H), 7.04 (t, *J* = 4.2 Hz, 1H), 2.37 (s, 3H).

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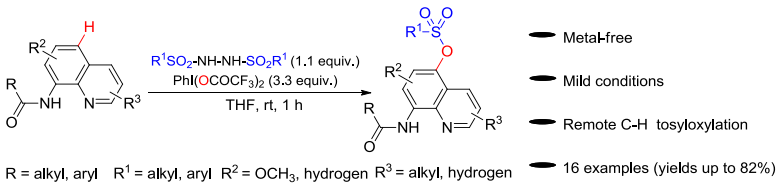

A novel and efficient method for direct tosyloxylation at C5 position of 8-aminoquinolines has been accomplished by nonmetal-catalyzed C-H functionalization at mild conditions. Although there are some reports of direct tosyloxylation of anilide, but it is the fist time to report that the 1, 2-disulfonyl hydrazides and PIDA as sulfonate source.

Key topic: 8-aminoquinolines, tosyloxylation.

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