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Nickel-Catalyzed Site-Selective C−H Bond Difluoroalkylation of 8-Aminoquinolines on the C5-Position

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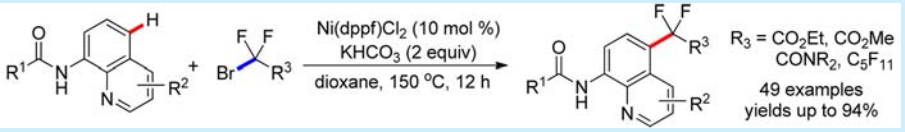
Supporting Information



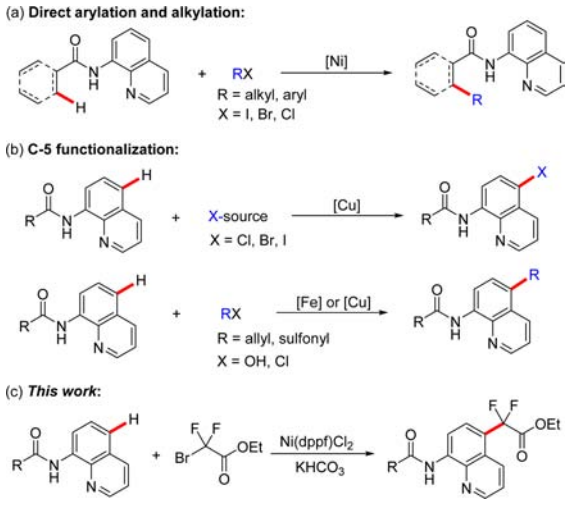
ABSTRACT: A simple and efficient protocol for nickel-catalyzed regioselective C−H bond difluoroalkylation of 8-aminoquinoline scaffolds with functionalized difluoromethyl bromides was developed. The reaction has broad substrate scope and provides a facile and useful access to the corresponding C5-functionalized difluoromethylated quinolines in good to excellent yields.

Nickel is one of the most widely used transition-metal catalysts in organic transformations, and Ni-catalyzed cross-coupling and C−H functionalization are of great interest to organic chemists.[1] Along with the extensively studied classical cross-coupling reactions, such as the Suzuki, Negishi, and Kumada reactions, Ni-catalyzed difluoroalkylation of aromatics between fluoroalkyl halides and aryl metals has also been well established in the past years. In 2014, Zhang's group reported an effective Ni-catalyzed cross-coupling of arylboronic acids with functionalized difluoromethyl bromides and chlorides.[2] Subsequently, Wang's group disclosed a Ni-catalyzed monofluoromethylation of arylboronic acids.[3] Moreover, they have also developed the Ni-catalyzed decarboxylative difluoroalkylation of α,β-unsaturated carboxylic acids.[4]

Although less studied, Ni-catalyzed directing C−H functionalizations have also been documented.[5] Recently, bidentate chelation-assisted organic transformation has become a powerful strategy for the regioselective functionalization of the C−H bond.[6] It is worth noting that a few examples of Ni-catalyzed *ortho* C−H functionalization with the aid of a bidentate directing group, 8-aminoquinoline, have been developed. Chatani realized a Ni-catalyzed direct functionalization of a C−H bond in benzamides and acrylamides with halogenated hydrocarbon or phenyltrimethylammonium salts via bidentate-chelation assistance (Scheme 1a).[7] Ge and co-workers reported a nickel-catalyzed site-selective alkylation and direct carbonylation of an unactivated C(sp^3)−H bond,[8] and Ackermann developed nickel-catalyzed direct alkylations and trifluoroethylations of arenes.[9]

Our initial aim was to realize a Ni-catalyzed *ortho* C−H difluoroalkylation of benzoic acid derivatives with the assistance of an 8-aminoquinoline auxiliary. Strangely, the difluoroalkylation reaction did not occur at the phenyl ring of the benzoic acid moiety but at the C5−H position of the quinoline ring. As we know, the C5-functionalization of quinolines has achieved much attention via transition-metal-catalyzed remote C−H functionalization, its chlorination being first reported by Stahl,[10] followed by Zhang.[11] Then, Zeng and co-workers described an Fe-catalyzed regioselective C5-allylation of quinolines through a remote C−H activation.[12] Subsequently, chalcogenation,[13] sulfonylation,[14] amination,[15] halogenation,[16] trifluoromethylation,[17] and nitration[18] of quinolines on the C5-position have been developed (Scheme 1b). In view of the synthetic utility for the functionalization of quinolines, development of the new synthetic methodology on these frameworks is highly desirable. To our knowledge, Ni-catalyzed regioselective fluoroalkylation of quinolines through remote C−H activation is not developed, representing a great challenge. As a part of ongoing efforts on

Scheme 1. Ni-Catalyzed C−H Functionalization of 8-Aminoquinolines



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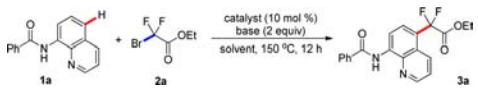
transition-metal-catalyzed direct C−H functionalization,[19] herein we demonstrate the first example of Ni-catalyzed difluoroalkylation of 8-aminoquinoline scaffolds on their C5-position with functionalized difluoromethyl bromides through the direct C−H activation/functionalization (Scheme 1c).

Initially, *N*-(quinolin-8-yl)benzamide (**1a**) and ethyl 2-bromo-2,2-difluoroacetate ($BrCF_2CO_2Et$, **2a**) were chosen as a model reaction for optimization of the reaction conditions, and the results are outlined in Table 1. When the reaction was carried out

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	base	solvent	yield[b] (%)
1	$NiCl_2$	Na_2CO_3	1,4-dioxane	26
2	$NiCl_2$	Na_2CO_3	1,4-dioxane	32[c]
3	$NiBr_2$	Na_2CO_3	1,4-dioxane	21[c]
4	$Ni(OAc)_2{\cdot}4H_2O$	Na_2CO_3	1,4-dioxane	14[c]
5	$Pd(OAc)_2$	Na_2CO_3	1,4-dioxane	n.r.[c]
6	$Cu(OAc)_2$	Na_2CO_3	1,4-dioxane	n.r.[c]
7	$Co(OAc)_2{\cdot}4H_2O$	Na_2CO_3	1,4-dioxane	n.r.[c]
8	$Fe(OAc)_2$	Na_2CO_3	1,4-dioxane	n.r.[c]
9	$Ni(PPh_3)_2Cl_2$	Na_2CO_3	1,4-dioxane	35
10	$Ni(PCy_3)Cl_2$	Na_2CO_3	1,4-dioxane	24
11	Ni(dppe)Cl_2	Na_2CO_3	1,4-dioxane	32
12	Ni(dppp)Cl_2	Na_2CO_3	1,4-dioxane	31
13	Ni(dppf)Cl_2	Na_2CO_3	1,4-dioxane	46
14	Ni(dppf)Cl_2	Cs_2CO_3	1,4-dioxane	<5
15	Ni(dppf)Cl_2	K_2CO_3	1,4-dioxane	38
16	Ni(dppf)Cl_2	$NaHCO_3$	1,4-dioxane	61
17	Ni(dppf)Cl_2	$KHCO_3$	1,4-dioxane	80
18	Ni(dppf)Cl_2	K_3PO_4	1,4-dioxane	36
19	Ni(dppf)Cl_2	K_2HPO_4	1,4-dioxane	43
20	Ni(dppf)Cl_2	pyridine	1,4-dioxane	21
21	Ni(dppf)Cl_2	$KHCO_3$	DMF	n.r.
22	Ni(dppf)Cl_2	$KHCO_3$	DMSO	n.r.
23	Ni(dppf)Cl_2	$KHCO_3$	toluene	35
24	Ni(dppf)Cl_2	$KHCO_3$	NMP	45
25	Ni(dppf)Cl_2	$KHCO_3$	DCE	53
26	Ni(dppf)Cl_2	$KHCO_3$	1,4-dioxane	51,[d] 76[e]
27	Ni(dppf)Cl_2	$KHCO_3$	1,4-dioxane	21,[f] 73[g]
28	Ni(dppf)Cl_2	$KHCO_3$	1,4-dioxane	60,[h] 82[i]

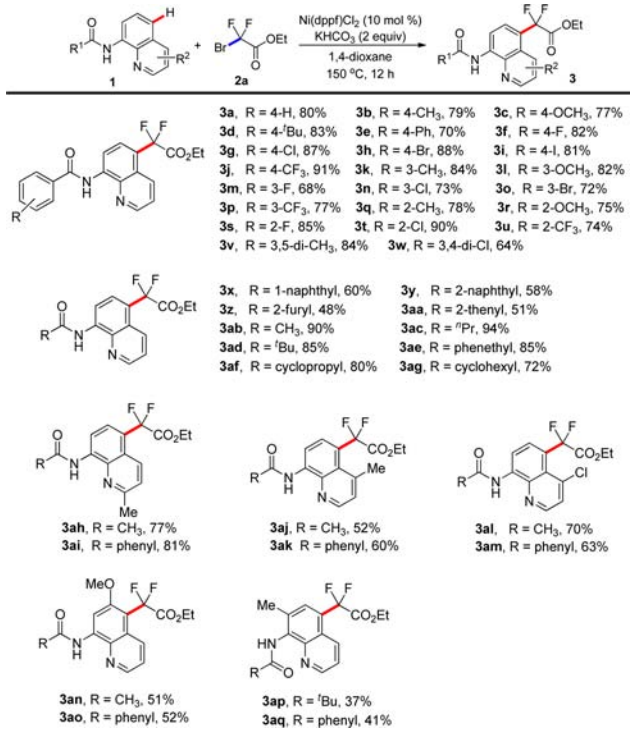
[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), catalyst (0.025 mmol, 10 mol %), base (0.50 mmol, 2.0 equiv), solvent (1.0 mL), 150 °C, 12 h. [b]Isolated yield. [c]PPh_3 (20 mol %). [d]Ni(dppf)Cl_2 (5 mol %). [e]Ni(dppf)Cl_2 (15 mol %). [f]140 °C. [g]160 °C. [h]8 h. [i]24 h. n.r. = no reaction.

in 1,4-dioxane at 150 °C for 12 h in the presence of a catalytic amount of $NiCl_2$ (10 mol %) using Na_2CO_3 as a base, the remote C5-difluoromethylation proceeded selectively and delivered a sole product **3a** in 26% yield (Table 1, entry 1). The structure of **3a** was characterized by ^1H and ^{13}C NMR, and the structure of **3r** was further confirmed by X-ray single crystal analysis.[20] An improved yield (32%) of **3a** was obtained when PPh_3 was added as a ligand, while $NiBr_2$ and $Ni(OAc)_2$ were found to be less effective (Table 1, entries 2−4). However, $Pd(OAc)_2$, $Cu(OAc)_2$, $Co(OAc)_2{\cdot}4H_2O$, and $Fe(OAc)_2$ failed to facilitate the reaction (Table 1, entries 5−8). Further screening showed that Ni(dppf)Cl_2 was the most effective catalyst for the reaction (Table 1, entries 9−13).

Among the examined bases, $KHCO_3$ was the best choice (Table 1, entries 14−20), while Cs_2CO_3 generated product **3a** in less than 5% yield. A numbers of solvents, such as DMF, DMSO, toluene, NMP, and DCE, were also examined, and none of them could match the efficacy of 1,4-dioxane (Table 1, entry 17 vs entries 21−25). The loading of the nickel catalyst, the reaction temperature, and time were optimized, also shown in Table 1 (entries 26−28).

With the optimized reaction conditions in hand, we subsequently explored the substrate scope with respect to 8-aminoquinoline amides, and the results are illustrated in Scheme 2. From Scheme 2, it can be seen that the protecting groups on

Scheme 2. Substrate Scope of 8-Aminoquinolines[a,b]



[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.50 mmol), Ni(dppf)Cl_2 (0.025 mmol, 10 mol %), $KHCO_3$ (0.50 mmol, 2.0 equiv), 1,4-dioxane (1.0 mL), 150 °C, 12 h. [b]Isolated yield

the amino moiety have no obvious influence on the reaction. Aromatic amides with a variety of substituted groups including electron-donating groups (Me, MeO, ^{t}Bu) and electron-withdrawing groups (Ph, F, Cl, Br, I, CF_3) on the benzene rings exhibited high reactivity to $BrCF_2CO_2Et$ (**2a**), and the desired products (**3a−w**) were obtained in good to excellent yields. It should be noted that naphthamides (1- and 2-naphthamide) and heterocyclic amides (furan-2- and thiophene-2-carboxamide) could also afford the corresponding difluoroalkylated products (**3x−aa**) in moderate to good yields. Furthermore, the reaction scope is beyond aromatic amides, aliphatic amides including acetamide, *n*-butyramide, pivalamide, cyclopropanecarboxamide, 3-phenylpropanamide, and cyclohexanecarboxamide which exhibit great suitability for the reaction with **2a**, providing the desired products (**3ab−ag**) in higher yields as compared to the corresponding aromatic amides. Moreover, the substituent effects on the quinoline ring were also studied. 2-Methyl-8-aminoquinoline amides could participate well in the reaction, affording the corresponding products (**3ah**

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and **3ai**) in good yields, while the installation of a sterically hindered methyl, chloro, or methoxy group at the C4-, C6-, and C7-position of quinolone rings has an obvious influence on reactivity, giving the corresponding C5-difluoromethylated quinolines in lower yields (**3aj**−**aq**).

To further explore the scope of substrates, a series of analogous of quinolones were investigated, and the results are listed in Figure 1. Under the optimized reaction conditions, the reaction

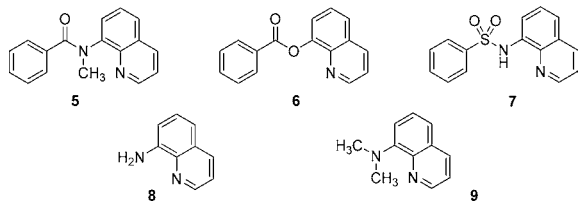
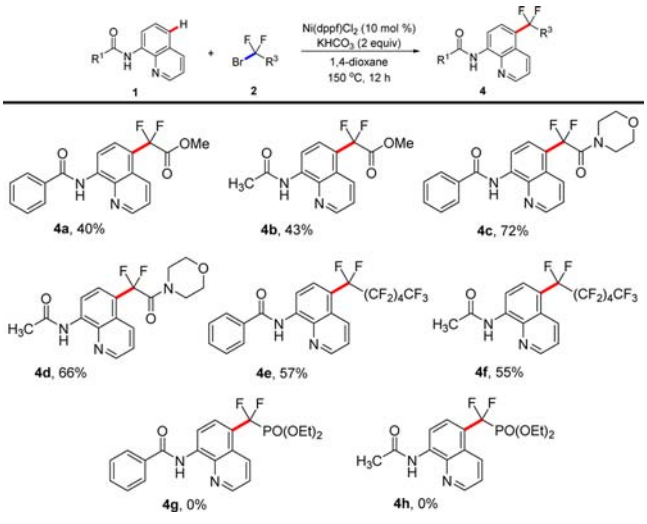


Figure 1. Ineffective Ni-catalyzed C5-difluoroalkylation of substrates (**5**−**9**).

of *N*-methyl-*N*-(quinolin-8-yl)benzamide (**5**) with **2a** failed to generate the difluoroalkylated product. However, quinolin-8-yl benzoate (**6**) and *N*-(quinolin-8-yl)benzenesulfon-amide (**7**) were also ineffective in the reaction despite the presence of the bidentate coordination site. Unfortunately, the C5-difluoroalkylation also failed with the electron-rich 8-aminoquinoline (**8**) and its derivative *N*,*N*-dimethyl-8-aminoquinoline (**9**). These results indicated that the chelation of the 8-aminoquinoline amide skeleton, as well as a free NH moiety, is essential for the reaction.

Subsequently, a variety of functionalized difluoromethyl bromides was investigated, and the results are summarized in Scheme 3. As expected, methyl bromodifluoroacetate could also

Scheme 3. Scope of R^3 in Difluoromethyl Bromides[a,b]

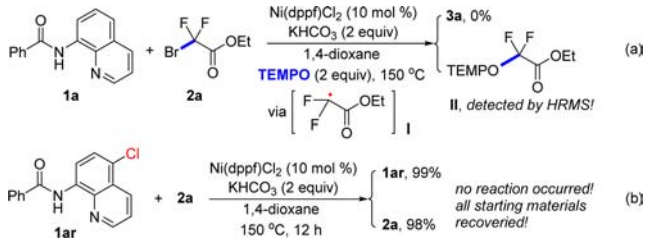


[a]Reaction conditions: **1** (0.25 mmol), **2** (0.50 mmol), Ni(dppf)Cl_2 (0.025 mmol, 10 mol %), $KHCO_3$ (0.50 mmol, 2.0 equiv), 1,4-dioxane (1.0 mL), 150 °C, 12 h. [b]Isolated yield.

be employed in the C5-difluoroalkylation of 8-aminoquinolines, providing the corresponding products **4a** and **4b** in 40% and 43% yield, respectively. Notably, 2-bromo-2,2-difluoro-1-morpholino-ethanone reacted with *N*-(quinolin-8-yl)benzamide (**1a**) and *N*-(quinolin-8-yl)acetamide to afford the desired products **4c** and **4d** in 72% and 66% yields. It should be noted that perfluorohexyl bromide was also a suitable reagent for the reaction under the optimized conditions and generated the anticipated coupling products (**4e** and **4f**) in 57% and 55% yields. However, bromodifluoromethyl diethylphosphonate failed in the reaction and the starting materials were recovered.

In order to gain insight into the reaction mechanism, some control experiments were performed, including free radical inhibition and trapping experiments. It was found that the remote C−H difluoroalkylation was completely inhibited in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a free radical scavenger. Meanwhile, the functionalized difluoromethyl radical (**I**) generated in situ from **2a** was captured, and the corresponding adduct **II** was detected by HRMS (Scheme 4a

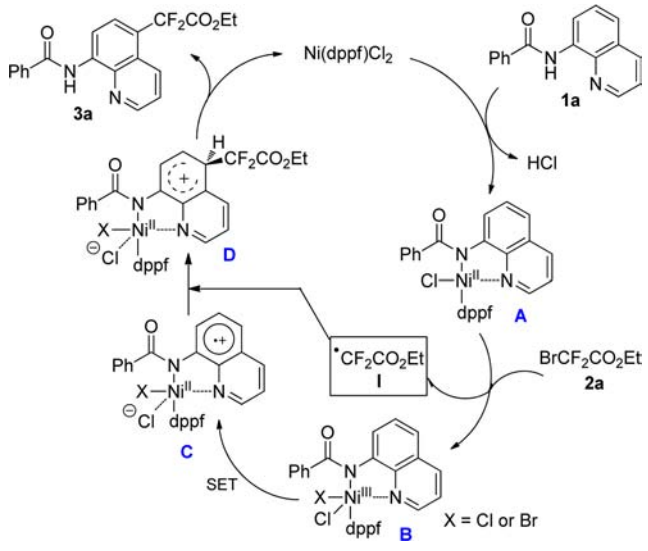
Scheme 4. Control Experiments



and Supporting Information). It is indicated that the radical process might be involved in the reaction. When the C5-position hydrogen of **1a** was substituted by chlorine (**1ar**), no product was obtained and the starting materials were recovered (Scheme 4b).

Although the exact mechanism remains unclear to date, on the basis of our experimental results and the literature,[12,15] a mechanistic hypothesis for the Ni-catalyzed remote C−H difluoroalkylation of 8-aminoquinoline amide is proposed, as shown in Scheme 5. First, Ni(dppf)Cl_2 reacts with 8-amino-

Scheme 5. Plausible Mechanism



quinoline amide (**1a**) to produce a chelated complex **A**. Then, a functionalized difluoromethyl radical **I** generated in situ from **2a** can be easily initiated by the oxidation of aryl-Ni(II) complex **A** to aryl-Ni(III) complex **B** through a SET process. Subsequently, an intermolecular SET between an electron-rich 8-aminoquinoline moiety with a highly oxidative Ni(III) center proceeds to generate a cationic quinoline radical/Ni(II) species **C**. The formed **C** reacts with radical **I** to afford an intermediate **D**. The

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obtained **D** undergoes a concerted proton transfer/demetalation step to provide the desired product **3a** along with the regeneration of a Ni(II)-complex for the next catalytic cycle. Further investigation is being conducted to afford evidence for the proposed mechanism.

In conclusion, we have established an efficient and convenient method for C5-difluoroalkylation of 8-aminoquinoline scaffolds making use of an inexpensive nickel catalyst. The reaction system shows tolerance toward numerous 8-aminoquinoline amides and functionalized difluoromethyl bromides, giving the corresponding products in good to excellent yields. On the basis of experimental investigations, a free radical cross-coupling pathway underlying the reaction mechanism was proposed. Further explorations for nickel catalyzed difluoroalkylation of other heteroarene systems are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02166.

Full experimental details and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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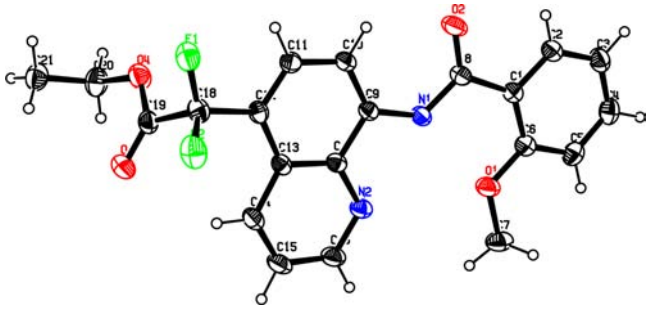
(20) X-ray single crystal structure of **3r** (CCDC: 1449577).



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