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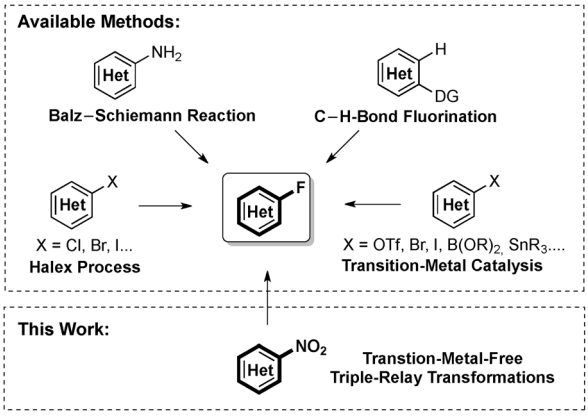
Synthesis of Fluorinated Heteroaromatics through Formal Substitution of a Nitro Group by Fluorine under Transition-Metal-Free Conditions

Ran-Ning Guo,[a, b] Xian-Feng Cai,[a] Lei Shi,*[a] Zhang-Pei Chen,[a] and Yong-Gui Zhou*[a]

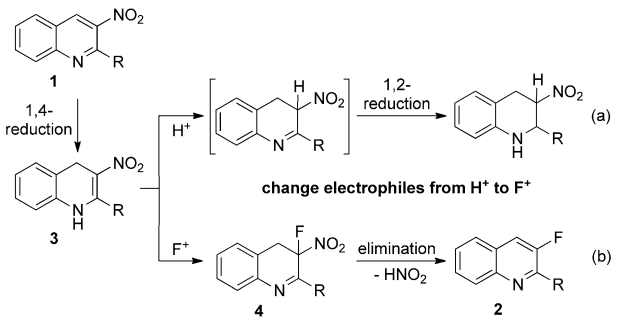
Abstract: An efficient and transition-metal-free approach was developed to access a series of fluorinated heteroaromatics in moderate to excellent yields. This one-pot procedure features a triple-relay transformation of rapid dearomatization, fluorination, and rearomatization processes, which represents a conceptually novel strategy of combining partial hydrogenation and electrophilic fluorination.

Fluorinated molecules are of remarkable significance in pharmaceuticals, agrochemicals, tracers for positron emission tomography and new materials due to their improved properties of lipophilicity, bioavailability, metabolic stability, etc.[1] To date, great achievements have been made in the construction of carbon–fluorine bonds, while the fluorination of aromatic compounds is still challenging.[2] Fluorination of medicinally relevant heteroaromatics, for example, mainly relies on classic fluorination methods,[3] such as the Halex (halogen exchange) process, the Balz–Schiemann reaction, and recently emerged transition-metal-mediated fluorination reactions.[2b,c,4–6] Transition metal-catalyzed fluorinations using palladium or silver have been proven to be highly efficient and encompass a broad substrate scope compared to traditional reactions; however, directing groups and high catalyst loading are unavoidable. Therefore, new and efficient fluorination methodologies are highly desirable in response to the ever-growing need of fluorinated aromatics in organic fluorine chemistry. Herein, we present a conceptually novel and transition-metal-free route to fluorinated heteroaromatics (Scheme 1).

In organic synthesis, the nitro group is viewed as a synthetically important functional group owing to its easy availability and transformation into a variety of diverse functionalities.[7,8] Very recently, as part of our ongoing efforts to promote the development of asymmetric hydrogenations of heteroaromatic compounds,[9,10] 3-nitroquinolines have been studied (Scheme 2a).[11] Due to the high electron-withdrawing and conjugative effect of the nitro group, the 1,4-reduction intermediate **3** was relatively stable in the asymmetric transfer hydrogenation (ATH) process; thus, it was isolated and used in further transformations to give more insights on the mechanism. The key-intermediate enamine **3**[12] also inspired us to investigate the possibility of combining the partial reduction process with other transformations. We envisioned that electrophilic fluorine could be introduced into the C3-position of **3** to yield the fluorinated intermediate **4**, and, driven by the strong force of rearomatization, nitrous acid would then subsequently be eliminated to yield the desired 3-fluoroquinoline (Scheme 2b). To achieve this sequential transformation, the reactivity of the enam-



Scheme 1. Different approaches to fluorinated heteroaromatics.



Scheme 2. a) ATH process of 3-nitroquinolines with Hantzsch ester. b) Synthesis of 3-fluoroquinolines through the partial reduction, fluorination, and elimination of nitrous acid.

[a] R.-N. Guo, X.-F. Cai, L. Shi, Z.-P. Chen, Prof. Y.-G. Zhou
State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics
Chinese Academy of Sciences, Dalian 116023 (P. R. China)
Fax: (+86) 411-84379220
E-mail: ygzhou@dicp.ac.cn

[b] R.-N. Guo
Department of Chemistry, Dalian University of Technology
Dalian 116012 (P. R. China)

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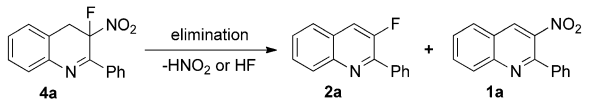
ine intermediate **3** with an electrophilic fluorine reagent and the selectivity of the elimination of nitrous acid or hydrogen fluoride are key considerations.

Following above hypothesis, the important step is how to trap the 1,4-reduction intermediate **3** by electrophilic fluorination. An original survey on common fluorine sources showed that both Selectfluor and *N*-fluorobenzenesulfonimide (NFSI) performed well in trapping the in situ generated 3-nitro-2-phenyl-1,4-dihydroquinoline (**3a**) in CH_3CN. In addition, the electrophilic attack by Selectfluor quantitatively converted **3a** to 3-fluoro-3-nitro-2-phenyl-3,4-dihydro-quinoline (**4a**) within 5 min.[13] With isolated **4a** in hand, further research focused on screening the conditions for the selective elimination of nitrous acid.[14] Preliminary trials revealed that a base could accelerate the eliminative rearomatization of **4a**, while acids, oxidants, or heating could not (Table 1, entries 1–3); a promising result (full conversion, 86% selectivity to **2a**) was obtained in the presence of Et_3N (Table 1, entry 4). Further evaluation of different bases illustrated that complete rearomatization could be achieved by a series of common bases, with inorganic bases performing better than organic bases in terms of selectivity and yield, and the best result was obtained with KO*t*Bu (Table 1, entries 6–9,). Notably, no deterioration of conversion or selectivity was observed when half amount of the base was used (Table 1, entry 10). With KO*t*Bu (2.0 equiv) as the optimized base, increasing or lowering the temperature only had a marginal influence on the selectivity and conversion (Table 1, entries 11–12).

After screening bases for the selective elimination, a >99:1 ratio of **2a**/**1a** was achieved (entry 10, Table 1). Therefore, we envisaged a one-pot transformation of 3-nitroquinolines to 3-fluoroquinolines. With diethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (HEH) as the hydrogen source for the initial partial reduction process and Selectfluor as the fluorinating reagent, a sequential transformation of **1a** to **2a** was conducted, as depicted in Table 2. A high conversion of 96% was obtained in CH_3CN, but other solvents diminished the first 1,4-reduction step and reduced the fluorination and elimination rate drastically (Table 2, entries 1–5). Strong acids such as L-CSA or *p*-TsOH·H_2O could replace 1,1′-binaphthyl-2,2′-diylhydrogenphosphate (BPA) perfectly (Table 2, entries 8–9), while weaker acids such as *o*-nitrobenzoic acid or acetic acid failed (Table 2, entries 6–7). Therefore, *p*-TsOH·H_2O was chosen as the alternative hydrogenation catalyst in consideration of its cost and availability. The optimized conditions for this mild and metal-free fluorination reaction were finally established as: HEH (1.1 equiv), *p*-TsOH·H_2O (5 mol%); Selectfluor (1.3 equiv); KO*t*Bu (2.0 equiv), CH_3CN.

With this newly developed triple-relay transformation strategy in hand, we next set out to demonstrate the generality and practicality in detail with various 3-nitroquinolines, and the results are summarized in Table 3. The reaction could be carried out with a series of substituted 3-nitroquinolines, affording the corresponding products in moderate to good yields. Both electron-donating and electron-withdrawing groups at the C2-position were tolerated under the reaction conditions and there was also no significant influence of the position of the 2-aryl substituents. Besides, the yield decreases with aryl > alkenyl ≈ alkynyl > alkyl substituents at the C2-position. Notably, in terms of reactivity, the dearomatization pro-

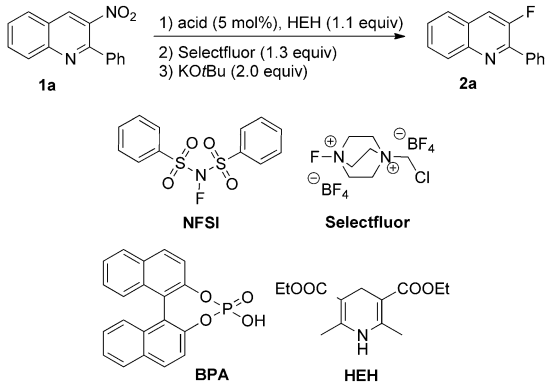
Table 1. Screening of conditions for the selective elimination of nitrous acid.[a]



Entry	Conditions	Conversion [%][b]	Ratio of **2a**/**1a**[b]
1	Heat (50 °C)	<5	–
2	DDQ (1.1 equiv)	<5	–
3	*p*-TsOH·H_2O (1.1 equiv)	<5	–
4	Et_3N (4.0 equiv)	>95	86:14
5	DABCO (4.0 equiv)	>95	82:18
6	Na_2CO_3 (2.0 equiv)	>95	93:7
7	K_2CO_3 (2.0 equiv)	>95	93:7
8	Cs_2CO_3 (2.0 equiv)	>95	93:7
9	KO*t*Bu (4.0 equiv)	>95	>99:1
10	KO*t*Bu (2.0 equiv)	>95	>99:1
11[c]	KO*t*Bu (2.0 equiv)	>95	99:1
12[d]	KO*t*Bu (2.0 equiv)	>95	>99:1

[a] Reaction condition: **4a** (0.20 mmol), CH_3CN (3.0 mL), RT, 12 h. [b] Determined by ^1H NMR spectroscopy. [c] At 0 °C. [d] At 50 °C. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; DABCO = 1,4-diazabicyclo[2.2.2]octane.

Table 2. Optimization of reaction parameters for the one-pot transformation.[a]



Entry	Solvents	Acid	Conversion [%][b]
1	CH_3CN	BPA	96
2	THF	BPA	76
3	1,4-dioxane	BPA	57
4	toluene	BPA	58
5	Et_2O	BPA	44
6	CH_3CN	AcOH	<5
7	CH_3CN	*o*-nitrobenzoic acid	<5
8	CH_3CN	L-CSA	94
9	CH_3CN	*p*-TsOH·H_2O	97

[a] Reaction conditions: **1a** (0.20 mmol), HEH (1.1 equiv), and acid (5 mol%) in solvent (3.0 mL) were stirred for 10 h at RT; then Selectfluor (1.3 equiv) was added and after about 20 h KO*t*Bu (2.0 equiv) was added and the mixture was stirred for 5.5 h. [b] Determined by ^1H NMR spectroscopy. L-CSA = (L)-camphorsulfonic acid; *p*-TsOH·H_2O = *p*-toluenesulfonic acid monohydrate; BPA = 1,1′-binaph-thyl-2,2′-diyl hydrogenphosphate.

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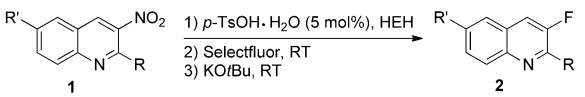
Table 3. Scope for the transformation of 3-nitroquinolines **1** to 3-fluoroquinolines **2**[a]



Entry	R	R′	Yield [%][b]
1	C_6H_5	H	94 (**2a**)
2	2-MeC_6H_4	H	95 (**2b**)
3	3-MeC_6H_4	H	93 (**2c**)
4	4-MeC_6H_4	H	91 (**2d**)
5	4-$MeOC_6H_4$	H	73 (**2e**)
6	4-FC_6H_4	H	93 (**2f**)
7	4-ClC_6H_4	H	78 (**2g**)
8	4-BrC_6H_4	H	93 (**2h**)
9	4-$CF_3C_6H_4$	H	81 (**2i**)
10	2-naphthyl	H	93 (**2j**)
11	(*E*)-styryl	H	80 (**2k**)
12	phenylethynyl	H	63 (**2l**)
13	4-chlorophenylethynyl	H	78 (**2m**)
14	Ph	F	87 (**2n**)
15	Ph	OMe	61 (**2o**)
16	*n*Bu	OMe	51 (**2p**)

[a] Reaction conditions: **1** (0.20 mmol), HEH (1.1 equiv), and *p*-TsOH·H_2O (5 mol%) in CH_3CN (3.0 mL) were stirred for 2 h at RT; then Selectfluor (1.3 equiv) was added and after about 5 min KO*t*Bu (2.0 equiv) was added and the mixture was stirred for 5.5 h. [b] Isolated yield.

cess of alkyl-, alkynyl-, and alkenyl-substituted substrates was faster than that of aryl-substituted ones, while in turn the fluorination and rearomatization process of the former substrates was slower than that of the latter ones.

In conclusion, we have developed an efficient and transition-metal-free procedure to synthesize a series of fluorinated heteroaromatics in moderate to excellent yields through formal substitution of a nitro group by fluorine. This one-pot procedure features a triple-relay transformation of rapid dearomatization, electrophilic fluorination, and eliminative rearomatization processes. This novel fluorination method also allows for the possibility of late-stage fluorination.[6e,6h,6k] Further investigations on new types of combinations of partial reductions and other reactions are underway in our laboratory.

Experimental Section

Typical procedure for the one-pot transformation

A solution of 2-phenyl-3-nitroquinoline (**1a**, 50 mg, 0.20 mmol), HEH (1.1 equiv), and *p*-TsOH·H_2O (5 mol%) in CH_3CN (3.0 mL) was stirred at RT for 2 h. A yellow solid formed gradually; then Selectfluor (1.3 equiv) was added and after about 5 min KO*t*Bu (2.0 equiv) was added and the mixture was stirred until the reaction was complete. All volatiles were removed under reduced pressure. Purification was performed on a silica gel column eluted with hexane/EtOAc (80:1–50:1) to give the desired product **2a** (42 mg, 0.19 mmol, 94% yield) as a white solid. M.p. = 36–38 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 7.3 Hz, 2H), 7.87–7.61 (m, 3H), 7.56–7.44 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2 (d, $^1J_{FC}$ = 261.0 Hz), 149.2 (d, $^2J_{FC}$ = 14.5 Hz), 145.4 (d, $^5J_{FC}$ = 2.9 Hz), 135.9 (d, $^4J_{FC}$ = 5.2 Hz), 129.7 (s), 129.5 (d, $^3J_{FC}$ = 5.3 Hz), 128.9 (d, $^5J_{FC}$ = 2.4 Hz), 128.7 (s), 128.4 (d, $^3J_{FC}$ = 5.4 Hz), 127.4 (s), 126.9 (d, $^4J_{FC}$ = 4.8 Hz), 119.8 ppm (d, $^2J_{FC}$ = 19.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −124.2 ppm (s); HRMS (ESI): *m/z* calcd for $C_{15}H_{10}FN$: 224.0877 $[M+H]^+$; found: 224.0870 (see the Supporting Information for spectroscopic data).

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Keywords: fluorination · heterocycles · hydrogenation · nitro compounds · rearomatization

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[13] Typical procedure: a solution of 2-phenyl-3-nitroquinoline (**1a**, 50 mg, 0.20 mmol), HEH (1.1 equiv), and BPA (5 mol%) in CH_3CN (3.0 mL) was stirred at RT for 2 h. A yellow solid formed gradually; then Selectfluor (1.3 equiv) was added and the reaction was monitored by TLC. Notably, Selectfluor should be added after the first transformation is complete, because otherwise HEH would be oxidized by Selectfluor preferentially.

[14] 3-Fluoro-3-nitro-2-phenyl-3,4-dihydroquinoline (**4a**) was comparatively stable when kept in cold storage. Once isolated, it should be subjected to the base evaluation experiments as soon as possible. Traces of eliminative by-product **2a** could be observed in the ^1H NMR spectrum due to the deterioration of **4a** in $CDCl_3$.

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