

Synthetic Methods

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

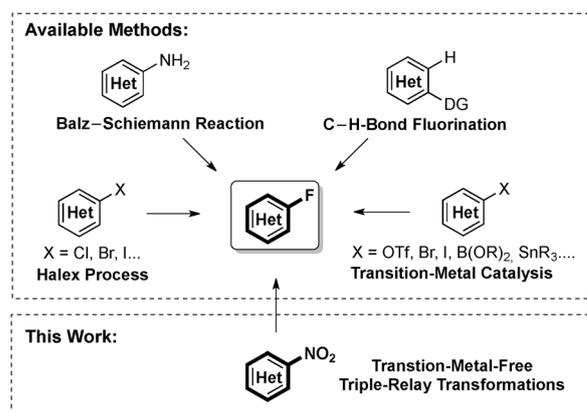
Ran-Ning Guo,^[a, b] Xian-Feng Cai,^[a] Lei Shi,^{*[a]} Zhang-Pei Chen,^[a] and Yong-Gui Zhou^{*[a]}

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.

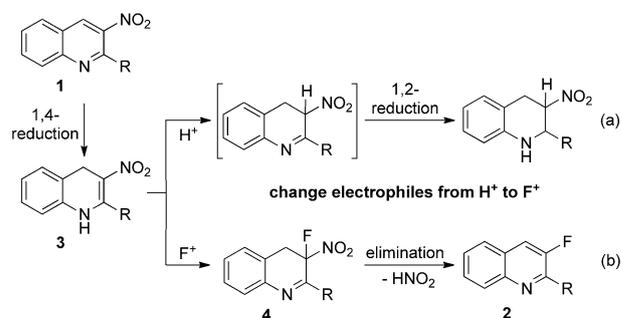
Fluorinated molecules are of remarkable significance in pharmaceuticals, agrochemicals, tracers for positron emission tomography and new materials due to their improved properties of lipophilicity, bioavailability, metabolic stability, etc.^[1] To date, great achievements have been made in the construction of carbon–fluorine bonds, while the fluorination of aromatic compounds is still challenging.^[2] Fluorination of medically 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 fluorination 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)

Supporting information for this article is available on the WWW under
<http://dx.doi.org/10.1002/chem.201402282>.

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 CH₃CN. 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 Et₃N (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 KOtBu (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 KOtBu (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 re-

agent, a sequential transformation of **1a** to **2a** was conducted, as depicted in Table 2. A high conversion of 96% was obtained in CH₃CN, 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·H₂O 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·H₂O 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·H₂O (5 mol %); Selectfluor (1.3 equiv); KOtBu (2.0 equiv), CH₃CN.

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	<i>p</i> -TsOH·H ₂ O (1.1 equiv)	<5	–
4	Et ₃ N (4.0 equiv)	>95	86:14
5	DABCO (4.0 equiv)	>95	82:18
6	Na ₂ CO ₃ (2.0 equiv)	>95	93:7
7	K ₂ CO ₃ (2.0 equiv)	>95	93:7
8	Cs ₂ CO ₃ (2.0 equiv)	>95	93:7
9	KOtBu (4.0 equiv)	>95	>99:1
10	KOtBu (2.0 equiv)	>95	>99:1
11 ^[c]	KOtBu (2.0 equiv)	>95	99:1
12 ^[d]	KOtBu (2.0 equiv)	>95	>99:1

[a] Reaction condition: **4a** (0.20 mmol), CH₃CN (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 ₃ CN	BPA	96
2	THF	BPA	76
3	1,4-dioxane	BPA	57
4	toluene	BPA	58
5	Et ₂ O	BPA	44
6	CH ₃ CN	AcOH	<5
7	CH ₃ CN	<i>o</i> -nitrobenzoic acid	<5
8	CH ₃ CN	<i>L</i> -CSA	94
9	CH ₃ CN	<i>p</i> -TsOH·H ₂ O	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 KOtBu (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·H₂O = *p*-toluenesulfonic acid monohydrate; BPA = 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate.

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

Entry	R	R'	Yield [%] ^[b]
1	C ₆ H ₅	H	94 (2a)
2	2-MeC ₆ H ₄	H	95 (2b)
3	3-MeC ₆ H ₄	H	93 (2c)
4	4-MeC ₆ H ₄	H	91 (2d)
5	4-MeOC ₆ H ₄	H	73 (2e)
6	4-FC ₆ H ₄	H	93 (2f)
7	4-ClC ₆ H ₄	H	78 (2g)
8	4-BrC ₆ H ₄	H	93 (2h)
9	4-CF ₃ C ₆ H ₄	H	81 (2i)
10	2-naphthyl	H	93 (2j)
11	(<i>E</i>)-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	<i>n</i> Bu	OMe	51 (2p)

[a] Reaction conditions: **1** (0.20 mmol), HEH (1.1 equiv), and *p*-TsOH·H₂O (5 mol%) in CH₃CN (3.0 mL) were stirred for 2 h at RT; then Selectfluor (1.3 equiv) was added and after about 5 min KO^tBu (2.0 equiv) was added and the mixture was stirred for 5.5 h. [b] Isolated yield.

cess of alkyl-, alkenyl-, 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·H₂O (5 mol%) in CH₃CN (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^tBu (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; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): δ = 155.2 (d, ¹*J*_{FC} = 261.0 Hz), 149.2 (d, ²*J*_{FC} = 14.5 Hz), 145.4 (d, ⁵*J*_{FC} = 2.9 Hz), 135.9 (d, ⁴*J*_{FC} = 5.2 Hz), 129.7 (s), 129.5 (d, ³*J*_{FC} =

5.3 Hz), 128.9 (d, ⁵*J*_{FC} = 2.4 Hz), 128.7 (s), 128.4 (d, ³*J*_{FC} = 5.4 Hz), 127.4 (s), 126.9 (d, ⁴*J*_{FC} = 4.8 Hz), 119.8 ppm (d, ²*J*_{FC} = 19.4 Hz); ¹⁹F NMR (376 MHz, CDCl₃): δ = –124.2 ppm (s); HRMS (ESI): *m/z* calcd for C₁₅H₁₀FN: 224.0877 [*M*+H]⁺; found: 224.0870 (see the Supporting Information for spectroscopic data).

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (21125208 & 21032003) and the National Basic Research Program of China (2010CB833300).

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

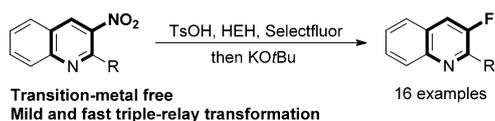
- [1] For selected reviews on the unique role of fluorine in organic, agricultural, medicinal, and material chemistry, see: a) H. Schofield, *J. Fluorine Chem.* **1999**, *100*, 7; b) H. J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; d) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359; e) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308; f) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; for books on fluorine in organic and medicinal chemistry, see: g) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**; h) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley, Chichester, **2009**.
- [2] For recent reviews on the construction of carbon–fluorine bonds, see: a) T. Furuya, C. A. Kuttruff, T. Ritter, *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803; b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470; c) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem.* **2013**, *125*, 8372; *Angew. Chem. Int. Ed.* **2013**, *52*, 8214.
- [3] For selected work and reviews on traditional fluorination reactions of aromatic compounds, see: a) G. Balz, G. Schiemann, *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1186; b) G. C. Finger, C. W. Kruse, *J. Am. Chem. Soc.* **1956**, *78*, 6034; c) G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, L. Kerekes, J. A. Olah, *J. Org. Chem.* **1979**, *44*, 3872; d) D. J. Adams, J. H. Clark, *Chem. Soc. Rev.* **1999**, *28*, 225.
- [4] For recent reviews on transition-metal-catalyzed fluorinations, see: a) V. V. Grushin, *Acc. Chem. Res.* **2010**, *43*, 160; b) T. Furuya, J. E. M. N. Klein, T. Ritter, *Synthesis* **2010**, 1804; c) A. Vignalok, *Organometallics* **2011**, *30*, 4802; d) C. Hollingworth, V. Gouverneur, *Chem. Commun.* **2012**, *48*, 2929; e) G. Liu, *Org. Biomol. Chem.* **2012**, *10*, 6243.
- [5] For selected reviews and work on typical catalytic fluorinations through C–H functionalization, see: a) K. M. Engle, T.-S. Mei, X. Wang, J.-Q. Yu, *Angew. Chem.* **2011**, *123*, 1514; *Angew. Chem. Int. Ed.* **2011**, *50*, 1478; b) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518; c) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; d) K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 7134; e) X. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 7520; f) K. S. L. Chan, M. Wasa, X. Wang, J.-Q. Yu, *Angew. Chem.* **2011**, *123*, 9247; *Angew. Chem. Int. Ed.* **2011**, *50*, 9081; g) B. Yao, Z.-L. Wang, H. Zhang, D.-X. Wang, L. Zhao, M.-X. Wang, *J. Org. Chem.* **2012**, *77*, 3336; h) S. J. Lou, D. Q. Xu, A. B. Xia, X. F. Wang, Y. K. Liu, X. H. Du, Z. Y. Xu, *Chem. Commun.* **2013**, *49*, 6218; i) T. Truong, K. Klimovica, O. Daugulis, *J. Am. Chem. Soc.* **2013**, *135*, 9342.
- [6] For selected work on transition-metal-mediated or -catalyzed C–F bond formations, see: a) T. Furuya, H. M. Kaiser, T. Ritter, *Angew. Chem.* **2008**, *120*, 6082; *Angew. Chem. Int. Ed.* **2008**, *47*, 5993; b) T. Furuya, T. Ritter, *Org. Lett.* **2009**, *11*, 2860; c) T. Furuya, A. E. Strom, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 1662; d) D. A. Watson, M. J. Su, G. Teverovskiy, Y. Zhang, J. Garcia-Fortanet, T. Kinzel, S. L. Buchwald, *Science* **2009**, *325*, 1661; e) P. Tang, T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 12150; f) P. Tang, T. Ritter, *Tetrahedron* **2011**, *67*, 4449; g) T. Noël, T. J. Maimone, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 9062; *Angew. Chem. Int. Ed.* **2011**, *50*, 8900; h) E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker, T. Ritter, *Science* **2011**, *334*, 639;

- i) T. J. Maimone, P. J. Milner, T. Kinzel, Y. Zhang, M. K. Takase, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 18106; j) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 10795; k) E. Lee, J. M. Hooker, T. Ritter, *J. Am. Chem. Soc.* **2012**, *134*, 17456; l) P. S. Fier, J. Luo, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 2552; m) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2013**, *135*, 4648; n) N. Ichiishi, A. J. Canty, B. F. Yates, M. S. Sanford, *Org. Lett.* **2013**, *15*, 5134; o) A. Mazzotti, M. Campbell, P. Tang, J. Murphy, T. Ritter, *J. Am. Chem. Soc.* **2013**, *135*, 14012; p) H. G. Lee, P. J. Milner, S. L. Buchwald, *Org. Lett.* **2013**, *15*, 5602; q) Y. Ye, S. D. Schimler, P. S. Hanley, M. S. Sanford, *J. Am. Chem. Soc.* **2013**, *135*, 16292; r) P. S. Fier, J. F. Hartwig, *Science* **2013**, *342*, 956; s) X. Mu, H. Zhang, P. Chen, G. Liu, *Chem. Sci.* **2014**, *5*, 275.
- [7] a) *Nitro Compounds: Recent Advances in Synthesis and Chemistry; Organic Nitro Chemistry Series* (Eds.: H. Feuer, A. T. Nielsen), Wiley-VCH, Weinheim, **1990**; b) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, Weinheim, **2001**.
- [8] For selected work on nucleophilic fluorodenitration processes, see: Ref. [3b]; see also: a) D. J. Adams, J. H. Clark, D. J. Nightingale, *Tetrahedron* **1999**, *55*, 7725; b) S. D. Kuduk, R. M. DiPardo, M. G. Bock, *Org. Lett.* **2005**, *7*, 577; c) P. D. O'Shea, D. Gauvreau, F. Gosselin, G. Hughes, C. Nadeau, A. Roy, C. S. Shultz, *J. Org. Chem.* **2009**, *74*, 4547; d) P. LaBeaume, M. Placzek, M. Daniels, I. Kendrick, P. Ng, M. McNeel, R. Afroze, A. Alexander, R. Thomas, A. E. Kallmerten, G. B. Jones, *Tetrahedron Lett.* **2010**, *51*, 1906; e) R. Song, W. Lin, Q. Jiang, *Tetrahedron Lett.* **2011**, *52*, 4965.
- [9] For reviews on asymmetric hydrogenations of aromatic compounds, see: a) P. J. Dyson, *Dalton Trans.* **2003**, 2964; b) F. Glorius, *Org. Biomol. Chem.* **2005**, *3*, 4171; c) S.-M. Lu, X.-W. Han, Y.-G. Zhou, *Chin. J. Org. Chem.* **2005**, *25*, 634; d) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357; e) R. Kuwano, *Heterocycles* **2008**, *76*, 909; f) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557; g) Q.-A. Chen, Z.-S. Ye, Y. Duan, Y.-G. Zhou, *Chem. Soc. Rev.* **2013**, *42*, 497.
- [10] For reviews on asymmetric transfer hydrogenations by using Hantzsch esters, see: a) S. G. Ouellet, A. M. Walji, D. W. C. Macmillan, *Acc. Chem. Res.* **2007**, *40*, 1327; b) S.-L. You, *Chem. Asian J.* **2007**, *2*, 820; c) S. J. Connon, *Org. Biomol. Chem.* **2007**, *5*, 3407; d) M. Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2010**, 852; e) M. Rueping, J. Dufour, F. R. Schoepke, *Green Chem.* **2011**, *13*, 1084; f) C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498.
- [11] X.-F. Cai, M.-W. Chen, Z.-S. Ye, R.-N. Guo, L. Shi, Y. Li, Y.-G. Zhou, *Chem. Asian J.* **2013**, *8*, 1381.
- [12] For selected work on electrophilic fluorinations of enamines, see: a) R. Surmont, B. De Corte, N. De Kimpe, *Tetrahedron Lett.* **2009**, *50*, 3877; b) P. N. Gichuhi, M. Kuriyama, O. Onomura, *Heterocycles* **2014**, *88*, 331; c) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051.
- [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 CH₃CN (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 CDCl₃.

Received: February 20, 2014

Published online on ■ ■ ■ ■, 0000

COMMUNICATION



An efficient and transition-metal-free approach was developed to access a series of fluorinated heteroaromatics in moderate to excellent yields through formal substitution of a nitro group by fluorine (see scheme). This one-pot pro-

cedure 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.

Synthetic Methods

R.-N. Guo, X.-F. Cai, L. Shi,* Z.-P. Chen, Y.-G. Zhou*



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

