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$Pd(OAc)_2$-catalyzed regioselective aromatic C–H bond fluorination†

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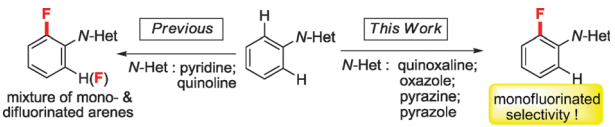
A novel $Pd(OAc)_2$–NFSI–TFA system was developed for the highly selective *ortho*-monofluorination directed by diverse aryl-*N*-heterocyclic directing groups *e.g.*, quinoxaline, pyrazole, benzo[*d*]oxazole, and pyrazine derivatives. A Pd(II/IV) catalytic cycle was proposed based on the ESI-MS/MS studies.

Given the remarkable properties of fluorine atoms, the late-stage introduction of fluorine into arenes is significant but still faces challenges.[1] The classic fluorination including Balz–Schiemann reaction[2] and the Halex process[3] is useful for the C_{aryl}–fluorine bond construction from aryldiazonium salts and electron-deficient aryl chlorides (or nitroarenes), respectively. Deoxyfluorination of phenols developed by the Ritter group recently represents an alternative efficient approach to prepare aryl fluorides.[4] Despite the nucleophilic attack process, electrophilic fluorination of aryl-lithium, -magnesium and -silicon reagents can also afford the corresponding fluoroarenes.[5] With much effort made in the past few years, transition metal catalysis exhibits high efficiency for the *ipso*-fluorination of aryl-halide, -silicon, -boron, -tin, -pseudohalide and -nickel as well as other reagents.[6] However, the use of prefunctionalized starting materials still limited the application of these strategies, the directed C–H bond fluorination potentially appears to be an improved approach.[7]

While much remarkable achievements have been made in ligand-directed C–H bond activation/functionalization in the recent decade, C–H bond fluorination is still rare and much less developed. A pyridine directing group was employed by the Sanford group in their early studies of Pd(II)-catalyzed C–H bond fluorination.[8] Recently, Yu and co-workers reported two examples of amide-directed *ortho*-fluorination of C–H bonds, and selective monofluorination of benzoic amides was developed by tuning the amide directing groups.[9] In addition, C–H bond fluorination of 8-methylquinoline derivatives with nucleophilic fluoride was recently reported by Sanford and co-workers.[10] In light of the previous C–H bond fluorination studies, the coordinating ability of the *N*-ligand directing group is sensitive to this type of transformation.[8,9] We reasoned that the quinoxaline directing group developed by our group in the C–H bond nitration[11] might be a feasible directing group for C–H bond fluorination (Scheme 1).



Scheme 1 Aryl-*N*-heterocycle directed C–H bond fluorination.

We initiated our research by treating the model substrate 2-phenyl quinoxaline (**1a**) with several fluorinating agents (**A**, **B**, **C**, **D**, and **E**), which were broadly used in the previous work, simple $Pd(OAc)_2$ as the catalyst and trifluoroacetic acid (TFA) as an additive in 1,2-chloroethane (DCE) in air. Unfortunately, only a trace amount of desired product was formed after 12 hours at 110 °C by using fluorinating agents **A–D** (Table 1, entries 1–4). To our delight, when NFSI (*N*-fluorobenzenesulfonimide, **E**) was employed as the fluorine source (entry 5), the monofluorinated product (**2a**) and the difluorinated product (**3a**) were obtained in 68% and 24% yields, respectively, with a trace amount of acetoxylated by-product.[12] After several solvents were screened (entries 6 and 7),[13] we found that DCE and CH_3NO_2 effectively promoted the conversion of **1a** while CH_3CN provided better selectivity. This phenomenon led us to assume that a mixed solvent of CH_3NO_2 (or DCE) and CH_3CN could meet the demands of both conversion and selectivity. Gratifyingly, an optimized result was obtained as anticipated by adjusting the ratio of the two types of solvents (entry 8). Various catalysts including Pd(0) and Pd(II) were surveyed subsequently (entries 10–14), $Pd(OAc)_2$ was found to exhibit the best efficiency and Pd(0) could also accelerate the reaction albeit in lower yields (entries 13 and 14). Importantly, the additives played a crucial role in this transformation, and TFA[14] performed the best among all the acidic additives tested (entries 15–20). However, *N*-methyl pyrrolidone (NMP)

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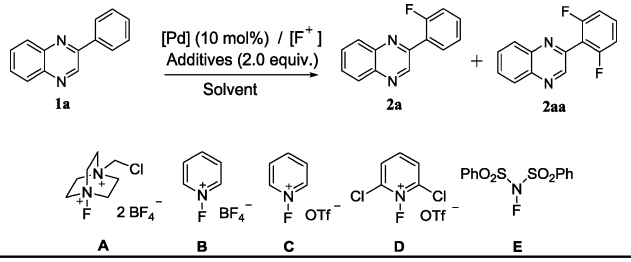
Table 1 Screening of the fluorination conditions[a]



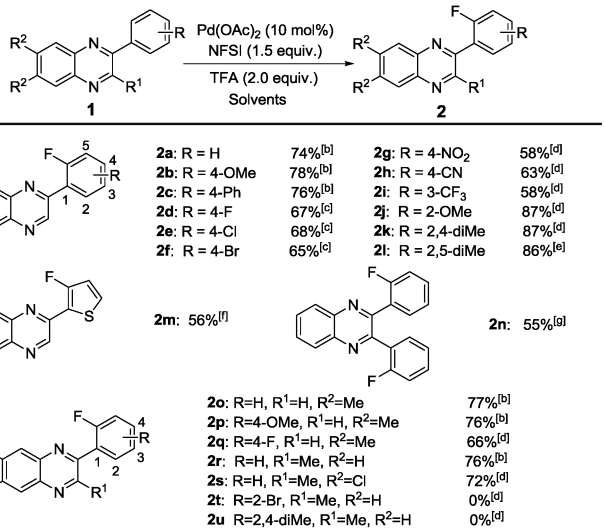
Entry	Cat.	[F$^+$]	Add.	Solvent	Yields of **2a**/**2aa**[b] (%)
1	$Pd(OAc)_2$	A	TFA	DCE	Trace/0
2	$Pd(OAc)_2$	B	TFA	DCE	5/0
3	$Pd(OAc)_2$	C	TFA	DCE	3/0
4	$Pd(OAc)_2$	D	TFA	DCE	5/trace
5	$Pd(OAc)_2$	E	TFA	DCE	68/24
6	$Pd(OAc)_2$	E	TFA	CH_3CN	53/1.5
7	$Pd(OAc)_2$	E	TFA	CH_3NO_2	54/33
8	**$Pd(OAc)_2$**	**E**	**TFA**	**MS 1**[c]	**78/3**
9	$Pd(OAc)_2$	E	TFA	MS 2	60/2
10	$Pd(OOCCF_3)_2$	E	TFA	MS 1	73/2
11	$PdCl_2$	E	TFA	MS 1	Trace/0
12	$Pd(PPh_3)_2Cl_2$	E	TFA	MS 1	58/2
13	$Pd_2(dba)_3$	E	TFA	MS 1	32/trace
14	$Pd(PPh_3)_4$	E	TFA	MS 1	65/2
15	$Pd(OAc)_2$	E	HOAc	MS 1	19/trace
16	$Pd(OAc)_2$	E	PivOH	MS 1	18/trace
17	$Pd(OAc)_2$	E	HOTf	MS 1	48/trace
18	$Pd(OAc)_2$	E	MSA	MS 1	64/15
19	$Pd(OAc)_2$	E	PTSA	MS 1	56/5
20	$Pd(OAc)_2$	E	TFAA	MS 1	70/3
21	$Pd(OAc)_2$	E	NMP	MS 1	7/trace
22	—	E	TFA	MS 1	0/0
23	$Pd(OAc)_2$	E	—	MS 1	10/2
24	$Pd(OOCCF_3)_2$	E	—	MS 1	55/3

[a] Reaction conditions: **1a** (0.1 mmol), [Pd] (10 mol%), additives (2.0 equiv.), [F$^+$] (1.5 equiv.), solvent (1.0 mL), 110 °C, in air, 12 h (unless otherwise noted), TFA = trifluoroacetic acid, MS1 = [CH_3NO_2–CH_3CN = 1 : 1 (v/v)], MS2 = [DCE–CH_3CN = 1 : 1 (v/v)], PivOH = pivalic acid, MSA = methanesulfonic acid, PTSA = *p*-toluenesulfonic acid, TFAA = trifluoroacetic anhydride, NMP = *N*-methyl pyrrolidone. [b] GC-MS yield. [c] For more detailed screening of mixed solvents, see the ESI.

used in Yu's studies[9] was inefficient in this case (entry 21). In addition, the reaction was sluggish in the absence of catalysts or additives (entries 22 and 23). Interestingly, when 10 mol% $Pd(TFA)_2$ was employed in place of $Pd(OAc)_2$, a catalytic amount of TFA that released in the C–H activation step[7,12] notably promoted the transformation and afforded monofluorinated product **2a** in 55% GC yield without external additives (entry 24). Finally, palladium-catalyzed selective C–H bond monofluorination using NFSI as a fluorinating agent and TFA as a promoter under ambient conditions was disclosed.

The scope of the quinoxaline-directed *ortho*-monofluorination was explored with the optimal reaction conditions established (Table 2). Notably, the ratio of the mixed solvent was sensitive to the quinoxaline derivatives of various substituents. Substrates containing electron-donating functionalities (**2b**, **2c**) were more favorable in this transformation, more CH_3CN was required in order to inhibit difluorination of the arenes. On the other hand, substrates bearing electron-withdrawing substituents fluorinated slowly under standard conditions,[13] thus a less amount of CH_3CN was added in these cases in order to obtain compromised yields (**2d**–**2f**). Furthermore, a single-component solvent of CH_3NO_2 was employed

Table 2 Scope of quinoxaline-directed *ortho*-monofluorination[a]



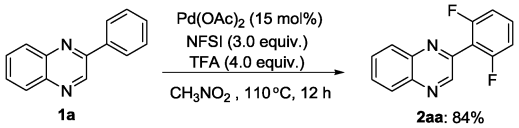
[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), TFA (2.0 equiv.), NFSI (1.5 equiv.), solvent (2.0 mL), 110 °C, in air, 12 h, isolated yields, (unless otherwise noted). [b] Solvent = [CH_3NO_2–CH_3CN = 1 : 1 (v/v)] (2.0 mL). [c] Solvent = [CH_3NO_2–CH_3CN = 10 : 1 (v/v)] (2.0 mL). [d] Solvent = CH_3NO_2 (2.0 mL). [e] $Pd(OAc)_2$ (15 mol%), TFA (2.0 equiv.), NFSI (2.0 equiv.), solvent = CH_3NO_2 (2.0 mL). [f] $Pd(OOCCF_3)_2$ (15 mol%), TFA (2.0 equiv.), NFSI (2.0 equiv.), solvent = CH_3NO_2 (2.0 mL). [g] $Pd(OAc)_2$ (15 mol%), TFA (2.0 equiv.), NFSI (3.0 equiv.), solvent = [CH_3NO_2–CH_3CN = 10 : 1 (v/v)] (2.0 mL).

to promote the fluorination of substrates containing strong electron-withdrawing groups, such as nitro (**2g**), cyano (**2h**), and trifluoromethyl (**2i**) substituents. *ortho*-Substituted substrates were monofluorinated smoothly to provide the desired products in 86% to 87% yields in the CH_3NO_2 system (**2j**, **2k**, **2l**). The heterocyclic ring was also tolerated with elevated loading of catalyst (**2m**). In addition, double-centered C–H fluorination occurred in a moderate isolated yield for inseparable fluorinated side products (**2n**).[9b]

Substrates substituted on the quinoxaline side also took part in the present protocol. Comparable results were obtained under suitable conditions (**2o**–**2s**). Notably, fluorination failed to proceed with the *ortho*-substituent at both the arene and quinoxaline moieties of the substrate, presumably due to the increase in the steric hindrance which was unfavorable for the formation of palladacyclic intermediates (**2t**, **2u**).[15]

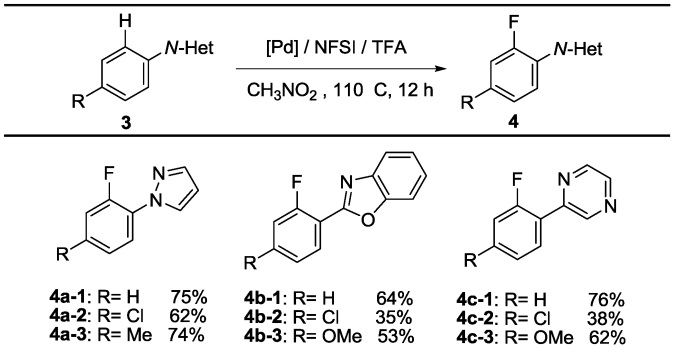
Meanwhile, the difluorinated product of **1a** was successfully afforded in 84% yield when 3 equiv. of NFSI was utilized (Scheme 2).

A series of different aryl-*N*-heterocycles other than quinoxaline were then investigated to examine the generality of this strategy. Through preliminary modification of the present conditions, pyrazole, benzo[*d*]oxazole, and pyrazine were determined to be practical directing groups (Table 3). In contrast, relatively strong coordinating groups, *e.g.*, pyridine and quinoline, were ineffective in this directed C–H bond fluorination.[13]

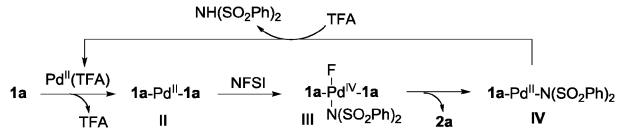


Scheme 2 Difluorination of **1a**.

Table 3 *ortho*-Monofluorination using other aryl-*N*-heterocyclic directing groups[a]



[a] See the ESI for detailed reaction conditions.



Scheme 3 Proposed mechanism.

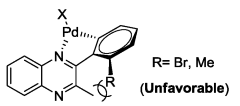
Preliminary mechanistic experiments were carried out to obtain further insight into the directed C–H bond fluorination. As monitored by kinetic studies, difluorination occurred as soon as the monofluorinated arene was formed.[13] A primary kinetic isotope effect was observed both in the intramolecular ($k_H/k_D \approx 2.3$) and intermolecular ($k_H/k_D \approx 2.3$) competition experiments, suggesting that the aromatic C–H activation might be involved in the rate-limiting step.[13]

Mass spectrometry experiments were also employed to gain a better understanding of the catalytic pathway of the present transformation.[16] The formation of cyclopalladation(II) intermediates **I**, **II** (ESI-MS signal at *m*/*z*: 466, 517, 535) and reductive eliminated Pd(II) intermediate **IV** (ESI-MS signal at *m*/*z*: 608, 626, 649, 667, 814, 832, 850; differed in the type of ligands that coordinated to the Pd centre) was detected unambiguously and assigned to the corresponding structures by MS/MS interpretation.[13] In addition, a competing coordination with Pd(II) complex **I** between **1a** and monofluorinated product **2a** was also observed (ESI-MS signal at *m*/*z*: 517 *vs.* 535), which led to the generation of difluorinated **2aa**.[13] A plausible mechanism[13] involving a Pd(II/IV) catalytic cycle was proposed based on the abovementioned mechanistic experiments and previous literatures[12] (Scheme 3).[13]

In summary, we have developed a new facile Pd(II)–NFSI–TFA system for the selective C–H bond monofluorination of aromatics *e.g.*, quinoxaline, pyrazole, benzo[*d*]oxazole, and pyrazine derivatives. The present procedure features high regio-selectivity, operational simplicity and special compatibility with multi-heteroaromatics. ESI-MS/MS studies provided a clear insight into the Pd(II/IV) catalytic cycle. Studies on the detailed mechanism and expanded substrate variations are currently underway in our lab.

Notes and references

1 For selected reviews on the formation of fluoroarenes, see: (*a*) D. J. Adams and J. H. Clark, *Chem. Soc. Rev.*, 1999, **28**, 225; (*b*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*c*) T. Furuya, J. E. M. N. Klein and T. Ritter, *Synthesis*, 2010, 1804; (*d*) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470; (*e*) C. Hollingworth and V. Gouverneur, *Chem. Commun.*, 2012, **48**, 2929.
2 (*a*) G. Balz and G. Schiemann, *Ber. Dtsch. Chem. Ges.*, 1927, **60**, 1186; (*b*) M. Döbele, S. Vanderheiden, N. Jung and S. Bräse, *Angew. Chem., Int. Ed.*, 2010, **49**, 5986.
3 H. Sun and S. G. DiMagno, *Angew. Chem., Int. Ed.*, 2006, **45**, 2720.
4 P. Tang, W. Wang and T. Ritter, *J. Am. Chem. Soc.*, 2011, **133**, 11482.
5 (*a*) V. Snieckus, F. Beaulieu, K. Mohri, W. Han, C. K. Murphy and F. A. Davis, *Tetrahedron Lett.*, 1994, **35**, 3465; (*b*) V. Gouverneur and B. Greedy, *Chem.–Eur. J.*, 2002, **8**, 766; (*c*) P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2010, **49**, 2219.
6 For selected transition metal-mediated or -catalyzed C–F bond formation, see: (*a*) T. Furuya, H. M. Kaiser and T. Ritter, *Angew. Chem., Int. Ed.*, 2008, **47**, 5993; (*b*) T. Furuya and T. Ritter, *Org. Lett.*, 2009, **11**, 2860; (*c*) D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. García-Fortanet, T. Kinzel and S. L. Buchwald, *Science*, 2009, **325**, 1661; (*d*) P. Tang, T. Furuya and T. Ritter, *J. Am. Chem. Soc.*, 2010, **132**, 12150; (*e*) T. Furuya, A. E. Strom and T. Ritter, *J. Am. Chem. Soc.*, 2009, **131**, 1662; (*f*) P. Tang and T. Ritter, *Tetrahedron*, 2011, **67**, 4449; (*g*) P. S. Fier and J. F. Hartwig, *J. Am. Chem. Soc.*, 2012, **134**, 10795; (*h*) E. Lee, J. M. Hooker and T. Ritter, *J. Am. Chem. Soc.*, 2012, **134**, 17456; (*i*) P. S. Fier, J. Luo and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, **135**, 2552; (*j*) Y. Ye and M. S. Sanford, *J. Am. Chem. Soc.*, 2013, **135**, 4648.
7 For selected reviews on the C–H functionalization, see: (*a*) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (*b*) J. F. Hartwig, *Nature*, 2008, **455**, 314; (*c*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*d*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*e*) For recent special issue on this topic, see: *Acc. Chem. Res.*, **2012**, issue 6, 777–958.
8 K. L. Hull, W. Q. Anani and M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 7134.
9 (*a*) X. Wang, T.-S. Mei and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 7520; (*b*) K. S. L. Chan, M. Wasa, X. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 9081.
10 K. B. McMurtrey, J. M. Racowski and M. S. Sanford, *Org. Lett.*, 2012, **14**, 4094.
11 Y.-K. Liu, S.-J. Lou, D.-Q. Xu and Z.-Y. Xu, *Chem.–Eur. J.*, 2010, **16**, 13590.
12 For mechanistic studies on C–F reductive elimination from high-valent palladium fluoride, see: (*a*) T. Furuya and T. Ritter, *J. Am. Chem. Soc.*, 2008, **130**, 10060; (*b*) N. D. Ball and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 3796; (*c*) L.-M. Xu, B.-J. Li, Z. Yang and Z.-J. Shi, *Chem. Soc. Rev.*, 2010, **39**, 712; (*d*) T. Furuya, D. Benitez, E. Tkatchouk, A. E. Strom, P. Tang, W. A. Goddard III and T. Ritter, *J. Am. Chem. Soc.*, 2010, **132**, 3793; (*e*) K. M. Engle, T.-S. Mei, X. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 1478.
13 For detailed information, see the ESI†.
14 TFA is known to generate highly electrophilic palladium cations, see: C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633.
15 The increase in the steric hindrance made the formation of palladacyclic intermediates sluggish.



16 (*a*) A. O. Aliprantis and J. W. Canary, *J. Am. Chem. Soc.*, 1994, **116**, 6985; (*b*) A. A. Sabino, A. H. L. Machado, C. R. D. Correia and M. N. Eberlin, *Angew. Chem., Int. Ed.*, 2004, **43**, 2514; (*c*) T. Gensch, M. Rönnefahrt, R. Czerwonka, A. Jäger, O. Kataeva, I. Bauer and H. Knölker, *Chem.–Eur. J.*, 2012, **18**, 770; (*d*) C. J. Shaffer, D. Schröder, C. Gütz and A. Lützen, *Angew. Chem., Int. Ed.*, 2012, **51**, 8097.

