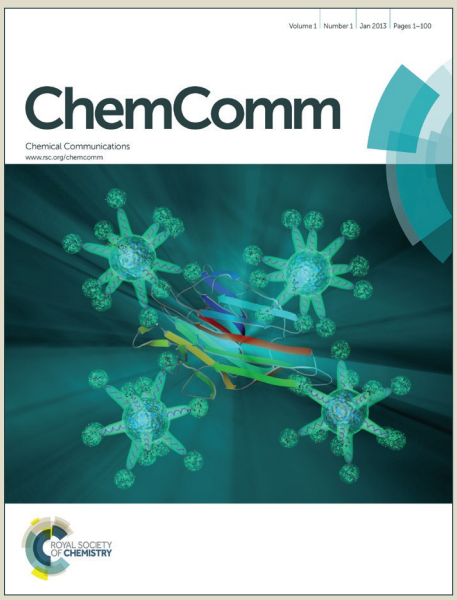
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

COMMUNICATION

Palladium-catalyzed cross-coupling of aryl fluorides with *N*-tosylhydrazones *via* C-F bond activation†

Received 00th January 20xx,
Accepted 00th January 20xx

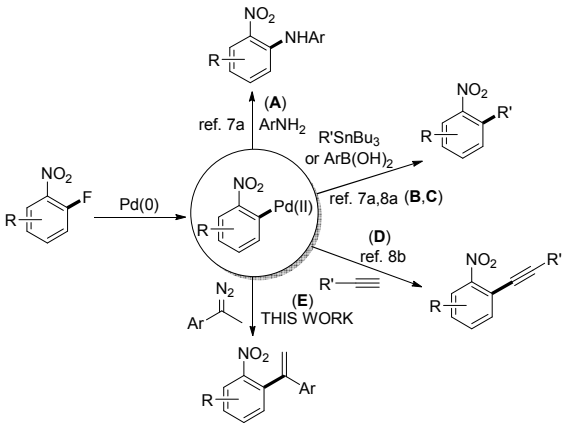
DOI: 10.1039/x0xx00000x

www.rsc.org/

Haiqing Luo,[ab] Guojiao Wu,[b] Shuai Xu,[b] Kang Wang,[b] Chaoqiang Wu,[b] Yan Zhang,[b] and Jianbo Wang*[b]

A palladium-catalyzed cross-coupling reaction of electron-deficient aryl fluorides with aryl *N*-tosylhydrazones has been reported. Mechanistically, this approach involves C-F bond activation and migratory insertion of palladium carbene as the two key steps.

Due to the high electronegativity of fluorine and the strong bonding energy of C-F bonds in organofluorine compounds, synthetically useful routes for the transformation of aromatic C-F bonds into C-C bonds are scarcely developed.[1-4] In this context, the activation of C–F bonds under transition-metal-catalyzed conditions has recently emerged as a very attractive approach toward C-F bond functionalization.[5,6] For example, *ortho*-nitro aryl fluorides have been elegantly illustrated as the electrophilic species for Pd-catalyzed cross-coupling reactions with various nucleophiles.[7,8] The nitro substituent not only activates the aromatic ring towards the nucleophilic attack by the palladium catalyst, but also control the selectivity by directing the palladium catalyst to the C-F bond adjacent to the nitro group (Scheme 1). The cross-coupling partners have been so far included amines (Buchwald-Hartwig coupling, Scheme 1A),[7a] organotin reagents (Stille coupling, Scheme 1B),[7a] organoboron reagents (Suzuki-Miyaura coupling, Scheme 1C),[7,8a] and terminal alkynes (Sonogashira coupling)[8b] (Scheme 1D).



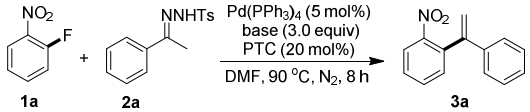
Scheme 1 Palladium-catalyzed cross-coupling with *ortho*-nitro aryl fluorides

On the other hand, *N*-tosylhydrazones, which are easily prepared from aldehydes or ketones, have received considerable attention as nucleophilic components in transition-metal-catalyzed cross-coupling reactions based on a metal carbene migratory insertion process.[9] In this context, we and others have explored a set of metal-catalyzed cross-coupling reactions with various coupling partners such as aryl halides,[10] aryl sulfonates,[11] benzyl halides,[12] alkynes,[13] azoles,[14] arylboronic acids,[15] and isocyanides.[16] However, among the various cross-coupling partners with carbenes, aryl fluorides are still lacking (Scheme 1E). As a continuation of our interest in the cross-coupling based on migratory insertion of palladium carbene, we herein report a palladium-catalyzed cross-coupling reaction of electron-deficient aryl fluorides with *N*-tosylhydrazones *via* C-F bond activation.

At the outset of the investigation, we examined the cross-coupling of 1-fluoro-2-nitrobenzene **1a** with *N*-tosylhydrazone **2a** in the presence of 5 mol% $Pd(PPh_3)_4$ in DMF at 90 °C. After preliminary screening of bases, Cs_2CO_3 turned out to be the suitable base (Table 1, entries 1-3). In view of the fact that phase-transfer catalysts (PTC) can facilitate the dissolution of Cs_2CO_3 and the subsequent conversion of the *N*-tosylhydrazone into the corresponding diazo intermediate, several typical PTC were tested in the reaction. We found that all the PTC except tetrabutylammonium acetate can effectively improve the reaction yield (Table 1, entries 4-11). The results revealed that tetrabutylammonium chloride (TBAC) was the best choice for the reaction; affording the desired product in a yield of 81% (Table 1, entry 8). On the contrary, using tetraethylammonium bromide (TEAB) as the PTC resulted in slightly diminished yield (Table 1, entry 9).

[a] *Department of Chemistry & Chemical Engineering, Gannan Normal University, Ganzhou 341000, China*
[b] *Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China. E-mail: wangjb@pku.edu.cn*
† Electronic supplementary information (ESI) available: Experimental details, Characterization data. See DOI: 10.1039/x0xx00000x

Table 1. Optimization of reaction conditions for the Pd-catalyzed cross-coupling of aryl fluoride **1a** with *N*-tosylhydrazone **2a**[a]



1a **2a** **3a**

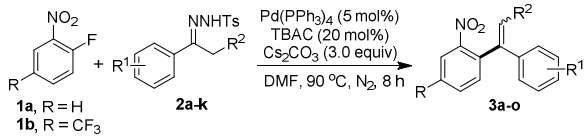
Entry	Base	PTC	Yield[b] (%)
1	*t*BuOLi	--	0
2	K_2CO_3	--	28
3	Cs_2CO_3	--	50
4[c]	Cs_2CO_3	--	5
5	Cs_2CO_3	nBu_4NI	54
6	Cs_2CO_3	nBu_4NI	72
7	Cs_2CO_3	$nBu_4NSO_2CF_3$	76
8	Cs_2CO_3	nBu_4NCl	81
9	Cs_2CO_3	Et_4NBr	78
10	Cs_2CO_3	nBu_4NAc	40
11	Cs_2CO_3	Et_3BnNBr	59

[a] Unless otherwise noted, the reaction conditions are as follows: **1a** (0.3 mmol), **2a** (0.6 mmol), DMF (3 mL). [b] Yield was determined by ^{1}H NMR using CH_3NO_2 as the internal standard. [c] Under open air.

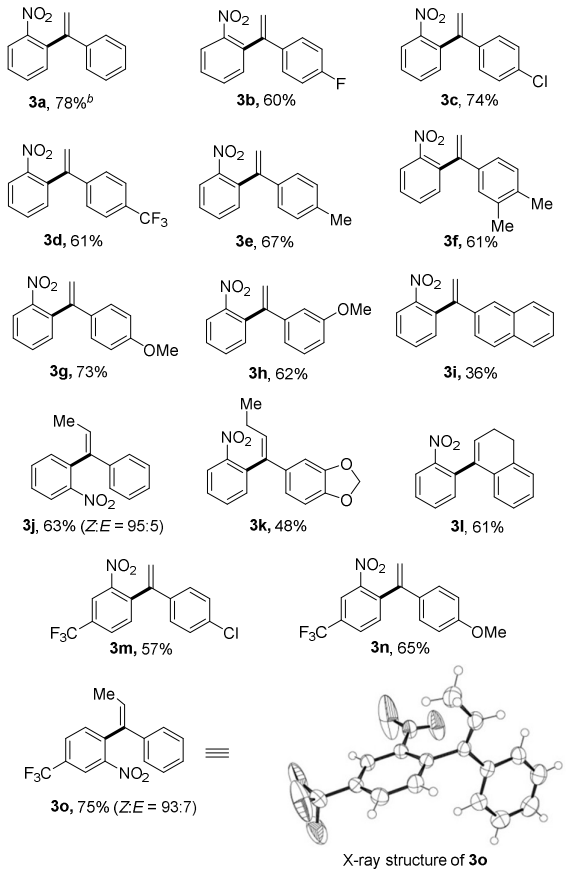
With the optimized reaction conditions, we then proceeded to explore the scope of the cross-coupling reaction with various *N*-tosylhydrazones and aryl fluorides, using 1-fluoro-2-nitrobenzene **1a** and 2-nitrofluorobenzene bearing *p*-CF_3 (**1b**) as the fluoride substrates. The results are summarized in Table 2. In general, the aryl *N*-tosylhydrazones bearing either electro-withdrawing or electro-donating groups react smoothly to afford the corresponding cross-coupling reaction products in moderate to good yields. For the substrate of *N*-tosylhydrazone with naphthalene group, the reaction gave a little diminished yield of the product **3i**. It is noted that the reaction could afford the trisubstituted olefins by using *N*-tosylhydrazones bearing alkyl substituents other than a methyl group (**3j-l** and **3o**). The excellent regioselectivity was observed, affording predominantly *Z*- isomers (**3j, 3k, 3o)**. The X-ray crystallographic analysis of **3o** has unambiguously confirmed that the cross-coupling product has a *Z*-configuration.[17] In addition, the aliphatic *N*-tosylhydrazones were also used to explore the possibility of the cross-coupling, but no desired product could be detected under the typical conditions.

We subsequently turned our attention to explore the substrate scope of this strategy. The reaction of 2-nitrofluorobenzenes bearing different groups with *N*-tosylhydrazone **2a** was investigated. The results are summarized in Table 3. The reactions could afford the cross-coupling products in moderate to good yields by using different 2-nitrofluorobenzenes bearing *m*-Me, *p*-Me, *p*-CN, and *p*-CF_3 groups. To our delight, good yields were obtained by using 1-fluoro-2-nitrobenzene and 2-nitrofluorobenzene bearing *p*-CF_3 group. The structure of **4f** was established by X-ray crystallographic analysis.[17] However, only trace product **4e** was detected by ^{1}H NMR, which may be attributed to the fact that the product is unstable and easy to polymerize.

Table 2. Pd-catalyzed cross-coupling of aryl fluorides with various *N*-tosylhydrazones[a]



1a, R = H
1b, R = CF_3 **2a-k** **3a-o**



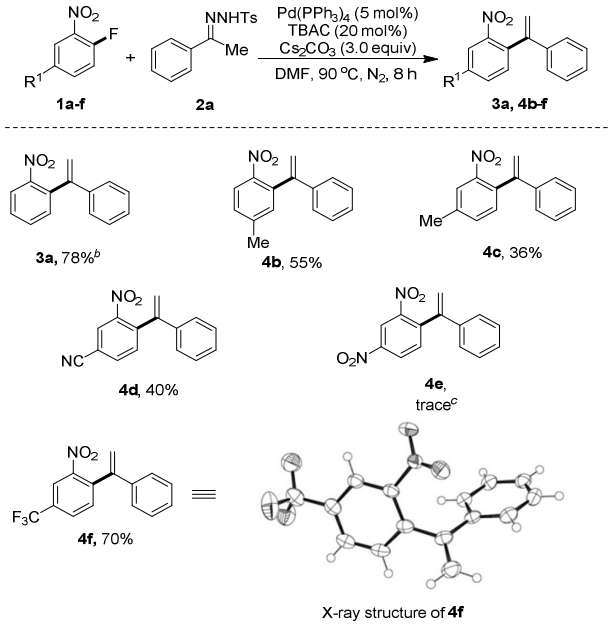
[a] Unless otherwise noted, the reaction conditions are as follows: **1** (0.3 mmol), **2** (0.6 mmol), DMF(3 mL). [b] All the yields refer to isolated yields.

A plausible mechanism is proposed as shown in Scheme 2. The reaction is initiated by the C-F activation reaction, in which the nitro group directs the S_NAr-type process to give the palladium(II) intermediate **A**,[6] leading directly to the C-F oxidative addition intermediate **B**.[18] Diazo compound **C** is generated *in situ* from *N*-tosylhydrazone **2a** with treatment of base.[19] The reaction of diazo compound **C** with aryl palladium complex **B** would produce palladium carbene intermediate **D**. Migratory insertion of the aryl group to the carbenic carbon gives the alkyl palladium complex **E**, from which β-hydride elimination would provide the arylated olefin **3a** and regenerate the Pd(0) catalyst with the aid of base.

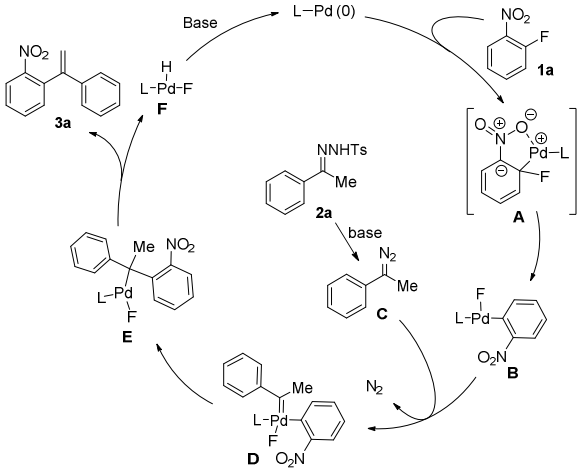
In summary, we have demonstrated a Pd-catalyzed cross-coupling reaction of aryl fluorides with various aryl *N*-tosylhydrazones. This reaction constitutes an efficient method for

the synthesis of di- and trisubstituted olefins. Mechanistically, this approach involves C-F bond activation and migratory insertion of palladium carbene as the two key steps. Since the reaction conditions are mild and the relevant aryl fluorides and palladium catalyst are commercially available, this reaction may find useful applications in organic synthesis.

Table 3. Pd-catalyzed cross-coupling of aryl fluorides with **2a**[a]



[a] Unless otherwise noted, the reaction conditions are as follows: **1a-f** (0.3 mmol), **2a** (0.6 mmol), DMF (3 mL). [b] Yields of isolated product unless otherwise noted. [c] Detected by ^{1}H NMR spectra.



Scheme 2 Proposed mechanism for the Pd-catalyzed cross-coupling of aryl fluorides with *N*-tosylhydrazones.

The project is supported by National Basic Research Program (973 Program, No. 2012CB821600) and Natural Science Foundation of China (Grant 21472004 and 21332002).

Notes and references

1 (a) J. L. Kiplinger, T. G. Richmond, C. E. Osterberg, *Chem. Rev.*,1994, **94**, 373; (b) H. Amii, K. Uneyama, *Chem. Rev.*, 2009, **109**, 2119.
2 V. V. Grushin, *Acc. Chem. Res.*, 2010, **43**, 160.
3 (a) C. Douvris, O. V. Ozerov, *Science*, 2008, **321**, 1188; (b) R. N. Perutz, *Science*, 2008, **321**, 1168.
4 E. Clot, O. Eisenstein, N. Jasim, S. A. Macgregor, J. E. McGrady, R. N. Perutz, *Acc. Chem. Res.*, 2011, **44**, 333.
5 See recent reviews: (a) T. Ahrens, J. Kohlmann, M. Ahrens, T. Braun, *Chem. Rev.*, 2015, **115**, 931; and references therein; (b) M. F. Kuehnel, D. Lent, T. Braun, *Angew. Chem., Int. Ed.*, 2013, **52**, 3328.
6 For selected examples, see: (a) T. Schaub, M. Backes, U. Radius, *J. Am. Chem. Soc.*, 2006, **128**, 15964; (b) L. Ackermann, R. Born, J. H. Spatz, D. Meyer, *Angew. Chem., Int. Ed.*, 2005, **44**, 7216; (c) M. Tobisu, T. Xu, T. Shimasaki, N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 19505; (d) J. Terao, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.*, 2003, **125**, 5646; (e) W.-H. Guo, Q.-Q. Min, J.-W. Gu, X. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, DOI: 10.1002/anie.201500124.
7 (a) Y. M. Kim, S. Yu, *J. Am. Chem. Soc.*, 2003, **125**, 1696; (b) D. A. Widdowson, R. Wilhelm, *Chem. Commun.*, 2003, 578.
8 (a) M. R. Cargill, G. Sandford, A. J. Tadeusiak, D. S. Yufit, J. A. K. Howard, P. Kilickiran, G. Nelles, *J. Org. Chem.*, 2010, **75**, 5860; (b) M. R. Cargill, G. Sandford, P. Kilickiran, G. Nelles, *Tetrahedron*, 2013, **69**, 512.
9 For reviews, see: (a) Y. Zhang, J. Wang, *Eur. J. Org. Chem.*, 2011, 1015; (b) J. Barluenga, C. Valdés, *Angew. Chem., Int. Ed.*, 2011, **50**, 7486; (c) Z. Shao, H. Zhang, *Chem. Soc. Rev.*, 2012, **41**, 560; (d) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.*, 2013, **46**, 236; (e) Y. Zhang, J. Wang, *Top. Curr. Chem.*, 2012, **327**, 239; (f) Y. Xia, Y. Zhang, J. Wang, *ACS Catal.*, 2013, **3**, 2586.
10 For selected examples, see: (a) J. Barluenga, P. Moriel, C. Valdés, F. Aznar, *Angew. Chem., Int. Ed.*, 2007, **46**, 5583; (b) J. Barluenga, N. Quiñones, M.-P. Cabal, F. Aznar, C. Valdés, *Angew. Chem., Int. Ed.*, 2011, **50**, 2350; (c) J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Chem. Eur. J.*, 2010, **16**, 12801; (d) J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Adv. Synth. Catal.*, 2010, **352**, 3235; (e) J. Barluenga, M. Tomas-Gamasa, P. Moriel, F. Amar, C. Valdés, *Chem. Eur. J.*, 2008, **14**, 4792; (f) Y. Xia, F. Hu, Z. Liu, P. Qu, R. Ge, C. Ma, Y. Zhang, J. Wang, *Org. Lett.*, 2013, **15**, 1784.
11 (a) B. Treguier, A. Hamze, O. Provot, J. D. Brion, M. Alami, *Tetrahedron Lett.*, 2009, **50**, 6549; (b) J. Barluenga, L. Florentino, F. Aznar, C. Valdés, *Org. Lett.*, 2010, **13**, 510.
12 (a) Q. Xiao, J. Ma, Y. Yang, Y. Zhang, J. Wang, *Org. Lett.*, 2009, **11**, 4732; (b) X. Wang, Y. Xu, Y. Deng, Y. Zhou, J. Feng, G. Ji, Y. Zhang, J. Wang, *Chem. Eur. J.*, 2014, **20**, 961.
13 (a) Q. Xiao, Y; Xia, H; Li, Y; Zhang, J. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 1114; (b) L. Zhou, Y. Shi, Q. Xiao, Y. Liu, F. Ye, Y. Zhang, J. Wang, *Org. Lett.*, 2011, **13**, 968; (c) F. Ye, X. Ma, Q. Xiao, H. Li, Y. Zhang, J. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 5742.
14 (a) T. Yao, K. Hirano, T. Satoh, M. Miura, *Angew. Chem., Int. Ed.*, 2012, **51**, 775; (b) X. Zhao, G. Wu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 3296.
15 X. Zhao, J. Jing, K. Lu, Y. Zhang, J. Wang, *Chem. Commun.*, 2010, **46**, 1724.
16 F. Zhou, K. Ding, Q. Cai, *Chem. Eur. J.*, 2011, **17**, 12268.
17 CCDC 1406907 and 1406908 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
18 (a) T. Braun, R. N. Perutz, M. I. Sladek, *Chem. Commun.*, 2001, 2254; (b) T. Braun, V. Schorlemer, B. Neumann, H. G. J. Stammler, *Fluorine Chem.*, 2006, **127**, 367; (c) V. V. Grushin, W. J. Marshall, *Angew. Chem., Int. Ed.*, 2002, **41**, 4476.
19 W. R. Bamford, T. S. Stevens, *J. Chem. Soc.*, 1952, 4735.