DOI: 10.1002/chem.200903235

Pd-Catalyzed C–N Bond Formation with Heteroaromatic Tosylates

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Dedicated to Professor Anders Kjær on the occasion of his 90th birthday

Abstract: A protocol for the palladium(0)-catalyzed amidation of heteroaromatic tosylates was successfully developed. The methodology proved to be effective for a variety of heteroaryl tosylates including the pyridine, pyrimidine, quinoline and quinoxaline ring systems. Successful carbon–nitrogen bond formation with these heteroaryl tosylates could be performed with a wide range of primary amides, oxazolidinones, lactams, anilines and indoles, including one cyclic urea. Moreover, this C–N bond forming reaction provided products with high structural diversity. The coupling reaction was also amenable to scale up applications.

Keywords: aryl tosylates · heterogeneous catalysis · C–N bond formation · heterocycles · palladium

Introduction

Palladium-catalyzed C–N bond forming reactions represent important transformations for the functionalization of aromatic ring systems with applications in both academia and industry.[1] Whereas these reactions have traditionally been performed with aryl halides and triflates, increasing efforts have been undertaken in recent years to extrapolate these transformations to other derivatives such as aryl tosylates.[2] In particular, this latter class of starting materials has several advantages such as 1) typically higher crystallinity compared with triflates or halides, which facilitates their handling, 2) superior chemical stability compared with the triflates, and 3) the generally greater accessibility of heteroaryl alcohols compared with the corresponding halides.

Nitrogen heterocycles are important constituents of many pharmacologically active compounds and organic materials and hence facile methods for the introduction of a range of ring substituents are of high interest.[3] We have recently reported the aptitude of 2-pyridyl tosylates and other heteroaryl tosylates, being easily accessible from the corresponding alcohols, to undergo effective Pd-catalyzed Mizoroki–Heck reactions with electron-rich alkenes, providing a rapid route to precursors of benzylic amines and aryl ketones.[4] Furthermore, we demonstrated that the same substrates could participate in Fe-mediated cross-coupling reactions with a variety of Grignard reagents.[5] In this paper, we expand the application of these heteroaromatic tosylates to include Pd-catalyzed amidation reactions with a variety of heteroaromatic tosylates. This protocol appears highly suitable for introducing a wide range of amide structures, as well as other related nitrogen-based nucleophiles such as anilines and indoles.

Results and Discussion

The work presented here began with the intention of developing general reaction conditions for the Mizoroki–Heck reaction between heteroaromatic tosylates and electron-poor olefins. Initial efforts in this line were not so successful and after considerable screening the best results obtained in the coupling of 2-pyridyl tosylate (**1**) with *tert*-butyl acrylamide (**2**) employed a palladium catalyst prepared from $Pd(OAc)_2$ and X-Phos, providing the desired coupling product **3** in approximately 30% yield (Scheme 1). Attempts to improve the yield by replacing the acrylamide with the *N*-acryloyl oxazolidinone (**4**) were not rewarding, but interestingly the amidation product **5** could be isolated in a 20% yield. Suspecting that this product arose from the high-temperature decomposition of the olefin **4** to 2-oxazolidinone (**6**) under

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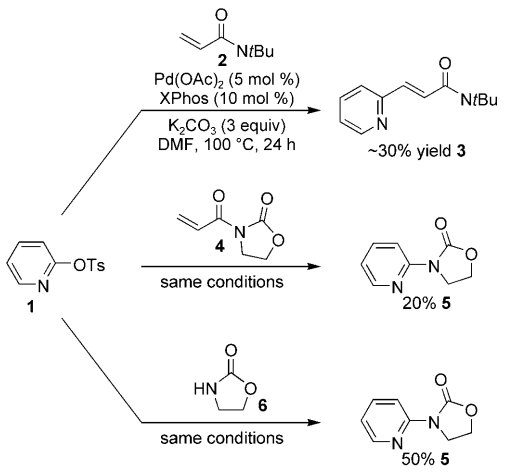
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903235.

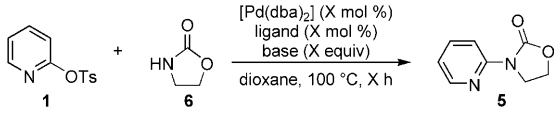


Scheme 1. Discovery of amidation protocol with heteroaromatic tosylates.

the reaction conditions followed by a Pd^0-catalyzed amidation, we decided to pursue the possibility of using the heteroaromatic tosylates for C–N bond formation. Hence, using the same reaction conditions and substituting **4** with **6**, the coupling yield of **5** could be improved to 50%.

In an effort to improve this amidation reaction, we examined other reaction conditions (ligand, base and solvent), the results of which are depicted in Table 1. The combination of $[Pd(dba)_2]$/DPPF as catalyst, K_2CO_3 as base and dioxane as solvent was chosen as starting point for the reaction between 2-pyridyl tosylate (**1**) and 2-oxazolidinone (**6**) and proved effective in promoting the reaction (entry 1).

Table 1. Optimization of amidation conditions.



Entry	Ligand ([%])	Base (equiv)	t [h]	Yield [%][a] (conversion [%])[b]
1[c]	DPPF (5)	K_2CO_3 (3)	24	99 (100)
2[c]	DPPP (5)	K_2CO_3 (3)	24	nd (76)
3[c]	DPPE (5)	K_2CO_3 (3)	24	nd (0)
4[c]	DPPPe (5)	K_2CO_3 (3)	24	nd (14)
5[c]	1,10-phenanthroline (5)	K_2CO_3 (3)	24	nd (0)
6[c]	BINAP (5)	K_2CO_3 (3)	24	91 (100)
7[c]	BDPPP (5)	K_2CO_3 (3)	24	88 (100)
8[c]	D*i*PrPF (5)	K_2CO_3 (3)	24	99 (100)
9[c]	D*t*BuPF (5)	K_2CO_3 (3)	24	99 (100)
10[c]	DPPF (3)	K_2CO_3 (3)	24	94 (100)
11[c]	DPPF (1)	K_2CO_3 (3)	24	nd (63)
12[d]	DPPF (3)	K_2CO_3 (3)	16	99 (100)
13[e]	DPPF (3)	K_2CO_3 (3)	16	nd (96)
14[d]	DPPF (3)	K_2CO_3 (2)	16	99 (100)
15[f]	DPPF (3)	K_2CO_3 (2)	16	95 (100)
16[d]	DPPF (3)	Na_2CO_3 (2)	16	91 (100)
17[d]	DPPF (3)	Cs_2CO_3 (2)	16	nd (0)

[a] Yield of the isolated product. nd = not determined [b] Conversions in parentheses are measured by ^{1}H NMR analysis of crude reaction mixture. [c] 3 equivalents of **6**. [d] 1.5 equivalents of **6**. [e] 1.2 equivalents of **6**. [f] 1 equivalent of **6**, 1.5 equivalents of **1**.

Screening other diphosphine ligands disclosed that the two ferrocene ligands, D*i*PrPF and D*t*BuPF, were equally effective as DPPF (entries 8 and 9).[6] Diphosphines bridged by aliphatic chains showed that a propyl spacer was more efficient than both ethyl and pentyl, suggesting that the bite angle of the bidentate ligands is important for catalytic activity (entries 2–4). Applying the nitrogen-based ligand phenanthroline resulted in a complex mixture of products (entry 5). On the other hand, BINAP and BDPPP also provided good coupling yields (entries 6 and 7), but still slightly less efficient than that of the ferrocene based ligands. Control experiments conducted in the absence of catalyst or ligand, resulted in no coupling yields (results not shown).

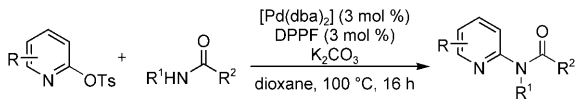
Changing the solvent to toluene lowered the yield to 74% (result not shown). The amount of DPPF was successfully lowered to 3 mol% (entry 10); however, 1 mol% of DPPF resulted in a considerable drop in conversion (entry 11). Likewise, the amount of **6** was lowered to 1.5 equivalents (entries 12 and 13) and the lower limit for K_2CO_3 was found to be 2 equivalents (entry 14). Switching the stoichiometry of the two starting materials lowered slightly the yield of the reaction to 95% (entry 15). Finally, two other bases were tested for this amidation reaction. Na_2CO_3 resulted in a comparable yield to K_2CO_3 (entry 16), whereas Cs_2CO_3 (entry 17) produced a complex mixture of products.

The optimized conditions were then tested on a variety of heteroaryl tosylates in combination with different types of amides and similar nitrogen-based nucleophiles. Generally, the amidations went to completion within 16 h and the products could be isolated by column chromatography in good to excellent yields. At first, a number of primary amides were applied in the amidation of heteroaromatic tosylates (Table 2, entries 1–8). The steric bulk of the amide influenced the yield in the coupling with **1**, as shown in entries 1–3. Whereas the isopentanoyl and isobutyryl amides led to high yields, coupling with the pivaloyl amide provided a 57% yield of the desired product. Other heteroaryl tosylates including the pyrimidine, quinoline and quinoxaline skeleton proved equally suitable for coupling with primary amides including cyclopropanecarboxamide (entries 5–8).

In entries 9–11, it is shown that 2-oxazolidinones can also be coupled to different heterocycles demonstrating the high efficiency of this coupling procedure for C–N bond formation with cyclic carbamates. Interestingly, the 2,4-ditosylated quinoline underwent selective monocoupling at the 2-position in a 91% isolated yield without formation of the double coupled product (entry 12).

While acyclic secondary amides failed to couple with the heteroaromatic tosylates in satisfactory yields under the applied conditions, lactams demonstrated to be good nucleophiles for the amidations (entries 13–16).[7] Five- and seven-membered lactams provided good yields of the amidation products and, gratifyingly, even a β-lactam could be exploited effectively for C–N bond formation with a pyrimidyl tosylate (entry 16).

Table 2. Primary amides, lactames and oxazolidinones in the amidation of heteroaromatic tosylates.



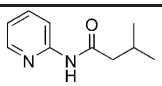
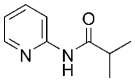
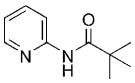
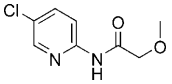
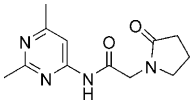
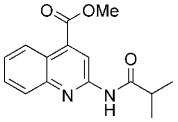
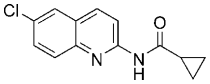
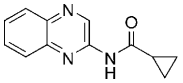
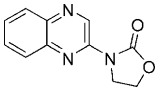
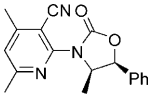
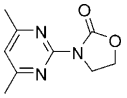
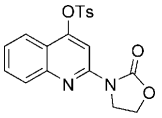
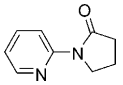
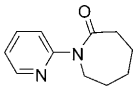
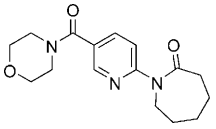
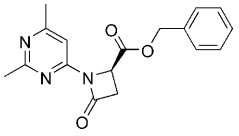
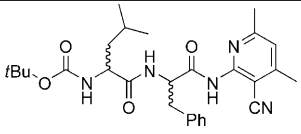
Entry[a]	Product	Cpd.	Yield [%][b]
1		**7**	92
2		**8**	99
3		**9**	57
4		**10**	86
5		**11**	99
6		**12**	99
7		**13**	65
8		**14**	94
9		**15**	98
10		**16**	95
11		**17**	97
12		**18**	91[c]
13		**19**	83
14		**20**	94
15		**21**	97
16		**22**	69

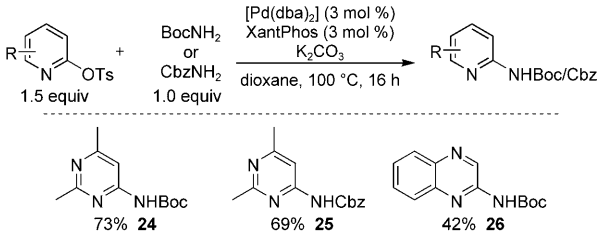
Table 2. (Continued)

Entry[a]	Product	Cpd.	Yield [%][b]
17		**23**	79[d]

[a] 1.5 equivalents of nitrogen-based nucleophile. [b] Yield of the isolated product. [c] Reaction performed on a 0.5 mmol scale with ditosylate 1.5 equiv and **6** 1 equiv [d] Obtained as epimers.

The tolerance of a tertiary carbon next to the amide carbonyl (entry 2) led us to examine a dipeptide with a *C*-terminal amide (entry 17). Its coupling with a substituted pyridyl tosylate could be effectively promoted and no traces of coupling products to the secondary amide or carbamate were observed. Nevertheless, epimerization proved to be problematic under this coupling protocol, which is undoubtedly related to the use of base at 100 °C in dioxane.[8]

On the other hand, primary carbamates were sluggish using this amidation protocol. However, a good yield of the desired coupling products could be obtained upon modifying the reaction conditions slightly and applying Xantphos as the ligand (Scheme 2).[9]



Scheme 2. Couplings with primary carbamates.

Double amidation reactions were also quite effective as illustrated with the products in Figure 1. Mono-substituted urea derivatives failed to provide more than 65% conversion (results not shown), however, the cyclic urea, 2-imidazolidinone, was applied in a double coupling with **1** providing the *N,N′*-disubstituted urea **27** in an excellent 99% yield. Double coupling with oxamide provided the double amidation product **28** in a 76% yield. Two C–N bond formations with ditosylates as starting materials likewise produced the double amidation products **29** and **30** in excellent yields.

We then tested the coupling protocol on aminations with anilines as the nitrogen nucleophile (Figure 2).[10] Three anilines with electron-donating and -withdrawing groups all provided coupling products **31**–**33** in excellent yields. Even indoles were satisfactory nucleophiles for these transformations as shown with the product **34** obtained in a 68% yield.[11] In Scheme 3, it is demonstrated how three consecutive transition-metal-catalyzed transformations can be exploited including the application of our C–N bond protocol for the synthesis of a highly functionalized indole skeleton. We recently published a two-step Au^{I}-catalyzed hydroami-

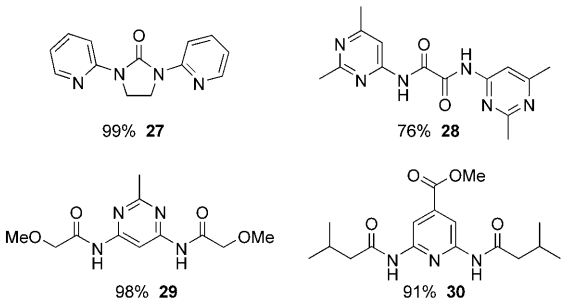


Figure 1. Double amidations.

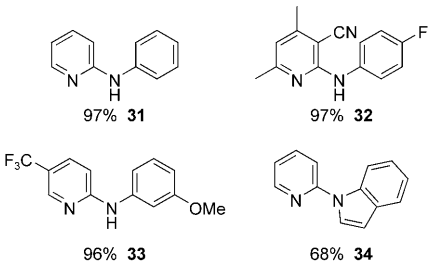
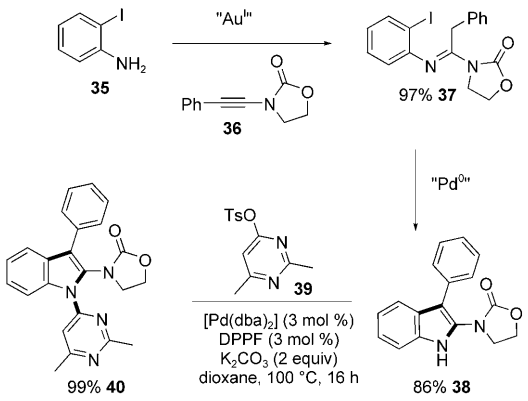


Figure 2. Indole and anilines as nucleophiles in the Pd-catalyzed amidation.

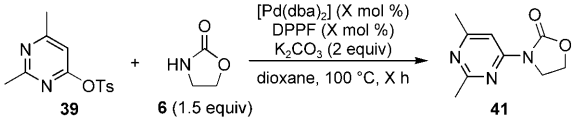


Scheme 3. Synthesis of highly substituted indole with Au and Pd catalysis.

nation of anilines with ynamides followed by a Pd^0-promoted cyclization step.[12] Subsequent amination of the 2,3-substituted indole **38** with the pyrimidyl tosylate **39** furnished the trisubstituted indole derivative **40** in a 99% yield.

Next, we decided to investigate the potential for scale-up application of the amidation reaction, which is illustrated in Table 3 for the coupling of the pyrimidyl tosylate **39** with **6**. Initial studies were conducted on a 3 mmol scale representing ten times the scale used in the previous couplings. Running these coupling reactions at a higher concentration and lowering the catalytic loading to 1 and 0.5 mol% provided **41** in quantitative yield (entries 1 and 2). Even a catalyst loading of 0.1% palladium and ligand provided **41** in quantitative yield in 1.5 h, corresponding to a TON of 3000

Table 3. Scale-up amidation.

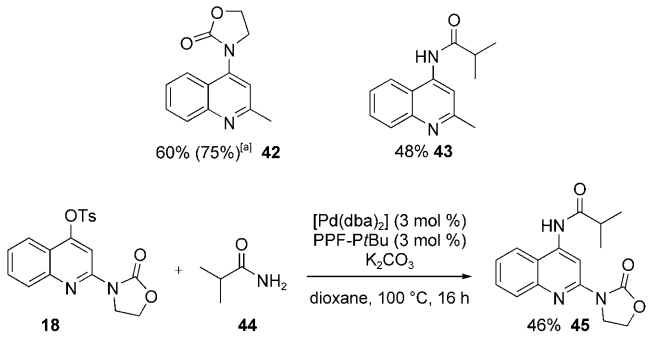


Entry	Scale [mmol]	Catalytic loading [%]	*t* [h]	Yield [%][a] (conversion [%])
1	3	1	16[b]	99
2	3	0.5	1.25	99
3	3	0.1	1.5	99
4	3	0.01	48	(41)[c]
5	20	0.1	1	96

[a] Yield of the isolated product. [b] Time not optimized. [c] Conversion based on **6**.

(entry 3). A catalytic loading of 0.01% resulted in 41% conversion after a reaction time of 48 h (entry 4). Finally, the scale was increased to 20 mmol of the pyrimidyl tosylate **39** and after one hour with 0.1% catalyst loading, the amidation product **41** could be isolated in an excellent 96% yield (3.7 g) (entry 5).

Finally, the possibility of applying pyridines with tosylates either in 3- or 4-position was investigated and the preliminary results are discussed below. Whereas attempts to apply 3-pyridyl tosylates in the amidation protocol failed, some interesting results were obtained using 2-methyl-4-tosyl quinoline.[2b] When this tosylate was subjected to the standard conditions using 2-oxazolidinone as the coupling partner a roughly 10% conversion was obtained (result not shown). Changing the ligand to D*t*BuPF resulted in a 60% isolated yield of **42** (Scheme 4). Also isobutyramide (**44**), a primary amide, proved sufficiently reactive affording **43** in a 48% isolated yield. Comparing **42** and **43** to the product obtained in Table 2, entry 12, suggests the possibility of sequential double couplings using **18** as reactant. Applying isobutyramide D*t*BuPF only afforded approximately 13% isolated yield of **45**. On the other hand, switching to the JosiPhos type ligand PPF-P*t*Bu,[6] **45** could be secured in an acceptable 46% isolated yield (Scheme 4).[13]



Scheme 4. Couplings with 4-tosylated quinolines. [a] Reaction run with $Pd(OAc)_2$.

Conclusion

We have successfully developed a protocol for the palladium-catalyzed amidation of heteroaromatic tosylates where the simple diphosphine ligand DPPF proved highly effective. A range of heteroaromatic tosylates including the pyridine, pyrimidine, quinoline and quinoxaline ring systems could be applied, in combination with a number of primary amides, lactams, oxazolidinones, anilines and indoles. Increased catalytic activity was observed in a large-scale reaction using catalyst loading of only 0.1%. Further efforts are currently underway to increase the scope of this methodology to include other heteroaromatic systems and to obtain an optimized protocol for the 4-pyridyl tosylate derivatives. This work will be reported in due course.

Experimental Section

General procedure for amidations of heteroaromatic tosylates with amides and carbamates: The pyridyl tosylate (1 equiv), amide/carbamate (1.5 equiv), K_2CO_3 (2 equiv), DPPF (0.03 equiv) and [Pd(dba)$_2$] (0.03 equiv) were dissolved in dioxane (2 mL) and the sample vial was fitted with a Teflon sealed screw cap and removed from the glove box. The reaction mixture was heated for 16 h at 100 °C. The crude reaction was filtered through Celite washing with CH_2Cl_2. After concentration in vacuo, the crude product was purified by column chromatography.

***N*-(2,6-Dimethylpyrimidin-4-yl)-2-(2-oxopyrrolidin-1-yl)acetamide (11)**: Compound **39** (83.5 mg, 0.30 mmol), 2-(2-oxopyrrolidin-1-yl)acetamide (64.0 mg, 0.45 mmol), K_2CO_3 (82.9 mg, 0.60 mmol), DPPF (5.0 mg, 0.009 mmol) and [Pd(dba)$_2$] (5.2 mg, 0.009 mmol) were dissolved in dioxane (2 mL) and reacted for 16 h at 100 °C. The crude product was purified by flash chromatography on silica gel using MeOH/CH_2Cl_2 3:97. This afforded 74.0 mg of the title compound (99% yield) as a colorless solid. M.p. 169–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (br s, 1H), 7.76 (s, 1H), 4.11 (s, 2H), 3.54 (t, 2H, J = 7.2 Hz), 2.55 (s, 3H), 2.50 (t, 2H, J = 8.0 Hz), 2.46 (s, 3H), 2.17–2.10 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 169.1, 167.7, 167.5, 156.9, 106.2, 48.6, 48.2, 30.3, 25.8, 24.6, 18.2 ppm; HRMS (ESI): m/z: calcd for $C_{12}H_{16}N_4O_2Na$: 271.1171, found: 271.1171 [M+Na$^+$].

General procedure for double amidations: The diamide or ditosylate (1 equiv), heteroaryl tosylate or amide (3 equiv), K_2CO_3 (4 equiv), DPPF (0.06 equiv) and [Pd(dba)$_2$] (0.06 equiv) were dissolved in dioxane (2 mL) and the sample vial was fitted with a Teflon sealed screw cap and removed from the glove box. The reaction mixture was heated for 16 h at 100 °C. The crude reaction was filtered through Celite washing with CH_2Cl_2. After concentration in vacuo, the crude product was purified by column chromatography.

1,3-Di(pyridin-2-yl)imidazolidin-2-one (27): 2-Imidazolidinone (25.8 mg, 0.3 mmol), **1** (224.4 mg, 0.9 mmol), DPPF (10.0 mg, 0.018 mmol) and [Pd(dba)$_2$] (10.4 mg, 0.018 mmol) were dissolved in dioxane (2 mL) and reacted for 16 h at 100 °C. The crude product was purified by flash chromatography on silica gel using Et_2O/CH_2Cl_2 3:97 as eluent. This afforded 71.5 mg of the title compound (99% yield) as a colorless solid. M.p. 182–183 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35–8.30 (m, 4H), 7.68 (ddd, 2H, J = 8.4, 7.2, 1.6 Hz), 6.98 (ddd, 2H, J = 7.2, 5.2, 1.2 Hz), 4.19 ppm (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 152.3, 147.6, 137.5, 118.5, 113.5, 40.8 ppm; HRMS (ESI): m/z: calcd for $C_{13}H_{12}N_4ONa$: 263.0909, found: 263.0905 [M+Na$^+$].

General procedure for aminations of heteroaromatic tosylates with anilines and indoles: The pyridyl tosylate (1 equiv), indole/aniline (1.5 equiv), K_2CO_3 (2 equiv), DPPF (0.03 equiv) and [Pd(dba)$_2$] (0.03 equiv) were dissolved in dioxane (2 mL) and the sample vial was fitted with a Teflon sealed screw cap and removed from the glove box. The reaction mixture was heated for 16 h at 100 °C. The crude reaction was filtered through Celite washing with CH_2Cl_2. After concentration in vacuo, the crude product was purified by column chromatography.

2-(4-Fluorophenylamino)-4,6-dimethylnicotinonitrile (32): 3-Cyano-4,6-dimethyl-2-pyridinyl tosylate (90.7 mg, 0.30 mmol), *p*-fluoroaniline (50.0 mg, 0.45 mmol), K_2CO_3 (82.9 mg, 0.60 mmol), DPPF (5.0 mg, 0.009 mmol) and [Pd(dba)$_2$] (5.2 mg, 0.009 mmol) were dissolved in dioxane (2 mL) and reacted for 16 h at 100 °C. The crude product was purified by flash chromatography on silica gel using CH_2Cl_2/pentane 33:67. This afforded 70.5 mg of the title compound (97% yield) as a colorless solid. M.p. 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (dd, 2H, J = 8.8, 4.8 Hz), 7.04 (dd, 2H, J = 8.8, 8.4 Hz), 6.89 (br s, 1H), 6.55 (s, 1H), 2.43 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 159.0 (d, J = 241.2 Hz), 156.1, 153.0, 135.2, 122.2 (d, J = 7.6 Hz), 116.4, 115.60, 115.59 (d, J = 22.2 Hz), 90.7, 25.0, 20.6 ppm; ^{19}F NMR (377 MHz, $CDCl_3$): δ = −120.0 ppm. HRMS (ESI) m/z: calcd for $C_{14}H_{12}FN_3Na$ [M+Na$^+$]: 264.0913, found: 264.0913.

Acknowledgements

We thank the Danish National Research Foundation, the Danish Council for Independent Research/Natural Science, the Lundbeck Foundation, the Carlsberg Foundation, the iNANO Graduate School and Aarhus University for generous financial support of this work.

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Received: November 26, 2009
Published online: April 6, 2010

