ORGANIC LETTERS

2012
Vol. 14, No. 7
1827–1829

N-Tosylcarboxamide as a Transformable Directing Group for Pd-Catalyzed C–H *Ortho*-Arylation

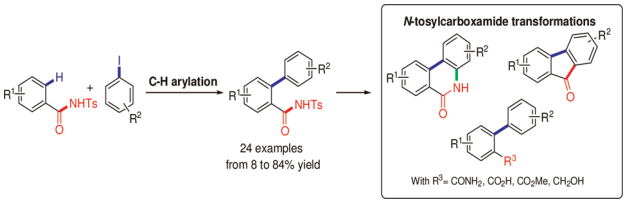
Florent Péron, Christine Fossey, Thomas Cailly, and Frédéric Fabis*

Université de Caen Basse-Normandie, EA 4258 CERMN - FR CNRS 3038 INC3M - SF 4206 ICORE, UFR des Sciences Pharmaceutiques, F-14032 Caen, France

frederic.fabis@unicaen.fr

Received February 21, 2012

ABSTRACT



The *N*-tosylcarboxamide group offers the possibility of directing the Pd-catalyzed C–H arylation of arenes providing a new entry to biarylcarboxamides. Moreover, its ability to react according to different reaction conditions including intramolecular reactions makes it a pivotal directing group for a divergent synthesis of biaryl-based compounds.

Palladium-catalyzed C–H arylation of directing-group-containing arenes has emerged as a powerful tool for the synthesis of biaryl compounds.[1] Numerous directing groups such as nitrogen-containing heterocycles,[2] anilides,[3] amides,[4] oximes,[5] benzylamines,[6] and carboxylic acids[7] have been used in the arylation of arenes, leading to a wide variety of important *ortho*-functionalized biaryl compounds. However, most of these groups were developed to achieve high regioselectivities and yields in the arylation step, but only a few of them were used for further transformations.[8,9] Very recently, the carboxylic acid group was described as a removable *ortho*-directing group for a formal *meta*-arylation reaction.[10] Some directing groups have been used in tandem *ortho*-arylation/intramolecular cyclization reactions to give straightforward access to biaryl-based heterocycles such as fluorenones[5,11] or phenanthrene derivatives.[11,12] Among them, *N*-substituted benzamides have been described for *ortho*-arylation and subsequent formation of fluorenone or phenanthridinone derivatives depending on the nitrogen substituent.[9,13] These cascade reactions using C–H arylation as the first step provide new perspectives for the construction of complex molecules starting from simple starting materials. Nevertheless, the issue of the second transformation is most often directing group-dependent. *O*-Acetyl oxime[14] and pyridylsilyl[15] groups have been recently described as

(1) For reviews, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (c) Daugulis, O.; Do, H. Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.

(2) Kaliani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331.

(3) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046–4048.

(4) Shabashov, D.; Daugulis, O. *Org. Lett.* **2006**, *8*, 2947–4949.

(5) (a) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9462–9465. (b) Sun, C. L.; Liu, N.; Li, B. J.; Yu, D. G.; Wang, Y.; Shi, Z. J. *Org. Lett.* **2010**, *12*, 184–187.

(6) Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211–5213.

(7) (a) Chiong, H. A.; Pham, Q. N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879–9884. (b) Giry, R.; Maugel, N.; Li, J. J.; Wang, D. H.; Breazzano, S. P.; Saunders, L. B.; Yu, J. Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511.

(8) Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720–7725.

(9) Shabashov, D.; Molina Maldonado, J. R.; Daugulis, O. *J. Org. Chem.* **2008**, *73*, 7818–7821.

(10) Cornella, J.; Righi, M.; Larrosa, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 9429–9432.

(11) Wang, D. H.; Mei, T. S.; Yu, J. Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676–17677.

(12) Gardeepan, P.; Parthasarathy, K.; Cheng, C. H. *J. Am. Chem. Soc.* **2010**, *132*, 8569–8571.

(13) (a) Karthikeyan, J.; Cheng, C. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 9880–9883. (b) Wang, G. W.; Yuan, T. T.; Li, D. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1380–1383.

(14) Neufeld, S. R.; Sanford, M. S. *Org. Lett.* **2010**, *12*, 532–535.

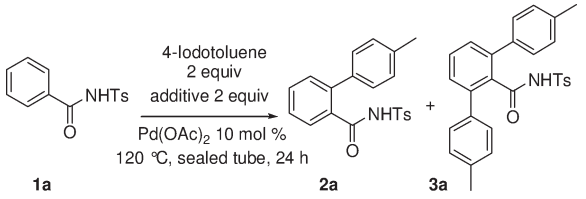
(15) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgian, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270–8272.

10.1021/ol3004244
Published on Web 03/22/2012

directing groups in the C−H acyloxylation of arenes and used for diverse subsequent transformations, but these examples remain rare, and suitable functional groups for C−H activation reactions followed by diverse transformations are still expected to extend this concept. Recently, the Falck group has disclosed, for the first time, the *N*-tosylcarboxamide group as an efficient directing group in the Pd- and Rh-catalyzed C−H olefination of arenes leading to isoindolinones in a one-pot procedure.[16] They also recently described the *N*-tosylcarboxamide-directed Rh-catalyzed C−H insertion of isocyanides followed by annulation leading to iminoisoindolinones.[17] In these works, the authors found that the NH acidity of the *N*-tosylcarboxamide group was essential for the reaction to take place. They postulated that the acidity of the NH facilitated the cyclometalation step. Starting from these results and the ability of the tosylamide to act as a good leaving group,[18] we reasoned that *N*-tosylcarboxamide could serve as an easily transformable directing group for Pd-catalyzed C−H arylation of arenes, allowing the synthesis of various biaryl-based compounds.

We started our investigations with the C−H arylation of *N*-tosylbenzamide **1a** with 4-iodotoluene, using $Pd(OAc)_2$ as a catalyst and silver salts as an additive in an acidic medium (Table 1). We found that *ortho*-arylation took place along with diarylation in a nearly 1:1 ratio using AcOH and Ag_2O at 120 °C (entry 1). Replacing AcOH by TFA led to decomposition of the starting material (entry 2). Whereas an excess of aryl iodide or Ag_2O did not allow any improvement of these results (entries 3 and 4), we found that AgOAc gave the best ratio of monoarylated/diarylated product (entries 5 and 6).

Table 1. Screening Conditions for the Pd-Catalyzed Arylation of **1a**



entry	solvent	additive	**1a/2a/3a**[a]
1	AcOH	Ag_2O	0/55/45
2	TFA	Ag_2O	0/0/0[b]
3[c]	AcOH	Ag_2O	0/28/72
4[d]	AcOH	Ag_2O	0/65/35
5[e]	AcOH	AgOAc	11/79/10
6	AcOH	AgOAc	9/82/9

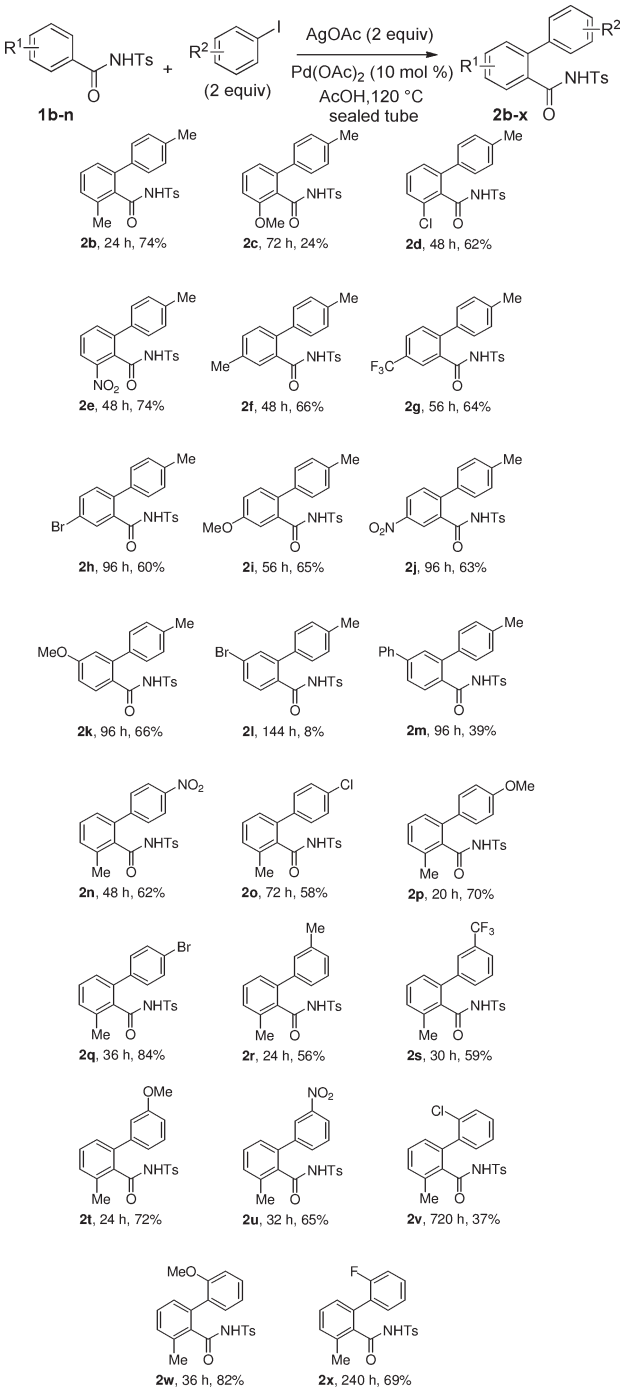
[a] HPLC/MS observed ratio using pure sample of material as references. [b] Degradation observed. [c] 4-Iodotoluene, 4 equiv. [d] Ag_2O, 4 equiv. [e] AgOAc, 4 equiv.

(16) (a) Zhu, C.; Falck, J. R. *Org. Lett.* **2011**, *13*, 1214–1217. (b) Zhu, C.; Falck, J. R. *Chem. Commun.* **2012**, *48*, 1674–1676.

(17) Zhu, C.; Xie, W.; Falck, J. R. *Chem.—Eur. J.* **2011**, *17*, 12591–12595.

(18) Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657–680.

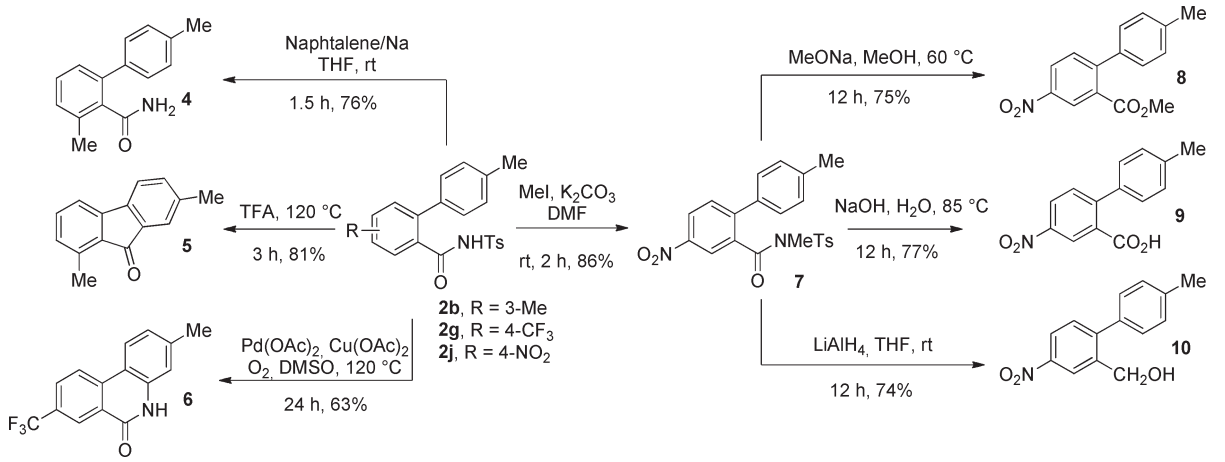
Scheme 1. Synthesis of Substituted *N*-Tosylbiphenyl-2-carboxamides **2b**−**x** by Pd-Catalyzed C−H Arylation[a]



[a] Reactions were carried out starting from 0.71 to 3.6 mmol of *N*-tosylbenzamides **1b**−**n**. Yields given are isolated yields.

With these optimized conditions, we evaluated the generality of the reaction using various substituted *N*-tosylbenzamides and iodoarenes. The results are summarized in Scheme 1. *Ortho*- and *meta*-substituted *N*-tosylbenzamides bearing either electron-withdrawing or -donating groups were efficiently arylated with 4-iodotoluene. Only the *para*-substituted benzamides were prone to diarylation leading to lower isolated yields in monoarylated compounds.

Scheme 2. Functional Transformations of *N*-Tosylbenzamides



The reaction was successfully applied to diversely substituted iodoarenes. Very interestingly, the reaction worked with *ortho*-substituted iodoarenes (compounds **2v**−**x**), even if extended reaction times were necessary for 2-chloro- and 2-fluoro- derivatives. These examples remain rare in Pd-catalyzed C−H arylation with *ortho*-substituted iodoarenes.[19] Overall, these results show that the *N*-tosylcarboxamide group can efficiently direct the Pd-catalyzed *ortho*-arylation of arenes.

We then turned our attention to the transformation of the *N*-acyl-*N*-tosyl group (Scheme 2). Starting from compound **2b**, the tosyl was easily removed using sodium/naphthalene in THF affording the primary biarylcarboxamide **4** in 76% yield. Activation of the carbonyl group of **2b** with TFA at 120 °C led to the fluorenone **5** in a clean and high yielding reaction exhibiting the ability of the tosylamide group to serve as a good leaving group.[18]

Using the conditions developed in the intramolecular palladium-catalyzed C−H amination of arenes for the construction of quinolones,[20] we were able, starting from **2g**, to directly access the detosylated phenanthridin-6(5*H*)-one **6** in a 63% isolated yield. We next investigated nucleophilic additions to *N*-tosylbenzenecarboxamides **2**. Due to its high acidity, previous methylation of the N−H group was necessary for nucleophilic additions to take place. Thus, basic hydrolysis of *N*-methylated biaryl compound **7** led to the carboxylic acid **9**, whereas addition of sodium methoxide led to the corresponding methyl ester **8**. Finally, the *N*-tosylcarboxamide group can easily be reduced to the corresponding benzyl alcohol **10** with $LiAlH_4$.

In summary, we have demonstrated that the *N*-tosylcarboxamide group represents one of the most efficient groups for both the Pd-catalyzed C−H arylation of arenes and further transformations including nucleophilic additions, electrophilic aromatic substitutions, and intramolecular C−H amination. The flexibility of this directing group allows, from a unique and simple starting material, for a wide variety of diversely *ortho*-functionalized biaryl compounds or substituted biaryl-based polycyclic structures to be easily obtained.

Acknowledgment. This work was supported by the CNRS and ERDF fundings. The IS:CE-Chem project and the Interreg IVA France-(Channel)-England program are gratefully thanked for their financial support.

Supporting Information Available. Detailed experimental procedures and characterization data. Copies of ^{1}H an ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) (a) René, O.; Fagnou, K. *Adv. Synth. Catal.* **2010**, *352*, 2116–2120. (b) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192–5196.

(20) Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. *J. Org. Chem.* **2010**, *75*, 3900–3903.

The authors declare no competing financial interest.