Pergamon

Tetrahedron Letters, Vol. 38, No. 36, pp. 6363-6366, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01464-0

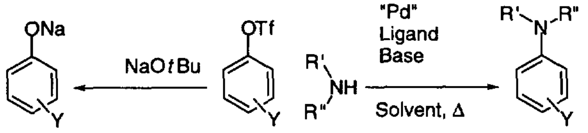
An Improved Method for the Palladium-Catalyzed Amination of Aryl Triflates

Jens Åhman and Stephen L. Buchwald*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139

Abstract: Aryl triflates are coupled with amines using catalytic amounts of $Pd(OAc)_2$ and BINAP and Cs_2CO_3 as a stoichiometric base. This protocol allows for the efficient amination of electron-poor as well as electron-rich aryl triflates and the reaction conditions are compatible with a wide variety of functional groups. © 1997 Elsevier Science Ltd.

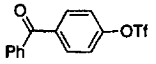
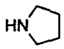
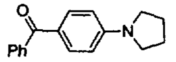
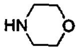
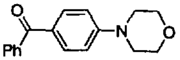
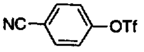
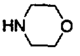
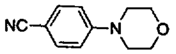
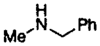
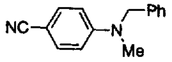
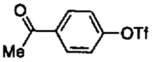
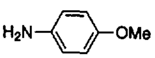
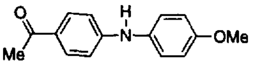
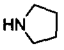
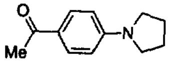
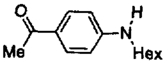
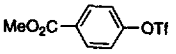
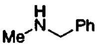
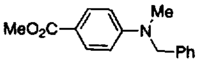
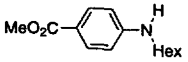
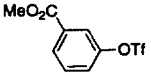
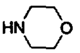
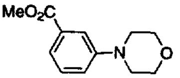
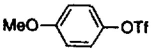
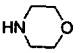
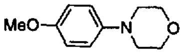
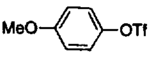
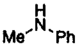
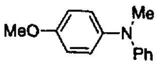
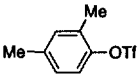
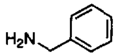
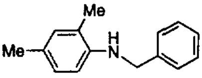
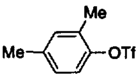
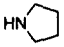
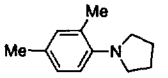
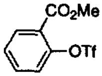
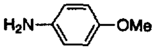
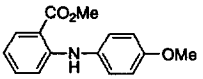
Recent reports from our laboratory and that of Hartwig described the palladium-catalyzed amination of aryl triflates.[1] These protocols employ palladium catalysts with chelating bis(phosphine) ligands and NaO*t*-Bu as base to couple aryl triflates with amines (Scheme 1). These procedures give moderate to excellent yields for electron-rich and electron-neutral aryl triflates but for electron-poor aryl triflates only modest yields were obtained. The low yields with electron-poor substrates were attributed to the rapid cleavage of the triflate by attack of NaO*t*-Bu on sulfur leading to the corresponding sodium phenoxide. The yields in these reactions could sometimes be improved by slow addition of the aryl triflate, but the effect of this procedure was very substrate dependent and it did not provide a general solution to the problem.[1b] Subsequent work in our laboratory led to the discovery that the use of Cs_2CO_3 in place of NaO*t*-Bu leads to improved functional group compatibility in the amination of aryl bromides.[2] Herein we report the use of Cs_2CO_3 as the base in the palladium-catalyzed amination of aryl triflates.



Scheme 1.

We found that a catalyst system composed of 3 mol % $Pd(OAc)_2$, 4.5 mol % BINAP, and Cs_2CO_3 as base is efficient for the coupling of electron-deficient aryl triflates with amines. Use of ligands such as DPPF, (*rac*)-PPF-OMe and P(*o*-tolyl)$_3$ gave, along with the desired anilines, considerable amounts of the reduced arene side products.[3] Use of other palladium sources such as $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ resulted in lower reaction rates. The catalyst system described above gave greatly improved yields in the amination of electron-deficient aryl triflates, compared to the corresponding yields reported for aminations using NaO*t*-Bu as base. For example, in the reactions of 4-benzoylphenyl triflate with pyrrolidine and morpholine the yields increased from 49% to 92% and 47%

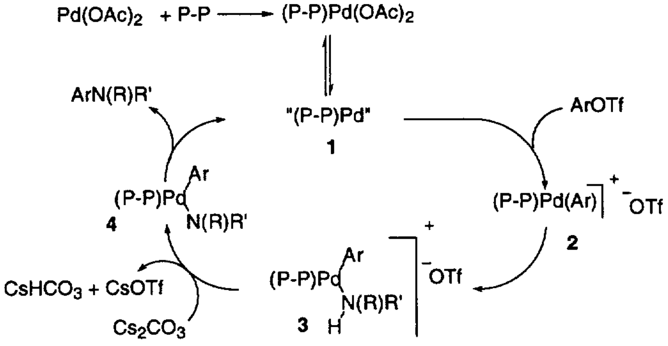
Table 1. Catalytic Amination of Aryl Triflates[a]

Entry	Triflate	Amine	Product	Conditions[b]	Temp.	Time	Yield(%)[e]
1				A	80 °C	6 h	92 (49)[f]
2				A	80 °C	16 h	86 (47)[f]
3				A	80 °C	16 h	84 (28)[f]
4				A	80 °C	5 h	78
5				B	65 °C	4 h	90
6				B[c]	65 °C	4 h	54
7		n-$C_6H_{13}NH_2$		B[c,d]	65 °C	4 h	46
8				A[c]	80 °C	19 h	85
9		n-$C_6H_{13}NH_2$		C[d]	80 °C	5 h	87
10				C	100 °C	16 h	91
11				A[c]	80 °C	5 h	76
12				A	80 °C	16 h	88
13				A[c,d]	100 °C	5 h	90 (72)[f]
14				A[c]	100 °C	5 h	83
15				A[c]	100 °C	7 h	78

---

[a] Reactions were performed with 1.0 equiv triflate, 1.2 equiv amine, 1.4 equiv Cs_2CO_3, cat. $Pd(OAc)_2$, cat. BINAP (1.5 ligand/Pd) and 2 mL solvent/1.0 mmol triflate. [b] A = 3 mol % $Pd(OAc)_2$, toluene, 80 °C under Ar; B = 3 mol % $Pd(OAc)_2$, THF, 65 °C, reaction run in a resealable tube under Ar; C = 5 mol % $Pd(OAc)_2$, 1,4-dioxane, 80 °C, reaction run in a resealable tube under Ar. [c] Performed with 5 mol % $Pd(OAc)_2$. [d] Two equiv of amine were used. [e] All yields are isolated yields (average of two runs) of compounds estimated to be 95% pure by ^1H NMR and GC or elemental analysis. [f] Yields in parenthesis were obtained using NaO*t*-Bu as base (see ref. 1).

to 86%, respectively (Table 1, entries 1–2).[4,5] In the reaction of 4-cyanophenyl triflate with morpholine, the yield increased from 28% to 84% (Table 1, entry 3).[6] The formation of phenol byproducts could not be detected when Cs_2CO_3 was employed instead of NaO*t*-Bu. Use of Cs_2CO_3 as base also allows for amination of enolizable ketones. For example 4-acetylphenyl triflate was coupled with *p*-anisidine in 90% yield (Table 1, entry 5). With amines such as pyrrolidine and *n*-hexylamine 5 mol % $Pd(OAc)_2$ was required and the corresponding anilines were obtained only in moderate yields of 54% and 46%, respectively (Table 1, entries 6 and 7).[9] In contrast to our previous procedure, methyl esters were also compatible with these reaction conditions, but 5 mol % $Pd(OAc)_2$ was necessary to prevent byproduct formation (Table 1, entries 8–10 and 15). Additionally, electron-rich aryl triflates, such as 4-methoxyphenyl triflate, could also be aminated (Table 1, entries 11 and 12). *Ortho*-substituted aryl triflates, such as 2,4-dimethylphenyl triflate and 2-carbomethoxyphenyl triflate, were transformed into anlines in high yields, but the reactions required higher temperatures and 5 mol % $Pd(OAc)_2$ to proceed to completion (Table 1, entries 13–15).[10] The reaction of aryl triflates with primary amines required the use of 2 equivalents of the amine and a more polar solvent such as THF or 1,4-dioxane in order to minimize diarylation of the amine. Coupling reactions with dibutylamine were inefficient and did not proceed beyond ~75% conversion. Compared to reactions with morpholine and pyrrolidine, aminations with piperidine were much slower, and these reactions only proceeded to full conversion with electron-poor aryl triflates.



Scheme 2.

The catalytic cycle for this reaction is probably very similar to the one proposed for aryl amination using NaO*t*-Bu as the base and likely involves the formation of zero valent Pd species **1** from $Pd(OAc)_2$ and the bidentate phosphine ligand (Scheme 2).[1a] Oxidative addition of the aryl triflate to **1** gives palladium aryl cation **2**. Coordination of amine followed by deprotonation by Cs_2CO_3 gives amido complex **4**. Reductive elimination from **4** gives the aniline with concomitant regeneration of the Pd(0) catalyst.

In conclusion we have developed a general and efficient method for the coupling of aryl triflates with primary and secondary amines and anilines. With this new protocol a wider variety of functional groups are tolerated, and, in many instances, higher yields can be obtained.

Acknowledgments. We thank the Wallenberg Foundation, the National Science Foundation, Pfizer and Eastman Kodak for support of this work. We thank John P. Wolfe for preparing 2,4-dimethylphenyl triflate. J.Å. is a Wallenberg Foundation Postdoctoral Fellow.

References and Notes.

(1) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264–1267. (b) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268–1273.

(2) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, preceding paper in this issue.

(3) DPPF = 1,1'-bis(diphenylphophino)ferrocene,
PPF-OMe = 1-[2-(Diphenylphosphino)ferrocenyl]ethyl methyl ether.

(4) All products were characterized by NMR (^{1}H, ^{13}C) and IR. Combustion analyses were obtained for new compounds.

(5) Prevously reported compounds: (a) N-(*p*-benzoylphenyl)pyrrolidine (entry 1).[1a] (b) N-(*p*-benzoylphenyl)morpholine (entry 2).[1a] (c) N-(*p*-cyanophenyl)morpholine (entry 3).[1a] (d) N-(4-acetylphenyl)-*p*-anisidine (entry 5): Itier, J.: Casadevall, A. *Bull. Soc. Chim. Fr.* **1969**, 3523–3538. (e) N-(4-acetylphenyl)pyrrolidine (entry 6): Ibata, T.; Isogami, Y.; Toyoda, J. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 42–49. (f) 4-(4-carbomethoxyphenyl)morpholine (entry 10).[2] (g) N-(4-methoxyphenyl)morpholine (entry 11): Tuji, Y.; Huh, K. T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365–1370. (h) N-(2,4-dimethylphenyl)benzylamine (entry 13).[1a] N-(2,4-dimethylphenyl)pyrrolidine (entry 14): Walkup, R. E.; Seareles, S., Jr. *Tetrahedron* **1985**, *41*, 101–106. (i) N-(2-carbomethoxymethylphenyl)-*p*-anisidine (entry 15).[2]

(6) Representative procedure: An oven-dried Schlenk tube was charged with Cs_2CO_3 (456 mg, 1.4 mmol) in a nitrogen-filled dry box.[7] The tube was capped with a rubber septum, removed from the dry box, and charged with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and BINAP (28.2 mg, 0.045 mmol). The tube was flushed with Ar for 5 min, then a solution of 4-cyanophenyl triflate (251 mg, 1.0 mmol) and morpholine (105 µl, 1.2 mmol) in toluene (2 mL) was added *via* cannula and the resulting mixture was first stirred under Ar at room temperature for 30 min and then at 80 °C for 16 h. The reaction mixture was allowed to cool to room temperature, diluted with ether (15 mL) and filtered through a pad of Celite and the filter cake was washed with ether (3 × 10 mL). Concentration and flash chromatography on silica gel afforded N-(*p*-cyanophenyl) morpholine (164 mg, 87%).[1a, 8]

(7) The Cs_2CO_3 was weighed out in a dry box for reasons of convenience. 4-Cyanophenyl triflate was coupled with morpholine to give a 77% yield of the corresponding aniline (entry 3) using Cs_2CO_3 stored in a desiccator and weighed in the air. Entries 13–15 were set up with Cs_2CO_3 weighed in the air.

(8) Efficient stirring is important in order to ensure short reaction times and optimum yields.

(9) We believe that the low yields are due to byproducts formed via enolization processes.

(10) Attempts to couple 2-carbomethoxyphenyl triflate with alkyl amines, such as pyrrolidine and benzyl amine, gave only low yields of the desired aniline.

(*Received in USA* 27 *May* 1997; *accepted* 8 *July* 1997)