Investigation on the Coupling Reactions of Aryltriflates with Aromatic Amines: Selection of the Metal Catalyst

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Abstract: *A simple and effective coupling reaction of aryl triflates with aniline derivatives in the presence of palladium catalyst is described, which appears to be a general and useful protocol for the preparation of functionalized arylamines starting from phenols.* © 1997 Elsevier Science Ltd.

Arylamines are an important class of compounds especially for the development of drugs, insecticides, and other chemicals of contemporary needs. Although a number of synthetic methods for these compounds have been collected, sometimes referred as a name reaction or unnamed ones,[1] there still exists a demand for novel protocols, which allow an effective transformation in the presence of wide range of functional groups under mild reaction conditions.

In the course of our synthetic study on the antibacterial compounds, a diaryl amine such as **1** was emerged as a key synthetic intermediate; for an efficient production of **1**, various methods were tested to find a practical route It was soon found that Ullmann-type coupling[1] between activated aromatic halides and aniline derivative was a choice for this transformation. **(Scheme-1)** Although this classical approach was proven to be successful in a large scale operation, we decided to find a more modern option for these types of transformation. It was then occurred to us to investigate a coupling reaction of the triflate (eg **2**) and aniline derivative,[2] which is considered to be of general synthetic value, opening a novel route to various amine derivatives starting from phenols.

Scheme-1
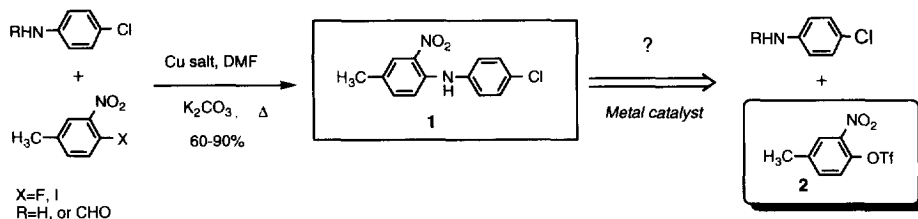
At the very beginning of our investigation, almost no general protocols had been developed for such transformation of phenol or corresponding triflate into amines, although some literature precedent indicated that these types of reaction were only possible with limited case or under harsh (high pressure) conditions with activated aromatics.[2]

Table-1
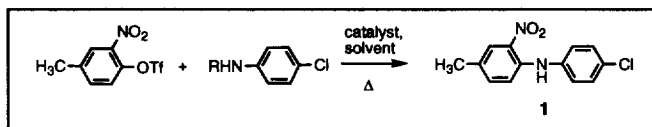
R=	solvent	cat.	conditions	yield
CHO	CH₃CN	-	reflux, 5h	a, b
CHO	DMF	Cu₂O, K₂CO₃	135-140°C, 5h	a
CHO	diisopropylethylamine	-	135-140°C, 5h	a
H	diisopropylethylamine	-	135-140°C, 5h	a
H	toluene	PdCl₂, Ph₃P, K₂CO₃	reflux, 1h	73%
H	toluene	Pd(Ph₃P)₄, Ph₃P, K₂CO₃	reflux, 2h	85%
H	toluene	10% Pd-C, K₂CO₃	reflux	a, b
H	toluene	Ni(OAc)₂, K₂CO₃	reflux, 5h	a

comments: a) No desired product was detected on TLC analysis.
          b) Starting material remained unchanged.

Table-2

X, Y=leaving Group or NH₂
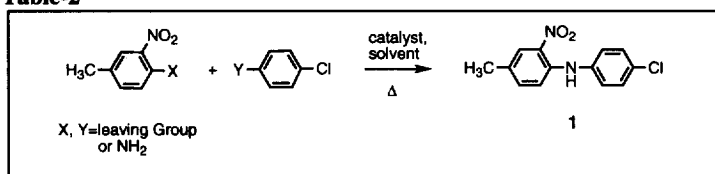
X=	Y=	solvent	cat.	conditions	yield
OTs	NH₂	toluene	Pd(Ph₃P)₄, Ph₃P, K₂CO₃	reflux, 4h	c
o-nitrobenzenesulfonyl	NH₂	toluene	Pd(Ph₃P)₄, Ph₃P, K₂CO₃	reflux, 4h	13%
NH₂	Br	toluene	Pd(Ph₃P)₄, Ph₃P, NaOMe	reflux, 9h	a
NH₂	Br	toluene	Pd(Ph₃P)₄, Ph₃P, K₂CO₃	reflux, 8h	37%
NH₂	Br	toluene	Pd(CH₃CN)₂Cl₂, dppp, K₂CO₃	reflux, 9h	c
NH₂	Br	toluene	Pd(CH₃CN)₂Cl₂, dppb, K₂CO₃	reflux, 8h	a
NH₂	Br	m-xylene	Pd(Ph₃P)₄, Ph₃P, K₂CO₃	reflux, 9h	16%
NH₂	Br	m-xylene	Pd(Ph₃P)₄, Ph₃P, iPr₂NEt	reflux, 9h	c
NH₂	Br	THF	Pd(Ph₃P)₄, Ph₃P, K₂CO₃	reflux, 9h	a
NH₂	OMs	toluene	Pd(Ph₃P)₄, Ph₃P, K₂CO₃	reflux, 4h	a
OMe	NH₂	EtOH	-	reflux, 3h	a

comments: a) No desired product was detected on TLC analysis.
          b) Starting material remained unchanged.
          c) Only trace of coupling product was detected on TLC.

According to these previous reports,[2] we initiated our reaction of the activated triflate (**2**) with *p*-chloroaniline without any metal catalyst.   In contrast to our expectation, no reaction took place even under reflux conditions. We thus focused our attention on the metal catalysts employed which enable the reaction to proceed under conventional experimental conditions, in comparison with the well-known Ullmann protocol,[1] where the copper catalyst play the key role.   The very recent paper by Buchwald and Hartwig concerning the Pd-catalyzed amination of aromatic compounds including triflates as substrates[3] prompted us to disclose here our own independent research in this area.

Results of our survey on the reaction conditions with regards to a suitable metal catalyst are summarized in **Table 1**, which clearly shows that Pd catalyst is promising and essential for this transformation.   Without the Pd catalyst no reaction took place, as mentioned before, which excludes either the classical direct substitution (SNAr) pathway, or benzyne process, both of which are often observed in nitroaromatics.[2]

Among the catalyst surveyed, conventional Pd(0) type catalyst such as (Ph3P)4Pd was found to be the most effective one, while the catalysts with bidentate ligand {Pd(dppe) or Pd(dppp)}, Ni(II) salts, and copper salts were found to be inefficient for this transformation.   Further exploitation for the selection of the ligand system will be carried out in due course.

After these brief examination, we tried several related reactions between the substrates other than triflats and amines to find the best reaction partners under these metal-catalyzed process.   Results are summarized in **Table 2**.   As can be seen from these examples, reaction between aryltriflate and aniline derivative described above gave the highest yield when compared with other sulfonate derivatives of phenols.

We also applied a Buchwald-Hartwig type coupling[4] using arylbromide and *o*-nitroaniline derivative as a reaction partner, which did give the desired coupling product in a moderate yield under unoptimized conditions. Further brief survey on other substrates indicated that the reaction worked well with both electron-rich and electron-deficient aryl triflate including triflate of phenol itself, thus demonstrating a general synthetic utility of this protocol.

Scheme-2

3 + H₂N—⟨⟩—Me → 4 22% (unoptimized)

Pd(PPh3)4, Ph3P, K2CO3, toluene, reflux, 2hr
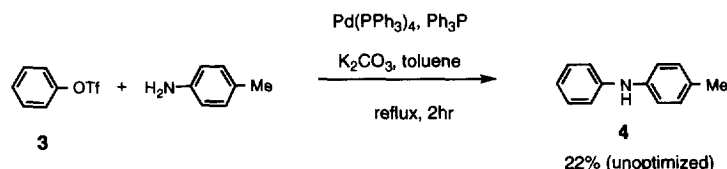
Results obtained here clearly indicate the effectiveness of the novel Pd-catalyzed coupling reactions between aryltriflate and anilines.   Although no precise study on the scope and limitations of these transformation has been carried out so far, we did not feel any difficulties in handling a reactive triflate as mentioned in the reports of the two pioneers.[3]   It is thus our future study to compare our protocol with the reported reaction conditions (especially catalyst ligand and base) [3] in order to clarify the key factor in the amination of triflates.

In summary, we have disclosed here a simple and effective method for the conversion of phenol to arylamine via corresponding triflate by making use of a simple Pd catalyst.   Considering the fact that even the activated triflate (**2**) could not react directly with amines, the selection of the Pd catalyst is critical and useful for the effective transformation of the triflate, as indicated in the recent work of Buchwald and Hartwig.[3]

It is our special aim to develop more simple and effective catalyst system than those reported by these pioneers especially in view of cost and cleanness of the reaction.   Thus, further search on the optimization of the reaction conditions especially with regards to the catalyst system with proper additives, and the potential of our protocol will be carefully investigated in this laboratory.

Typical experimental procedure:[5]

N-(*p*-Chlorophenyl)-4-methyl-2-nitroaniline (**1**):   A mixture of the triflate (**2**, 731 mg), *p*-chloroaniline (480 mg), triphenylphopsphine (66 mg), K_2CO_3 (345 mg) and tetrakis(triphenylphosphine)palladium (0) (144 mg) in toluene (5 mL) was heated under reflux for 2hr.   TLC then indicated the complete consumption of the starting triflate.   Filtration of the insoluble material and concentration of the filtrate under reduced pressure gave a crude product, which was purified by SiO_2 column chromatography to afford the desired amine (**1**, 560 mg, 85.3%).

N-Phenyl-*p*-toluidine (**4**):   A mixture of the triflate (**3**, 565 mg), *p*-toluidine (402 mg), triphenylphopsphine (66 mg), K_2CO_3 (345 mg) and tetrakis(triphenylphosphine)palladium (0) (144 mg) in toluene (5 mL) was heated under reflux for 2hr.   TLC then indicated the complete consumption of the starting triflate.   After filtration of the solid material, filtrate solution was concentrated to give a crude residue, which was purified by SiO_2 column chromatography to afford **4** (101 mg, 22.1%).

References and Notes:

1. See for example: a) Lindsay, R. J. in *Comprehensive Organic Chemistry*; Barton, D.H.R.; Ollis, W. D. Eds, *Pergamon Press*, Oxford, **1979**, vol 2, p. 131-184; b) Hassner, A.; Stumer, C. *Organic Syntheses Based on Name Reactions and Unnamed Reactions, Elsevir Science Ltd.*, Oxford, **1994**; c) Larock, R. C. in *Comprehensive Organic Transformations, VCH Publisher* **1989**, pp. 397-398; d) Mitsunobu, O. in *Comprehensive Organic Synthesis,* Trost, B. M., Fleming, I., Eds.; *Pergamon Press*, **1991**, vol 6, pp. 65-101.

2. Recent examples: a) Kotsuki, H.; Kobayashi, S.; Suenaga, H.; Nishizawa, H. *Synthesis,* **1990**, 1145-1146; b) Kraus, G. A.; Maeda, H. *Tetrahedron Lett.,* **1995**, *36*, 9189-9190.

3. 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.

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5. All the experiments shown here were carried out under conventional conditions (no argon exchange) and no special precautions have been taken for the selection of the solvent and reagents.