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This paper is dedicated to Professors Xiyan Lu and Lixin Dai for their life-long contributions to the development of organic chemistry

Abstract: The bulky and electron-rich MOP-type ligand was efficient for the Pd-catalyzed amination of aryl tosylates. The in situ generated Pd(0) was a more efficient catalyst precursor than Pd(dba)₂. In the presence of Pd(OAc)₂, PhB(OH)₂, and a hindered and electron-rich MOP-type ligand, a variety of primary aryl amines reacted with various aryl tosylates to form the corresponding secondary aryl amines in high yields with high selectivity. Furthermore, the catalyst system was also efficient for the arylation of indoles and hydrazones with aryl tosylates.

Key words: palladium, ligand, monoarylation, aryl tosylate, aryl amine

Palladium-catalyzed sp² C-N bond-forming reactions have evolved into a highly versatile and synthetically attractive transformation in targeting pharmaceutically useful intermediates and material science.¹ In these transformations, electrophilic substrates have been largely limited to aryl halides.² As synthetic equivalents of aryl halides, aryl tosylates are easily prepared from cheap and readily available starting materials, convenient to handle, as well as stable, crystalline solids. Furthermore, use of these compounds has advantages over the corresponding aryl halides because the phenol is a useful directing group for the introduction of other functional groups on the aromatic ring, and this fact can allow access to a wider substrate scope.³ Therefore, aryl sulfonates are very attractive as coupling partners for the transition-metal-catalyzed processes. They are also a challenging class of coupling substrates because of their very low activity toward oxidative addition, which is a critical initial step in the metalcatalyzed coupling reaction.⁴ Since Hartwig realized the amination of inactive aryl tosylates by the application of hindered, chelating alkyl phosphine ligands and hindered bases,⁵ some ligands have been investigated to tackle the difficult palladium-catalyzed couplings of aryl tosylate.⁶ Nevertheless, the couplings of primary amines with aryl tosylates are rare.⁷

We recently reported the synthesis of the bulky and electron-rich MOP-type ligand (Figure 1), which was readily

SYNLETT 2011, No. 7, pp 0955–0958 Advanced online publication: 10.03.2011 DOI: 10.1055/s-0030-1259728; Art ID: W34910ST © Georg Thieme Verlag Stuttgart · New York prepared from inexpensive, commercially available materials, and turned out to be an excellent catalyst for palladium-catalyzed amination of aryl chlorides.⁸ As part of our continuing work, we explored the possibility for the amination of aryl tosylates by utilizing such ligand. Herein, we report our findings in this study.

Figure 1 The structure of the bulky and electron-rich MOP-type ligand

Diarylamines are important synthetic intermediates of dyestuffs, pesticides, and pharmaceuticals,9 and are used as antioxidants for rubbers and elastomers,¹⁰ or as the important intermediate of organic electroluminescent and photoconductors materials.¹¹ The research of the efficient synthesis of diarylamines appears attractive. Therefore, we chose the coupling reaction of phenyl tosylate and aniline as the model reaction to test the limit on activity and selectivity of our ligand. The results are summarized in Table 1. The coupling reaction of aniline with phenyl tosylate occurred in low yield under the identical conditions as for the amination of aryl chloride (Table 1, entry 1).⁸ On the basis of the report that the oxidative additions of aryl tosylates were faster in more polar solvents,¹² the solvent was replaced by t-BuOH, however, still no coupled product was obtained. As Pd(dba)₂ was used as a Pd(0) source, the backbond existed between Pd(0) and the electron-poor dba ligand. Using the strongly electrondonating phosphine as ligand increased the backbonding, therefore, it inhibited the dissociation of dba to form the active species Pd(0)-L1,⁷ and consequently, the concentration of the active species and the rate of the oxidative addition decreased.¹³ Thus, an alternative precatalyst Pd(0) was needed. $Pd(OAc)_2$ in combination with $PhB(OH)_2$ is an efficient method to generate Pd(0) by double transmetalation and reductive elimination. Gratifyingly, the monoaryl product of aniline was obtained in



38% yield (Table 1, entry 3) and no diaryl product was formed when 2 mol% of Pd(OAc)₂, 5 mol% of PhB(OH)₂, and 3 mol% of L1 were used. In the absence of $PhB(OH)_2$, no reaction occurred (Table 1, entry 4). Decreasing the basicity of bases favored controlling the O-S cleavage of the tosylates. When the weaker bases, K_3PO_4 and Cs_2CO_3 , were used, the monoaryl yield was increased to 85% and 99%, respectively (Table 1, entries 5 and 6). However, when the reaction was run in the presence of K_2CO_3 , only 19% yield was obtained (Table 1, entry 7). With respect to the applicability and availability, K₃PO₄ was employed as the base in further studies. By replacing solvent t-BuOH with *n*-BuOH, elevating reaction temperature to 110 °C led to a higher yield of 99% (Table 1, entry 9). In addition, the coupling reaction could be finished in short time, the yield of coupling product reached 99% after two hours (Table 1, entry 10). Thus, under the optimized reaction conditions illustrated in entry 9 (Table 1), the catalytic system was efficient for the coupling reaction of inactivated aryl tosylates with aniline and showed high selectivity for monoarylation vs. diarylation.

Table 1 Optimization of Reaction Conditions for Coupling of Benzyl Tosylate**1a** with Aniline $2a^a$

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	OTs +	NH ₂ -F	Pd, ligand	Ň	
1a		2a		3aa	
Entry	Pd	Base	Solvent	Additive	Yield (%) ^b
1	Pd(dba) ₂	NaOt-Bu	toluene	-	17
2	Pd(dba) ₂	NaOt-Bu	t-BuOH	-	0
3	Pd(OAc) ₂	NaOt-Bu	t-BuOH	PhB(OH) ₂	38
4 ^c	Pd(OAc) ₂	NaOt-Bu	t-BuOH	-	0
5	Pd(OAc) ₂	K ₃ PO ₄	t-BuOH	PhB(OH) ₂	85
6	Pd(OAc) ₂	Cs ₂ CO ₃	t-BuOH	PhB(OH) ₂	99
7	Pd(OAc) ₂	K ₂ CO ₃	t-BuOH	PhB(OH) ₂	19
8	Pd(OAc) ₂	K_3PO_4	dioxane	PhB(OH) ₂	4
9	Pd(OAc) ₂	K ₃ PO ₄	n-BuOH	PhB(OH) ₂	99
10 ^d	Pd(OAc) ₂	K ₃ PO ₄	n-BuOH	PhB(OH) ₂	99

^a Reaction condition: PhOTs (1mmol), PhNH₂ (1.2 mmol), Pd (2 mol%), L1 (3 mol%), PhB(OH)₂ (5 mol%), base (1.5 mmol), solvent (2 mL), 15 h. ^b GC vield.

° L1 (5 mol%).

^d Reaction time: 2 h.

The scope of the catalytic system $Pd(OAc)_2-PhB(OH)_2-$ L1 was examined by reacting various aryl tosylates and amines under the optimized reaction conditions (Table 2).¹⁴ Alkyl-substituted aryl tosylates reacted in excellent yields with aniline without formation of any diarylamine (Table 2, entries 1–3). Even inactive electron-rich aryl tosylates were coupled in excellent yields and selectivities (Table 2, entries 4 and 5). Generally, the strongly electron-withdrawing groups could promote both the C-O cleavage (the desired reaction) and the O-S cleavage (side reaction).¹⁵ When *p*-benzoyl-substituted phenyl tosylate was used as substrate, an excellent yield of the desired product was obtained (Table 2, entry 6). Due to the steric hindrance of the ligand, the reaction was slightly sensitive to the steric effects of the substrates. The reaction of aryl tosylates with only one substituent (ortho) occurred in good yield (Table 2, entry 2); when 2,6-dimethylphenyl tosylate was employed as substrate, the coupling yield decreased to 74% (Table 2, entry 7). The steric effects of the aryl amine were similar. For example, when 2,6-dimethylaniline was used, a decreased yield was afforded (Table 2, entry 10). Furthermore, the reaction was also slightly influenced by the electronic properties of aryl amines. The electron-rich aryl amines were coupled in good yields (Table 2, entries 8 and 12); for the electrondeficient aryl amines, the decreased nucleophilicity led to decreased coupling yields. For instance, *p*-methylaniline was monoarylated in 91% yield (Table 2, entry 8), while p-trifluoromethylaniline was monoarylated in 59% yield (Table 2, entry 11). Consistent with the high selectivity for reactions of primary arylamines, the reactions of secondary amines were much slower. The reactions of aryl tosylates with diphenylamine gave no coupled products (Table 2, entry 13).

 Table 2
 Palladium-Catalyzed Amination of Aryl Tosylates^a

Entry	Aryl tosylate	Amine	Yield (%)
1	1b 4-MeC ₆ H ₄ OTs	2a PhNH ₂	3ba 94
2	1c 2-MeC ₆ H ₄ OTs	2a PhNH ₂	3ca 93
3	1d C ₁₀ H ₇ -2-OTs	2a PhNH ₂	3da 96
4	1e 4-MeOC ₆ H ₄ OTs	2a PhNH ₂	3ea 96
5	1f 4-NHBocC ₆ H ₄ OTs	2a PhNH ₂	3fa 81
6	1h 4-C(O)PhC ₆ H ₄ OTs	2a PhNH ₂	3ha 95
7	1i 2,6-Me ₂ C ₆ H ₃ OTs	2a PhNH ₂	3ia 74
8	1a PhOTs	2b 4-MeC ₆ H ₄ NH ₂	3ba 91
9	1a PhOTs	2c 2-MeC ₆ H ₄ NH ₂	3ca 88
10	1a PhOTs	2d 2,6-Me ₂ C ₆ H ₃ NH ₂	3ia 54
11	1a PhOTs	2e 4-F ₃ CC ₆ H ₄ NH ₂	3ae 59
12	1a PhOTs	$2\mathbf{f}$ 4-MeOC ₆ H ₄ NH ₂	3ea 95
13	1a PhOTs	2h Ph ₂ NH	0
14	1a PhOTs	2i indole	3ai 67
15	1a PhOTs	2k Ph ₂ C=NNH ₂	3ak 62

^a Reaction conditions: ArOTs (1 mmol), amine (1.2 mmol), Pd(OAc)₂ (2 mol%), **L1** (3 mol%), PhB(OH)₂ (5 mol%), K₃PO₄ (2.0 mmol), *n*-BuOH (2 mL), 110 °C, 15 h.

Nitrogen-containing heterocycles are interesting substrates for the N-arylation since many pharmaceuticals possess such functionality.¹⁶ The catalyst system was efficient for the coupling reaction of indole and aryl tosylates. *N*-Benzylindole (**3ai**) was obtained in 67% (Table 2, entry 14), and no C-arylation product was isolated. The weaker nucleophilicity and more steric hindrance of indole relative to primary amine led to the decrease of the coupling yield.

Moreover, the catalytic system was efficient for the coupling reaction of aryl tosylate and (diphenylmethylene)hydrazine, the desired product *N*-aryl hydrazone, an important intermediate for the synthesis of indoles,¹⁷ was obtained in 62% yield (Table 2, entry 15).

In addition, the activity of tosylates relative to chlorides was also investigated. In our catalytic system, aryl chlorides reacted faster than aryl tosylates. The reaction of 4-chlorophenyl tosylate led to a coupling product at the C–Cl bond (Scheme 1). These results were in parallel to those catalyzed by Pd-Buchwald ligand,¹⁸ but different from those catalyzed by Pd-Josiphos.⁷



Scheme 1 The coupling reaction of 4-chlorophenyl tosylate with aniline

In summary, the bulky and electron-rich MOP-type ligand was efficient for the Pd-catalyzed amination of aryl tosylates. The active catalyst was formed in situ from $Pd(OAc)_2$, $PhB(OH)_2$, and air- and moisture-stable phosphines. The optimized system showed high catalytic activity for monoarylation of aryl amines, indoles, and hydrazones. In the competitive reaction, the reaction rates of aryl chlorides are faster than those of aryl tosylates.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **Typical Procedure** A flame-dried Schlenk t

A flame-dried Schlenk tube was charged with Pd(OAc)₂ (4.5 mg, 0.02 mmol), L1 (13.7 mg, 0.03 mmol), PhB(OH)₂ (6.1 mg, 0.05 mmol), and *n*-BuOH (2 mL) under an atmosphere of nitrogen. The solution was stirred at r.t. for 15 min then K_3PO_4 (424.5 mg, 2.0 mmol) and ArOTs 1 (1mmol) were added, followed by aryl amine 3 (1.2 mmol). The reaction was heated to 110 °C and stirred for 15 h. The reaction mixture was cooled to r.t. and diluted with Et₂O (5 mL) and H₂O (3 mL). After separation of the layers, the aqueous phase was extracted with Et₂O (3 × 5 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Purification of the crude product by flash column chromatography (silica gel; PE–Et₃N, 99:1) yielded compound 3.

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