EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201402475

# Nickel-Catalyzed One-Pot Suzuki–Miyaura Cross-Coupling of Phenols and Arylboronic Acids Mediated by *N*,*N*-Ditosylaniline

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**Keywords:** Nickel / Chemoselectivity / Boronic acids / Biaryls / Cross-coupling

An efficient method for the construction of two distinct $C_{aryl}$–$C_{aryl}$ bonds through the Ni-catalyzed Suzuki–Miyaura cross-coupling of phenols with arylboronic acids has been developed. This reaction proceeds through the in situ tosylation of phenols by using *N*,*N*-ditosylaniline as the sulfonylating reagent, which is highly active, markedly stable, and easily prepared. The scope with respect to the coupling partners – phenols and boronic acids – is broad, and sensitive functional groups are tolerated. Phenols, especially those containing an unprotected amino group, which are generally problematic for coupling under conventional one-pot conditions, are also viable substrates in this transformation.

## Introduction

The transition-metal-catalyzed Suzuki–Miyaura cross-coupling reaction constitutes one of the most powerful $C_{aryl}$–$C_{aryl}$ bond-forming transformations.[1] This reaction has been successfully applied to a wide range of academic areas, but it has also been used in the pharmaceutical, agrochemical, and fine-chemical industries.[2] Over the history of Suzuki–Miyaura cross-coupling, the starting materials have been limited to aryl iodides, aryl bromides, and certain activated aryl chlorides until 20 years ago. A broad range of aryl electrophiles have attracted much interest, and they are more commonly used in coupling chemistry.[3] These electrophiles, according to the atoms of the leaving groups, can be classified as N-,[4] S-,[5] P-,[6] C-,[7] as well as O-based. Among these leaving groups, O-based electrophiles are much more appealing owing to the ubiquitous presence of their starting materials – phenols – both in the natural world and in synthetic systems.[8]

Previous work using phenols as coupling partners involved prior activation of the phenols to more active precursors.[9] These activation strategies included the formation of aryl triflates, sulfonates, ethers, esters, carbamates, sulfamates, and phosphoramides.[10,11] However, such a preparatory process limits their efficiency for overall yields and step economy. Very recently, several direct coupling reactions have been reported by the in situ activation of phenols through the formation of inorganic salts (e.g., ArOM),[9] organic phenolic phosphonium salts,[12] pivalate esters,[13] and aryl nonaflates.[3] These novel strategies merged phenol activation and subsequent cross-coupling into a single operation,[14] and therefore, they made the transformation more practical in terms of efficiency, economy, and environmental impact,[15] but their limitation to specific substrates, generality to labile functional groups, in addition to a high loading of expensive Pd catalysts and ligands[16,17] [e.g., 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos)] made it imperfect. Consequently, a more general, efficient, and direct approach for phenol coupling has been long awaited. In this communication, we successfully obtained the coupling products by one operation of the phenols in a single flask by using a novel sulfonylating reagent, *N*,*N*-ditosylaniline ($ArNTs_2$).

## Results and Discussion

Recently, an investigation on $ArNTs_2$ drew our attention to their ability to donate a Ts group in the presence of a base. This inspired us to test the feasibility of tosylating phenolic hydroxy groups, and we envisioned the domino sulfonylation and cross-coupling reaction of phenols [Scheme 1, Equation (1)].

First, the sulfonylation of phenols worked smoothly with $ArNTs_2$ (1.1 equiv.) in 1,4-dioxane by using anhydrous $K_3PO_4$ (2 equiv.) as base, and the corresponding sulfonated products were obtained in quantitative yield. Afterwards, we were very surprised to find that phenols **1** containing a naked amino group could undergo tosylation and coupling to afford desired product **5** with the intact amino group [Scheme 1, Equation (2)].

Optimization of the critical reaction conditions was conducted on the model reaction of 4′-hydroxyacetophenone

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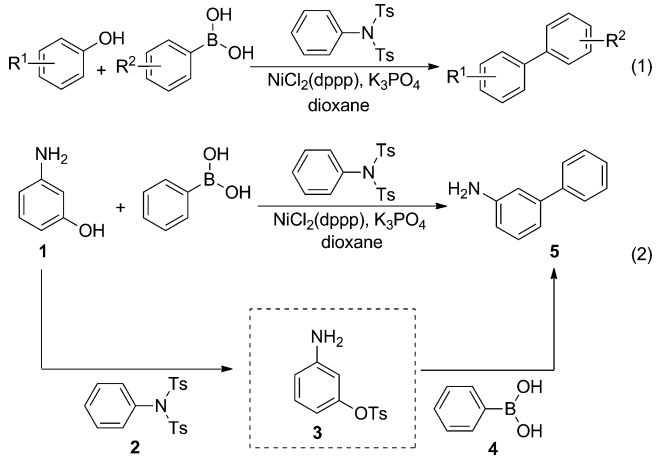
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402475.




Scheme 1. Stepwise Suzuki–Miyaura coupling of phenols. dppp = 1,3-bis(diphenylphosphino)propane.

(**1a**) with phenylboronic acid (**4e**) (Table 1). Various specific nickel-catalyzed systems were tested (Table 1, Entries 1–5). In stark contrast, $NiCl_2$(dppp) proved to be a much more effective catalyst coordinated with $K_3PO_4$ as base in dioxane at 110 °C. $K_3PO_4$ was irreplaceable, as $Cs_2CO_3$, *t*BuOK, *t*BuOLi, and $K_2CO_3$ provided much lower yields of the products (Table 1, Entries 6–9). Furthermore, the use of 1,2-dichloroethane (DCE), 1,2-dimethoxyethane (DME), THF, and toluene as solvents for the reaction gave dissatisfactory results (Table 1, Entries 10–13).

Then, a variety of sulfonylating reagents were examined for the optimized catalyst system, and the results are summarized in Figure 1. Substituents on the aniline ring slightly influenced the efficiency of the domino coupling reaction. Among all the sulfonylating reagents, unsubstituted **2a** and 4-methoxy-substituted **2b** gave the best results, both of which provided **5ae** in 93% yield. Naphthyl-, *n*-butyl-, and 3,4-dimethyl-substituted **2f**, **2g**, and **2d** also provided the products in yields of 87, 90, 90%, respectively. Benzyl-substituted **2e** gave the product in a decreased yield of 72%, whereas strongly electron-withdrawing 4-nitro-substituted **2c** gave the product in a similarly dissatisfying yield of 61%. Furthermore, we replaced the Ts group with Ms (methylsulfonyl) and Ns (4-nitrobenzenesulfonyl) groups (see **2h** and **2i**) (Figure 1), and the yield dropped sharply to 20 and 31%, respectively. By comparison, sulfonated secondary amines **2j** and **2k**, TsCl (**2l**), and $Ts_2O$ (**2m**) failed to give desired product **5ae**, except for TsCl, which provided the product in only 7% yield.

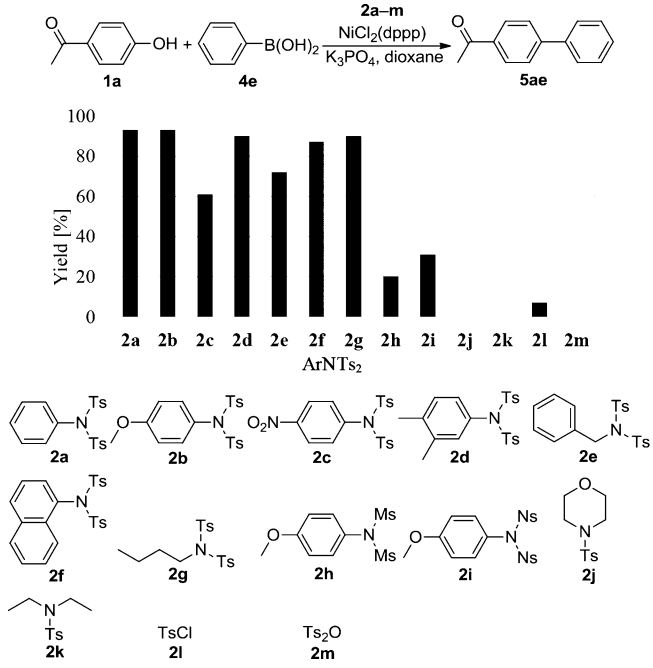
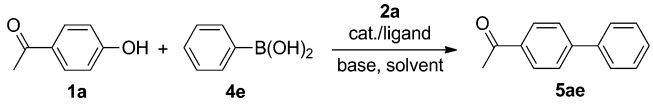



Figure 1. Screening of sulfonylating reagents from **2a** to **2m**.

Table 1. Selected results of the screening of the optimal conditions.[a]



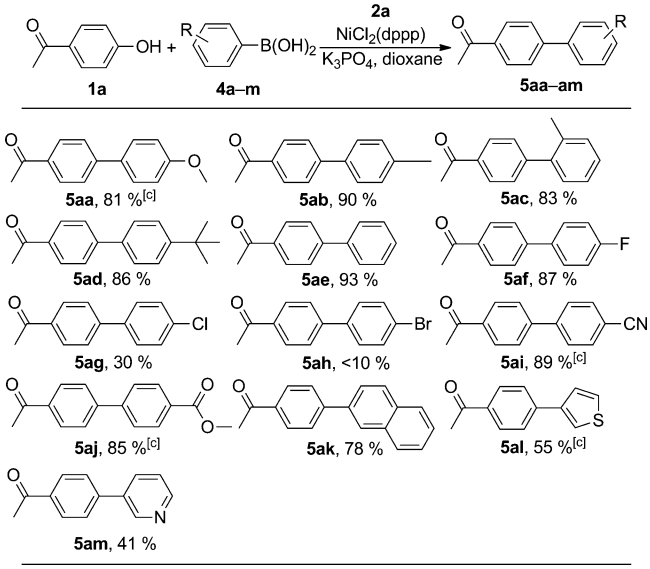

| Entry | Catalyst (mol-%) | Base | Solvent | *T* [°C] | Time [h] | Yield[b] [%] |
|---|---|---|---|---|---|---|
| 1 | $Ni(cod)_2$ (3)/$PCy_3$ (12) | $K_3PO_4$ | THF | 70 | 24 | trace |
| 2 | $NiCl_2(PCy_3)_2$ (3)/$PCy_3$ (12) | $K_3PO_4$ | dioxane | 130 | 36 | 76 |
| 3 | $Ni(PPh_3)_2$(1-naphthyl)Cl (5)/$PPh_3$ (5) | $K_2CO_3$ | toluene | 120 | 24 | n.r. |
| 4 | $NiCl_2$(dppf)/Zn (5) | $K_3PO_4$ | THF | 70 | 24 | n.r. |
| 5 | $NiCl_2$(dppp) (5) | $K_3PO_4$ | dioxane | 110 | 36 | 93 |
| 6 | $NiCl_2$(dppp) (5) | $Cs_2CO_3$ | dioxane | 110 | 36 | 10 |
| 7 | $NiCl_2$(dppp) (5) | *t*BuOK | dioxane | 110 | 36 | 25 |
| 8 | $NiCl_2$(dppp) (5) | *t*BuOLi | dioxane | 110 | 36 | trace |
| 9 | $NiCl_2$(dppp) (5) | $K_2CO_3$ | dioxane | 110 | 36 | 17 |
| 10 | $NiCl_2$(dppp) (5) | $K_3PO_4$ | DCE | 90 | 36 | 34 |
| 11 | $NiCl_2$(dppp) (5) | $K_3PO_4$ | DME | 110 | 36 | 21 |
| 12 | $NiCl_2$(dppp) (5) | $K_3PO_4$ | THF | 70 | 36 | trace |
| 13 | $NiCl_2$(dppp) (5) | $K_3PO_4$ | toluene | 120 | 36 | n.r. |

[a] Reaction conditions: **1a** (0.50 mmol), **4e** (1.00 mmol), **2a** (0.55 mmol), $K_3PO_4$ (2.50 mmol), dioxane (6.00 mL), under $N_2$. cod = 1,5-cyclooctadiene, Cy = cyclohexyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene. [b] Yield of isolated product. n.r. = no reaction.

Thus, with the optimized reaction conditions available, we first investigated the effects of electronic and structural variations of the boronic acids. The results are presented in Table 2. Generally, the products were isolated in excellent yields, and the overall reaction efficiency was not sensitive to the electronic properties of the groups on the phenyl ring of the boronic acids, as cross-couplings of boronic acids modified with an electron-rich OMe group (see **5aa**) (Table 2), electron-neutral Me and H groups (see **5ab** and **5ae**) (Table 2), and electron-deficient CN and $CO_2Me$ groups (see **5ai** and **5aj**) (Table 2) all proceeded very smoothly. The hindrance of the phenyl ring had a slight effect on the efficiency (see **5ac** and **5ad**) (Table 2). Notably, halo groups on the phenyl ring of the boronic acids behaved very differently: an F substituent survived the procedure without being affected, whereas Cl and Br were modified in the presence of the highly active catalyst system, and much lower yields of the products were obtained (see **5af**, **5ag**, and **5ah**) (Table 2). Moreover, 2-naphthyl-, 3-thienyl-, and 3-pyridylboronic acids also gave arylation products in moderate yields (see **5ak**, **5al**, and **5am**) (Table 2).

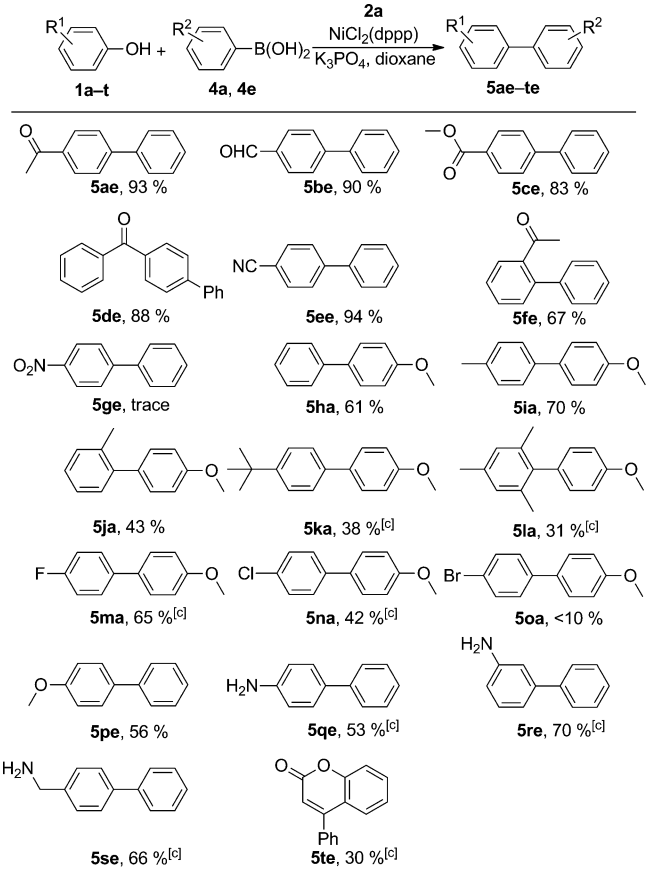
Table 2. Suzuki–Miyaura cross-coupling of 4′-hydroxyacetophenone (**1a**) with boronic acids **4a**–**m** mediated by *N*,*N*-ditosylaniline (**2a**).[a,b]




[a] Reaction conditions: **1a** (0.50 mmol), **4a**–**m** (1.00 mmol), **2a** (0.55 mmol), $NiCl_2$(dppp) (5.00 mol-%), $K_3PO_4$ (2.50 mmol), dioxane (6.00 mL), 110 °C, under $N_2$, 24–60 h. [b] Yields of isolated products are given. [c] Compound **2b** was used instead of **2a**.

Next, the reaction efficiency of the direct Suzuki–Miyaura coupling was further inspected by varying the phenol components (Table 3). As expected, a series of functional groups on the phenol ring, such as chloro, fluoro, cyano, ether, ester, formyl, acetyl, and even amino, were compatible under this procedure. Generally, we observed that electron-deficient phenol compounds such as those with a CN, $CO_2Me$, or C(O)Me substituent, could be transformed smoothly into the corresponding products in 83–95% yield (**5ae**–**ee**) (Table 3). Comparatively, analogues containing a strongly electron-withdrawing $NO_2$ group failed in the reaction (see **5ge**) (Table 3), and substrates with electron-rich and electron-neutral groups such as OMe, $NH_2$, Me, *t*Bu, and H gave slightly lower yields (see **5ha**, **5ia**, **5ka**, **5pe**–**se**) (Table 3). Most interestingly, F and Cl were retained under the coupling conditions with acceptable efficiency, whereas Br was not immune (see **5ma**–**oa**) (Table 3). *ortho*-Substituted phenols gave lower yields than *para*-substituted analogues (see **5fe**, **5ja** vs. **5ae**, **5ia**) (Table 3). If there were two substituents in the *ortho* position, an even lower yield was obtained (see **5la**) (Table 3). Notably, the direct arylation of 4-hydroxycoumarin was somewhat challenging, and the desired product was provided in 30% yield (see **5te**) (Table 3).

Table 3. Suzuki–Miyaura cross-coupling of phenols **1a**–**s** with phenylboronic acid (**4e**) or 4-methoxyphenylboronic acid (**4a**) mediated by **2a**.[a,b]




[a] Reaction conditions: **1a**–**s** (0.50 mmol), **4a** or **4e** (1.00 mmol), **2a** (0.55 mmol), $NiCl_2$(dppp) (5.00 mol-%), $K_3PO_4$ (3.00 mmol), dioxane (6.00 mL), 110 °C, under $N_2$, 24–60 h. [b] Yields of isolated products are given. [c] **2a** (0.75 mmol) and **4e** or **4a** (1.50 mmol) were used.

Of particular note is that the coupling of phenols containing a free amino group (see **5qe**–**se**) (Table 3) occurred exclusively at the hydroxy position, and the unprotected $NH_2$ functional group remained intact, which was discussed in Scheme 1. To the best of our knowledge, such a highly chemoselective cross-coupling with the use of phenols has

not been observed for known protocols. In contrast, similar conventional Pd-catalyzed cross-coupling reactions require prior protection of the amino group.[18] Thus, one of the foreseeable advantages with the direct use of unprotected amino phenols is that it provides a much more straightforward pathway for the construction of polyaromatic-ring-containing amines. Besides, the orthogonal use of this protocol with Buchwald–Hartwig coupling[19] is a good prospect for selective C($sp^2$)–C($sp^2$) and C($sp^2$)–N bond formation through proper control of the catalyst system and the reaction sequences.[20]

## Conclusions

We developed a novel, practical sulfonylating reagent – $ArNTs_2$ – and successfully applied it to the direct coupling of phenols with arylboronic acids. This method does not require the isolation of the intermediary sulfonate, and therefore, it is much more convenient and useful than known traditional ways. In addition, the method also shows broad applicability and high efficiency towards various functional groups on the aromatic rings, and even a naked amino group was tolerated. We highlight its use for the construction of polyaromatic-ring-containing amines, which are core motifs and important building blocks in the synthesis of pharmaceuticals, functional materials, and coordination compounds by orthogonal use with Buchwald–Hartwig coupling.

As a stable source of the Ts group, $ArNTs_2$ exhibits a lot of incomparable superiority towards conventional reagents such as TsCl and $Ts_2O$. We described its highly chemical selectivity between phenols and amines; its stability in strong base, its high activity in the metal catalyst system, and the lack of the generation of an acid such as HCl are impressive as well. Studies on these properties of $ArNTs_2$ are currently underway in our laboratory.

## Experimental Section

**General Procedure for the Suzuki–Miyaura Cross-Coupling Reactions of Phenols with Arylboronic Acids:** Into a 25 mL Schlenk tube equipped with a magnetic bar were added $NiCl_2$(dppp) (0.025 mmol, 13.5 mg), the phenol (0.5 mmol), the arylboronic acid (1.0 mmol), the *N*,*N*-ditosylamine (0.55 mmol), and anhydrous $K_3PO_4$ (2.5 mmol). The tube was then evacuated (3× 10 min) and backfilled with $N_2$. Dried dioxane (5.0 mL) was injected by syringe, and the mixture was stirred at 110 °C until the phenol had disappeared, as monitored by TLC. The mixture was poured into water (20 mL) and then extracted with $CH_2Cl_2$ (3× 20 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, filtered, and concentrated to dryness. The crude material was purified by flash chromatography (silica gel; hexane/ethyl acetate or hexane/$CH_2Cl_2$) to give the desired cross-coupled product.

**General Procedure for the Synthesis of the *N*,*N*-Ditosylamines:** The amine was treated with sulfonyl chloride (2.1 equiv.) and $Et_3N$ (3 equiv.) in dry $CH_2Cl_2$ (3 mL mmol$^{-1}$ of amine). After 24 h of stirring at room temperature, the mixture was washed with water; the final organic layer was dried ($Na_2SO_4$), and the solvents were evaporated under vacuum. Purification by column chromatography (cyclohexane/dichloromethane, 5:1–1:1) afforded the target compound as a white solid.

**Supporting Information** (see footnote on the first page of this article): Experimental details and copies of the $^1$H NMR and $^{13}$C NMR spectra.

## Acknowledgments

The work was supported by the National Nature Science Foundation of China (NSFC, 21272069, 20672035), the Fundamental Research Funds for the Central Universities, and the Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

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Received: April 23, 2014
Published Online: July 8, 2014

  