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$NiCl_2(PCy_3)_2$: A Simple and Efficient Catalyst Precursor for the Suzuki Cross-Coupling of Aryl Tosylates and Arylboronic Acids

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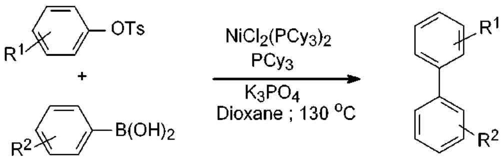
ABSTRACT



$NiCl_2(PCy_3)_2$ associated with PCy_3 promotes the selective cross-coupling of aryltosylates with arylboronic acids under relatively mild reaction conditions, and a variety of functional groups are tolerated in both arenes. This is one of the simplest and most efficient experimental procedures for the coupling of arylboronic acids with aryl tosylates reported to date.

The transition metal catalyzed Suzuki cross-coupling reaction is one of the most efficient methods for the construction of $C_{aryl}-C_{aryl}$ bonds.[1] Indeed, in recent years various efficient Pd catalyst precursors have been developed that allow aryl iodides, bromides, triflates, and chlorides to be effectively coupled with aryl boronic acids under mild reaction conditions.[2] Moreover, Ni-based catalysts have also been successfully used for the Suzuki reaction of aryl chlorides.[3] Aryl triflates and sulfonates are regarded as synthetic equivalents of aryl halides; however, the propensity of triflates to hydrolyze readily, associated with the higher price of triflating agents, restricts their application. From a synthetic point of view, the use of aryl sulfonates (in particular tosylates) is a very attractive alternative because they are easily prepared from phenols, are more stable than triflates, and are cheap and easily available starting materials. However, there are only few reports on the application of arene sulfonates in catalytic Suzuki coupling reactions. Yields up to 81% have been obtained using large quantities (∼10%) of $NiCl_2$(dppf) and Zn (1.7 equiv) for the coupling of aryl mesylates with boronic acids.[4] Higher yields have been obtained employing lithium arylborates.[5] However, this reaction is limited to mesylates and tosylates containing an electron-withdrawing group. Herein, we report the use of a simple and general catalyst system for the nickel-catalyzed Suzuki cross-coupling reaction of aryl tosylates.

A series of experiments were performed in order to determine the feasibility of using aryl tosylates in the Ni-catalyzed Suzuki reaction. Initially, we examined the cou-

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[1] Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147 and references therein.

[2] (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561. (b) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (c) Littke, A. F.; Daí, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387. (e) Bei, X.; Crevier, T.; Guran, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855−3858. (f) Zhang, C. M.; Huang, J. K.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. (g) Zim, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881−2884.

[3] (a) Saito, S.; Oh-tani, S.; Miayaura, N. *J. Org. Chem.* **1997**, *62*, 8024−8030. (b) Indolese, A. F. *Tetrahedron Lett.* **1997**, *38*, 3513−3516. (c) Lipshutz, B. H.; Sclafani, A.; Blomgren, P. A. *Tetrahedron* **2000**, *56*, 2139−2144.

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[5] Kobayashi, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 8531−8534.

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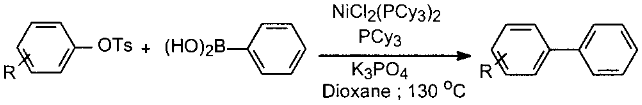
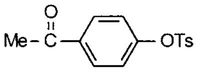
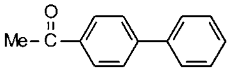
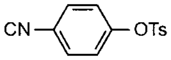
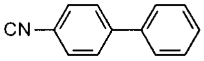
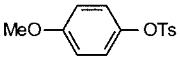
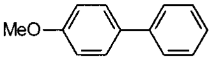
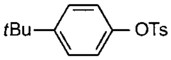
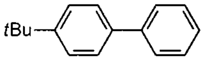
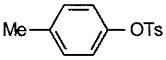
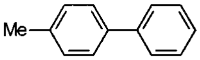
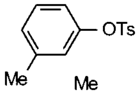
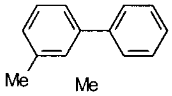
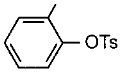
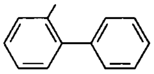
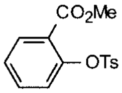
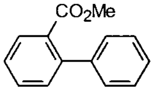
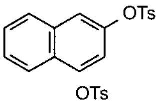
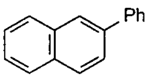
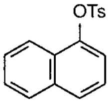
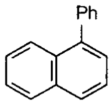
pling of 4-*tert*-butylphenyltosylate with $PhB(OH)_2$ using Ni(0) viz. [$Ni(cod)_2$] in the presence of phosphine ligands, or $NiCl_2L_2$ (L = PPh_3 and PCy_3) under various reaction conditions. 1,4-Dioxane was found to be the most effective solvent, and K_3PO_4 was the base of choice. The addition of further phosphine ligands is necessary, and PCy_3 gave the best results. Similar results were obtained using Ni(0) or Ni(II) catalyst precursors in the presence of an excess of PCy_3. Since $NiCl_2(PCy_3)_2$ is a stable complex and easy to prepare and manipulate, we used it instead of the unstable and air-sensitive $Ni(cod)_2$.[6] To our surprise, we found that the reaction can be carried out using 1.5−3 mol % of $NiCl_2(PCy_3)_2$ in the absence of reducing agents such as Zn.[4] The coupling of a wide variety of aryl tosylates with $PhB(OH)_2$ was examined using $NiCl_2(PCy_3)_2$ under optimized reaction conditions (Table 1).

Aryl tosylates containing electron-withdrawing groups (entries 1 and 2) and naphthyl tosylates (entries 9 and 11) are efficiently coupled to provide the corresponding biaryl products in excellent isolated yields (>94%). Although complete conversion was not observed for the coupling of the aryl tosylates containing electron-donating groups, the corresponding biaryl products were isolated in good yields (79−89%, entries 3−6). Side reactions such as the homocoupling of aryl boronic acid and aryl tosylate hydrolysis were negligible. Ortho methyl-substituted aryl tosylates (entry 7) gave lower yields as compared to meta- and para-substituted analogues (entries 5 and 6, respectively). Lower yields were found for the Suzuki reaction of $2\text{-}CH_3O_2CC_6H_4\text{-}OTs$ with $PhB(OH)_2$ (entry 8). Ni-catalyzed reactions are more sensitive to steric hindrance than those involving Pd-catalysis.[2a,3a] Attempts to perform the cross-coupling of 2,4,6-trimethylphenyltosylate with $PhB(OH)_2$ gave only modest yields (30%) of biphenyl product. However, the promising results obtained for para- and meta-substituted aryl tosylates render this system a new and useful tool in the Suzuki cross-coupling reaction. For instance, the combination of the present reaction and the Pd-catalyzed Suzuki reaction[7] can be used to produce unsymmetrically substituted terphenyl compounds in high yields (Scheme 1).

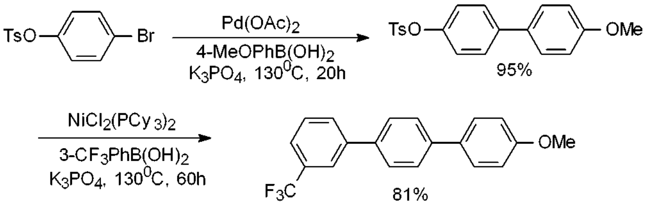
Table 1. $NiCl_2(PCy_3)$-catalyzed Suzuki Cross-Coupling of Aryl Tosylates and $PhB(OH)_2$[a]



entry	aryl tosylate	product	yield (%)
1			94
2			96
3			89
4			83
5			79
6			88
7			60
8			47
9			99
10			95

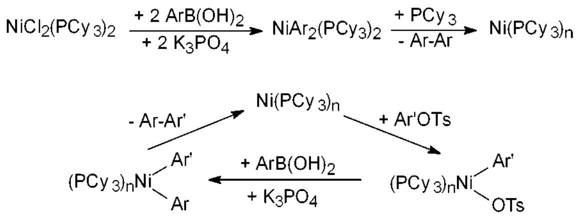
[a] Reaction conditions: 1.0 equiv of aryl tosylate, 1.5 equiv of $PhB(OH)_2$, 2.0 equiv of K_3PO_4, 1.5 mol % $NiCl_2(PCy_3)_2$ (entries 1, 2, 9, and 10), 3 mol % $NiCl_2(PCy_3)_2$ (entries 3−8), $PCy_3/NiCl_2(PCy_3)_2$ = 4, dioxane (5 mL), 130 °C, 14−60 h. Isolated yields (average of two runs).

Scheme 1. Synthesis of an Unsymmetric Terphenyl Compound



The catalytically active species are probably $Ni(PCy_3)_n$ formed from the sequence involving aryl boronic acid transmetalation and reductive elimination (Scheme 2). Indeed, in all cases 2−3% of the aryl boronic acid homocoupled product was observed. The general mechanism of a transition metal catalyzed cross-coupling reaction between

Scheme 2. Reaction Path for Ni-Catalyzed Suzuki Cross-Coupling Reaction of Aryltosylates



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(6) This compound is easily prepared by reaction of PCy_3 with $NiCl_2 \cdot 6H_2O$. Barnett, K. W. *J. Chem. Educ.* **1974**, *51*, 422−423.

(7) Zim, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2000**, *41*, 8199−8202.

organo-electrophiles and organometallic reagents involving sequential oxidative addition, transmetalation, and reductive elimination can explain the observed results. In the first step, the electron-rich Ni(0) complex formed is stabilized by PCy_3, and it undergoes the oxidative addition to aryl tosylates.

The low reactivity of aryl sulfonates and chlorides can be correlated with their poor reactivity toward oxidative addition in the catalytic cycle. A plot of the relative reactivity of substituted aryl tosylates against the σ constant gave a value of $\rho = 2.0$ and 1.6 for the coupling with 4-$MePhB(OH)_2$ and 4-$MeOPhB(OH)_2$, respectively, as shown in Figure 1.

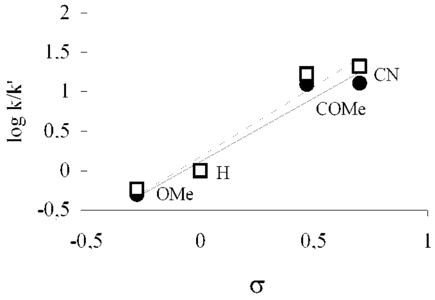

Figure 1. Effects of substituents on aryl tosylates: 4-$MePhB(OH)_2$ (●) and 4-$MeOPhB(OH)_2$ (☐).

This electronic effect is not surprising, since electron-withdrawing groups are expected to accelerate the Ar-OTs oxidative step. However, the ρ value is too low compared to those observed for aryl chlorides.[8] These values suggest that oxidative addition is not the rate-determining step in the case of aryl tosylates. We have noted that in a competitive experiment using $NiCl_2(PCy_3)_2$, aryl tosylates react twice as fast as aryl chlorides.[9]

The plot of the relative reactivity of substituted aryl tosylates against the σ constant shows that the relative reactivity is sensitive to the substituents on the aryl boronic acids (Figure 2). The correlation yields a value of $\rho \approx 0.8$ independent of the substituents on the aryl tosylate (4-NCC_6H_4OTs $\rho = 0.76$; PhOTs $\rho = 0.81$; 4-$MeOC_6H_4OTs$ $\rho = 0.85$). This indicates a subsequent rate-determining step such as transmetalation or reductive elimination. A concerted process with the participation of the π-orbitals of aryl groups has been proposed for the reductive elimination of biaryls.[10] Since the relative reactivity increases when aryl boronic acids containing electron-withdrawing groups are used, the transmetalation step is more likely to be the rate-determining step. Further evidence that transmetalation is the rate-determining step for aryl tosylates is that the reaction of 4-*t*BuC_6H_4OTs with $PhB(OH)_2$ proceeds more rapidly once the amounts of boronic acid and K_3PO_4 are increased. A yield of 35% in biaryl product was obtained after 1.5 h with 1.5 equiv of $PhB(OH)_2$ and 2.0 equiv of K_3PO_4, whereas a 50% yield was observed after the same period of time when 3.0 equiv of $PhB(OH)_2$ and 4.0 equiv of K_3PO_4 were employed.

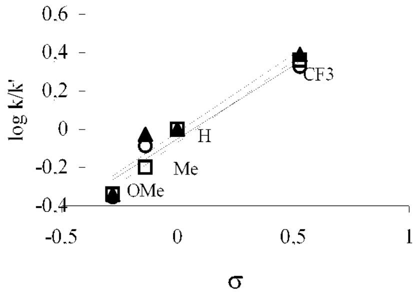

Figure 2. Effects of substituents on aryl boronic acids: 4-NCC_6H_4-OTs (○), PhOTs (▲), and 4-$MeOC_6H_4OTs$ (☐).

In conclusion, we have developed the first active and general system for the Suzuki coupling of aryl tosylates based on $NiCl_2(PCy_3)_2$, which is stable and easy to prepare and manipulate. From a synthetic point of view, these results open new possibilities for exploiting the Suzuki reaction, since aryl tosylates are easily prepared from phenols, are less susceptible to hydrolysis than aryl triflates, and are cheap and easily available starting materials. Moreover, in the case of aryl tosylates the transmetalation reaction is the rate-determining step. Further mechanistic studies are currently under investigation.

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Supporting Information Available: Detailed experimental procedure and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) $R = 8.6$ for substituent groups with $\sigma > 0.23$ (see ref 3a).

(9) The reaction of 4-*t*BuC_6H_4OTs (10 mmol) and 4-MeC_6H_4Cl (10 mmol) with $PhB(OH)_2$ (1 mmol) gave 15% conversion based on $PhB(OH)_2$ after 1 h (67:33 proportion of 4-*t*butylbiphenyl to 4-methylbiphenyl).

(10) Ozawa, F.; Yamamoto, A. *J. Chem. Soc. Jpn.* **1987**, 773−784.