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Ni^{II}–(σ-Aryl) Complex Catalyzed Suzuki Reaction of Aryl Tosylates with Arylboronic Acids

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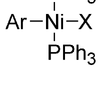
A practical, efficient protocol was developed for the Suzuki reaction of aryl tosylates with arylboronic acids. The process was promoted by a nickel-based catalyst system consisting of the easily available Ni^{II}–(σ-aryl) complex and the simple ligand PPh_3 in toluene in the presence of the base K_2CO_3. The convenient operation, high yield, generality, and low cost make this method viable for most common laboratories and applicable in large-scale preparations.

Introduction

The transition-metal-catalyzed Suzuki cross-coupling reaction has become a powerful and routine tool in organic synthesis for the construction of biaryl motifs commonly found in natural products, pharmaceuticals, and material chemicals. Over the past decades, palladium-based catalyst systems have been fully developed that allow aryl halides/pseudohalides to be effectively coupled with arylboronic acids under mild reaction conditions.[1] On the other hand, the use of cheaper nickel complexes as catalysts has also been attracting considerable interest. Since the first report by Percec in 1995,[2] remarkable advance has been made in the nickel-catalyzed version of the Suzuki reaction.[3–9] One of the advantages of Ni systems over Pd is their high reactivity toward relatively inert substrates such as aryl chlorides and sulfonates without the need of special ligands that are often expensive and/or air sensitive. For the cross-coupling reactions, aryl sulfonates, particularly tosylates, are very attractive as electrophilic substrates in place of haloarenes because of their ease of preparation and handling, pronounced stability to air and moisture, as well as low cost.

Several examples of the nickel-catalyzed Suzuki aryl–aryl couplings of aryl tosylates have been reported. Monterio et al.[5] reported the first active and efficient nickel catalyst system based on the expensive and air-sensitive ligand PCy_3. Percec et al.[6a] made a systematic investigation into the effects of $NiCl_2R_2$ precatalysts (R = PPh_3, PCy_3, 1/2dppf, and 1/2dppe), phosphane-type ligands, and solvents on the reactions, and although only a very limited number of aryl tosylates (electron-deficient ones) were studied, they gave good yields under the conditions reported. Hu et al. demonstrated the room-temperature Suzuki reaction of aryl tosylates based on the $Ni(cod)_2/PCy_3$[7a] or $Ni(cod)_2$/Fc-MP[7b] system. Despite their high catalytic activities, the Ni^0 precursor is not only costly (more expensive than normal Pd sources) but also hard to handle because of its toxicity and high instability in air. Very recently, Doi described NHC-derived Ni^{II} pincer complexes as precatalysts in Suzuki aryl–aryl couplings; but this system is effective only for electron-poor aryl tosylates.[8] Accordingly and considering the need for large-scale or even industrial preparation, it remains highly desirable to develop more practical protocols (i.e., cost efficient, convenient, and general) for Suzuki aryl–aryl cross-coupling reactions.

Recently, we have been exploring the possibility of employing Ni^{II}–(σ-aryl) complexes, *trans*-haloarylbis(triphenylphosphane)nickel(II) (Figure 1), as catalysts in cross-coupling reactions,[10] which turned out to be efficient for some C–C/C–N bond-forming coupling reactions.[3g,11] These nickel complexes, easily prepared from cheap and commercially available starting materials,[12] display good stability to air and moisture, making them highly applicable catalyst precursors. Herein, we wish to disclose our new findings concerning the Ni^{II}–(σ-aryl) complex-catalyzed Suzuki reaction of aryl tosylates with arylboronic acids.



$$\text{Ar}-\underset{\text{PPh}_3}{\overset{\text{PPh}_3}{\text{Ni}}}-\text{X}$$

Figure 1. Ni^{II}–(σ-aryl) complexes.

Results and Discussion

Initially, a combination of the simple ligand PPh_3 and different Ni^{II} complexes was chosen as catalyst system, and

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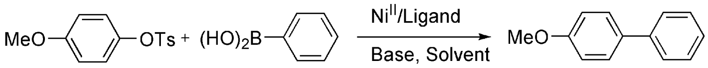
Table 1. Screening of reaction conditions for the Ni^{II}-catalyzed Suzuki reaction of aryl tosylate and phenylboronic acid.[a]



Entry	$[Ni^{II}]$[b] (mol-%)	Ligand (mol-%)	Base	Solvent	Temp. [°C]	Time [h]	Yield[c] [%]
1	$Ni(acac)_2$ (5)	PPh_3 (5)	K_2CO_3	toluene	100	5	5
2	$Ni(PPh_3)_2Cl_2$ (5)	PPh_3 (5)	K_2CO_3	toluene	100	5	51
3	**1** (5)	PPh_3 (5)	K_2CO_3	toluene	100	5	50
4	**2** (5)	PPh_3 (5)	K_2CO_3	toluene	100	5	65
5	**3** (5)	PPh_3 (5)	K_2CO_3	toluene	100	5	83
6	**3** (5)	none	K_2CO_3	toluene	100	5	66
7	**3** (5)	PPh_3 (10)	K_2CO_3	toluene	100	5	71
8	**3** (5)	IPrHCl[d] (2.5)	K_2CO_3	toluene	100	5	67
9	**3** (5)	bipy[e] (2.5)	K_2CO_3	toluene	100	5	16
10	**3** (5)	phena[f] (2.5)	K_2CO_3	toluene	100	5	8
11	**3** (5)	PPh_3 (5)	K_3PO_4	toluene	100	5	70
12	**3** (5)	PPh_3 (5)	KOH	toluene	100	5	26
13	**3** (5)	PPh_3 (5)	Na_2CO_3	toluene	100	5	20
14	**3** (5)	PPh_3 (5)	K_2CO_3	dioxane	100	5	36
15	**3** (5)	PPh_3 (5)	K_2CO_3	THF	70	5	6
16	**3** (5)	PPh_3 (5)	K_2CO_3	toluene	80	5	50
17	**3** (3)	PPh_3 (3)	K_2CO_3	toluene	100	5	79

[a] Reagents: *p*-anisyl tosylate (1 mmol), phenylboronic acid (1.5 mmol), K_2CO_3 (4 mmol), toluene (5 mL). [b] **1**: $Ni(PPh_3)_2$(1-naphthyl)Br; **2**: $Ni(PPh_3)_2$(phenyl)Br; **3**: $Ni(PPh_3)_2$(1-naphthyl)Cl. [c] Isolated yield. [d] IPrHCl: 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride. [e] bipy: 2,2′-bipyridine. [f] phena: 1,10-phenanthroline.

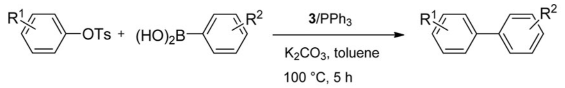
the reaction of *p*-anisyl tosylate with phenylboronic acid was performed to optimize the reaction conditions (Table 1). The effect of the source of Ni^{II} on the reaction is significant: the use of $Ni(acac)_2$ led to only 5% yield (Table 1, Entry 1); $Ni(PPh_3)_2Cl_2$ promoted substantially the reaction with 51% yield (Table 1, Entry 2); $Ni(PPh_3)_2$(1-naphthyl)Br (**1**) and $Ni(PPh_3)_2$(phenyl)Br (**2**) provided comparable yields (Table 1, Entries 3 and 4); and $Ni(PPh_3)_2$-(phenyl)Cl (**3**) was found to display the highest activity, giving a high isolated yield of 83% (Table 1, Entry 5).

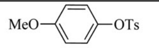
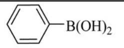
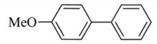
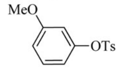
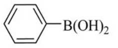
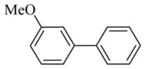
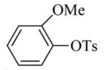
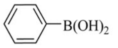
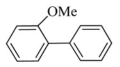
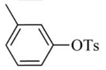
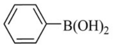
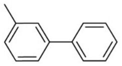
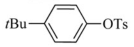
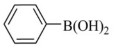
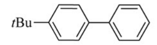
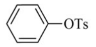
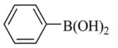
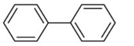
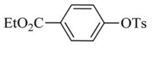
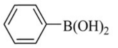
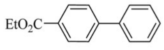
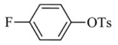
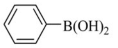
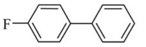
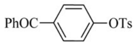
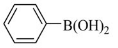
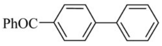
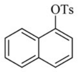
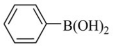
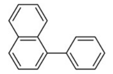
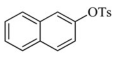
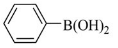
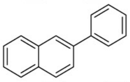
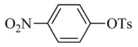
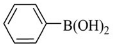
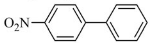
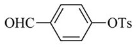
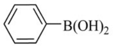
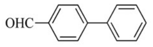
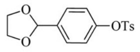
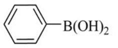
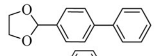
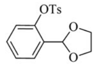
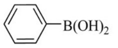
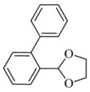
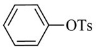
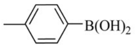
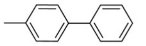
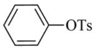
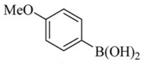
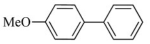
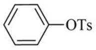
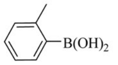
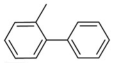
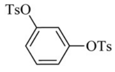
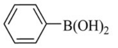
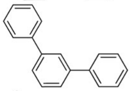
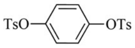
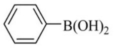
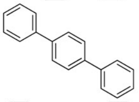
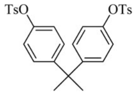
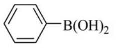
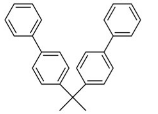
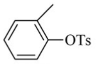
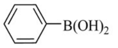
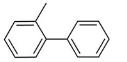
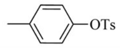
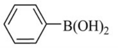
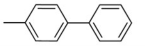
After Ni^{II}–(σ-aryl) complex **3** was determined as the preferred precatalyst, a further investigation was made into other factors that would affect the reaction, such as ligands, bases, solvents, and the like (Table 1). Without the help of additional PPh_3 ligand (Table 1, Entry 6), the reaction yield decreased substantially. Interestingly, the use of an excess amount of PPh_3 did not favor this reaction (Table 1, Entry 7). The N-heterocyclic carbene ligand IPrHCl did not seem to be superior to PPh_3 (Table 1, Entry 8), whereas the nitrogen-based bidentate ligands 2,2′-bipyridine (Table 1, Entry 9) and 1,10-phenanthroline (Table 1, Entry 10) were almost ineffective for this reaction. For the bases used, K_3PO_4 (Table 1, Entry 11) was not as effective as K_2CO_3, although it has been the most commonly used base in nickel-catalyzed Suzuki reactions;[3–9] strongly basic KOH (Table 1, Entry 12) or the weak base Na_2CO_3 (Table 1, Entry 13) was far inferior to K_2CO_3. Toluene seemed to be the solvent of choice for the reaction. For example, a considerably low yield was afforded upon replacing toluene with dioxane (Table 1, Entry 14) or THF (Table 1, Entry 15). Additionally, lowering the reaction temperature caused a substantial decrease in the yield (Table 1, Entry 16 vs. 5), and an attempt to reduce the catalyst loading also resulted in a negative effect (Table 1, Entry 17 vs. 5). Finally, the optimal reaction conditions were set as Entry 5 in Table 1.

Next, a wide range of aryl tosylates was coupled with several representative arylboronic acids under the optimized reaction conditions to examine the substrate scope of this reaction (Table 2). Generally, electron-neutral (Table 2, Entries 6, 10, 11, and 16–18), -poor (Table 2, Entries 7–9), and -rich (Table 2, Entries 1–5, 14, 15, 22, and 23) aryl tosylates were coupled smoothly in high isolated yields. Although the electronic effect of the substituents did not hamper the reaction substantially, aryl tosylates with electron-withdrawing groups (Table 2, Entries 2, 7–9) were more reactive than those with electron-donating groups (Table 2, Entries 1, 5, 14, and 23). However, 4-nitrophenyl tosylate (Table 2, Entry 12) and *p*-tosyloxybenzaldehyde (Table 2, Entry 13) indeed quenched the reaction due to the role of the nitro[13a] and formyl[13b] groups, as is well documented. The *ortho* substituents of the tosylate substrate seemed to be favorable, or they, at least, do not impose a detrimental effect on the reaction (Table 2, compare Entries 3, 10, 15, and 22 to Entries 1, 11, 14, and 23). The nickel-based catalyst, different from other transition-metal systems, is not sensitive to the steric hindrance of the electrophilic substrates, as recorded earlier.[14] In addition, the reaction was highly tolerable to some sensitive functional groups such as ester (Table 2, Entry 7) and acetal (Table 2, Entries 14 and 15) with excellent yields of the desired products. For arylboronic acid substrates, both electronic and steric effects slightly disfavored the reaction under the standard reaction conditions (Table 2, compare Entry 6 with Entries 16–18). Further, double cross-coupling proceeded in excellent yields under similar conditions when phenylene-bistosylates were treated with phenylboronic acid (Table 2, Entries 19 and

20), but the bistosylate of bisphenol-A, somehow, cannot afford a satisfactory result even upon increasing the catalyst loadings (Table 2, Entry 21).

Table 2. Ni^{II}–aryl complex catalyzed Suzuki cross-couplings of aryl tosylates with arylboronic acids.[a]



Entry	ArOTs	ArB(OH)$_2$	Product	Yield[b] [%]
1				83
2				95
3				92
4				86
5				83
6				90
7				99
8				99
9				99
10				98
11				92
12				NR
13				trace
14				81
15				85
16				80
17				83
18				79
19[c]				90
20[c]				92
21[c]				35 57[c,d]
22				83
23				85

[a] Reagents: aryl tosylate (1 mmol), arylboronic acid (1.5 mmol), **3** (0.05 mmol), PPh_3 (0.05 mmol), K_2CO_3 (4 mmol), toluene (5 mL). [b] Isolated yield. [c] Arylboronic acid (3.0 mmol). [d] **3** (0.1 mmol), PPh_3 (0.1 mmol).

Conclusions

In summary, as part of our ongoing effort, we developed a general, practical method for the Suzuki reaction of aryl tosylates with arylboronic acids catalyzed by the simple Ni^{II}–(σ-aryl) complex/PPh_3 system. The advantages of convenient operation, high yield, milder conditions, generality, and low cost make this protocol extremely attractive as an alternative and complement to metal-catalyzed Suzuki aryl–aryl cross-coupling reactions.

Experimental Section

Synthesis of $Ni(PPh_3)_2$(1-naphthyl)Cl (3) as a Representative Example for the Synthesis of Ni^{II}–(σ-aryl) Complexes:[12] A stirred mixture of $NiCl_2{\cdot}6H_2O$ (4.8 g, 0.02 mol), triphenylphosphane (11.53 g, 0.044 mol), and 95% ethanol (90 mL) was heated until a gentle reflux started. 1-Chloronaphthalene (6.5 g, 0.04 mol, excess) was then added, followed by zinc dust (1.3 g, 0.02 mol) over 5 min. The dark-green mixture very soon turned yellow. After stirring and heating under reflux for 1.5 h (under an atmosphere of nitrogen), the mixture was cooled to room temperature. Hydrochloric acid (30% aq., 4 × 2 mL) was added over 15 min. After stirring for 1.5 h, the solid was filtered off on a sintered-glass funnel and successively washed with ethanol (20 mL), hydrochloric acid (1 M aq., 2 × 20 mL), ethanol (2 × 20 mL), petroleum ether (30–60 °C, 1 × 20 mL). The yellow solid was dried in vacuo with a bath temperature of not higher than 45 °C. The yield was above 80%.

General Procedure for the Ni^{II}–(σ-Aryl) Complex-Catalyzed Reaction of Aryl Tosylates with Arylboronic Acids: An oven-dried 50-mL, three-necked flask was charged with K_2CO_3 (4 mmol), $Ni(PPh_3)_2$(1-naphthyl)Cl (0.05 mmol), and PPh_3 (0.05 mmol). Then, the aryl tosylate (1 mmol) and arylboronic acid (1.5 mmol) were added. The flask was evacuated and backfilled with nitrogen, with the operation being repeated twice. Dried PhMe (5 mL) was added by syringe at this time. The reaction mixture was heated in an oil bath of 100 °C for 5 h and then allowed to cool to room temperature; it was then filtered through a silica gel pad that was washed with ethyl acetate. The combined organic phase was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give the desired products.

Supporting Information (see footnote on the first page of this article): General considerations and characterization data of all compounds prepared.

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