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Suzuki cross-coupling of aryl halides with aryl boronic acids catalyzed by phosphine-free $NiCl_2·6H_2O$

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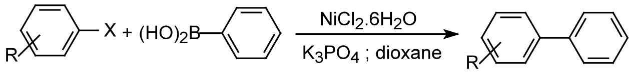
Abstract—Aryl bromides and iodides can be coupled with phenylboronic acid in good yields using $NiCl_2·6H_2O$ as a catalyst precursor. This nickel complex is cheap, widely available and can be used without any auxiliary ligand or reducing agent.

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, various efficient Pd catalyst precursors have been developed in the last several years 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] Recently, we have demonstrated that the $NiCl_2(PCy_3)_2$ complex promotes the selective cross-coupling of aryl tosylates with arylboronic acids under relatively mild reaction conditions, tolerating a variety of functional groups in both arenes.[4] During these studies we have observed in control experiments, that for some aryl halides, the complex $NiCl_2·6H_2O$ (a cheap and readily available compound) is active in the Suzuki cross-coupling reaction. More interestingly, these reactions were performed without adding any auxiliary ligand or reducing agent. From a synthetic point of view, it would be important to determine in which cases we can use this catalyst precursor. Here we demonstrate the application of $NiCl_2·6H_2O$ as a one component catalyst precursor for the Suzuki cross-coupling reaction of aryl halides.



Initially, we examined the coupling of 4-bromoanisole with phenylboronic acid using $NiCl_2·6H_2O$ under the optimized conditions developed earlier for aryl tosylates (Table 1).[4]

The Suzuki reaction carried out using 0.5 mol% of $NiCl_2·6H_2O$ furnished 4-methoxybiphenyl in 74% yield (Table 1, entry 1). Biphenyl generated from the homocoupling of phenylboronic acid was obtained in less than 1% yield. Higher concentrations of nickel (Table 1, entries 2–4) do not improve the conversion and yields of biaryl product. Low conversion was obtained using 0.01 mol% of Ni (entry 5) although this result represents a turnover number of 1300. A temperature of 130°C is the optimal temperature for this reaction (compare Table 1, entries 1, 6 and 7). The low conversion obtained at 170°C could be associated with rapid catalyst decomposition under these conditions (Table 1, entry 6). When the reaction temperature was lowered to

Table 1. $NiCl_2·6H_2O$-catalyzed Suzuki cross-coupling of 4-bromoanisole with phenylboronic acid[a]

Entry	$NiCl_2·6H_2O$ (%)	Temp. (°C)	Yield (%)[b]
1	0.5	130	74
2	1	130	63[c]
3	3	130	60
4	5	130	64
5	0.01	130	14
6	0.5	170	30[c]
7	0.5	100	6[c]

[a] Reactions conditions: 1.0 mmol of 4-bromoanisole, 1.5 mmol of phenylboronic acid, 2.0 mmol of K_3PO_4, dioxane (5 mL), 19 h (entries 2–5), 60 h (entries 1, 6 and 7).
[b] GC yield based on 4-bromoanisole.
[c] Average of two runs.

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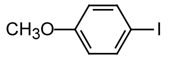
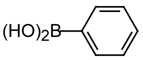
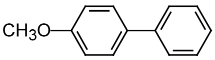
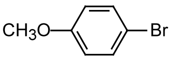
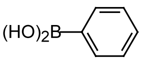
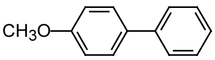
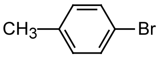
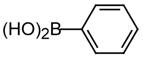
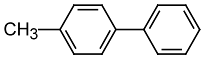
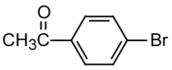
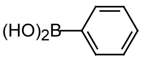
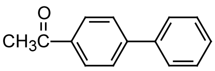
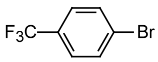
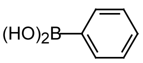
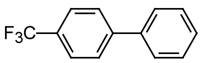
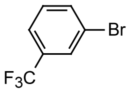
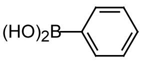
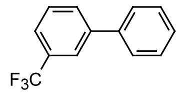
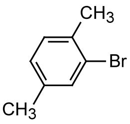
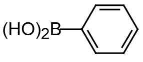
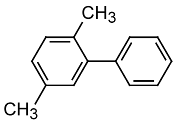
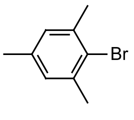
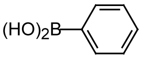
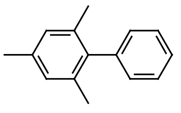
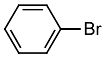
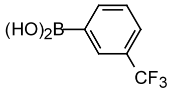
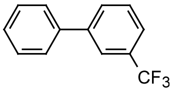
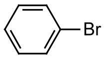
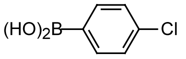
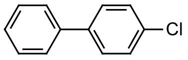
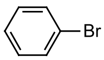
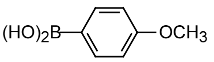
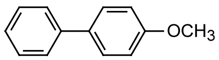
100°C, the yield also decreased (Table 1, entry 7). This could be due to the decreased solubility of K_3PO_4 and/or decreased reactivity of 4-bromoanisole. Other attempts to find reaction conditions that enabled the complete conversion of 4-bromoanisole to product, such as increased phenylboronic acid concentration or the addition of more nickel catalyst or $PhB(OH)_2$ during the reaction, also failed. The reason for this incomplete reaction is not yet clear.[5] However, the good yields obtained using such a simple, inexpensive and widely available catalyst precursor encouraged us to investigate the extension of this reaction to other aryl halides.

The coupling of several aryl halides with phenylboronic acid was examined using $NiCl_2·6H_2O$ (Table 2).[6] 4-Iodoanisole was coupled with phenylboronic acid to give 4-methoxybiphenyl in 65% yield (entry 1). Aryl bromides containing electron-withdrawing and electron-donating groups were coupled to furnish the corresponding biaryl products in good yields (61–87% yield, Table 2, entries 2–7). Ni-catalyzed Suzuki reactions are sensitive to steric hindrance and the coupling of bromomesitylene afforded very low yields of product (entry 7).[7] Attempts to perform the cross-coupling of aryl chlorides and tosylates gave only modest yields. For these substrates the addition of a phosphine ligand is essential to achieve high yields.[3,4] Substituted arylboronic acids were also investigated. $NiCl_2·6H_2O$ also promotes the coupling of bromobenzene with 3-trifluoromethylphenylboronic acid in 68% yield. However, low yields in biaryl product are obtained when 4-chlorophenylboronic acid (entry 10) and 4-methoxyphenylboronic acid (entry 11) were used. It is interesting to note that in these cases the cleavage of the aryl–boron bond, affording the arene product, was observed in significant amounts (60% of chlorophenylboronic acid is converted to chlorobenzene and 30% of

Table 2. $NiCl_2·6H_2O$-catalyzed Suzuki cross-coupling of aryl halides with arylboronic acids[a]

Entry	ArX	ArB(OH)2	Biaryl	Yield (%)[b]
1				65
2				74[c]
3				61
4				87 (85)
5				76 (72)
6				67 (61)
7				71[c]
8				6
9				68
10				31[d]
11				33[e]

[a] Reactions conditions: $NiCl_2.6H_2O$ (0.5 mol%), 1.0 mmol of aryl halide, 1.5 mmol of arylboronic acid, 2.0 mmol of K_3PO_4, dioxane (5 mL), 12 h (entry 1), 60 h(entries 2,3, 8-11), 110 h (4-7).

[b] GC Yields based on aryl halide (isolated yields in parentheses).

[c] Average of two runs.

[d] Chlorobenzene formed from 4-chlorophenylboronic acid was obtained in 60% yield.

[e] Anisole formed from 4-metoxyphenylboronic acid was obtained in 32% yield.

methoxyphenylboronic acid is converted to anisole). Attempts to improve the cross-coupling reaction by using a higher arylboronic acid concentration or adding more aryl boronic acid during the reaction did not increase the yield in byphenyl product. This secondary reaction could be associated with the deactivation of the nickel catalyst and the incomplete conversion of aryl bromide observed in this system. A study of this reaction is underway in our laboratory.

In summary, we have found that aryl bromides and iodides can be coupled with phenylboronic acid in good yields using $NiCl_2 \cdot 6H_2O$ as catalyst precursor. This nickel complex is cheap, widely available and can be used without any auxiliary ligand or reducing agent. From a synthetic point of view this protocol is cheap and an easy alternative for the synthesis of biaryls from aryl bromides and iodides.

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5. Incomplete conversion in nickel-catalyzed Suzuki cross-coupling has been observed in several cases. See Refs. 3a, 3b, 4a and: Percec, V.; Bae, J. Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060.
6. In a typical experiment an oven-dried resealable Schlenk flask was evacuated and back-filled with argon and charged with K_3PO_4 (2 mmol), arylboronic acid (1.5 mmol), and $NiCl_2 \cdot 6H_2O$ (0.005 mmol). The flask was evacuated and back-filled with argon and then the aryl halide (1 mmol) and dioxane (5 mL) were added. The reaction mixture was stirred at the desired temperature until the conversion of starting aryl halide stopped, as judged by GC analysis. The solution was then taken up in ether (20 mL) and washed with aqueous NaOH (1 M, 5 mL) and brine (2×5 mL), and then dried over $MgSO_4$. After purification by flash chromatography the biaryl product was characterized by ^1H and ^{13} C NMR, IR and GC–MS.
7. For an active Pd-catalyst for the synthesis of sterically hindered biaryls see: Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163.