

Cross-Coupling of Chloroarenes with Boronic Acids using a Water-Soluble Nickel Catalyst.

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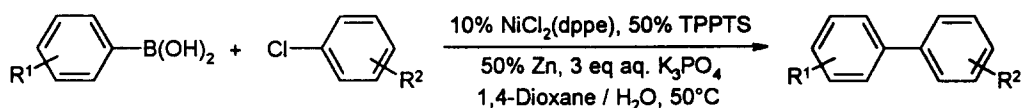
Abstract: Various biaryl compounds are prepared by cross-coupling reactions between arylboronic acids and aromatic chlorides in organoaqueous medium. These reactions are performed using an hydrosoluble Ni(0) catalyst preformed from NiCl₂(dppe) and TPPTS. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Biaryls have aroused a great interest in organic chemistry since they have found many industrial and biological applications¹. Elaboration of liquid crystals, for example, often relies on the synthesis of a biaryl framework. On the other hand, many important natural products contain this molecular substructure as illustrated by biphenomycin^{2a} or steganacin^{2b}.

The synthesis of biaryl compounds is often based on a palladium catalyzed coupling between an aromatic halide and a phenylboronic acid³. These Suzuki type reactions are efficiently carried out with aromatic bromides or iodides. Moreover, we have recently shown that biaryls can be cleanly generated from arenediazonium salts and arylboronic acids or aromatic potassium trifluoroborates under very mild conditions⁴. However the use of the more accessible chlorides remains challenging since they are generally unreactive towards the oxidative addition of the Pd(0) species and require harsh experimental conditions⁵.

The use of nickel instead of palladium appear as a good alternative to this problem⁶. Various biaryl compounds have been recently synthesized from phenylboronic acids and aromatic chlorides by using a Ni(0) catalyst⁷. Although quite effective, these methods require the use of the expensive NiCl₂(dppf) precursor and are incompatible with an aqueous medium.

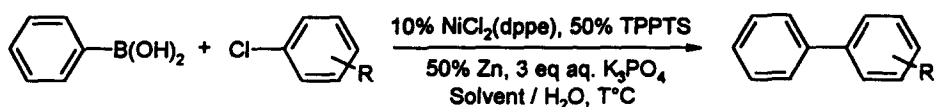
In our continuous interest in organometallic catalysis in organoaqueous medium⁸, we wish to report herein that biaryls can be efficiently synthesized by using a water-soluble Ni(0) catalyst preformed from NiCl₂(dppe) and TPPTS (Scheme 1).



Scheme 1

Although hydrosoluble Ni(TPPTS)₃ complex is thoroughly described⁹, we looked for a more expeditious way to generate a water-soluble Ni(0) species. We have found that such a catalyst could be easily preformed by heating a mixture of NiCl₂(dppe), TPPTS¹⁰ and Zn at 80°C in neat water. Obtention of the requisite biaryl compound is achieved by adding to this solution a diluted mixture of phenylboronic acid and complementary arylchloride in an appropriate solvent, as well as 3 equivalents of a 3.7 molar K₃PO₄ aqueous solution (Table 1).

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Entry	R	Solvent	T(°C)	Product	Yield ^a
1	4-COCH ₃	1,4-Dioxane	50		(79%)
2	4-CHO	1,4-Dioxane	50		81% (85%)
3	4-COPh	1,4-Dioxane	50		70%
4	4-CF ₃	DMF ^b	80		80% (85%)
5	4-CH ₃	NMP	80		70% (76%)

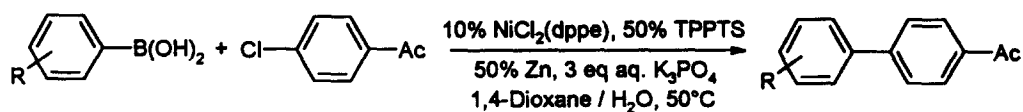
^a: Isolated yield. GPC conversions are given inside brackets. See ref. 11 for a typical experimental procedure.

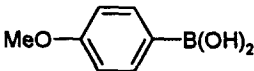
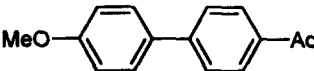
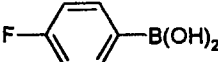
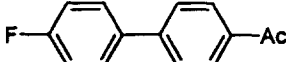
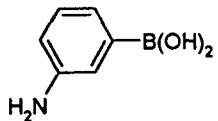
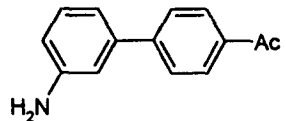
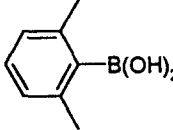
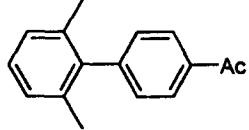
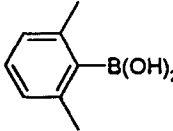
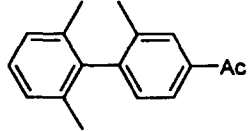
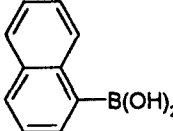
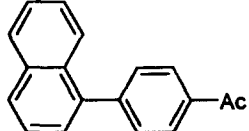
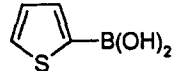
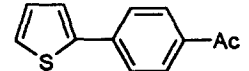
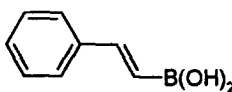
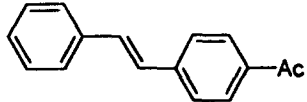
^b: The use of 1,4-dioxane as solvent gave a lower yield (35%).

Table 1

Aromatic chlorides substituted with an electronic withdrawing group undergo smoothly clean cross-coupling reactions at 50°C in 1,4-dioxane with good yields and selectivities since only traces of homocoupling products could be detected (entries 1-3). Good results can also be obtained with 4-chlorotrifluoromethylbenzene by performing the reaction in DMF (entry 4) or, in the case of more electron-rich substrates such as 4-chlorotoluene, in N-methylpyrrolidinone (entry 5). On the other hand, no reaction took place in the absence of Zn or TPPTS which supports the presumed intervention of a true Ni(0) species.

We next turned our attention to the cross-coupling reactions between 4-chloroacetophenone and several substituted arylboronic acids. As depicted in table 2, these reactions offer an efficient access to a large variety of biaryls under mild conditions and with satisfactory yields ranging from 47% to 99%. Important features include the possible use of arylboronic acids bearing electronic withdrawing or donating substituents (entries 1-3). Moreover, the reaction turns out to be independent of steric effects, as evidenced by the formation of di or even tri-*o-o'*-substituted structures (entries 4 and 5). Heteroaromatic substrates may also be used (entry 7), as well as vinylboronic acids offering an interesting route to styrene derivatives (entry 8).

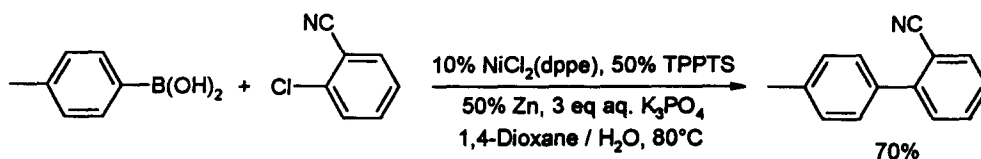


Entry	ArB(OH) ₂	Product	Yield ^a
1			81%
2			86%
3			47%
4			94%
5 ^b			67%
6			99%
7			72%
8			88%

^a: Isolated yield. ^b: 3-Methyl-4-chloroacetophenone was used.

Table 2

These new conditions may find valuable laboratory synthetic applications, as shown in the non-optimized preparation of 2-*p*-tolylbenzonitrile known as an important pharmaceutical intermediate¹² (Scheme 2).



Scheme 2

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10. TPPTS = sodium triphenylphosphinitrimetasulfonate.
11. Typical procedure (Table 2, entry 6): Water and solvents were degazed before use and experiments are carefully run under argon. TPPTS (0.5 eq; 0.25 mmol; 473 mg of a 30% wt. solution in water), Zn (0.5 eq; 0.25 mmol; 16.4 mg) and NiCl₂(dppf) (10% mol.; 0.05 mmol; 26.4 mg) were placed in a Schlenk tube under argon. 0.3 ml of water was added and the suspension was vigorously stirred at 80°C for 2h. The bright red solution was cooled to 50°C after what a solution of 1-naphtaleneboronic acid (1.1 eq; 0.55 mmol; 95 mg) in 1 ml of 1,4-dioxane was added. 4-chloroacetophenone (1.0 eq; 0.5 mmol; 65 µl) and 0.4 ml (3.0 eq) of a 3.7 M aqueous K₃PO₄ solution were quickly introduced and the resulting mixture was stirred overnight at 50°C, then quenched with 7 ml of sat. NH₄Cl solution and extracted by 3×20 ml of ether. The organic layer was washed with 20 ml of brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash-chromatography on silica gel to give 123 mg (99%) of the expecting product. ¹H NMR (CDCl₃; 200 MHz; δ): 8.11 (2H, d, ³J = 8.5 Hz, 2×CH_{arom}), 8.0-7.8 (3H, m, H_{arom}), 7.7-7.4 (6H, m, H_{arom}); 2.7 (3H, s, CH₃); ¹³C NMR (CDCl₃; 50 MHz; δ): 197.7, 145.7, 138.9, 135.9, 133.7, 131.1, 130.2, 128.3, 126.8, 126.3, 125.9, 125.5, 125.3, 26.6; MS (EI, m/z): 246 (M⁺); 231 (M - CH₃)⁺; 202 (M - COCH₃ - H)⁺.
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