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LETTERS

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

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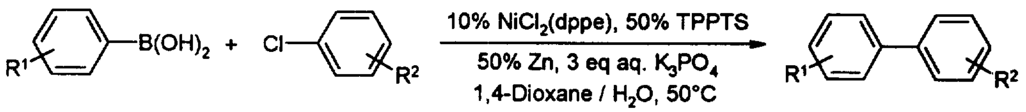
Abstract: Various biarylic coumpounds are prepared by cross-coupling reactions between arylboronic acids and aromatic chlorides in organoaqueous medium. These reactions are performed using an hydrosoluble Ni(0) catalyst preformed from $NiCl_2$(dppe) and TPPTS.

Biaryls have aroused a great interest in organic chemistry since they have found many industrial and biological applications[1]. Elaboration of liquid cristals, for example, often relies on the synthesis of a biarylic framework. On the other hand, many important natural products contain this molecular substructure as illustrated by biphenomycin[2a] or steganacin[2b].

The synthesis of biarylic compounds is often based on a palladium catalyzed coupling between an aromatic halide and a phenylboronic acid[3]. 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 conditions[4]. 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 conditions[5].

The use of nickel instead of palladium appear as a good alternative to this problem[6]. Various biarylic compounds have been recently synthesized from phenylboronic acids and aromatic chlorides by using a Ni(0) catalyst[7]. Although quite effective, these methods require the use of the expensive $NiCl_2$(dppf) precursor and are incompatible with an aqueous medium.

In our continuous intererest in organometallic catalysis in organoaqueous medium[8], we wish to report herein that biaryls can be efficiently synthesized by using a water-soluble Ni(0) catalyst preformed from $NiCl_2$(dppe) and TPPTS (Scheme 1).



Scheme 1

Although hydrosoluble $Ni(TPPTS)_3$ complex is thoroughly described[9], 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 $NiCl_2$(dppe), TPPTS[10] and Zn at 80°C in neat water. Obtention of the requisite biarylic 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 K_3PO_4 aqueous solution (Table 1).

Fax: 01-44-07-10-62 E-Mail: genet@ext.jussieu.fr

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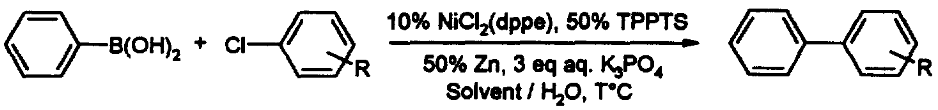
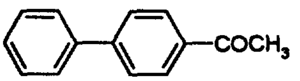
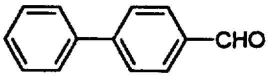
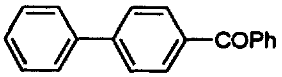
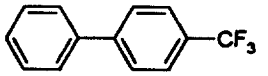
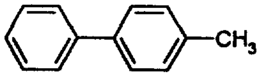


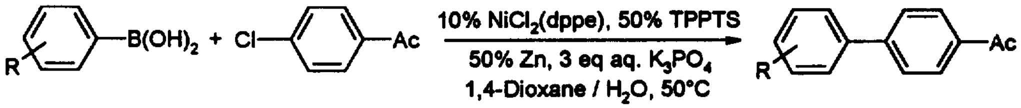
Entry	R	Solvent	T(°C)	Product	Yield[a]
1	4-$COCH_3$	1,4-Dioxane	50		(79%)
2	4-CHO	1,4-Dioxane	50		81% (85%)
3	4-COPh	1,4-Dioxane	50		70%
4	4-CF_3	DMF[b]	80		80% (85%)
5	4-CH_3	NMP	80		70% (76%)

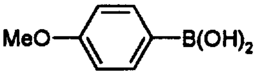
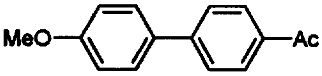
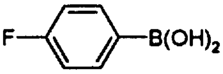
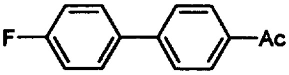
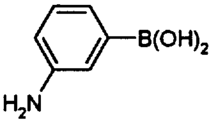
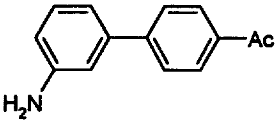
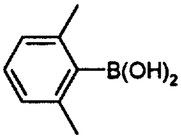
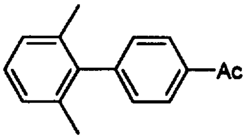
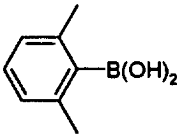
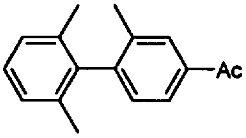
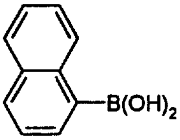
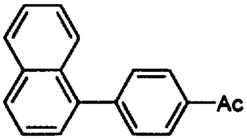
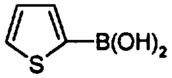
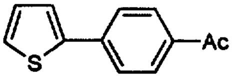
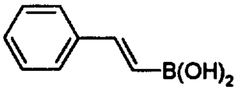
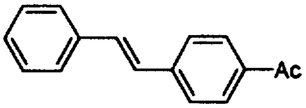
[a]: Isolated yield. GPC conversions are given inside brackets. See ref. 11 for a typical experimental procedure.
[b]: The use of 1,4-dioxane as solvent gave a lower yield (35%).

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 fomation 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).

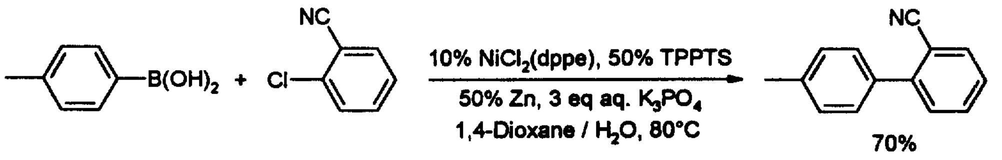


Entry	$ArB(OH)_2$	Product	Yield[a]
1			81%
2			86%
3			47%
4			94%
5[b]			67%
6			99%
7			72%
8			88%

[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 intermediate[12] (Scheme 2).



Scheme 2

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10. TPPTS = sodium triphenylphosphinotrimetasulfonate.
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 NiCl$_2$(dppe) (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 K$_3$PO$_4$ solution were quickly introduced and the resulting mixture was stirred overnight at 50°C, then quenched with 7 ml of sat. NH$_4$Cl solution and extracted by 3×20 ml of ether. The organic layer was washed with 20 ml of brine, dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash-chromatography on silical gel to give 123 mg (99%) of the expecting product. ^{1}H NMR (CDCl$_3$; 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, CH$_3$); ^{13}C NMR (CDCl$_3$; 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 - CH$_3$)$^+$; 202 (M - COCH$_3$ - H)$^+$.
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