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Suzuki-Type Coupling of Chloroarenes with Arylboronic Acids Catalysed by Nickel Complexes

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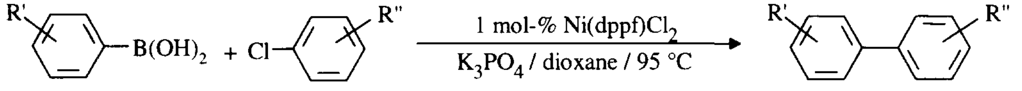
Abstract: A Suzuki-type cross-coupling reaction of aryl chlorides with arylboronic acids using nickel-catalysts is described. The best results were obtained at 95 °C in the presence of K_3PO_4 and in dioxane using Ni(dppf)Cl_2. Unsymmetrical biaryls with both electron-withdrawing and electron-donating functional groups were obtained in high yields. © 1997 Elsevier Science Ltd.

The palladium-catalysed cross-coupling of aryl electrophiles with arylboronic acids, the so called „Suzuki-coupling“, is a powerful tool for the synthesis of substituted biaryls.[1] High yields can be obtained with coupling partners bearing a variety of functional groups. Aryl bromides, iodides and triflates are easily activated by palladium catalysts and are therefore often employed for the Suzuki-coupling. The more economical but less reactive aryl chlorides do not react except when they are activated by electron-withdrawing groups.[2]

Nickel complexes are known to activate chloroarenes more easily.[3] Percec et al. recently developed a Suzuki-coupling for aryl mesylates and tosylates using a nickel catalyst.[4] With a similar protocol it was possible to couple aryl chlorides, too.[5] However, in both studies the nickel-catalysts were only active in the presence of a reducing agent. Here we report a convenient procedure for the Suzuki-coupling of various chloroarenes and arylboronic acids that does not need an activating agent. TON (turn over number) up to 200 were observed compared to 10 in the previous studies.[4,5]



R', R'' = Alkyl, F, OR, SR, NH_2, CN, CHO, CF_3

We adopted the conditions that Percec et al.[4] had used for aryl mesylates (Ni(dppf)Cl_2, Zn, K_3PO_4 in dioxane) to the reaction of 4-chloro-anisole with phenylboronic acid (Table 1). With 10 mol-% catalyst 4-methoxy-biphenyl was obtained in 76 % yield. However it was not possible to lower the amount of catalyst without a decrease in yield (entry 2). Percec et al.[4] reported that in the coupling of aryl mesylates the presence of zinc is absolutely essential to get an active catalyst. Surprisingly, in the case of chloroarenes the catalyst performed much better when the reducing agent was omitted. It was possible to lower the amount of catalyst to 1 mol-% without a substantial loss in yields (entries 3 -7).

Table 1: Nickel-catalysed Suzuki-coupling of 4-chloro-anisole with phenylboronic acid using K_3PO_4 as the base.[a]

entry	solvent[6]	temp.	catalyst[b]	[mol-%]	conversion[c]	biphenyl	remarks
		°C			[%]	[%]	
1	dioxane	95	Ni(dppf)Cl_2	10	76	4	with Zn[d]
2	dioxane	95	Ni(dppf)Cl_2	5	38	2	with Zn[d]
3	dioxane	95	Ni(dppf)Cl_2	10	82	4	
4	dioxane	95	Ni(dppf)Cl_2	5	78	4	
5	dioxane	95	Ni(dppf)Cl_2	1	77	3	
6	dioxane	95	Ni(dppf)Cl_2	0.5	46	3	
7	dioxane	95	Ni(dppf)Cl_2	0.1	3	4	
8	dioxane	95	Ni(dppf)Cl_2	1	84	5	1.6 eq. $PhB(OH)_2$
9	anisole	130	Ni(dppf)Cl_2	1	2	9	
10	anisole	95	Ni(dppf)Cl_2	1	67	3	
11	anisole	70	Ni(dppf)Cl_2	1	70	3	
12	anisole	25	Ni(dppf)Cl_2	1	2	1	
13	anisole	95	Ni(dppf)Br_2	1	70	3	
14	anisole	95	$Ni(PPh_3)_2Cl_2$	1	68	6	
15	anisole	95	Ni(dppb)Cl_2	1	70	8	
16	anisole	95	Ni(dppp)Cl_2	1	17	7	
17	anisole	95	Ni(dppe)Cl_2	1	11	8	
18	anisole	95	$Ni(PPh_3)_2$(naph)Cl[e]	1	16	11	
19	anisole	95	$Ni(PPh_3)_2$(tol)Cl[e]	1	13	7	

a. Reactions were carried out under argon using K_3PO_4 (3 mmol), arylboronic acid (1.1 mmol), chloroarene (1 mmol) and the indicated amount of catalyst in 4 ml solvent. The reaction mixture was stirred for 16 hours.

b. dppf: 1,1'-bis(diphenylphosphino)ferrocene, PPh_3: triphenylphosphine, dppb: 1,4- bis(diphenylphosphino)butane, dppp: 1,3- bis(diphenylphosphino)propane, dppe: 1,2- bis(diphenylphosphino)ethane.

c. Determined by GC.

d. 3 equivs Zn / Ni were used.

e. naph: 1-naphthyl, tol: 2-tolyl. see ref. 7

In general, the reactions were very clean. Less than 10 % biphenyl was found formed either by homocoupling[8] of the phenylboronic acid or the coupling with a phenyl group of the ligand via aryl-phenyl scrambling.[9] Besides of biphenyl, only 4,4'-dimethoxy-biphenyl (less than 1 %) was detected, so the conversions of the chloroarene in Table 1 also represent the yields of 4-methoxy-biphenyl very well.

Similar results were found in anisole (see ref. 6). At 95 °C, the conversion reached 67 % after 4 hours (entry 10), and did not improve further with longer reaction time. The conversion was therefore slightly lower than in dioxane. At 70 °C, the reactions also stopped at a conversion of 70 %, but 24 hours were needed. Very low conversions were obtained at 130 °C (fast catalyst decomposition) and at room temperature (very slow reaction) (entries 9 and 12).

It is not yet clear why the reaction did not go to completion both in anisole and in dioxane (entries 3 and 10). When more phenylboronic acid was added after the reaction had stopped, the conversion was increased by about 15 % under these conditions. This indicates that the phenylboronic acid was decomposed rather than that the catalyst was deactivated. The finding that adding more phenylboronic acid resulted in a more pronounced improvement than increasing the amount of catalyst points in the same direction (compare entries 3, 5 and 8).

Different nickel complexes were examined as catalyst precursors in anisole (entries 13 - 17). With dppf the chloride or the bromide complex gave almost the same yields. The PPh_3 and dppb complexes were as effective as the dppf complex. Ligands like dppp and dppe that form very stable five and six membered chelates gave only poor results. A similar trend was found by Saito et al..[5] We suggest that one phosphorus dissociates during a step of the catalytic cycle. Surprisingly, nickel aryl complexes (entries 18 and 19) which are assumed to be intermediates in a nickel(0)-nickel(II) catalytic cycle were less effective than the nickel dichloride complexes, indicating that an alternative catalytic cycle might be active.

Table 2: Synthesis of biaryls via Suzuki-coupling of chloroarenes and arylboronic acid.[a]

entry	R'	R"	catalyst	mol-%	GC yield [%]	isolated yield [%]
20	H	4-COMe	$Ni(dppf)Cl_2$	1	100	80
21	H	2-CN	$Ni(dppf)Cl_2$	0.5	100	-
22	H	2-CN	$Ni(dppf)Cl_2$	1	100	95
23	4-Me	2-CN	$Ni(dppf)Cl_2$	3	83	76
24	2-Me	$4-CF_3$	$Ni(dppf)Cl_2$	3	88	26
25	H	3-CHO	$Ni(dppf)Cl_2$	3	86	66
26	H	$3-NH_2$	$Ni(dppf)Cl_2$	1	88	79
27	H	4-OMe	$Ni(dppf)Cl_2$	1	77	68
28	H	2-S-*i*-Pr,$3-NH_2$	$Ni(dppf)Cl_2$	10	80	50
29	2-Me	2-F, 5-F	$Ni(dppf)Cl_2$	1	69	40
30	$3-NO_2$	4-COMe	$Ni(dppf)Cl_2$	5	0	-
31	A[b]	H	$Ni(dppf)Cl_2$	1	79	51
32	H	B[b]	$Ni(PPh_3)_2Cl_2$	1	100	66
33	H[c]	2-Cl	$Ni(dppf)Cl_2$	1	73 (6 : 100)[d]	-
34	H[c]	2-Cl	$Ni(PPh_3)_2Cl_2$	1	62 (10 : 8)[d]	-

a. Reactions were carried out under argon using K_3PO_4 (6 mmol), arylboronic acid (2.2 mmol), chloroarene (2 mmol) and the indicated amount catalyst in dioxane (8 ml). The reaction mixture was stirred for 16 hours at 95 ° C.

b. A : 2-thiophenylboronic acid. B: 1-chloro-naphthalene.

c. 4.4 mmol phenylboronic acid were used.

d. Ratio of monoarylated to diarylated product.

With the standard protocol a variety of substrates baring different functional groups could be coupled to the corresponding unsymmetrical biaryls in high yields (Table 2). Some aryl chlorides activated by electron-withdrawing groups gave quantitative yields with TON of 100 and higher (entries 20 - 22). With groups like amine and thioether the yields were still very satisfactory (entries 26 - 28), although somewhat lower. On the other hand, a nitro group was not tolerated (entry 30); no reaction was observed in this case. The reaction is not very sensitive to steric hindrance like ortho substituents (entries 21 - 24, 28 and 29), and also heterocyclic and polycyclic compounds can be employed (entries 31 and 32).

In the reaction of 1,2-dichloro-benzene with 2 equivalents of phenylboronic acid a noteworthy difference in selectivity between the dppf and the PPh_3 complex was observed. (entries 34 and 35). With Ni(dppf)Cl_2, o-terphenyl was formed almost exclusively, whereas with Ni$(PPh_3)_2Cl_2$ a 10 : 8 mixture of o-chloro-biphenyl and o-terphenyl was obtained.

In summary, we found a convenient and broadly applicable method for the synthesis of unsymmetrical biaryls starting from aryl chlorides and arylboronic acids.[10] A variety of functional groups is tolerated. The airstable nickel complexes are easily prepared and can be used as catalyst without any activation. Since many aryl chlorides are commercially available and are less expensive than aryl bromides and iodides, this new method allows an easier and more cost efficient synthesis of biaryls.

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References and Notes

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6. Several solvents were tested using 1 mol-% Ni(dppf)Cl_2 and K_3PO_4 as the base. Dioxane (77 %), pyridine (69 %), anisole (67 %) and toluene (63 %) were the best solvents. Poor results were obtained in water (0 %), tributylamine (0 %), acetic acid (0 %), n-propanol (0 %), acetonitrile (1 %), heptane (1 %), N,N-dimethylacetamide (1 %) and dichloroethane (2 %). In between were *n*-butyl acetate (10 %), THF (16 %), xylene (23 %), dibutyl ether (49 %) and dimethoxyethane (50 %).
   K_3PO_4 as the base gave the best results (67 %), using 1 mol-% Ni(dppf)Cl_2 in anisole. With $Ba(OH)_2$, the yields were only 35 %. All other bases (NaOH, NaH, $NaHCO_3$ and Na_2CO_3) gave yields below 10 %. K-t-butylate and tributylamine were completely ineffective. We can not excluded that an other base in combination with an other solvent than anisole might be suitable as well.
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10. *Representative procedure:* To Ni(dppf)Cl_2 (0.01 mmol), K_3PO_4 (3 mmol) and phenylboronic acid (1.1 mmol) under argon 4-chloro-anisole (1 mmol) and degassed dioxane (4 ml) were added. The reaction mixture was stirred at 95 °C overnight. Water was added and the product was extracted with ether and purified by distillation. The products were identified by NMR spectroscopy.

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