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SUZUKI ARYL COUPLINGS MEDIATED BY PHOSPHINE-FREE NICKEL COMPLEXES

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Abstract: Suzuki aryl cross-couplings employing phenylboronic acid and a range of aryl halides proceed under mild conditions with high efficiency using the phosphine-free nickel complexes $NiCl_2(NEt_3)_2$ and $NiCl_2$(bipy), both derived from $NiCl_2$. © 1999 Elsevier Science Ltd. All rights reserved.

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Palladium-mediated cross-coupling reactions are versatile methods for carbon-carbon bond formation.[1] Of particular interest is the coupling of aryl boronic acids and aryl halides, the so called Suzuki reaction, due to the fact that the biaryl unit and its homologues are frequently found in natural products.[2] The most frequently used catalyst for the Suzuki reaction is $Pd(PPh_3)_4$ but often a number of by-products are formed in the reaction. In particular, with a catalyst containing PPh_3 ligands, there is scope for activation of one of the phenyl rings of the ligand and coupling of this with the aryl boronic acid, this forming an undesired biaryl product.[3] Here we show the application of two phosphine free nickel complexes to metal-mediated biaryl formation. Nickel catalysed Suzuki reactions are not unprecedented[4,5] but this represents the first development of an air stable triphenylphosphine free catalyst.

Reaction of anhydrous $NiCl_2$ with two equivalents of the monodentate ligand triethylamine or one equivalent of the bidentate ligand 2,2'-bipyridine (bipy) in methanol under reflux leads, within a few minutes, to the quantitative formation of the nickel(II) complexes $NiCl_2(NEt_3)_2$ and $NiCl_2$(bipy) respectively, as characterised by comparison of spectroscopic data with that in the literature and by analysis (Scheme 1).[6,7]

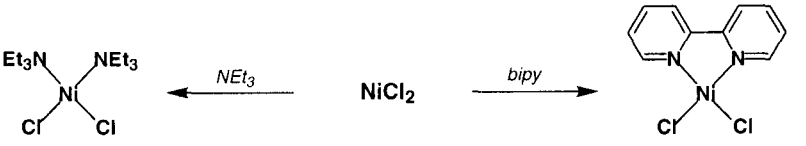

Figure 1: Synthesis of phosphine-free nickel complexes for use in the Suzuki reaction

Although the Ni(II) complexes are slightly air sensitive and are stored under nitrogen prior to use, the key advantage of these over Ni(0) complexes used previously, such as $Ni(COD)_2$,[8] is that these are easily handled and are not prone to decomposition by oxidation or protonolysis.

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The complexes were assessed for their activity in the Suzuki protocol initially by studying the coupling of 4-bromotoluene with phenylboronic acid to form 4-phenyltoluene. (Figure 2). The effects of base, catalyst concentration, solvent and reaction time were investigated, reaction conditions and yields being shown in Tables 1 and 2. 4-Bromotoluene was chosen in preference to bromobenzene because, with the former, it is possible to distinguish between the heterocoupling of the aryl halide and boronic acid and the homocoupling of the reactants.

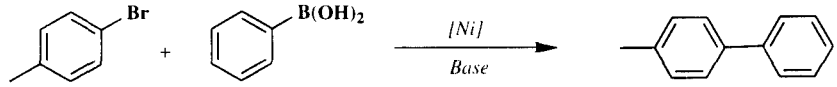


Figure 2: The Suzuki coupling reaction

Table 1: The effect of catalyst concentration on the coupling of 4-methyltoluene with phenylboronic acid [a]

Catalyst	Quantity	Yield
$NiCl_2(bipy)$	1 mol%	30
"	3 mol%	70
"	6 mol%	70
"	12 mol%	80
$NiCl_2(NEt_3)_2$	1 mol%	20
"	3 mol%	80
"	6 mol%	80
"	12 mol%	80

[a] Reaction performed using dioxane as the solvent and Na_3PO_4 as base at 95 °C for 16 hours

Table 2: The effects of solvent, base and time on the coupling of 4-bromotoluene with phenylboronic acid [a]

Catalyst	Solvent	Base	Biaryl yield	
			8h	16h
$NiCl_2(bipy)$	Dioxane	Na_3PO_4	70	70
		NaOH	50	50
		Na_2CO_3	40	40
$NiCl_2(bipy)$	Toluene	Na_3PO_4	30	50
		NaOH	20	40
		Na_2CO_3	15	40
$NiCl_2(bipy)$	Hexane	Na_3PO_4	10	30
		NaOH	5	20
		Na_2CO_3	5	20
$NiCl_2(NEt_3)_2$	Dioxane	Na_3PO_4	80	80
		NaOH	50	50
		Na_2CO_3	20	20
$NiCl_2(NEt_3)_2$	Toluene	Na_3PO_4	25	50
		NaOH	15	20
		Na_2CO_3	2	10
$NiCl_2(NEt_3)_2$	Hexane	Na_3PO_4	5	20
		NaOH	0	0
		Na_2CO_3	0	0

[a] Reaction run for 16 hours at reflux temperature of the solvent using 3 mol% of the catalyst

The main findings of the studies are that:

- The rate and yield of the reaction is optimised using polar, weakly coordinating solvents such as dioxane. The reaction reaches completion within 8 hours and leads to up to 80% yields of the biaryl. DMF, the most common solvent employed in Suzuki (and Stille) coupling reactions, shows similar results to dioxane. Toluene slightly inhibits cross coupling leading to up to 50% yields of the biaryl but only after the full 16 hours. Solvents such as hexane and dichloromethane slow the reaction markedly, almost to the point of inhibition. This trend is not totally unexpected and has been seen previously in Suzuki reactions using nickel phosphine complexes.[5]

- The best results are found using potassium phosphate as base, this leading to the highest yields of biaryl (around 90% using dioxane as a solvent). The use of mineral bases such as sodium hydroxide and sodium carbonate leads to less satisfactory results (around 60% using dioxane as a solvent).

- The best results are obtained using the triethylamine coordinated nickel complexes as opposed to the bipy coordinated examples. This points towards the fact that the mechanism of the reaction at some point may involve dissociation of a triethylamine ligand in the case of $NiCl_2(NEt_3)_2$ or one of the pyridyl groups of bipy in the case of $NiCl_2$(bipy). This being said, relative rate of ligand dissociation is only one explanation for the observation.[9]

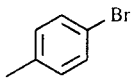
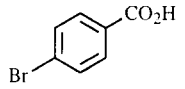
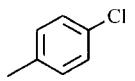
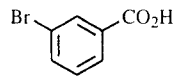
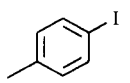
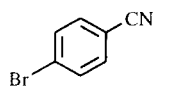
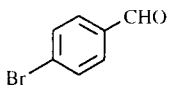
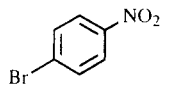
- A study of the concentration of metal necessary to optimise the yield of coupled product shows that the reaction was best performed using between 3 and 6 mol% of the reagent. Any more than 6 mol% of catalyst is unnecessary as the yield does not increase any further and less than 3 mol% results in a significant drop in yield.

- The reactions are very clean, the absence of any triphenylphosphine ligands meaning that no biaryl is formed as a result of coupling with a phenyl group of the ligand.

- Unlike some other nickel-mediated aryl coupling reactions where contaminants such as water cause substantial reduction in yields, in the present studies trace quantities of water have little effect on the overall yield of product.

In an attempt to illustrate the generality of the procedure, the coupling of phenyl boronic acid with a range of aryl halides was investigated, products being isolated (Table 3). The results from these screening experiments indicate that, although $NiCl_2(NEt_3)_2$ can be used for the coupling of aryl chlorides, the bromides give far better results under the conditions used here. This may be due to the fact that, in the aryl halides, the more labile C-Br bond is activated more easily than the less labile C-Cl bond under the relatively mild conditions used here. In addition, the influence of substituent on the aryl halide has only a negligible effect on the yield of coupled product compared with phenyl boronic acid. Similar observations have been reported in other Suzuki coupling reactions, the effects of both electron donating and withdrawing groups on the rate of reaction and yield of coupled product being inconsequential, with the notable exception of a nitro group where no reaction occurs. This anomaly with nitro-substituted arenes has been seen in other studies.[5]

Table 3: The effect of substituents on the Ni-mediated coupling of aryl halides with phenylboronic acid [a]

Aryl halide	Yield	Aryl halide	Yield
	80		72
	48		62
	84		65
	68		0

[a] Reaction performed using $NiCl_2(NEt_3)_2$ as the catalyst (3 mol%), dioxane as solvent and Na_3PO_4 as base for 16 hours at 95 °C. Isolated yields are reported.

In conclusion, we have found a convenient method for the synthesis of biaryls using amine and diimine coordinated nickel(II) complexes. The reaction was found to be highly dependent on the solvent in which the reaction was performed, on the base used and on the molar percentage of metal complex used. The optimum conditions were found to be when dioxane was used as a solvent, K_3PO_4 as used as the base, 3 mol% $NiCl_2(NEt_3)_2$ added and the reaction performed at 95 °C overnight.

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EXPERIMENTAL

Unless stated otherwise, all syntheses were performed under an inert atmosphere of dry nitrogen using standard Schlenk techniques. Routine separation of products was performed by chromatography using Merck silica gel 60 (70-230 mesh, 60 Å). All reagents were purchased from commercial sources and used as received unless noted otherwise. Literature methods were used to prepare the starting material compounds $NiCl_2(NEt_3)_2$[7] and $NiCl_2(bipy)$[6]. ^1H- and ^{13}C- NMR spectra were recorded in $CDCl_3$ using a Bruker AM400 or WM250 Fourier transform NMR spectrometer and data reported using the chemical shift scale in units of ppm relative to $SiMe_4$ (d = 0). Fast atom bombardment (FAB) mass spectra were recorded using a KRATOS MS-50 spectrometer, with either 3-nitrobenzylalcohol or thioglycerol as a matrix and CsI as calibrant.

Representative experimental for the coupling of 4-bromotoluene and $PhB(OH)_2$: In a general reaction the nickel complex was added to a solution (35 ml) of phenylboronic acid (1.00 g, 8.2 mmol), 4-bromotoluene (1.2g, 0.86 ml, 7.0 mmol), and base (20 mmol) under a nitrogen atmosphere. The reaction mixture was then stirred and refluxed at the boiling point of the solvent for 16 hours, monitoring the reaction regularly by removing aliquots of the solution and analysing them by LC-MS. After this time, the reaction mixture was cooled, water added and organics extracted with ether and evaporated to dryness *in vacuuo*. Purification of the product mixture by column chromatography (using hexane as eluent) led to the recovery of the desired biaryl, 4-phenyltoluene. mp = 49-50 °C; ^{1}H-NMR δ = 7.59 (m, 2H), 7.52 (m, 2H), 7.35 (m, 2H), 7.29 (m, 2H), 7.21 (m, 1H), 2.23(s, 3H); ^{13}H-NMR δ = 141.0, 138.3, 136.9, 129.4, 128.6, 21.04; m/z = 168, $C_{13}H_{12}$ requires 168.

Optimisation of conditions: The effects of catalyst ($NiCl_2$(bipy) and $NiCl_2(NEt_3)_2$), catalyst concentration (1-12 mol%), solvent (dioxane, toluene and hexane), base (Na_3PO_4, NaOH and Na_2CO_3) and reaction time (8-16 hours) were each investigated. The results are shown in Tables 1 and 2.

Coupling of 4-chlorotoluene and $PhB(OH)_2$: $NiCl_2(NEt_3)_2$ (3 mmol) was added to a dioxane solution (35 ml) of phenylboronic acid (1.00 g, 8.2 mmol), 4-chlorotoluene (0.88 g, 0.82 ml, 7.0 mmol), and Na_3PO_4 (3.26 g, 20 mmol) under a nitrogen atmosphere. The reaction mixture was then stirred at 95 °C for 16 hours. The reaction mixture was then cooled, water added and organics extracted with ether and evaporated to dryness *in vacuuo*. Purification of the product mixture by column chromatography (using hexane as eluent) led to the recovery of 4-phenyltoluene (0.56 g, 3.36 mmol) in 48% yield based on 4-chlorotoluene.

Coupling of 4-Iodotoluene and $PhB(OH)_2$: The reaction was performed as in the case of 4-chlorotoluene using 4-iodotoluene (1.52 g, 7.0 mmol) in the place of the chloro analogue. Purification of the product mixture led to the recovery of 4-phenyltoluene (0.98 g, 5.88 mmol) in 84% yield based on 4-iodotoluene. MASS =

Coupling of 4-bromobenzaldehyde and $PhB(OH)_2$: The reaction was performed as in the case of 4-chlorotoluene but using 4-bromobenzaldehyde (1.30 g, 7.0 mmol). Purification of the product mixture by column chromatography (using dichloromethane / hexane 1:10 as eluent) led to the recovery of 4-phenylbenzaldehyde (0.94 g, 4.76 mmol) in 68% yield. mp = 60-61 °C; ^{1}H-NMR δ = 10.2 (s, 1H), 8.05 (m, 2H), 7.71 (m, 2H), 7.61 (m, 2H), 7.45 (m, 3H); ^{13}H-NMR δ = 191.6, 147.0, 139.6, 135.2, 130.2, 128.9, 128.3, 127.6, 127.3; m/z = 182, $C_{13}H_{10}O$ requires 182.

Coupling of 4-bromobenzoic acid and $PhB(OH)_2$: The reaction was performed as in the case of 4-chlorotoluene but using 4-bromobenzoic acid (1.41 g, 7.0 mmol). Purification of the product mixture by column chromatography (using dichloromethane / hexane 3:7 as eluent) led to the recovery of 4-phenylbenzoic acid (1.00 g, 5.04 mmol) in 72% yield. mp = 227-229 °C; ^{1}H-NMR δ = 8.05 (m, 2H), 7.72 (m, 4H), 7.43 (m, 3H), 2.55 (s, 1H); ^{13}H-NMR δ = 167.3, 144.5, 139.3, 130.0, 129.7, 128.8, 127.9, 126.8; m/z = 198, $C_{13}H_{10}O_2$ requires 198.

Coupling of 3-bromobenzoic acid and $PhB(OH)_2$: The reaction was performed as in the case of 4-bromobenzoic acid but using 3-bromobenzoic acid (1.41 g, 7.0 mmol). Purification of the product mixture by column chromatography (using dichloromethane / hexane 3:7 as eluent) led to the recovery of 3-phenylbenzoic acid (0.93 g, 4.69 mmol) in 67% yield. mp = 112-114 °C; ^{1}H-NMR δ = 7.74 (m, 2H), 7.58 (m, 1H), 7.52 (m, 1H), 7.38 (m, 5H), 2.51 (s, 1H); ^{13}H-NMR δ = 169.3, 141.5, 140.3, 132.0, 130.7, 129.8, 129.1, 128.8, 127.7, 126.7; m/z = 198, $C_{13}H_{10}O_2$ requires 198.

Coupling of 4-bromobenzonitrile and $PhB(OH)_2$: The reaction was performed as in the case of 4-chlorotoluene but using 4-bromobenzonitrile (1.27 g, 7.0 mmol). Purification of the product mixture by column chromatography (using dichloromethane / hexane 1:10 as eluent) led to the recovery of 4-phenylbenzoic acid (0.82 g, 4.55 mmol) in 65% yield. mp = 86-87 °C; ^{1}H-NMR δ = 7.71 (m, 2H), 7.62 (m, 3H), 7.45 (m, 4H); ^{13}H-NMR δ = 145.6, 139.1, 132.5, 129.0, 128.6, 127.6, 127.1, 118.9, 110.8; m/z = 179, $C_{13}H_9N$ requires 179.

Coupling of 1-bromo-4-nitrobenzene and $PhB(OH)_2$: The reaction was performed as in the case of 4-chlorotoluene but using 4-bromonitrobenzene (1.41 g, 7.0 mmol). No 4-nitrobiphenyl was formed.

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9. It is likely that Ni(I) and Ni(III) intermediates with geometries ranging from square planar through tetrahedral to octahedral may well be involved in the reaction mechanism. Furthermore, the very different hybridisation and bite angle of the two ligands will undoubtedly play a role in determining the rate of reaction.