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Nickel-catalyzed reductive coupling of chlorodiphenylphosphine with aryl bromides into functionalized triarylphosphines

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Abstract—Functionalized triarylphosphines are obtained with good yields in a one-step reaction of an equimolar mixture of chlorodiphenylphosphine and an aromatic bromide in NMP or DMF at 110°C in the presence of zinc dust and a catalytic amount of $NiBr_2(bpy)$. A possible catalytic pathway is discussed.

1. Introduction

The modern synthetic chemistry counts increasingly on catalysis to obtain more efficient and clean procedures. In the field of homogeneous catalysis, tertiary arylphosphines form an important class of ligands of transition metals which has attracted considerable interest in the past few decades. The presence of functional groups on at least one aryl moiety can obviously offer the advantage of fitting the catalytic properties of a phosphine-ligated metallic center. However, the preparation of functionalized phosphines excludes the usual methods of synthesis based on reactions involving aryllithium or aryl Grignard reagents in the case of base-sensitive functional groups. Since the pioneering work of Stille,[1] which reported in 1987 a palladium-catalyzed coupling reaction between functionalized aryl iodides and either trimethylstannyl- or trimethylsilyl-diphenylphosphine, several studies have been devoted to transition metal-catalyzed cross-coupling reactions leading to arylphosphines. For example, aryl triflates react with diphenylphosphine in the presence of $Pd(OAc)_2$ and dppb (dppb=bis-diphenylphosphinobutane),[2] or in the presence of $NiCl_2(dppe)$ (dppe=bis-diphenylphosphinoethane).[3] Recent papers relate that triphenylphosphine can also be used in order to obtain aryldiphenylphosphine through Pd-catalyzed couplings with either aryltriflates[4] or aromatic bromides.[5] Interestingly, Laneman et al.[6] reported some years ago that the nickel complex $NiCl_2(dppe)$ is also an efficient catalyst for the synthesis of triarylphosphines, with moderate yields from aryl bromides and with good yields from aryl triflates. These substrates are coupled with chlorodiphenylphosphine in a one-pot reaction using zinc dust as reductant. More recently, $NiCl_2(PPh_3)_2$ was found to be an effective catalyst towards phosphination of biaryl triflates with chlorodiphenylphosphine.[7] In a related approach, a group in this laboratory showed that such a reductive cross-coupling between an aryl bromide or an heteroaromatic chloride and Ph_2PCl can be achieved by an electrochemical way where the catalyst is generated by electroreduction of $NiBr_2(bpy)$ (bpy=2,2′-bipyridine).[8] This method is however rather delicate to perform since its requires a well controlled addition rate of Ph_2PCl all over the electrolysis in order to avoid side reactions. Even in optimized reaction conditions, yields in arylphosphine are only moderate.

We then decided to reinvestigate the chemical approach on the basis of both Laneman's work and our electrochemical investigations. Actually, it is known that the reduction of a Ni^{II}-dppe salt leads to a zerovalent complex $Ni^0(dppe)$ which is very reactive towards carbon−halogen bonds.[9] On the contrary, the stable $Ni^0(dppe)_2$ complex is quite unreactive.[10] It may form by disproportionation between two $Ni^0(dppe)$, thus accounting for a loss of the catalyst in the form of nickel metal. Such a drawback does not exist when the ligand is bipyridine (bpy), since zerovalent nickel reacts with aryl halides, even in the presence of an excess of bpy.[11]

We report in this paper our results on the reductive coupling between functionalized aryl bromides and Ph_2PCl by a chemical reaction employing zinc as the reductant and complexes of nickel associated with 2,2′-bipyridine (bpy) or 2,2′-dipyridylamine (dpa) as catalysts.

Keywords: triarylphosphine; chlorodiphenylphosphine; aromatic bromide; reductive cross-coupling; nickel-bipyridine catalysis.

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2. Results and discussion

Our first goal was the synthesis of m-CF_3–$C_6H_4PPh_2$ (product **1a**) from m-CF_3–C_6H_4Br and $ClPPh_2$, and we conducted new experiments either in DMF or NMP (*N*-methylpyrrolidinone), and using nickel complexes associated to bidentate nitrogenous ligands, either bpy or dpa instead of dppe, as catalyst precursor. In a typical experiment, an equimolar mixture of m-CF_3–C_6H_4Br and $ClPPh_2$ was heated at 110°C in DMF or NMP, in the presence of a slight excess of zinc and a catalytic amount of $NiBr_2$(bpy) or $NiBr_2$(dpa). The reactions were conducted until more than 95% of the aryl halide was consumed. The results are reported in Table 1.

It is worth noting that the yields in **1a** are higher when NMP is used as solvent instead of DMF, and also with $NiBr_2$(bpy) (entries 1 and 2 of Table 1) as catalyst rather than $NiBr_2$(dpa) (entries 3 and 4 of Table 1). Both catalysts are indeed efficient. However, if the Ni-dpa system allows rather higher yields (entries 3 and 4 of Table 1), it also tends to favor the partial oxidation of the phosphine **1a** into the corresponding oxide **1b** during the work up. A crucial experimental parameter is the reaction temperature. Indeed, two experiments corresponding to entries 2 and 4 of Table 1 were performed at 80°C instead of 110°C. After an overnight reaction, the aryl bromide was not fully consumed and the yield in coupling products (**1a**+**1b**) was only 20–25%. On the other hand, no difference in the yield was observed when zinc was added either after cooling the solution at 5–10°C, as recommended with the Ni-dppe catalyst,[6] or at room temperature, this being followed by immediate heating up to 110°C. Other parameters were studied, while keeping the following unchanged, i.e. reaction temperature at 110°C, $NiBr_2$(bpy) as the catalyst precursor, and NMP as the solvent. As shown in Table 1, entries 5–8, the reaction remained very efficient when the concentration of both reactants was increased up to 2 mol L^{-1} while lowering the molar ratio of the catalyst to 2.5%. Even with 1.25% of $NiBr_2$(bpy) (entry 9 of Table 1), the yield was high, though the reaction rate was slowed down. The reaction conditions corresponding to entry 8 of Table 1 were thus considered as being satisfactory.

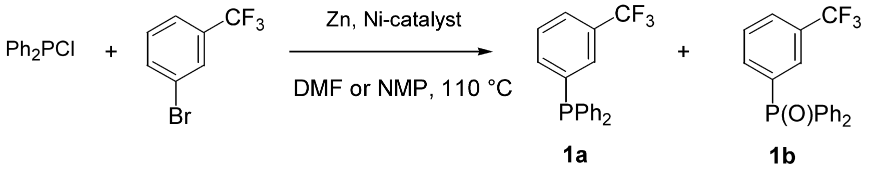
We then extended this method to other substituted aryl bromides. In NMP with a 2.5% ratio of $NiBr_2$(bpy), the cross-coupling with chlorodiphenylphosphine was performed with moderate to good yields by heating at 110°C an equimolar mixture of both reactants and zinc dust. Results are reported in Table 2.

It can be seen that the position of the substituent has a high influence on the efficiency of the cross-coupling reaction. Indeed, *meta*- and *para*-trifluoromethyl-bromobenzene furnishes the coupling products in high yields (entries 1 and 3 of Table 2) whereas *ortho*-trifluoromethyl-bromobenzene leads to only 30% of the related triarylphosphine (entry 2 of Table 2), several by-products being formed along with. When very reactive *para*-substituted aryl bromides are used, the amount of catalyst has to be reduced to 1.25% and even in these conditions, the reaction proceeds very fast (entries 7 and 8 of Table 2). We also found that the oxide is easily formed when the functional group on the starting aryl halide is electron-donating like the methoxy group (Table 2, entry 9). These results also show again that the use of DMF as solvent and $NiBr_2$(dpa) as catalyst (Table 2, entries 10–12) leads to significant amounts of the product in the form of the oxide.

To our knowledge, the mechanism of this nickel-catalyzed reductive cross coupling between chlorodiphenylphosphine and an aryl halide has not been described. We propose the following catalytic mechanism (Scheme 1), notably on the basis of previous electroanalytical studies.

Since no coupling product is obtained in the absence of nickel complexes, this indicates that the reaction proceeds via an homogeneous catalysis involving organonickel complexes. This catalytic cycle is initiated by the zinc reduction of the divalent nickel precursor into a zerovalent complex, either Ni^0(bpy) or Ni^0(dpa) in this work, or

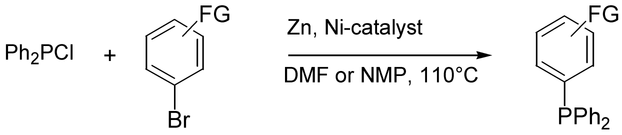
Table 1. Nickel-catalyzed reductive cross-coupling between chlorodiphenylphosphine and *m*-trifluoromethylbromobenzene



Entry	Solvent	Volume (mL)	Catalyst (mol%)	Reaction time (h)	GC Yield (%)		Isolated (%)
					1a	**1b**	**1a**
1	DMF	20	$NiBr_2$(bpy) (5)	4	60	5	–
2	NMP	20	$NiBr_2$(bpy) (5)	1	70	10	68
3	DMF	20	$NiBr_2$(dpa) (5)	3	60	20	55
4	NMP	20	$NiBr_2$(dpa) (5)	2	75	24	63
5	NMP	10	$NiBr_2$(bpy) (5)	1.25	88	5	–
6	NMP	7.5	$NiBr_2$(bpy) (5)	0.75	85	6	–
7	NMP	7.5	$NiBr_2$(bpy) (2.5)	1.5	84	6	–
8	NMP	5	$NiBr_2$(bpy) (2.5)	2	95	4	86
9	NMP	5	$NiBr_2$(bpy) (1.25)	4	80	6	–

Standard reaction conditions: Ph_2PCl (10 mmol), ArBr (10 mmol), Zn dust (16 mmol), 110°C under argon.

Table 2. Nickel-catalyzed reductive cross-coupling between chlorodiphenylphosphine and functionalized aryl bromides



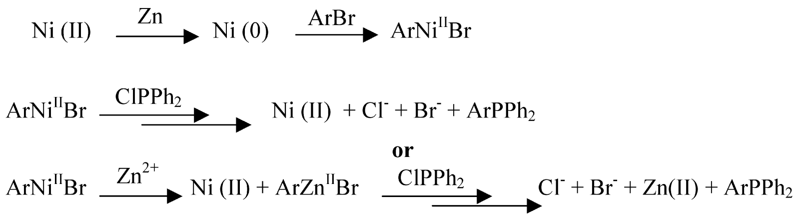
Entry	FG	Solvent	Catalyst (mol%)	Reaction time (h)	Product and isolated yield (%)		
1	*m*-CF_3	NMP	$NiBr_2$(bpy) (2.5%)	2	**1a**	*m*-$F_3C-C_6H_4PPh_2$	86
2	*o*-CF_3	NMP	$NiBr_2$(bpy) (2.5%)	4	**2a**	*o*-$F_3C-C_6H_4PPh_2$	30
3	*p*-CF_3	NMP	$NiBr_2$(bpy) (2.5%)	3	**3a**	*p*-$F_3C-C_6H_4PPh_2$	75
4	*m*-CN	NMP	$NiBr_2$(bpy) (2.5%)	1.25	**4a**	*m*-$NC-C_6H_4PPh_2$	73
5	*m*-CO_2Et	NMP	$NiBr_2$(bpy) (2.5%)	3	**5a**	*m*-$EtO_2C-C_6H_4PPh_2$	69
6	*p*-CO_2Et	NMP	$NiBr_2$(bpy) (2.5%)	3	**6a**	*p*-$EtO_2C-C_6H_4PPh_2$	76
7	*p*-COMe	NMP	$NiBr_2$(bpy) (1.25%)	1	**7a**	*p*-$MeOC-C_6H_4PPh_2$	75
8	*p*-CHO	NMP	$NiBr_2$(bpy) (1.25%)	0.5	**8a**	*p*-$HOC-C_6H_4PPh_2$	70[a]
9[b]	*p*-MeO	NMP	$NiBr_2$(bpy) (2.5%)	3	**9a**	*p*-$MeO-C_6H_4PPh_2$	49[c]
10	*m*-CF_3	DMF	$NiBr_2$(dpa) (5%)	3	**1a**	*m*-$F_3C-C_6H_4PPh_2$	55[c]
11	*m*-CN	DMF	$NiBr_2$(dpa) (5%)	3	**4a**	*m*-$NC-C_6H_4PPh_2$	62[c]
12	*m*-CO_2Et	DMF	$NiBr_2$(dpa) (5%)	3	**5a**	*m*-$EtO_2C-C_6H_4PPh_2$	61[c]

Standard reaction conditions: solvent (5 mL), Ph_2PCl (10 mmol), ArBr (10 mmol), Zn dust (16 mmol), 110°C, under argon.

[a] GC yield, the coupling product leads to degradation products during work-up.

[b] The starting compound was *p*-$MeO-C_6H_4I$.

[c] Actually, large amounts of phosphine oxides were detected in the crude mixture.



Scheme 1. A possible catalytic mechanism of the Ni-catalyzed cross-coupling reaction between $ClPPh_2$ and an aromatic bromide.

Ni^0(dppe) in Laneman's work.[6] These zerovalent nickel complexes are known to react by oxidative addition with aryl halides (ArX) to give the corresponding σ-aryl-nickel complex, $ArNi^{II}XL$.[11,12] At this stage, two routes can be envisaged. Either $ClPPh_2$ can react with ArNiX to yield the aimed product, or a transmetallation reaction first occurs between ArNiX and Zn^{2+} cations thus providing ArZnX.[13] Thus, as demonstrated elsewhere,[14] the aryl phosphine would be obtained by coupling of an organozinc intermediate with the electrophile $ClPPh_2$. However, in the absence of ArBr, we have found that the addition of $NiBr_2$(bpy) and zinc dust into a solution of $ClPPh_2$ induces the transformation of the chlorophosphine into unidentified product(s). Therefore, we can assume that the zerovalent complex Ni^0(bpy) can also reacts with $ClPPh_2$, either by electron transfer or by oxidative addition with the P–Cl bond but we have any information on a possible mechanism leading to a coupling product with an aryl halide by this way.

3. Conclusion

We have demonstrated several examples of cross coupling reactions between commercially available chlorophosphine and aromatic bromides. Functionalized triarylphosphines, potentially useful as ligands in homogeneous catalysis, are obtained with good yields by this way which uses zinc as a cheap reductant and $NiBr_2$(bpy) as an efficient catalyst. The main features of this versatile method are the simplicity of the reaction conditions and the compatibility with various functional groups. We propose a possible catalytic mechanism for this Ni-bpy catalyzed reaction.

4. Experimental

Solvents (NMP or DMF in analytical grades) and starting materials were purchased from commercial suppliers and used without further purification. The catalytic precursor $NiBr_2$(bpy) was prepared according to a reported method[15] by precipitation in absolute ethanol of an equimolar mixture of $NiBr_2\cdot xH_2O$ and 2,2′-bipyridine, filtration, ethanol rinsing and drying. The same method was applied to the synthesis of the complex $NiBr_2$(dpa). Chromatographic purifications were realized using Merck 60 ACC (70–200 mesh) silica gel.

4.1. Typical experimental procedure for a Ni-catalyzed cross-coupling reaction between chlorodiphenylphosphine and an aromatic bromide

A mixture of ArBr (10 mmol), chlorodiphenylphosphine (1.8 mL, 10 mmol) and either $NiBr_2$(bpy) (93 mg, 0.25 mmol) or $NiBr_2$(dpa) (97 mg, 0.25 mmol) were dissolved in 5 mL NMP (*N*-methyl-pyrrolidinone). Zinc dust (1.1 g, 16 mmol) was added portion wise in a few minutes. The solution was then heated under argon up to 110°C until GC analysis of samples indicated the quasi consumption of ArBr. The solution was allowed to cool at room temperature and the solvent was evaporated under a reduced pressure in the presence of celite. The triarylphosphine was recovered by a chromatographic purification on a silica gel (Merck 60 ACC, 70–200 mesh) column and elution with a suitable pentane/diethyl ether mixture.

4.2. Analytical data

GC analyses were performed on a 5 m CPSIL-5CB column using a Varian 3400 CX chromatograph. Mass spectra were recorded on a Finnigan GC/MS GCQ spectrometer. ^{1}H (200 MHz), ^{31}P (81 MHz) and ^{19}F (188 MHz) NMR spectra were recorded in CDCl$_3$ on a Bruker AC200 spectrometer. Analytical data of synthesized triarylphophines fit with analytical data found in given references.

4.2.1. [(3-Trifluoromethyl)phenyl]-diphenylphosphine 1a.[16,17] Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 7.80–7.10 (m, 14H); ^{31}P NMR, δ (ppm): -9.99; ^{19}F NMR, δ (ppm): -62.38; MS, *m*/*z* (relative intensity): 330 (M,100), 251 (M$-$79, 19), 203 (M$-$127, 18), 183 (M$-$147, 48), 108 (M$-$222, 22).

4.2.2. [2-(Trifluoromethyl)phenyl]-diphenylphosphine 2a.[18] White solid; ^{1}H NMR, δ (ppm): 7.65–7.55 (m, 1H), 7.20–7.05 (m, 13H); ^{31}P NMR, δ (ppm): -16.15 (q, J=47 Hz); ^{19}F NMR, δ (ppm): -56.45 (d, J=47 Hz); MS, *m*/*z* (relative intensity): 330 (M,100), 241 (M$-$89, 60), 183 (M$-$147, 33), 165 (M$-$165, 18), 107 (M$-$223, 8).

4.2.3. [4-(Trifluoromethyl)phenyl]-diphenylphosphine 3a.[1] Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 7.53 (m, 2H), 7.41–7.27 (m, 12H); ^{31}P NMR, δ (ppm): -10.33; ^{19}F NMR, δ (ppm): -62.52; MS, *m*/*z* (relative intensity): 330 (M,100), 251 (M$-$79, 20), 203 (M$-$127, 18), 183 (M$-$147, 36), 108 (M$-$222, 27).

4.2.4. (3-Cyanophenyl)-diphenylphosphine 4a.[19] Pale brown solid; ^{1}H NMR, δ (ppm): 7.80–7.20 (m, 14H); ^{31}P NMR, δ (ppm): -10.04; MS, *m*/*z* (relative intensity): 287 (M, 100), 208 (M$-$79, 33), 183 (M$-$104, 36), 108 (M$-$179, 35).

4.2.5. Ethyl 3-(diphenylphosphino)benzoate 5a.[8] Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 8.30–8.10 (m, 2H), 7.70–7.35 (m, 12H), 4.48 (q, ^{3}J=7.1 Hz, 2H), 1.49 (t, ^{3}J=7.1 Hz, 3H); ^{31}P NMR, δ (ppm): -10.44; MS, *m*/*z* (relative intensity): 334 (M, 100), 306 (M$-$28, 19), 181 (M$-$153, 49).

4.2.6. Ethyl 4-(diphenylphosphino)benzoate 6a.[8] Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 8.12 (m, 2H), 7.60–7.35 (m, 12H), 4.48 (q, ^{3}J=7.1 Hz, 2H), 1.48 (t, ^{3}J=7.1 Hz, 3H); ^{31}P NMR, δ (ppm): -10.18; MS, *m*/*z* (relative intensity): 334 (M, 100), 306 (M$-$28, 16), 181 (M$-$153, 57), 152 (M$-$182, 10).

4.2.7. (4-Acetylphenyl)-diphenylphosphine 7a.[1] White solid; ^{1}H NMR, δ (ppm): 7.86 (m, 2H), 7.40–7.25 (m, 12H), 2.56 (s, 3H); ^{31}P NMR, δ (ppm): -9.95; MS, *m*/*z* (relative intensity): 304 (M, 100), 261 (M$-$43, 16), 225 (M$-$79, 10), 183 (M$-$121, 52).

4.2.8. (4-Methoxyphenyl)-diphenylphosphine 9a.[1] White solid; ^{1}H NMR, δ (ppm): 7.22–7.14 (m, 12H), 6.77 (m, 2H), 3.66 (s, 3H); ^{31}P NMR, δ (ppm): -12.03; MS, *m*/*z* (relative intensity): 292 (M, 100), 277 (M$-$15, 9), 213 (M$-$79, 19), 199 (M$-$93, 11), 184 (M$-$108, 38), 170 (M$-$122, 9), 138 (M$-$154, 9), 108 (M$-$184, 9).

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