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Electrochemical Cross-coupling Between 2-Halopyridines and Aryl or Heteroaryl Halides Catalysed by Nickel-2,2'-Bipyridine Complexes.

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Abstract : 2-Arylpyridines can be obtained in good to high yields by electrochemical reduction using the sacrificial anode process and catalysis by nickel-2,2'-bipyridine (bpy) complexes. In a first approach functionalized arylzinc species are prepared in DMF as solvent by electrolytic reduction of the corresponding aryl-bromides or -chlorides in the presence of $ZnBr_2$ and Ni(II)-bpy complexes and then coupled with 2-chloropyridine. In a second approach the cross-coupling occurs from the electrochemical reduction of a stoichiometric mixture of an aryl halide and 2-halopyridine in DMF in the presence of $NiBr_2$bpy as catalyst.

INTRODUCTION

The nickel catalyzed electroreduction of organic halides offers an easy way of activation of carbon-halogen bonds at potentials ranging between -1 and -1.5 V/SCE, i.e. quite higher than those necessary for the cathodic reduction of most organic halides.[1] This method has mostly been used for the reductive dimerisation of organic halides, notably of arylhalides to prepare biaryls, or of aryldihalides to prepare polymers.[1,2] When combined with the sacrificial anode process, these reactions can be conducted efficiently under very simple reaction conditions. More challenging are the cross-coupling reactions. We have already reported[3] on the efficient synthesis of α-aryl-esters, -ketones, or -nitriles by reduction of mixtures of arylhalides and α-halo-esters, -ketones, or -nitriles in the presence of Ni-catalyst and a sacrificial aluminium anode (eq 1).

$$FG\text{-}C_6H_4X + Cl\text{-}CH(R)A \xrightarrow{e,\ cat} FG\text{-}C_6H_4CH(R)A \qquad (1)$$

with X = Br, Cl; R = H, Me, Ph; A = CO_2R', COR', CN;
FG = Me, OMe, CO_2R', COR', F, CN

We have also described another approach for the synthesis of unsymmetrical biaryls. This method is based on the nickel catalyzed electrochemical formation of an arylzinc intermediate from FG-C_6H_4X[4] followed by palladium catalyzed chemical coupling of the arylzinc halide with FG'-C_6H_4X (eq 2).[5]

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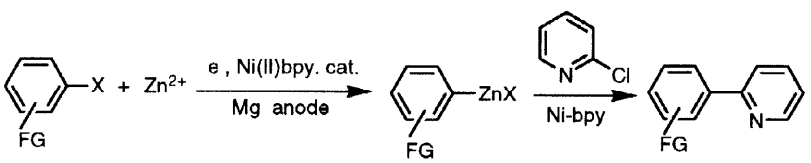
Though already applied to a large variety of aromatic structures, this coupling reaction has be used with very only few heteroaromatic compounds. We have already reported[6] on the electrosynthesis of 3-thienylzinc bromide from 3-bromothiophene and its coupling with aromatic halides.

$$FG\text{-}C_6H_4X + ZnBr_2 \xrightarrow[e,\ DMF]{Ni^{II}\ cata} FG\text{-}C_6H_4ZnX \xrightarrow[FG'\text{-}C_6H_4X]{Pd(0)} FG\text{-}C_6H_4\text{-}C_6H_4\text{-}FG' \qquad (2)$$

The arylation of halopyridines developed by Negishi et al[7] goes through the formation of the organozinc compound from the halopyridine or the aromatic halide followed by their coupling by a palladium catalysis with respectively aryl or pyridyl halides. The organozinc compound from 2-iodo- or bromo-pyridine can be prepared directly by reaction of Rieke's active zinc on this halide;[8] this method is compatible with an ester group on the ring.

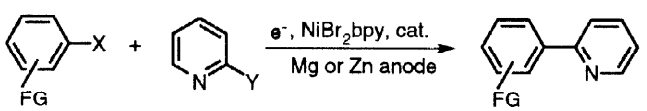
Recently, the one-step coupling of pyridyl triflate and a variety of arylbromides mediated by a stoichiometric amount of hexamethylditin, LiCl and $Pd(0)(PPh_3)_4$ as catalyst has been reported.[9] In this reaction, the palladium likely allows the in situ formation of a pyridylstanane from the pyridyl compound and its coupling with the aryl halide.

In this paper, we present two electrochemical processes for the arylation of halopyridines. The first one involves the electrochemical preparation of an arylzinc compound followed by its reaction with 2-chloropyridine (eq 3), the two steps being catalyzed by the same nickel-bipyridine complex.



(3)

The second one is the electroreduction of a mixture of aryl or heteroaryl halide and 2-halopyridine in DMF as solvent in the presence of a catalytic amount of $NiBr_2bpy$ (eq 4).



(4)

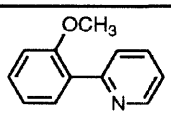
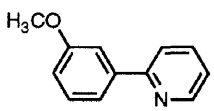
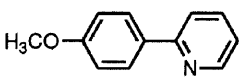
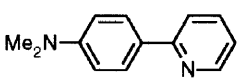
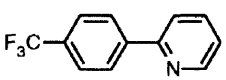
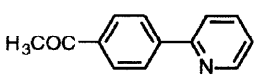
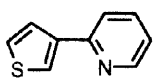
X, Y = Cl or Br; FG = electron-donating or electron-withdrawing group

RESULTS AND DISCUSSION

1. Electrosynthesis of arylzinc compounds and their coupling with 2-chloropyridine.

We have recently shown that various functionalized aryl bromides or chlorides can be converted into aryl zinc species by an electrochemical method using a nickel catalyst and zinc ions.[4,5] These electrogenerated organometallics react with aryl halides in the presence of a catalytic amount of palladium phosphine to give unsymmetrical biaryls in good yields.[5] In all cases previously studied, the catalysis by palladium is necessary because the nickel-bpy complex present in the medium does not catalyze this coupling reaction even with some electricity supply to generate the zero-valent nickel. In contrast, with 2-chloropyridine as the aryl halide added in the second stage, the coupling is efficiently catalyzed by Ni-bpy, and 2-arylpyridines are obtained in good yields. Results are reported in Table 1 for the arylation of 2-chloropyridine according to eq 4.

Table 1. Nickel-Catalyzed Electrochemical Arylation of 2-Chloropyridine via the Formation of an Arylzinc Intermediate

Entry	FG-C_6H_4ZnX	Coupling Product	Isolated Yield % based on starting FG-C_6H_4X
1	*o*-CH_3O-C_6H_4ZnCl	 **A**	55
2	*m*-CH_3O-C_6H_4ZnBr	 **B**	60
3	*p*-CH_3O-C_6H_4ZnBr	 **C**	55
4	*p*-$(CH_3)_2N$-C_6H_4ZnBr	 **D**	60
5	*p*-CF_3-C_6H_4ZnBr	 **E**	40
6	*p*- CH_3CO-C_6H_4ZnBr	 **F**	40
7	3-thienylZnBr	 **G**	50

The organozinc compounds were prepared in an undivided electrochemical cell flushed with argon and fitted with a magnesium rod as the anode and a nickel foam as the cathode. The aryl halide FG-C_6H_4X (1 eq),

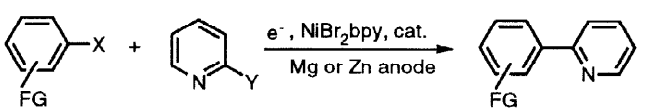
$ZnBr_2$ (1 eq), Ni(II)bpy (6.5 %) and 2,2'-bpy (13 %) were added to DMF. A constant current intensity of 0.2 A was applied at room temperature until a charge of 2.2 F per mole of halide was passed to ensure both the complete conversion of the aryl halide and the generation, in the end, of the zerovalent nickel complex. The nickel-bpy complex was usually $Ni(BF_4)_2bpy_3$ (Table 1, entries 1-6).

The use of extra bipyridine (2 eq vs $Ni(BF_4)_2bpy_3$) was necessary to avoid the formation of biaryl. However, in the case of 3-thienylzinc compound, $NiBr_2bpy$ was used as catalyst and without excess of bpy (Table 1, entry 7). After the electrolysis, 1 equivalent of 2-chloropyridine was added to the solution; the coupling reaction occurred rapidly, at room temperature for para- and meta-substituted organozinc compounds, and at 60 °C for the ortho-substituted derivatives.

Other nitrogen heterocycles like 2-chloro-5-trifluoromethylpyridine or 2-chloropyrimidine were also coupled with *p*-$CH_3OPhZnBr$ in 33 % and 54 % yields respectively. Under the same reaction conditions, no coupling was observed with 3-chloropyridine.

2. *Electroreductive coupling between aryl halides and halopyridines*

Usually, the electroreductive coupling between two arylhalides ArX and Ar'X of comparable reactivity catalyzed by nickel complexes gives a statistical product distribution (i.e. 25 % ArAr, 50 % ArAr' and 25 % Ar'Ar'). But expecting a specific behavior of 2-chloropyridine as compared to aryl halides because of the presence of the nitrogen atom close to the carbon-halogen bond, we tried to investigate the reduction of 1:1 mixtures of 2-chloropyridine and several aryl halides (eq 4).

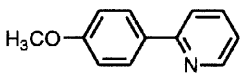
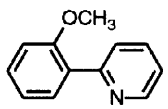
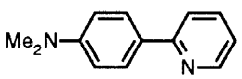
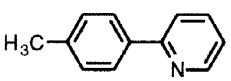
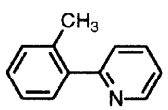
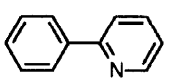
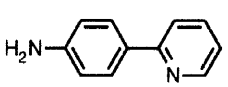
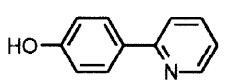
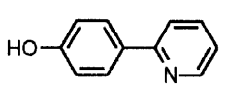


(4)

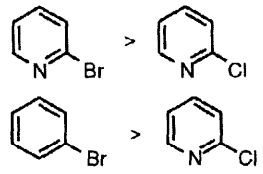
Fortunately, we obtained the cross-coupling products in good yields. Results are given in Table 2 for this reaction with X = Br, Y = Cl, FG = electron-donating group.

The reactions were carried out in an undivided electrolysis cell flushed with argon and fitted with a magnesium rod as the anode and a nickel foam as the cathode. FG-C_6H_4Br (1 eq), 2-chloropyridine (1 eq) and $NiBr_2bpy$ (13 %) were added to a solution of DMF containing NBu_4BF_4 as the supporting electrolyte. The electrolyses were conducted at room temperature at constant current intensity of 0.2 A until a charge of 2 F per mole of FG-C_6H_4Br was passed. When an arylchloride was used instead of the arylbromide, no cross-coupling was observed; only 2-chloropyridine was consumed leading to a mixture of 2,2'-bipyridine and pyridine. This indicates indicates that Ni(0) likely reacts faster with FG-C_6H_4X than with 2-chloropyridine.

Table 2. Nickel-Catalyzed Electrochemical Cross-Coupling Between Aryl Bromides Substituted with Electron-Donating Groups and 2-Chloropyridine

Entry	FG	Coupling Product	Isolated Yields %
8	*p*-OMe	 **C**	77
9	*o*-OMe	 **A**	58
10	*p*-NMe_2	 **D**	67
11	*p*-Me	 **H**	80
12	*o*-Me	 **I**	30
13	H	 **J**	70
14	*p*-NH_2	 **K**	55
15	*p*-OH	 **L**	55
16	*p*-$OCOCH_3$	 **L**	55

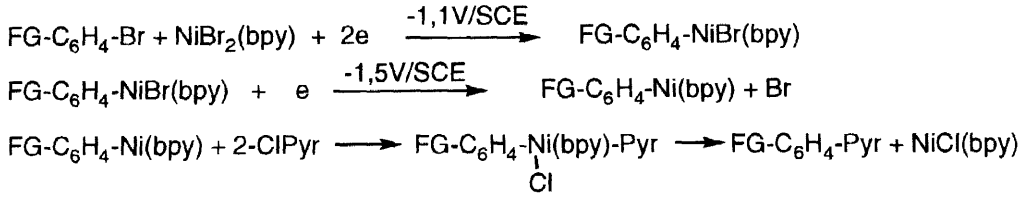
In a previous study on the coupling of aryl halides with activated alkyl halides[3] we showed that the electroreductive coupling between PhI and $ClCH_2CO_2Et$ in equimolar amount, in DMF, is very efficient because the oxidative addition of Ni(0) to PhI is more rapid than to the α-chloroester.[10] Thus, in order to understand the processes involved here it was useful to compare the reactivity of Ni(0)-bpy with several typical aryl halides including 2-halopyridines. Voltammetric measurements made in DMF gave the following order of reactivity of 2-halopyridines towards electrogenerated Ni(0)bpy (Scheme 1):



Scheme 1

Thus, 2-chloropyridine is less reactive than PhBr and it should be possible to attach 2-chloropyridine to an aryl bromide (FG-C_6H_4Br) which has a reactivity similar to PhBr (FG : electron-donating group).

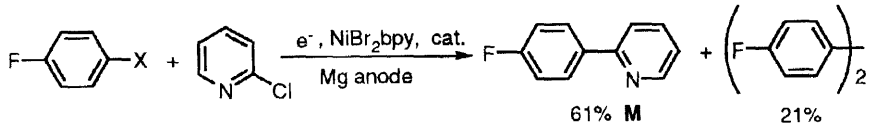
The organonickel compound *o*-$CH_3C_6H_4NiBrbpy$ is stable in DMF. It can be formed quantitatively by eletroreduction of $NiBr_2bpy$ in DMF in the presence of *o*-$CH_3C_6H_4Br$. This organometallic species reacts with 2-chloropyridine (or 2-bromopyridine) only when the cathode potential reaches -1.5 V/SCE corresponding to the potential of formation of *o*-$CH_3C_6H_4Nibpy$ from *o*-$CH_3C_6H_4NiBrbpy$ and the cross coupling product is formed quantitatively. This result prompts us to propose a mechanism (Scheme 2, with 2-ClPyr for 2-chloropyridine) similar to that for the coupling reaction of ArX with ClCH(R)COOEt referred to above.



Scheme 2

For an efficient coupling to occur, FG-C_6H_4NiBr must be formed but also the reduced intermediate (FG-C_6H_4Ni) must react with 2-chloropyridine faster than with FG-C_6H_4X. This is the case for reactions of entries 8-16 of Table 2 in which no dimer was detected.

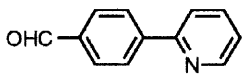
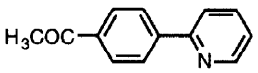
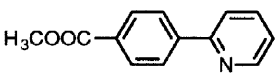
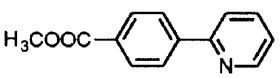
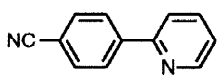
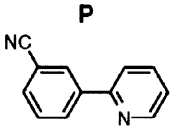
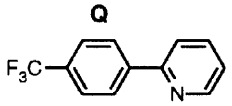
In the same reaction conditions the use of *p*-F-C_6H_4Br leaded to the difluorodiphenyl in 21 %, along with 61% of the cross-coupling product (eq 5), indicating a competition between the two reactions.



(5)

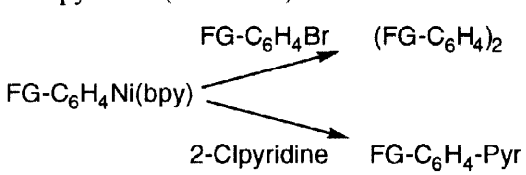
For aryl halides substituted with electron-withdrawing groups we had to care about such a competition as discussed below. Results are reported in Table 3.

Table 3. Nickel-Catalyzed Electrochemical Cross-Coupling Between Aryl Halides Substituted with Electron-Withdrawing Groups and 2-Halopyridine

Entry	FG'	X	Y	Coupling Product	Isolated Yield % vs FG'ArX
17	*p*-CHO	Br	Br	 **N**	52
18	*p*-$COCH_3$	Br	Br	 **F**	60
19	*p*-CO_2CH_3	Cl	Cl	 **O**	76
20	*p*- CO_2CH_3	Br	Br	 **O**	64
21	*p*-CN	Br	Br	 **P**	60
22	*m*-CN	Br	Br	 **Q**	62
23	*p*-CF_3	Cl	Cl	 **E**	63

The experimental conditions are the same as those described above for FG = electron-donating group except that a zinc was used instead of magnesium as anode material. Aryl bromides substituted with an electron-withdrawing group are more reactive towards the Ni(0)-oxidative addition than those substituted with an electron-donating group, and a fortiori more reactive than 2-chloropyridine. Zinc(II) ions formed by anodic oxidation of Zn allow the cathode potential to remain higher than -1.6 V to prevent the direct reduction of the aryl halide when FG is an electron-withdrawing group.

However, the increase in reactivity of FG-C_6H_4Br leads to the homocoupling which is more rapid than the cross-coupling with 2-chloropyridine (Scheme 3).

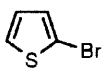
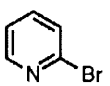
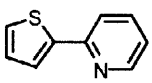
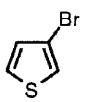
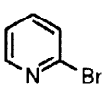
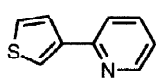
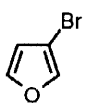
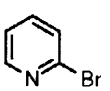
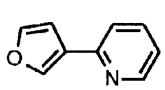


Scheme 3

Then, when X = Br with FG an electron-withdrawing group and Y = Cl, the biaryl is the major product. By increasing the reactivity of the halopyridine, i.e. using the 2-bromo instead of the 2-chloro derivative (Table 3, entries 17,18 and 20-22) or decreasing that of the aryl halide by, for example, choosing chlorine instead of bromine (Table 3, entry 19, 23) one can make of the cross-coupling to occur in good yields.

The electroreductive coupling process can also be applied to reactions involving heteroaryl halides instead of aryl halides. Results are given in Table 4.

Table 4. Nickel-Catalyzed Cross-Coupling Between 2-Bromopyridine and Bromothiophene or Bromofurane

Entry	Heteroaryl halide	Pyr-X	Coupling product	Yields % /ArX
24			 **R**	50+ 21 RR
25			 **G**	78
26			 **S**	60

CONCLUSION

The results reported here illustrate the specific behavior of 2-halopyridines in the two cross-coupling reactions described in this paper. We have shown in the first approach that 2-chloropyridine can be coupled with electrogenerated arylzinc reagents using, as catalyst, the nickel complex involved in the formation of the arylzinc reagent, whereas palladium-catalysts are usually required in these coupling reactions. We have also shown that the arylation of 2-halopyridines can more interestingly be conducted in one operation by nickel-catalyzed electroreduction of 1/1 mixtures of an aryl- (or heteroaryl) halide and either 2-chloro- or 2-bromo-pyridine according to the reactivity of the aryl halide. To our knowledge, this reaction is the most straightforward method of preparation of functionalized arylpyridines in high yields.

EXPERIMENTAL

General procedures

1. Electrosynthesis of arylzinc halides and their coupling with aryl halides.

The electrochemical cell was similar to that described previously.[12] The anode was a cylindrical rod of magnesium (diameter 0.5 cm) surrounded by a nickel foam cathode (apparent surface 40 cm^2). A solution in DMF (40 mL) of F-C_6H_4X (7.5 mmol), $Ni(BF_4)_2bpy_3$ (0.5 mmol), bpy (1 mmol) and $ZnBr_2$ (8 mmol) was electrolyzed under argon at I = 0.2 A until 1600 C had passed. When the electrolysis was stopped, 2-chloropyridine (7.5 mmol) was added and the solution stirred at room temperature for para- and meta-substituted compounds or at 60 °C for the ortho-substituted compounds. The reaction was monitored by gas chromatography (GC) and run until the disappearance of FG-C_6H_4ZnX (ca. 1 hour). The solution was hydrolyzed with NH_4Cl and extracted with diethyl ether; the organic layer washed with brine, dried and the solvent evaporated. The products were purified by flash column chromatography on silica gel with pentane/ether mixture as eluent and characterized by NMR (^1H, ^{13}C and ^{19}F), mass spectrometry, and elemental analysis.

2. Electrochemical cross-coupling between aryl halides and 2-halopyridines.

The single compartment electrochemical cell was fitted by a magnesium or zinc anode surrounded by a nickel foam cathode. A solution in DMF (40 mL) of FG-C_6H_4X (7.5 mmol) and 2-halopyridine (7.5 mmol) and $NiBr_2bpy$ (1 mmol) $Bu_4N^+BF_4^-$ (0.1 mmol) was electrolyzed under argon at I = 0.2 A until a charge of 1500 C had passed. The solution was hydrolyzed with NH_4Cl and extracted with diethyl ether, the organic layer washed with brine, dried, and the solvent evaporated. The products were isolated by flash column chromatography on silica gel with pentane/ether mixture as eluent and were characterized by NMR (^1H, ^{13}C and ^{19}F) mass spectrometry and elemental analysis.

Product analysis

^1H, NMR (δ, ppm from TMS) ^{13}C NMR (δ, ppm from TMS) and ^{19}F (δ, ppm from $CFCl_3$) spectra were recorded on AC200 Bruker NMR spectrometer ($CDCl_3$ solution); mass spectra were measured on a Finnigan GC/MS ITD 800 spectrometer.

2-(4-Trifluoromethylphenyl)pyridine **E** : colorless solid, ^1H NMR ($CDCl_3$): 8.6(1H, d, J=4.7Hz); 8(2H, d, J=8.3Hz); 7.8-7.7 (2H, m); 7.65 (2H, d, J=8.3Hz); 7.3-7.2 (1H, m, J=8.6,4.7 and 2.1 Hz). ^{13}C NMR ($CDCl_3$) : 155.6; 149.8; 142.6; 136.8; 130.6 (q, J= 32Hz); 127; 125.6; 125.5; 125.4; 124.1 (q, J=272Hz). ^{19}F NMR ($CDCl_3$): -62 (s). MS m/z (relative intensity) : 223 (M^+,96); 204 (M^+-F,(23)); 175 (M^+-CF_2,18); 154 (M^+-CF_3,93); 126 (43); 101 (15); 78 (36); 69 (CF_3^+,78); 51 (100). Anal. Calcd for $C_{12}H_8F_3N$: C, 64.58; H, 3.61; N, 6.27. Found: C, 64.55; H, 3.52; N, 6.25.

2(4-Carboxyaldehydephenyl) pyridine **N**: colorless solid, ^1H NMR ($CDCl_3$): 9.8(1H, s); 8.5(1H, dd, J= 4.8-1.1Hz); 7.9(2H, d, J=8.3Hz); 7.7 (2H,d; J=8.3Hz); 7.6-7.5 (2H, m); 7.1-7.0 (1H, m). ^{13}C NMR ($CDCl_3$) :

191.7; 155.5; 149.7; 144.6; 136.8; 136.2 130.1; 129.9; 127.7; 127.2; 122.9; 120.9. (s). MS m/z (relative intensity) : 183 (M^+,80); 154 (M^+-CHO,79); 127 (42); 101 (31); 77 (42); 51 (100). Anal. Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.64. Found: C, 78.60; H, 4.94; N, 7.60.

The following products were identified by comparison of their spectral data with those given in the cited references : 2-(2-methoxyphenyl)pyridine **A**;[13] 2-(3-methoxyphenyl)pyridine **B**;[14] 2-(4-methoxy-phenyl) pyridine **C**;[14] 2-(4-Dimethylaminophenyl)pyridine **D**;[15] 2-(4-acetoxyphenyl)pyridine **F**;[7] 3-(2-pyridyl) thiophene **G**;[16] 2-(4-methylphenyl)pyridine **H**;[14] 2-(2 methylphenyl) pyridine **I**;[14] 2-phenylpyridine **J**;[6] 2-(4 aminophenyl)pyridine **K**;[17] 2-(4-hydroxyphenyl) pyridine **L**;[14] 2-(4-fluorophenyl)pyridine **M**;[17] 2-(4-methoxycarbonylphenyl)pyridine **O**;[14] 2-(4-cyanophenyl) pyridine **P**;[18] 2-(3-cyanophenyl)pyridine **Q**;[18] 2-(2-pyridyl)thiophene **R**;[19] 3-(2-pyridyl)furane **S**.[20]

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