Articles

Is Selective Monosubstitution of Dihalides *via* $S_{RN}1$ Reaction Feasible? An Electrochemical Approach for Dichloroarenes

Christian Amatore,*,† Catherine Combellas,*,‡ Nour-Eddine Lebbar,*,‡ André Thiébault,*,‡ and
Jean-Noël Verpeaux*,†

*Ecole Normale Supérieure, Département de Chimie, U.R.A. CNRS 1679, 24 rue Lhomond
F-75231 Paris Cédex 05, France, and Ecole Supérieure de Physique et Chimie Industrielles,
U.R.A. CNRS 429, 10 rue Vauquelin, F-75231 Paris Cédex 05, France*

Received August 2, 1994®

1,4-Dichlorobenzene and dichloropyridines undergo $S_{RN}1$ reactions with various nucleophiles upon electrochemical initiation. Substitution can compete with reduction only when indirect electrolyses at low current are performed. Selective formation of monosubstitution products is observed when the nucleophiles used behave as electron-donating groups when attached to the aromatic moiety, a situation which is just the opposite of what had been observed when the same reactions were initiated photochemically. This surprising difference in behavior can be rationalized in terms of different capabilities of both activation methods to generate the key monosubstitution anion radical, $ArNuX^{\bullet-}$. Kinetic and thermodynamic data concerning the reactivity of dichloroarenes in such processes are presented and discussed.

Introduction

If nucleophilic displacement of aromatic halides *via* a radical chain mechanism—the so-called $S_{RN}1$ reaction—is a well-documented, fully understood process,[1] its application to selective monosubstitution of dihaloarenes remains an open question.[2] However, dihaloarenes and especially dichlorobenzenes are cheap and abundant compounds, and their clean monosubstitution, opening the way to further unsymmetrical disubstitution, would be highly rewarding.

$$ArX_2 \rightarrow ArNuX\ (+\ ArNu_2) \rightarrow ArNuNu'$$

A few specific cases involving photochemical initiation have been reported showing that the selectivity for mono- or disubstitution is strongly dependent on the nature of the halogen, the electrophile, and the experimental conditions.[3] The key role of the fate of the intermediate anion radical ($ArNuX^{\bullet-}$) was recognized early: its oxidation yields the monosubstituted product, whereas its cleavage, leading to $ArNu^{\bullet}$, which can readily couple with a second molecule of nucleophile, allows the formation of the disubstituted product. Consequently, "stable" anion radicals, *i.e.* those formed from nucleophiles that can stabilize the extra electron, are expected to oxidize *via* electron transfer to the starting dihalide and therefore to undergo monosubstitution, whereas those lacking such stabilization will cleave before having the opportunity to meet an oxidant. This dichotomy provides a satisfactory explanation of the good yield of monosubstituted product obtained under photochemical initiation from *m*-chloroiodobenzene and diethyl phosphite anion and the very poor yield from the same dihalide and thiophenoxide.[2,3a]

A more recent study of the photostimulated reactions of dihalobenzenes with various aromatic thiolates[4] pointed out the possible triggering of a supplementary radical chain that consumes some of the valuable monosubstituted product whenever electron transfer from $ArNu_2^{\bullet-}$ to ArNuX can compete with transfer to other molecules, mainly ArX_2, (see Scheme 1, dotted arrow). The occurrence of this side reaction is responsible for partial conversion of mono- to disubstituted product; its contribution to the overall process increases with conversion of the starting dihalide.

Although electrochemistry is also a very efficient means to trigger $S_{RN}1$ reactions, it has almost never been used to study dihalide reactivity[5] or to address the question of mono *vs* disubstitution. The reason probably resides in the reductive driving force associated with electrochemical initiation. Schematically, a competitive reduction of the aromatic radical to the corresponding anion, taking place either at the electrode or in solution by reducing species continuously flowing from the electrode, is responsible for the lower yield of substitution product (compared to the yield from photochemical initiation). In the case of dihalides, four products (ArH_2, ArNuH, $ArNu_2$, ArNuX) are now expected to be formed, instead of the two major ones ($ArNu_2$, ArNuX) obtained upon photoinitiation. Moreover, under electrochemical initiation, the monosubstituted product (ArNuX) can be reduced, and this reduction initiates the second radical chain (see above), which converts ArNuX into $ArNu_2$ or ArNuH. For these reasons, the situation did not look

---

† Ecole Normale Supérieure.

‡ Ecole Supérieure de Physique et Chimie Industrielles.

® Abstract published in *Advance ACS Abstracts*, December 1, 1994.

[1] (a) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. (b) Savéant, J. M. *Acc. Chem. Res.* **1980**, *13*, 323. (c) Rossi, R. A.; Rossi, R. H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*; ACS Monograph Series 178; American Chemical Society; Washington, D.C., 1983.

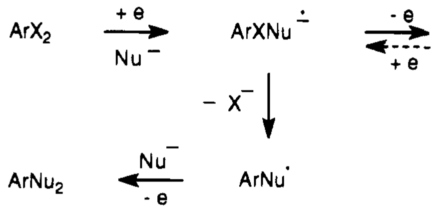
[2] See ref 1c, pp 205–217.

[3] (b) Bunnett, J. F.; Creary X. *J. Org. Chem.* 1974, *39*, 3611 and 3612. (b) Bunnett, J. F.; Traber, R. P. *J. Org. Chem.* **1978**, *43*, 1867. (c) Bunnett, J. F.; Shafer, S. J. *J. Org. Chem.* **1978**, *43*, 1873. (d) Beugelmans, R.; Bois-Choussy, M. *Tetrahedron* **1986**, *42*, 1381.

[4] Amatore, C.; Beugelmans, R.; Bois-Choussy, M.; Combellas, C.; Thiébault, A. *J. Org. Chem.* **1989**, *54*, 5688.

0022-3263/95/1960-0018$09.00/0

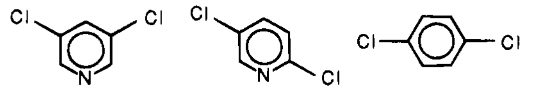
Scheme 1



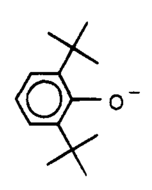
very promising. However, it has been shown in several cases that using a redox mediator M could significantly modify the course of electrochemical $S_{RN}1$ reactions.[5-7] Such a mediator would allow the reaction to take place far away from the electrode, allow the flux of the reducing species $M^{\bullet-}$ to be controlled, and allow the introduction of a molecule (the neutral mediator) that can efficiently oxidize the various anion radicals formed. This last function may be crucial in the case of selective monosubstitution of dihalides, since the mediator should accelerate the oxidation of $ArNuX^{\bullet-}$ and hence disfavor the cleavage pathway. Electrochemically induced $S_{RN}1$ reactions between some dihaloarenes and various electrophiles have been performed, and the results obtained upon direct or indirect electrolysis are presented and discussed here.

Results

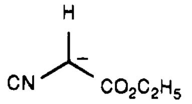
It was clear, from previously reported photochemical reactions[3] that the key intermediate anion radical ($ArNuX^{\bullet-}$) had to be chlorinated (X = Cl) in order to be stable enough to have the opportunity to meet an oxidant before cleaving.[8] In other words, dihalides would be likely to lead to monosubstituted product only if bearing at least one chlorine atom. For this reason and because of availability, this study was restricted to dichlorides; the following compounds were used:



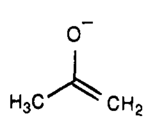
Various nucleophiles were considered: 2,6-di-*tert*-butylphenoxide ($tBPh^-$), cyanacetate (CA^-), acetone enolate (AE^-), and several arenethiolates (PhS^-, PyS^-, and $PrmS^-$) with different capabilities to stabilize the key anion radical ($ArNuX^{\bullet-}$); in this respect, and when substituted, tBuPh, CA, and AE groups are clearly electron donating whereas PyS, PrmS, and even PhS are electron attracting:[9]



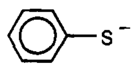
*t*BPh$^-$



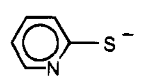
CA$^-$



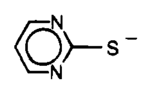
AE$^-$



PhS$^-$



PyS$^-$



PrmS$^-$

Direct Electrolysis. A few direct electrolyses performed in liquid ammonia confirmed the rather pessimistic analysis of the possibility for monosubstitution: indeed, even at a partial (30–70%) conversion of ArX_2 (so that the potential remained locked on the dihalide reduction wave), the monosubstituted product ArXNu could not be obtained in a significant yield (see Table 1). The disubstituted product ($ArNu_2$) was not formed either, except when $PrmS^-$ was used. Reduction of aromatic radicals $ArX^{\bullet}$ (and $ArNu^{\bullet}$ to a lesser extent) leading to ArXH (and ArNuH) was definitely the main pathway. This is visible in the product distribution, even though yield of the rather volatile ArXH (the major product) could not be properly determined because of our workup procedure.

The number of electrons consumed during the electrolysis should normally give the same information: since $S_{RN}1$ is a zero-electron process but reduction is a two-electron process, the theoretical number of faradays per mole of converted dihalide should be $N = 2y_{ArNuH} + 2y_{ArXH}$, assuming that ArXH is not reducible under these conditions. However, in all the electrolyses performed, the experimental number of faradays was greater than what could be calculated from the various yields according to the expression above, mainly because of the presence of residual reducible impurities. Not unexpectedly, a lower current disfavored the reduction of $ArX^{\bullet}$ and consequently increased the yield of monosubstituted product (compare 3rd and 4th rows).

Indirect Electrolysis Using a Redox Mediator. A theoretical study of the preparative use of indirect electrolysis in radical chain and especially $S_{RN}1$ reactions has been reported and gave adequate criteria for selecting a suitable mediator.[7] 4,4′-Bipyridine was found to be convenient for both dichloropyridines used, since it is soluble in NH_3, is stable both as neutral and anion radical in the medium, and reduces some 350 mV before the substrate (see below). For the same reasons, benzonitrile was used with 1,4-dichlorobenzene except when the nucleophile was potassium acetone enolate. Since benzonitrile is not stable in liquid ammonia in the presence of a strong base such as this enolate, 2-phenylpyridine was used instead. Indirect electrolyses were performed at a constant low current (50 mA) corresponding to reduction of the mediator as the major electrode process. In our standard conditions, 2 mmol of mediator and 3 mmol of dihalide were dissolved in 80 mL of liquid ammonia. However, the anion radicals of 4,4′-bipyridine and 2-phenylpyridine were found to be rather basic species and were readily protonated by the coupling products initially formed when either 2,6-di-*tert*-butylphenoxide or cyanoacetate were used (Scheme 2). When one of these nucleophiles was associated with one of these two mediators, extra base (potassium hydroxide, 3 mmol) was added prior to electrolysis.

Electrolysis could be performed up to nearly complete consumption of the starting dihalide, as confirmed by

---

[5] To our knowledge, there is only one reported example involving 4,4′-dibromobiphenyl and heavy chalcogenides: Degrand, C. *Tetrahedron* **1990**, *46*, 5237.

[6] (a) Swartz, J. E.; Stenzel, T. T. *J. Am. Chem. Soc.* **1984**, *106*, 2520. (b) Alam, N.; Amatore, C.; Combellas, C.; Thiébault, A.; Verpeaux, J. N. *Tetrahedron Lett.* **1987**, *28*, 6171. (c) Alam, N.; Amatore, C.; Combellas, C.; Pinson, J.; Savéant, J. M.; Thiébault, A.; Verpeaux, J. N. *J. Org. Chem.* **1988**, *53*, 1496.

[7] Alam, N.; Amatore, C.; Combellas, C.; Thiébault, A.; Verpeaux, J. N. *J. Org. Chem.* **1990**, *55*, 6347.

[8] For values of cleavage rate constants for aromatic iodide, bromide, and chloride anion radicals in DMF, see Andrieux, C. P.; Savéant, J. M.; Zann, D. *Nouv. J. Chim.* 1984, *8*, 107 and references therein; in liquid ammonia, at −38 °C the following values have been determined for 4-halobenzonitrile anion radical: iodo 5×10^{11} s^{-1}, bromo 4×10^{10} s^{-1}, chloro 8×10^{9} s^{-1} Thiébault, A. Unpublished results.

Table 1. Product Distribution after Partial Direct Electrolysis at Constant Current of ArX_2 (3 mmol) in the Presence of Nucleophile (18 mmol) in 80 mL of Liquid Ammonia at −38 °C

dihalide	nucleophile	current, mA	C^a (%)	$ArNuX^b$	$ArNu_2{}^b$	$ArNuH^b$
3,5-dichloropyridine	$tBuPh^-$	30	54	2		35
2,5-dichloropyridine	$PrmS^-$	30	70		38	
1,4-dichlorobenzene	$tBPh^-$	50	40	2	traces	25
1,4-dichlorobenzene	$tBPh^-$	15	32	16		16

[a] Conversion of starting ArX_2. [b] Yields (%) per mole of ArX_2 converted.

Scheme 2

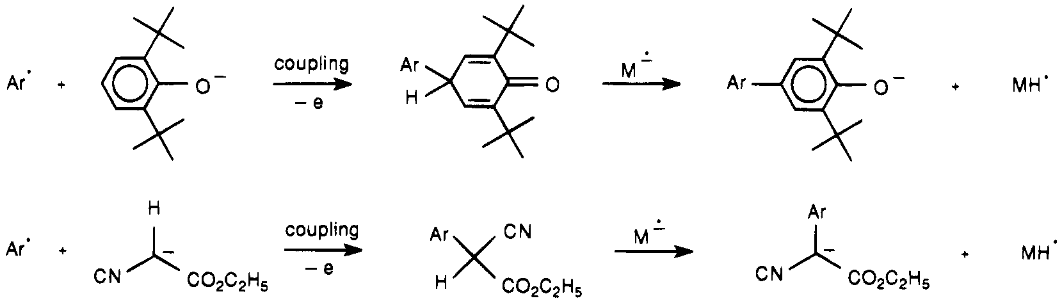


Table 2. Product Distribution after Indirect Electrolysis of ArX_2 (3 mmol) and Nucleophiles (*n* mmol) in 80 mL of Liquid Ammonia −38 °C; Current 50 mA on the Reduction Wave of a Suitable Redox Mediator (2 mmol)

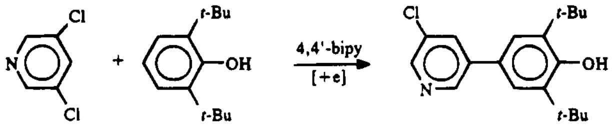
dihalide	nucleophile (*n*)	mediator[a]	C(%)[b]	$ArNuX^c$	$ArNu_2{}^c$	$ArNuH^c$
3,5-dichloropyridine	$tBPh^-$ (18)[d]	4,4′-bipy	92	58	–	–
	CA^- (24)[d]	4,4′-bipy	83	49	–	–
	PhS^- (10)	4,4′-bipy	100	–	60	–
2,5-dichloropyridine	$tBPh^-$ (24)[d]	4,4′-bipy	90	15[e]	–	4[e]
	PyS^- (18)	4,4′-bipy	100	–	40	–
	$PrmS^-$ (18)	4,4′-bipy	100	–	45	–
1,4-dichlorobenzene	$tBPh^-$ (18)	BN		25	–	2.5
	AE^- (18)[b]	2-PhPy	96	48	–	–
	$PrmS^-$ (18)	BN	99	10	52	–

[a] BN: benzonitrile; 2-Phpy: 2-phenylpyridine; 4,4′-bipy: 4,4′-bipyridine. [b] Conversion of starting ArX_2. [c] Yields (%) per mole of ArX_2 converted. [d] 3 mmol of potassium hydroxide added, see text. [e] Mixture of isomers.

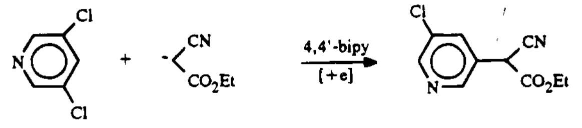
cyclic voltammetry. The main results are given in Table 2. Formation of ArNuH is always negligible, and either the monosubstituted (ArNuX) or the disubstituted ($ArNu_2$) product is formed, depending on the nucleophile. Electron-donating nucleophiles[9] ($tBPh^-$ or CA^- and AE^-) led to ArNuX, whereas electron-withdrawing ones (ArS^-) led to $ArNu_2$. It must be emphasized that this selectivity is just the opposite of that observed upon photochem-photochemical activation.[3,4] In this respect, electrochemistry appears to be a complementary method, even if the yields of ArNuX are only fair at this stage. It is obvious from results in Table 2 that reduction to ArXH occurs to a significant extent since the sum of the yields of the three products carrying at least one Nu group is always in the 40−60% range.

Influence of Current and Mediator Concentration. The influences of current and concentration of the mediator were therefore investigated. A lower current corresponding to a smaller flow of reducing species was expected to disfavor reduction processes and consequently increase the yield of monosubstituted product (ArNuX). By the same argument, an increase in the mediator concentration at constant current was expected to lead to a faster oxidation of $ArNuX^{•-}$ and therefore to improve the yield of monosubstituted product.

Monosubstitution of 3,5-Dichloropyridine. Indeed, when 3,5-dichloropyridine (3 mmol) was coelectrolyzed with 2,6-di-*tert*-butylphenoxide (18 mmol) in the presence of 4,4′-bipyridine (2 mmol) in 80 mL of liquid ammonia, the yield of 3-chloro-5-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)pyridine was found to be dependent on the current: at 50 mA the yield was 58% (Table 2), at 100 mA it was 43%, and at 25 mA a yield as high as 74% could be obtained.

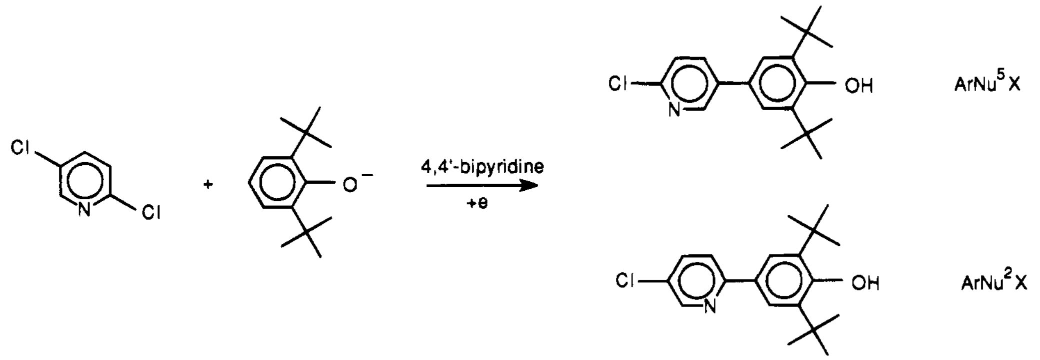


In the same way, coupling of 3,5-dichloropyridine with cyanacetate anion gave the expected monosubstituted product in a 64% yield when the 4,4′-bipyridine-catalyzed electrolysis was performed at 25 mA (constant current); a 75% yield was obtained when the current was decreased to 15 mA.



Monosubstitution of 1,4-Dichlorobenzene. The reaction between 1,4-dichlorobenzene and 2,6-di-*tert*-butylphenoxide gave a rather poor yield (25% see Table 2) of monosubstituted product upon standard treatment. Once more, decreasing the current from 50 to 15 mA proved highly favorable: the yield increased to 62%. Several electrolyses were then performed using the same current of 15 mA but with various concentrations of benzonitrile used as the mediator. Doubling the concentration of benzonitrile from 2.5×10^{-2} M (standard conditions) to 5×10^{-2} M resulted in a barely significant improvement: 64% yield of ArNuX. Using a large excess of benzonitrile did not allow anything better than 67%.

Scheme 3



Conversely, a similar electrolysis performed with a 10^{-2} M concentration of benzonitrile led to a 58% yield of monosubstituted product. It is then clear that the amount of mediator available influences the selectivity of the process and that the higher the concentration the higher the yield. However, at least in this range of concentration (which corresponds to 26–133% molar equivalent of mediator *vs* starting dichloride), the role of mediator concentration appears much less dramatic than the role of current.

Monosubstitution of 2,5-Dichloropyridine. Analysis of the products obtained upon indirect electrolysis of 2,5-dichloropyridine in the presence of nucleophiles is obviously complicated by the fact that two monosubstituted products are now expected because of the unsymmetrical positions of the two chlorine atoms (Scheme 3).

Using standard conditions (namely, a 50 mA current) an overall 15% yield was obtained (see Table 2) with $tBuPh^-$; 5-chloro-2-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)pyridine, hereafter called $ArNu^2X$, was the major isomer, the ratio $ArNu^2X/ArNu^5X$ being approximately 90/10. In this case also, a lower current improved the yield, but nothing better than 35% monosubstituted product ($ArNu^2X/ArNu^5X \approx 85/15$) could be obtained when the electrolysis was performed at 15 mA. Despite the poor yield and the formation of two isomers, this reaction may be worth considering, since it gives compounds that are not so easily prepared and opens the way to 2-substituted pyridines upon dechlorination (see below).

Kinetic Aspects of the Nucleophilic Displacement of Chlorides from Dichloroarenes. The results given above show that electrochemical initiation of an $S_{RN}1$ reaction can be an efficient means to convert a dichloroarene ($ArCl_2$) into the monosubstituted compound (ArNuCl) provided that the current is kept low and the nucleophile used is electron donating (phenoxide, enolates).[9] Since electrochemical techniques are highly suited to kinetic investigations, we decided to determine the rate constants of the key steps of this process to gain a more quantitative understanding of the reason why the ArNuX *vs* $ArNu_2$ selectivity is just the opposite of what had been reported for photochemical initiation.[4]

First Anion Radical Cleavage Rate Constant k_1. Redox catalysis experiments, *i.e.*, indirect reduction of the dichloroarene in the *absence* of nucleophile, were performed for the various dichlorides used in this study. This method has been thoroughly described for many monohalides or pseudohalides;[10,11] it can also be used for dihalides provided that the anion radical of the mediator is able to transfer an electron to ArX_2 in the time scale of the voltammetric scan and cannot affect the monoreduced product ArXH. Such a condition is fulfilled if the difference between the reduction potentials of ArX_2 and ArXH is greater than 200 mV.[12]

$$M + e \rightleftharpoons M^{\bullet -}$$

$$M^{\bullet -} + ArX_2 \rightleftharpoons M + (ArX_2)^{\bullet -} \qquad \text{(eq a)}$$

$$(ArX_2)^{\bullet -} \rightarrow ArX^{\bullet} + X^- \qquad \text{rate constant } k_1 \qquad \text{(eq b)}$$

$$M^{\bullet -} + ArX^{\bullet} \rightarrow M + ArX^- \rightarrow ArXH \qquad \text{(eq c)}$$

but

$$M^{\bullet -} + ArXH \not\rightleftharpoons M + (ArXH)^{\bullet -}$$

For each dichloride used, sets of catalytic currents of the mediator reduction wave, corresponding to various potential scan rates and excess levels of substrate, were collected. Treatment[7,10,11] of these data led to the values of standard potential (E^0) and anion radical cleavage rate constant (k_1) given in Table 3; the standard potential for the corresponding monoreduced product ArXH is also indicated in Table 3. In all three cases, the [E^0 (ArX_2) − E^0 (ArXH)] value satisfies the requirement and therefore validates the determination; as expected, the dichloride was found to be much more easily reduced than the monochloride in terms of thermodynamics. The anion radical of 3,5-dichloropyridine cleaves very rapidly, the

---

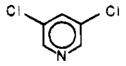
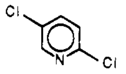
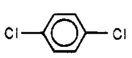
[9] It may be surprising to find arylthio groups and especially phenylthio in the electron-attracting category. It must be kept in mind that the qualification does not refer to the nucleophile itself but to the effect of the group when it is linked to the aromatic moiety. If ArNu is more electron rich than ArH, Nu will be called an electron-donating group or nucleophile, conversely if ArNu is less electron rich (*i.e.*, more easily reduced) than ArH, Nu will be called an electron-attracting group. In this respect, ArS belongs to the latter series: compare, for benzonitrile, $CN-C_6H_4-H$: $E^0 = -1.78$ V and $CN-C_6H_4-SPh$: $E^0 = -1.52$ V *ortho* isomer, $E^0 = -1.58$ V *meta* isomer, $E^0 = -1.51$ V *para* isomer, see ref 13.

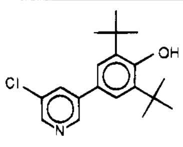
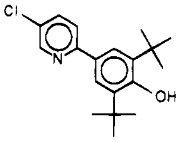
[10] Amatore, C.; Oturan, M. A.; Pinson, J.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1985**, *107*, 3451.

[11] For a simplified discussion and various aspects of the method see: Amatore, C.; Bayachou, M.; Boutejengout, F.; Verpeaux, J. N. *Bull. Soc. Chim. Fr.* **1993**, 371 and references therein.

[12] Under our conditions, the relative rates of electron transfer from $M^{\bullet -}$ to ArX_2 (k_0^1) and ArXH (k_0^2) is given by: $k_0^1/k_0^2 \approx \exp[F(E^0_1 - E^0_2)/RT]$ where E^0_1 and E^0_2 are the standard reduction potentials of ArX_2 and ArXH, respectively, since the backward electron transfers are expected to be diffusion limited.[9] Thus a $\Delta E^0 = E^0_1 - E^0_2$ close to 200 mV results in $k_0^1/k_0^2 \approx 2 \times 10^4$, showing that electron transfer from $M^{\bullet -}$ to ArXH cannot compete kinetically with that to ArX_2. The *situation may be slightly different if the overall competition involves* contribution from cleavage of the $ArX_2^{\bullet -}$ (k_1^1) and $ArXH^{\bullet -}$ (k_1^2) anion radicals. Then the relative overall rate of electron transfer is given by: $k^1/k^2 = (k_1^1/k_1^2) \exp[F(E^0_1 - E^0_2)/RT]$, showing that the above result may be invalidated if the ratio k_1^1/k_1^2 is small enough. This was not the case here (*vide infra*).

Table 3. Standard Potential E^0 and Cleavage Rate Constant k_1 of the Anion-Radical of the Dichloroarenes ArX_2 (and some monosubstituted products ArNuX) used and Determined by Redox Catalysis; Potentials Given in Volts *vs* Ag/Ag$^+$ 0.01 M in Liquid Ammonia at −38 °C

ArX_2	mediator (E^0)	E^0 (ArX_2)	E^0 (ArXH)	k_1 (s^{-1})
	4,4′-bipy (−1.33)	−1.66	−1.95[a]	3.6×10^8
	4,4′-bipy (−1.33)	−1.70	−1.95[a,b] (−1.97)[a,b]	5.3×10^7[c]
	4-MePhCN (−1.87)	−2.19	−2.42[d]	4.2×10^7

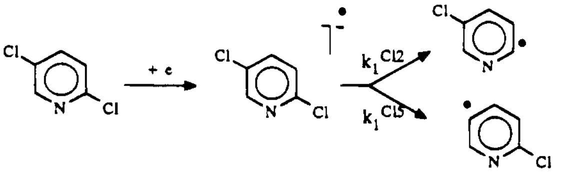
ArNuX	mediator (E^0)	E^0 (ArNuX)	k_1 (s^{-1})
	PhCN (−1.78)	−2.10	3×10^9
	2-PhPy (−1.85)	−2.37	3×10^8

[a] From ref 7. [b] −1.95 V for 3-chloropyridine and −1.97 V for 2-chloropyridine. [c] This experimental value is in fact the sum of two different partial cleavage rate constants corresponding to departure of one chloride or the other, see text. [d] From ref 13.

rate constant 3.6 10^8 s^{-1} being approximately double that previously measured[7] for 3-chloropyridine (1.7×10^8 s^{-1}).

A similar situation was observed for 1,4-dichlorobenzene, with a cleavage rate constant for the anion radical being 4.2×10^7 s^{-1}, identical within experimental error to the rate constant of monochlorobenzene anion radical cleavage measured elsewhere.[13]

The results are quite different for 2,5-dichloropyridine. The experimental value 5.3×10^7 s^{-1} is now lower than that of any of the two monochloropyridine anion radicals (6.5×10^8 and 1.7×10^8 s^{-1} for 2-chloro and 3-chloropyridine, respectively). Moreover, this overall cleavage rate constant is in fact the sum of two partial contributions corresponding to departure of each chloride:



Redox catalysis does not allow the determination of the two real rate constants separately, but this could be achieved by performing an incomplete electrolysis of 2,5-dichloropyridine in the absence of nucleophile and measuring the ratio of 3-chloro- and 2-chloropyridine formed. Under such conditions, the ratio of yields is equal to the ratio of rate constants. It was found that 90% of the reduced dichloride had been converted into 3-chloropyridine and only 10% into 2-chloropyridine.

$$[3\text{-ClPy}]/[2\text{-ClPy}] = k_1^{Cl2}/k_1^{Cl5} = 9$$

Since $k_1^{Cl2} + k_1^{Cl5} = 5.3 \times 10^7$ s^{-1}, one can easily deduce that k_1^{Cl2} for cleavage of the chlorine located on carbon 2 is 4.8×10^7 s^{-1} and that k_1^{Cl5} for cleavage of the other one is disfavored, with a rate constant of 0.5×10^7 s^{-1}. Even if no satisfactory explanation for these values can be given, they are in good agreement with the regioselectivity of the monosubstitution by di-*tert*-butylphenoxide reported in the previous paragraph.

Rate Constant k_2 of the Coupling between the Monochloroaryl Radical and the Nucleophile. The coupling between the aromatic radical and the nucleophile is definitely a crucial step in the process; it has to be fast enough to compete efficiently with the very easy reduction of the radical, which generally requires with a second-order rate constant k_2 in the range of 10^9 M^{-1} s^{-1}. A number of data concerning such rate constants for various nucleophiles and aromatic radicals are now available,[10] and it was of interest to see whether the presence of a chlorine atom on the aromatic radical had an effect on this rate constant. A significant decrease of k_2 is expected to be responsible for a very poor $S_{RN}1$ process and lead to extensive formation of ArXH and products deriving from it.

Determination of k_2 by Perturbed Redox Catalysis. This method, which has been used in the case of $S_{RN}1$ reactions of monohaloarenes,[13,14] consists of measuring the decrease in catalytic efficiency in a redox catalysis scheme upon addition of the nucleophile. This decrease is related to the fact that, instead of consuming another $M^{\bullet -}$ (eq c), part of the aromatic radical is now trapped by the nucleophile (reaction in eq d, the rate constant of which is to be determined) in a zero-electron process regenerating $M^{\bullet -}$ (eqs d + e); kinetic competition between reactions shown in eq d and eq c can be solved by analysis of electron consumption at the level of the reduction wave of the mediator (M).

$$ArX^{\bullet} + Nu^- \rightarrow ArNuX^{\bullet -} \qquad \text{rate constant } k_2 \quad \text{(eq d)}$$

$$ArNuX^{\bullet -} + M \rightarrow ArNuX + M^{\bullet -} \qquad \text{(eq e)}$$

$$ArNuX^{\bullet -} + ArX_2 \rightarrow ArNuX + ArX_2^{\bullet -} \qquad \text{(eq e')}$$

The general scheme written here is in fact identical to the scheme corresponding to the substitution of a monohalide; indeed, it remains appropriate for dihalides provided that any subsequent reactions taking place on either ArNuX or ArXH and made possible by the presence of the remaining halogen atom do not alter the electron consumption. A similar condition has been met in the preceding paragraph, where we checked that reduction of the monohalides ArXH by $M^{\bullet -}$ was a very slow process because of its very negative standard potential. The same point has to be considered for ArNuX: if its reduction by any electron-rich species present in the medium is negligible, or if its reduction to the new aromatic radical $ArNu^{\bullet}$ (eqs f, g) is followed by coupling with the nucleophile (eq h) in a still zero-electron process, the experimental data of this perturbed redox catalysis can be worked out as in the simple case of monohalides.

$$ArNuX + M^{\bullet -} \rightleftharpoons ArNuX^{\bullet -} + M \qquad \text{(eq f)}$$

$$ArNuX^{\bullet -} \rightarrow ArNu^{\bullet} + X^- \qquad \text{(eq g)}$$

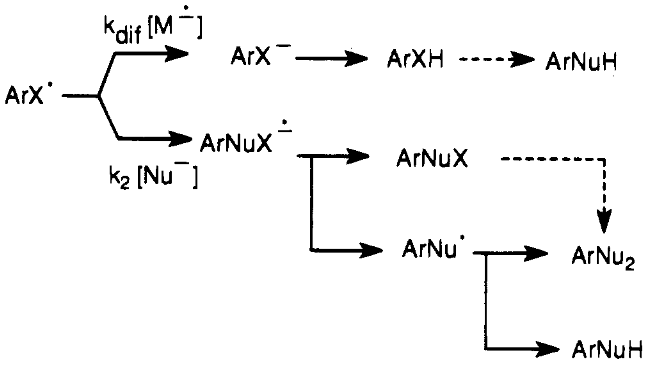
$$ArNu^{\bullet} + Nu^- \rightarrow ArNu_2^{\bullet -} \qquad \text{(eq h)}$$

Conversely, reduction of the aromatic radical $ArNu^{\bullet}$ to $ArNu^-$ and subsequent protonation (eq i) will interfere in the treatment. The results given in Table 2 show that

$$ArNu^{\bullet} + M^{\bullet -} \rightarrow ArNu^{-} + M \rightarrow ArNuH \quad \text{(eq i)}$$

in all the cases studied, the yield of ArNuH is very low. Since this compound is not prone to react further, this very low yield guarantees that eq i is not really significant in the overall process and that the usual treatment of perturbed redox catalysis can therefore be applied. The values $k_2^{\text{cat.}}$ obtained for the three radicals and some nucleophiles are given in Table 4.

Determination of k_2 from the Yield of Preparative Electrolyses. Although redox catalysis is a powerful method for kinetic investigations, it remains rather blind in terms of chemistry itself because all the information is extracted from the peak current of the mediator reduction wave on the assumption that the mechanistic sequence described above is valid. Since the present mechanism involves many intermediates and many steps, we managed to cross-check the values of k_2 by another method based on the chemical yields of the products. For the fate of $ArX^{\bullet}$, two competitive routes are to be considered; the first one is reduction by the mediator anion radical (rate constant k_{dif}), and the second one is coupling with the nucleophile; the first one leads to ArXH, and the second one leads to $ArNuX^{\bullet -}$ which, in turn, opens the way to ArNuX, $ArNu_2$, or ArNuH.



Accordingly, the initial yield of ArX^{-} is $k_{dif}[M^{\bullet -}]/(k_{dif}[M^{\bullet -}] + k_2[Nu^{-}])$, and the initial yield of $ArNuX^{\bullet -}$ is $k_2[Nu^{-}]/(k_{dif}[M^{\bullet -}] + k_2[Nu^{-}])$. It has been shown that this latter yield could be rewritten:[7]

$$y_{Nu} = 1/\{1 + (k_{dif}/k_2)[M^{\bullet -}]/[Nu^{-}]\} = 1/\{1 + \epsilon\gamma_M(i/i_M^{\,lim})(k_{dif}/k_2)\}$$

where γ_M is equal to the ratio of concentrations of mediator and nucleophile, and i is the electrolysis current. The term i_M^{lim}, the limiting current corresponding to the plateau of the mediator reduction wave for the given concentration of the mediator alone, can also be written as $i_M^{lim} = [M]i^{lim}$, where i^{lim} can be determined definitively for a given mediator, since it depends on the size and geometry of the cathode; it also depends on the stirring efficiency. ϵ is a factor smaller than one that has been evaluated previously[7,13] ($\epsilon \approx 0.63$) and k_{dif} is the diffusion limit rate constant. Its value is 3×10^{10} $M^{-1}\,s^{-1}$ in liquid ammonia at -38 °C. The equation is valid provided that the current remains lower than i_M^{lim}. Using this equation, and taking for y_{Nu} the sum of the yields of the three products containing the nucleophile (ArNuX, $ArNu_2$, and ArNuH), it was possible to derive a new set of values for the rate constants k_2 reported in Table 4 as k_2^y:

$$k_2^y/k_{dif} = 0.63\,(i/[Nu^{-}]i^{lim})\,(y_{Nu}/1 - y_{Nu})$$

The values of k_2 extracted from the two methods are in quite good agreement even when k_2^y is generally slightly smaller than k_2^{cat}. It can also be noticed that the experimental value found for k_2^y generally increases up to $k_2^{\text{cat.}}$ when the current increases; indeed when the current of the electrolysis is high, a large low of reducing species is produced at the electrode, and some ArXH can undergo a substitution reaction yielding ArNuH. At such current intensities, a significant amount of ArNuH is produced (see Table 4 notes c–e), although it is impossible to decide whether this product derives from a further reaction of ArXH or from reduction of $ArNu^{\bullet}$ (see scheme above). In any case, this may lead to the integration of some product initially deriving from reduction of $ArX^{\bullet}$ into y_{Nu} and therefore to the overestimation of $k_2[Nu^{-}]$. The situation is similar in redox catalysis experiments where data are extracted from the peak current of the mediator reduction wave, *i.e.* when the concentration of reducing species is high in the diffusion layer. For this reason, we believe the lower values of k_2^y to be more accurate than those obtained at higher current but wish to underline the fact that the values obtained from the two methods are, in most cases, quite similar, their difference not exceeding greatly the usual accuracies in redox catalysis experiments.[10,11]

Discussion

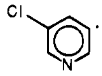
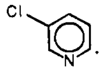
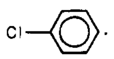
Reactivity of Dichloroarenes in $S_{RN}1$ Reactions. *Formation and Stability of $ArX^{\bullet}$.* It can be seen, from data given in Table 3, that the standard reduction potentials of the three dichloroarenes are roughly 250 mV more positive than the standard reduction potentials of the corresponding monochloro derivatives. This of course corresponds to a lower energy for the LUMO of the aromatic compound when a second chlorine atom is present. However, if the anion radical is now more easily formed (thermodynamics), its half-life is not significantly altered. Indeed, the first-order cleavage rate constants of 3,5-dichloropyridine and 1,4-dichlorobenzene anion radicals remain very similar to that of the corresponding monohalogeno compound, 3-chloropyridine ($1.7 \times 10^8\ s^{-1}$) and chlorobenzene ($4.1 \times 10^7\ s^{-1}$),[13] respectively. The probability of the transfer of the extra electron into the carbon chlorine σ^* orbital appears not to be significantly modified by the presence of the second halogen, except perhaps for a statistical factor of two. The situation is different for the unsymmetrical 2,5-dichloropyridine, the anion radical of which cleaves far slower ($k_1 = 5.3 \times 10^7$ s^{-1}) than either 2-chloropyridine ($k_1 = 6.5 \times 10^8\ s^{-1}$)[7] or 3-chloropyridine ($k_1 = 1.7 \times 10^8\ s^{-1}$).[7] The higher reactivity of the *ortho* compared to the *meta* position observed in monochloropyridines is still more obvious in 2,5-dichloropyridine ($k_1^{Cl2}/k_1^{Cl5} = 9$) despite the overall kinetic stabilization due to the presence of the second chlorine atom. The reason for this kinetic stabilization is not clear. It certainly involves, besides the interactions with the nitrogen ring, a direct interaction between the two carbon halogen bonds, which is also responsible for the fact that the relative rates of cleavage at positions 2 and 5 are in a ratio of 9 to 1 while the ratio of the rates

---

[13] Amatore, C.; Combellas, C.; Pinson, J.; Oturan, M. A.; Robveille, S.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1985**, *107*, 4846.

[14] Amatore, C.; Oturan, M. A.; Pinson, J.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* 1984, *106*, 6318.

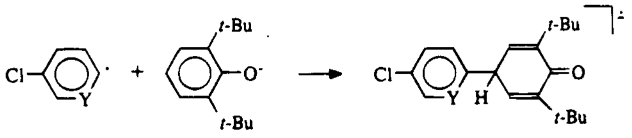
Table 4. Determination of the Second-Order Rate Constant k_2 for Coupling of Monohalogenoaryl Radicals and Nucleophiles: Data Obtained from Perturbed Redox Catalysis are Given in the Right-Hand Column, Data Obtained from Preparative Indirect Electrolysis were Extracted from Experiments Where the Substrate ArX_2 (0.037 M) was Coelectrolyzed with the Nucleophile on the Reduction Wave of the Mediator Indicated in Table 2 (0.025 M) in 80 mL of Liquid Ammonia −38 °C. The Conditions Used were Associated with a Limiting Current i^{lim} = 2 A M^{-1} for Cathode A and 7.2 A M^{-1} for Cathode B

					k_2 (M^{-1} s^{-1})	
$ArX^{\bullet}$	nucleophile	cathode	i (mA)	y_{Nu}[a]	k_2^{y}	$k_2^{cat.}$
	$tBPh^-$ (0.225 M)	A	25	74	3.0×10^9	4×10^9
	$tBPh^-$ (0.225 M)	A	50	58	3.0×10^9	
	$tBPh^-$ (0.225 M)	A	100	44	3.3×10^9	
	$tBPh^-$ (0.225 M)	A	200[b]	30[c]	3.6×10^9	
	CA^- (0.3 M)	A	15	75	1.4×10^9	2×10^9
	CA^- (0.3 M)	A	25	64	1.4×10^9	
	CA^- (0.3 M)	A	50	49	1.5×10^9	
	CA^- (0.3 M)	A	100	38[d]	1.9×10^9	
	CA^- (0.3 M)	A	200[b]	24[e]	2.0×10^9	
	PhS^- (0.125 M)	A	50	60	9×10^8	10^9
	PyS^-	A				2×10^9
	$PrmS^-$	A				8×10^8
	$tBPh^-$ (0.225 M)	B	15	38	1.1×10^8	3×10^8
	$tBPh^-$ (0.225 M)	B	50	19	1.4×10^8	
	$tBPh^-$ (0.225 M)	B	100	10	1.3×10^8	
	PyS^- (0.225 M)	B	50	40	3.9×10^8	2×10^8
	$PrmS^-$ (0.225 M)	B	50	45	4.8×10^8	2×10^8
	$tBPh^-$ (0.237 M)	B	15	65	3.0×10^8	4×10^8
			50	27	2.0×10^8	

[a] Total yield of substituted products, *i.e* sum of the yields of ArNuX, $ArNu_2$ and ArNuH. [b] To achieve such a current, a 0.05 M concentration of the mediator was used. [c] 15% of ArNuX and 15% of ArNuH. [d] 20% of ArNuX and 18% of ArNuH. [e] 4% of ArNuX and 20% of ArNuH.

of cleavage of the 2-chloropyridine and 3-chloropyridine anion radicals is only *ca.* 4 (*viz.* 6.5/1.7). Apparently, no similar extra interaction takes place in 3,5-dichloropyridine (see above). Moreover, this kind of interaction is visible in kinetic data (cleavage rate constants) but does not affect thermodynamic parameters: indeed, the difference between standard potentials of ArX_2 and ArXH (see Table 3) is similar to that determined for 3,5-dichloropyridine, where such interactions are absent. We may therefore conclude that the chlorine−chlorine interaction under discussion is operative in the transition state of the cleavage reaction.

Reactivity of ArX• with Nucleophiles (k_2). The chloroaryl radicals so formed were expected to be at least as reactive as the corresponding nonchlorinated analogues: indeed the presence of the electron-withdrawing chlorine should enhance the overall electrophilicity of the radical and stabilize the anion radical formed upon coupling by lowering the antibonding orbital in which the extra electron is to be located in this reactive intermediate. Comparison of the values of k_2 determined in this work with the related second-order rate constants previously reported for the nonchlorinated analogues shows that for those radicals which are already very reactive in $S_{RN}1$ processes, the presence of the chlorine atom does not bring real increase of the reactivity: the coupling constants k_2 of 3-(5-chloropyridinyl) radical with 2,6-di-*tert*-butylphenoxide or thiophenoxide are in the same range (a few 10^9 M^{-1} s^{-1}) as the constants reported for 3-pyridinyl radical.[7,10] For those radicals which proved rather inefficient in $S_{RN}1$ processes, such as 2-pyridinyl or phenyl radicals, with k_2 values[7,15] for coupling with 2,6-di-*tert*-butylphenoxide being smaller than 10^8 M^{-1} s^{-1}, the effect of the extra chlorine atom becomes significant, and k_2 values become high enough to allow the $S_{RN}1$ coupling to proceed in fair or even good yield. Such a difference may be related only to the simple fact that contributions of activation components affect the overall rate constant more severely when the latter is much smaller than the diffusion limit. Whatever the real origin of this enhanced reactivity, an indirect scheme can be designed for $S_{RN}1$ reactions from very poorly reactive substrates taking advantage of this observation.



Y = CH $k_2 \approx 3\ 10^8\ M^{-1}\ s^{-1}$

Y = N $k_2 \approx 2\ 10^8\ M^{-1}\ s^{-1}$

Indirect $S_{RN}1$ Reactions from Very Poorly Reactive Substrates. If ArXH does not react in $S_{RN}1$ reactions, the substitution product ArNuH can be obtained by means of a two-step pathway involving (i) $S_{RN}1$ reaction with the corresponding dichloride $ArCl_2$ and formation of the monosubstitution product ArNuCl and (ii) subsequent reduction of this product by chemical or electrochemical means to eventually lead to ArNuH. Such a route has been used in the preparation of 5-chloro-2-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)pyridine from the reaction of 2,5-dichloropyridine with 2,6-di-*tert*-butylphenoxide followed by dechlorination by electrochemical reduction in a 16% overall yield.[16] The same pathway should also be feasible with 1,4-dichlorobenzene.

Comparison between Photochemical and Electrochemical Initiation. As already pointed out, properties of nucleophiles required for monosubstitution products upon electrochemically and photochemically induced $S_{RN}1$ reactions from dichloro arenes are opposite

---

(15) The second-order rate constant for coupling of phenyl radical with 2,6-di-*tert*-butylphenoxide in liquid ammonia was shown to be smaller than 10^8 M^{-1} s^{-1}, Thiébault, A. Unpublished result.

(16) Boy, P.; Combellas, C.; Suba, C.; Thiébault, A. *J. Org. Chem.* **1994**, *59*, 4482.

each other. In photochemical processes, the key factor is the half-life of the anion radical ($ArNuCl^{\bullet -}$); a fast cleavage, corresponding to electron-releasing nucleophiles, leads to disubstitution, whereas a somewhat longer lifetime, which allows oxidation by the starting dichloride to proceed, leads to monosubstitution, a condition that is normally achieved with electron-withdrawing nucleophiles.[4,9] In electrochemical reactions, the reductive driving force is the most important drawback. Because of the presence of the oxidized form of the mediator, the electron transfer from $ArNuCl^{\bullet -}$ is more easily achieved, and the crucial point is now the stability of the monosubstituted product in the reductive medium. Those with electron-withdrawing groups are obviously more easily reduced and eventually transformed into disubstitution (or monosubstitution monoreduction) products.

Conclusion

It was possible to find conditions under which dichloroarenes gave the corresponding monosubstituted product after an electrochemically induced $S_{RN}1$ reaction. The nucleophiles involved must behave as electron-donating groups when attached to the aromatic moiety; in this respect, phenoxides and enolates are good candidates. The electrolysis has to be performed in the presence of a redox mediator at a rather low current to secure a good yield and be useful on a preparative scale.[17]

One of the most interesting aspects of this reaction resides in its complementarity, in terms of suitable nucleophiles, with photochemically induced substitution. The qualitative analysis of reactivity presented in this work can probably be applied to aliphatic radical chain substitutions, as shown by results obtained by Rossi *et al.* with dihalides in the presence or absence of *p*-dinitrobenzene.[18] This compound is expected to play the same role as our oxidized redox mediator and accordingly to shift the reactivity toward the formation of monosubstitution product in agreement with the experimental observations by Rossi *et al.*[18]

Experimental Section

Starting chemicals, nucleophiles, aromatic dichlorides, and mediators were all commercially available and were used without further purification. Kieselgel Merck 60, 230–400 mesh ASTM was used for column chromatography. HPLC was performed with a Shimadzu LC-6A chromatograph equipped with UV detector (λ_{max} 254 nm) and a reverse-phase column Lichrosorb RP-18 (5 mm), 4 × 150 mm; water/acetonitrile mixtures were used for elution. ^1H and ^{13}C NMR spectra were recorded on a Brücker spectrometer operating at 300 and 75.5 MHz, respectively, in $CDCl_3$ with Me_4Si as internal standard. A Nermag R-10-10B instrument was used for mass spectra with electronic impact at 70 eV. Combustion analyses were performed by the Service de microanalyse de l'Université Pierre et Marie Curie, Paris.

All the experiments, cyclic voltammetry as well as preparative electrolyses, were run in an undivided cell filled with 80 mL of liquid ammonia at −38 °C, and potassium bromide 0.1 M was used as supporting electrolyte. The reference electrode was a Ag/Ag^+ (0.01 M) electrode. The working electrode was a gold disk (0.5 mm diameter) for cyclic voltammetry (CV) and a 7.5 cm^2 platinum grid (1024 mesh per cm^2) for preparative-scale electrolysis. A platinum wire worked as auxiliary electrode for CV, whereas a sacrificial magnesium anode was used in preparative experiments.

In the cyclic voltammetry experiments, a solid-state amplifier potentiostat with positive feedback resistance compensation was used together with a function generator (Tacussel TPPRT), a storage oscilloscope (Nicolet), and an X-Y recorder (Sefram TGM 164). Ohmic drop compensation was required, since the resistance between reference and working electrode was on the order of 100–200 Ω. For kinetic measurements the mediators and substrates varied from 10^{-3} to 5×10^{-2} M and the scan rates from 10^{-1} to 5×10^{-1} V s^{-1}. A stabilizer power supply (Sodilec) was used for the preparative experiments.

General Procedure for Direct Electrolysis. To 80 mL of a 0.1 M KBr solution in liquid ammonia, kept at −38 °C, were added first 18 mmol of nucleophile and then 18 mmol of potassium *tert*-butoxide. A 0.225 M concentration of nucleophile was then obtained. When acetone enolate was used as nucleophile, 1 mmol extra of potassium *tert*-butoxide was required to neutralize residual water, which is a stronger acid than acetone. To this solution was added 3 mmol of aromatic halide. The electrolysis was carried out at −38 °C, at a constant current; it was not performed till total consumption of the starting aromatic dichloride had been obtained in order to avoid a negative shift of the cathode potential at the end of the electrolysis. Conversion rate was about 50–60%.

General Procedure for Indirect Electrolysis. The procedure described above was used except that 2 mmol of mediator was added prior to nucleophile addition. When 4,4′-bipyridine and 2-phenylpyridine were used, 3 mmol extra of potassium hydroxide (obtained *in situ* from 3 mmol of water and 3 mmol of potassium *tert*-butoxide were required. This extra base was not necessary when acetone enolate was the nucleophile. The conversion rate was about 80–100%.

Workup and Extraction of the Biaryls. At the end of the electrolysis, 20 mmol of ammonium bromide was added to the solution to protonate the nucleophile (23 mmol with acetone enolate), and ammonia was allowed to evaporate slowly. Extraction of the crude reaction mixture with 250 mL of dichloromethane left a solid residue. This solid mineral residue was dissolved in 100 mL of diluted aqueous nitric acid solution. Titration of the free chloride ions ($AgNO_3$, 0.5 M solution) gave a measurement of the amount of starting aromatic dichloride consumed during the electrolysis. The dichloromethane extract was pumped off to dryness, and the organic residue was chromatographed with petroleum ether, dichloromethane, and diethyl ether mixtures as eluent. Each biarylic product was isolated and fully characterized. However, in some experiments where only the measurement of the yield was needed, the crude reaction mixture was analyzed by HPLC, and the yield was determined by calibration with an internal standard.

Description of the Products. 2,5-Bis(2-pyrimidylthio)pyridine: mp = 119 °C; ^1H NMR (250 MHz, $CDCl_3$), δ (ppm) 7.2 to 7.5 (m, 2 H), 7.9_5 to 8.3_5 (m, 2 H), 8.6 to 9.0 (m, 5 H); MS (CI), *m/z* = 300 (M + 1), 223, 190; MS (EI) *m/z* = 299 (M), 298, 241, 188. Anal. Calcd for $C_{13}H_9N_5S_2$: C 52.14, H 3.03, N 23.29. Found: C, 52.25, H 3.16, N 23.10.

2,5-Bis(2-pyridylthio)pyridine: mp = 150 °C; ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 6.5–7.5 (m, 8 H), 8.0 (dd, J_1 = 10 Hz, J_2 = 2 Hz, 1 H); MS (CI) *m/z* = 298 (M + 1), 189.

3,5-Bis(phenylthio)pyridine: mp = 55 °C; ^1H NMR (250 MHz, $CDCl_3$), δ (ppm) 7.45–7.55 (m, 11 H), 8.40 (d, J = 2 Hz, 2 H); MS (CI) *m/z* = 296 (M + 1), 188, 109, 77. Anal. Calcd for $C_{17}H_{13}NS_2$: C 69.15, H 4.40, N 4.76. Found: C 68.89, H 4.32, N 4.61.

3-Chloro-5-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)pyridine: mp = 143 °C; ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.6 (s, 18 H), 5.5 (s, 1 phenolic H), 7.6 (s, 2 H), 8.0 (br s, 1 H), 8.8 (br s, 1 H), 9.0 (br s, 1 H); MS (CI) *m/z* = 318 (M + 1), 262.

---

[17] In view of the low current required in these electrolyses, one referee questioned the real synthetic usefulness of the reaction. It must be emphasized that in the case of a zero electron reaction such as $S_{RN}1$ coupling, a low current is not a drawback, since the electrons passed through the solution only initiate the radical chain and eventually convert the starting material into an unwanted reduction byproduct. A low current density does not necessarily mean a very slow conversion; in fact it can be shown that the amount of product formed as a function of time in independent of the current.

[18] Lukach, A. E.; Santiago, A. N.; Rossi, R. A. *J. Phys. Org. Chem.* **1994**, in press.

Anal. Calcd for $C_{19}H_{24}NOCl$: C 71.80, H 7.61, N 4.41. Found: C 71.66, H 7.56, N 4.46.

2-Chloro-5-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)pyridine: mp = 168 °C; ^1H NMR (90 MHz, $CDCl_3$) δ (ppm) 1.5 (s, 18 H), 5.3_5 (s, 1 phenolic H), 7.3, 7.7_5 and 8.5_5 (AMX, $J_{AM} = 9$ Hz, $J_{AX} = 3$ Hz, $J_{MX} = 1$ Hz), 7.3_5 (s, 2 H); MS (CI) $m/z = 318$ (M + 1), 284. Anal. Calcd for $C_{19}H_{24}NOCl$: C 71.80, H 7.61, N 4.41. Found: C 71.69, H 7.56, N 4.31.

5-Chloro-2-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)pyridine: mp = 122 °C; ^1H NMR (90 MHz, $CDCl_3$) δ (ppm) 1.5 (s, 18 H), 5.4 (s, 1 phenolic H), 7.4_5 to 7.6 (m, 2 H), 7.7_5 (s, 2 H), 8.6 (dd, $J_1 = 2$ Hz, $J_2 = 1$ Hz, 1 H); MS (CI) $m/z = 318$ (M + 1), 302, 284. Anal. Calcd for $C_{19}H_{24}NOCl$: C 71.80, H 7.61, N 4.41. Found: C 71.90, H 7.64, N 4.48.

(5-Chloro-3-pyridinyl)cyanoacetic acid ethyl ester: mp = 80 °C; ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.3 (t, J = 7 Hz, 3 H), 4.3 (q, J = 7 Hz, 2 H), 4.8 (s, 1 H), 7.8_5 (t, J = 2 Hz, 1 H), 8.5_5 to 8.7 (m, 2 H); MS (CI) $m/z = 225$ (M + 1), 191; MS (EI) $m/z = 224$ (M), 197, 152. Anal. Calcd for $C_{10}H_9N_2O_2Cl$: C 53.47, H 4.04, N 12.47. Found: C 53.38, H 3.88, N 12.71.

3′,5′-Di-*tert*-butyl-4-chloro-4′-hydroxy-1,1′-biphenyl: already described in ref 19.

1-(4-Chlorophenyl)-2-propanone: in agreement with literature data.[20]

Registry Numbers (supplied by author). 3,5-dichloropyridine, 2457-47-8; 2,5-dichloropyridine, 16110-09-1; 1,4-dichlorobenzene, 106-46-7; 2,6-di-*tert*-butylphenol, 128-39-2; ethyl cyanoacetate, 105-56-6; acetone, 67-64-1; 108-98-5; 2-mercaptopyridine 2637-34-5; 2-mercaptopyrimidine, 1450-85-7; 4,4′-dipyridyl, 553-26-4; benzonitrile, 100-47-0; 3′,5′-di-*tert*-butyl-4-chloro-4′-hydroxy-1,1′-biphenyl, 20031-73-6; 1-(4-chlorophenyl)-2-propanone, 5586-88-9.

JO941317I

---

(19) Combellas, C.; Marzouk, M., Suba, C.; Thiébault, A. *Synthesis* **1993**, 788.

(20) Ohwada, T.; Okabe, K.; Ohta, T.; Shudo, K. *Tetrahedron* **1990**, *46*, 7539.