

Electrochemically Catalyzed Aromatic Nucleophilic Substitution. Phenoxide Ion as Nucleophile

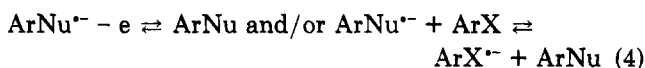
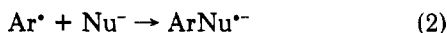
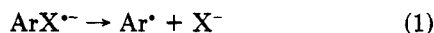
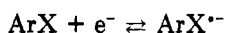
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Cyclic voltammetry and preparative-scale electrolysis of aryl halides in the presence of phenoxide ions, a nucleophile reputed as unreactive in $S_{RN}1$ reactions, show the formation, in liquid ammonia or in dimethyl sulfoxide, of coupling products along an electrochemically catalyzed $S_{RN}1$ aromatic substitution process. Coupling occurs at carbons of the phenyl ring rather than at the phenolic oxygen. The mechanism of the reaction is established on kinetic grounds. Determination of the coupling rate constant between phenoxide ions and aryl radicals and comparison with other nucleophiles shows that phenoxide ions are quite efficient nucleophiles in $S_{RN}1$ reactions. The reaction can as well be viewed as an homolytic aromatic substitution. Mechanistic implications concerning the latter type of reaction are discussed. With mediated electrochemical induction of the substitution reaction, it is possible to raise the yield in coupling product up to about 80%, which renders the reaction an attractive route to the synthesis of electron donor-electron acceptor biaryls.

Nucleophilic aromatic substitution catalyzed by electron injection, i.e., occurring along a $S_{RN}1^2$ mechanism,^{3d} is now



a well-documented reaction with various manners of injecting electrons, electrochemically,³ photochemically,⁴ by solvated electrons from alkali metals dissolved in liquid ammonia,⁴ or by other electron-transferring reagents.^{3b,e,f,h,5} A large variety of nucleophiles have been shown to react on aromatic substrates in $S_{RN}1$ processes: carbanions (including cyanide ions^{3b,f,i}) and their silicium, germanium, and tin analogues, phosphorus, arsenic, and antimony

anionic nucleophiles, and thiolates and their selenium and tellurium analogues.⁶

It is noteworthy that alkoxides and phenoxides do not seem to react. Although halobenzenes have been reported^{7a} to react with phenoxide ions in aqueous *tert*-butyl alcohol upon stimulation by sodium amalgam, yielding diphenyl ether, these results could not be reproduced by other workers.^{7b} Other attempts to make phenoxide ions react have also been unsuccessful.^{7c-e,8}

In a recent preliminary paper,⁹ it was shown, with the example of 4-bromobenzophenone as the starting aryl halide, that phenoxide ions can couple with aryl radicals, yielding carbon coupling products. The purpose of what follows is to provide a more complete description of the reaction both from the mechanistic and synthetic standpoints. It is shown that the reaction can be carried out with other aryl halides. The mechanism of the reaction is established on kinetic grounds with identification of the competition side reactions, i.e., the termination steps in the chain process, that lead to the undesired hydrogenolysis product ArH. Determination of the rate constant of the coupling step allows the comparison of phenoxide ions with other nucleophiles previously investigated in $S_{RN}1$ reactions. The reaction can also be viewed as an homolytic aromatic substitution of aromatic halides by an aromatic reactant. Starting from the mechanism we have established, mechanistic implications concerning this type of reaction will be discussed. The discussion of the mechanism, especially of the nature of the undesired reactions and the way in which they compete with the formation of the target coupling products also allows one to optimize the yield in the latter compounds. With redox-mediated electrochemical induction, it is possible to raise the yields up to ca. 80%. This renders the reaction an

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(8) It is also noteworthy that ketone enolates, which are powerful nucleophiles in $S_{RN}1$ aromatic reactions were never found to react at oxygen but always at carbon.^{4f}

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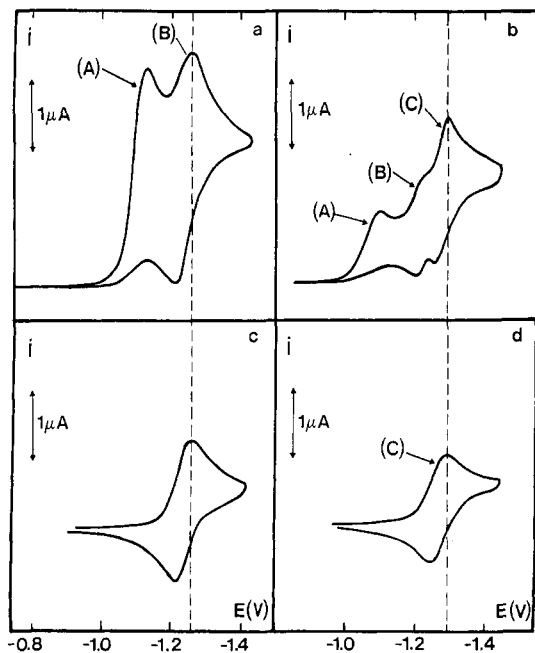
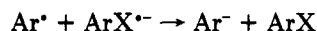
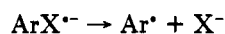
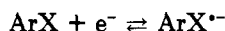


Figure 1. Cyclic voltammetry of 4-bromobenzophenone (1.7 mM) in liquid NH_3 + 0.1 M KBr at -40°C on a hanging mercury drop in the absence (a) and presence of phenoxide ions (22 mM) (b). Reduction of PhCOPhOPh (2 mM) (c) and of PhCOPhPhO^- (2 mM) (d). Sweep rate: 0.2 V s^{-1} : (A) reduction of 4-bromobenzophenone; (B) reduction of benzophenone; (C) reduction of the coupling phenate.

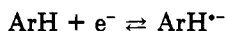
attractive route to the synthesis of important chemicals, namely, electron-donor-electron-acceptor biaryls as discussed in the following.

Results

Figure 1 shows the cyclic voltammetry of 4-bromobenzophenone in liquid ammonia in the absence and presence of phenoxide ions. In the absence of PhO^- , two successive waves are observed. The first (A) is irreversible and has a peak height corresponding to two electrons per molecule. It features the reaction sequence^{10a}

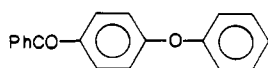


The second wave B is reversible and has a peak height corresponding to the exchange of one electron per molecule. It features the reduction of the benzophenone, ArH , formed at the level of the first wave, into its anion radical



Upon addition of phenoxide ions, the two waves of 4-bromobenzophenone decrease in height, a new, reversible, wave C appears at a more negative potential and increases at the expense of the first wave, as the concentration of PhO^- is raised (Figures 1a,b and 2).

The product giving rise to a reversible wave negative to that of benzophenone (Figure 1b) is not the ether resulting from substitution of Br^- by PhO^-



as seen in Figure 1c: an authentic sample of this compound exhibits a reversible wave which is significantly less negative than that of the compound formed upon addition of PhO^- ions to the 4-bromobenzophenone solution. In

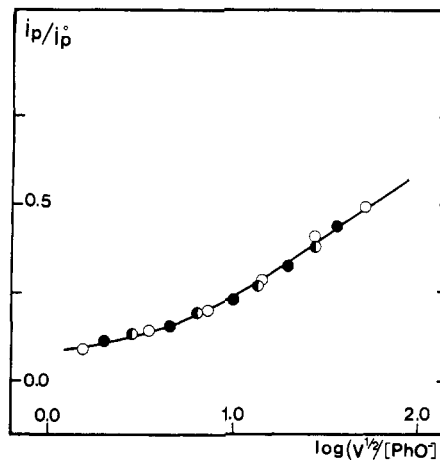
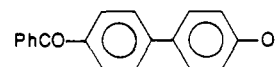


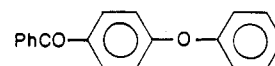
Figure 2. Cyclic voltammetry of 4-bromobenzophenone (1.65 mM) in liquid NH_3 + 0.1 M KBr + 0.06 M urea. Variations of the current ratio i_p/i_p° (i_p and i_p° : peak current in the presence and absence of phenoxide ions, respectively). Sweep rate: 0.115 (O), 0.200 (●), and 0.380 (●) V s^{-1} . From left to right: $[\text{PhO}^-] = 210, 93, 44, 22, 13 \text{ mM}$.

contrast, an authentic sample of the para C-substitution phenoxide

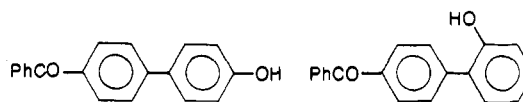


gives rise to a reversible wave located at the same potential as that of the product resulting from the reaction of PhO^- with 4-bromobenzophenone in cyclic voltammetry (compare Figure 1d with Figure 1b).

Preparative-scale electrolyses carried out at the reduction potential of 4-bromobenzophenone confirm the above results and allow a more precise identification of the reaction products. It was first checked that 4-bromobenzophenone and phenoxide ions do not react spontaneously. Upon electrolysis at the reduction potential of 4-bromobenzophenone, a reaction occurs which leads to a mixture of benzophenone and coupling products. It was shown by VPC, HPLC, mass spectrometry, and ^{13}C NMR that these do not contain the oxygen coupling ether



but consist in a mixture of para and ortho carbon coupling phenols.



No meta isomer was found in the reaction mixture, and the yields of the ortho and para isomer were 2/3 and 1/3, respectively, corresponding to the statistical distribution. The yield of coupling products was 60%, the remainder of the 4-bromobenzophenone being converted into benzophenone. The electric charge passed during the electrolysis is exclusively consumed in the formation of benzophenone according to a two-electron per molecule stoichiometry whereas the formation of the coupling products consumes no electricity, i.e., arises from an electrocatalytic process.

Similar results were obtained in DMSO. Upon addition of 0.05 M sodium phenoxide (which is about the solubility limit) the wave of 4-bromobenzophenone decreases to 55% of its original height. With tetramethylammonium phenoxide (0.2 M) the decrease is even larger, the wave height being then 20% of its original value. At the preparative

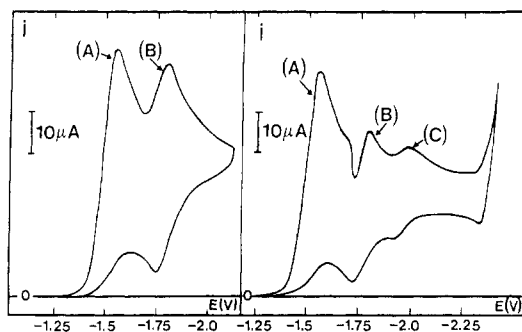


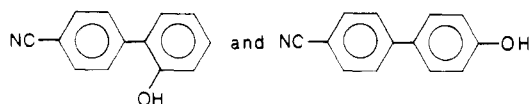
Figure 3. Cyclic voltammetry of 4-chlorobenzonitrile (2.4 mM) in liquid NH_3 + 0.1 M KBr in the absence (a) and presence (b) of phenoxide ions (200 mM): (A) reduction of 4-chlorobenzonitrile; (B) reduction of benzonitrile; (C) reduction of the coupling product. Sweep rate: 0.2 V s^{-1} .

scale, 50% coupling product is obtained, i.e., a little less than in liquid NH_3 , with an electricity consumption which corresponds to the formation of the other product, viz., benzophenone, along a two-electron stoichiometry reaction. The ratio of the ortho and para coupling phenoxides is again close to two.

Another example is the reaction of phenoxide ions with 4-chlorobenzonitrile under electrochemical stimulation. Cyclic voltammetry (Figure 3) shows that the reaction does occur, although it is less efficient than in the case of 4-bromobenzophenone.

In the absence of phenoxide ions, 4-chlorobenzonitrile exhibits a first two-electron irreversible wave featuring the reductive cleavage of the C–Cl bond and leading to benzonitrile, the one-electron reversible wave of which appears at a more negative potential. There is no significant decrease of the first wave upon addition of phenoxide ions. However, a small new reversible wave shows up at a potential negative to that of benzonitrile. This corresponds to the reduction of the carbon-coupling phenates as shown by the comparison to an authentic sample 4-hydroxy-4'-cyanobiphenyl. We also note the presence of a current dip at the foot of the benzonitrile wave. The reason for this particular feature will be given in the Discussion section.

At the preparative scale also, the results obtained with 4-chlorobenzonitrile and 4-bromobenzophenone were similar. Coupling products were obtained and shown to be a mixture of



the ratio of the ortho to the para isomer being close to 2. No other resulting from oxygen-carbon coupling was detected. The overall yield of coupling phenols was, however, lower, ca. 10%, than in the case of 4-bromobenzophenone. The charge consumed in the electrolysis, 1.8 electrons per chlorobenzonitrile molecule, was again consistent with an electrocatalytic generation of the coupling phenols and a two electrons per molecule stoichiometry for the formation of benzonitrile resulting from reductive cleavage of the starting compound.

The cyclic voltammetry of 4-chlorobenzonitrile in the presence of 2,6-di-*tert*-butylphenoxide is similar to the case of phenoxide. The reaction is somewhat more efficient as attested by a stronger decrease of the peak current of wave A ($i_p/i_p^\circ = 0.61$ for 206 mM di-*tert*-butylphenoxide instead of 0.91 for 200 mM phenoxide) and by the fact that the new reversible wave that appears at more negative potential (wave C) is larger. As in the case of phenoxide ions there is a dip in the current at the foot of the benzonitrile

wave. Although the decrease of wave A upon addition of 2,6-di-*tert*-butylphenoxide is not very large, it is sufficient to estimate the rate constant, k_2 , of the coupling with the 4-cyanophenyl radical, bearing in mind that the competition with the reductive of the latter takes place in an ECE context as discussed above. Then^{10b,c}

$$\frac{i_p}{i_p^\circ} = \frac{k_1^{1/2}}{k_1^{1/2} + (k_2[\text{Nu}^-])^{1/2}}$$

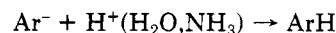
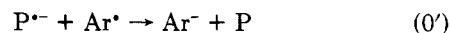
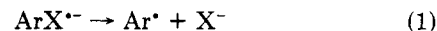
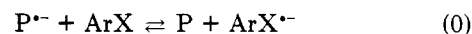
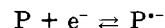
and thus since, $i_p/i_p^\circ = 0.61$ for $[\text{Nu}^-] = 206 \text{ mM}$ and $k_1 = 9.3 \times 10^8 \text{ s}^{-1}$ ^{10d}, it follows that $k_2 = 1.9 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.

At preparative scale also, 2,6-di-*tert*-butylphenoxide ions are slightly more reactive than phenoxide ions. Another advantage of 2,6-di-*tert*-butylphenoxide over phenoxide is that the possibility of obtaining an ortho coupling product is eliminated (the phenoxide coupling product may then be obtained easily by a retro-Friedel-Craft reaction). Upon reduction at the 4-chlorobenzonitrile wave, the para coupling product is obtained in 22% yield (25% when referred to the consumed 4-chlorobenzonitrile) after the passage of 1.5 electrons per consumed ArX molecules. The electricity consumption again corresponds to the formation of benzonitrile according to a two electron per molecule stoichiometry.

As in other $\text{S}_{\text{RN}}1$ processes, the main side reaction leading to the undesired hydrogenolysis product consists of the reduction of Ar \cdot radicals at the electrode or in the solution.

This is the main reason why a rather low yield of coupling products is obtained in the case of 4-chlorobenzonitrile as compared to 4-bromobenzophenone. It derives from the fact that the anion radical decomposes much more rapidly in the first case than in the second (the rate constant is $9.3 \times 10^8 \text{ s}^{-1}$ ^{10d} instead of 590 s^{-1} ^{10a}). As discussed in more detail below, the resulting aryl radical is formed, under these conditions, close to the electrode surface where it is rapidly reduced, having thus little time to react with phenoxide ions. A strategy for overcoming this difficulty is to trigger the reaction by means of a redox catalyst, such as an aromatic or heteroaromatic anion radical, generated electrochemically from the parent compound at a potential positive to the reduction of the aryl halide.^{3d,5a}

This is what was done with 4-chlorobenzonitrile, by using 2,6-di-*tert*-butylphenoxide ions as the nucleophile and 4,4'-bipyridine as the redox catalyst. Figure 4 shows the results of the redox catalysis experiments. The catalyst, 4,4'-bipyridine exhibits (Figure 4a) two reversible waves, the first of which is positive of the reduction wave of 4-chlorobenzonitrile. Upon addition of the latter, this wave increases and becomes irreversible because of the redox catalysis of the reduction of 4-chlorobenzonitrile by the anion radical of 4,4'-bipyridine according to the reaction sequence¹¹



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Table I. Cyclic Voltammetry of Aryl Halides in the Presence of Phenoxide Ions in DMSO

ArX (conc)	phenoxides	countercation	[phenoxide ions], M	rel decrease of ArX wave, %	reductn peak of the substitutn product, ^a V	
4-bromobenzophenone (1 mM)	phenoxide	Na ⁺	0.05	45	-1.77	
		NMe ₄ ⁺	0.20	80		
	3-hydroxyphenoxide	Na ⁺	0.05	46	-1.78	
		NMe ₄ ⁺	0.10	63		
		3,5-dihydroxyphenoxide	NBu ₄ ⁺	0.1		76
		3,5-dimethoxyphenoxide	NBu ₄ ⁺	0.1		89
2-chloroquinoline (1 mM)	3,5-dimethylphenoxide	NBu ₄ ⁺	0.1	94	-1.78	
		NMe ₄ ⁺	0.57	24	-2.00	
	phenoxide	NBu ₄ ⁺	0.1	18	-1.95	
2-chloropyrazine (1 mM)	phenoxide	NMe ₄ ⁺	0.45	35	-1.89	
1-bromonaphthalene (1 mM)	phenoxide	NMe ₄ ⁺	0.25	0		
		NMe ₄ ⁺	0.11	12		

^a Scan rate 0.2 V s⁻¹.

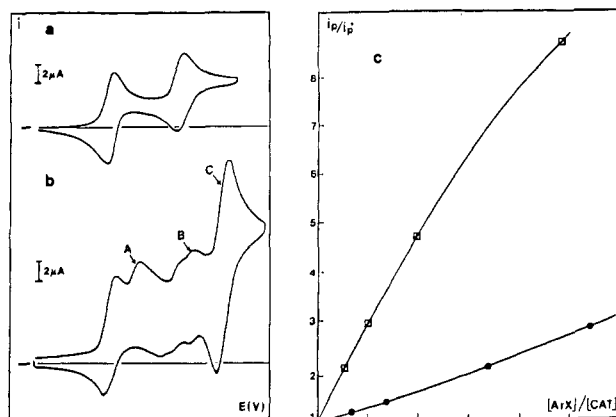


Figure 4. Cyclic voltammetry of 4,4'-bipyridine (4.7 mM) in liquid NH₃ + 0.1 M KBr in the absence (a) and presence (b) of 4-chlorobenzonitrile (6.4 mM) and of 2,6-di-*tert*-butylphenoxide ions (240 mM). The designations of the waves (A-C) are the same as in Figure 3: (c) variations of the normalized peak height, i_p/i_p^0 (i_p^0 peak current of the one-electron reversible catalyst wave) with the substrate over catalyst concentration ratio in the absence (□) and presence (●) of 2,6-di-*tert*-butylphenoxide ions (240 mM). Sweep rate: 0.2 V s⁻¹.

The variations of the peak height with the substrate to catalyst concentration ratio are represented in Figure 4c. The effect of a variation of the catalyst concentration shows that the rate-determining step of the catalytic sequence is the forward electron transfer (eq 0).¹¹ Analysis of these variations¹¹ indicates that $k_0 = 1.2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ and that the standard potential for the reduction of 4-chlorobenzonitrile is -1.64 V, a value in good agreement with that previously determined by independent means.^{10d} The fact that reaction 0 rather than reaction 1 is the rate-determining step of the catalytic process derives from the fact that the latter reaction is very fast ($k_1 = 9 \times 10^8 \text{ s}^{-1}$), faster than the second-order backward electron transfer (eq 0).

If the series of experiments is repeated in the presence of 2,6-di-*tert*-butylphenoxide ions, the peak height decreases back as a consequence of the competition between the second electron transfer (eq 0') and the reaction between the 4-cyanophenyl radical and the phenoxide ions. It is seen on the cyclic voltammograms (Figure 4b) that

the waves A and B corresponding to the reduction of ArX are now quite small as compared to the wave of the reaction product (C), indicating that the use of the redox catalyst leads to an efficient induction of the substitution process.

The variations of i_p/i_p^0 with the substrate to catalyst concentration ratio in the presence of 2,6-di-*tert*-butylphenoxide ions are shown in Figure 4c. The coupling rate constant, k_2 , was derived from these data by using a previously described procedure,^{3g,h} leading to a value of $2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.

Another method was used to estimate the rate constant k_2 . It consists^{3h} of adding a reference nucleophile for which the rate constant k_2 is independently known, here diethyl phosphite ions,^{3h} to a solution of 4-bromobenzonitrile and measuring the height, i_p^0 , of the resulting reversible wave of the substitution product. Upon addition of 2,6-di-*tert*-butylphenoxide ions to the solution, the peak height decreases to a value of i_p . Then

$$\frac{i_p^0 - i_p}{i_p} = \frac{k_{2,\text{PhO}}}{k_{2,(\text{EtO})_2\text{PO}}} \frac{[\text{PhO}^-]}{[(\text{EtO})_2\text{PO}^-]}$$

This was verified for several values of the concentration ratio. It was also confirmed that this current ratio is independent of the ArX concentration; k_2 was found equal to $1.2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ from the ratio of the rate constants thus determined.

The various methods give values of k_2 that are in satisfactory agreement ($k_2 = 1.6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$).

On the basis of these results, redox-mediated (with again 4,4'-bipyridine as the redox mediator) electrochemical induction was also used at the preparative scale in an attempt to improve the yield of coupling product with 4-chlorobenzonitrile and 2,6-di-*tert*-butylphenoxide ions. Indeed, upon electrolysis at -1.22 V, i.e., at the foot of the mediator wave, a yield of 78% (83% vis-à-vis the 4-chlorobenzonitrile consumed in the reaction) was obtained as compared to 22% in the direct electrochemical induction experiments.

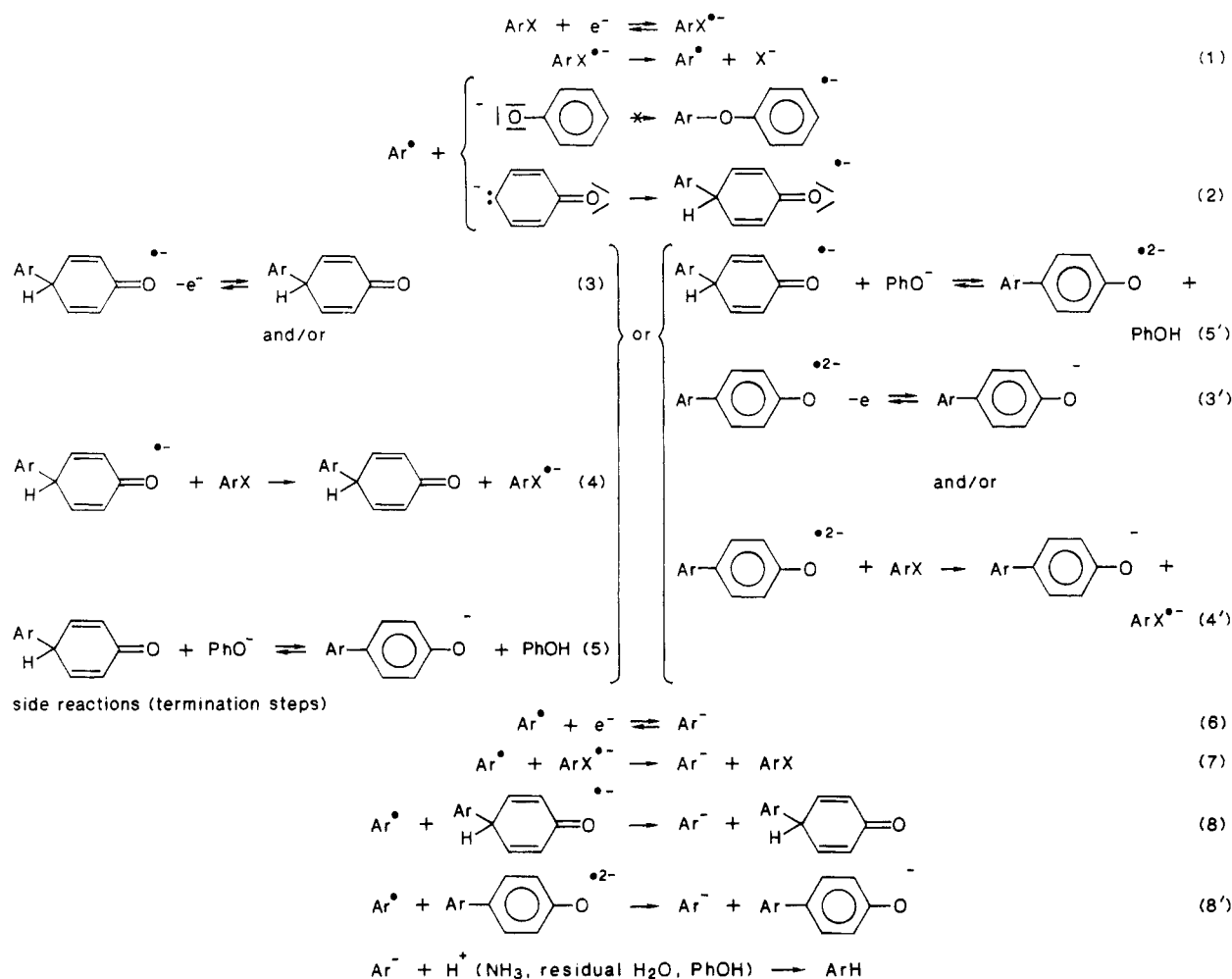
Several other systems, involving a change in the substrate and/or the phenoxide, have been tested by means of cyclic voltammetry in DMSO (Table I). The relative decrease of the ArX reduction wave upon addition of the phenoxide ions is a measure of the possibility and rate of the substitution reaction, bearing in mind that even when no decrease is observed the reaction may nevertheless proceed as shown in the case of 4-chlorobenzonitrile in liq. NH₃.

Among the systems listed in Table I, the reaction of

(11) (a) Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; Savéant, J. M. *J. Am. Chem. Soc.* 1979, 101, 3431. (b) Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; M'Halla, F.; Savéant, J. M. *J. Electroanal. Chem.* 1980, 113, 19. (c) Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; M'Halla, F.; Savéant, J. M. *J. Am. Chem. Soc.* 1980, 102, 3806.

Scheme I^a

electrocatalytic process



^a Only the reaction of Ar[•] with the para carbon of the phenoxide ion is represented. The scheme should be completed by the same reactions involving the ortho carbons.

2-chloroquinoline with phenoxide ions was also investigated at the preparative scale in DMSO. Upon electrolysis at the reduction potential of 2-chloroquinoline, the coupling phenoxide is obtained with a 27% yield and quinoline with a 68% yield. In this case, only the ortho isomer is formed.

Discussion

The above described results show that phenoxide ions can act as nucleophiles in a S_{RN}1 nucleophilic aromatic substitution. This is demonstrated by the possibility of electrochemically inducing the reaction just as with numerous other nucleophiles.³ Coupling of the aryl radical with the nucleophile does not, however, occur at the oxygen but rather at the ortho and para carbons or exclusively at the para carbon when the ortho carbons are blocked. The general applicability of the reaction is attested by the fact that it has been shown to take place with several different aryl halide-phenoxide couples.

The side reactions that tend to lower the yield of coupling products are, as with other electrochemically catalyzed S_{RN}1 reactions, the electron-transfer reduction of the aryl radical at the electrode surface or in the solution in all solvents and, in organic solvents such as DMSO, H atom abstraction from the solvent.³ A high cleavage rate of the aryl halide radical favors the first of these side reactions, hindering the substitution process at the reduction potential of the ArX substrate. A typical example of this

situation is provided by 4-chlorobenzonitrile where the ArX reduction peak shows a very small decrease upon addition of phenoxide ions. The substitution reaction, however, takes place at more negative potential thanks to the formation of the benzonitrile anion radical which is able to trigger the substitution process in the solution, i.e., under conditions where it competes more favorably with the side reactions. The appearance of a current dip at the foot of the benzonitrile wave is typical of this phenomenon.^{3,10e} The possibility of dramatically improving the substitution process (the yield in coupling product with 2,6-di-*tert*-butylphenoxide increases from 25% to 83%) with the same substrate, by adding a redox catalyst and setting the potential at its reduction wave, derives from the same displacement of the induction process from the electrode surface to the solution.

In DMSO, an additional side reaction, viz., H atom abstraction from the solvent, is expected to interfere, tending to decrease the substitution. This is indeed what is observed in cyclic voltammetry (Figure 2, Table I).

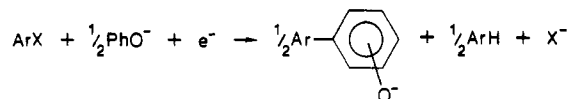
Scheme I summarizes the various possible pathways that lead to the substitution product and the side reactions which hinder its formation yielding the hydrogenolysis ArH compound, in the case of a poor H atom-donor solvent, such as liquid ammonia (for simplicity only the case of phenoxide itself has been represented).

In the scheme, the final product is considered to be the coupling phenoxide ion rather than the corresponding

phenol. In most cases, the phenoxide reactant is indeed more basic than the coupling phenoxide.^{12,13b}

The initial electron transfer is followed by cleavage of the carbon-halogen bond of the ensuing anion radical, Ar⁻ (eq 1). The resulting aryl radical, Ar[•], then couples with phenoxide ion at the ortho or para carbons. The cyclohexadienone anion radical thus obtained is likely to be rapidly and irreversibly converted to the more stable coupling phenol anion radical along a sigmatropic intramolecular proton transfer. In the following, we thus regard eq 2 as a single irreversible reaction representing either two successive or concerted steps.

The final product is obtained from this adduct by formally removing an hydrogen atom. H atom abstraction does not, however, actually occur due to the following reasons. The only efficient H atom scavenger present is the aryl radical itself. The charge consumed would thus correspond to one electron per ArX molecule, the yield of coupling being 50% at maximum:



As seen for 4-bromobenzophenone, the electron stoichiometry can be much lower, approaching zero upon addition of increasing amounts of phenoxide ions (Figure 2).

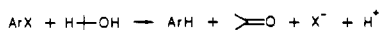
The formation of the final coupling products therefore rather involves the combination of a deprotonation and an oxidation step. Oxidation may precede deprotonation (left-hand side) or vice versa (right-hand side). As in other electrochemically induced S_{RN}1 reactions,³ oxidation may occur at the electrode (eq 3) and/or in the solution (eq 4). In the latter case, the oxidant is the starting molecule ArX, which confers a chain character to the overall process.

The deprotonation step (eq 5, 5') is an additional step which has no equivalent in the electrochemically catalyzed S_{RN}1 reactions investigated so far:^{3,14} it is likely to involve

(12) (a) The pK_a of phenol in water is 9.89^{12b} whereas those of 2- and 4-cyanophenol are 6.90 and 7.96, respectively.^{12cd} This is not the case of the ortho-coupling phenol of 2-quinolyl, which has a pK_a of 12.86.^{12d} (b) *Handbook of Chemistry Physics*, 52nd Ed., Weast, R. C., Ed.; CRC: Cleveland, 1971; p D-121. (c) Vandenberg, J. M.; Henrich, C.; Vandenberg, S. G. *Anal. Chem.* 1954, 25, 726. (d) Fickling, M. M.; Fischer, A.; Mann, B. R.; Packer, J.; Vaughan, J. *J. Am. Chem. Soc.* 1959, 81, 4226. (e) Johnston, W. D.; Freiser, H. *Anal. Chim. Acta* 1954, 11, 301.

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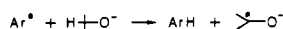
(14) (a) Precedence can, however, be found in the electrochemically catalyzed conversion of alcohols into ketones by aryl halides^{14b}



as compared to the same reaction occurring with alcoholates^{14c}



The crucial step, after reductive cleavage of ArX into Ar[•], is, in the latter case, the abstraction of an H atom from the alcoholate



leading to the ketone anion radical, which is the formal equivalent of eq 2 in S_{RN}1 reactions. This is followed by an oxidation step yielding the ketone. The side reaction results from the electrode and/or solution reduction of Ar[•] to Ar⁻. On the overall, the kinetics and selectivity rules of the system are identical to those of the usual S_{RN}1 process. In the case of alcohols, eq 2 can be written as



and the resulting radical deprotonates, yielding the ketone anion radical which undergoes the same reactions as above.^{14b} This is thus a process which is formally similar to the one investigated here. (b) Andrieux, C. P.; Badoz-Lambling, J.; Combellas, C.; Lacombe, D.; Savéant, J. M.; Thiébaud, A.; Zann, D. *J. Am. Chem. Soc.* 1987, 109, 1518. (c) Amatore, C.; Badoz-Lambling, J.; Bonnel-Huygès, C.; Pinson, J.; Savéant, J. M.; Thiébaud, A. *J. Am. Chem. Soc.* 1982, 104, 1979.

phenoxide ions which are the strongest bases present in the reaction medium. It may precede (right-hand side of the above scheme) or follow (left-hand side) the oxidation steps.

The side reactions, which are the termination steps of the chain process, result from the various possible ways of transferring an electron to the aryl radical, heterogeneously or homogeneously (eq 6, 7, 8, 8').³

In the case of 4-chlorobenzonitrile, the cleavage reaction 1 is very fast ($k_1 = 9 \times 10^8 \text{ s}^{-1}$),^{3e} the aryl radical, Ar[•], is thus formed close to the electrode surface. For this reason,³ it will prevalently be reduced to Ar⁻ and ultimately ArH, at the electrode surface rather than in the solution (eq 7, 8, 8'). Likewise, the oxidation of the substituted radicals into the final substituted product prevalently takes place at the electrode surface (eq 3, 3') rather than in the solution (eq 4, 4'). The speed of the cleavage reaction is also a cause of the poor efficiency of the substitution process as observed both in cyclic voltammetry and preparative-scale electrolysis, since the reduction of Ar[•] at the electrode surface strongly competes with the coupling with phenoxide ion.

The situation is more favorable in the case of 4-bromobenzophenone due to the cleavage of its anion radical being much slower ($k_1 = 590 \text{ s}^{-1}$).^{10a} For this reason, the oxidation of the substituted radicals occurs in the solution (eq 4, 4') rather than at the electrode (eq 3, 3'), triggering an efficient chain process. Likewise, reduction of Ar[•] to Ar⁻ occurs in the solution (eq 7, 8, 8'), allowing the addition reaction to proceed more efficiently.

Coupling with phenoxide ion only yields the ortho isomer in the case of the 2-quinolyl radical in contrast with the cases of the 4-benzoylphenyl and the 4-cyanophenyl radicals, where a statistical distribution of the ortho and para isomers is observed. This can be rationalized by regarding, in the first case, the intramolecular proton transfer and the coupling step in reaction 2 as concerted processes. Under such conditions, the driving force for the formation of the ortho compound is larger than for the para compound owing to internal H bonding with the quinolyl nitrogen (this internal H bonding manifests itself in the fact that the pK_a of the ortho coupling phenol is three units larger than that of phenol in water¹²).

It is remarkable that the reaction of phenoxide ions with aryl radicals only involves the ring carbons and not the phenolic oxygen. This is quite similar to what happens with ketone enolates where carbon-carbon coupling is likewise exclusively observed.^{3,4} It also falls in line with the absence of S_{RN}1 substitution with alkoxides as nucleophiles.¹⁵ This is in sharp contrast with the case of thiophenoxide ions and aliphatic thiolate ions which readily give rise to carbon-sulfur coupling S_{RN}1 reactions.^{3,4,16}

The lack of reactivity of aryl radicals toward the oxygen atom of phenoxide ions as opposed to the sulfur atom in thiophenoxide ions may be due to both driving force and activation factors. As regards the former factor, we note that the anion radical of the O-coupling ether appears quite stable in cyclic voltammetry even at low sweep rates, in

(15) (a) *tert*-Butoxide ions do not react at all (note, however, that the reaction has only been tested with phenyl halides which do not bear electron-withdrawing substituents).^{4b} Primary and secondary alkoxides react in a different manner. They give rise to H atom abstraction by aryl radicals,^{14b,15b-d} leading to the electrocatalytic formation of the corresponding carbonyl compounds. (b) Bunnett, J. F.; Wamser, C. C. *J. Am. Chem. Soc.* 1967, 89, 6712. (c) Bunnett, J. F.; Takayama, H. *J. Am. Chem. Soc.* 1968, 90, 5173. (d) Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* 1973, 38, 1407.

(16) Pinson, J.; Savéant, J. M. *J. Chem. Soc., Chem. Commun.* 1974, 933.

the case of benzophenone (Fig. 1c), just as that of its sulfur analogue. Thermodynamics are thus in favor of the formation of the aromatic carbon-oxygen bond. The lack of reactivity of the oxygen atom should thus be related to activation factors. As discussed previously, on quantum mechanical grounds,¹⁷ a likely picture of the transition state of the bond-cleavage and bond-forming processes in the $\text{ArNu}^{\cdot-} \rightleftharpoons \text{Ar}^{\cdot} + \text{Nu}^-$ reaction corresponds to the location of the odd electron in the σ^* orbital of the Ar-Nu bond. The high activation energy required to form the aromatic carbon-oxygen bond in the Ar-O-Ph^- anion radical would thus correspond to an exceptionally high C-O σ^* orbital as compared to the π^* orbital of the aromatic Ar system.^{4b,18} Similar considerations apply in the case of benzonitrile. Yet in the context of carbon-carbon rather than carbon-oxygen coupling, phenoxide ions appear as rather powerful nucleophiles^{3h} having a coupling rate constant just below the diffusion limit.

We have so far considered the substitution of halide by phenoxide ions as a $\text{S}_{\text{RN}}1$ process, involving as an essential step the reaction of an aryl radical with a nucleophile. It can, however, also be viewed as a homolytic aromatic substitution reaction involving, as an essential step, the reaction of an aryl radical with a particular aromatic reactant, the phenoxide ion. Homolytic aromatic substitution is a well-documented reaction especially from the synthetic point of view.¹⁹ The most commonly used sources of aryl radicals in this reaction have been the decomposition of benzoyl peroxide and of azo compounds.¹⁹ Although the phenoxide ion itself was not investigated, the reactivity of the ortho, meta, and para positions of the aromatic substrate was estimated as a function of electron-donating and electron-withdrawing substituents introduced in the aromatic substrate as well as in the aryl radical.^{19k} It was observed that the reactivity of the meta position falls to a very low value when more and more electron-withdrawing substituents are introduced in the aryl radical and more and more electron-donating substituents are introduced in the aromatic substrate. This is consistent with the fact that, in the present case, with PhCO and CN as electron-withdrawing substituents in the aryl radical and with a very powerful electron-donating substituent, O⁻, in the aromatic substrate, we find no detectable substitution at the meta position. Note, however, that with a *p*-nitrophenyl radical and anisole as substrate, the differential reactivity of the ortho position vs the para

position appears to be much larger^{19k} than the statistical factor we found in the present case.

On the other hand, substitution of aryl halides by aromatic reactants, including phenoxide ion, has been investigated using photolysis of the carbon-halogen bond as a means for generating the aryl radical.^{20,21} Both intermolecular and intramolecular coupling were investigated. Besides H atom abstraction from the arylcyclohexadienyl radical by the initial aryl radical, oxidation by added dioxygen has been demonstrated.^{21c} Intramolecular cyclization from aryl radicals generated by electrochemical reductive cleavage of aryl halides has also been described.²² It appears that, in several cases,^{22a,b} the yield of coupling products is significantly larger than that of the hydrogenolysis product, allowing us to infer that a chain process involving the starting halide as oxidant takes place. The occurrence of such a chain process is clearly established in the present work. This is an indication that it is likely to also take place in other homolytic aromatic substitution reactions where the aryl radical is generated from an aryl halide, photochemically or electrochemically.

To conclude let us come back to the synthetic aspects of the reaction. With redox-mediated electrochemical induction, it was possible to reach yields as high as 80%. Yields of the same order were also reached by using the same approach with several other substrate-phenoxide couples.²³ The reaction thus appears as a valuable route to electron donor-electron acceptor substituted biaryls. The other methods for synthesizing these molecules generally involve several successive steps leading to products in rather poor overall yields, when starting from simple commercial products or in the absence of metal catalyst.²⁴ On the other hand, nickel,²⁵ palladium,²⁶ and other metal²⁷ catalyses have been used to obtain good yields in cross coupling of aromatic halides to unsymmetrical biaryls. Yet those methods seem difficult to adapt to the direct syn-

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thesis of unsymmetrical biphenyls bearing electron-acceptor substituents on one ring and electron-donor ones on the other, except for few particular cases where, e.g., ortho effects could help in avoiding homocoupling products. Alternative routes can be envisioned such as palladium-catalyzed coupling of aryl Grignard reagents with aryl halides,^{26a,28} provided that the substituents are compatible with the Grignard reactant. Similarly methods using aryltin²⁹ or arylpalladium³⁰ as one of the starting materials proved to be effective and versatile in the synthesis of electron-acceptor biaryls without isomer formation but involve stoichiometric amounts of metal or not readily available reactants. Another interesting approach to the problem consists in using the Diels-Alder reaction,³¹ but again the starting materials need to be independently synthesized.

Experimental Section

Instrumentation and procedures for cyclic voltammetry in liquid ammonia were the same as previously described.^{3h,10b} The working electrode was a mercury drop hung on a gold disk of 0.5-mm diameter or a platinum or gold disk of the same diameter. No appreciable variation in the voltammograms occurs when changing the electrode. The reference electrode was an Ag/Ag⁺ (0.01 M) electrode.^{13a} A platinum electrode of 20-cm² surface area was used in the preparative-scale electrolysis. KBr (0.1 M) was used as supporting electrolyte. The temperature was -40 °C in all experiments. Two types of cells were used: one had separate compartments and a platinum anode,^{10b} while the other was an undivided cell with a magnesium anode.^{13c} In DMSO the reference electrode was an aqueous SCE, the working electrode was a mercury drop hung on a 3-mm diameter gold disk for cyclic voltammetry and a 20-cm² mercury pool for preparative-scale electrolysis. The experiments were carried out at 20 °C.

The procedures used in preparative-scale electrolysis for analysis of the solutions and identification of the products were as follows.

Reaction of 4-Bromobenzophenone with Phenoxide Ions in Liquid NH₃. The title substrate (1.6 mmol) was dissolved in 60 mL of liquid NH₃ containing 0.1 M KBr and 8.9 mmol of sodium phenoxide. Electrolysis was carried out at -1.1 V (reduction of 4-bromobenzophenone) and stopped after consumption of 0.66 electron per molecule. Ammonia was evaporated, and the residue was taken up with water and dichloromethane. The organic phase was analyzed by GPC (3% OV17 on Chromosorb 100/120) showing the presence of benzophenone, 4-bromobenzophenone, and a mixture of 2- and 4-hydroxy-4'-benzoylbiphenyl. The two isomers appear at the same retention time as an authentic sample of 4-hydroxy-4'-benzoylbiphenyl³² and at a different retention time from an authentic sample of the isomeric 4-benzoylphenyl phenyl ether.³³ This was confirmed by reverse-phase HPLC (20-cm Lichrosorb RP18, 5 μm, 70/30 MeOH/H₂O) where the 2- and 4-isomers are separated. Their ratio obtained from peak integration was 2/1. The analysis of this solution under the above conditions with authentic samples as external standards gave 17% benzophenone, 4% 4-bromobenzophenone, and 57% of a mixture of the 2- and 4-isomers. The mass spectrum obtained by GC-MS is in agreement with the proposed formula although it does not allow the distinction between the 2- and 4-hydroxy-4'-benzoylbiphenyl and the 4-benzoylphenyl phenyl ether: *m/z* (relative intensity) 274 (38), 197 (100), 169 (15), 141 (12), 115 (12), 105 (45), 77 (80). The coupling product was recovered from the CH₂Cl₂ solution by extraction with 1 M NaOH followed by acid neutralization. A

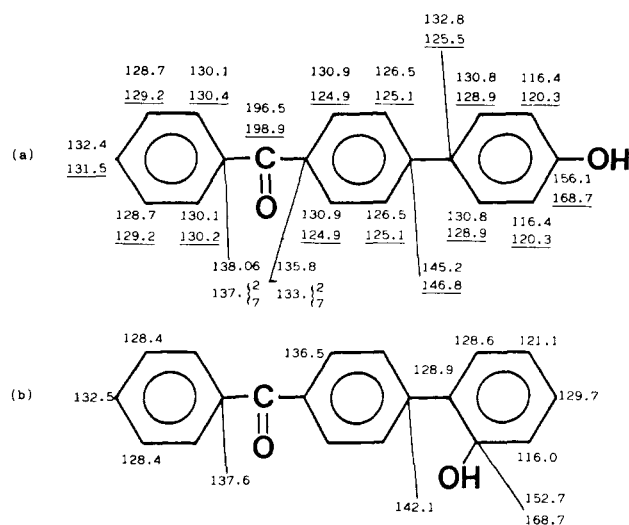


Figure 5. Assignment of the ¹³C NMR spectra of 4-hydroxy-4'-benzoylbiphenyl as an authentic sample and as the electrolysis product (a) and of 2-hydroxy-4'-benzoylbiphenyl as the electrolysis product (b). The numbers are the location of the bands in ppm for the phenols and the underlined numbers for the phenoxide ions.

white precipitate was obtained (131 mg, 0.48 mmol, 30% yield) which appeared in reverse-phase HPLC as a mixture of the two isomers. The structure was assigned on the basis of the ¹³C NMR spectra (in CDCl₃, TMS reference), by comparison of the spectrum of the isomer mixture with that of an authentic sample of 4-hydroxy-4'-benzoylbiphenyl (Figure 5).³⁴ The same comparison was also made in NaOH, where the phenols are converted into the phenoxide ions. The observed displacement of the band of the carbon bearing the OH function is typical of biphenyls.³⁵

Reaction of 4-Bromobenzophenone with Phenoxide Ions in DMSO. 4-Bromobenzophenone (3.8 mmol) and 36 mmol of tetramethylammonium phenoxide were dissolved in 70 mL of DMSO. Electrolysis was carried out at -1.50 V vs SCE (reduction of 4-bromobenzophenone) and stopped after consumption of 0.68 electron per molecule. The solution was analyzed by HPLC in the same conditions as above: 33% benzophenone, 3% 4-bromobenzophenone, 47% 2- and 4-hydroxy-4'-benzoylbiphenyl.

Reaction of 4-Chlorobenzonitrile with Phenoxide Ions in Liquid NH₃. 4-Chlorobenzonitrile (6.8 mmol, 940 mg) was electrolyzed in 80 mL of liquid NH₃ + 100 mmol of KBr at -1.65 V, in the presence of 28 mmol (3.268 g) of PhONa. After evaporation of NH₃ and acidification with dilute HCl, the residue from the cathodic compartment was extracted with dichloromethane. The CH₂Cl₂ layer was dried and evaporated. The residue (2.4 g) was then dissolved in 100 mL of butanone and heated at 70 °C during 18 h with excess Me₂SO₄ (40 mmol) and K₂CO₃ (40 mmol) in order to methylate the phenols.³⁶ After hydrolysis of the reaction mixture, extraction with dichloromethane, and evaporation of the solvent together with some of the anisole formed, the crude product was analyzed by coupled capillary VPC-mass spectrometry. It contained mostly anisole and a mixture of ortho and para isomers of the methoxybiphenyl-carbonitrile. After purification by chromatography (silica gel, dichloromethane/pentane mixture), 127 mg (6.08 mmol, 9% yield) of methoxybiphenylcarbonitrile was obtained as a mixture of both the ortho and para isomers in a 2/1 ratio (capillary GPC and ¹H NMR spectroscopy).

2'-Methoxy-1,1'-biphenyl-4-carbonitrile (major isomer): mp 79 °C. MS, *m/z* 209 (mass peak), 194, 166, 140. ¹H NMR (250 MHz): δ 3.83 (s, 3 H); 7.02 (d, *J* = 8.5 Hz, d, *J* = 1.5 Hz, 1 H); 7.08 (t, *J* = 8 Hz, d, *J* = 1.5 Hz, 1 H); 7.32 (d, *J* = 8 Hz, d, *J* =

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2 Hz, 1 H); 7.40 (d, $J = 8.5$ Hz, d, $J = 8$ Hz, d, $J = 2$ Hz, 1 H); 7.67 and 7.74 (A_2B_2 , $J_{app} = 9$ Hz, 4 H). ^{13}C NMR: δ 55.3 (OCH₃); 110.2 (C); 111.3 (CH); 119.0 (C); 120.9 (CH); 128.4 (C); 129.8 (CH); 130.0 (2 CH); 130.4 (CH); 131.5 (2 CH); 143.2 (C); 156.2 (C).

4'-Methoxy-1,1'-biphenyl-4-carbonitrile (minor isomer): mp 103 °C (lit.³⁷ mp 104 °C). MS, m/z 209 (mass peak), 194, 166, 140. 1H NMR (250 MHz): δ 3.87 (s, 3 H); 7.02 (d, $J = 9$ Hz, 2 H); 7.56 (d, $J = 9$ Hz, 2 H); 7.67 and 7.74 (A_2B_2 , $J_{app} = 9$ Hz, 4 H). ^{13}C NMR: δ 55.3 (OCH₃); 110.1 (C); 114.5 (2CH); 118.9 (C); 127.0 (2CH); 128.2 (2CH); 131.4 (C); 132.4 (2CH); 145.1 (C); 160.2 (C). The reaction mixture did not contain any detectable amount of the oxygen-coupling ether: *p*-CNC₆H₄OC₆H₅ as shown by comparison with an authentic sample.³⁸

Reaction of 4-Chlorobenzonitrile with 2,6-Di-*tert*-butylphenoxide in Liquid NH₃. Direct Electrochemical Induction. The electrolysis was performed in a compartmented cell containing 80 mL of NH₃ and 1.67 g of potassium bromide. A magnesium rod was used as the anode; the cathode was a platinum grid. 2,6-Di-*tert*-butylphenol (18.05 mmol, 3.72 g), water (3.24 mmol, 58.3 mg), and then potassium *tert*-butoxide (21.3 mmol, 2.39 g) were added. 4-Chlorobenzonitrile (3.01 mmol, 413.8 mg) was added just before electrolysis. The current density was kept constant throughout the electrolysis (13.3 mA/cm² at the cathode), until 436 C (1.5 F per mole of chlorobenzonitrile) was consumed. After addition of excess ammonium chloride and evaporation of the solvent, the crude residue was extracted with acetonitrile. The reaction mixture was purified by chromatography (silica gel, dichloromethane/pentane as the eluent). The starting unreacted

phenol is eluted first. Then the following eluted.

4'-Hydroxy-2',6'-di-*tert*-butyl-1,1'-biphenyl-4-carbonitrile: yield, 203 mg, 22%; mp 155 °C. MS m/z 307 (mass peak), 292, 57, 84, 264. 1H NMR (250 MHz): δ 1.50 (s, 18 H); 5.47 (s, 1 phenolic H); 7.47 (s, 2 H); 7.70 and 7.77 (A_2B_2 , $J_{app} = 9$ Hz, 4 H). ^{13}C NMR: δ 30.3 (6 CH₃); 34.4 (2 C); 109.8 (C); 119 (C); 124.0 (2 CH); 127.3 (2 CH); 130.4 (C); 132.4 (2 CH); 136.8 (2 C); 146.6 (C); 154.6 (C). IR (KBr pellet): 3650, 2245, 1620, 1445, 847 cm⁻¹. Anal. Calcd C, 82.08; H, 8.15; N, 4.56. Found: C, 81.87; H, 8.23; N, 4.84.

4-Chlorobenzamide: yield, 56 mg, 12%; compared (mp, NMR) with a commercial sample.

Redox-Mediated (4,4'-Bipyridine) Electrochemical Induction. The experimental procedure was the same as described above except that 4,4'-bipyridine (2.07 mmol, 323 mg) was added before electrolysis. The electrolysis was stopped after consumption of 0.3 F per mole of substrate (87.2 C), leading to the following.

4'-Hydroxy-2',6'-di-*tert*-butyl-1,1'-biphenyl-4-carbonitrile: 720.7 mg, 78%.

4-Chlorobenzamide: 6%.

Reaction of 2-Chloroquinoline with Phenoxide Ions in DMSO. 2-Chloroquinoline (6.1 mmol) was mixed with 14 mmol of tetramethylammonium phenoxide in 50 mL of DMSO containing 0.1 M NBu₄BF₄. Electrolysis was carried out at -1.75 V vs SCE (reduction of 2-chloroquinoline). The resulting solution was analyzed by reverse-phase HPLC (Lichrosorb R18, 70-30 MeOH-H₂O). In addition to 68% quinoline, 27% of the 2-(2-quinolinyl)phenol coupling product was found as shown by comparison with authentic samples of this compound and of the 4-isomer.³⁹

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Ceric Ammonium Nitrate Oxidative-Cleavage Reaction of Some Lignin Model Compounds: Role of the Benzylic Hydroxyl Group

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A series of β -1 lignin model compounds was synthesized and then oxidized with ceric ammonium nitrate (CAN) in aqueous acetonitrile. The compounds studied were 1,2-diarylethanol with either a *p*-hydroxy (1a-e) or a *p*-methoxy (2a-e) on the 1-ring and the following para substituents on the 2-ring: (a) H, (b) Cl, (c) Me, (d) OMe, and (e) NO₂. Reactions of *p*-hydroxyl compounds 1a-e with CAN resulted in the formation of a red cerium complex that did not oxidize under the conditions of the reaction. In contrast, all of the methoxy compounds 2a-e were rapidly oxidized by CAN at room temperature to give *p*-anisaldehyde in near quantitative yield. The relative rates of these oxidative-cleavage reactions were found to be 0.11, 0.16, 1.00, 1.58, and 2.37 for the 1,2-diarylethanol 2e, 2b, 2a, 2c, and 2d, respectively. A Hammett treatment of this data revealed an excellent correlation with σ ($\rho = -1.24$). Methylation of the benzylic hydroxy group of 2a gave 1-methoxy-1-(4-methoxyphenyl)-2-phenylethane, which was found to be inert to CAN oxidation.

The alkaline oxidative-cleavage reaction of softwood lignin to vanillin using such oxidants as nitrobenzene and copper(II) is one of the more important reactions of wood chemistry. Until recently the mechanism of this reaction was assumed to be a two-electron process involving quinone methide intermediates.¹ Evidence from our laboratories²⁻⁵ is more consistent with a one-electron process

that does not involve quinone methide intermediates. The precise roles that the *p*-hydroxy and benzylic hydroxy groups of lignin play in this reaction are also not clearly established.

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