Nickel-Catalyzed Direct Electrochemical Cross-Coupling between Aryl Halides and Activated Alkyl Halides

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The electrochemical reduction of a mixture of aryl halides and activated alkyl halides in DMF in the presence of catalytic amount of $NiBr_2$bipy leads to cross-coupling products in good to high yields. The method applies to the synthesis of α-aryl ketones, α-aryl esters, and allylated compounds from readily available organic halides. Optimization of the process has been obtained by slowly adding the most reactive organic halide (usually the activated alkyl halide) during the electrolysis which is best conducted at 70 °C when aryl bromides are involved.

Introduction

Aryl compounds, like α-aryl ketones, α-aryl esters, or allylated aryl derivatives, are of high interest due to their versatile properties as pharmaceuticals, agrochemicals, perfumes, etc. Many synthetic strategies are available to prepare these compounds, but the most straightforward approach is the direct introduction of the aryl group on the substate. Selective one-step reductive cross-coupling between aryl halides and alkyl halides (eq 1) has never been achieved efficiently, as far as we know.

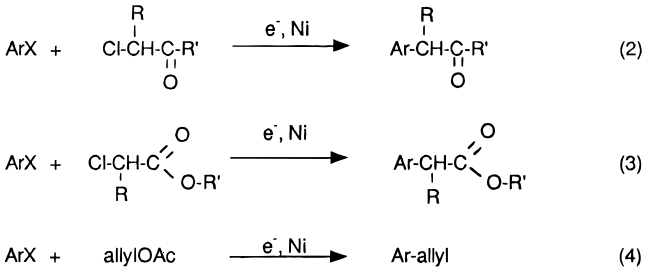
$$ArX + RX \xrightarrow{\text{reductant}} Ar\text{-}R + 2X^- \qquad (1)$$

Such coupling requires the preliminary preparation of an organometallic, either ArM or RM, which is then reacted with the other organic halide, eventually in the presence of transition metal catalyst. Grignard organometallics are often involved in these reactions. However, they cannot be prepared from organic halides having sensitive functional groups. Zinc organometallics are less reactive and often prepared from the corresponding organomagnesium compound.

The coupling reaction between arylmagnesium bromides and activated alkyl halides is more or less efficient. Thus the coupling with allylic bromides occurs in good yield. However, the reaction is not regioselective, and two isomeric products are formed from for example crotyl bromide.[1] Pd-,[2] Ni-,[3] or Cu-[4] catalysis of these reactions can both increase the reaction rate and control the regioselectivity. Alternatively, the allylation reaction can be carried out from organozinc intermediates and in the presence of a transition metal catalyst.[5]

The direct reaction of ArMgX with α-halo carbonyls, esters or ketones, only leads to addition to the carbonyl, unless a catalyst (usually a nickel complex) is used, with, however, modest yields.[6] Organozinc compounds can also be used, in the presence of a nickel complex as catalyst, but these reactions are not widely applicable.

Over the past decade, research in these laboratories has developed new methods of electroreductive C−C bond-forming reactions based on the use of a sacrificial anode,[7] eventually in the presence of a catalyst. Notably, we have found that cross-coupling between aryl halides and activated alkyl halides, α-chloro ketones (eq 2), α-chloro esters (eq 3), or allylic derivatives (eq 4), can be easily carried out with a simple electrosynthesis using nickel−bipyridine complexes as catalysts in *N*,*N*-dimethylformamide (DMF).



Since the publication of some preliminary results,[8,9] the process has been both optimized on the basis of a better understanding of the reaction mechanism and extended to a wide range of organic halides. Here we present a full account of these reactions.

Results and Discussion

Optimization of the Cross-Coupling. The electroreduction of a mixture of an aryl halide and an α-chloro ketone or α-chloro ester, in the absence of catalyst, does not afford the expected cross-coupling product. We only obtain the reduction products from the alkyl halide RX, namely RH and RR. On the contrary, as previously shown,[8] aryl iodides or activated aryl bromides couple electroreductively with an α-chloro ester

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(1) Kharash, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Coustable: London, 1954.

(2) (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5531. (b) Bumagin, N. A.; Kasatkin, A.; Beletskaya, I. P. *Bull. Acad. Sci. USSR* **1984**, *33*, 1696.

(3) (a) Wenkert, E.; Fernandes, J. B.; Michelotti, E. L.; Swindell, C. S. *Synthesis* **1983**, 701. (b) Okamura, H.; Takei, H. *Tetrahedron Lett.* **1979**, *20*, 3425.

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(9) Durandetti, M.; Sibille, S.; Nédélec, J.-Y.; Périchon, J. *Synth. Commun.* **1994**, *2*, 145.

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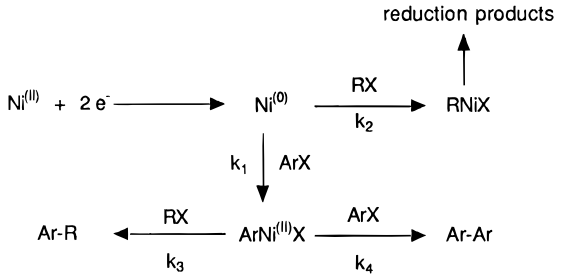
Scheme 1



used in excess at room temperature, in the presence of a catalytic amount (5−10%) of $NiBr_2$bipy (bipy = 2,2′-bipyridine) and a zinc or aluminum anode. However, when the electrolysis is carried out with PhBr, the cross-coupling does not occur and RR is first formed and then biphenyl after consumption of RX. Improvements were obtained as follows: the running of the reaction at 70 °C from a mixture of PhBr and RX afforded 5−10% of cross-coupling, and high yields were obtained by slowly adding RX, during the electrolysis at elevated temperature. Thus at 70 °C and with a slow addition of the α-chloro carbonyl the reaction between bromobenzene and, respectively, chloropropanone and methyl 2-chloropropionate gave 62% of phenylacetone and 70% of methyl phenylacetate. With aryl iodides, and if the α-halo ester or the α-halo ketone is added slowly, the reaction is best carried out at room temperature. Also, electron-withdrawing groups on the aromatic ring slightly favor the cross-coupling, as compared to electron-releasing substituents, though the influence of the nature of the substituent on Ar is not very large.

Other features of these reactions are worth noting: for a given ArX, the efficiency of the cross-coupling also depends on the nature of X in RX and on the RX vs ArX molar ratio. Thus the coupling reaction between PhI and $ClCH_2CO_2Me$ is efficiently performed at room temperature by slow (5 mmol/h) addition of 1.2 equiv of the α-halo ester. On the contrary, only the reduction of the α-halo ester occurs when $BrCH_2CO_2Me$ is used instead of $ClCH_2CO_2Me$, even with a very slow addition of methyl bromoacetate. Similarly, allylation reactions are more efficently performed with allylic acetates than with the corresponding chlorides, while no cross-coupling occurs with allylic bromides.

The reactions were usually conducted at constant current density, and we found that during the electrolyses the potential of the working electrode remained constant at *ca* −1.2 V/SCE, which corresponds to the reduction of $Ni^{(II)}$ to $Ni^{(0)}$.[10] The subsequent step is an oxidative addition of $Ni^{(0)}$ to one of the two organic halides. There are indeed two possible competitive pathways, *i.e.* the formation of ArNiX and the formation of RNiX (Scheme 1). Rate constants value for the reaction of $Ni^{(0)}$ (electrogenerated from $NiBr_2$bipy) with typical organic halides in DMF was obtained by the method described by Nicholson and Shain[11] which is based on the measurement of the ratio of the intensity of cyclic voltametry peaks of the $Ni^{(II)}/Ni^{(0)}$ system in the presence of various amounts of RX *vs* Ni $(i_{ox}/i_{red})^{[RX]}$ as compared the system in the absence of RX $(i_{ox}/i_{red})^0$. It them comes out that α-chloro carbonyls compounds add more rapidly to $Ni^{(0)}$ than aryl halides.[12] We also found that the cross-coupling does not occur at all with the more reactive alkyl bromides. This clearly indicates that for the cross-coupling to occur it should involve, as the key step, the formation of a σ-arylnickel intermediate (Scheme 1, step 1). The formation of RNiX likely occurs in all cases (Scheme 1, step 2); it can, however, be minimized by keeping the ArX/RX molar ratio elevated over the duration of electrolysis by slow addition of RX. We must also avoid forming biaryl (Scheme 1, step 4), so the excess of ArX must be kept within a certain range. We found an optimum addition rate of 5 mmol/h via a syringe pump to keep a ArX/RX molar ratio of *ca*. 15 in the cell.

We already mentioned that with aromatic bromides, yields of cross-coupling increased with the reaction temperature. This means that the rate of the oxidative addition of $Ni^{(0)}$ increases more rapidly with the temperature for ArBr than for RX. Indeed the activation energy for the oxidative addition of $Ni^{(0)}$ to PhBr and to $ClCH_2COCH_3$ was found to be, respectively, 76 kJ mol^{-1} and 28 kJ mol^{-1}.

($NiBr_2$bipy + bipy) was found to be less reactive than $NiBr_2$bipy (only 30% of *m*-$CF_3PhCH_2COCH_3$ was obtained in the electroreductive cross-coupling between *m*-CF_3PhBr and $ClCH_2COCH_3$ with $NiBr_2bipy_2$ instead of 80% with $NiBr_2$bipy), and with $Ni(BF_4)_2bipy_3$ ArX was not consumed. This can be explained by the decrease of the rate constant of the oxidative addition of ArX to $Ni^{(0)}$ with added bipy. As a consequence, when the ratio bipyridine/nickel is increased, the formation of RNiX prevails (Scheme 1, step 2) over the formation of ArNiX (Scheme 1, step 1) and R−R and RH are mainly formed. Changing 1,10-phenanthroline (phen) for bipyridine does not change the chemical yields: the reaction between PhI and $ClCH(CH_3)CO_2Me$ gave 70% cross-coupling with $NiBr_2$bipy and 73% with $NiCl_2$(phen). With $NiBr_2(PPh_3)_2$ or $NiBr_2$diphos in DMF, the oxidative addition to ArX is too slow, and the Ni^0 zero species only reacts with RX.

The effect of the nature of the metal used as anode material on the chemical and faradaic yields of 1-phenyl-2-propanone from iodobenzene and chloroacetone at room temperature was also studied and found not to be a highly critical factor in the process. Thus the yield of 1-phenyl-2-propanone was 54% with a zinc anode and 53% with an aluminum anode, but 39% with a magnesium anode. The decrease in the chemical yield with a magnesium anode can be explained by the occurrence of side reactions at the electroeroded metal.[7] To sum up, the kind of the electrogenerated ion does not greatly affect the chemical yield. This may rule out a transmetalation reaction, as described in other reactions.[13]

To gain further insight into the mechanism of the coupling step between ArNiX and RX (Scheme 1, step 3), we have undertaken voltametric studies of this cross-coupling process.[12] Here again, two processes may occur, as outlined in Scheme 2.

ArNiX can be reduced to ArNi (Scheme 2, step 1), which would then react by oxidative addition with RX (Scheme 2, step 2). The coupling product results from the reductive elimination reaction (Scheme 2, step 3). However, an exhaustive electrolysis of a mixture PhI/$ClCH_2COCH_3$ in the molar ratio 15/1 conducted at −1

(10) Rollin, Y.; Troupel, M.; Tuck, D.; Périchon J. *J. Organomet. Chem.* **1986**, *303*, 131.
(11) Nicholson, R. S.; Shain, I. *Anal. Chem.* **1964**, *36*, 706.
(12) Results to be published.
(13) (a) Durandetti, S.; Sibille, S.; Périchon, J. *J. Org. Chem.* **1989**, *54*, 2198. (b) Conan, A.; Sibille, S.; Périchon, J. *J. Org. Chem.* **1991**, *56*, 2018. (c) Sibille, S.; Ratovelomanana, V.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1992**, 283.

Scheme 2

$$ArNi^{(II)}X + e^- \longrightarrow ArNi^{(I)} + X^- \quad (1)$$

$$ArNi^{(I)} + RX \longrightarrow ArRNi^{(III)}X \quad (2)$$

$$ArRNi^{(III)}X \longrightarrow Ar\text{-}R + Ni^{(I)}X \quad (3)$$

$$\text{or} \begin{cases} ArNi^{(II)}X + RX \longrightarrow ArRNi^{(IV)}X_2 & (4) \\ ArNi^{(II)}X + RX \longrightarrow [ArNiX^{\cdot+}RX^{\cdot-}] & (5) \end{cases}$$

$$[ArNiX^{\cdot+}RX^{\cdot-}] \longrightarrow ArNiX^{+} + R^{\cdot} + X^-$$

$$ArNi^{(II)}X + R^{\cdot} \longrightarrow ArRNiX^{\cdot} \quad (6)$$

$$ArRNiX^{\cdot} \longrightarrow Ar\text{-}R + NiX^{\cdot} \quad (7)$$

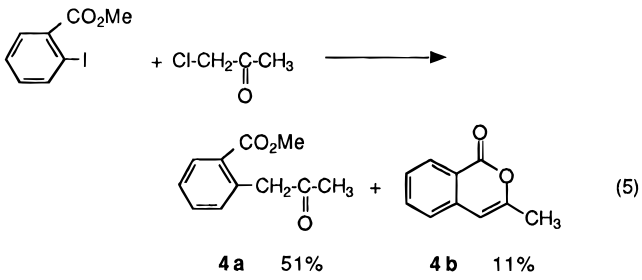
V/SCE yielded the heterocoupling product nearly quantitatively. This indicates that the reduction of ArNiX is not necessary for the coupling reaction to occur. In keeping with this, a previous report showed that ArNiX-$(PPh_3)_2$ prepared electrochemically from ArX and $NiBr_2$-$(PPh_3)_2$ in the presence of exces of PPh_3 reacts with α-chloro esters in the absence of electricity to give the corresponding α-aryl ester.[14] A second oxidative addition between ArNiX and RX could then be postulated, thus leading to $ArRNiX_2$ which is formally a $Ni^{(IV)}$ species (Scheme 2, step 4). We were unable to detect such an intermediate by electrochemical analysis. An alternative route would involve an electron transfer between these two species leading to $ArNiX^{\bullet+}RX^{\bullet-}$ (scheme 2, step 5) as already proposed by Hegedus[15a] for the coupling of π-allylnickel bromide and alkyl iodide and more recently by Yamamoto[(15b)] for the coupling of arylnickel(II) and alkyl iodide. This would involve the formation of a radical from RX which would then react with ArNiX to give nickel species $ArRNiX^{\cdot}$ (Scheme 2, step 6), as through step 7. To test this hypothesis we ran some reactions involving chiral methyl chloropropionate. This resulted in the formation of a racemic α-aryl ester. We can then conclude that there is more than one reaction mechanism, and the main mechanism leading to the cross-coupling depends on the experimental conditions, notably the cathode potential. A full mechanistic investigation will be reported.[12]

The investigation of the effect of the various parameters led us to employ the following experimental procedure. Freshly distilled DMF (40 mL), Bu_4NBF_4 (0.6 mmol), $NiBr_2$bipy (1 mmol), ArX (10 mmol), and a portion of RX (*ca*. 0.3 mmol) were introduced into a one-compartment cell fitted with an Al or Zn rod as the anode, and a nickel or stainless-steel-sponge, or carbon fiber as the cathode (cathode area: *ca* 20 cm^2). RX was added constantly to the solution via a syringe pump at a rate of 5 mmol/h up to the disappearance of ArX, monitored by GC, and the electricity was supplied at constant current intensity of 0.2−0.25 A under argon. Reactions involving aryl iodides were run at room temperature and those with bromides at 70 °C. The electrolyses were usually run until the aromatic halide was totally consumed.

Synthetic Applications. (a) Arylation of α-Chloro Ketones. Arylacetones and α-aryl ketones are key intermediates in the synthesis of many target molecules, notably amphetamine-like drugs. They can be prepared in two or more steps from aryl compounds (halides,[16] boranes,[17] or azo sulfides[18]) from benzylic compounds,[19] or from aromatic aldehydes.[20] They can also be easily obtained using the method reported here (eq 2).

Results for the electrochemical coupling reaction between chloroacetone and aryl iodides or bromides under the standard reaction conditions defined above are given in Table 1. Reactions involving aryl iodides were run at room temperature and those with aryl bromides were run at 70 °C. Because of the high reactivity of chloroacetone with $Ni^{(0)}$, the addition of 2−4 equiv of chloroacetone with respect to ArX was needed to totally consume ArX.

We can see that the chemical yields are good to excellent and that they are roughly identical from both types of aryl halides. As mentioned above there is no great influence of the ring substituent on the yield. However, with two electron-releasing groups the yields are low. Also, the functional compatibility is worth noting, illustrated here with the ester group. If the substituent is at the ortho position, like with methyl 2-iodobenzoate, the yield was good regardless of the steric hindrance. A lactone was formed as a secondary product by cyclocondensation (eq 5).



(5)

The method can be used with other α-chloro ketones such as 3-chloro-2-butanone and 2-chloroacetophenone. Results are given in Table 2.

Results are generally good. The excess of ketone *vs* ArX needed with 3-chloro-2-butanone is less than for chloroacetone. This is due to a decrease of the rate constant of the oxidative addition of $Ni^{(0)}$bipy with 3-chloro-2-butanone as compared to chloroacetone.

With 2-chloroacetophenone the reaction should be run at a cathode potential of *ca* −1.1 V/SCE because this chloroketone is easily reduced ($E_{1/2} = -1.4$ V/SCE). For that reason the reactions were conducted at a slightly lower current intensity ($i \leq 0.2$ A) than for the other reagents.

(b) Arylation of α-Chloro Esters. Nonsteroidal antiinflammatory arylacetic and α-arylpropionic acids are one of the largest class of drugs. Many routes to the various structures of therapeutic interest have been described, from either a benzylic[21] or an aromatic deriva-

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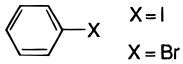
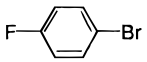
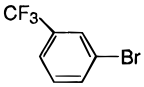
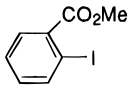
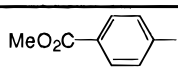
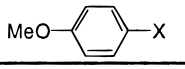
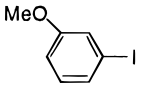
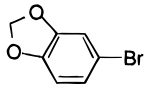
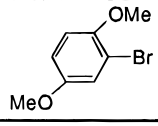
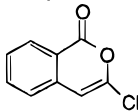
(15) (a) Hegedus, L. S.; Miller, L. L. *J. Am. Chem. Soc.* **1975**, *97*, 459. (b) Kim, Y. J.; Sato, R.; Maruyama, T.; Osakada, T.; Yamamoto, T. *J. Chem. Soc., Dalton Trans.* **1994**, 943.
(16) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.
(17) Brown, H. C.; Nambu, H.; Rogic, M. M. *J. Am. Chem. Soc.* **1969**, *91*, 6852.
(18) (a) Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1992**, *48*, 325. (b) Dell'Erba, C.; Novi, M.; Petrillo, G. Tavani, C. *Tetrahedron* **1994**, *50*, 3529.
(19) D'Incan, E.; Sibille, S.; Périchon, J. *Tetrahedron Lett.* **1986**, *27*, 4175.
(20) Binovic, K.; Vrancea, S. *Chim. Ther.* **1968**, *5*, 313.
(21) Bakshi, S. P.; Turner, E. E. *J. Chem. Soc.* **1961**, 171.

Table 1. Electroreductive Cross-Couplings between Aryl Halides and $ClCH_2COCH_3$

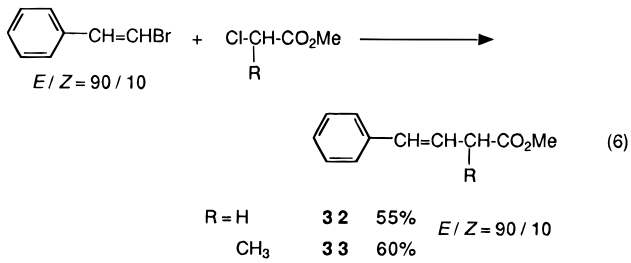
Entry	ArX (10 mmol)	$ClCH_2\overset{O}{\overset{\|}{C}}CH_3$ (mmol)	Product (yields %)[a]
1	 X = I X = Br	29 35	**1** (54) (62)
2		35	**2** (56)
3		27	**3** (80)
4		39	**4a** (51)[b]
5		30	**5** (52)
6	 X = I X = Br	22 36	**6** (65) (53)
7		28	**7** (56)
8		35	**8** (34)
9		35	**9** (34)

a : Isolated yields, based on initial ArX. All products gave satisfactory analytical data. b : by-product lactone  **4b** 11%

tive,[22] or by rearrangement of propiophenone.[23] We already described the electrochemical carboxylation of benzylic halides.[24] The method described here offers an interesting alternative leading directly to the ester of the desired arylacetic and α-arylpropionic acid (eq 3). Results are given in Table 3.

Methyl chloroacetate is slightly less reactive than chloroacetone toward $Ni^{(0)}$. The reactions can then be conducted in the presence of 2 equiv or less of the chloro ester relative to the aryl halide. The yields are good to excellent and do not seem to greatly depend on the nature of the ring substituent.

The method can also be applied to alkenyl bromides. Thus, as a preliminary study, the direct coupling between β-bromostyrene and α-chloro esters proceeds in good yield (eq 6). The stereochemical aspect has not been investigated yet.



(c) Arylation of Allylic Derivatives. The arylallyl skeleton is the basic structure of many natural products[3a] like estragol (p-CH_3O-$C_6H_4CH_2CH{=}CH_2$), eugenol (2-CH_3O-C_6H_4OH-4-$CH_2CH{=}CH_2$), methyleugenol (1,2-di-CH_3O-C_6H_4-4-$CH_2CH{=}CH_2$), osmorhyzol (1,3-di-CH_3O-C_6H_4-4-$CH_2CH{=}CH_2$), etc. It is also a useful building block. Substitution reactions of allylic halides with aromatic organometallic reagents have provided an important route for the synthesis of these allylic compounds.[1−3,5]

Cross-coupling reactions between aromatic halides and allylic derivatives were performed with two kinds of allylic compounds: allylic chloride and allylic acetate. The results are summarized in Table 4.

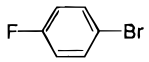
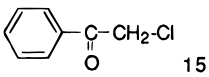
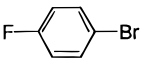
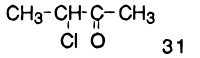
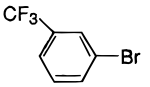
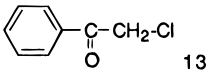
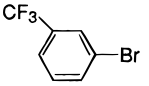
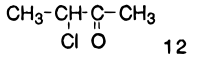
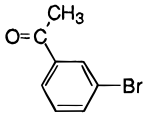
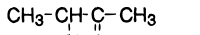
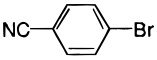
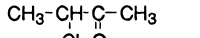
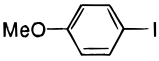
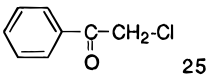
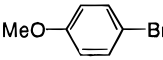
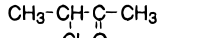
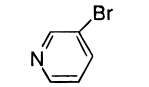
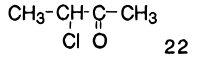
Reactions involving allylic derivatives generally give

(22) (a) Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833. (b) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1977**, *132*, C17. (c) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273. (d) Yamanaka, H.; An-naka, M.; Kondo, Y.; Sakamoto, T. *Chem. Pharm. Bull.* **1985**, *33*, 4309. (e) Klingstedt, T.; Frejd, T. *Organometallics* **1983**, *2*, 598.

(23) Rieu, J. P.; Boucherle, A.; Cousse, H. Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.

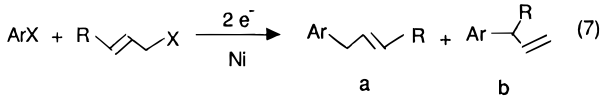
(24) Sock, O.; Troupel, M.; Périchon, J. *Tetrahedron Lett.* **1985**, *26*, 1509.

Table 2. Electroreductive Cross-Couplings between Aryl Halides and α-Chloro Ketones

Entry	ArX (10mmol)	α-chloroketone (mmol)	Product (yields %)[a]
1		 15	**10** (40)
2		 31	**11** (43)
3		 13	**12** (63)
4		 12	**13** (70)
5		 14	**14** (35)
6		 13	**15** (70)
7		 25	**16** (52)
8		 26	**17** (53)
9		 22	**18** (45)

a : Isolated yields, based on initial ArX. All products gave satisfactory analytical data.

two isomeric products due to allylic transposition: this is also observed in the reactions reported here (eq 7).



(7)

However, contrary to many other methods, the major product formed in these reactions is the unbranched product **a**, and the ratio of the two products is about 9:1 (Table 4, entries 4−6).

Identical or better results were obtained with allylic acetates than with allylic chlorides. The oxidative addition of $Ni^{(0)}$bipy is faster with allylic chlorides than with allylic acetates, so the competition in the formation of RNiX or ArNiX is in favor of RNiX in the reaction with allylic chlorides.

We can notice that an aromatic chloride, when activated by an electron-withdrawing group, can couple with allyl acetate in medium yield, at 70 °C (Table 4, entry 2).

(d) Arylation of Other Organic Halides. α-Chloropropiononitrile, benzyl chloride, methyl β-bromopropionate, and 1-bromopropene can also participate in such cross-coupling reactions (Table 5), though the procedure has to be adapted to each case.

α-Chloropropiononitriles (Table 5, entry 1) or benzyl chloride (Table 5, entries 2−3) react under the same procedure as for α-chloro esters or α-chloro ketones. The less reactive methyl β-bromopropionate and 1-bromopropene required a modified experimental procedure. 1-Bromopropene (Table 5, entries 5−7) was introduced initially (10 mmol) into the cell with the aromatic bromide and then constantly added to the solution during the electrolysis with a syringe pump at a rate of 5 mmol/h, at room temperature. Unreacted vinylic bromide was recovered at the end of the electrolysis. The stereochemical aspect has not yet been investigated. Methyl β-bromopropionate (Table 5, entry 4) was introduced initially into the cell, and bromobenzene was added slowly (*ca.* 4 mmol/h) to the electrolytic solution containing $BrCH_2$-CH_2CO_2Me. A great amount of benzene was formed along with the cross-coupling product.

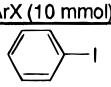
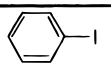
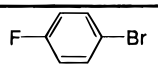
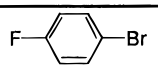
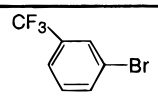
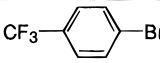
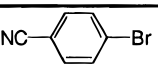
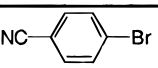
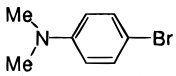
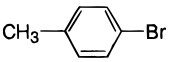
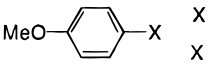
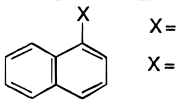
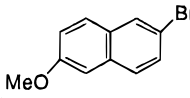
Conclusion

We have reported in this paper a staightforward method of efficient cross-coupling of aryl and alkyl halides, enabling the preparation of valuable target molecules such as α-aryl esters or α-aryl ketones. The scope of the method is wide concerning the type of organic halides involved: besides aryl and activated alkyl halides, alkenyl or alkyl halides can also be interestingly used. The method is also of large functional tolerance as regards the substituents on the aromatic ring. In addition, because of the use of a simple undivided electrolytic cell and sacrificial anode,[25] a possible scale up of the process can be envisaged.

The important part played by the nickel catalysis in the electroreductive coupling of aromatic halide with

(25) Chausard, J.; Troupel, M.; Jacob, G.; Juhasz, J. P. *J. Appl. Electrochem.* **1989**, *19*, 345.

Table 3. Electroreductive Cross-Couplings between Aryl Halides and α-Chloro Esters

Entry	ArX (10 mmol)	RX (mmol)	Product (yields %)[a]
1		$ClCH_2CO_2Me$ 12	**19** (74)
2		CH_3-CH(Cl)-CO_2Me 16	**20** (69)
3		$ClCH_2CO_2Me$ 20	**21** (75)
4		CH_3-CH(Cl)-CO_2Me 20	**22** (65)
5		CH_3-CH(Cl)-CO_2Me 11	**23** (59)
6		CH_3-CH(Cl)-CO_2Me 20	**24** (66)
7		$ClCH_2CO_2Me$ 20	**25** (60)
8		CH_3-CH(Cl)-CO_2Me 20	**26** (70)
9		$ClCH_2CO_2Me$ 27	**27** (67)
10		CH_3-CH(Cl)-CO_2Me 20	**28** (65)
11	 X = I, X = Br	CH_3-CH(Cl)-CO_2Me 20 20	**29** (85) (51)
12	 X = I, X = Br	CH_3-CH(Cl)-CO_2Me 20 20	**30** (80) (55)
13		CH_3-CH(Cl)-CO_2Me 20	**31** (55)

a : Isolated yields, based on initial ArX. All products gave satisfactory analytical data.

alkyl halide has been clearly demonstrated. The best catalysts for these reactions are $NiBr_2$bipy and $NiBr_2$-phen. The optimization of the cross-coupling reactions has led to a fine tuning of the experimental parameters (concentration, temperature). Metallic ions (Al^{3+} or Zn^{2+}) derived from the anode do not have a vital role in these reactions with respect to either the efficiency or the selectivity. Notably, a transmetalation reaction can be ruled out. A full study of the reaction mechanism will be published separately.

Experimental section

Nickel bromide, nickel tetrafluoroborate, and 2−2′-bipyridine were used as obtained commercially. NBu_4BF_4 was dried by heating overnight at 70 °C in vacuum.

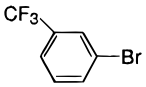
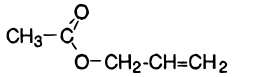
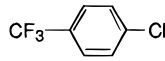
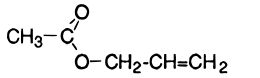
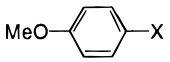
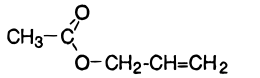
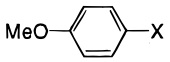
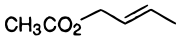
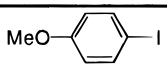
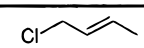
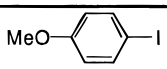
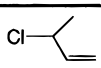
A zinc, magnesium, or aluminum rod was used as the anode. The cathode was made of carbon fiber or nickel- or stainless-steel-sponge. Other reagents were generally used as received. *N*,*N*-Dimethylformamide was distilled in the presence of copper sulfate under reduced pressure and was dried over molecular sieves (3 Å). DMF (analytical grade) was just dried over molecular sieves. *N*-methylpyrrolidone was distilled in the presence of alcoholic potassium hydroxide under reduced pressure. The reaction products were identified by the usual techniques. ^1H, ^{19}F, ^{13}C NMR spectra were recorded at 200 MHz. TMS served as an internal standard for ^1H or ^{13}C NMR spectra. For ^{19}F NMR spectra, $CFCl_3$ served as an external standard. Mass spectra were recorded with an ITD spectrometer coupled to a gas chromatograph (DB1, 30 m). High resolution mass spectra were performed by the Service Central de Spectrométrie de Masse (C.N.R.S., Lyon).

Preparation of Ni$^{(II)}$ Complexes. $NiBr_2$bipy,[26] $Ni(BF_4)_2$-bipy$_3$,[27] $NiBr_2(PPh_3)_2$,[28] and $NiCl_2$diphos[29] were prepared according to literature methods.

Preparation of Crotyl Acetate. We mixed 43 mL of crotyl alcohol, 95 mL of acetic anhydride, and a catalytic amount of (dimethylamino)pyridine (DMAP). A mixture of pyridine−CH_2Cl_2 (40 mL:40 mL) was added slowly, and the solution was allowed to react for 30 min at 0 °C. When all the pyridine was added, the mixture was set at room temperature. Then the reaction mixture was poured into 30 mL of 4 N HCl and was extracted with diethyl ether (3 × 30 mL). The combined

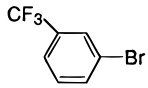
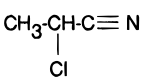
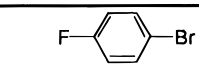
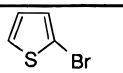
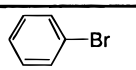
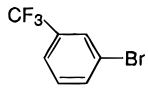
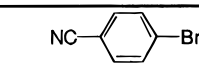
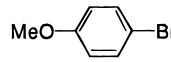
(26) Uchino, M.; Asagi, K.; Yamamoto, A. Ikeda, S. *J. Organomet. Chem.* **1975**, *84*, 93.
(27) Dunach, E.; Périchon, J. *J. Organomet. Chem.* **1988**, *352*, 239.
(28) Venanzi, L. *J. Chem. Soc.* **1958**, 719.
(29) Van Hecke, G. R.; Horrocks, W. W. *Inorg. Chem.* **1966**, *5*, 1968.

Table 4. Electroreductive Cross-Couplings between Aryl Halides and Allylic Compounds

Entry	ArX (10mmol)	Allylic derivative (mmol)		Product (yield %)[a]	
1			15	**34** (56)	
2			15	**35** (38)	
3	 X = I X = Br		17 15	**36** (40) (52)	
4	 X = I X = Br		10 11	**37** (68) (63)	**37a**[b] / **37b** 94 / 6 86 / 14
5			14	(43)	88 / 12
6			11	(56)	96 / 4

a : Isolated yields, based on initial ArX. All products gave satisfactory analytical data. b : see eq 7

Table 5. Electroreductive Cross-Couplings between Aryl Halides and Other Organic Halides

Entry	ArX (10 mmol)	RX (mmol)	Product (yields %)[a]
1		 22	**38** (62)
2		$PhCH_2Cl$ 10	**39** (83)
3		$PhCH_2Cl$ 13	**40** (56)[b]
4		$BrCH_2CH_2CO_2Me$ 15	**41** (38)
5		Br-CH=CH-CH_3[c] 20	**42** (60)[b] (Z / E = 2 / 8)
6		Br-CH=CH-CH_3[c] 29	**43** (66) (Z / E = 2 / 8)
7		Br-CH=CH-CH_3[c] 49	**44** (44) (Z / E = 25 / 75)

a : Isolated yields, based on initial ArX. All products gave satisfactory analytical data. b : GC yields, based on internal standard. c : mixture of *Z* / *E* = 50 / 50

extracts were washed with dilute aqueous HCl to ensure the complete removal of pyridine, with aqueous $NaHCO_3$ to remove acetic acid, and finally with water. The extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. We obtained 57 g of crotyl acetate (100%). ^1H NMR ($CDCl_3$): 1.7 (d, J = 5 Hz, 3H); 2.1 (s, 3H); 4.6 (d, J = 5 Hz, 2H); 5.7 (m, 2H).

General Procedure for the Electrosynthesis. The electrolysis cell has already been described.[7] It was fitted with a nickel-sponge cathode (20 cm^2) and a zinc or aluminum rod (1 cm diameter) anode. To a DMF solution (40 mL) containing 0.6 mmol of NBu_4BF_4 and 1 mmol of $NiBr_2$bipy were added the aromatic halide (10 mmol) and the α-chloro ester or the α-chloro ketone or the allylic derivative (*ca.* 0.3 mmol). Reactions were performed at room temperature (aromatic iodide) or at 70 °C (aromatic bromide), under argon. The electrolysis (*i* = 250 mA or 200 mA for the coupling with 2-chloroacetophenone) was monitored by GC and was run until the aromatic halide was totally consumed (2−6 h). The reactions were then quenched with 4 N HCl (or 2 N to aryl esters) and extracted with diethyl ether (3 × 40 mL). The combined extracts were washed with water (5 × 40 mL) to ensure complete removal of DMF. The extracts were dried ($MgSO_4$), and solvent was removed under reduced pressure. The product was isolated by silica-gel column chromatography eluted with 90:10 or 85:15 pentane/diethyl ether.

Characterization of the Products. Benzoic acid, 4-(2-oxopropyl)-methyl ester (5): ^1H NMR ($CDCl_3$, 200 MHz) δ 2.17

(3H, s), 3.77 (2H, s), 3.89 (3H, s), 7.27 and 8 (2H each, AA′-BB′ system $J = 8.2$ Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 29.2 (1C, CH_3), 50.2 (1C, CH_2), 51.7 (1C, CH_3), 128.6 (1C, arom), 129.2 (2C, arom), 129.6 (2C, arom), 139.1 (1C, arom), 166.4 (1C, CO_2), 204.8 (1C, CO); MS 192 (M), 161 (M − 31), 149 (M − 43, base), 135 (M − 57), 118 (M − (31 + 43)), 90.

3-(3-Acetylphenyl)-2-butanone (14): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (3H, d, J = 6.99 Hz), 2.09 (3H, s), 2.62 (3H, s), 3.89 (1H, q, J = 6.99 Hz), 7.45−7.51 and 7.86−7.91(4H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.0 (1C, CH_3), 26.3 (1C, CH_3), 28.2 (1C, CH_3), 53.0 (1C, CH), 127.1 (1C, arom), 127.4 (1C, arom), 129 (1C, arom), 132.1 (1C, arom), 137.5 (1C, arom), 141 (1C, arom), 197.4 (1C, CO), 207.7 (1C, CO); high resolution MS 190.1 (M), 175.1 (M − 15), 148.1 (M − 43), 105.1, 43.0 (base).

Benzeneacetic acid, 4-fluoro-methyl ester (21): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.59 (2H, s), 3.69 (3H, s), 6.96−7.04 (2H, m), 7.20−7.27 (2H, m); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ -115.52 (1F, m)/$CFCl_3$; MS 168 (M), 109 (M − 59, base).

2-[3-(Trifluoromethyl)phenyl]propiononitrile (38): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.64 (3H, d, J = 7.3 Hz), 4.02 (1H, q, J = 7.3 Hz), 7.47−7.66 (4H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.9 (1C, CH_3), 30.9 (1C, CH), 120.9 (1C, CN), 123.5 (1C, arom, q, J_{CCCF} = 3.78 Hz), 123.8 (1C, CF_3, q, J_{CF} = 272.33 Hz), 124.9 (1C, arom, q, J_{CCCF} = 3.72 Hz), 129.7 (1C, arom), 130.2 (1C, arom), 131.3 (1C, arom, q, J_{CCF} = 32.48 Hz), 138.3 (1C, arom); ^{19}F NMR ($CDCl_3$, 188.3 MHz) δ -62.66 (3F, s)/$CFCl_3$; high resolution MS 199.1 (M), 184.1 (M − 15, base), 145.1, 130.1 (M − 69).

The following products were characterized by comparison of their GC and spectral data with those for commercially available samples: 1-phenyl-2-propanone **(1)**; 1-(4-fluorophenyl)-2-propanone **(2)**; 1-[3-(Trifluoromethyl)phenyl]-2-propanone **(3)**; 1-(4-methoxyphenyl)-2-propanone **(6)**; methyl phenylacetate **(19)**; 1-methoxy-4-(2-propenyl)benzene **(36)**; benzene, 1-methoxy-4-(1-propenyl) **(44)**.

The following compounds were identified by comparison of their physical and spectral data with those given in the cited references: Benzoic acid, 2-(2-oxopropyl)-methyl ester **(4a)**;[30] 3-methylisocoumarin **(4b)**;[31] 1-(3-methoxyphenyl)-2-propanone **(7)**;[18a] 1-(1,3-benzodioxol-5-yl)-2-propanone **(8)**;[32] 1-(2,5-Dimethoxyphenyl)-2-propanone **(9)**;[33] 2-(4-Fluorophenyl)-1-phenylethanone **(10)**;[34] 3-(4-Fluorophenyl)-2-butanone **(11)**;[35] 2-[3-(Trifluoromethyl)phenyl]-1-phenylethanone **(12)**;[34] 3-[3-(Trifluoromethyl)phenyl]-2-butanone **(13)**;[20] 3-(4-cyanophenyl)-2-butanone **(15)**;[36] 2-(4-methoxyphenyl)-1-phenylethanone **(16)**;[37] 3-(4-methoxyphenyl)-2-butanone **(17)**;[35] 3-(3-pyridyl)-2-butanone **(18)**;[38] Benzeneacetic acid, α-methyl-methyl ester **(20)**;[39] Benzeneacetic acid, 4-fluoro-α-methyl-methyl ester **(22)**;[39] benzeneacetic acid, α-methyl-3-(trifluoromethyl)-methyl ester **(23)**;[40] benzeneacetic acid, α-methyl-4-(trifluoromethyl)-methyl ester **(24)**;[40] benzeneacetic acid, 4-cyano-methyl ester **(25)**;[8] benzeneacetic acid, 4-cyano-α-methyl-methyl ester **(26)**;[41] benzeneacetic acid, 4-(dimethylamino)-methyl ester **(27)**;[42] benzeneacetic acid, α-methyl-4-methyl-methyl ester **(28)**;[39] 4-methoxybenzeneacetic acid, α-methyl-methyl ester **(29)**;[39] 1-naphthylacetic acid, α-methyl-methyl ester **(30)**;[43] [2-(6-methoxynaphthyl)]acetic acid, α-methyl-methyl ester **(31)**;[44] 3-butenoic acid, 4-phenyl-methyl ester **(32)**;[45] 3-butenoic acid, 2-methyl-4-phenyl-methyl ester **(33)**;[8] 1-(2-propenyl)-3-(trifluoromethyl)benzene **(34)**;[46] 1-(2-propenyl)-4-(trifluoromethyl)benzene **(35)**;[47] 1-(2-butenyl)-4-methoxybenzene **(37a)**;[3a] 1-methoxy-4-(1-methyl-2-propenyl)benzene **(37b)**;[48] benzene, 1-fluoro-4-(phenylmethyl) **(39)**;[49] thiophene, 2-(phenylmethyl) **(40)**;[50] benzenepropanoic acid, methyl ester **(41)**;[51] benzene, 1-(1-propenyl)-3-(trifluoromethyl) **(42)**;[46] benzonitrile, 4-(1-propenyl) **(43)**.[52]

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Registry Numbers (provided by the author). (**1**), 103-79-7; **(2)**, 459-03-0; **(3)**, 21906-39-8; **(4a)**, 7115-18-6; **(4b)**, 25539-21-7; **(5)**, 22744-50-9; **(6)**, 122-89-9; **(7)**, 3027-13-2; **(8)**, 4676-39-5; **(9)**, 14293-24-4; **(10)**, 347-91-1; **(11)**, 79341-86-9; **(12)**, 30934-66-8; **(13)**, 21906-07-0; **(15)**, 79341-85-8; **(16)**, 24845-40-7; **(17)**, 7074-12-6; **(18)**, 66702-67-8; **(19)**, 101-41-7; **(20)**, 31508-44-8; **(21)**, 34837-84-8; **(22)**, 50415-71-9; **(23)** (-), 145983-12-6; **(24)**, 125670-61-3; **(25)**, 52798-01-3; **(26)**, 125670-62-4; **(27)**, 6767-29-9; **(28)**, 79443-97-3; **(29)**, 50415-73-1; **(30)**, 72221-62-6; **(31)**, 30012-51-2; **(32)**, 29891-75-5; **(33)**, 94041-87-9; **(34)**, 1813-96-3; **(35)**, 1813-97-4; **(36)**, 140-67-0; **(37a)**, 18322-84-4; **(37b)**, 18272-83-8; **(39)**, 587-79-1; **(40)**, 13132-15-5; **(41)**, 103-25-3; **(42)** (*E*), 588879-30-4; **(42)** (*Z*), 154309-36-1; **(43)**, 140675-27-0; **(43)** (*E*), 74254-13-0; **(44)**, 4180-23-8.

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