Electrochemical Cross-Coupling of Alkyl Halides in the Presence of a Sacrificial Anode

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The electrochemical trichloromethylation of various alkyl halides has been obtained in high yields in an undivided cell in the presence of a sacrificial anode. This cross-coupling process has been extended to the preparation of numerous *gem*-dichloro compounds from trichloro-substituted methanes and alkyl halides. Zinc, magnesium, or aluminium were used as anodes according to the reduction potentiel of the reagents. Mixtures of polar aprotic solvents, e.g. THF–TMU or THF–NMP, were found more appropriate than pure solvents. The critical role of the metallic ions from the consumption of the anode has been clearly evidenced.

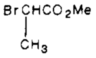
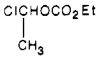
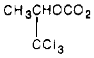
Coupling of organic halides has been an attractive way for carbon–carbon bond formation since the disclosure of the Wurtz reaction. Important improvements have obviously been reached to avoid side reactions, which are quite common in classical Wurtz reactions, especially by using preformed organometallic species, usually with a transition metal catalyst, e.g. Ni, Pd.[1] If homocoupling of alkyl, alkenyl, alkynyl, or aryl halides can then be performed in simple efficient ways, cross-coupling is usually less feasible, notably because of the number of products obtained. Moreover, access to α-halogenated organometallic compounds through classical methods are quite difficult because of the low thermal stability of these species.[2] Thus, such reactions as trihalomethylation of organic halides via organometallic intermediates remain hardly feasible. The alternative approach by phase-transfer catalysis is not more suitable since α-halomethylanions rapidly give carbenes.[3]

We have recently published a preliminary account[4] on a very simple electrochemical trichloromethylation of various alkyl halides (eq 1, R = Cl) and a related synthesis of *gem*-dichloro compounds (eq 1, R = alkyl, aryl, methoxycarbonyl), performed in an undivided cell with a sacrificial anode.[5] We report herein the full details of this study.

$$RCCl_3 + R'X + 2e \rightarrow RCCl_2R' + Cl^- + X^- \qquad (1)$$

Recent papers[6,7] have demonstrated the successful use of consumable anode in electroreductive organic syntheses performed in a one-compartment cell, one of the most important feature of the process being the uselessness of a membrane because the anodic process does not involve any organic compound. Stemming from our current studies on electroreductive functionnalization of organic halides with sacrificial anode are some premises relevant to the present work. Notably, the direct electroreduction of an alkyl halide (RX) in an undivided cell in the presence of a Mg anode in dimethylformamide (DMF) mainly gives the homocoupling product (RR)[8] instead of the reduced product (RH) usually obtained in a divided cell.[9] Moreover, we have already obtained cross-coupling between various alkyl halides and mono- and dichlorophosphines in DMF or *N*-methylpyrrolidone (NMP) by using magnesium as anode.[6c] We have also demonstrated that the reduction of CCl_4 in presence of a Zn or Al anode in DMF gives CCl_3^-, which is reasonably stable to, as an example, efficiently add to carbonyl bonds of aldehydes, meanwhile the CCl_2 carbene is reportedly obtained when the reduction is carried out in a divided cell.[10]

Table I. Electrochemical Trichloromethylation of Aliphatic Halides in the Presence of a Sacrificial Anode of Zinc[a]

entry	R'X	products[b]	% yield[c]	recovery[d] of R'X, %
1	$PhCH_2Br$	$PhCH_2CCl_3$ (**1a**)	70	20
2	$PhCH{=}CH\text{-}CH_2Br$	$PhCH{=}CH\text{-}CH_2CCl_3$ (**3a**)	35	20
		$PhCH{=}CH\text{-}CH{=}CCl_2$ (**10a**)	5	
3	$BrCH_2CO_2Me$	$Cl_3CCH_2CO_2Me$ (**5a**)	30	20
		$Cl_2C{=}CHCO_2Me$ (**8a**)	45	
4	 $Br\underset{\underset{CH_3}{\vert}}{C}HCO_2Me$	$CH_3CH(CCl_3)CO_2Me$ (**6a**)	55	10
		$Cl_2C{=}C(CH_3)CO_2Me$ (**9a**)	25	
5	 $Cl\underset{\underset{CH_3}{\vert}}{C}HOCO_2Et$	 $CH_3\underset{\underset{CCl_3}{\vert}}{C}HOCO_2Et$ (**7a**)	98	40

[a] CCl_4 (40 mmol), R'X (20 mmol), Zn anode, THF (20 mL), TMU (20 mL), NBu_4BF_4 (0.5 mmol), NBu_4I (0.5 mmol), I = 0.2 A, 3 mol of electron for 1 mol of R'X, room temperature. [b] Isolated by column chromatography. [c] Isolated yield based on R'X consumed. [d] GC determination.

The conjunction of these observations prompted us to test the feasibility of a cross-coupling process between easily reducible alkyl polychlorides (CCl_4 and $RCCl_3$) on one side and less easily reducible alkyl halides which would be sensitive to S_N2 reaction. We will show that the process offers a simple and general access to a variety of di- and trichloro compounds of potential synthetic as well as biological value.

Results and Discussion

Results of the trichloromethylation of various types of alkyl halides in presence of a Zn anode are given in Table I. The electrochemical cell used in this work has already

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[1] (a) Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic: New York, 1978; Chapter 14. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

[2] (a) Villieras, J. *Bull. Soc. Chim. Fr.* **1967**, 1520. (b) Helmchen, G.; Wegner, G. *Tetrahedron Lett.* **1985**, *26*, 6047. (c) Tarhouni, R.; Kirschleger, B.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1984**, *25*, 835.

[3] Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*; VCH Verlagsgesellschaft: Weinheim, 1980; p 177.

[4] Nédélec, J. Y.; Aït-Haddou-Mouloud, H.; Folest, J. C.; Périchon, J. *Tetrahedron Lett.* **1988**, *29*, 1699.

[5] Nédélec, J. Y.; Folest, J. C.; Périchon, J.; Aït-Haddou-Mouloud, H. French Pat. 87 15975.

[6] (a) Sock, O.; Troupel, M.; Périchon, J. *Tetrahedron Lett.* **1985**, *26*, 1509. (b) Sibille, S.; d'Incan, E.; Leport, L.; Périchon, J. *Tetrahedron Lett.* **1986**, *27*, 3129. (c) Folest, J. C.; Nédélec, J. Y.; Périchon, J. *Tetrahedron Lett.* **1987**, *28*, 1885.

[7] (a) Silvestri, G.; Gambino, S.; Filardo, G.; Greco, G.; Gulotta, A. *Tetrahedron Lett.* **1984**, *25*, 4307. (b) Silvestri, G.; Gambino, S.; Filardo, G.; Gulotta, A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 979. (c) Silvestri, G.; Gambino, S.; Filardo, G. *Tetrahedron Lett.* **1986**, *27*, 3429.

[8] Folest, J. C.; Mabrouk, S.; Périchon, J., unpublished.

[9] See, for example: Cleary, J. A.; Mubarak, M. S.; Vieira, K. L.; Anderson, M. R.; Peters, D. G. *J. Electroanal. Chem.* **1986**, *198*, 107.

[10] (a) Wawzonek, S.; Duty, R. T. C. *J. Electrochem. Soc.* **1961**, *108*, 1135. (b) Fritz, H. P.; Kornrumpf, W. *Justus Liebigs Ann. Chem.* **1978**, 1416.

0022-3263/88/1953-4720$01.50/0

Table II. Electrochemical Synthesis of *gem*-Dichloro Compounds[a]

entry	$RCCl_3$	R′X	anode	product(s)[b]	% yield[c]	recovery[d] of R′X, %
1	$PhCCl_3$	$CH_3(CH_2)_3CH_2Br$	Zn	$PhCCl_2(CH_2)_4CH_3$ (**4b**), $PhCCl{=}CH(CH_2)_3CH_3$ (**11b**)	45, 30	20
2	$PhCCl_3$	$PhCH_2Br$	Al[e]	$PhCCl_2CH_2Ph$ (**1b**), $PhCCl{=}CHPh$ (**12b**)	70, 10	10
3	$PhCCl_3$	$BrCH_2CO_2Me$	Zn	$PhCCl_2CH_2CO_2Me$ (**5b**), $PhCCl{=}CHCO_2Me$ (**8b**)	70, 10	5
4	$PhCCl_3$	$BrCH(CH_3)CO_2Me$	Zn	$PhCCl_2CH(CH_3)CO_2Me$ (**6b**), $PhCCl{=}C(CH_3)CO_2Me$ (**9b**)	75, 5	10
5	CCl_3CO_2Me	$PhCH_2Br$	Zn	$PhCH_2CCl_2CO_2Me$ (**1f**)	70	10
6	CCl_3CO_2Me	$CH_2{=}CHCH_2Br$	Zn	$CH_2{=}CHCH_2CCl_2CO_2Me$ (**2f**)	70	20
7	CH_3CCl_3	$ClCH(CH_3)OCO_2Et$	Mg	$CH_3CCl_2CH(CH_3)OCO_2Et$ (**7d**), $CH_3CHClCH(CH_3)OCO_2Et$ (**13**)	50, 20	30
8	CF_3CCl_3	$PhCH_2Br$	Al[e]	$PhCH_2CCl_2CF_3$ (**1e**)	60	25
9	$HCCl_3$	$PhCH_2Br$	Al[e]	$PhCH_2CCl_2H$ (**1c**), $PhCH_2CCl_3$ (**1a**)	60, 30	5

[a] Unless otherwise stated: R′X (20 mmol), $RCCl_3$ (40 mmol), THF (20 mL), TMU (20 mL), NBu_4BF_4 (0.5 mmol), NBu_4I (0.5 mmol), I = 0.2 A, 3 mol electron per mol RX, room temperature. [b] Isolated by column chromatography. [c] Isolated yield based on R′X consumed. [d] Determined by GC. [e] NBu_4Br (1 mmol) was used as electrolyte.

Table III. Trichloromethylation of Benzyl Bromide in a Divided Electrochemical Cell in the Presence of Preformed Zn(II) Ions[a]

entry	$ZnBr_2$, mmol	electricity,[b] F/mol	yield[c] of $PhCH_2$-CCl_3, %	yield[c] of $PhCH_2Cl$, %	yield[c] of $PhCH_2)_2$, %
1	0	1.2	<5	80	10
2	5	1.4	13	65	<5
3	10	1.6	15	50	<5
4	20	2	35	30	5

[a] Cathodic compartment: $PhCH_2Br$ (10 mmol), CCl_4 (20 mmol), THF (20 mL), TMU (20 mL), NBu_4BF_4 (24 mmol), I = 0.1 A, Au cathode. [b] Amount of electricity needed to convert around 80% of $PhCH_2Br$. [c] Determined by GC.

been described.[5] In a typical reaction, 2 equiv of CCl_4 and 1 equiv of alkyl halide (R′X) were mixed in 1:1 mixture of tetrahydrofuran (THF) and *N*,*N*′-tetramethylurea (TMU) as solvent containing an ammonium salt as supporting electrolyte in a cylindrical undivided cell fitted with a rod of zinc as the anode and a cylindrical grid of stainless steel as the cathode. Three equivalents of electron relative to R′X were passed at constant current with a current density of 2 A/dm^2, at room temperature under argon. Good to high yields of trichloromethylated products were obtained, and further reduction of these products was not detected. Dehydrochlorination, when observed (entries 2, 3, 4, Table I), mainly occurred during the workup and the silica gel column chromatography. Indeed, no unsaturated product was detected during the reaction by GC analysis of a nonhydrolyzed aliquot. With magnesium instead of zinc as the anode, yields were lower, partially because of the reduction of the product.

We have also investigated the reaction of trichlorosubstituted methanes (eq 1, R = H, Ph, CH_3, CF_3, CO_2CH_3) with various alkyl halides. As indicated in Table II, many *gem*-dichloro compounds can be obtained in high yields by using this very simple procedure. The nature of the anode had nevertheless to be selected according to the reduction potentiel of $RCCl_3$.[11] Thus with R = Ph, CO_2Me, CF_3, the reduction potentials being less negative for $RCCl_3$ than for Zn(II), a Zn anode is quite convenient, more especially as the reduction of the product is prevented; an Al anode can also be used but only with NBu_4Br as electrolyte (entries 2, 8, Table II). With R = H or CH_3, zinc cannot be used, for we mainly observe the reduction of Zn(II) produced at the anode; instead we can use magnesium with NBu_4BF_4 or aluminium with NBu_4Br, and good yields are obtained (entries 7, 9, Table II), but partial reduction of the product can occur (see entry 7, Table II). The coupling reaction between $PhCH_2Br$ and $HCCl_3$ (entry 9, Table II) gives rise to two products: the expected *gem*-dichloro compound **1c** along with **1a**, the formation of this latter being readily explained by an acid–base equilibrium (eq 2) leading to appreciable amount

$$HCCl_2^- + HCCl_3 \rightleftarrows CH_2Cl_2 + CCl_3^- \qquad (2)$$

of CCl_3^- ion. On prolonged electroreduction (up to 5 F/mol), **1a** was totally transformed into **1c**.

All these reactions were performed with 2 equiv of $RCCl_3$ relative to R′X to better ensure the selective reduction of the former. Only small amount of supporting electrolyte is necessary for the conductivity to be sufficient at the beginning of the reaction, and a mixture of salts (NBu_4BF_4–NBu_4I) were found convenient to avoid passivation of the anode. That the reaction is not a chemical reaction between CCl_4 and an electroactivated reducing metal (Zn, Mg) was ascertained by switching off the current at different stages and following the evolution of reagents and products with and without electricity.

As already proposed for other reactions with sacrificial anodes, the mechanism of this reaction can be summarized as follows:

$$\text{at the anode} \qquad M \rightarrow M^{n+} + ne \qquad (3)$$

$$\text{at the cathode} \quad RCCl_3 + 2e \rightarrow RCCl_2^- + Cl^- \qquad (4)$$

$$\text{in solution} \quad RCCl_2^- + R'X \rightarrow RCCl_2R' + X^- \qquad (5)$$

However, the role of the M^{n+} ions from the consumption of the anode (eq 3) is not clearly evidenced in this mechanism (eq 3–5). Indeed, very little of the cross-coupling product is formed in a diaphragm cell in the absence of metallic ions, whatever the reagents are.[12] This indicates that CCl_3^- or $RCCl_2^-$ are not efficiently stabilized by NBu_4^+ ions.

To tentatively enlighten the basic properties of the process, a careful examination of the features of the reaction has been conducted with the trichloromethylation of benzyl bromide as the model (eq 6).

$$PhCH_2Br + CCl_4 + 2e \rightarrow \underset{\mathbf{1a}}{PhCH_2CCl_3} + Cl^- + Br^- \qquad (6)$$

The critical role of the M^{n+} ions from the anode oxidation was demonstrated by the following experiments. The model reaction has been comparatively studied in a divided cell with increasing amounts of Zn(II) ions, which were preliminarily formed in the cathodic chamber used as a one-compartment cell, by electrochemical reduction

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(11) The following half-peak reduction potentials have been measured in (1:1) THF–TMU/NBu_4BF_4 with a gold cathode for various R in $RCCl_3$ (value in volt vs sce): Cl (−0.9); CO_2Me (−1.6); Ph (−1.75); CF_3 (−1.7); H (−2.2); CH_3 (−2.4); and for $ZnBr_2$ and $ZnCl_2$ (−2.2).

(12) The electrochemical trichloromethylation of alkyl halide was observed by Baizer et al. as a side reaction in a process using CCl_4 as source of electrogenerated base in a divided cell. See: Nugent, S. T.; Baizer, M. M.; Little, R. D. *Tetrahedron Lett.* **1982**, *23*, 1339.

Table IV. Electrochemical Trichloromethylation of Benzyl Bromide: Solvent Effect[a]

entry	solvent	GC yield[b] of $PhCH_2CCl_3$, %	GC yield[b] of $(PhCH_2)_2$, %	GC yield[b] of $PhCH_2Cl$, %	GC recovery of $PhCH_2Br$, %
1	DMF	30	50	20	20
2	NMP	25		60	15
3	DMSO	30	70		10
4	TMU	40	20	30	10
5	DMF-THF (1:1)	25	50	20	20
6	DMF-TMU (1:1)	80	10		10
7	DMF-NMP (1:1)	50	30	20	20
8	DMF-DEC (1:1)	75	5	20	20
9	NMP-THF (1:1)	60	35	5	20
10	NMP-THF (2:1)	80	20		20
11	TMU-THF (1:1)	80	5	10	10

[a] CCl_4 (40 mmol), $PhCH_2Br$ (20 mmol), Zn anode, solvent (40 mL), NBu_4BF_4 (0.5 mmol), NBu_4I (0.5 mmol), $I = 0.2$ A, 3 F/mol of $PhCH_2Br$. [b] Based on consumed $PhCH_2Br$.

of 1,2-dibromoethane in the presence of a zinc rod as the anode in a 1:1 THF–TMU mixture containing NBu_4BF_4 (eq 7, 8). We thus have found (Table III) that in the

$$Zn \rightarrow Zn^{2+} + 2e \quad (7)$$

$$BrCH_2CH_2Br + 2e \rightarrow 2\ Br^- + CH_2{=}CH_2 \quad (8)$$

absence of zinc ions only traces of the cross-coupling product were formed, and that $PhCH_2Br$ was essentially transformed into $PhCH_2Cl$ with slightly more than 1 mol equiv of electron. The material balance thus implies that two chlorine ions are produced per molecule of CCl_4. The effect of Zn(II) ions is clearly pointed out by the increasing amount of product **1a** paralleling the amount of Zn(II) present in the medium. Nevertheless, the efficiency of this "salt effect" is less in a divided cell than in an undivided one where fresh zinc ions are continuously produced as the reaction proceeds. The same observations have been made for the coupling reaction between $PhCCl_3$ and $PhCH_2Br$ in similar experimental conditions.

The reaction was also found to be quite sensitive to the nature of the solvent, as well as the nature of the anode and the nature of the supporting electrolyte in connection with the type of anode.

As indicated in Table IV yields of $PhCH_2CCl_3$ were low in pure DMF, TMU, NMP, or dimethyl sulfoxide (DMSO) and high in mixtures of solvents such as 1:1 DMF–TMU, 2:1 NMP–THF, or 1:1 mixture of DMF and diethyl carbonate (DEC). This contrasts with the results obtained for other reactions based on the same procedure as the alkylation of carbonyl compounds in DMF,[6b] even with CCl_4 as reagent, or the cross-coupling of alkyl halides and chlorophosphines in DMF or NMP.[6c] THF-HMPA (hexamethylphosphoramide) mixture was also positively tested, but toxic HMPA is advantageously replaced with TMU. The observed solvent effect could be indicative of a low rate of the nucleophilic displacement involved here (eq 5) compared to the nucleophilic addition to C=O or the S_N2 reaction involving the more reactive Ph_2P^- ion previously studied in similar conditions. Therefore, a highly stabilizing medium is necessary to avoid the evolution of CCl_3^- into dichlorocarbene. If we assume that the reactive intermediate is a complexed ion such as $CCl_3^-M^{n+}X_{(n-1)}$, we can find close analogies between our observations and the studies of the properties of α-halogenated organomagnesium or organolithium compounds, whose stability and reactivity show the same type of solvent dependence.[2] Nevertheless, our process does not require preformation of the organometallic, and then it can occur at room temperature and without reaction with the solvent; in this sense, we can define our reacting species as a mild organometallic.

Table V. Trichloromethylation of Benzyl Bromide: Conjugated Influence of the Anode and the Supporting Electrolyte[a,b]

entry	anode	supporting electrolyte	GC yield[c] of $PhCH_2CCl_3$, %	GC yield[c] of $PhCH_2Cl$, %	GC recovery of $PhCH_2Br$, %
1	Zn	NBu_4BF_4	85	5	10
2	Zn	NBu_4Br	50	25	20
3	Mg	NBu_4BF_4	43	25	25
4	Mg	NBu_4Br	45	20	25
5	Al	NBu_4BF_4	10	85	5
6	Al	NBu_4Br	85	5	10
7	Mn	NBu_4BF_4	30	41	15
8	Mn	NBu_4Br	6	70	25
9	Cd	NBu_4BF_4	25	45	5
10	Cd[d]	NBu_4Br	20	25	5

[a] CCl_4 (40 mmol), $PhCH_2Br$ (20 mmol), TMU (20 mL), THF (20 mL), $I = 0.2$ A, 3 F/mol of $PhCH_2Br$, supporting electrolyte (1 mmol). [b] Unless otherwise indicated, less than 5% (GC) of $(PhCH_2)_2$ was detected. [c] Relative to consumed $PhCH_2Br$. [d] 50% of $(PhCH_2)_2$ was formed.

It is also remarkable that the formation of the cross-coupling depends on the nature of the metal used as the anode and on the nature of the supporting electrolyte (Table V). Of the potentially possible reactions in the electrochemical reduction of a mixture of halides such as $PhCH_2Br$–CCl_4 (homo- and cross-coupling, halogen exchange, and reduction of the reagents) two were found predominant: the cross-coupling reaction giving $PhCH_2CCl_3$, which was observed with Zn in presence of NBu_4BF_4 or NBu_4BF_4–NBu_4I mixture, the halogen exchange (eq 9) prevailing with Mn or Cd, whatever the

$$PhCH_2Br \rightarrow PhCH_2Cl \quad (9)$$

electrolyte was, whereas both reactions occurred with Zn in the presence of NBu_4Br and with Mg with NBu_4Br or NBu_4BF_4. Finally, Al was found very peculiar inasmuch as $PhCH_2Br$ was converted into $PhCH_2Cl$ with NBu_4BF_4 but was cross-coupled with CCl_4 in the presence of NBu_4Br.

These results can be rationalized in terms of halogen scrambling mediated by the Lewis acid that is formed as the reaction proceeds. This would normally give the less reactive benzyl chloride in variable amounts depending on the efficiency of the competing nucleophilic displacement by CCl_3^- (eq 5). When aluminium is used, and in presence of bromide ions, the aluminium bromide progressively produced as the reaction proceeds can favor a back halogen exchange when benzyl chloride has been formed (eq 10),

$$PhCH_2Cl + {>}AlBr \rightarrow PhCH_2Br + {>}AlCl \quad (10)$$

such reaction being possibly favored by the lower solubility in organic solvents of $AlCl_3$ compared to $AlBr_3$.[13] Indeed, $AlBr_3$ has been used to prepare alkyl bromides from chlorides.[14] We then have verified that such reaction actually occurs in our system when both aluminium and bromide ions are present in the medium. Thus, benzyl

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(13) *Comprehensive Inorganic Chemistry*; Trotman-Dickinson, A. F., Ed.; Pergamon: Oxford, 1973; Vol. 1, p 1019 sq.

(14) *Bromine and its Compounds*; Jolles, Z. E., Ed.; Benn: London, 1966; p 383.

chloride was efficiently converted (>60%), at room temperature, into the bromide in presence of aluminium bromide produced by electroreduction of $C_2H_4Br_2$ with an Al anode in 1:1 THF–TMU.

With this result in hand, it was interesting to confirm the postulated mechanism with a revised reaction mixture, i.e., with alkyl chlorides as reagents instead of the alkyl bromides and aluminium instead of zinc operating in presence of NBu_4Br. Thus benzyl (eq 11) and allyl (eq 12) chlorides as well as α-chloro esters (eq 13) were conveniently cross-coupled with CCl_4 in THF–TMU with 2 equiv of CCl_4 relative to R′Cl.

$$PhCH_2Cl + CCl_4 + 2e \xrightarrow{Al/NBu_4Br} \underset{\mathbf{1a}\ (70\%)}{PhCH_2CCl_3} \quad (11)$$

$$PhCH{=}CHCH_2Cl + CCl_4 + 2e \xrightarrow{Al/NBu_4Br} \underset{\mathbf{3a}\ (45\%)}{PhCH{=}CHCH_2CCl_3} + \underset{\mathbf{10a}\ (10\%)}{PhCH{=}CHCH{=}CCl_2} \quad (12)$$

$$ClCH_2CO_2Me + CCl_4 + 2e \xrightarrow{Al/NBu_4Br} \underset{\mathbf{5a}\ (40\%)}{CCl_3CH_2CO_2Me} + \underset{\mathbf{8a}\ (60\%)}{CCl_2{=}CHCO_2Me} \quad (13)$$

In conclusion, we have shown that the trichloromethylation of alkyl halides as well as the preparation of *gem*-dichloro compounds can be performed efficiently in very simple mild conditions by electroreduction with a consumable anode. We have pointed out in the discussion that, in some respects, these reactions are close to some organometallic syntheses. However, the alternative Grignard reactions have only been applied to a very limited number of syntheses of *gem*-polyhalo compounds, because even at very low temperature carben side reactions are hardly avoided. The proposed electrochemical method offers quite valuable advantages. Indeed, this process does not require the preparation of unstable α-halogenated organometallic compounds and can be carried out at room temperature. Additionally, our approach is more versatile than the organometallic approach, and, for comparable syntheses, our yields are higher. Finally, due to its simpleness and safeness, industrial scaling up of the process is reliably foreseeable.

Experimental Section

^1H NMR spectra were recorded on a Varian 360A (60 MHz) or a Brucker WH-90 (90 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 577 spectrometer. Mass spectra were obtained on a Nermag R-10-10 spectrometer coupled with a Girdel gas chromatograph with a 25 CP-SIL5 capillary column, either by electron impact or with NH_3 as ionizing agent, at Département de Chimie Organique, Orsay. Gas chromatography analyses were performed on a Girdel 75 chromatograph equipped with a stainless steel ($^1/_8$ in. × 13 ft) column packed with SE 30 (15%) or a Varian 3700 equipped with a 25-m CP-SIL5 capillary column. Analytical TLC analyses were performed on Merck silica gel 60F254 precoated aluminium sheets. Products were isolated by flash silica gel (230–240 mesh) column chromatography. Elemental analyses and high-resolution mass spectra were performed by the service de Microanalyse du CNRS, Lyon.

All reagents and supporting electrolytes were used as obtained commercially. Solvents were distilled by using the usual procedures. Metals used as anode were of high purity (Ventron, Alfa Produkte).

Electrochemical Reactions in the Presence of a Sacrificial Anode in a Diaphragmless Cell: Trichloromethylation of Benzyl Bromide (Typical Procedure). In a 50-mL cylindrical undivided glass cell fitted with a Zn rod as the anode and a cylindrical stainless steel grid as the cathode were introduced 40 mL of a 1:1 THF–TMU mixture as solvent, $NBuBF_4$ (0.165 g, 0.5 mmol) and NBu_4I (0.185 g, 0.5 mmol) as supporting electrolyte, CCl_4 (4 mL, 40 mmol), and $PhCH_2Br$ (2.4 mL, 20 mmol). Three moles of electrons were passed per mole of $PhCH_2Br$ under argon at constant current with a current density of 2A/dm^2. The reaction mixture was then poured into a cold mixture of 1 N HCl (50 mL) and diethyl ether (50 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (25 mL). The combined ethereal extracts were washed with water, dried over $MgSO_4$, and evaporated. Flash chromatography on silica gel with pentane gave 2,2,2-trichloroethylbenzene (**1a**)[15] (2.9 g, yield 70%): ^1H NMR ($CDCl_3$, 60 MHz) δ 3.9 (s, 2 H), 7.3 (s, 5 H).

Electrochemical Reactions in a Divided Cell in the Presence of Electrogenerated Zinc Halides. The reactions were conducted in two steps in a cell divided in two compartments by a fritted disk. Both compartments were preliminarily charged under argon with the electrolytic medium (30 mL), i.e. 0.3 M NBu_4BF_4 in 1:1 THF–TMU. For the first step, the cathodic chamber was fitted with a grid of inox and a rod of zinc, respectively acting as cathode and anode, with the inox electrode of the anodic chamber being not connected. In the cathodic chamber were then introduced the amount of $C_2H_4Br_2$ required to prepare 5, 10, or 20 mmol of $ZnBr_2$, with the corresponding amount of electricity (I = 0, 1 A) according to the stoichiometry. For the second step, the Zn rod was removed, $PhCH_2Br$ (1.2 mL, 10 mmol) and CCl_4 (2 mL, 20 mmol) were introduced in the cathodic compartment, and each chamber was properly connected to the DC power supply. Then was passed the amount of electricity corresponding to the consumption of more than 80% of $PhCH_2Br$ (GC analysis), at a current density of 1 A/dm^2. Workup and analysis were performed as usual.

Identification of the Products. The following products were identified by comparison of their physical and spectral data with those given in the cited references: 2,2-dichloroethylbenzene (**1c**),[16] methyl 2,2-dichlororo-3-phenylpropanoate (**1f**),[17] methyl 3,3-dichloroacrylate (**8a**),[18] methyl 2,2-dichloro-4-pentenoate (**2f**),[19] methyl 3-chlorocinnamate (**8b**),[20] methyl 2-methyl-3,3-dichloroacrylate (**9a**),[21] α,α-dichlorobibenzyl (**1b**),[22] α-chlorostilbene (**12b**).[22]

The other products were characterized by spectroscopic and elemental analyses as described below.

1-Phenyl-4,4,4-trichloro-1-butene (3a): ^1H NMR ($CDCl_3$) δ 3.54 (2 H, dd, J = 1.2, 7 Hz), 6.32 (1 H, dt, J = 7, 15 Hz), 6.63 (1 H, d, J = 15 Hz); ^{13}C NMR ($CDCl_3$) δ 61.2, 97.6, 122.4, 127.3, 129.1, 129.7, 136.4, 137.6; GC–MS, m/z (relative intensity) 234/236/238/240 (M$^+$, 7.9/7.1/2.1/0.3), 165 (1), 163 (3.2), 138 (2.5), 128 (14), 127 (8.9), 118 (10), 117 (100), 115 (22.6), 91 (7.5). Anal. Calcd for $C_{10}H_9Cl_3$: C, 50.99; H, 3.85; Cl, 45.15. Found: C, 50.79; H, 3.84; Cl, 44.99.

Methyl 3,3,3-trichloropropanoate (5a): ^1H NMR ($CDCl_3$) δ 3.73 (s, 2 H), 3.78 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 52.37, 57.4, 92.6, 165.6; GC–MS, m/z (relative intensity) 190/192/194 (M$^+$, 0.9/0.7/0.2), 163 (8), 161 (23.8), 159 (32.3), 157 (52.4), 155 (80.3), 137 (0.3), 135 (4.1), 133 (10.9), 131 (12.5), 119 (15), 117 (16). Treatment of **5a** (128 mg) with 1 N alcoholic NaOH at room temperature for 12 h gave **8a** (87 mg, yield 85%).

Methyl 2-methyl-3,3,3-trichloropropanoate (6a): ^1H NMR ($CDCl_3$) δ 1.57 (d, 3 H, J = 7 Hz), 3.58 (q, 1 H, J = 7 Hz), 3.73 (s, 3 H); GC–MS (CI with NH_3), m/z (relative intensity) 236/238/240/242 (MNH_4^+, 100/96/32.7/3.4), 183/185 (2.1/1.3), 137/139/141 (7.8/5.2/1.7). Treatment of **6a** (97 mg) with 1 N alcoholic NaOH at 40 °C gave **9a** (72 mg).

Ethyl 1-methyl-2,2,2-trichloroethyl carbonate (7a): ^1H NMR ($CDCl_3$) δ 1.36 (3 H, t, J = 7.1 Hz), 1.64 (3 H, d, J = 6.2 Hz), 4.29 (2 H, q, J = 7.1 Hz), 5.37 (1 H, q, J = 6.2 Hz); ^{13}C NMR

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[15] (a) Walling, C.; Lepley, A. R. *J. Am. Chem. Soc.* **1972**, *94*, 2007. (b) Freidlina, R. Kh.; Dostovalova, V. I.; Kuz'Mina, N. A.; Chukovskaya, E. C. *Org. Magn. Reson.* **1981**, *15*, 133.

[16] Lin, M. T.; Subramanian, R. *J. Org. Chem.* **1985**, *50*, 3218.

[17] De Buyck, L.; Verhé, R.; De Kimpe, N.; Courtheyn, D.; Schamp, N. *Bull. Soc. Chim. Belg.* **1980**, *89*, 441.

[18] Ellern, J. B.; Gray, H. B. *J. Org. Chem.* **1972**, *37*, 4485.

[19] Grignon, J.; Servens, C.; Pereyre, M. *J. Organomet. Chem.* **1975**, *96*, 225.

[20] Jalander, L.; Broms, M. *Acta Chem. Scand., Ser. B.* **1983**, *B37*, 174.

[21] Raulet, C.; Levas, E. *Bull. Soc. Chim. Fr.* **1971**, 2598.

[22] Alberde, A.; Delgado, J. A.; Recio, M. N. *An. Quim.* **1977**, *73*, 877.

($CDCl_3$) δ 14.2, 16.3, 65, 81.6, 99.8, 153.8; GC–MS (CI with NH_3), *m/z* (relative intensity) 252/254/256/258 ($MNH4^+$, 100/94.7/30.5/3.1), 220 (1.9), 218 (2.4). Anal. Calcd for $C_6H_9Cl_3O_3$: C, 30.60; H, 3.85; Cl 45.16. Found: C, 30.43; H, 3.81; Cl, 45.10.

1-Phenyl-4,4-dichloro-1,3-butadiene (10a): ^1H NMR ($CDCl_3$) δ 6.8 (3 H, m), 7.6 (5 H, m); GC–MS, *m/z* (relative intensity) 198/200/202 (M^+, 35.2/20.5/2.9), 165 (4.4), 164 (5.8), 163 (17.6), 162 (10.2), 129 (10.2), 128 (100), 127 (85.2), 126 (13.2), 115 (2.9).

1-Phenyl-1,1-dichlorohexane (4b): ^1H NMR ($CDCl_3$) δ 0.85 (3 H, m), 1.3 (4 H, m), 1.6 (2 H, m), 2.83 (2 H, t, J = 7.5 Hz), 7.45 (3 H, m), 7.8 (2 H, m). Anal. Calcd for $C_{12}H_{16}Cl_2$: C, 62.35; H, 6.98; Cl, 30.67. Found: C, 62.53; H, 7.03; Cl, 30.55.

Methyl 3-phenyl-3,3-dichloropropanoate (5b): IR ($CDCl_3$) 2960, 1750, 1600, 1445, 1435, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.53 (3 H, s), 3.63 (2 H, s), 7.3 (3 H, m), 7.7 (2 H, m); HRMS 232.0065, calcd for $C_{10}H_{10}Cl_2O_2$ 232.0058.

Methyl 2-Methyl-3,3-dichloro-3-phenylpropanoate (6b). Compound **6b** was found not stable as pure sample and was analyzed in presence of **9b**: ^1H NMR ($CDCl_3$) δ 1.34 (3 H, d, J = 7 Hz), 3.4 (3 H, s), 3.45 (1 H, q, J = 7 Hz), 7.25 (3 H, m), 7.4 (2 H, m); GC–MS (CI with NH_3), *m/z* (relative intensity) 264/266/268 (MNH_4^+, 32.7/21.5/3.6), 232 (3.7), 230 (16), 228 (16.6), 213 (14.6), 211 (41.5), 192 (100). Treatment of **6b** (120 mg) with 1 N alcoholic NaOH gave **9b** (95 mg).

Methyl 2-methyl-3-chlorocinnamate (9b): GC analysis, two isomers in 3/1 ratio; stereochemistry not determined; IR (neat) 1750, 1600, 1490, 1460, 1450, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (3 H, s), 3.5 (3 H, s), 7.33 (5 H, s); GC–MS (CI with NH_3), *m/z* (relative intensity) 228/230 (MNH_4^+, 100/34.7), 211/213 (MH^+, 61.9/19.9), 175 (13), 115 (13); HRMS 210.0435, calcd for $C_{11}H_{11}ClO_2$ 210.0444.

1-Chloro-1-phenyl-1-hexene (11b): ^1H NMR ($CDCl_3$) δ 0.85 (3 H, m), 1.35 (4 H, m), 2.31 (2 H, m), 6.1 (1 H, t, J = 8 Hz), 7.3 (3 H, m), 7.5 (2 H, m). Anal. Calcd for $C_{12}H_{15}Cl$: C, 74.02; H, 7.76; Cl, 18.20. Found: C, 74.09; H, 7.75; Cl, 18.10.

Ethyl 1-methyl-2,2-dichloropropyl carbonate (7d): ^1H NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7 Hz), 1.46 (3 H, d, J = 6.7 Hz), 2.05 (3 H, s), 4.18 (2 H, q, J = 7 Hz), 5.04 (1 H, q, J = 6.7 Hz); GC–MS (CI with NH_3), *m/z* (relative intensity) 232/234/236 (MNH_4^+, 100/66.6/10.3). Anal. Calcd for $C_7H_{12}Cl_2O_3$: C, 39.09; H, 5.62; Cl, 32.97. Found: C, 39.22; H, 5.60; Cl, 33.09.

3-Phenyl-2,2-dichloro-1,1,1-trifluoropropane (1e): ^1H NMR ($CDCl_3$) δ 3.53 (2 H, s), 7.37 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 45.2, 114.9, 128.2, 128.4, 128.7, 131.1, 131.3. Anal. Calcd for $C_9H_7Cl_2F_3$: C, 44.47; H, 2.90; Cl, 29.17. Found: C, 44.46; H, 2.89; Cl, 29.20.

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Registry No. **1a**, 3883-13-4; **1b**, 53617-93-9; **1c**, 4412-39-9; **1e**, 115395-69-2; **1f**, 1552-80-3; **2f**, 55039-88-8; **3a**, 115560-82-2; **4b**, 115560-84-4; **5a**, 20618-02-4; **5b**, 30693-80-2; **6a**, 115560-83-3; **6b**, 115560-86-6; **7a**, 115395-70-5; **7d**, 115395-68-1; **8a**, 2257-46-7; **8b**, 87541-87-5; **9a**, 86164-40-1; **9b**, 115560-87-7; **10a**, 56772-77-1; **11b**, 115560-85-5; **12b**, 1460-06-6; **13**, 115560-88-8; THF, 109-99-9; TMU, 632-22-4; Mg, 7439-95-4; Al, 7429-90-5; Zn, 7440-66-6; NBu_4BF_4, 429-42-5; NBu_4I, 311-28-4; $ZnBr_2$, 7699-45-8; $PhCH_2Br$, 100-39-0; $PhCH{=}CHCH_2Br$, 4392-24-9; $BrCH_2CO_2Me$, 96-32-2; $CH_3CHBrCO_2Me$, 5445-17-0; $CH_3CHClOCO_2Et$, 50893-36-2; $PhCCl_3$, 98-07-7; CCl_3CO_2Me, 598-99-2; CH_3CCl_3, 71-55-6; CF_3CCl_3, 354-58-5; $HCCl_3$, 67-66-3; $CH_3(CH_2)_3CH_2Br$, 110-53-2; $BrCH(CH_3)CO_2Me$, 5445-17-0; $CH_2{=}CHCH_2Br$, 106-95-6; $ClCH(CH_3)OCO_2Et$, 50893-36-2; $PhCH_2Cl$, 100-44-7; $PhCH_2CH_2Ph$, 103-29-7.

Total Synthesis of (±)-Wikstromol

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The antineoplastic prototype lignan natural product wikstromol was synthesized in racemic form by a straightforward sequence involving, as its key transformations, oxidative coupling of a carboxylic acid dianion, generation and stereoselective oxidation of a potassium enolate, and a deprotection step. The overall yield for nine steps is 29%. Depending on the choice of oxidants for the enolate, considerable modification in the ratio of stereoisomeric products is possible.

The lignans,[1] an important class of natural products derived formally from the dimerization of substituted 3-phenylpropane precursors,[2] exhibit many useful biological activities.[3] Medicinal chemists have been especially intrigued by those lignans that display cytotoxicity since such compounds may serve as valuable leads in the search for novel antitumor agents.[4] Complex lignan prototypes such as steganacin (**1**),[5] and podophyllotoxin (**2**),[6] as well as simpler lignans, have attracted considerable synthetic attention.[7]

In Chinese medical folklore "Nan-Ling-Jao-Hua" or "Po-Lun", *Wikstroemia indica* C. A. Mey (Thymelaeaceae), has been recommended as a herbal remedy for a number of maladies including cancer.[8] Recent work by Lee[9] has demonstrated that methanolic extracts of the stems of this plant have inhibitory activity in vivo against Ehrlich ascites carcinoma and P-388 lymphocytic leukemia. Several antitumor constituents were isolated as pure substances by a combination of solvent extraction followed by chromatography. Wikstromol ((+)-nortrachelogenin), a lignan of unusual structure, is a particularly interesting constituent. Additional studies by Lee confirmed the significant antineoplastic activity of wikstromol. Other

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(1) Rao, C. B. S. *Chemistry of Lignans*; Andhra University Press: Andhra Pradesh, 1978.

(2) Geissman, T. A.; Crout, D. H. *Organic Chemistry of Secondary Plant Metabolism*; Freeman, Cooper, & Co.: San Francisco, 1969; pp 398–399.

(3) (a) Pratt, W. B.; Ruddon, R. W. *The Anticancer Drugs*; Oxford University Press: New York, 1979; pp 221–235. (b) MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207.

(4) For example: Glinski, M. B.; Freed, J. C.; Durst, T. *J. Org. Chem.* **1987**, *52*, 2749.

(5) Becker, D.; Hughes, L. R.; Raphel, R. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1674 and references cited within.

(6) Van der Eycken, J.; DeClercq, P.; Vandewalle, M. *Tetrahedron Lett.* **1985**, *26*, 3871 and references cited within.

(7) Ward, R. S. *Chem. Soc. Rev.* **1982**, 75.

(8) Sugi, M.; Nagashio, Y. In *Cancer Therapy in Modern China*; Kondo, K., Ed.; Shizen Sha: Japan, 1977; p 256.

(9) Lee, K.-H.; Tagahara, K.; Suzuki, H.; Wu, R.-Y.; Haruna, M.; Hall, I. H.; Huang, H.-C.; Ito, K.; Iida, T.; Lai, J.-S. *J. Nat. Prod.* **1981**, *44*, 530.