

Electroreductive Radical Cyclization of Ethyl 2-Bromo-3-allyloxy- and -3-(propargyloxy)propanoates Catalyzed by (Tetramethylcyclam)nickel(I) Electrogenerated at Carbon Cathodes in Dimethylformamide

Ana P. Esteves,^[a] Danielle M. Goken,^[b] Lee J. Klein,^[b] Luis F. M. Leite,^[a] Maria J. Medeiros,^[a] and Dennis G. Peters^{*[b]}

Keywords: Electroreduction / Intramolecular cyclization / Redox catalysis / (Tetramethylcyclam)nickel(I) / Bromo propargyloxy ester / Bromo allyloxy ester

Reductive intramolecular cyclization of ethyl 2-bromo-3-(3',4'-methylenedioxyphenyl)-3-(propargyloxy)propanoate (**1**) and ethyl 3-allyloxy-2-bromo-3-(3',4'-dimethoxyphenyl)propanoate (**2**) promoted by (1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane)nickel(I), [Ni(tmc)]⁺, electrogenerated at glassy-carbon cathodes in dimethylformamide containing tetraalkylammonium salts, has been investigated. Cyclic voltammograms for reduction of [Ni(tmc)]²⁺ in the presence of **1** and **2** reveal that [Ni(tmc)]⁺ catalytically reduces these two compounds at potentials significantly more positive than those required for direct reduction of the bromo

esters. During controlled-potential electrolyses of solutions of [Ni(tmc)]²⁺ in the presence of **1** and **2**, catalytic reduction of each substrate proceeds by one-electron cleavage of the carbon–bromine bond to form a radical intermediate that undergoes cyclization to afford, respectively, ethyl 2-(3',4'-methylenedioxyphenyl)-4-methylenetetrahydrofuran-3-carboxylate (**3**) and ethyl 2-(3',4'-dimethoxyphenyl)-4-methyltetrahydrofuran-3-carboxylate (**6**). A mechanistic Scheme is proposed to account for the formation of each major product. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2005)

Introduction

Carbon–carbon bond formation by radical cyclization has been an important tool in organic chemistry, especially for the total synthesis of complex natural products.^[1,2] Until relatively recently, most synthetically useful radical-mediated carbon–carbon bond-forming reactions have been carried out by use of tri-*n*-butyltin hydride (Bu₃SnH);^[2–4] this approach ordinarily requires an excess of Bu₃SnH along with a small amount of radical initiator, usually azobis(isobutyronitrile) (AIBN). For example, Roy and Adhikari^[5] utilized such a procedure for the highly stereocontrolled total synthesis of paulownin (a furofuran lignan), a key reaction being the intramolecular radical cyclization of ethyl 2-bromo-3-(3',4'-methylenedioxyphenyl)-3-(propargyloxy)propanoate (**1**) to afford ethyl 4-methylene-2-(3',4'-methylenedioxyphenyl)tetrahydrofuran-3-carboxylate (**3**).

Unfortunately, triorganotin hydrides are toxic, and separation of tin-containing residues from the desired products is a time-consuming operation. As substitutes for Bu₃SnH, tri-*n*-butylgermanium hydride (Bu₃GeH) was employed by Dolbier et al.^[6] and tris(trimethylsilyl)silane [(Me₃Si)₃SiH] was used by Quirante and co-workers;^[7] both reagents are

less toxic and easier to remove by conventional work-up procedures than Bu₃SnH. In addition, 1-ethylpiperidinium hypophosphite and hypophosphorous acid can serve as effective reducing agents for organic halides.^[8,9] For processes involving radicals, a recent advance has been the introduction of solid-phase organic synthesis,^[10–12] for which the radical precursor is attached to a resin and the Bu₃SnH used in the reaction is removed by simple washing of the resin after the intramolecular cyclization is complete; thus, the desired product can be obtained easily and in a highly pure state.

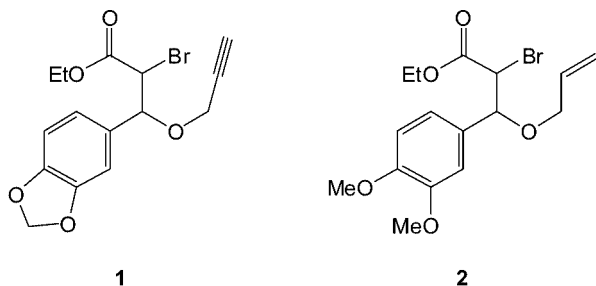
Another convenient way to initiate radical reactions is to employ a nickel(I) complex as an electron-transfer mediator.^[13] Reports pertaining to electrogenerated nickel(I) species as catalysts for the reductive radical cyclization of various organic halides,^[14] bromoacetals possessing electron-deficient olefinic moieties,^[15] and 2-haloaryl ethers containing unsaturated side chains^[16] have demonstrated that the electrochemical method is an excellent alternative to the use of organometallic reagents. Reductive intramolecular cyclization of 6-iodo- and 6-bromo-1-phenyl-1-hexyne, catalyzed by electrogenerated (salen)nickel(I), affords benzylidenecyclopentane in 84–95% yield;^[17] (salen)nickel(I)-catalyzed reduction of 6-bromo-1-hexene involves homolytic scission of the carbon–bromine bond to give the 5-hexen-1-yl radical which cyclizes intramolecularly to form methylcyclopentane as well as dimeric species arising from coupling of both cyclic and acyclic radicals.^[18] In other investi-

[a] Centro de Química, Universidade do Minho, Largo do Paço, 4704-553 Braga, Portugal

[b] Department of Chemistry, Indiana University, Bloomington, Indiana 47405, USA
E-mail: peters@indiana.edu

gations,^[19–21] it was reported that electrogenerated nickel(I) complexes catalyze the reduction of unsaturated halides to yield alkenyl radicals, which react intramolecularly to give carbocyclic products. Finally, the use of nickel(I) complexes as mediators for radical cyclization has been applied to the synthesis of substituted tetrahydrofurans, for which the furan moiety is an important subunit in a wide range of biologically active natural products.^[22,23]

In this research we have examined the reductive intramolecular cyclizations of ethyl 2-bromo-3-(3',4'-methylenedioxyphenyl)-3-(propargyloxy)propanoate (**1**) and ethyl 3-allyloxy-2-bromo-3-(3',4'-dimethoxyphenyl)propanoate (**2**) that are promoted by electrogenerated (1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane)nickel(I), $[\text{Ni}(\text{tmc})]^+$. Cyclic voltammetry has been used to ascertain if bromo esters **1** and **2** undergo catalytic reduction as well as to find the optimal conditions for preparative-scale controlled-potential electrolyses. Experimental parameters, such as the initial ratio of parent nickel(II) complex to bromo ester and the effects of an added proton donor (1,1,1,3,3,3-hexafluoro-2-propanol) and of an added hydrogen atom donor (diphenylphosphane), have been investigated to ascertain how these variables affect the yield and identity of cyclic products.



Results and Discussion

Cyclic Voltammetric Behavior of Ethyl 2-Bromo-3-(3',4'-methylenedioxyphenyl)-3-(propargyloxy)propanoate (**1**) and Ethyl 3-Allyloxy-2-bromo-3-(3',4'-dimethoxyphenyl)propanoate (**2**)

Cyclic voltammograms recorded at a scan rate of 100 mV s^{-1} for the direct reduction of **1** and **2** are shown in Figure 1 (curve A) and Figure 2 (curve A), respectively, at a glassy-carbon electrode in DMF containing 0.10 M TEABF_4 . Except for the values of peak potentials, both compounds exhibit the same cyclic voltammetric characteristics: an initial irreversible sharp spike, followed by three irreversible peaks at more negative potentials (the first actually appearing to be an unresolved double peak, and the third being a shoulder preceding the final current rise). For compound **1**, these four voltammetric features have peak potentials of -0.69 , -1.11 , -1.51 , and -1.83 V , whereas for compound **2** the corresponding four peak potentials are -0.80 , -1.22 , -1.57 and -1.94 V . On the basis of our earlier detailed investigation^[24] of the cyclic voltammetric behavior of ethyl 2-bromo-3-(3',4'-dimethoxyphenyl)-3-(propargyloxy)pro-

panoate at a glassy-carbon electrode, we conclude that the first sharp spike is associated with irreversible two-electron reductive cleavage of the carbon–bromine bond of **1** and **2**, and that the second, third, and fourth peaks are due to subsequent reduction of *trans*-3-(3',4'-methylenedioxyphenyl)prop-2-enoate and *trans*-3-(3',4'-dimethoxyphenyl)-

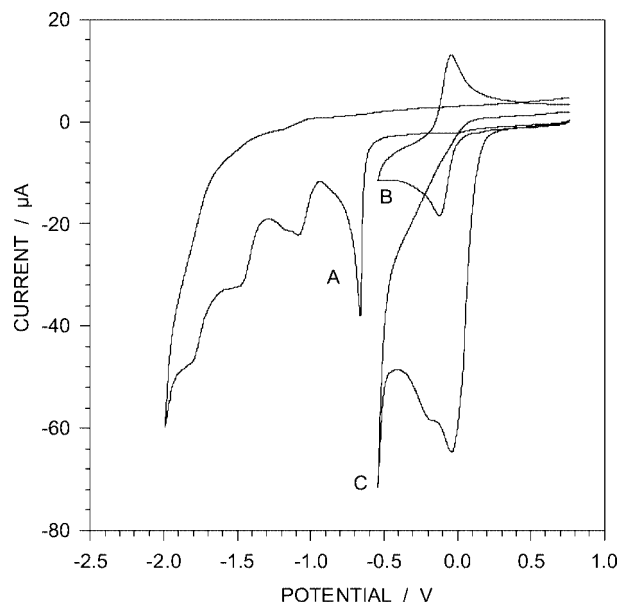


Figure 1. Cyclic voltammograms recorded with a glassy-carbon electrode (area = 0.077 cm^2) at 100 mV s^{-1} in DMF containing 0.10 M TEABF_4 : (A) 1.0 mM **1**; (B) 2.0 mM $[\text{Ni}(\text{tmc})]\text{Br}_2$; (C) 2.0 mM $[\text{Ni}(\text{tmc})]\text{Br}_2$ and 20.0 mM **1**. For curve A, the scan goes from $+0.70$ to -2.00 to $+0.70 \text{ V}$; for curves B and C, the scan goes from $+0.70$ to -0.50 to $+0.70 \text{ V}$.

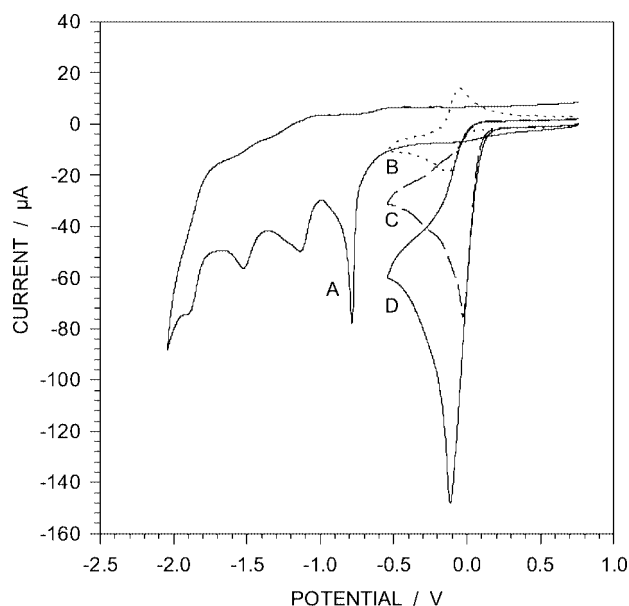


Figure 2. Cyclic voltammograms recorded with a glassy-carbon electrode (area = 0.077 cm^2) at 100 mV s^{-1} in DMF containing 0.10 M TEABF_4 : (A) 2.0 mM **2**; (B) 2.0 mM $[\text{Ni}(\text{tmc})]\text{Br}_2$; (C) 2.0 mM $[\text{Ni}(\text{tmc})]\text{Br}_2$ and 4.0 mM **2**; (D) 2.0 mM $[\text{Ni}(\text{tmc})]\text{Br}_2$ and 20.0 mM **2**. For curve A, the scan goes from $+0.70$ to -2.00 to $+0.70 \text{ V}$; for curves B–D, the scan goes from $+0.70$ to -0.50 to $+0.70 \text{ V}$.

prop-2-enoate, which arise, respectively, during the first stage of reduction of **1** and **2**.

Behavior of (1,4,8,11-Tetramethyl-1,4,8,11-tetraazacyclotetradecane)nickel(II) Bromide, [Ni(tmc)]Br₂, in Cyclic Voltammetry and Controlled-Potential Electrolysis Experiments

Cyclic voltammograms were recorded at a series of scan rates (ν) between 20 and 200 mV s⁻¹ at a glassy-carbon electrode for 2.0 mM solutions of [Ni(tmc)]Br₂ in DMF containing 0.10 M TEABF₄. Representative cyclic voltammograms obtained at 100 mV s⁻¹ for the reversible one-electron reduction of [Ni(tmc)]²⁺ to [Ni(tmc)]⁺ are shown in curve B of both Figure 1 and Figure 2. From an analysis of these cyclic voltammograms, we found that the separation of cathodic and anodic peak potentials ($\Delta E_p = E_{pc} - E_{pa}$) is close to 60 mV, the ratio of the peak currents (I_{pc}/I_{pa}) is unity, and $I_{pc}/\nu^{1/2}$ is independent of the scan rate. In addition, the formal potential for the reversible [Ni(tmc)]²⁺/[Ni(tmc)]⁺ couple was determined to be -0.15 V, and no further electron-transfer process involving the nickel complexes occurs within the potential range of the medium.

Controlled-potential electrolyses were performed at potentials approximately 150 mV more negative than the peak potential for reduction of [Ni(tmc)]²⁺, and the coulometric n value was 1.0. Thus, [Ni(tmc)]⁺ is stable on the time scale of a bulk electrolysis. Furthermore, the electron added to [Ni(tmc)]²⁺ is known to be nickel-centered, and the electron-transfer process is fast and is known to occur without significant changes in the geometry of the complex.^[25–29]

Cyclic Voltammetric Behavior of [Ni(tmc)]Br₂ in the Presence of Ethyl 2-Bromo-3-(3',4'-methylenedioxyphenyl)-3-(propargyloxy)propanoate (**1**) and Ethyl 3-Allyloxy-2-bromo-3-(3',4'-dimethoxyphenyl)propanoate (**2**)

Cyclic voltammograms were recorded for reduction of 2.0 mM [Ni(tmc)]Br₂ at a glassy-carbon electrode in DMF containing 0.10 M TEABF₄ and different concentrations of each bromo ester. Figure 1 (curve C) and Figure 2 (curve C) show the cyclic voltammetric behavior of [Ni(tmc)]Br₂ in the presence of 20.0 mM **1** and 4.0 mM **2**, respectively, at a scan rate of 100 mV s⁻¹.

Even in the presence of a relatively low concentration of bromo ester, the reduction of [Ni(tmc)]²⁺ becomes completely irreversible; although the cathodic peak increases in height upon addition of substrate, the anodic peak vanishes because electrogenerated [Ni(tmc)]⁺ is consumed by the substrate. When the initial concentration of bromo ester is increased, the cathodic peak current grows, but not in proportion to the concentration of the substrate. Furthermore, with progressive increases in the concentration of bromo ester, the cathodic peak potential shifts toward more negative values (as a comparison of curves C and D in Figure 2 reveals). Table 1 and Table 2 provide a compilation of data obtained from experiments carried out in DMF–0.10 M

TEABF₄, for different bromo ester/[Ni(tmc)]²⁺ ratios, where (I_{pc})_c is the cathodic peak current in the presence of bromo ester, and (I_{pc})_d is the cathodic peak current in its absence. From these results, it can be concluded that, for a fixed initial concentration of [Ni(tmc)]²⁺, the extent of the catalytic reaction increases when the concentration of bromo ester is larger, and the effect is greater in the case of **2** than in the case of **1**. However, it is obvious that the peak current ratio, (I_{pc})_c/ $(I_{pc})_d$, does not increase linearly with the bromo ester/[Ni(tmc)]²⁺ ratio. These findings indicate that the efficiency of electrogenerated [Ni(tmc)]⁺ is diminished as it engages in repetitive catalytic cycles, presumably due to sluggish regeneration of [Ni(tmc)]²⁺. Similar results were obtained in our previous work dealing with the [Ni(tmc)]⁺-catalyzed electroreductive intramolecular cyclization of ethyl 2-bromo-3-(3',4'-dimethoxyphenyl)-3-(propargyloxy)propanoate.^[21]

Table 1. Peak-current ratios obtained from cyclic voltammograms of solutions of DMF containing 0.10 M TEABF₄, 2 mM [Ni(tmc)]²⁺, and various concentrations of **1** at 100 mV s⁻¹.

	Concentration of 1 [mM]			
	2	4	20	40
(I_{pc}) _c / $(I_{pc})_d$ ^[a]	1.62	2.89	3.68	3.80

[a] (I_{pc})_c = catalytic peak current in the presence of substrate and (I_{pc})_d = diffusion peak current in the absence of substrate.

Table 2. Peak-current ratios obtained from cyclic voltammograms of solutions of DMF containing 0.10 M TEABF₄, 2 mM [Ni(tmc)]²⁺, and various concentrations of **2** at 100 mV s⁻¹.

	Concentration of 2 [mM]			
	4	10	20	28
(I_{pc}) _c / $(I_{pc})_d$ ^[a]	4.09	9.81	10.90	12.24

[a] (I_{pc})_c = catalytic peak current in the presence of substrate and (I_{pc})_d = diffusion peak current in the absence of substrate.

Controlled-Potential Reduction of [Ni(tmc)]Br₂ in the Presence of Ethyl 2-Bromo-3-(3',4'-methylenedioxyphenyl)-3-(propargyloxy)propanoate (**1**) and Ethyl 3-Allyloxy-2-bromo-3-(3',4'-dimethoxyphenyl)propanoate (**2**)

Controlled-potential reductions of [Ni(tmc)]²⁺ in the presence of either **1** or **2** were performed at either platinum or reticulated vitreous carbon cathodes in DMF containing 0.10 M TEABF₄; the potential was 100 mV more negative than the peak potential for reduction of [Ni(tmc)]²⁺ in the presence of each bromo ester. Several substrate/[Ni(tmc)]²⁺ ratios were employed; in each experiment, current–time data were used to calculate the number of electrons (n) transferred to a molecule of bromo ester. At the end of an electrolysis, the current dropped to a steady and low value, all of the starting material was consumed, and the products were separated, identified, and quantitated with the aid of gas chromatography.

Table 3. Coulometric data and product distributions for catalytic reduction of **1** by $[\text{Ni}(\text{tmc})]^+$ electrogenerated at platinum and reticulated vitreous carbon cathodes in DMF containing 0.10 M TEABF₄.

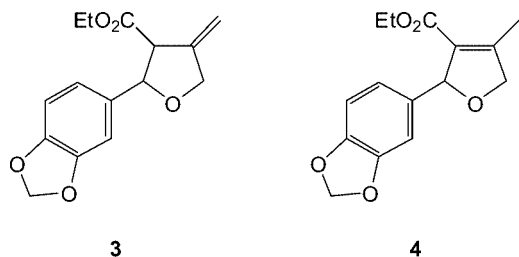
Entry	$[\text{Ni}(\text{tmc})]^{2+}$ [mM]	1 [mM]	[HFIP] [mM] ^[b]	[DPP] [mM] ^[c]	<i>n</i> ^[d]	Product distribution [%] ^[a]			Total
						3	4	5	
1 ^[e]	0.5	1	–	–	0.9	81	23	–	104
2 ^[f]	0.4	2	–	–	0.9	74	26	–	100
3 ^[f]	0.2	2	–	–	0.8	79	17	–	96
4 ^[e]	0.5	1	4	–	0.9	<1	89	–	90
5 ^[e]	0.5	1	10	–	0.8	<1	85	–	86
6 ^[e]	0.5	1	–	4	0.8	63	11	11	85
7 ^[e]	0.5	2.5	–	10	0.8	66	10	11	87
8 ^[e]	0.5	5	–	20	0.9	67	4	14	85

[a] % = yield expressed as the percentage of **1** incorporated into each product. [b] HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. [c] DPP = diphenylphosphane. [d] Number of electrons per molecule of starting material. [e] Platinum gauze cathode. [f] Reticulated vitreous carbon cathode.

Catalytic Reduction of Ethyl 2-Bromo-3-(3',4'-methylenedioxyphenyl)-3-(propargyloxy)propanoate (**1**)

Table 3 presents coulometric data and product distributions obtained from the catalytic reduction of **1**; each Entry is an average of two or three individual experiments. Two general conclusions can be drawn from the results: (i) An *n* value of essentially 1 was observed, indicating that catalytic reduction of **1** is a one-electron process which leads to formation of a radical intermediate; (ii) the product distribution and coulometric *n* value do not depend on the initial concentration of $[\text{Ni}(\text{tmc})]^{2+}$, as revealed by Entries 1–3 of Table 3.

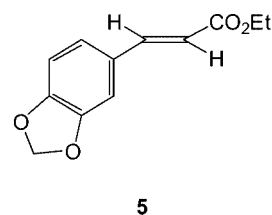
Entries 1–3 in Table 3 show that, in the absence of a deliberately added proton source or hydrogen atom donor, catalytic reduction of **1** by electrogenerated $[\text{Ni}(\text{tmc})]^+$ gives rise to two major products: ethyl 4-methylene-2-(3',4'-methylenedioxyphenyl)tetrahydrofuran-3-carboxylate (**3**), formed in 74–81% yield, and ethyl 4-methyl-2-(3',4'-methylenedioxyphenyl)-2,5-dihydrofuran-3-carboxylate (**4**), obtained in 17–26% yield. Although the sum of the yields of **3** and **4** accounts for less than 100% of the original starting material in some experiments, we found no evidence (e.g., additional gas chromatographic peaks) for any other product.



To probe the effect of an added proton donor, solutions of 1.0 mM **1**, 0.50 mM $[\text{Ni}(\text{tmc})]\text{Br}_2$, and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) in DMF containing 0.10 M TEABF₄ were electrolyzed. Entries 4 and 5 of Table 3 show that increasing amounts of HFIP lead to no change in the coulometric *n* value. On the other hand, the product distribution is significantly altered; **4** is obtained almost quantitatively, whereas **3** is formed in trace amounts only. Thus, a deliberately added proton donor exerts a profound influ-

ence on the product distribution. An interpretation of these observations will be presented in the following mechanistic section.

In a study of the homogeneous interaction of alkyl halides with the (octaethylisobacteriochlorin)nickel(I) anion, $[\text{Ni}^{\text{I}}\text{OEiBC}]^-$, generated through reduction with a sodium amalgam in DMF, Helveston and Castro^[30] investigated the influence of hydrogen atom donors on the behavior of the system. To determine the source of the hydrogen atom in methane derived from methyl iodide, various proton and hydrogen atom donors were added to the reaction medium. It was found that, when diphenylphosphane was added to the reaction mixture, the yield of methane was greatly enhanced, an observation leading to the conclusion that diphenylphosphane acts as a hydrogen atom donor and not as an acid ($\text{p}K_{\text{a}} = 23.7$ in DMF^[31,32] at 25 °C). Furthermore, Ozaki and co-workers reported that reduction of a vinyl bromide^[33] or a bromo amide^[34,35] mediated by electrogenerated nickel(I) species in the presence of diphenylphosphane led to a significant enhancement in the yield of the desired cyclic product as well as that of an acyclic product. Thus, in an effort to maximize the formation of **3**, we surveyed what effect would result from the addition of a hydrogen atom donor (diphenylphosphane) to the system. We carried out a series of electrolyses of DMF/0.10 M TEABF₄ solutions containing 0.50 mM $[\text{Ni}(\text{tmc})]\text{Br}_2$ and three different concentrations of **1**, along with diphenylphosphane at a concentration level four times that of **1**. Entries 6–8 of Table 3 list the coulometric *n* values and product distributions for these experiments. It can be seen (in comparison with Entries 1–3 of Table 3) that diphenylphosphane does not exert a major effect on the ratio of yields of **3** and **4**. However, the absolute yields of these two cyclic products are diminished, due to the accompanying



formation of ethyl 3-(3',4'-methylenedioxyphenyl)prop-2-enoate (**5**) in 11–14% yield.

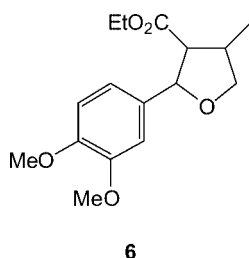
Catalytic Reduction of Ethyl 3-Allyloxy-2-bromo-3-(3',4'-dimethoxyphenyl)propanoate (**2**)

Summarized in Table 4 are coulometric data and product distributions, obtained from the reduction of compound **2** by electrogenerated $[\text{Ni}(\text{tmc})]^+$ in DMF/0.10 TEABF₄. As expected, the $[\text{Ni}(\text{tmc})]^+$ -catalyzed reduction of **2** is a one-electron process, which implies the intermediacy of an alkyl radical. At the end of the electrolyses, two major products – both isomers of ethyl 2-(3',4'-dimethoxyphenyl)-4-methyltetrahydrofuran-3-carboxylate (**6**) – were found by means of gas chromatographic analysis. In the absence of a proton donor, the product distributions are not sensitive to the initial concentration of $[\text{Ni}(\text{tmc})]^{2+}$ (Table 4, Entries 1–3). Moreover, when a proton donor (HFIP) is introduced into the system (Table 4, Entry 4), neither the coulometric n value nor the product distribution is altered.

Table 4. Coulometric data and product distributions for catalytic reduction of 2 mM **2** by $[\text{Ni}(\text{tmc})]^+$ electrogenerated at reticulated vitreous carbon cathodes in DMF containing 0.10 M TEABF₄.

Entry	$[\text{Ni}(\text{tmc})]^{2+}$ [mM]	[HFIP] [mM] ^[b]	n ^[c]	Product distribution [%] ^[a]
				6 (<i>dr</i>) ^[d]
1	1	–	1.2	100 (92:8)
2	0.4	–	1.2	96 (92:8)
3	0.2	–	1.1	107 (92:8)
4	0.4	8	1.0	104 (92:8)

[a] % = yield expressed as the percentage of **2** incorporated into each product. [b] HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. [c] Number of electrons per molecule of starting material. [d] Diastereomeric (*cis*-to-*trans*) ratio.



Mechanistic Aspects of the $[\text{Ni}(\text{tmc})]^+$ -Catalyzed Reductions of Ethyl 2-Bromo-3-(3',4'-methylenedioxyphenyl)-3-(propargyloxy)propanoate (**1**) and Ethyl 3-Allyloxy-2-bromo-3-(3',4'-dimethoxyphenyl)propanoate (**2**)

To account for the various products that arise from the $[\text{Ni}(\text{tmc})]^+$ -catalyzed reductions of **1** and **2**, the mechanistic steps outlined in Scheme 1 are proposed. After $[\text{Ni}(\text{tmc})]^{2+}$ is reversibly reduced to $[\text{Ni}(\text{tmc})]^+$ [reaction (1)], the latter species transfers an electron to a bromo ester, cleaving the carbon–bromine bond homolytically, to give radical intermediates **7** [reaction (2)] and **9** [reaction (3)]. According to

Halcrow and Christou,^[36] who published an extensive review of catalytic processes involving nickel(I) complexes and alkyl halides, a nickel(I) species can transfer one electron to an alkyl halide through an inner-sphere mechanism, and an alkylnickel intermediate might be formed; the subsequent decomposition of which could generate alkyl radicals. Once produced, **7** and **9** would be expected to undergo rapid intramolecular cyclization to yield the carbocyclic radicals **8** and **10**, respectively, which, after abstracting a hydrogen atom from DMF, will afford **3** [reaction (2)] and **6** [reaction (3)], respectively. Considerable evidence exists that DMF can act as a hydrogen atom donor.^[37–40]

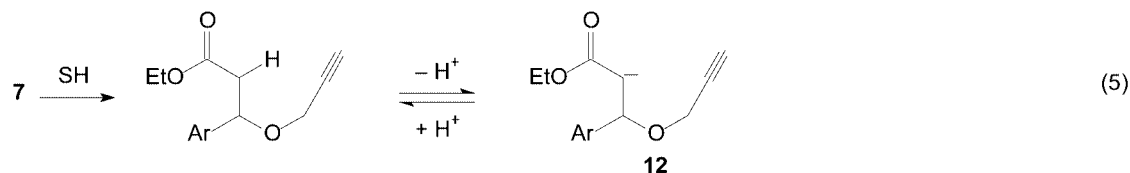
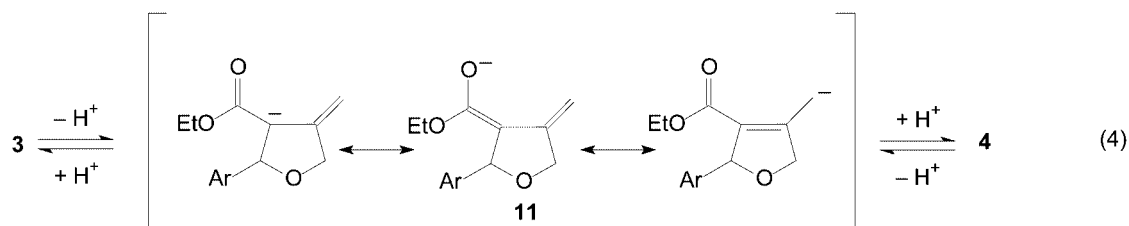
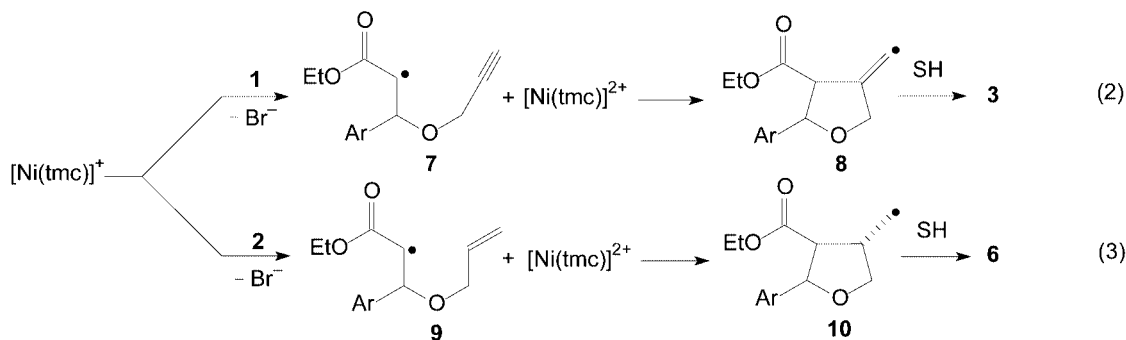
An inevitable consequence of electrolytic reductions in DMF is that small quantities of electrogenerated bases are produced.^[41] Under such conditions, **3** can undergo deprotonation, due to the acidity of the proton adjacent to the carbonyl moiety, to give the corresponding resonance-stabilized carbanion **11**; protonation of this carbanion results in the formation of **4** [reaction (4)]. This process is in agreement with that described in our previous work.^[21]

As shown by Entries 4 and 5 of Table 3, when HFIP is added to the catholyte prior to the start of an experiment, **4** is formed almost exclusively, whereas **3** is detected in trace amounts only. Similar results, observed in our earlier work,^[21] suggest that the enhanced isomerization of **3** to **4** occurs because the conjugate base of HFIP (arising from its reaction with electrogenerated base) can deprotonate **3**, whereas HFIP itself can readily protonate **11**. In a sense, HFIP acts as a buffer to facilitate the isomerization.

To account for the formation of the acyclic product **5** [obtained when **1** is catalytically reduced in the presence of diphenylphosphane (Entries 6–8 of Table 3)], it is reasonable to assert that **7** can abstract a hydrogen atom from diphenylphosphane, followed by deprotonation to give the carbanion **12** [reaction (5)]. Then, as soon as **12** is formed, it could eliminate the propargyloxy anion, leading to the formation of **5** [reaction (6)]. This latter process is termed an E1cB mechanism, which is most likely to be encountered with substrates containing acidic hydrogen atoms or poor leaving groups, or when the carbanion is stabilized by resonance.^[42] In previous work^[24] dealing with direct electrochemical reduction of ethyl 2-bromo-3-(3',4'-dimethoxyphenyl)-3-(propargyloxy)propanoate at a vitreous carbon cathode in DMF, we rationalized the formation of a cinnamic acid ester by means of the same process.

Finally, with respect to the stereochemistry of the two starting materials and the various cyclic products, it should be noted that the original *trans*-ester-to-aryl group orientation of compounds **1** and **2** is retained in **3**, **4**, and **6**. However, as revealed in Table 4, the electroreductive ring closure of **2** to **6** affords a mixture of isomers in which the ester and methyl groups are *cis* and *trans* to each other in a 92:8 ratio. A review chapter by Renaud^[43] discusses the factors that govern the stereochemistry of radical cyclization reactions.

In conclusion, we have shown that the method described here can afford a desired cyclized product in good yield through the use of a catalytic amount of an appropriate



1: Ar = 3',4'-methylenedioxyphenyl

2: Ar = 3',4'-dimethoxyphenyl

Scheme 1.

electrogenerated metal complex under mild experimental conditions at room temperature starting from bromo esters **1** and **2**, which makes this procedure an attractive alternative to other synthetic methods.

Experimental Section

Reagents: Each of the following chemicals was used as received: Nickel(II) bromide (Aldrich, 98%), 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (tetramethylcyclam, tmc, Fluka, 97%), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, Aldrich, 99.8+%), diphenylphosphane (Aldrich, 95%), *n*-tetradecane (Aldrich, 99+%), and *n*-hexadecane (Aldrich, 99+%). Dimethylformamide (DMF), “distilled-in-glass” reagent from Aldrich, was used as received. We obtained tetraethylammonium tetrafluoroborate (TEABF₄) with a purity of 98.5% from GFS Chemicals; this electrolyte was stored in a vacuum oven at 80 °C to remove traces of water. Deaeration

procedures were carried out with zero-grade argon (Air Products). Published procedures were employed for the preparation of [Ni(tmc)]Br₂^[44] and of ethyl 2-bromo-3-(3',4'-methylenedioxyphenyl)-3-(propargyloxy)propanoate (**1**) and ethyl 3-allyloxy-2-bromo-3-(3',4'-dimethoxyphenyl)propanoate (**2**).^[5]

A method described by McCague et al.^[9] provided the basis for the syntheses of ethyl 4-methylene-2-(3',4'-methylenedioxyphenyl)-tetrahydrofuran-3-carboxylate (**3**), ethyl 4-methyl-2-(3',4'-methylenedioxyphenyl)-2,5-dihydrofuran-3-carboxylate (**4**), and ethyl 2-(3',4'-dimethoxyphenyl)-4-methyltetrahydrofuran-3-carboxylate (**6**). We identified the compounds by means of ¹H NMR spectrometry with a Varian Unity Plus 300-MHz instrument.

3: ¹H NMR (CDCl₃): δ = 1.28 (t, *J* = 7.2 Hz, 3 H, OCH₂CH₃), 3.42–3.47 (m, 1 H, 3-H), 4.21 (qABq, *J* = 11.0, 7.2 Hz, 2 H, OCH₂CH₃), 4.49 (apparent dq, *J* = 13.0, 2.4 Hz, 1 H, 5-H), 4.63 (br. apparent d, *J* = 13.0 Hz, 1 H, 5-H), 5.10 (apparent q, *J* = 2.4 Hz, 1 H, =CH), 5.15 (d, *J* = 8.7 Hz, 1 H, 2-H), 5.18 (apparent

q, $J = 2.4$ Hz, 1 H, =CH), 5.96 (s, 2 H, OCH₂O), 6.77 (d, $J = 8.0$ Hz, 1 H, 5'-H), 6.88 (dd, $J = 8.0$, 1.8 Hz, 1 H, 6'-H), 6.90 (d, $J = 1.8$ Hz, 1 H, 2'-H) ppm.

4: ¹H NMR (CDCl₃): $\delta = 1.16$ (t, $J = 7.2$ Hz, 3 H, OCH₂CH₃), 2.18 (apparent d, $J = 1.2$ Hz, 3 H, 4-CH₃), 4.09 (qABq, $J = 10.8$, 7.2 Hz, 2 H, OCH₂CH₃), 4.71 (apparent ddd, $J = 15.0$, 3.5, 1.0 Hz, 1 H, 5-H), 4.87 (apparent ddd, $J = 15.0$, 5.0, 1.0 Hz, 1 H, 5-H), 5.83–5.87 (m, 1 H, 2-H), 5.94 (s, 2 H, OCH₂O), 6.76 (d, $J = 8.0$ Hz, 1 H, 5'-H), 6.77 (d, $J = 1.8$ Hz, 1 H, 2'-H), 6.82 (dd, $J = 8.0$, 1.8 Hz, 1 H, 6'-H) ppm.

6: ¹H NMR (CDCl₃): $\delta = 1.07$ (d, $J = 6.9$ Hz, 2.55 H, 4-CH₃), 1.18 (d, $J = 6.6$ Hz, 0.45 H, 4-CH₃), 1.25 (t, $J = 7.0$ Hz, 0.45 H, OCH₂CH₃), 1.28 (t, $J = 7.2$ Hz, 2.55 H, OCH₂CH₃), 2.55 (apparent t, $J = 9.0$, 8.7 Hz, 0.15 H, 3-H), 2.70–2.85 (m, 1 H, 4-H), 3.00 (apparent dd, $J = 9.0$, 7.8 Hz, 0.85 H, 3-H), 3.66 (apparent dd, $J = 8.7$, 6.6 Hz, 1 H, 5-H_a), 3.87 (s, 3 H, OCH₃), 3.89 (s, 3 H, OCH₃), 4.12–4.24 (m, 2 H, OCH₂CH₃), 4.28 (dd, $J = 8.4$ and 6.6 Hz, 1 H, 5-H_b), 5.05 (d, $J = 9.0$ Hz, 0.15 H, 2-H), 5.19 (d, $J = 7.8$ Hz, 0.85 H, 2-H), 6.83 (d, $J = 9.0$ Hz, 1 H, 5'-H), 6.88–6.92 (m, 2 H, 2'-H and 6'-H) ppm. These compounds were utilized as standards for the determination of gas chromatographic response factors.

Electrodes: For cyclic voltammetry we fabricated a planar, circular working electrode with an area of 0.077 cm² by press-fitting a short length of 3-mm-diameter glassy-carbon rod (Grade GC-20, Tokai Electrode Manufacturing Company, Tokyo, Japan) into a Teflon shroud. Working electrodes for controlled-potential electrolyses were of two kinds: (i) platinum gauze (area of 2.4 cm²) and (ii) disks (0.4 cm in thickness, 2.4 cm in diameter, and approximately 200 cm² in geometric area) sliced from reticulated vitreous carbon logs (RVC, 2X1–100S, Energy Research and Generation, Oakland, CA). Procedures for the cleaning and handling of reticulated vitreous carbon electrodes have been described previously.^[45] All potentials are quoted with respect to a reference electrode consisting of a cadmium-saturated mercury amalgam in contact with DMF saturated with both cadmium chloride and sodium chloride.^[46,47] This electrode has a potential of –0.76 V vs. the aqueous saturated calomel electrode (SCE) at 25 °C.

Cells and Instrumentation: Cells for cyclic voltammetry^[48] and for controlled-potential electrolysis^[49] have been described in earlier publications. Cyclic voltammograms were obtained with the aid of a Princeton Applied Research Corporation (PARC) model 175 universal programmer coupled to a PARC model 173 potentiostat–galvanostat and were recorded with a Yokogawa model 3023 X–Y plotter. Controlled-potential electrolyses were carried out by means of the above-mentioned potentiostat–galvanostat equipped with a PARC model 176 current-to-voltage converter. Electrolyses were programmed and current–time curves were acquired, stored, and integrated with the aid of locally written software, which controlled a data acquisition board installed in a personal computer.

Identification and Quantitation of Products: Gas chromatographic analyses were accomplished with the aid of a Hewlett–Packard 5890 Series gas chromatograph equipped with dual flame-ionization detectors and coupled to a Hewlett–Packard model 3392A integrator. Products were separated with a 30 m × 0.32 mm i.d. capillary column (EC-5, Alltech Associates) with a stationary phase of poly(methylphenylsiloxane). A known quantity of an electroinactive internal standard (*n*-tetradecane or *n*-hexadecane) was added to a solution before each experiment to allow quantitation of the electrolysis products. Gas chromatographic response factors were measured experimentally with authentic samples of each product, and all product yields tabulated in this paper represent the absolute percentage of starting material incorporated into a particular spe-

cies. Due to uncertainties in various analytical measurements (i.e., quantities of internal standards and starting materials as well as gas chromatographic peak areas and response factors), the absolute error in the average yield of each product is typically ±3–4%. Consequently, it is not surprising that, for several Entries in Tables 3 and 4, the total recovery of products slightly exceeds 100%. Such analytical results are not uncommon in electrochemical studies involving gas chromatographic determinations of product distributions.^[21,40,49–52]

Identities of the products were confirmed with the aid of a Hewlett–Packard 5890 Series II gas chromatograph coupled to a Hewlett–Packard 5971 mass-selective detector: **3:** MS (70 eV): $m/z = 276$ (35) [M⁺], 247 (3) [M – C₂H₅]⁺, 202 (18) [M – CO₂C₂H₅ – H]⁺, 149 (45) [CH₂O₂C₆H₃CO]⁺, 126 (59) [H₅C₂O₂CC₄H₅]⁺, 98 (100) [C₃H₆O₂]⁺. **4:** MS (70 eV): $m/z = 276$ (100) [M⁺], 261 (17) [M – CH₃]⁺, 247 (34) [M – C₂H₅]⁺, 202 (82) [M – CO₂C₂H₅ – H]⁺, 149 (64) [CH₂O₂C₆H₃CO]⁺, 77 (7) [C₆H₅]⁺, 29 (22) [COH]⁺. **5:** MS (70 eV): $m/z = 220$ (100) [M⁺], 205 (1) [M – CH₃]⁺, 192 (16) [M – C₂H₄]⁺, 175 (69) [M – C₂H₅O]⁺, 145 (39) [H₅C₇O₂C≡C]⁺, 117 (17) [C₆H₅OC≡C]⁺, 89 (36) [C₇H₅]⁺, 29 (9) [COH]⁺. **6:** MS (70 eV): $m/z = 294$ (84) [M⁺], 279 (26) [M – CH₃]⁺, 265 (69) [M – C₂H₅]⁺, 220 (10) [M – CO₂C₂H₅ – H]⁺, 205 (35) [M – CO₂C₂H₅ – CH₃ – H]⁺, 165 (100) [(CH₃O)₂C₆H₃CO]⁺, 29 (16) [COH]⁺. These identifications were checked by comparison of gas chromatographic retention times for the suspected products, under carefully controlled conditions, with those of the authentic compounds prepared above.

Acknowledgments

Most of this research was conducted while M. J. M. was a Visiting Scholar at Indiana University. In addition, we are grateful to the Fundação Calouste Gulbenkian, CRUP and FCT for partial financial support of this work. During the course of this work, D. M. G. was the holder of a Government Assistance in Areas of National Need (GAANN) Fellowship awarded by Indiana University.

- [1] B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press, Oxford, **1986**.
- [2] A. L. J. Beckwith, *Chem. Soc. Rev.* **1993**, 22, 143–151.
- [3] B. Venugopalan, P. J. Karnik, S. Shinde, *J. Chem. Soc. Perkin Trans. 1* **1996**, 1015–1020.
- [4] G. Stork, R. Mook Jr., *J. Am. Chem. Soc.* **1983**, 105, 3720–3722.
- [5] S. C. Roy, S. Adhikari, *Tetrahedron* **1993**, 49, 8415–8422.
- [6] W. R. Dolbier Jr., X. X. Rong, B. E. Smart, Z.-Y. Yang, *J. Org. Chem.* **1996**, 61, 4824–4826.
- [7] J. Quirante, C. Escolano, A. Merino, J. Bonjoch, *J. Org. Chem.* **1998**, 63, 968–976 (and references cited therein).
- [8] S. R. Graham, J. A. Murphy, D. Coates, *Tetrahedron Lett.* **1999**, 40, 2415–2416.
- [9] R. McCague, R. G. Pritchard, R. J. Stoodley, D. S. Williamson, *Chem. Commun.* **1998**, 2691–2692.
- [10] C. Bokelmann, W. P. Neumann, M. Peterseim, *J. Chem. Soc. Perkin Trans. 1* **1992**, 3165–3166.
- [11] A. Routledge, C. Abell, S. Balasubramanian, *Synlett* **1997**, 61–62.
- [12] X. Du, R. W. Armstrong, *Tetrahedron Lett.* **1998**, 39, 2281–2284 (and references cited therein).
- [13] E. Duñach, D. Franco, S. Olivero, *Eur. J. Org. Chem.* **2003**, 1605–1622.
- [14] S. Ozaki, E. Matsui, J. Waku, H. Ohmori, *Tetrahedron Lett.* **1997**, 38, 2705–2708 (and references cited therein).
- [15] M. Ihara, A. Katsumata, F. Setsu, Y. Tokunaga, K. Fukumoto, *J. Org. Chem.* **1996**, 61, 677–684.

- [16] S. Olivero, J.-P. Rolland, E. Duñach, *Organometallics* **1998**, *17*, 3747–3753 (and references cited therein).
- [17] M. S. Mubarak, D. G. Peters, *J. Electroanal. Chem.* **1992**, *332*, 127–134.
- [18] D. M. Fang, D. G. Peters, M. S. Mubarak, *J. Electrochem. Soc.* **2001**, *148*, E464–E467.
- [19] A. P. Esteves, A. M. Freitas, M. J. Medeiros, D. Pletcher, *J. Electroanal. Chem.* **2001**, *499*, 95–102.
- [20] E. Duñach, A. P. Esteves, A. M. Freitas, M. J. Medeiros, S. Olivero, *Tetrahedron Lett.* **1999**, *40*, 8693–8696.
- [21] A. P. Esteves, D. M. Goken, L. J. Klein, M. A. Lemos, M. J. Medeiros, D. G. Peters, *J. Org. Chem.* **2003**, *68*, 1024–1029.
- [22] S. C. Bobzin, J. D. Faulkner, *J. Nat. Prod.* **1991**, *54*, 225–232.
- [23] A. Merritt, S. V. Ley, *Nat. Prod. Rep.* **1992**, *9*, 243–287 (and references cited therein).
- [24] A. P. Esteves, D. M. Goken, L. J. Klein, M. A. Lemos, M. J. Medeiros, D. G. Peters, *J. Electroanal. Chem.* **2003**, *560*, 161–168.
- [25] C. Gosden, K. P. Healy, D. Pletcher, *J. Chem. Soc. Dalton Trans.* **1978**, 972–976.
- [26] K. P. Healy, D. Pletcher, *J. Organomet. Chem.* **1978**, *161*, 109–120.
- [27] C. Gosden, D. Pletcher, *J. Organomet. Chem.* **1980**, *186*, 401–409.
- [28] J. Y. Becker, J. B. Kerr, D. Pletcher, R. Rosas, *J. Electroanal. Chem.* **1981**, *117*, 87–99.
- [29] C. Gosden, J. B. Kerr, D. Pletcher, R. Rosas, *J. Electroanal. Chem.* **1981**, *117*, 101–107.
- [30] M. C. Helveston, C. E. Castro, *J. Am. Chem. Soc.* **1992**, *114*, 8490–8496.
- [31] E. S. Petrov, M. I. Terekhova, I. G. Malakhova, E. N. Tevetkov, A. I. Shatenshtein, M. I. Kabachnik, *Zh. Obshch. Khim.* **1979**, *49*, 2410–2414.
- [32] F. Maran, D. Celadon, M. G. Severin, E. Vianello, *J. Am. Chem. Soc.* **1991**, *113*, 9320–9329.
- [33] S. Ozaki, I. Horiguchi, H. Matsushita, H. Ohmori, *Tetrahedron Lett.* **1994**, *35*, 725–728.
- [34] S. Ozaki, H. Matsushita, H. Ohmori, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2339–2344.
- [35] S. Ozaki, H. Matsushita, M. Emoto, H. Ohmori, *Chem. Pharm. Bull.* **1995**, *43*, 32–36.
- [36] M. A. Halcrow, G. Christou, *Chem. Rev.* **1994**, *94*, 2421–2481.
- [37] C. P. Andrieux, C. Blocman, J. M. Dumas-Bouchiat, F. M'Halla, J. M. Savéant, *J. Am. Chem. Soc.* **1980**, *102*, 3806–3813.
- [38] F. M'Halla, J. Pinson, J. M. Savéant, *J. Am. Chem. Soc.* **1980**, *102*, 4120–4127.
- [39] J. M. Savéant, *Bull. Soc. Chim. Fr.* **1988**, 225–237.
- [40] M. S. Mubarak, D. G. Peters, *J. Electroanal. Chem.* **1995**, *388*, 195–198.
- [41] J. H. P. Utley, M. F. Nielsen, in: *Organic Electrochemistry*, 4th ed. (Ed.: H. Lund, O. Hammerich), Dekker, New York, **2001**, pp. 1227–1257.
- [42] M. B. Smith, J. March, in: *March's Advanced Organic Chemistry*, 5th ed., Wiley, New York, **2001**, pp. 1308–1312.
- [43] P. Renaud, in: *Radicals in Organic Synthesis* (Ed.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, pp. 400–415.
- [44] B. Bosnich, M. L. Tobe, G. A. Webb, *Inorg. Chem.* **1965**, *4*, 1109–1112.
- [45] J. A. Cleary, M. S. Mubarak, K. L. Vieira, M. R. Anderson, D. G. Peters, *J. Electroanal. Chem.* **1986**, *198*, 107–124.
- [46] L. W. Marple, *Anal. Chem.* **1967**, *39*, 844–846.
- [47] C. W. Manning, W. C. Purdy, *Anal. Chim. Acta* **1970**, *51*, 124–126.
- [48] K. L. Vieira, D. G. Peters, *J. Electroanal. Chem.* **1985**, *196*, 93–104.
- [49] C. E. Dahm, D. G. Peters, *Anal. Chem.* **1994**, *66*, 3117–3123.
- [50] W. A. Pritts, D. G. Peters, *J. Electroanal. Chem.* **1995**, *380*, 147–160.
- [51] M. S. Mubarak, D. G. Peters, *J. Org. Chem.* **1995**, *60*, 681–685.
- [52] M. S. Mubarak, D. G. Peters, *J. Electrochem. Soc.* **1996**, *143*, 3833–3838.

Received: June 28, 2005

Published Online: September 27, 2005