

DOI: 10.1002/ange.200600951

Self-Supported and Clean One-Step Cathodic Coupling of Activated Olefins with Benzyl Bromide Derivatives in a Micro Flow Reactor**

Ping He, Paul Watts, Frank Marken, and
Stephen J. Haswell*

Electrosynthesis offers a clean and versatile method for the generation of anion and cation radical intermediates.^[1] The addition of electrons to, or the removal of electrons from, neutral organic substrates can be achieved under relatively mild reaction conditions and may lead to powerful electro-synthetic strategies. A possible role of electrosynthesis in “green chemistry” has been highlighted by several authors,^[2] particularly in combination with the recently emerging microreactor technology.^[3a–c] Microreactors have numerous practical advantages including safe operating, easy modulation, and easy scale-up for industrial production when compared with batch reactors.^[3d,e] The combination of electrosynthesis with microreactors has made electrochemistry more accessible even in the absence of electrolyte.^[4]

In synthetic chemistry, C–C-bond-formation processes are of considerable importance and new methods are constantly sought with the aim of obtaining clean, simple, and efficient synthetic routes. Herein, we describe a C–C-bond-formation method based on the electro-reductive coupling of activated olefins and benzyl bromide derivatives. The coupling products such as 2-benzyl succinic acid dimethyl ester are important classes of compounds owing to their utility as intermediates in the synthesis of important targets such as natural antibiotics,^[5a] pyrrolidines,^[5b] metalloproteinase inhibitors,^[5c] inhibitors towards human leukocytes,^[5d] cephalotaxine,^[5e] and monoesters of alkylated succinic acids.^[5f] Several methods have been reported^[5b,g,h] for this class of compounds, most of which involve multi-step processes and require the presence of metal catalysts. Alternatively, a photochemical procedure based on electron transfer to a photo-sensitizer has been proposed for the coupling of methylbenzene and dimethylsuccinate,^[5i] but the method resulted in a complex mixture of reaction products. In contrast, the process described herein is based on a clean one-step cathodic coupling process carried out under micro-

reactor flow through conditions to generate higher yields of products when compared with conventional synthetic methods. Considerable benefits of the novel electrochemical process are 1) simple operation, 2) no need for chemical reagents or electrolytes, 3) simple work-up, and 4) a surprisingly high yield.

Initially, the coupling of dimethyl fumarate with benzyl bromide was selected for study by cyclic voltammetry experiments. Both dimethyl fumarate and dimethyl maleate are known to be reduced in one-electron processes, both leading to the dimethyl fumarate radical anions as the intermediate followed by slow hydrodimerization.^[6] The reduction of benzyl bromide is usually found to be chemically irreversible leading to the formation of dibenzyl products. The one-electron reduction of benzyl bromide proceeds through the benzyl radical intermediate. The two-electron reduction of benzyl bromide to give a benzyl carbanion may occur at sufficiently negative potentials, at mercury pool electrodes,^[7] or in the presence of electrophilic reagents such as protons. Figure 1A shows typical (conventional) cyclic voltammograms for the reduction of benzyl bromide (curve a), dimethyl fumarate (curve b), and dimethyl fumarate in the presence of benzyl bromide (curve c). The reduction of dimethyl fumarate occurs as a reversible one-electron process. In the presence of benzyl bromide, the peak current of the reduction wave for dimethyl fumarate remains and the re-oxidation wave after reversal of the scan direction completely disappears. A complete loss of the anodic peak reveals a rapid chemical reaction of the dimethyl fumarate radical anion with benzyl bromide. From the peak current in Figure 1A (and based on additional microelectrode experiments, see Supporting Information), the process can be identified as a one-electron process. As will be shown below, on a longer time scale during the course of electrolysis, transfer of a second electron occurs and is attributed to a further unidentified processes.

During the main electrode reaction, the interaction of the primary fumarate radical anion and benzyl bromide is believed to lead to rapid C–C coupling. The coupling, followed by loss of bromide, occurs only if a sufficient driving force for this process is available. The parameter ΔE ($E_{1/2,df} - E_{1/2,bb}$) describes the potential difference for the reduction of the dimethyl fumarate (df) and for benzyl bromide (bb) and is obtained here as an approximate measure of the energy balance in the intermolecular electron transfer. If ΔE becomes too high, the energy for the C–Br bond heterolysis will be insufficient.

Preparative microreactor electrolyses were conducted in a flow cell (see Figure 2) to isolate and identify products by using GC/MS as well as ¹H and ¹³C NMR spectroscopy and to optimize yields for the coupling of dimethyl fumarate (or dimethyl maleate) with benzyl bromide. The solution containing 5 mM dimethyl fumarate (or dimethyl maleate) and 5 mM benzyl bromide in DMF (*N,N*-dimethylformamide) was continuously pumped through the cell in which two platinum electrodes with a working area of 45 mm² were positioned with an inter-electrode gap of 160 μ m or 320 μ m. The coupling reactions were conducted galvanostatically and product samples were collected in a product vial for 5 min. Table 1 summarizes the conversion and product distribution for the

[*] Dr. P. He, Dr. P. Watts, Prof. S. J. Haswell
Department of Chemistry
University of Hull, Hull, HU6 7RX (UK)
Fax: (+44) 148-246-6416
E-mail: s.j.haswell@hull.ac.uk

Dr. F. Marken
Department of Chemistry
University of Bath, Bath, BA2 7AY (UK)

[**] We thank the EPSRC for funding.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

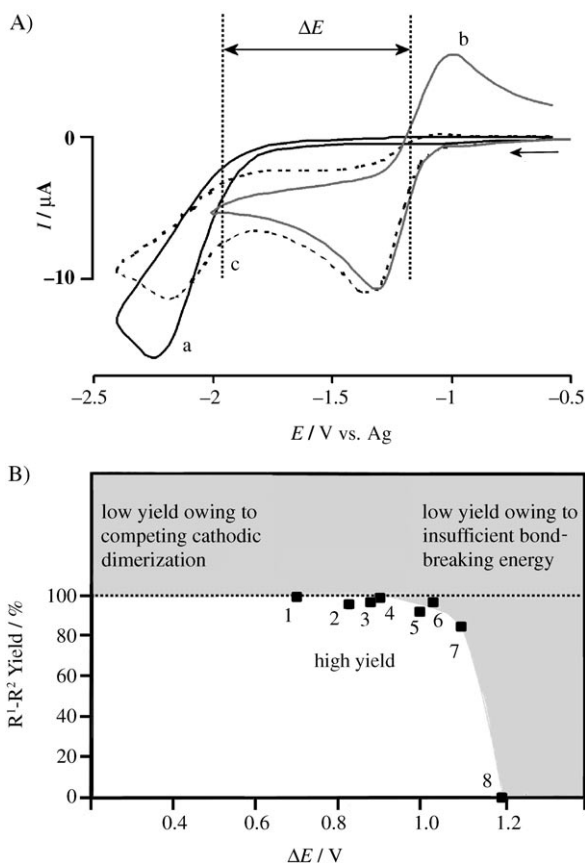


Figure 1. A) Cyclic voltammograms (scan rate 10 V s^{-1}) obtained at a platinum disc electrode (diameter 0.5 mm) immersed in $0.1 \text{ M } n\text{Bu}_4\text{NBF}_4/\text{DMF}$ for: a) 3 mM benzyl bromide, b) 3 mM dimethyl fumarate, and c) 3 mM dimethyl fumarate in the presence of 3 mM benzyl bromide. The parameter ΔE when compared to the energy for heterolytic C–Br bond fission allows the driving force for the reaction to be assessed (see text). B) Plot of the yield of the $\text{R}^1\text{--R}^2$ coupling product (see Table 1) versus the gap in halfwave potential for:

1) dimethyl fumarate/benzyl bromide, 2) dimethyl fumarate/4-bromobenzyl bromide, 3) dimethyl fumarate/1-phenylethylbenzyl bromide, 4) fumaronitrile/benzyl bromide, 5) dimethyl fumarate/4-methoxybenzyl bromide, 6) fumaronitrile/4-bromobenzyl bromide, 7) maleic anhydride/bisbromomethylbenzene, 8) maleic anhydride/benzyl bromide.

range of conditions employed in this study. Both conversion and product distribution are strongly dependent on the electrode gap, the flow rate, and the applied current. For a $320\text{-}\mu\text{m}$ inter-electrode gap (Table 1, entries 1 and 2), 47% and 77% conversion to the desired coupling product can be achieved with significant homo-coupling side products. An increase in current was found to enhance only homo-dimerization of the olefin or benzyl bromide. For an inter-electrode gap of $160 \text{ }\mu\text{m}$ (Table 1, entries 3–7), relatively lower voltages (4–4.4 V) were required to obtain sufficiently high levels of conversion ($> 95\%$). Inter-

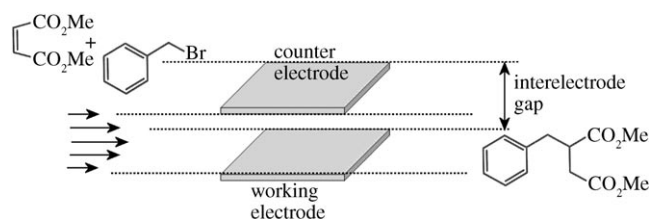


Figure 2. Schematic representation of the C–C coupling reaction during electrosynthesis in a microreactor. A flow of reagents through a rectangular duct with the working and counter electrodes facing each other results in the formation of products.

estingly, unwanted dimerization of olefins was found to be less than 2% plus a very small amount of toluene (from debromination of benzyl bromide) and no dimerization of benzyl bromide was detected. The best result obtained was 98% of 2-benzyl dimethylsuccinate with only 2% of the homo-dimer tetramethyl butanetetracarboxylate and toluene at a flow rate of 10 or $15 \text{ }\mu\text{L min}^{-1}$ (Table 1, entries 5 and 6, respectively). At higher flow rates, the possibility of homo-dimerization of the olefin was observed (Table 1, entry 7).

This electrochemical procedure was also scaled up in a “parallel” microreactor cell containing two equally sized sets of electrodes. Again, dimethyl fumarate was completely converted to give the cross-coupling product 2-benzyl dimethylsuccinate with only 2% of olefin dimer and toluene. In this case, a volumetric flow rate equivalent to $30 \text{ }\mu\text{L min}^{-1}$ (i.e. $15 \text{ }\mu\text{L min}^{-1} \times 2$ flow cells) was achieved, which is double the flow rate of the single cell and hence producing twice the quantity of the product in a given time. Other benzyl bromide derivatives such as 4-methoxybenzyl bromide, 4-methylbenzyl bromide, 4-bromobenzyl bromide, 4-iodobenzyl bromide, and 1-phenylethyl bromide were also examined for coupling reactions with dimethyl fumarate using the same microreactor

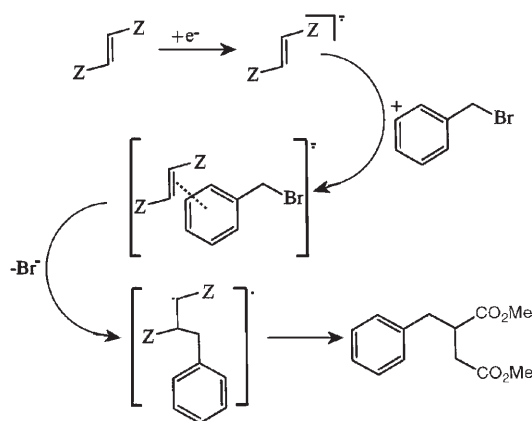
Table 1: Data for the preparative electrolysis of activated olefins in the presence of benzyl bromides in a micro flow cell without intentionally added supporting electrolyte.^[a]

No.	I [mA]	Olefin R^1	$\text{R}^2\text{-Br}$ R^2	Flow [$\mu\text{L min}^{-1}$]	Conv. [%] ^[b]	Distribution [%] $\text{R}^1\text{-R}^2$ others ^[c]
1	0.6	dimethyl maleate	benzyl	20	47	89 11
2	1.5	dimethyl maleate	benzyl	20	77	70 30
3	0.6	dimethyl maleate	benzyl	10	100	98 2
4	0.6	dimethyl maleate	benzyl	15	100	98 2
5	0.6	dimethyl fumarate	benzyl	10	100	98 2
6	0.6	dimethyl fumarate	benzyl	15	100	98 2
7	0.6	dimethyl fumarate	benzyl	20	100	94 6
8	0.6	dimethyl fumarate	4-methoxybenzyl	10	100	94 6
9	0.6	dimethyl fumarate	4-methylbenzyl	10	100	94 6
10	0.6	dimethyl fumarate	4-bromobenzyl	10	100	99 1
11	0.6	dimethyl fumarate	4-iodobenzyl	10	100	99 1
12	0.6	dimethyl fumarate	1-phenylethyl	10	100	98 2
13	0.5	fumaronitrile	benzyl	10	100	96 4
14	0.5	fumaronitrile	4-methylbenzyl	10	100	93 7
15	0.5	fumaronitrile	4-bromobenzyl	10	100	95 5
16	0.3	maleic anhydride	dibromide	10	82	84 16 ^[d]

[a] Olefin 5 mm , halide 5 mm , solvent DMF; the electrode gap is $320 \text{ }\mu\text{m}$ for entries 1 and 2, and $160 \text{ }\mu\text{m}$ for entries 3–16. [b] Conversion was determined based on the quantity of olefin before and after reaction using n -decane as an internal standard. [c] Other products result from dimerization of olefin and debromination of benzyl bromides; no dimerization of benzyl bromides is detected except for entry 2. [d] Other side products are 1,2-dimethylbenzene and 2-methylbenzyl bromide.

as that used in entry 3 in Table 1. All preparative electrolyses gave excellent yields (94 %) of cross-coupling products with very small amount of olefin dimer and debrominated products (Table 1, entries 8–12). The formation of bromine due to oxidation of bromide was not observed presumably owing to the limited overlap of diffusion layers within the flow cell. Current efficiencies for all processes are typically 40–50 %. These data suggest that overall two moles of electrons are consumed for each mole of product formed by electrolysis. Cyclic voltammetry data (short time scale) do not show evidence for the transfer of the second electron. However, the time scale for the electrolysis process is different and the second electron transfer may occur in the later stages of the process, for example, involving solvent.

From the results obtained, it can be seen that the presence of benzyl bromide suppresses olefin hydromerization, indicating that the reaction between olefin radical anion and benzyl bromide is fast. The neutral benzyl radical intermediate,^[4d] which is short-lived^[8] and known to either dimerize (to give bibenzyl) or to abstract a hydrogen atom to produce toluene,^[9] appears to be an unlikely free intermediate. The absence of bibenzyl and only a small amount of toluene indicate fast direct coupling of the dimethyl fumarate radical anion with benzyl bromide. Scheme 1 describes a



Scheme 1. Plausible mechanistic reaction pathway for the C–C coupling process.

plausible reaction pathway. The mild conditions employed during electrolysis are consistent with a one-electron pathway, and a related transition metal complex mediated reduction of benzyl bromide also has been shown to proceed through a one-electron pathway.^[10] However, in this particular study it is not clear whether the final step proceeds through a second-electron transfer process or not and this will require further study.

Further coupling reactions between fumaronitrile and benzyl bromides as well as between maleic anhydride and 1,2-bis(bromomethyl)benzene were investigated. Formally equivalent (but more laborious and less effective) conventional synthetic reactions have been described in the literature, for example, a photochemical process in the presence of organometallic catalysts for the coupling of benzyl bromide with fumaronitrile,^[11] a sacrificial zinc approach,^[12a] a photochem-

ical approach,^[12b] and a direct Diels–Alder reaction^[12c,d] for coupling of maleic anhydride with dibromides. Interestingly, in a flow microreactor cell excellent yields (> 93 %) for coupling of fumaronitrile and bromides (Table 1, entries 13–15) and 84 % yields for coupling of maleic anhydride and 1,2-bis(bromomethyl)benzene (Table 1, entry 16) can be obtained.

For the proposed mechanism, the differences between the approximate reduction halfwave potentials for the olefin and benzyl bromide, ΔE , may be understood as part of a thermodynamic cycle.^[13] It is observed that conversion is dependent on the reduction potential difference ΔE . For the coupling reaction of dimethyl fumarate and benzyl bromide with ΔE of 0.7 V up to 100 % conversion can be achieved, and for the coupling reaction of dimethyl fumarate and 4-methoxybenzyl bromide with ΔE of 1.1 V 91 % conversion are obtained at a flow rate of 15 $\mu\text{L min}^{-1}$ under the same conditions. It is also observed that coupling reactions of benzyl chloride with dimethyl fumarate, and that of maleic anhydride with all benzyl bromide derivatives ($\Delta E > 1.2$ V) except 1,2-bis(bromomethyl)benzene ($\Delta E = 1.1$ V) fail to produce any cross-coupling products. The benzyl bromides are recovered unreacted. A schematic plot of maximum yield versus ΔE (Figure 1 B) suggests a threshold of $\Delta E \approx 1.1$ V for successful coupling. This value is in approximate agreement (ΔE is slightly high due to uncertainty in half wave potential for the benzyl bromide reduction) with the value expected for dissociation of the C–Br bond: $\Delta E = 0.85$ V (the gas phase bond energy for benzyl bromide is $D_0 = 82 \text{ kJ mol}^{-1}$).^[14]

We have demonstrated that clean microreactor-based electrosyntheses in the absence of supporting electrolyte are feasible even with very simple cell geometries. The height of the microfluidic cell and the flow rate have been shown to be crucial for the minimization of unwanted side products and optimization of yields. More work will be required for a better understanding of the spatial distribution of reagents, the electron transfer process in microreactor systems, as well as for the optimization and scale up of processes in the microreactor cell. For an energy-efficient use of microreactor electrosynthesis, the resistive losses during electrosynthesis will need further investigation and better electrode designs may help in optimizing the efficiency of the process. It is very likely that clean one-step electrosynthetic coupling processes in microfluidic reactors are applicable for a wider range of reactions.

Experimental Section

Cyclic voltammetric (CV) experiments were carried out with an Autolab PGSTAT30 system in a conventional three-electrode cell and in the presence of supporting electrolyte. A Pt disc (diameter 0.5 mm), a Pt wire, and a silver wire (both diameter 0.1 mm) were used as the working electrode, the counter electrode, and the reference electrode, respectively. For preparative microreactor electrolyses, a Harvard PHD 2000 syringe pump was used to pump the reaction solution containing olefin (5 mm) and benzyl bromide (5 mm) in DMF without the addition of electrolyte through the microreactor cell in which two platinum foil electrodes with a working area of 45 mm² were positioned with an inter-electrode distance of 160 μm and 320 μm .^[4d] All reactions were conducted galvanostatically and

product samples were continuously collected 5 times and each run took 5 min. Reactions were analyzed by GC (Shimadzu GC-17 A, FID, column CPSIL8) using decane as an internal standard. The replicate analysis shows RSD less than 5%. The products were also identified using ^1H and ^{13}C NMR spectroscopy (Jeol GX400) in CDCl_3 as well as mass spectrometry (Varian 2000).

Received: March 10, 2006
Published online: May 23, 2006

Keywords: C–C coupling · electrochemical synthesis · flow cells · microreactors · olefins

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