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Continuous electrochemical synthetic system using a multiphase electrolyte solution

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ABSTRACT

A continuous electrochemical synthetic system has been developed using a cyclohexane-based multiphase electrolyte solution composed of lithium perchlorate and nitromethane. The upper cyclohexane phase functioned as both substrate supply and product assembly phases, whereas the electrochemical reactions took place in the lower electrolyte solution phase, achieving spatial separation of the electrolyte solution phase.

1. Introduction

Radical ion-based cyclizations have widely been investigated to give several ring skeletons [1–9]. In this respect, transition metals have extensively employed as catalysts to generate radical ions that established a large number of elegant synthetic approaches [10–14]. In this context, electrochemical processes have also proven to be effective for generating both nucleophilic and electrophilic carbons, and provide a unique way to construct several carbon skeletons [15–22]. In particular, there are many reports on intra- and intermolecular cyclization reactions that produce a wide variety of ring products, including natural product frameworks possessing several biological activities [23–28]. In these processes, electrodes function as both oxidizing and reducing reagents and the consumption of additional reagents is avoidable, thus, they are promising methodologies from an environmental viewpoint. However, in these reactions, the use of a large amount of electrolyte solution composed of polar organic solvent and supporting electrolytes is generally necessary, usually requiring further separation and/or purification procedures. One of the common procedures employed to remove these supporting electrolytes is liquid–liquid extraction containing water. This procedure quenches the electrolyte solution and lowers the productivity of the reaction, decreasing the "green" possibilities of electrochemical reactions. Several elegant approaches, e.g., electrolytic systems using solid-supported reagents [29–30], thin layer flow cells [31], and ionic liquids [32–33], have been reported to solve these problems. In this context, an electrochemical synthetic system where the electrolyte solution phase is spatially separated is expected to improve the "green" nature of electrochemical reactions (Scheme 1).

Previously, we reported an oxidative carbon–carbon bond formation system using a cyclohexane-based thermomorphic multiphase electrolyte solution composed of lithium perchlorate (LPC) and nitromethane (NM) [34]. In this system, a thermomorphic middle phase formed between the upper cyclohexane phase and the lower LPC/NM electrolyte solution phase, which provided an effective reaction field for the [3+2] cycloaddition reactions. The electrochemical reaction took place in the lower LPC/NM electrolyte solution phase and the desired products were assembled in the upper cyclohexane phase, enabling the separation of the desired products from the LPC/NM electrolyte solution via simple liquid–liquid extraction with cyclohexane (Scheme 2).

We envisioned that this system could be applied to establish a novel electrochemical synthetic system where the electrolyte solution phase was spatially separated to improve the "green" nature of electrochemical reactions. Here, we report a continuous electrochemical synthetic system using a cyclohexane-based multiphase electrolyte solution composed of LPC and NM.

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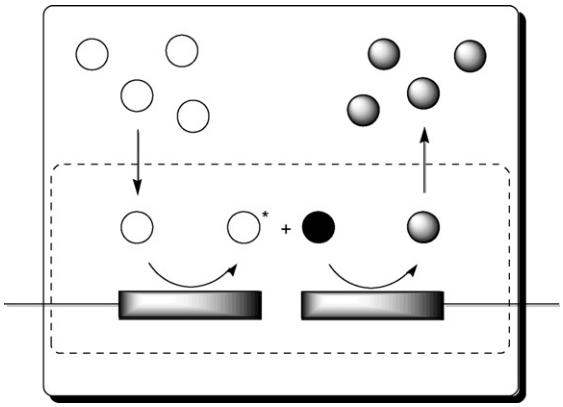


Scheme 1. The electrochemical synthetic system where the electrolyte solution phase is spatially separated.

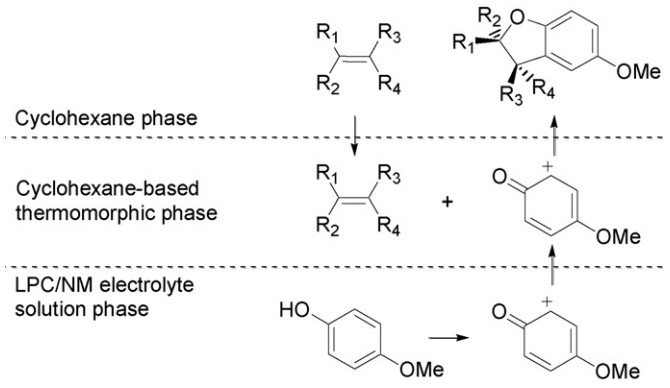
2. Experimental

2.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the initial standard (600 MHz and 150 MHz, respectively). The following abbreviations were used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; sept, septet; m, multiplet. TLC analysis was carried out with the plates containing the fluorescent indicator, detection of compounds was achieved by UV absorption (254 nm) and by charring after spraying with 12 molybdo (VI) phosphoric acid n-hydrate in 95% ethanol. Column chromatography was performed with silica gel (0.04–0.063 mm).

2.2. General procedure of anodic oxidation

Aliphatic olefins (4.0 mmol) and prop-1-enyloxybenzenes (0.20 mmol) were added to 1.0 M $LiClO_4$–CH_3NO_2 (20 mL). The undivided reaction cell used was capped with a septum equipped with the both carbon felt (CF) anode and cathode (20 mm × 20 mm), and the Ag/AgCl reference electrode. The electrolysis was then performed at 1.2 V (*vs.* Ag/AgCl). After the reaction was completed, the desired products were extracted by cyclohexane and concentrated. The configurations of the products were confirmed by nuclear Overhauser effect spectroscopy (NOE). All percentage values including the yields and purities of the products and the partition ratios in the multiphase electrolyte solution were determined by NMR, based on internal standards.



Scheme 2. Oxidative carbon–carbon bond formation system using a cyclohexane-based thermomorphic multiphase electrolyte solution composed of LPC and NM.

2.2.1. 1-(2-Butyl-4-methylcyclobutoxy)-4-propylbenzene **3a** (all cis, minor)

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.04 (2H, d, J = 8.1 Hz), 6.76 (2H, d, J = 8.1 Hz), 4.71 (1H, t, J = 7.3 Hz), 2.67 (1H, sept, J = 7.3 Hz), 2.50 (3H, t, J = 7.3 Hz), 2.22–2.16 (1H, m) 1.70–1.63 (1H, m), 1.60 (2H, sext, J = 7.3 Hz), 1.52–1.43 (1H, m) 1.43–1.36 (1H, m), 1.33–1.11 (4H, m), 1.05 (3H, d, J = 7.3 Hz), 0.92 (3H, t, J = 7.3 Hz), 0.86 (3H, t, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 157.5, 134.2, 129.1, 114.7, 75.7, 38.6, 37.2, 33.4, 31.6, 29.8, 29.5, 24.8, 22.7, 15.7, 14.1, 13.8 IR (NaCl, cm^{-1}) 2958, 2929, 1611, 1510, 1456, 1242, 1173, 825 MS (rel. int.) m/z 260 (M^+, 17), 218 (30), 176 (51), 154 (100), 136 (74), 107 (47) HRMS calc. for $C_{18}H_{28}O$ 260.2140, found 260.2142.

2.2.2. 1-(2-Butyl-4-methylcyclobutoxy)-4-propylbenzene **3b** (all trans, major)

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.06 (2H, d, J = 8.8 Hz), 6.82 (2H, d, J = 8.8 Hz), 3.86 (1H, t, J = 7.3 Hz), 2.51 (2H, t, J = 7.3 Hz), 2.25–2.13 (2H, m), 2.10 (1H, q, J = 9.5 Hz), 1.65–1.55 (3H, m), 1.43–1.33 (1H, m), 1.33–1.18 (4H, m) 1.16 (3H, d, J = 7.3 Hz), 0.93 (3H, t, J = 7.3 Hz), 0.86 (3H, t, J = 7.3 Hz), 0.80 (1H, q, J = 9.5 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.4, 134.9, 129.2, 115.8, 84.1, 41.1, 37.2, 36.2, 34.4, 29.5, 27.1, 24.7, 22.7, 19.7, 14.1, 13.8 IR (NaCl, cm^{-1}) 2957, 2927, 1609, 1510, 1456, 1242, 1065, 831 MS (rel. int.) m/z 260 (M^+, 30), 218 (16), 176 (20), 154 (100), 136 (85), 107 (32) HRMS calc. for $C_{18}H_{28}O$ 260.2140, found 260.2143.

2.2.3. 1-(2-Butyl-4-methylcyclobutoxy)-4-propylbenzene **3c–d** (diastereomixture)

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.05 (2H, d, J = 8.8 Hz), 6.75 (2H, d, J = 8.8 Hz), 4.19 (1H, t, J = 7.3 Hz), 2.76–2.65 (1H, m), 2.65–2.56 (1H, m), 2.51 (2H, t, J = 7.3 Hz), 1.69–1.55 (4H, m), 1.53–1.45 (1H, m), 1.45–1.35 (1H, m) 1.35–1.20 (4H, m), 1.03 (3H, d, J = 7.3 Hz), 0.93 (3H, t, J = 7.3 Hz), 0.88 (3H, t, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.6, 134.5, 129.2, 114.5, 78.2, 40.8, 38.3, 37.2, 36.1, 29.5, 27.5, 24.8, 22.7, 19.1, 14.1, 13.8 IR (NaCl, cm^{-1}) 2959, 2927, 1613, 1510, 1456, 1240, 1075, 829 MS (rel. int.) m/z 260 (M^+, 25), 218 (28), 176 (35), 154 (100), 136 (87), 69 (50) HRMS calc. for $C_{18}H_{28}O$ 260.2140, found 260.2142.

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.05 (2H, d, J = 8.8 Hz), 6.75 (2H, d, J = 8.8 Hz), 4.17 (1H, t, J = 7.3 Hz), 2.76–2.65 (1H, m), 2.65–2.56 (1H, m), 2.51 (2H, t, J = 7.3 Hz), 1.82–1.69 (1H, m), 1.69–1.55 (3H, m), 1.53–1.45 (1H, m), 1.45–1.35 (1H, m) 1.35–1.20 (4H, m), 1.15 (3H, d, J = 7.3 Hz), 0.93 (3H, t, J = 7.3 Hz), 0.84 (3H, t, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.8, 134.5, 129.2, 114.5, 79.5, 38.3, 36.1, 34.2, 32.6, 29.5, 27.7, 27.3, 22.8, 19.1, 14.1, 13.8.

2.2.4. 1-(2,2-Diethyl-4-methylcyclobutoxy)-4-propylbenzene **7a** (cis)

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.04 (2H, d, J = 8.8 Hz), 6.75 (2H, d, J = 8.8 Hz), 4.32 (1H, d, J = 7.3 Hz), 2.73–2.64 (1H, m), 2.50 (2H, t, J = 7.3 Hz), 1.80–1.72 (2H, m), 1.66–1.56 (3H, m), 1.50 (2H, q, J = 7.3 Hz), 1.40 (1H, q, J = 5.8 Hz) 1.02 (3H, d, J = 7.3 Hz), 0.92 (3H, t, J = 7.3 Hz), 0.81 (3H, t, J = 7.3 Hz), 0.80 (3H, t, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 157.4, 134.3, 129.1, 114.8, 79.5, 45.1, 37.2, 35.5, 30.0, 29.9, 24.8, 24.7, 15.7, 13.8, 8.2, 7.7 IR (NaCl, cm^{-1}) 2961, 2929, 1612, 1510, 1458, 1240, 1102, 825 MS (rel. int.) m/z 260 (M^+, 8), 218 (7), 176 (100), 154 (48), 136 (31), 69 (25) HRMS calc. for $C_{18}H_{28}O$ 260.2140, found 260.2142.

2.2.5. 1-(2,2-Diethyl-4-methylcyclobutoxy)-4-propylbenzene **7b** (trans)

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.04 (2H, d, J = 8.8 Hz), 6.79 (2H, d, J = 8.8 Hz), 3.97 (1H, d, J = 7.3 Hz), 2.51 (2H, t, J = 7.3 Hz), 2.42–2.32 (1H, m), 1.79 (1H, t, J = 10.3 Hz), 1.73 (1H, sext, J = 7.3 Hz), 1.64–1.55 (3H, m), 1.55–1.43 (2H, m) 1.16 (3H, d, J = 6.6 Hz), 0.99–0.92 (1H, m), 0.92 (3H, t, J = 7.3 Hz), 0.83 (3H, t, J = 7.3 Hz), 0.80 (3H, t, J = 7.3 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz) δ 157.0, 134.8, 129.2, 115.7, 85.2, 45.3, 37.2, 33.7, 31.7, 30.9, 24.8, 24.0, 19.9, 13.8, 8.4, 8.3 IR (NaCl, cm^{-1}) 2960, 2931, 1610, 1510, 1457, 1240, 1059, 822 MS (rel. int.) *m/z* 260 (M^+, 22), 218 (6), 176 (100), 154 (100), 136 (73), 125 (51) HRMS calc. for $C_{18}H_{28}O$ 260.2140, found 260.2142.

*2.2.6. 2-Methyl-1-(4-propylphenoxy)spiro[3.5]nonane **8a** (cis)*

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.04 (2H, d, *J* = 8.8 Hz), 6.75 (2H, d, *J* = 8.8 Hz), 4.27 (1H, d, *J* = 7.3 Hz), 2.70 (1H, m), 2.51 (2H, t, *J* = 7.7 Hz), 1.81 (1H, ddd, *J* = 11.4 Hz, 9.2 Hz, 1.1 Hz), 1.71–1.64 (2H, m), 1.60 (2H, sext, *J* = 7.3 Hz), 1.55–1.51 (2H, m), 1.51–1.41 (2H, m), 1.45 (1H, dd, *J* = 11.4 Hz, 5.9 Hz), 1.40–1.30 (2H, m), 1.29–1.20 (2H, m), 1.04 (3H, d, *J* = 7.3 Hz), 0.92 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 157.2, 134.0, 128.9, 114.5, 80.3, 42.6, 38.5, 37.1, 36.1, 32.9, 29.9, 26.1, 24.8, 23.0, 22.2, 15.7, 13.8 IR (NaCl, cm^{-1}) 2954, 2925, 2852, 1610, 1508, 1240, 1060, 821 MS (rel. int.) *m/z* 272 (M^+, 3), 230 (25), 176 (100), 147 (76), 107 (96), 81 (80) HRMS calc. for $C_{19}H_{28}O$ 272.2140, found 272.2144.

*2.2.7. 2-Methyl-1-(4-propylphenoxy)spiro[3.5]nonane **8b** (trans)*

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.05 (2H, d, *J* = 8.8 Hz), 6.82 (2H, d, *J* = 8.8 Hz), 3.90 (1H, d, *J* = 7.0 Hz), 2.51 (2H, t, *J* = 7.7 Hz), 2.38 (1H, m), 1.96 (1H, t, *J* = 10.3 Hz), 1.72–1.66 (1H, m), 1.60 (2H, sext, *J* = 7.3 Hz), 1.54–1.33 (7H, m), 1.28-1.19 (1H, m), 1.18–1.08 (1H, m), 1.16 (3H, d, *J* = 7.0 Hz), 0.95 (1H, m), 0.93 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 157.0, 134.6, 129.1, 115.3, 85.5, 43.0, 39.6, 37.2, 33.5, 32.8, 30.1, 26.2, 24.7, 23.1, 22.1, 19.8, 13.8 IR (NaCl, cm^{-1}) 2954, 2925, 2852, 1612, 1508, 1238, 1020, 823 MS (rel. int.) *m/z* 272 (M^+, 3), 176 (73), 147 (59), 136 (30), 107 (95), 81 (100) HRMS calc. for $C_{19}H_{28}O$ 272.2140, found 272.2150.

*2.2.8. 1-Propyl-4-(2,2,4-trimethylcyclobutoxy)benzene **9a** (cis)*

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.04 (2H, d, *J* = 8.4 Hz), 6.74 (2H, d, *J* = 8.4 Hz), 4.30 (1H, d, *J* = 7.8 Hz), 2.71 (1H, tsept, 7.2 Hz, *J* = 1.5 Hz), 2.51 (2H, t, *J* = 7.7 Hz), 1.84 (1H, ddd, *J* = 11.4 Hz, 8.8 Hz, 1.5 Hz), 1.60 (2H, quint, *J* = 7.3 Hz), 1.44 (1H, dd, *J* = 12.0 Hz, 6.0 Hz), 1.20 (3H, s), 1.16 (3H, s), 1.08 (3H, d, *J* = 7.2 Hz), 0.92 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 157.2, 134.3, 129.1, 114.7, 80.1, 38.6, 38.3, 37.1, 29.7, 29.4, 24.8, 24.0, 15.4, 13.8 IR (NaCl, cm^{-1}) 2956, 2927, 2869, 1612, 1510, 1240, 1097, 827 MS (rel. int.) *m/z* 232 (M^+, 8), 190 (22), 176 (82), 161 (36), 147 (78), 107 (100) HRMS calc. for $C_{16}H_{24}O$ 232.1827 found 232.1836.

*2.2.9. 1-Propyl-4-(2,2,4-trimethylcyclobutoxy)benzene **9b** (trans)*

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.05 (2H, d, *J* = 8.4 Hz), 6.80 (2H, d, *J* = 8.4 Hz), 3.91 (1H, d, *J* = 7.8 Hz), 2.51 (2H, t, *J* = 7.7 Hz), 2.41 (1H, tsept, *J* = 6.6 Hz, 2.6 Hz), 1.77 (1H, t, *J* = 10.2 Hz), 1.60 (2H, quint, *J* = 7.5 Hz), 1.20 (3H, s), 1.15 (3H, d, *J* = 6.6 Hz), 1.1 (3H, s), 1.05 (1H, t, *J* = 10.2 Hz), 0.92 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 156.8, 134.67, 129.2, 115.3, 85.3, 38.5, 37.2, 35.7, 33.3, 29.5, 24.7, 21.7, 19.52, 13.8 IR (NaCl, cm^{-1}) 2956, 2929, 2865, 1610, 1510, 1240, 1062, 829 MS (rel. int.) *m/z* 232 (M^+, 9), 190 (12), 176 (59), 161 (21), 147 (62), 107 (100) HRMS calc. for $C_{16}H_{24}O$ 232.1827, found 232.1834.

*2.2.10. 1-(2,2-Diethyl-4-methylcyclobutoxy)-2-propylbenzene **11a** (cis)*

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.17–7.04 (2H, m), 6.82 (1H, t, *J* = 7.3 Hz), 6.65 (1H, d, *J* = 8.1 Hz), 4.38 (1H, d, *J* = 7.3 Hz), 2.72 (1H, sept, *J* = 7.3 Hz), 2.70–2.50 (2H, m), 1.88–1.72 (2H, m), 1.72–1.57 (3H, m), 1.57–1.47 (3H, m), 1.42 (1H, q, *J* = 5.9 Hz) 1.00 (3H, d, *J* = 7.3 Hz), 0.96 (3H, t, *J* = 7.3 Hz), 0.83 (3H, t, *J* = 7.3 Hz), 0.82 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.7, 131.0, 129.9, 126.6, 119.6, 115.5, 78.8, 45.2, 35.5, 32.9, 30.1, 29.9, 24.8, 23.2, 15.8, 14.2, 8.1, 7.7 IR (NaCl, cm^{-1}) 2961, 2931, 1600, 1490, 1454, 1237, 1126, 748 MS (rel. int.) *m/z* 260 (M^+, 4), 218 (4), 176 (49), 154 (100), 136 (59), 69 (25) HRMS calc. for $C_{18}H_{28}O$ 260.2140, found 260.2122.

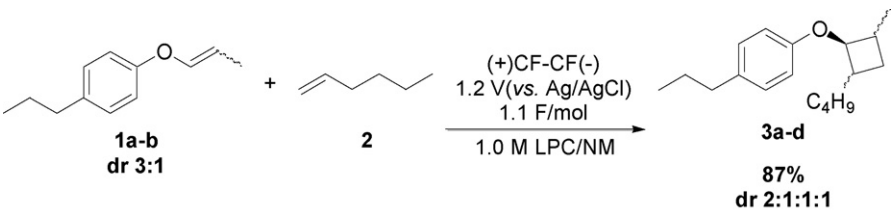
*2.2.11. 1-(2,2-Diethyl-4-methylcyclobutoxy)-2-propylbenzene **11b** (trans)*

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.12–7.06 (2H, m), 6.83 (1H, t, *J* = 7.3 Hz), 6.79 (1H, d, *J* = 8.1 Hz), 4.03 (1H, d, *J* = 7.3 Hz), 2.58 (2H, t, *J* = 7.3 Hz), 2.40–2.29 (1H, m), 1.84 (1H, t, *J* = 10.3 Hz), 1.79 (1H, sept, *J* = 7.3 Hz), 1.56–1.47 (2H, m), 1.19 (3H, d, *J* = 7.3 Hz) 1.00–0.95 (1H, m), 0.94 (3H, t, *J* = 7.3 Hz), 0.86 (3H, t, *J* = 7.3 Hz), 0.82 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.4, 131.6, 129.9, 126.6, 120.0, 112.7, 84.3, 45.0, 34.0, 32.7, 32.1, 31.0, 23.8, 23.2, 20.2, 14.1, 8.3, 8.2 IR (NaCl, cm^{-1}) 2961, 2932, 1601, 1490, 1454, 1239, 1126, 749 MS (rel. int.) *m/z* 260 (M^+, 8), 218 (5), 176 (62), 154 (100), 136 (62), 69 (39) HRMS calc. for $C_{18}H_{28}O$ 260.2140, found 260.2142.

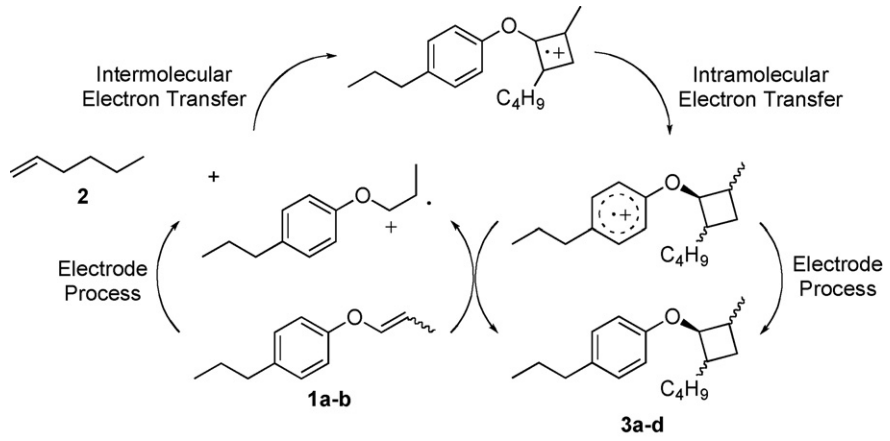
3. Results and discussion

Our present study began with the investigation of a model reaction that could realize a desirable synthetic system. Initially, anodic oxidation of prop-1-enyloxy-4-propylbenzene **1a**–**b** (0.20 mmol), which was prepared using the previously reported method [35], in the presence of an excess amount (4.0 mmol, 20 mol equiv.) of 1-hexene **2** in the LPC/NM electrolyte solution was attempted, affording the corresponding [2+2] cycloadducts **3a**–**d** in high yield (Scheme 3) [36].

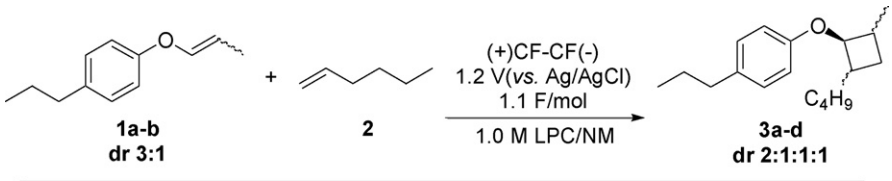
A plausible reaction mechanism is depicted below. **1a**–**b** was anodically oxidized to generate the corresponding radical cation, which was trapped by **2** to give **3a**–**d** (Scheme 4). In this reaction, an excess amount of **2** was essential for the effective trapping of the radical cation of **1a**–**b**, possibly due to its short lifetime [37–39]. The yields of **3a**–**d** were dramatically decreased as amounts of **2** decreased (Scheme 5). The configuration of **3a**–**d** was not derived from **1a**–**b**, suggesting that some sort of stepwise process was involved in the reaction. We then attempted to incorporate the second phase, cyclohexane, to the reaction system to form a multiphase electrolyte solution composed of LPC and NM. Since both substrates **1a**–**b** and **2** are soluble in cyclohexane, they could be introduced into this system as a cyclohexane solution. The reaction was carried out in the cyclohexane-based multiphase electrolyte solution composed of LPC and NM to give **3a**–**d** in excellent yield. The amounts of **1a**–**b** and **2** were the same as in Scheme 5, Entry 1. In this system, 5 mL of cyclohexane and 20 mL of LPC/NM electrolyte solution were used, and 79% (0.158 mmol) of **1a**–**b** and 63% (2.52 mmol) of **2** were partitioned in the upper cyclohexane phase,



Scheme 3. The anodic oxidation of **1a**–**b** in the presence of an excess amount of **2** in the LPC/NM electrolyte solution.



Scheme 4. Plausible reaction mechanism.



Entry	**1a-b** (mmol)	**2** (mmol, mol equiv.)	Yield (%)[a]
1	0.20	4.0, 20	**87**
2	0.20	1.0, 5	**46**

[a]Determined by NMR

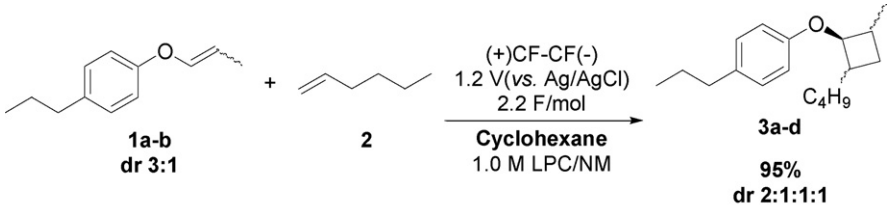
Scheme 5. The effects of concentration on **2**.

while 21% of (0.042 mmol) of **1a**–**b** and 37% (1.48 mmol) of **2**, i.e., "35 mol equiv." for **1a**–**b**, were partitioned in the lower LPC/NM electrolyte solution phase (Scheme 6).

It can be explained reasonably that because **1a**–**b** is more hydrophobic than **2** due to their respective molecular weights, a larger ratio of **1a**–**b** was portioned in the upper cyclohexane phase. At the end of the reaction, **3a**–**d** could be completely separated from the lower LPC/NM electrolyte solution phase via simple liquid-liquid extraction with cyclohexane to give **3a**–**d** with high chemoselectivity (Fig. 1). Thus, in this system, cyclohexane plays dual roles as the substrate supply and the product assembly phases. There is no conductivity in the upper cyclohexane phase, clearly suggesting that activation of **1a**–**b** takes place in the lower LPC/NM electrolyte solution phase. Namely, the lower LPC/NM electrolyte solution phase is spatially separated (Scheme 7).

It was noteworthy that only a moderate yield (65%) of **3a**–**d** was obtained through anodic oxidation of **1a**–**b** (0.042 mmol) without cyclohexane even in the presence of an excess amount (1.48 mmol, 35 mol equiv.) of **2** in the LPC/NM electrolyte solution. These results suggested that a continuous supply of **1a**–**b** from the upper cyclohexane phase to the lower LPC/NM electrolyte solution phase was crucial for the reaction and that the amount of **1a**–**b** was also correlated to the reaction progress (Scheme 8).

This was strongly supported by the fact that excellent yields of **3a**–**d** were obtained using the condition depicted below (Scheme 9). In this case, 15 mL of cyclohexane and 10 mL of LPC/NM electrolyte solution were used, while the concentrations of both **1a**–**b** and **2** in the lower LPC/NM electrolyte solution phase were intended to be comparable to those of Scheme 6, with a continuous supply of **1a**–**b** from the upper cyclohexane phase to reduce the amount of the LPC/NM electrolyte solution. The productivity of



	1a-b (0.20 mmol)	**2** (4.0 mmol, 20 mol equiv.)
Cyclohexane (5 ml)	79% (1.58 mmol)	63% (2.52 mmol)
LPC/NM (20 ml)	21% (0.042 mmol)	37% (1.48 mmol, **"35 mol equiv."**)

Scheme 6. The anodic oxidation of **1a**–**b** in the presence of an excess amount of **2** in the cyclohexane-based multiphase electrolyte solution composed of LPC and NM (5 mL of cyclohexane and 20 mL of LPC/NM were used, respectively).

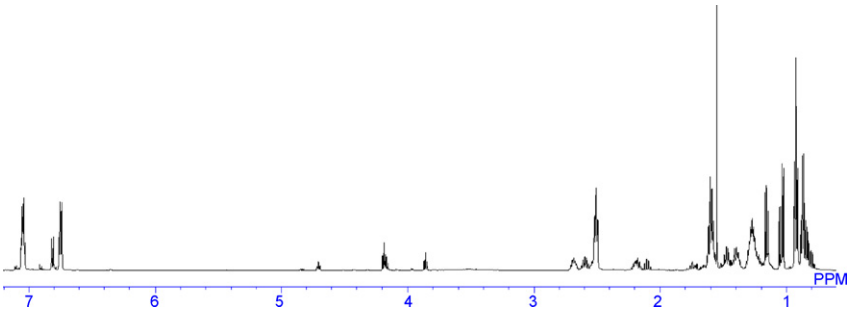
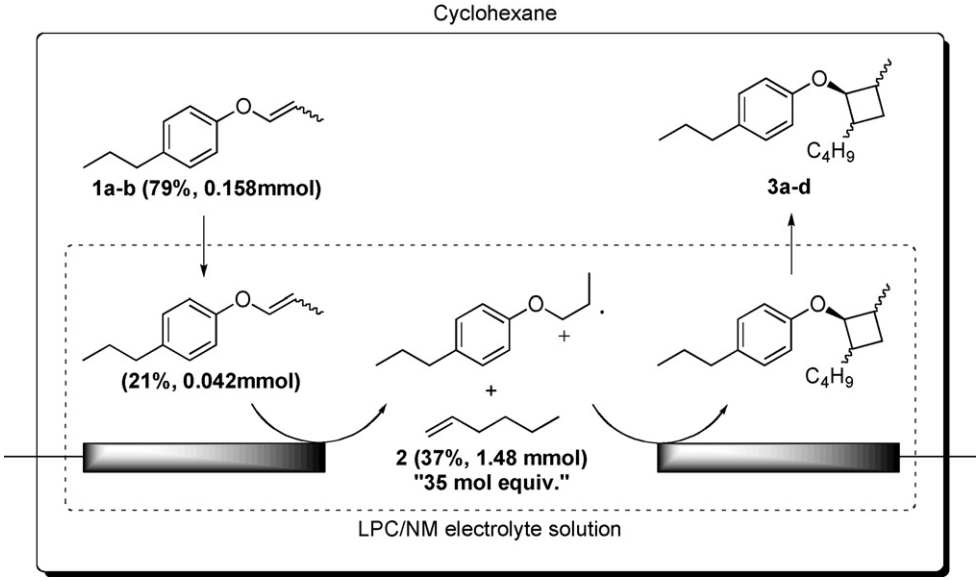


Fig. 1. The ^{1}H NMR spectra of **3a–d** separated via simple liquid–liquid extraction with cyclohexane.

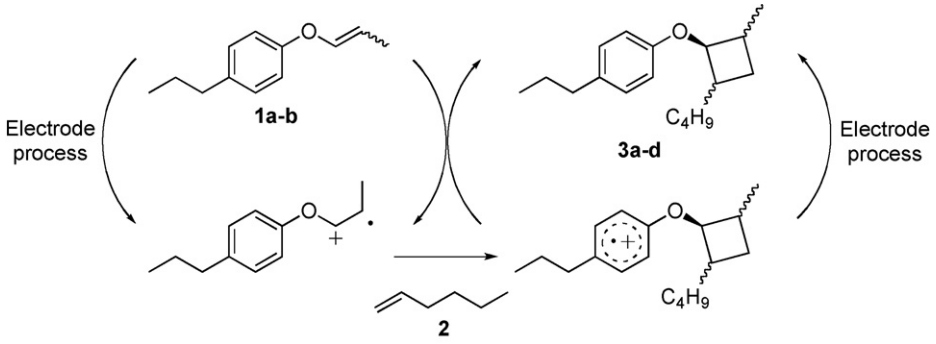


Scheme 7. The concept of the cyclohexane-based multiphase electrolyte solution composed of LPC and NM.

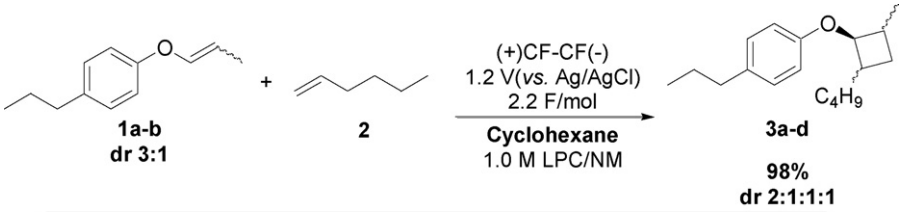
the LPC/NM electrolyte solution was clearly improved through this system.

It was also noteworthy that the anodic oxidation of **1a–b** (0.20 mmol) in the presence of **2** (1.0 mmol, 5 mol equiv.) in cyclohexane-based multiphase electrolyte solution composed of LPC and NM with 5 mL of cyclohexane and 20 mL of LPC/NM electrolyte solution afforded **3a–d** in moderate yield (63%), in sharp contrast to that in LPC/NM electrolyte solution without cyclohexane (46%, see Scheme 5, Entry 2). These results also suggested that **1a–b** was preferentially partitioned in the upper cyclohexane phase and was continuously supplied to the lower LPC/NM electrolyte solution phase, whereas a larger ratio of **2** was partitioned in the lower LPC/NM electrolyte solution such that the amount of **2** in the lower LPC/NM electrolyte solution phase was relatively high compared to that in LPC/NM electrolyte solution without cyclohexane (Scheme 10). It could be concluded that a continuous supply of **1a–b** from the upper cyclohexane phase to the lower LPC/NM electrolyte solution phase was critical for the reaction.

We next examined the reusability of the LPC/NM electrolyte solution in this system. After extraction of **3a–d**, additional

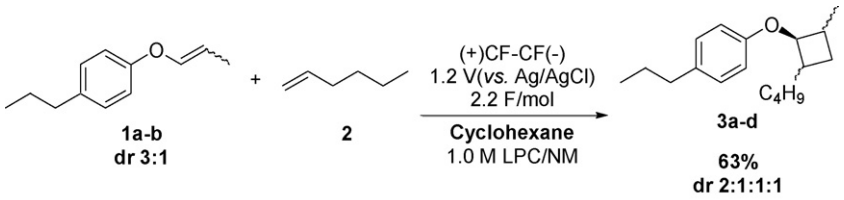


Scheme 8. Plausible reaction mechanism.



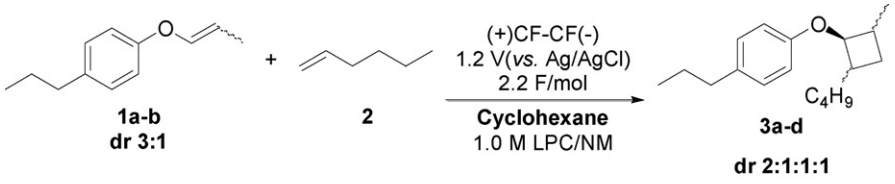
	1a-b (0.49 mmol)	2 (8.2 mmol, 17 mol equiv.)
Cyclohexane (15 ml)	96% (31 mM)	91% (497 mM)
LPC/NM (10 ml)	4% (**2 mM**)	9% (**74 mM**, "35 mol equiv.")

Scheme 9. The anodic oxidation of **1a**–**b** in the presence of an excess amount of **2** in the cyclohexane-based multiphase electrolyte solution composed of LPC and NM (15 mL of cyclohexane and 10 mL of LPC/NM electrolyte solution were used, respectively).



	1a-b (0.20 mmol)	2 (1.0 mmol, 5 mol equiv.)
Cyclohexane (5 ml)	79% (1.58 mmol)	63% (0.63 mmol)
LPC/NM (20 ml)	21% (0.042 mmol)	37% (0.37 mmol, "**9 mol equiv.**")

Scheme 10. The anodic oxidation of **1a**–**b** in the presence of an excess amount of **2** in the cyclohexane-based multiphase electrolyte solution composed of LPC and NM (5 mL of cyclohexane and 20 mL of LPC/NM electrolyte solution were used, respectively).

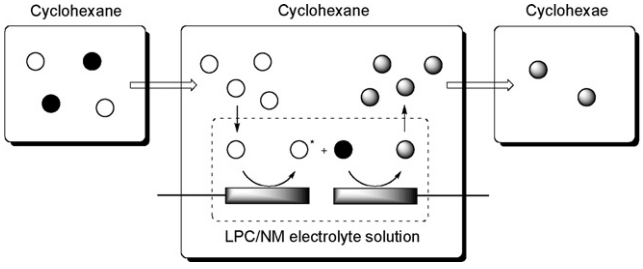


Entry	1	2	3	4	5
Yield	95%	95%	96%	96%	95%

Scheme 11. Reusability of the LPC/NM electrolyte solution.

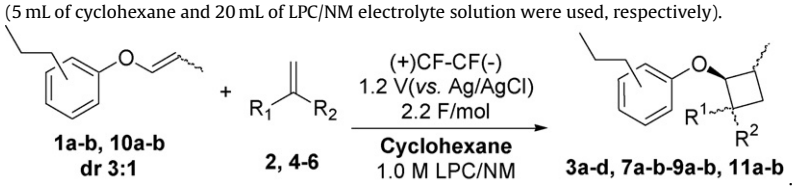
amounts of **1a**–**b** and **2** in a cyclohexane solution were introduced to the residual LPC/NM electrolyte solution. In this case, 5 mL of cyclohexane and 20 mL of LPC/NM electrolyte solution were used. The yields of **3a**–**d** were excellent for at least five cycles, indicating the reusability of the LPC/NM electrolyte solution (Scheme 11). The amount of the LPC/M electrolyte solution necessary for the reaction was reduced significantly through this system.

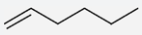
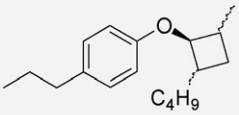
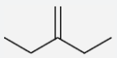
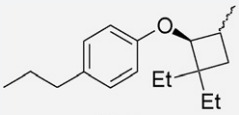
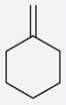
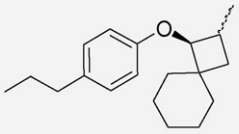
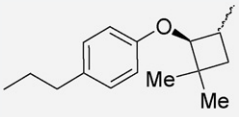
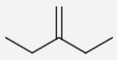
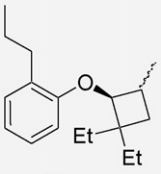
In order to demonstrate the generality of this system, the anodic oxidation of **1a**–**b** in the presence of an excess amount (20 mol equiv.) of several olefins **4**–**6** was attempted in the cyclohexane-based multiphase electrolyte solution composed of LPC and NM. In this case, 5 mL of cyclohexane and 20 mL of LPC/NM electrolyte solution were used (Table 1). After extraction of the corresponding [2+2] cycloadducts at the end of the reaction, the residual LPC/NM electrolyte solution was then reused for the next reaction. The overall experimental procedures are illustrated below (Scheme 12). Surprisingly, several [2+2] cycloadducts **7a**–**b**, **8a**–**b**, **9a**–**b** were obtained in excellent yields, which could be completely separated from the LPC/NM electrolyte solution via simple liquid–liquid extraction with cyclohexane to give the cycloadducts with high chemoselectivity. Prop-1-enyloxy-2-propylbenzene **10a**–**b** could also be introduced into this system to give the corresponding [2+2] cycloadducts **11a**–**b** in excellent yield. It should be emphasized that



Scheme 12. Overall experimental procedures.

Table 1
Anodic oxidation of **1a–b** in the presence of an excess amount of **2**, **4–6** in the cyclohexane-based multiphase electrolyte solution composed of LPC and NM (5 mL of cyclohexane and 20 mL of LPC/NM electrolyte solution were used, respectively).



Entry	Olefin	Products	Yield (%)[a]
1	 **2**	 **3a-d**	95 dr 2:1:1:1
2	 **4**	 **7a-b**	96 dr 1:1
3	 **5**	 **8a-b**	**79**[b] dr 1:1
4	 **6**	 **9a-b**	>99 dr 1:1
5[c]	 **4**	 **11a-b**	96 dr 1:1

[a] Determined by NMR.
[b] Non-cyclized product was obtained in 20% yield (see Ref. [36]).
[c] Prop-1-enyloxy-2-propylbenzene **10a–b** was used.

since all reactions were conducted in the residual LPC/NM electrolyte solution, the amount of the LPC/NM electrolyte solution used was effectively decreased, thus improving the productivity of the LPC/NM electrolyte solution significantly.

4. Conclusion

In conclusion, we constructed a continuous electrochemical synthetic system using a cyclohexane-based multiphase electrolyte solution composed of LPC and NM. In this system, the upper cyclohexane phase functioned as both the substrate supply and the product assembly phases, whereas the electrochemical reaction took place in the lower LPC/NM electrolyte solution phase, achieving spatial isolation of the electrolyte solution phase. Thus, the amount of the LPC/NM electrolyte solution used was decreased significantly, improving the productivity of the LPC/NM electrolyte solution. In this system, electrochemical [2+2] cycloaddition reactions proceeded effectively, and the products could be separated from the LPC/NM electrolyte solution via simple liquid–liquid extraction with cyclohexane to give the corresponding [2+2] cycloadducts with high chemoselectivity. A continuous supply of the substrates from the upper cyclohexane phase to the lower LPC/NM electrolyte solution phase played a key role in establishing this system.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.electacta.2010.02.085.

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