DOI: 10.1002/ejoc.201101313

Efficient Intermolecular Carbon–Carbon Bond-Formation Reactions Assisted by Surface-Condensed Electrodes

Yohei Okada,[a] Yusuke Yamaguchi,[a] and Kazuhiro Chiba*[a]

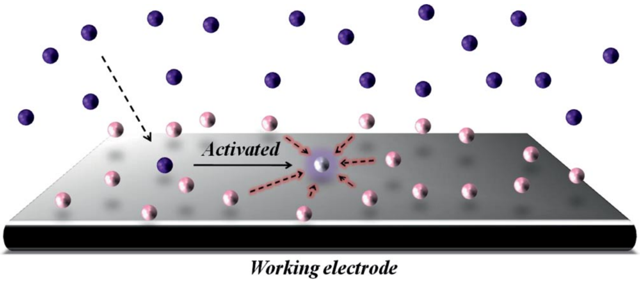
Keywords: Electrochemistry / Radicals / Cations / Cycloaddition

Transient radical cation intermediates generated at electrodes were effectively trapped by reaction partners noncovalently condensed at the surface of an electrode, enabling efficient intermolecular carbon–carbon bond-formation reactions. When the reactions were conducted with surface-condensed electrodes, high reaction efficiencies remained even in the presence of a significantly smaller amount of olefin nucleophiles. The concept of surface-condensed electrodes could offer opportunities for rapid intermolecular reactions.

Introduction

Intermolecular reactions are triggered by the collision of reaction component molecules of which the efficiency is essentially dependent upon the homogeneity of the reaction solution. Several mixing techniques have been established to achieve such homogeneity and realize effective intermolecular reactions. In this context, the concept of "flash chemistry" has been proposed, where extremely fast reactions occur by utilizing microreactors that can benefit from rapid mass and thermal transfer better than conventional macroreactors, which leads to enhancement in both the kinetics and selectivity of chemical transformations.[1] Microreactors have also been well combined with continuous flow systems to direct multistep chemical processes.[2] In particular, flash chemistry enables the use of transient intermediates prior to their decomposition, because the residence times can be controlled in the range of milliseconds to seconds by simply adjusting the flow rates and length of the microchannels.

On the other hand, several types of heterogeneous reaction fields have been created to offer unique opportunities for intermolecular reactions. Both supramolecular[3] and micellar systems[4] have been noncovalently constructed to facilitate various intermolecular reactions in their cavities or at their surfaces. Electrochemical approaches have also been employed to regulate chemical transformations at the surfaces of electrodes.[5] From the synthetic aspect, an electrochemical approach can be used to generate transient intermediates such as ions, radicals, or radical ions through electron transfer at the electrodes to afford not only functional group transformations, but also carbon–carbon bond-formation reactions. We have previously developed electron-transfer-induced intermolecular carbon–carbon bond-formation reactions.[6] When such intermolecular reactions are addressed, reaction partners noncovalently condensed at the electrode surfaces would be efficient to trap transient intermediates generated at the electrodes (Scheme 1).



Scheme 1. Concept of surface-condensed electrodes.

Results and Discussion

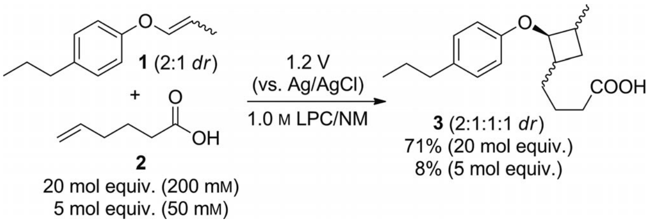
The present work began with investigation of an appropriate model to demonstrate the concept of surface-condensed electrodes. For this purpose, the electron-transfer-induced intermolecular [2+2] cycloaddition reaction between 1-(prop-1-en-1-yloxy)-4-propylbenzene (**1**) and hex-5-enoic acid (**2**) in $LiClO_4/CH_3NO_2$ (LPC/NM) electrolyte solution was selected. In this reaction, the anodically generated transient radical cation of **1** is trapped by **2** to give the corresponding [2+2] cycloadduct **3** in good yield as a diastereomeric mixture (Scheme 2). The radical cation of **1** has a short lifetime; therefore, an excess amount (20 mol equiv., 200 mM) of **2** was essential for effective trapping. The yields of **3** decreased rapidly in response to the

---

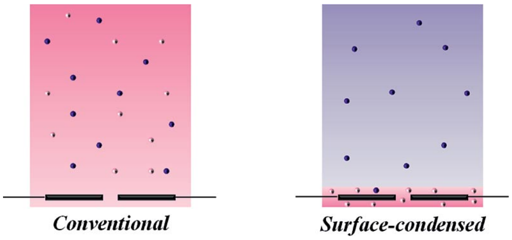
[a] Department of Applied Life Science,
Tokyo University of Agriculture and Technology,
3-5-8 Saiwai-cho, Fuchu, Tokyo 183-8509, Japan
Fax: +81-42-360-7167
E-mail: chiba@cc.tuat.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101313.

amount of **2**, whereas the use of a higher concentration of **1** resulted in a dimerization reaction. Following these results, we attempted to design the surface-condensed conditions at the electrodes. To this extent, a multiphase reaction solution was formed by the combination of a large amount of cyclohexane (*c*-Hex) and a small amount of LPC/NM electrolyte solution, in which the electrodes were soaked (Scheme 3). Less polar *c*-Hex and polar LPC/NM electrolyte solutions were immiscible, forming a multiphase reaction solution and **2** was expected to selectively dissolve into a polar electrolyte solution due to its free carboxyl group; therefore, **2** might be condensed at the surface of the electrodes.



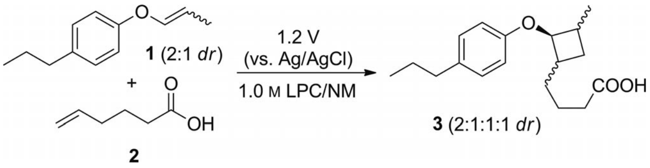
Scheme 2. Electron-transfer-induced intermolecular [2+2] cycloaddition reaction between 1-(prop-1-en-1-yloxy)-4-propylbenzene (**1**) and hex-5-enoic acid (**2**).



Scheme 3. Surface-condensed conditions based on a multiphase reaction solution formed by the combination of a large amount of *c*-Hex (blue) and a small amount of LPC/NM electrolyte solution (red).

When the electron-transfer-induced intermolecular [2+2] cycloaddition reaction between **1** and **2** was conducted with surface-condensed electrodes, **3** was obtained in high yield as a diastereomeric mixture (Table 1). It should be noted that a relatively small amount (5 mol equiv.) of **2** could also effectively trap the transient radical cation of **1** to afford **3** in good yield as a diastereomeric mixture, which is in marked contrast to the result achieved through conventional "nonsurface-condensed" electrolysis. Moreover, the same level of reaction efficiency was maintained even in the presence of a smaller amount (2 mol equiv.) of **2**. In both cases, more than 95% of **2** was dissolved in a small amount of electrolyte solution (ca. 200 mM, respectively), into which the electrodes were soaked, and therefore, condensed at the surface of electrodes, whereas more than 95% of **1** was dissolved in a large amount of *c*-Hex.

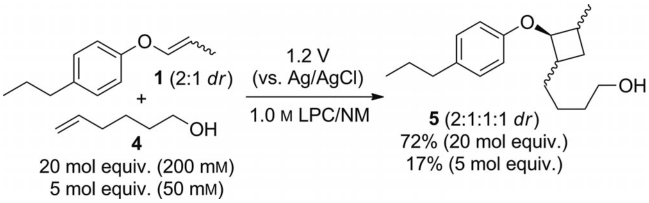
Table 1. Electron-transfer-induced intermolecular [2+2] cycloaddition reaction between 1-(prop-1-en-1-yloxy)-4-propylbenzene (**1**) and hex-5-enoic acid (**2**) with the use of surface-condensed electrodes.



Reaction partner **2** [equiv.]	Yield [%]	
	Conventional[a]	Surface condensed[b]
20	71	85
5	8	63 (65)
2	6	37 (72)

[a] Yield using monophasic electrolysis. [b] Yield using multiphasic electrolysis (based on consumed starting material).

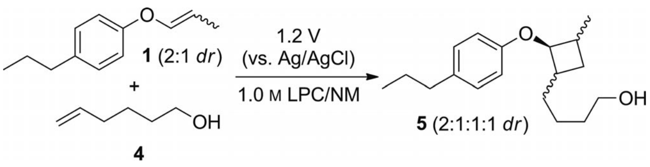
Subsequently, the electron-transfer-induced intermolecular [2+2] cycloaddition reaction between **1** and hex-5-en-1-ol (**4**) in LPC/NM electrolyte solution was attempted (Scheme 4). Although the anodic oxidation of **1** in the presence of an excess amount (20 mol equiv., 200 mM) of **4** gave the corresponding [2+2] cycloadduct **5** in good yield as a diastereomeric mixture, a relatively small amount (5 mol equiv.) of **4** was less effective for trapping the transient radical cation of **1**. When this reaction was conducted with surface-condensed electrodes, **5** was produced in excellent yield as a diastereomeric mixture, even in the presence of a relatively small amount (5 mol equiv.) of **4** (Table 2). Furthermore, high reaction efficiency remained even in the presence of a smaller amount (2 mol equiv.) of **4**. In both cases, more than 99% of **4** was dissolved in a small amount of the electrolyte solution (ca. 200 mM, respectively), which indicates that **4** was efficiently condensed at the surface of the electrodes, whereas more than 95% of **1** was dissolved in a large amount of *c*-Hex.



Scheme 4. Electron-transfer-induced intermolecular [2+2] cycloaddition reaction between 1-(prop-1-en-1-yloxy)-4-propylbenzene (**1**) and hex-5-en-1-ol (**4**).

With these results in hand, finally the electron-transfer-induced intermolecular [2+2] cycloaddition reactions between **1** and hex-5-en-2-one (**6**) or but-3-en-1-yl acetate (**8**) were attempted with the use of surface-condensed electrodes (Table 3). Although the polarities of these olefin nucleophiles were expected to be much lower than those of **2** or **4**, more than 90% (ca. 180 mM) of **6** and **8** were dissolved in a small amount of electrolyte solution, respectively, which could still efficiently trap the transient radical cation

Table 2. Electron-transfer-induced intermolecular [2+2] cycloaddition reaction between 1-(prop-1-en-1-yloxy)-4-propylbenzene (**1**) and hex-5-en-1-ol (**4**) with the use of surface-condensed electrodes.

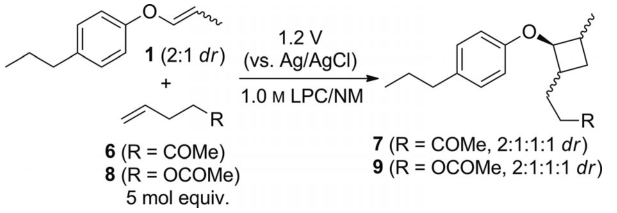


Reaction partner **4** [equiv.]	Yield [%] Conventional[a]	Surface condensed[b]
20	72	95
5	17	97
2	14	80 (96)

[a] Yield using monophasic electrolysis. [b] Yield using multiphasic electrolysis (based on consumed starting material).

of **1**. The corresponding cycloadducts **7** and **9** were obtained in good yields as diastereomeric mixtures, respectively, even in the presence of relatively small amounts (5 mol equiv.) of **6** or **8**.

Table 3. Electron-transfer-induced intermolecular [2+2] cycloaddition reaction between 1-(prop-1-en-1-yloxy)-4-propylbenzene (**1**) and hex-5-en-2-one (**6**) or but-3-en-1-yl acetate (**8**) with the use of surface-condensed electrodes.



Reaction partner	Yield [%] Conventional[a]	Surface condensed[b]
6 (R = COMe)	35	65 (77)
8 (R = OCOMe)	28	65 (70)

[a] Yield using monophasic electrolysis. [b] Yield using multiphasic electrolysis (based on consumed starting material).

Conclusions

We have demonstrated the concept of surface-condensed electrodes that enables efficient intermolecular carbon–carbon bond-formation reactions. Reaction partners were noncovalently condensed at the electrode surfaces, which could effectively trap transient radical cation intermediates generated at the electrodes to offer opportunities for rapid intermolecular reactions. The concept of surface-condensed electrodes would be a significant aid for directing intermolecular reactions.

Experimental Section

General Procedure: A multiphase reaction solution (25 mL) was formed by combining a large amount of *c*-Hex (20–23 mL) and a small amount of 1.0 M LPC/NM electrolyte solution (2–5 mL), in which carbon felt (CF) electrodes (10 mm × 10 mm) were soaked by using an undivided reaction cell capped with a septum. Electrolysis was performed at 1.2 V (vs. Ag/AgCl), which was measured by cyclic voltammetry with the use of a glassy carbon working electrode, a platinum wire counter electrode, and a Ag/AgCl reference electrode. After the electrolysis (1–3 F/mol), the reaction mixture was poured into EtOAc, and the EtOAc solution was successively washed with brine. The organic layer was dried with anhydrous $MgSO_4$. After filtration and evaporation under reduced pressure, the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to give products. Partition ratios in the multiphase reaction solution were determined by NMR, based on internal standards.

Supporting Information (see footnote on the first page of this article): General information, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra of new compounds.

Acknowledgments

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

---

[1] a) Y. Tomida, A. Nagaki, J. Yoshida, *J. Am. Chem. Soc.* **2011**, *133*, 3744–3747; b) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi, J. Yoshida, *Angew. Chem. Int. Ed.* **2010**, *49*, 7543–7547; c) P. J. Nieuwland, K. Koch, N. van Harskamp, R. Wehrens, J. C. M. van Hest, F. P. J. T. Rutjes, *Chem. Asian J.* **2010**, *5*, 799–805; d) J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450–7459; e) J. Yoshida, *Chem. Commun.* **2005**, 4509–4516.

[2] a) S. Mozharov, A. Nordon, D. Littlejohn, C. Wiles, P. Watts, P. Dallin, J. M. Girkin, *J. Am. Chem. Soc.* **2011**, *133*, 3601–3608; b) Y. S. M. Vaske, M. E. Mahoney, J. P. Konopelski, D. L. Rogow, W. J. McDonald, *J. Am. Chem. Soc.* **2010**, *132*, 11379–11385; c) D. Horii, T. Fuchigami, M. Atobe, *J. Am. Chem. Soc.* **2007**, *129*, 11692–11693; d) K. Saito, K. Ueoka, K. Matsumoto, S. Suga, T. Nokami, J. Yoshida, *Angew. Chem. Int. Ed.* **2011**, *50*, 5153–5156; e) A. Sniady, M. W. Bedore, T. F. Jamison, *Angew. Chem. Int. Ed.* **2011**, *50*, 2155–2158; f) J. R. Naber, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2010**, *49*, 9469–9474; g) P. P. Lange, L. J. Gooßen, P. Podmore, T. Underwood, N. Sciammetta, *Chem. Commun.* **2011**, *47*, 3628–3630; h) A. G. O'Brien, F. Lévesque, P. H. Seeberger, *Chem. Commun.* **2011**, *47*, 2688–2690; i) F. Amemiya, K. Fuse, T. Fuchigami, M. Atobe, *Chem. Commun.* **2010**, *46*, 2730–2732.

[3] a) T. Murase, S. Horiuchi, M. Fujita, *J. Am. Chem. Soc.* **2010**, *132*, 2866–2867; b) Y. Nishioka, T. Yamaguchi, M. Kawano, M. Fujita, *J. Am. Chem. Soc.* **2008**, *130*, 8160–8161; c) K. Ikemoto, Y. Inokuma, M. Fujita, *Angew. Chem. Int. Ed.* **2010**, *49*, 5750–5752; d) M. Yoshizawa, J. K. Klosterman, M. Fujita, *Angew. Chem.* **2009**, *121*, 3470; *Angew. Chem. Int. Ed.* **2009**, *48*, 3418–3438; e) T. Iwasawa, R. J. Hooley, J. Rebek Jr., *Science* **2007**, *317*, 493–496; f) M. D. Pluth, R. G. Bergman, K. N. Raymond, *Science* **2007**, *316*, 85–88; g) D. Fiedler, D. H. Leung, R. G. Bergman, K. N. Raymond, *Acc. Chem. Res.* **2005**, *38*, 349–358; h) F. Hof, S. L. Craig, C. Nuckolls, J. Rebek Jr., *Angew. Chem.* **2002**, *114*, 1556; *Angew. Chem. Int. Ed.* **2002**, *41*, 1488–1508; i) D. L. Caulder, K. N. Raymond, *Acc. Chem. Res.* **1999**, *32*, 975–982; j) J. Kang, J. Rebek Jr., *Nature* **1997**, *385*, 50–52.

[4] a) K. Manabe, S. Iimura, X.-M. Sun, S. Kobayashi, *J. Am. Chem. Soc.* **2002**, *124*, 11971–11978; b) K. Manabe, X.-M. Sun, S. Kobayashi, *J. Am. Chem. Soc.* **2001**, *123*, 10101–10102; c) K. Nishimoto, S. Kim, Y. Kitano, M. Tada, K. Chiba, *Org.*

Lett. **2006**, *8*, 5545–5547; d) K. Chiba, Y. Kono, M. Kitayama, R. Uchiyama, S. Kim, Y. Kitano, M. Tada, *Electrochem. Commun.* **2001**, *3*, 63–66.

[5] a) H.-C. Xu, K. D. Moeller, *J. Am. Chem. Soc.* **2010**, *132*, 2839–2844; b) H.-C. Xu, K. D. Moeller, *J. Am. Chem. Soc.* **2008**, *130*, 13542–13543; c) J. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, *Chem. Rev.* **2008**, *108*, 2265–2299; d) K. Matsumoto, S. Fujie, S. Suga, T. Nokami, J. Yoshida, *Chem. Commun.* **2009**, 5448–5450; e) T. Sawamura, S. Kuribayashi, S. Inagi, T. Fuchigami, *Adv. Synth. Catal.* **2010**, *352*, 2757–2760; f) K. Hosoi, Y. Kuriyama, S. Inagi, T. Fuchigami, *Chem. Commun.* **2010**, *46*, 1284–1286; g) Y. S. Park, R. D. Little, *Electrochim. Acta* **2009**, *54*, 5077–5082; h) Y. S. Park, R. D. Little, *J. Org. Chem.* **2008**, *73*, 6807–6815; i) R. Francke, G. Schnakenburg, D. Cericola, R. Kötz, S. R. Waldvogel, *Chem. Eur. J.* **2011**, *17*, 3082–3085; j) J. Kulisch, M. Nieger, F. Stecker, A. Fischer, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2011**, *50*, 5564–5567; k) A. V. Shtelman, J. Y. Becker, *J. Org. Chem.* **2011**, *76*, 4710–4714.

[6] a) T. Nokami, K. Ohata, M. Inoue, H. Tsuyama, A. Shibuya, K. Soga, M. Okajima, S. Suga, J. Yoshida, *J. Am. Chem. Soc.* **2008**, *130*, 10864–10865; b) T. Maruyama, Y. Mizuno, I. Shimizu, S. Suga, J. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 1902–1903; c) F. Amemiya, K. Fuse, T. Fuchigami, M. Atobe, *Chem. Commun.* **2010**, *46*, 2730–2732; d) R. Asami, T. Fuchigami, M. Atobe, *Chem. Commun.* **2008**, 244–246; e) M. Ohkoshi, J. Michinishi, S. Hara, H. Senboku, *Tetrahedron* **2010**, *66*, 7732–7737; f) Y. Yamauchi, S. Hara, H. Senboku, *Tetrahedron* **2010**, *66*, 473–479; g) A. Kirste, G. Schnakenburg, F. Stecker, A. Fischer, S. R. Waldvogel, *Angew. Chem.* **2010**, *122*, 983; *Angew. Chem. Int. Ed.* **2010**, *49*, 971–975; h) J. Barjau, G. Schnakenburg, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1415–1419; i) Y. Okada, T. Yoshioka, M. Koike, K. Chiba, *Tetrahedron Lett.* **2011**, *52*, 4690–4693; j) Y. Okada, A. Nishimoto, R. Akaba, K. Chiba, *J. Org. Chem.* **2011**, *76*, 3470–3476; k) Y. Okada, K. Chiba, *Electrochim. Acta* **2011**, *56*, 1037–1042; l) Y. Okada, K. Chiba, *Electrochim. Acta* **2010**, *55*, 4112–4119; m) Y. Okada, R. Akaba, K. Chiba, *Tetrahedron Lett.* **2009**, *50*, 5413–5416; n) Y. Okada, R. Akaba, K. Chiba, *Org. Lett.* **2009**, *11*, 1033–1035.

Received: September 9, 2011