

An Oxidative Carbon–Carbon Bond  
Formation System in Cycloalkane-Based  
Thermomorphic Multiphase Solution

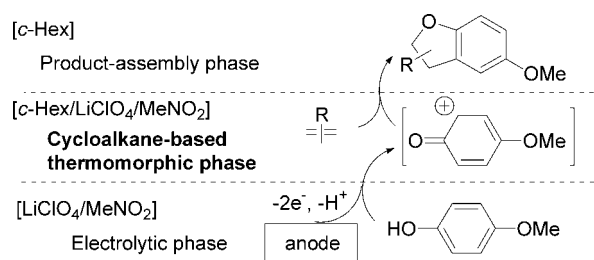
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## ABSTRACT



A selective anodic oxidation system in which a carbocation intermediate is generated exclusively by use of a temperature-controlled multiphase solution to separate the different stages of the reaction from each other and from the products is described. The formation of a thermomorphic middle layer in an electrolytic solution composed of *c*-Hex and LPC/MeNO<sub>2</sub> results in enhanced interaction between aliphatic alkenes and polar unstable cation.

It has recently been shown that electrochemical reactions provide an efficient means of carbon–carbon bond formation.<sup>1</sup> Anodic electrochemistry is used to generate extremely useful carbocation intermediates for the construction of a wide variety of carbon skeletons under mild conditions.<sup>2</sup> However, with conventional electrochemical systems, it is often difficult to selectively generate reactive carbocation intermediates by anodic oxidation of the target precursor substrates in the presence of other species, such as nucleophiles and reaction products, because they are also easily oxidized during the anodic carbon–carbon bond formation reaction.

To address this problem, efforts have been made to develop effective methodologies for direct oxidative C–C bond formation reactions.<sup>3</sup> In particular, microflow reactors

allow precise control of reactive intermediates in a designed reaction space, thereby facilitating highly selective reactions.<sup>4</sup> In previous work, we developed a selective anodic C–C bond formation system in which the incorporation of PTFE (poly tetrafluoroethylene) resin supports in a lithium perchlorate/nitromethane (LPC/MeNO<sub>2</sub>) medium enabled cy-

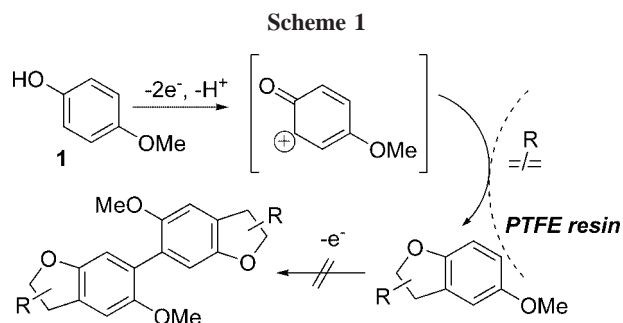
(1) For a recent review of electroorganic synthesis, see: (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (c) Moeller, K. D. In *Organic Electrochemistry*; Schafer, H. J., Ed.; Wiley-VCH: Weinheim, Germany, **2004**; Vol. 8, p 277. (d) Huang, Y.; Moeller, K. D. *Tetrahedron* **2006**, *62*, 6536. (e) Tang, F.; Moeller, K. D. *J. Am. Chem. Soc.* **2007**, *129*, 12414.

(2) (a) Schaefer, H. J. In *Organic Electrochemistry*, 4th ed.; Lund, H., Hammerich, O., Eds.; Marcel Dekker: New York, **2001**; pp 883. (b) Little, R. D.; Schwabe, M. K. In *Electrochemistry VI: Electroorganic Synthesis: Bond Formation at Anode and Cathode, Topics in Current Chemistry 185*; Steckhan, E., Ed.; Springer: Berlin, **1997**; p 1. (c) Quideau, S.; Pouysegue, L.; Deffieux, D. *Curr. Org. Chem.* **2004**, *8*, 113.

(3) (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 30. (c) Yoshida, J.; Suga, S. *Chem.—Eur. J.* **2002**, *8*, 2650. (d) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (e) Suga, S.; Nishida, T.; Yamada, D.; Nagaki, A.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14338. (f) Okajima, M.; Suga, S.; Itami, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 6930.

(4) (a) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 7941. (b) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *QSAR Comb. Sci.* **2005**, *24*, 728. (c) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 11666.

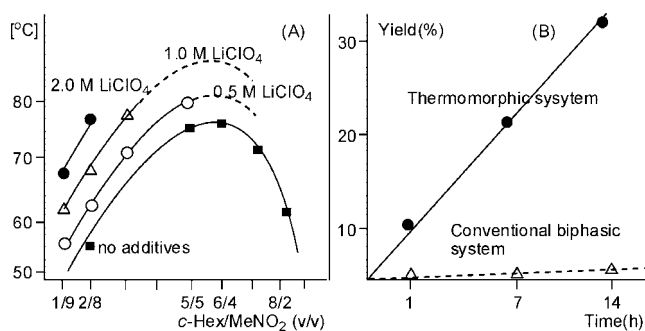
coaddition of phenoxonium cations with aliphatic alkenes, allowing the construction of various dihydrobenzofuran derivatives while avoiding overoxidation of the products (Scheme 1).<sup>5</sup> The success of this approach relied on the



presence of two separate “fields” in the reaction solution—one for C–C bond formation and one for product assembly—which was based on the unique properties of the LPC/MeNO<sub>2</sub> solution system. However, these fields are limited to the PTFE solid-phase surface. Thus, the targeted creation of a specific field may enhance the interaction between the cationic intermediates and trapped nucleophiles. Enhancing the affinity of the synthesized product for a single phase is also desirable.

During recent research on thermomorphic processes, we found that cyclohexane (*c*-Hex) shows thermosensitive phase transitions with a wide variety of typical polar organic solvents under moderate conditions.<sup>6</sup> It was thought that a methodology involving the use of an appropriate cycloalkane-based thermomorphic (CBT) system and a LPC/MeNO<sub>2</sub> medium would overcome the problems of interfacial reactivity and affinity associated with solid–liquid conditions. Furthermore, this system was expected to be highly useful in enabling selective separation of the product into the cycloalkane phase, which might prevent overoxidation. This gave us an incentive to develop an effective electrochemical synthetic system with a CBT process. We report herein an oxidative C–C bond formation reaction system in a multiphase solution using a CBT method.

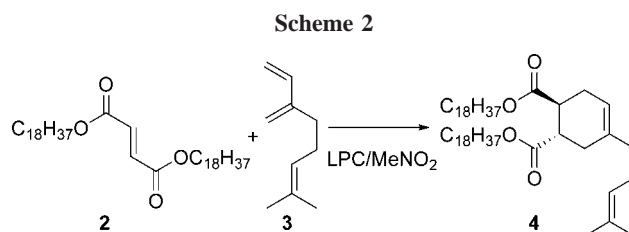
We initially studied the relationship between the miscible temperature and the ratio of *c*-Hex to MeNO<sub>2</sub>. As shown in Figure 1A, the maximum miscible temperature was observed at a *c*-Hex/MeNO<sub>2</sub> ratio of 6:4 (v/v), and the miscible temperature decreased as the *c*-Hex/MeNO<sub>2</sub> ratio decreased. For example, at 25 °C, a 2:8 (v/v) *c*-Hex/MeNO<sub>2</sub> solution consisted of an upper *c*-Hex phase and a lower MeNO<sub>2</sub> phase, but after heating to 60 °C, mixing occurred to form a



**Figure 1.** (A) Effect of solvent composition on miscible temperature. (B) Effect of different media on the rate of the Diels–Alder reaction between dienophile **2** and diene **3**.

homogeneous phase. Between ca. 50 and 80 °C, a reversible phase transition was clearly observed. Notably, the system consisting of *c*-Hex/0.5–2.0 M LPC/MeNO<sub>2</sub> was found to exhibit thermomorphic phase transition. This allows for an effective CBT process at a temperature and solvent ratio suitable for phase separation according to target reaction conditions.

In order to compare the CBT method with a conventional biphasic reaction and thus determine the effect of the medium used, a Diels–Alder reaction between dienophile **1** and myrcene **2** was examined (Scheme 2). As shown in Figure



1B, in a thermomorphic solution system formed by a combination of *c*-Hex and 1.0 M LPC/MeNO<sub>2</sub>, the Diels–Alder reaction showed moderate acceleration (33%, 14 h), while the reaction rate was very low in a conventional biphasic solution system using *n*-hexane (3%, 14 h). These results show that cyclohexane mixes successfully with the highly polar LPC/MeNO<sub>2</sub> solution, resulting in an effective thermomorphic medium.

It was expected that this system might stabilize unstable intermediates during anodic dihydrobenzofuran synthesis, thus accelerating the target reaction, and might also facilitate separation of the product from the electrolytic solution via simple liquid–liquid extraction. Furthermore, it was suggested that the introduction of a heated area at the liquid–liquid interface of the *c*-Hex/LPC/MeNO<sub>2</sub> electrolytic solution, which is biphasic at 25 °C, might result in the concomitant presence of three solution phases (Table 1), which would allow for selective oxidation of polar substrates in LPC/MeNO<sub>2</sub> and C–C bond formation reaction and product separation in *c*-Hex.

(5) (a) Fukuda, M.; Kim, S.; Kitano, Y.; Tada, M. *J. Org. Chem.* **1999**, *64*, 7654. (b) Chiba, K.; Jinno, M.; Kuramoto, R.; Tada, M. *Tetrahedron Lett.* **1998**, *39*, 5527.

(6) (a) Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345. (b) Bergbreiter, D. E.; Osburn, P. L.; Smith, T.; Li, C.; Frels, J. D. *J. Am. Chem. Soc.* **2003**, *125*, 6254. (c) Bergbreiter, D. E.; Li, J. *Chem. Commun.* **2004**, *1*, 42. (d) Huang, X.; Witte, K. L.; Bergbreiter, D. E.; Wong, C. H. *Adv. Synth. Catal.* **2001**, *343*, 675. (e) Chiba, K.; Kono, Y.; Kim, S.; Nishimoto, K.; Kitano, Y.; Tada, M. *Chem. Commun.* **2002**, 1766. (f) Hayashi, K.; Kim, S.; Kono, Y.; Tamura, M.; Chiba, K. *Tetrahedron Lett.* **2006**, *47*, 171.

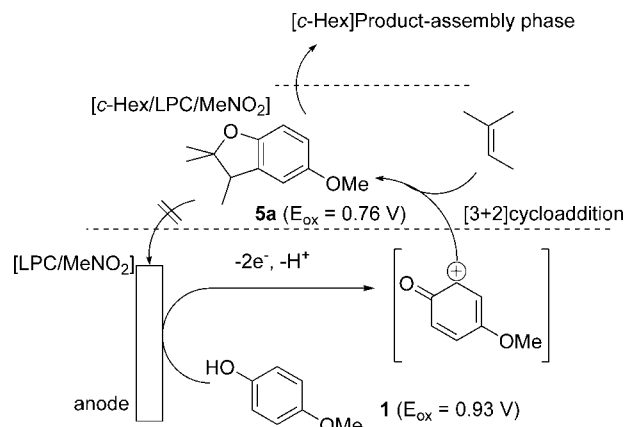
**Table 1.** Anodic Intermolecular [3 + 2] Cycloaddition Reactions Using a Solution Multiphase System<sup>a</sup>

Entry	Phenol	Alkene	Product	Yield(%) <sup>b</sup>
1	1			97
2	1			88
3	1			79
4	1			86
5	6			93

<sup>a</sup> All reactions were performed under constant current conditions (1.0 mA/cm<sup>2</sup>, 2.2 F/mol). <sup>b</sup> Isolated yield in the *c*-Hex layer.

To examine this, we developed a selective anodic C–C bond formation reaction system in a multiphase solution using a CBT method, in which electrolytic benzofuran synthesis was carried out as follows. The upper and lower layers of an electrolytic solution were cooled to 25 °C, while the middle layer was heated to 60 °C. Methoxyphenol derivatives **1** and **6** were oxidized in the presence of aliphatic alkenes using a glassy carbon anode, which was situated at the lower area. As shown in Table 1, the expected [3 + 2] cycloaddition reactions proceeded successfully to afford dihydrobenzofuran skeletons **5a–e** in the *c*-Hex phase in excellent yields. In contrast, when *n*-Hex was used at 60 °C, the desired product **5a** was obtained in very low yield (26%), and no dimerized product was observed. These results show that this system allows effective trapping of anodically generated phenoxonium cations with the relatively unreactive aliphatic alkenes, followed by the corresponding reactions. The CBT phase in the middle layer plays a significant role by enhancing the interaction between the polar carbocations in the electrolytic phase and the hydrophobic nucleophiles

**Scheme 3**



in the *c*-Hex phase (Scheme 3). In particular, selective distribution of the electron-rich trisubstituted dihydrobenzofuran ring system (e.g., **5a**,  $E_{\text{ox}} = 0.76$  V) in the *c*-Hex phase allows selective oxidation of the starting material **1** ( $E_{\text{ox}} = 0.91$  V), generating the target cations exclusively while avoiding overoxidation of the products, which are distributed only into the upper and middle layers. The remarkable affinity of the resulting cycloadducts for the *c*-Hex phase greatly facilitates their isolation in highly pure form from the electrolytic solution via simple liquid–liquid extraction.

In conclusion, we have developed a selective anodic oxidation system which can generate the appropriate carbocation exclusively by use of a temperature-controlled multiphase solution to separate the different stages of the reaction from each other and from the products. The formation of a thermomorphic middle layer in an electrolytic solution composed of *c*-Hex and LPC/MeNO<sub>2</sub> results in enhanced interaction between hydrophobic aliphatic alkenes and polar unstable cation intermediates in the expanded solution-phase field, effectively accelerating the target C–C bond formation reaction. In addition, this system facilitates separation of the desired products from the electrolytic solution at the end of the reaction via simple liquid–liquid extraction, thereby eliminating the need for a cumbersome electrolyte removal process. The applicability and limitations of this system for various electrolytic carbon–carbon bond formation reactions are currently under investigation.

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**Supporting Information Available:** Experimental procedures and characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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