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Cyclohexane-Based Liquid-Biphasic Systems for Organic Electrochemistry

Yohei Okada and Kazuhiro Chiba

Additional information is available at the end of the chapter

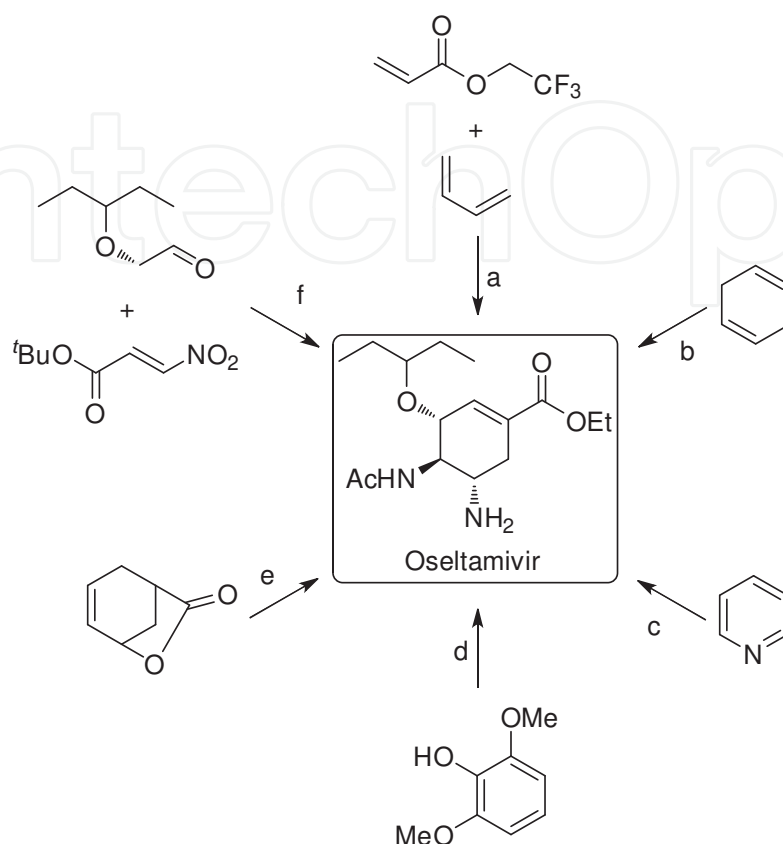
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1. Introduction

Organic chemistry research comprises three fundamental elements, including synthesis, separation, and analysis. The long and untiring efforts of synthetic chemists have established countless useful reactions to enable the preparation of nearly anything. Beneficial and complex structures can be elaborated from abundant and simple starting materials. For example, several elegant synthetic strategies for Oseltamivir (commonly known as “Tamiflu”), an effective antiviral drug for the flu virus, have been proposed (Fig. 1) [1-6]. With concerns about the environmental aspects of these syntheses, various green processes, e.g., transition-metal-free transformations or the use of water as a reaction solvent, have been studied intensively. In addition, outstanding technological advances have been achieved in the field of analysis, realizing numerous powerful methods. Spectroscopy in particular can yield much information about the structure of both naturally-occurring and artificial compounds.

In these contexts, separation has assumed a key role in organic chemistry. It is generally meaningless if the desired compound cannot be isolated from the reaction mixture even though it was prepared and characterized in a precise manner. Typically, recrystallization and silica gel column chromatography are employed as isolation methodologies in industrial and academic fields. While these separation techniques offer high-performance compound isolation, time-consuming preliminary experiments and the use of large amounts of silica gel are required. Solid-phase techniques are one solution to provide great advantages with respect to compound separation and have also proven to be effective for automated synthesis and combinatorial chemistry. Reaction substrates are generally bound to a solid-phase, enabling their separation from the reaction mixture merely through filtration and washing with solvents. Based on this strategy, efficient multistep chemical transformations, especially for peptide synthesis, can be accomplished. Additionally, the immobilization of

reaction catalysts on a solid-phase is efficient for their consecutive recycling, and can also serve as a promising application in combination with a flow strategy.



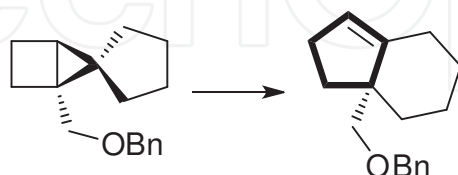
- (a) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310-6311.
 (b) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312-6313.
 (c) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5734-5736.
 (d) Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895-4902.
 (e) Trost, B. M.; Zhang, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 3759-3761.
 (f) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 1304-1307.

Figure 1. Synthetic strategies for Oseltamivir

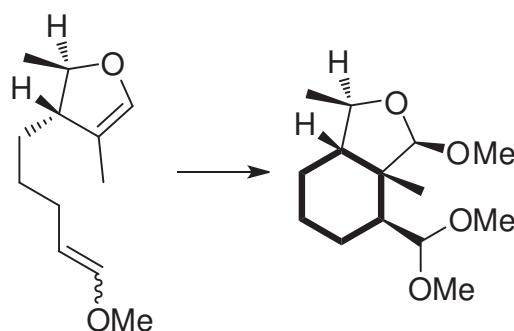
In addition to the solid-phase technique, the liquid-biphasic technique can also provide a facile separation of compounds by simple liquid-liquid extraction. A representative liquid-biphasic technique is based on the insolubility of perfluorinated hydrocarbons with both polar and less-polar organic solvents, known as fluorous systems [7-11]. In these systems, fluorous compounds, including substrates, products, and catalysts, or designed fluorous platforms, are preferentially dissolved into the fluorous phase to enable their rapid separation. Moreover, “thermomorphic” systems have been developed to offer unique liquid-biphasic separation techniques that change thermally from biphasic conditions to monophasic conditions [12-19].

In organic electrochemistry, electrodes have been utilized as solid-phase redox reagents to trigger either one- or two-electron transfers that afford various functional group transforma-

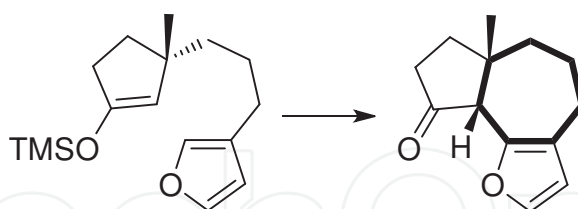
tions and a wide variety of carbon-carbon bond formations in a controlled manner [20-25]. In particular, there is good chemistry between electrochemical approaches and cyclic compounds to produce complex ring systems in one step. For example, five-, six-, and seven-membered rings can be constructed through ring rearrangement or intramolecular cycloaddition (Fig. 2) [26-28]. We have also been developing a series of electrochemical intermolecular cycloadditions initiated by anodic oxidation to give four-, five, and six-membered rings (Fig. 3) [29-31].



Park, Y. S.; Wang, S. C.; Tantillo, D. J.; Little, R. D. *J. Org. Chem.* **2007**, 72, 4351-4357.



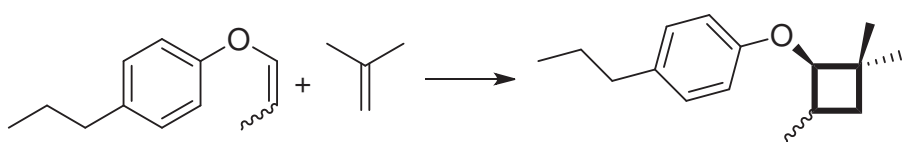
Tang, F.; Moeller, K. D. *J. Am. Chem. Soc.* **2007**, 129, 12414-12415.



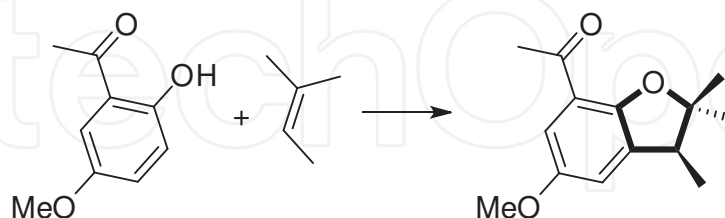
Sperry, J. B.; Wright, D. L. *J. Am. Chem. Soc.* **2005**, 127, 8034-8035.

Figure 2. Electrochemical intramolecular five-, six-, and seven-membered ring formations

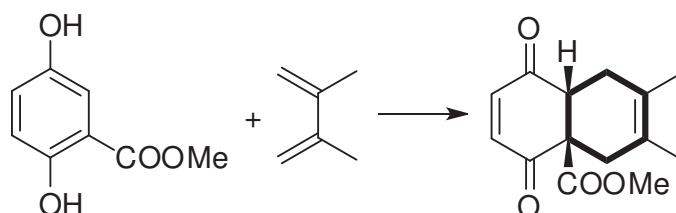
Although electrodes can be rapidly removed from the reaction mixtures after the completion of electrochemical transformations, the separation of products from supporting electrolytes that are necessary for imparting electrical conductivity to polar organic solvents is still required. In order to address this problem, various ingeniously designed electrochemical reaction systems have been developed [32-36]. In this chapter, we describe cyclohexane-based liquid-biphasic systems as unique separation techniques that are well-combined with organic electrochemistry. The combination of electrodes as solid-phase redox reagents and cyclohexane-based liquid-biphasic systems has paved the way for organic electrochemistry.



Arata, M.; Miura, T.; Chiba, K. *Org. Lett.* **2007**, 9, 4347-4350.



Kim, S.; Hirose, K.; Uematsu, J.; Mikami, Y.; Chiba, K. *Chem. Eur. J.* **2012**, 18, 6284-6288.

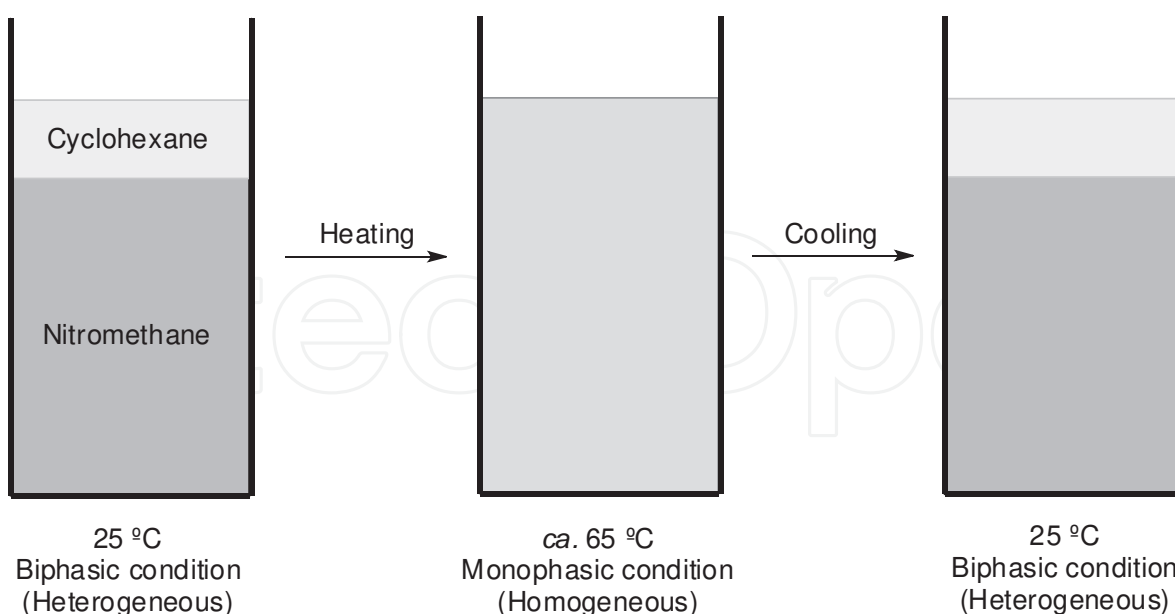


Nishimoto, K.; Okada, Y.; Kim, S.; Chiba, K. *Electrochim. Acta* **2011**, 56, 10626-10631.

Figure 3. Electrochemical intermolecular four-, five-, and six-membered ring formations

2. Cyclohexane-based liquid-biphasic systems

Cyclohexane-based liquid-biphasic systems have their roots in the initial discovery that cyclohexane has unique thermomorphic properties [37]. Numerous investigations aimed at constructing new liquid-biphasic systems have led to the finding that cyclohexane can be used to successfully form thermomorphic biphasic solutions with typical polar organic solvents and that the regulation of their separation and mixing can be achieved by moderate control in a practical temperature range. A 1:4 (v/v) mixture of cyclohexane and nitromethane, for example, exhibits biphasic conditions at 25 °C, then forms a monophasic condition at *ca.* 60 °C and higher (Fig. 4). In this system, the thermally-mixed monophasic condition can serve as an effective homogeneous reaction field between a less polar substrate that dissolves selectively into the cyclohexane phase and a polar substrate that dissolves selectively into the nitromethane phase. This monophasic solution is cooled to reform the biphasic condition after completion of the reaction, and the hydrophobic products or designed hydrophobic platforms dominantly partition into the cyclohexane phase, which can be recovered rapidly [38-41].



Chiba, K.; Kono, Y.; Kim, S.; Nishimoto, K.; Kitano, Y.; Tada, M. *Chem. Commun.* **2002**, 1766-1767.

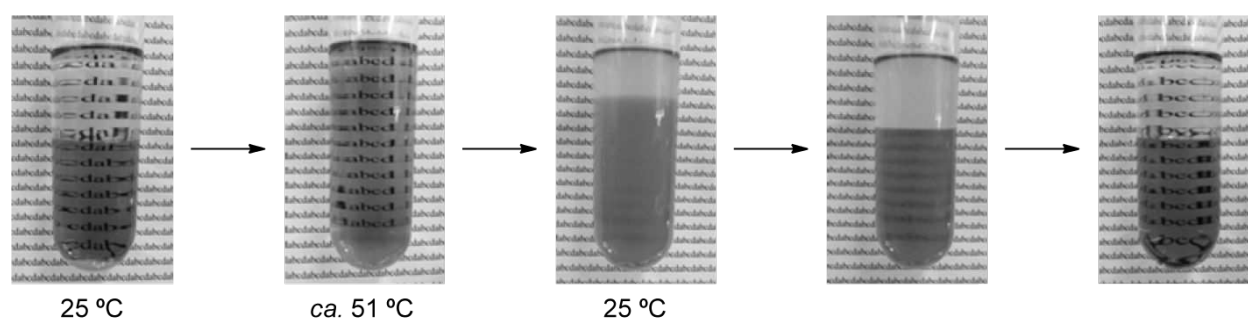
Figure 4. Thermomorphing property of cyclohexane in combination with nitromethane

Moreover, several other polar organic solvents can be introduced into the cyclohexane-based liquid-biphasic system and their phase switching temperatures are tunable based on the choice of polar organic solvents and their ratio to cyclohexane. For instance, a 1:3 (v/v) mixture of cyclohexane and acetonitrile is heated to form a monophasic condition at *ca.* 53 °C and higher, whereas heating to *ca.* 40 °C and higher is enough for a 1:1 (v/v) mixture of cyclohexane and methanol to be thermally mixed into a monophasic condition. In light of these studies, organic electrochemistry will benefit from cyclohexane-based liquid-biphasic systems, especially over the issue of separation.

3. Kolbe-coupling assisted by cyclohexane-based liquid-biphasic systems

In order to apply cyclohexane-based liquid-biphasic techniques to organic electrochemistry, we initially investigated a wide variety of compositions of electrolyte solutions composed of polar organic solvents and supporting electrolytes that showed practical thermomorphing properties in combination with cyclohexane. Through numerous trials, we found that a 1:1:2:4 (v/v/v/v) mixture of pyridine, methanol, acetonitrile, and cyclohexane could be thermally mixed to form a monophasic condition even in the presence of saturated potassium hydroxide as a supporting electrolyte. Heating to *ca.* 48 °C and higher was sufficient to create monophasic conditions, while biphasic conditions were reformed when the solvent mixture was cooled to 25 °C [42]. Furthermore, a 0.10 M concentration of lithium perchlorate could be employed as a supporting electrolyte to show reversible thermal phase switching (Fig. 5).

With these results in hand, Kolbe-coupling, known as a representative electrochemical reaction in organic chemistry, was then carried out in the cyclohexane-based liquid-biphasic system (Fig. 6). Essentially, electrochemical approaches have the requirement that both substrates and products should be soluble in polar electrolyte solutions. This is due to the following reasons. First, electron transfer events take place only at the surface of the electrodes such that insoluble compounds are unable to access their neighborhood, which means that the use of hydrophobic compounds is generally restricted. Second, the formation of insoluble hydrophobic products during the electrochemical transformations might result in electrode passivation in which the surface of the electrodes is covered with polymeric films that severely suppress electric current. In this regard, the thermally-mixed monophasic conditions in the cyclohexane-based liquid-biphasic system can be deemed as a “less-polar” electrolyte solution because it contains an equal volume of less-polar cyclohexane as the polar electrolyte solution.



A 1:1:2:4 (v/v/v/v) mixtures of pyridine, methanol, acetonitrile, and cyclohexane in the presence of 0.10 M concentration of lithium perchlorate as supporting electrolyte was gradually heated with stirring. The upper cyclohexane phase was colored by coenzyme Q10 and the lower electrolyte solution phase was colored by methylene blue.

Okada, Y.; Kamimura, K.; Chiba, K. *Tetrahedron* **2012**, 68, 5857-5862.

Figure 5. Reversible thermal phase switching of the cyclohexane-based liquid-biphasic system

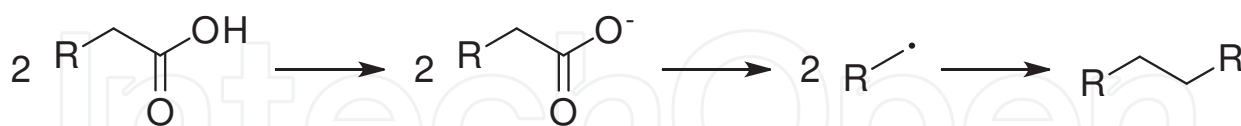
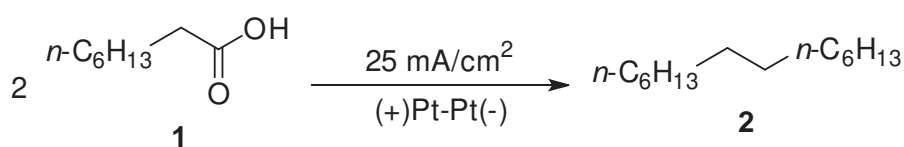


Figure 6. Kolbe-coupling including its proposed reaction mechanism

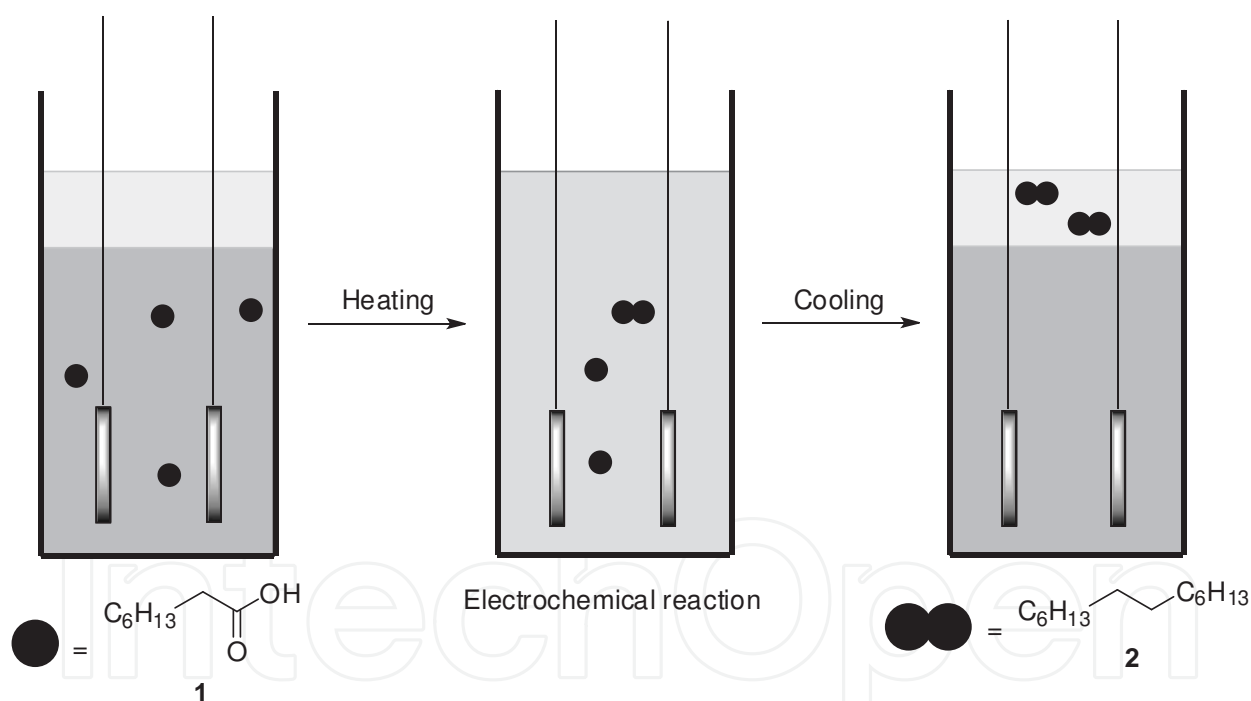
To test this idea, octanoic acid (**1**) was chosen as a simple model for Kolbe-coupling. Not surprisingly, the reaction proceeded nicely to give the coupled product (**2**) in excellent yield using conventional conditions, i.e., the electrolysis was carried out without cyclohexane (Fig. 7). As expected, the Kolbe-coupling also took place effectively in the cyclohexane-based liquid-biphasic system to suggest its possibility for applications to organic electrochemistry. In this case, the electrochemical reaction was carried out in the thermally-mixed monophasic condition, which was cooled to reform the biphasic condition, realizing rapid separation of the product (**2**) simply through liquid-liquid extraction (Fig. 8). The coupled product (**2**) was so hydrophobic that it was dissolved selectively in the cyclohexane phase.



electrolyte solution	yield (%)
pyridine:MeOH:MeCN = 1:1:2	93
pyridine:MeOH:MeCN:c-Hex = 1:1:2:4	95

Okada, Y.; Kamimura, K.; Chiba, K. *Tetrahedron* **2012**, 68, 5857-5862.

Figure 7. Evaluation of the cyclohexane-based liquid-biphasic system for organic electrochemistry

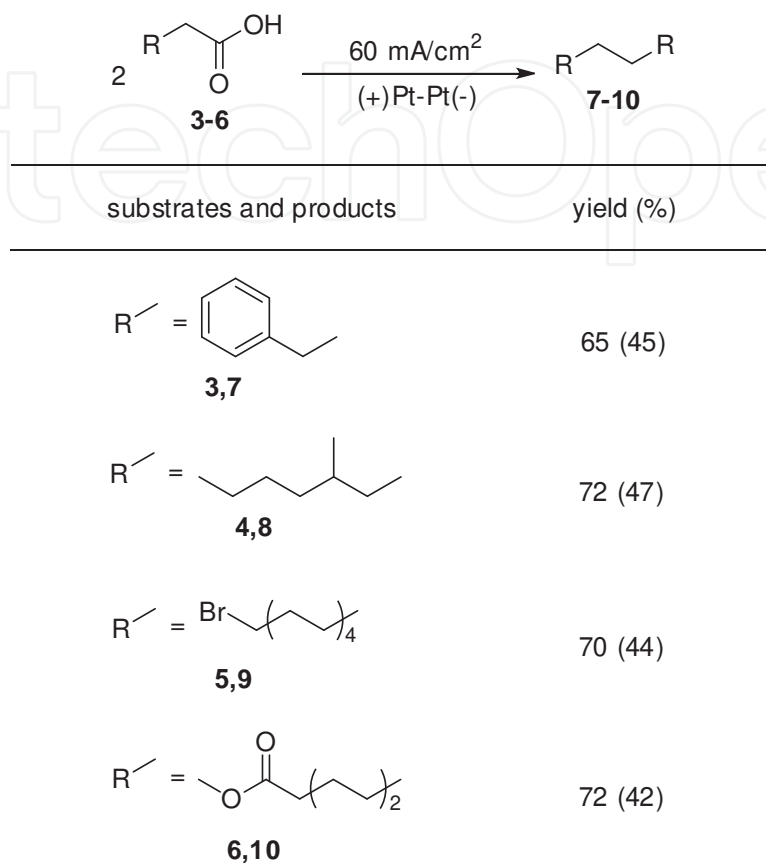


Okada, Y.; Kamimura, K.; Chiba, K. *Tetrahedron* **2012**, 68, 5857-5862.

Figure 8. Overall reaction procedure of the Kolbe-coupling

Several carboxylic acids (**3-6**) were subsequently used for the Kolbe-coupling in the cyclohexane-based liquid-biphasic system to give the corresponding coupled products (**7-10**) effectively (Fig. 9). These coupled products were poorly soluble in polar electrolyte solution, generally causing electrode passivation to decrease the reaction yield. In contrast, the reaction yields were significantly improved when the cyclohexane-based liquid-biphasic system

was used. After the electrochemical reaction, the biphasic condition was reformed through cooling to enable the facile separation of the coupled products (**7-10**). These results show the possibility of using cyclohexane-based liquid-biphasic systems in organic electrochemistry.



Yields using conventional conditions are shown in parentheses.

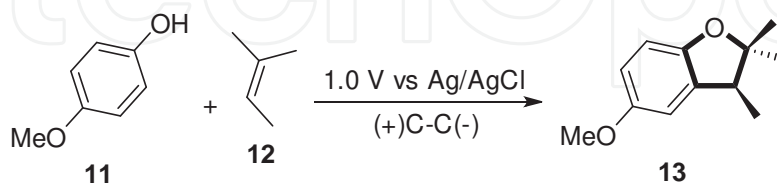
Okada, Y.; Kamimura, K.; Chiba, K. *Tetrahedron* **2012**, 68, 5857-5862.

Figure 9. Kolbe-coupling in the cyclohexane-based liquid-biphasic system

4. Five-membered ring formation assisted by cyclohexane-based liquid-biphasic systems

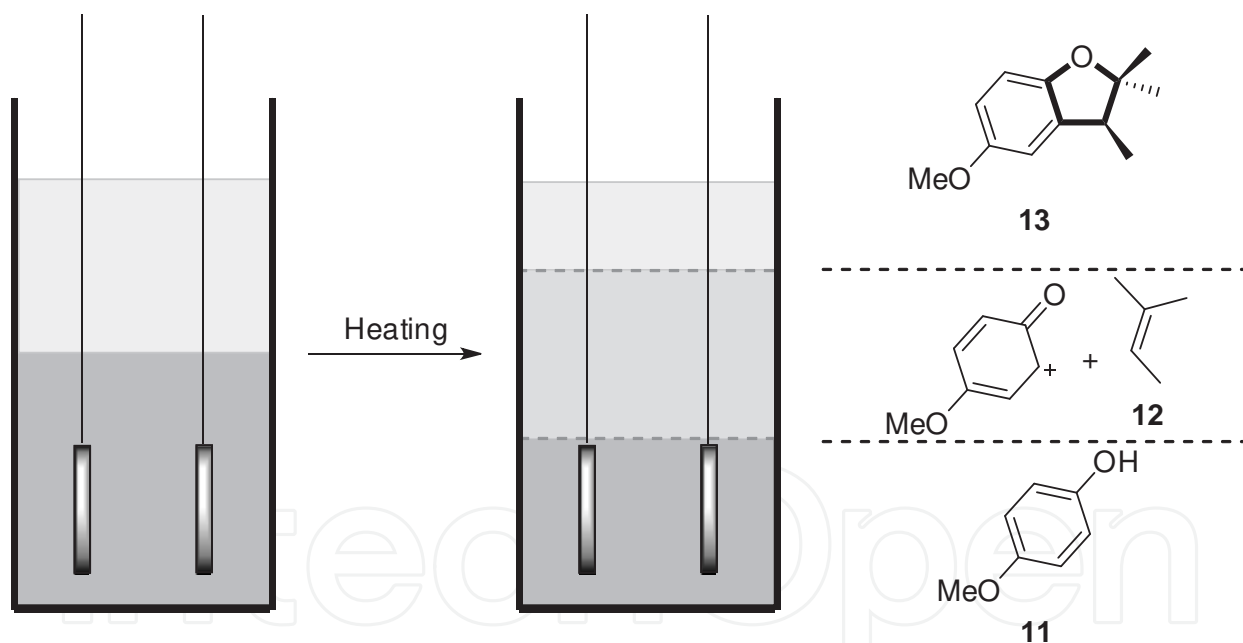
Undesired overoxidation also becomes problematic in organic electrochemistry. While this is not a concern for the Kolbe-coupling because the oxidation potential of the product is generally lower than that of the substrate, it might severely decrease the reaction yield in some instances. For example, a creative solution to the electrochemical five-membered ring formation between 4-methoxyphenol (**11**) and 2-methylbut-2-ene (**12**) must be developed to avoid this problem (Fig. 10) [43]. The oxidation potential of the five-membered ring product (**13**) is lower than that of 4-methoxyphenol (**11**), thus, undesired overoxidation is possible. As de-

scribed above, the electron transfer events in organic electrochemistry occur only at the surface of the electrodes. Using this situation to its best advantage can be a great aid for problematic overoxidation, namely, if the products can be rapidly removed from the electrodes, their overoxidation could be avoided. For this purpose, the cyclohexane-based liquid-biphasic system is promising because the less-polar cyclohexane phase does not have dissolving power for supporting electrolytes, thus there is no electrical conductivity. In other words, the cyclohexane phase is isolated from the electron transfer events.



Chiba, K.; Fukuda, M.; Kim, S.; Kitano, Y.; Tada, M. *J. Org. Chem.* **1999**, 64, 7654-7656.

Figure 10. Electrochemical five-membered ring formation

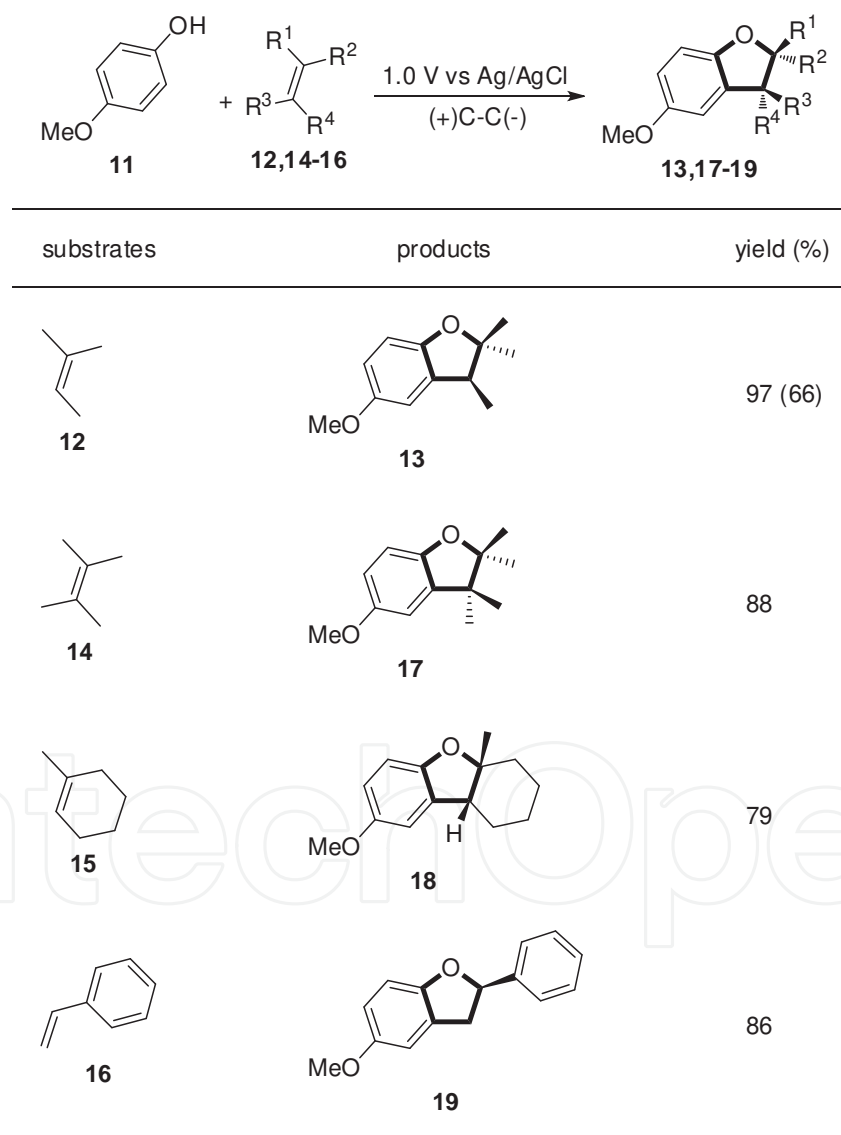


Kim, S.; Noda, S.; Hayashi, K.; Chiba, K. *Org. Lett.* **2008**, 10, 1827-1830.

Figure 11. Experimental outline of the electrochemical five-membered ring formation

On the basis of this concept, the electrochemical five-membered ring formation between 4-methoxyphenol (**11**) and 2-methylbut-2-ene (**12**) was carried out in the cyclohexane-based liquid-biphasic system (Fig. 11) [44]. This time, the interfacial surface between the cyclohexane phase and the electrolyte solution was partially heated in order to maintain a certain amount of the cyclohexane phase, which was expected to remove the five-membered ring

product (**13**) from the electrodes. Less-polar 2-methylbut-2-ene (**12**) was selectively dissolved into the cyclohexane phase, while relatively polar 4-methoxyphenol (**11**) preferred the electrolyte solution phase. The overoxidation of the product (**13**) was effectively avoided to improve the reaction yield significantly (Fig. 12). In addition to 2-methylbut-2-ene (**12**), various olefin nucleophiles (**14-16**) could be introduced into this system to construct the corresponding five-membered ring products (**17-19**), which were recovered into the cyclohexane phase such that their separation required only liquid-liquid extraction. These results have also highlighted the power of cyclohexane-based liquid-biphasic systems in organic electrochemistry. In addition to facile separation of the products, this system protects the products from their overoxidation.



Yield using conventional condition is shown in parenthesis.

Kim, S.; Noda, S.; Hayashi, K.; Chiba, K. *Org. Lett.* **2008**, *10*, 1827-1830.

Figure 12. Electrochemical five-membered ring formations in the cyclohexane-based liquid-biphasic system

5. Four-membered ring formation assisted by cyclohexane-based liquid-biphasic systems

From the environmental viewpoint, the separation process of products and supporting electrolytes is not the only problem in organic electrochemistry. The use of a large amount of supporting electrolytes, which are essential to impart electrical conductivity to polar organic solvents, also causes disposal issues. As described above, although various ingeniously designed electrochemical reaction systems have been reported so far that avoid the use of supporting electrolytes, there are also many electrochemical reactions that are dependent on the presence of a high concentration of supporting electrolytes. We have been developing several electrochemical four-membered ring formations between enol ethers and olefins in nitromethane using high concentrations of lithium perchlorate [45-51]. Because a high concentration of lithium perchlorate in nitromethane can effectively stabilize carbocations and enhance nucleophilicity of olefins, these reactions only take place under such conditions. Therefore, not only organic electrochemistry without supporting electrolytes but also the possibility of their reuse should be considered. For this purpose, cyclohexane-based liquid-biphasic systems are powerful. The less-polar cyclohexane phase does not have dissolving power for supporting electrolytes, thus, they can be confined in the polar electrolyte solution phase, which can be reused for the next reaction (Fig. 13).

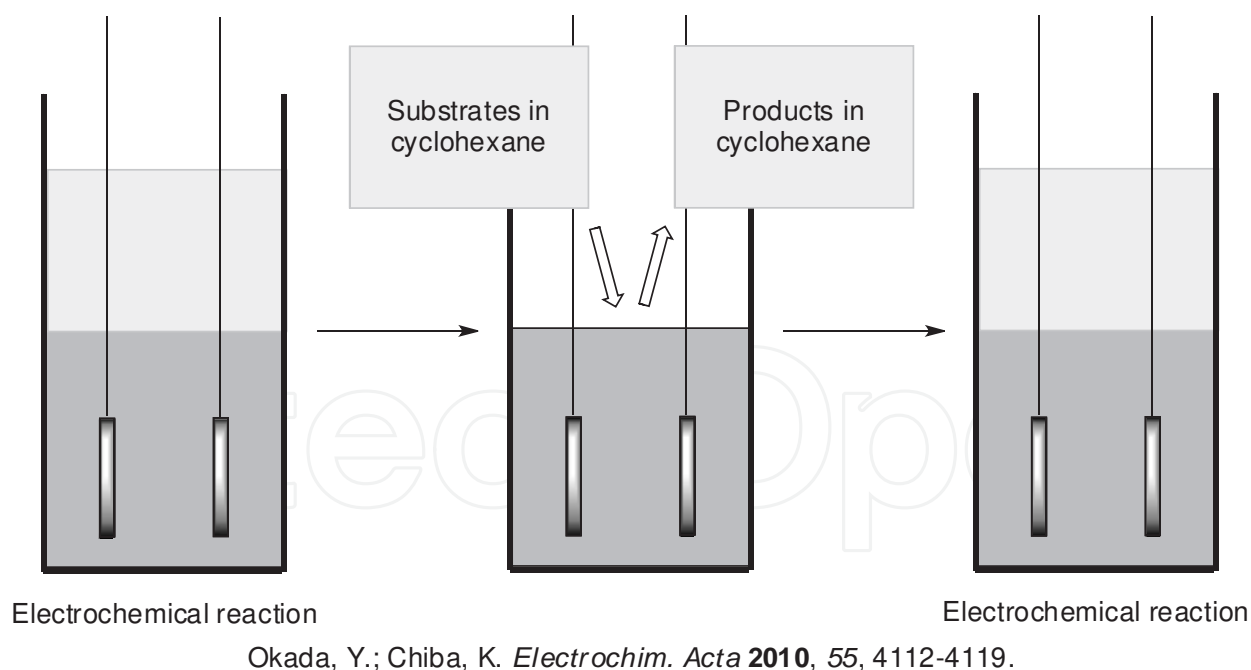
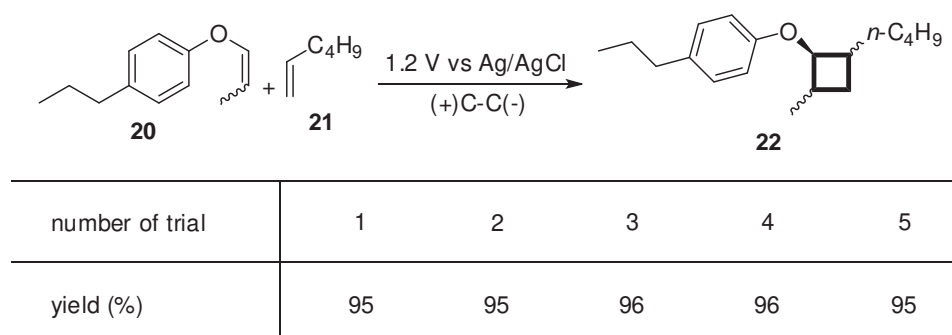


Figure 13. Reuse of supporting electrolytes based on the cyclohexane-based liquid-biphasic system

Based on this concept, the electrochemical four-membered ring formation between 1-(prop-1-en-1-yloxy)-4-propylbenzene (**20**) and hex-1-ene (**21**) was carried out in the cyclohexane-based liquid-biphasic system (Fig. 14) [52]. In this case, the reaction was found to

take place even under biphasic conditions without heating to construct the corresponding four-membered ring product (**22**) nicely. The product (**22**) was dominantly partitioned into the cyclohexane phase, where it could be isolated rapidly and purely simply through liquid-liquid extraction. To examine the reusability of the supporting electrolyte, additional amounts of 1-(prop-1-en-1-yloxy)-4-propylbenzene (**20**) and hex-1-ene (**21**) in cyclohexane were introduced to the residual electrolyte solution to find that the yield of the four-membered ring product (**22**) was excellent for at least five cycles. This indicated that the supporting electrolytes could be reused in the cyclohexane-based liquid-biphasic system at least five times in the absence of their degradation, also meaning that the productivity of the product was improved five times. In other words, the required amount of the supporting electrolyte for the reaction was reduced significantly through this system. In addition to hex-1-ene (**21**), several olefin nucleophiles (**23-25**) were then introduced to this system (Fig. 15). This time, too, the four-membered ring product was recovered simply by liquid-liquid extraction at the end of each reaction, and the residual supporting electrolyte was reused five times. Even in this situation, several types of four-membered ring products (**22**, **26-28**) could be completely separated from the electrolyte solution to give the corresponding products with high selectivity by simple liquid-liquid extraction. Low productivity, which is one of the weak points of organic electrochemistry, was improved significantly by using the cyclohexane-based liquid-biphasic system.



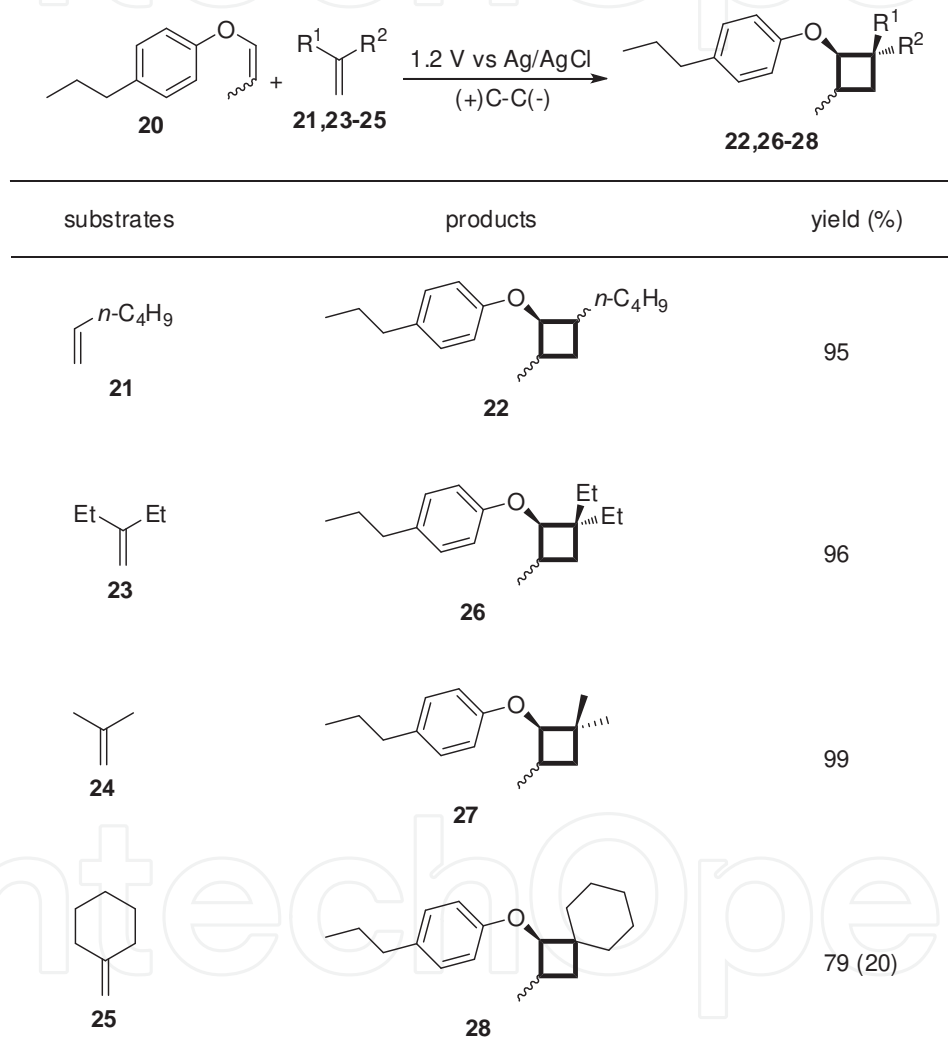
Okada, Y.; Chiba, K. *Electrochim. Acta* **2010**, 55, 4112-4119.

Figure 14. Reusability of supporting electrolyte in the cyclohexane-based liquid-biphasic system

6. Continuous flow electrochemical synthesis assisted by cyclohexane-based liquid-biphasic systems

Cyclohexane-based liquid biphasic systems have been well combined with three types of organic electrochemistry, including Kolbe-couplings, five-, and four-membered ring formations, to realize rapid separation of the resulting products. In all cases, the products were selectively dissolved in the cyclohexane phase and could be isolated by simple liquid-liquid extraction to give the desired compounds in almost pure fashion without additional separation steps. Moreover, cyclohexane-based liquid-biphasic systems also offer many valuable

functions as follows. In Kolbe-couplings, the biphasic condition was thermally mixed to a monophasic condition to form a less-polar electrolyte solution, which avoided electrode passivation effectively to improve the reaction efficiency. In electrochemical five-membered ring formations, the cyclohexane phase selectively dissolved the products to protect them from undesired overoxidation. High reusability of the supporting electrolyte was also demonstrated and improvement of productivity was achieved in electrochemical four-membered ring formations. Here we have set an ultimate aim to accomplish flow electrochemical synthesis assisted by cyclohexane-based liquid-biphasic systems.



Yield of non-cyclized product is shown in parenthesis.

Okada, Y.; Chiba, K. *Electrochim. Acta* **2010**, 55, 4112-4119.

Figure 15. Electrochemical four-membered ring formations in the cyclohexane-based liquid-biphasic system

For the construction of a flow electrochemical synthetic device, the composition of several cyclohexane-based liquid-biphasic systems was studied in detail (Fig. 16). Three electrolyte solutions were prepared using 1.0 M lithium perchlorate as a supporting electrolyte in meth-

anol, acetonitrile, or nitromethane. The same volume of cyclohexane was then added to investigate the compositions of both upper and lower phases.

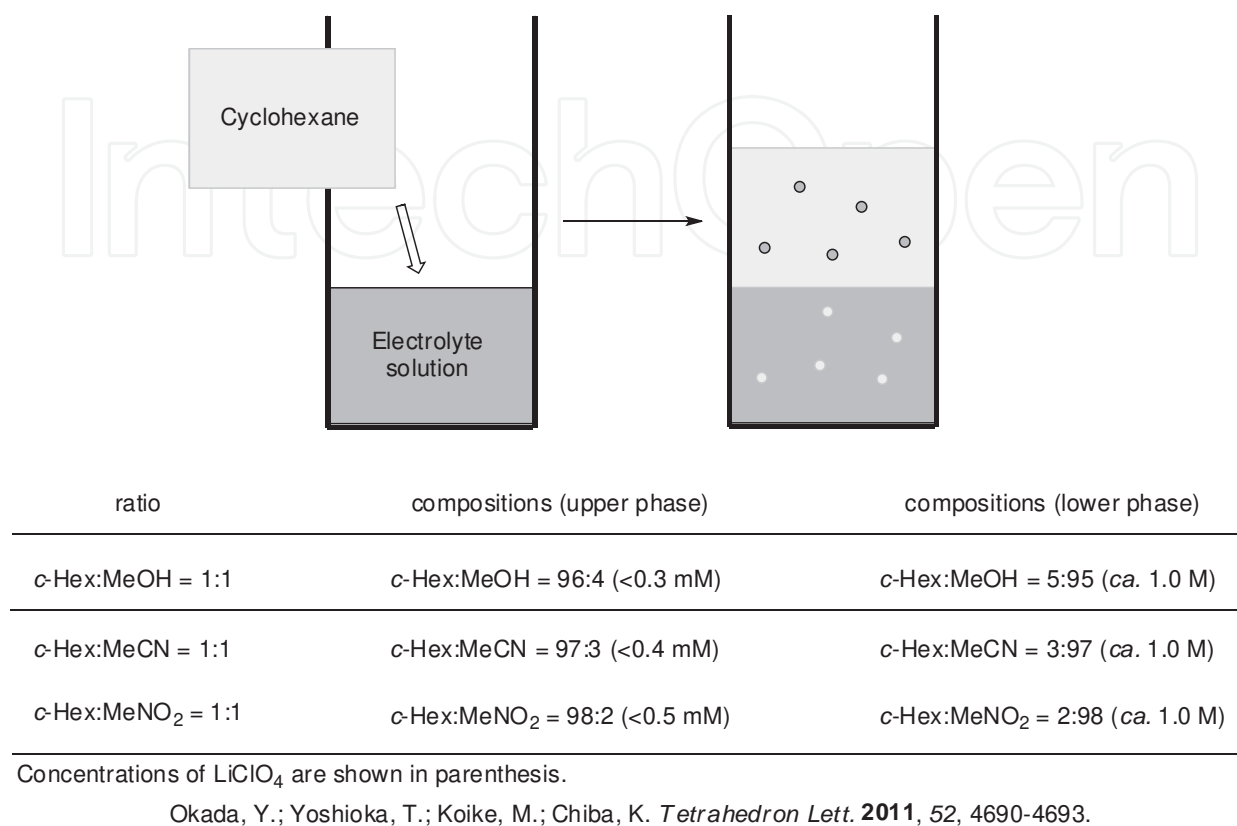
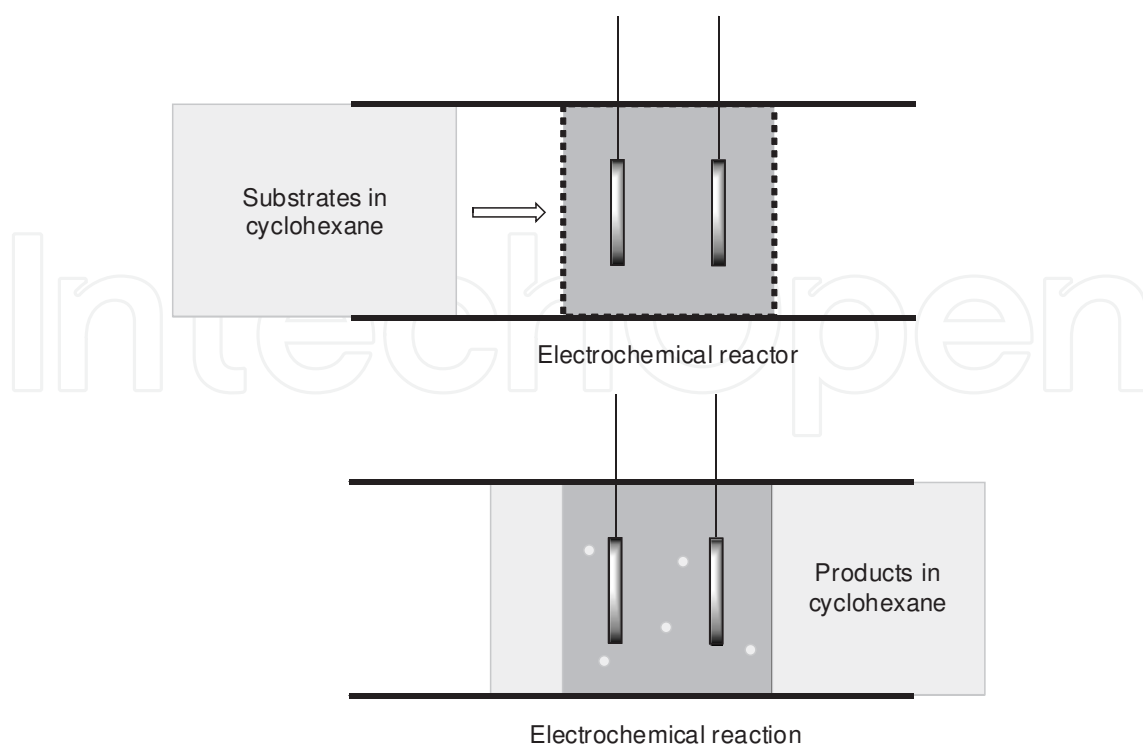


Figure 16. Compositions of cyclohexane-based liquid-biphasic systems

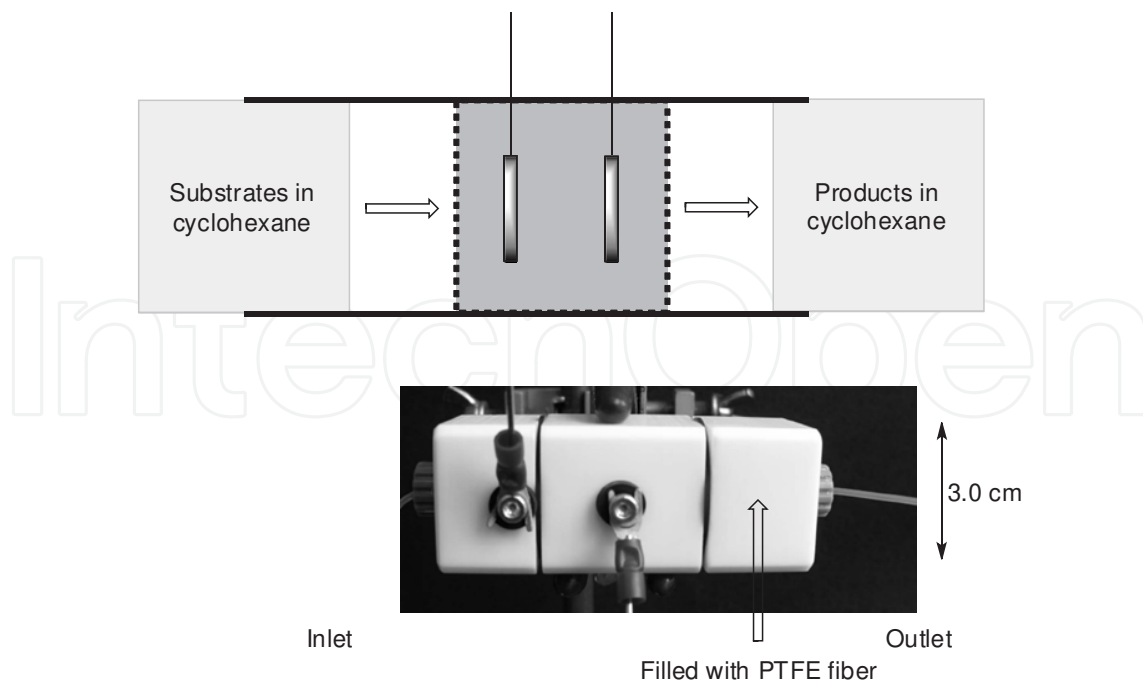
Remarkably, although cyclohexane and these polar solvents were partially miscible even at ambient temperature, only a trace amount of lithium perchlorate was recovered from the cyclohexane phase. This meant that the supporting electrolyte could be confined in polar solvents. As described, electrodes function as solid-phase redox reagents; therefore, they should be well combined with a flow strategy (Fig. 17) [53]. Substrates in cyclohexane are injected into an electrochemical reactor, which is equipped with electrodes and a filter that is selectively permeable to cyclohexane. In this system, the outlet ejected from the reactor might be almost pure product in cyclohexane.

Based on these preliminary experiments, we designed and prepared a new flow electrochemical synthetic device (Fig. 18). The device was built with three compartments, which are mainly made of polytetrafluoroethylene, and could contain 5.0 mL of electrolyte solution. The third compartment was filled with polytetrafluoroethylene fiber that is known to be permeable for less-polar cyclohexane rather than polar electrolyte solutions. Substrates could be pumped into the reactor as a cyclohexane solution from the inlet, which would then emerge from the outlet after the electrochemical reaction.



Okada, Y.; Yoshioka, T.; Koike, M.; Chiba, K. *Tetrahedron Lett.* **2011**, 52, 4690-4693.

Figure 17. Outline of flow electrochemical synthesis based on the cyclohexane-based liquid-biphasic system



Okada, Y.; Yoshioka, T.; Koike, M.; Chiba, K. *Tetrahedron Lett.* **2011**, 52, 4690-4693.

Figure 18. Design of new flow electrochemical synthetic device

With this device in hand, initially, electrochemical methoxylation, another representative electrochemical reaction in organic chemistry, was attempted (Fig. 19). The methoxylation of hydrophobic furan (**29**) nicely took place in the reactor to afford the methoxylated product (**30**) in a selective manner (Fig. 20). Vacuum concentration of the outlet cyclohexane solution ejected from the reactor was all that was required to give nearly pure product.

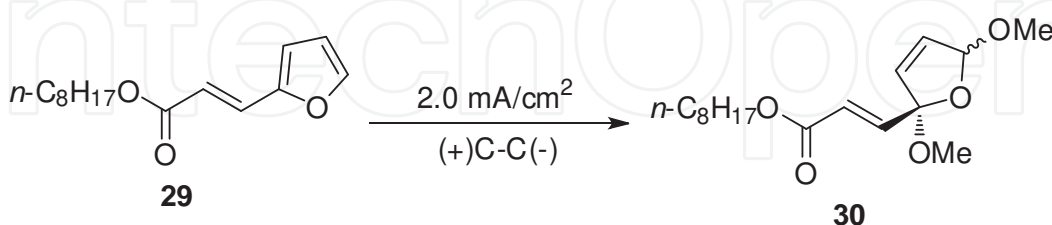


Figure 19. Electrochemical methoxylation

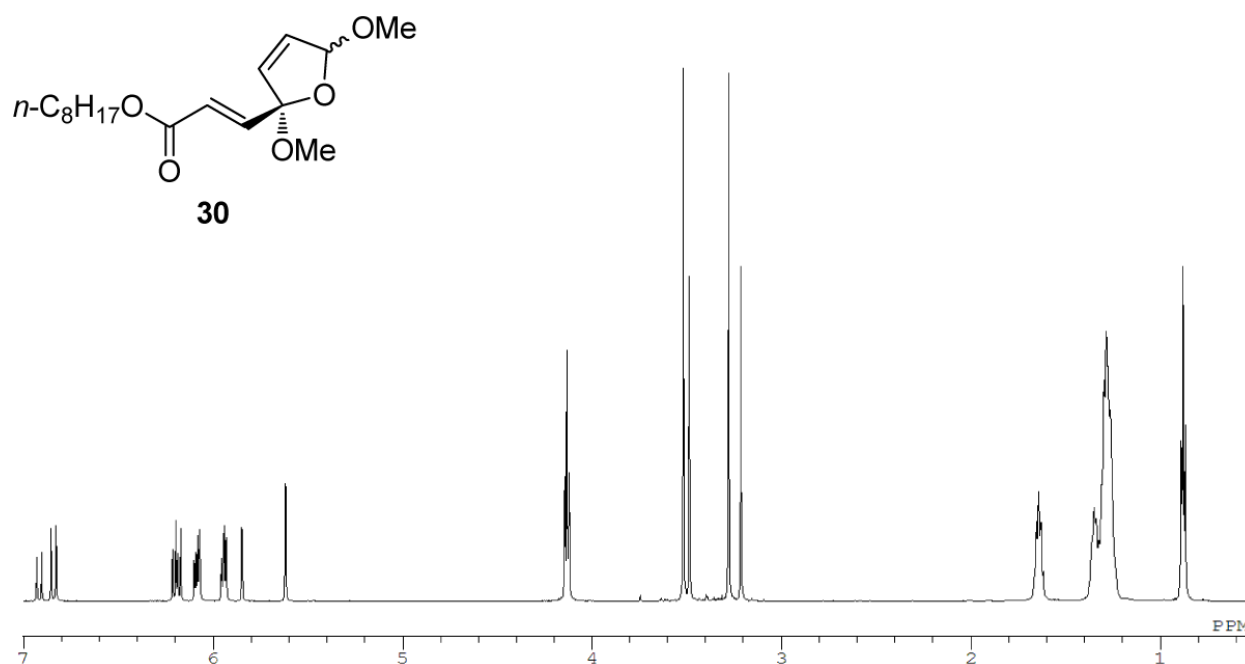


Figure 20. NMR spectrum of the methoxylated product (**30**)

Finally, electrochemical four-, five-, and six-membered ring formations were carried out in this flow system (Fig. 21). All reactions took place selectively in the reactor and it should be noted that only vacuum concentration of the outlet cyclohexane solution was required. The corresponding ring products could be obtained in almost pure fashion without any additional separation processes. It is perhaps fair to say that the desired products emerge automatically from the flow electrochemical synthetic device assisted by the cyclohexane-based liquid-biphasic system.

substrates	products	yield (%)
 20 + 21 → 22	95	
 31 + 23 → 32	96	
 11 + 12 → 13	97	
 11 + 16 → 19	86	
 33 + 34 → 35	99	

Okada, Y.; Yoshioka, T.; Koike, M.; Chiba, K. *Tetrahedron Lett.* **2011**, 52, 4690-4693.

Figure 21. Flow electrochemical synthesis assisted by the cyclohexane-based liquid-biphasic system

7. Conclusion

As described in this chapter, the discovery that cyclohexane had a unique thermomorphic nature has led to the development of cyclohexane-based liquid-biphasic systems, which can be well-combined with organic electrochemistry. Rapid and high-performance separations, which have been assuming a larger role in modern organic chemistry, were accomplished

by this system. Cyclohexane-based liquid-biphasic systems offer not only effective separation but also several additional functions of value, including suppressing electrode passivation, protecting products from overoxidation, and enabling reuse of supporting electrolytes.

Desired compounds can be synthesized precisely, and then characterized carefully. Organic chemists have made significant advances in these techniques to realize the preparation of almost anything with detailed structural information. In this context, the development of effective separation methodologies should maximize their vitality. For this purpose, the cyclohexane-based biphasic-system is one of the most promising techniques, especially in organic electrochemistry.

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