A new approach to anodic substitution reaction using acoustic emulsification

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We have developed a novel electrolytic system for anodic substitution reactions using acoustic emulsification. This new system involves the generation of a carbocation by anodic oxidation of a substrate, and then its reaction with a nucleophile droplet formed by ultrasonication. In this system, even if the oxidation potential of the nucleophile is lower than that of the substrate, the substrate was predominantly oxidized to give the corresponding cation intermediate because the nucleophile phase, which was insoluble in the electrolytic medium, was electro-inactive. In addition, the overoxidation of the desired products was considerably suppressed by the extraction of products from the electrolyte solution into the nucleophile phase. As a result, the anodic substitution reaction of several carbamates with allyltrimethylsilane was carried out to provide the corresponding products in good to moderate yields.

Introduction

Nucleophilic reactions between chemically and electrochemically generated carbocations from organic substrates and nucleophiles are one of the most important reactions in organic syntheses.[1–3] Since carbocations are usually unstable intermediates, the oxidative generation of carbocations often has to be conducted in the presence of nucleophiles so that the nucleophile can trap the carbocation immediately as it is generated. However, the oxidation potentials of the nucleophiles are usually lower than those of the organic substrates, and therefore the presence of nucleophiles would prevent oxidation of the organic substrates. In this regard, introduction of an electro-auxiliary into substrates[4–8] and the "cation pool" method[9–12] have been developed, but these necessarily include laborious multi-step reactions.

On the other hand, recently we have reported that direct electropolymerization of water-insoluble monomers proceeded successfully in aqueous electrolytes using acoustic emulsification.[13,14] Ultrasonication of the water-insoluble monomer–aqueous electrolyte mixtures allowed the formation of very stable emulsions without added surfactants, and smooth electropolymerization in the emulsions took place *via* direct electron transfer between the electrode and the water-insoluble monomer droplets. In this kind of biphasic electron transfer system, the supporting electrolyte should be dissolved not only in the aqueous phase but also in the monomer droplets and should contribute to the formation of an electric bilayer inside the droplets. Hence, when the droplet did not contain any supporting electrolytes, the direct electron transfer occurred only to a small extent.

These findings gave us the incentive to develop a novel electrochemical system that would realize anodic substitution reactions without affecting the oxidation of the nucleophile in a one-step electrochemical operation. In this system, illustrated in Fig. 1 the nucleophile is insoluble in the electrolytic medium and is dispersed as submicrometer sized droplets by ultrasonication. In this situation, if the nucleophile droplet does not contain any supporting electrolyte, it becomes electro-inactive, and therefore the substrate is oxidized preferentially at the anode. Consequently, the desired coupling-product can be formed if the carbocation generated can be rapidly trapped by the coexisting nucleophile droplet before its decomposition. Thus, this system could realize the anodic substitution reaction and overcome the constraints such as the oxidation potentials of the nucleophiles and the stability of the carbocations.

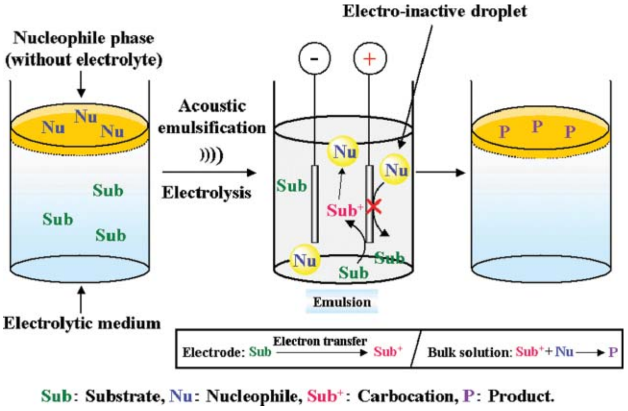

Fig. 1 Schematic illustration of the anodic substitution reaction system using acoustic emulsification.

In fact, we preliminarily reported that this concept worked successfully in the anodic substitution reaction of *N*-(methoxycarbonyl)pyrrolidine **1** (oxidation potential $E_{ox} = 1.91$ V *vs.* Ag/AgCl) with allyltrimethylsilane **2** (E_{ox} = 1.75 V *vs.* Ag/AgCl) (Scheme 1).[15] The successful results prompted us to perform a systematic study of the anodic substitution reaction of a variety of carbamates. Herein, we report the full details of the anodic substitution reaction of carbamates using acoustic emulsification.

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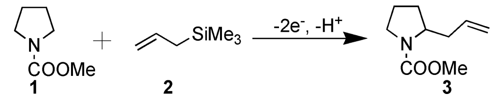


Scheme 1 Anodic substitution reaction of *N*-(methoxycarbonyl)pyrrolidine **1** with allyltrimethylsilane **2**.

Results and discussion

Investigation of suitable electrolytic medium for our electrosynthetic system

In this system, the electrolytic medium needs to possess solubilizing ability for the substrate **1**, but should not exhibit it for a nucleophile such as allyltrimethylsilane **2**. From the above point of view, we explored suitable electrolytic media, and as a result an ionic liquid like 1-ethyl-3-methylimidazolium tetrafluoroborate (EMIM BF$_4$) was found to show the desired properties as shown in Fig. 2. Recently, one of us (M.A.) reported that ionic liquids have an excellent stabilizing ability for carbocations.[16] Together, these facts indicated that EMIM BF$_4$ is a suitable electrolytic medium for our system.

Linear sweep voltammetry

We measured linear sweep voltammograms of compounds **1**, **2** and a mixture of them. Since both **1** and **2** can be dissolved in CH$_3$CN, **2** which has lower oxidation potential, was oxidized as shown in Fig. 3a. In contrast, Fig. 3b indicates that the anodic oxidation of **2** hardly occurred in EMIM BF$_4$. As mentioned above, **2** was insoluble in the electrolytic medium. Moreover boron atom was not detected in the nucleophile phase by inductively coupled plasma spectrometry (ICP). This result suggested that the nucleophile phase contained very little of the electrolyte (EMIM BF$_4$). Hence, the droplet of **2** should be electro-inactive and thereby **1** was oxidized preferentially even in the presence of **2** in the same reactor as shown in Fig. 3b. This accords with our observations.

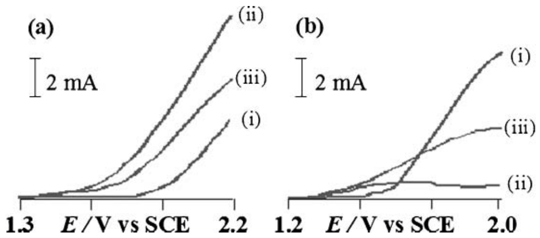


Fig. 3 Linear sweep voltammograms of (i) 0.1 M *N*-(methoxycarbonyl)pyrrolidine **1**, (ii) 0.1 M allyltrimethylsilane **2**, and (iii) 0.1 M **1** with **2** in (a) 0.1 M n-Bu$_4$NBF$_4$–CH$_3$CN solution and (b) EMIM BF$_4$ under ultrasonication. Scan rate was 0.1 V s^{-1}.

Preparative scale electrolysis

We then carried out on a preparative scale the anodic substitution reaction (Scheme 1). 1 mmol of *N*-(methoxycarbonyl)pyrrolidine **1** was galvanostatically electrolyzed at 5 mA in the presence of allyltrimethylsilane **2** by passing 2 F mol^{-1} of charge under ultrasonication with 150 W cm^{-2} intensity. As shown in entry 1 of Table 1, the desired product **3** was obtained in only 11% yield and 76% of substrate was recovered from the CH$_3$CN solution. In this case, nucleophile **2** was probably oxidized preferentially. In sharp contrast, the use of the emulsion system resulted in an improvement of the conversion of **1** as shown in entry 2. However, the low yield persisted. The low yield was ascribed to the fact that the amount of **2** was insufficient to trap the carbocations generated. In fact, the addition of further amounts of **2** was effective for improving the yield and gave **3** in 70% yield when 10 equivalents of **2** were added (entry 4). It should be noted that the nucleophilic substitution reaction barely proceeded

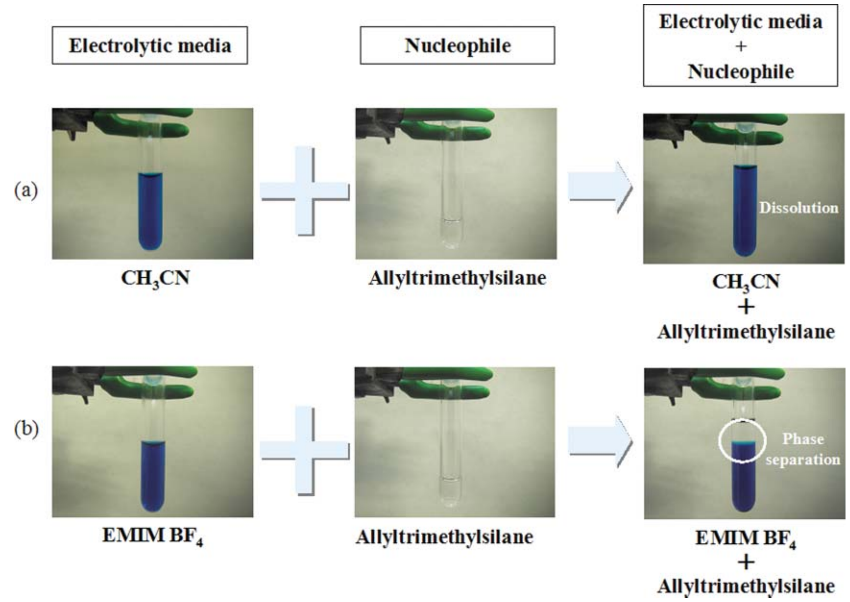


Fig. 2 Dissolution and phase separation of allyltrimethylsilane in (a) CH$_3$CN, and (b) EMIM BF$_4$ (CH$_3$CN and EMIM BF$_4$ layers were colored by methylene blue).

Table 1 Anodic substitution reaction of *N*-(methoxycarbonyl)pyrrolidine with allyltrimethylsilane

Entry	Electrolytic media	**2** (mmol)	Yield of **3** (%)[a]	Conversion of **1** (%)[a]
1	0.1 M Bu_4NBF_4–CH_3CN	10	11	24
2	EMIM BF_4	2	16	88
3	EMIM BF_4	5	32	81
4	EMIM BF_4	10	70 (62)[b]	78
5[c]	EMIM BF_4	10	11	69
6[d]	EMIM BF_4	10	8	57

[a] Determined by GC. [b] Isolated yield in parentheses. [c] Mechanical stirring (1500 rpm) was used instead of ultrasonication. [d] Electrolysis was conducted without ultrasonication in acoustically pre-emulsified solution.

under mechanical stirring conditions, although the substrate was oxidized smoothly as shown in entry 5. In this case, mechanical stirring could not form an emulsion because of the high viscosity of the EMIM BF_4. We presume that the cation that was generated decomposed before being trapped by the nucleophile.

It is noteworthy that emulsion droplets formed by ultrasonication can often exist for a long period, and hence continuous sonication is not necessary to maintain the emulsion after droplet formation.[17–20]

Subsequently, we carried out the anodic substitution reaction without continuous ultrasonication in an acoustically pre-emulsified solution. However, the product yield was very low (entry 6 of Table 1) compared to the case with continuous ultrasonication (entry 4). This can be ascribed to de-emulsification of the nucleophile droplets during the electrolysis. Indeed, as shown in Fig. 4, the de-emulsification was observed immediately after acoustic emulsification in EMIM BF_4; few emulsion droplets were found in the beaker after 60 min, although the presence nanometer size droplets of allyltrimethylsilane was confirmed by dynamic light scattering (DLS) measurement from a freshly prepared emulsion (see Fig. 5). These results suggested that the nucleophile emulsion droplets are relatively unstable in EMIM BF_4, and therefore continuous ultrasonication is required for maintaining the emulsion during the electrolysis.

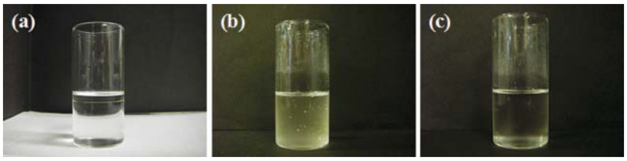


Fig. 4 Photographic observations of emulsification and de-emulsification of allyltrimethylsilane in EMIM BF_4. (a) Before acoustic emulsification, (b) right after acoustic emulsification, and (c) after 60 min.

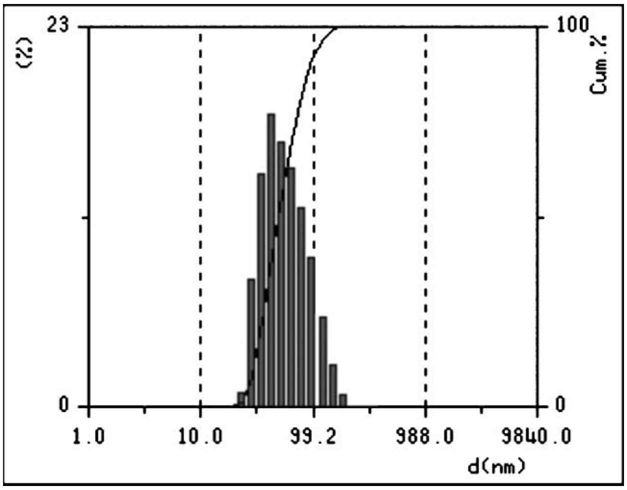


Fig. 5 DLS number size distribution of allyltrimethylsilane droplets from freshly prepared emulsion showing a monomodal distribution with an average diameter of 62.9 ± 30.7 nm.

Avoidance of overoxidation

The oxidation potential of product **3** ($E_{ox} = 1.90$ V *vs.* Ag/AgCl) is very close to that of substrate **1** implying that overoxidation of **3** could be a problem for this reaction.[9] However, in our case, the overoxidized products were not detected at all. From this fact, it can be considered that introduction of an allyl group into **1** greatly decreases its solubility in the electrolytic medium (EMIM BF_4) and, consequently, allylated product **3** would be extracted from EMIM BF_4 into the nucleophile phase. To confirm this conjecture, we measured the partition ratio of **1** and **3** between EMIM BF_4 and the nucleophile phase (Fig. 6). As a result, it was found that about 75% of **3** was extracted into the nucleophile phase while only 16% of **1** was dissolved in this phase. Moreover, this conjecture was also supported by the linear sweep voltammetry. As shown in Fig. 7, trace i, the anodic oxidation of **3** proceeded smoothly in the absence of nucleophile droplets of allyltrimethylsilane. In contrast, the oxidation current was decreased appreciably in the presence of the droplets (Fig. 7, trace ii). This also means apparently that allylated product **3** was extracted from the EMIM BF_4 electrolytic medium into the nucleophile phase. Thus, it is likely that the allyl group serves as a "phase tag" for extraction of the product from the electrolytic medium, and the *in situ* extraction results in reducing the chances of overoxidation of the product.[21,22]

Anodic substitution reaction of other carbamates with allyltrimethylsilane

In order to demonstrate the generality of this new methodology, we investigated the anodic substitution reactions of other carbamates with allyltrimethylsilane. As shown in Table 2, the anodic substitution reactions of both cyclic and linear carbamates with allyltrimethylsilane proceeded smoothly to give the corresponding allylated products in good to moderate yields, while the anodic substitution reaction of compound **12** did not proceed and the starting material was mostly recovered after the electrolysis. This may be due to the higher oxidation potential of **12**. Actually,

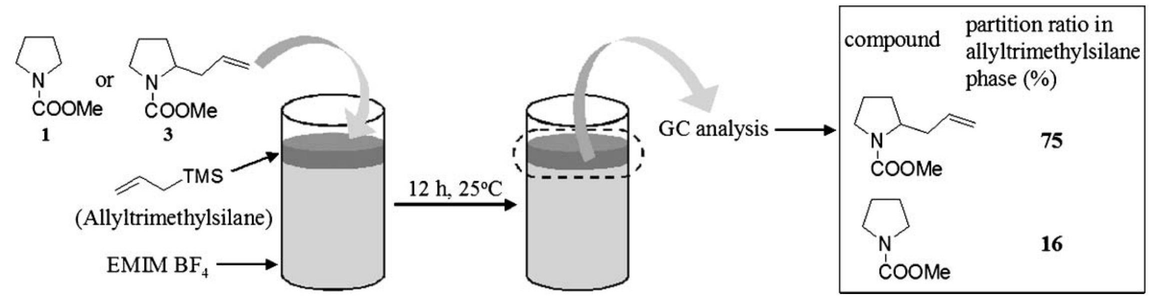


Fig. 6 Schematic illustration of the experimental procedures for the measurement of partition ratio of **1** and **3** between EMIM BF$_4$ and allyltrimethylsilane phase.

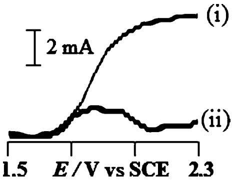


Fig. 7 Linear sweep voltammograms of (i) 0.1 M methyl 2-(2-propenyl)-pyrrolidinecarboxylate **3** and (ii) 0.1 M methyl 2-(2-propenyl)pyrrolidinecarboxylate **3** with 0.1 M allyltrimethylsilane **2** in EMIM BF$_4$ under ultrasonication. Scan rate was 0.1 V s^{-1}.

as shown in Fig. 8, trace ii, the current for the oxidation of **12** was small because the electrolytic medium (EMIM BF$_4$) was discharged more easily although the current for **1** oxidation was clearly confirmed, as shown in Fig. 8, trace i.

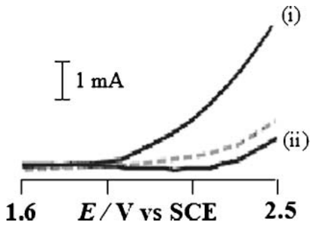


Fig. 8 Linear sweep voltammograms of (i) 0.1 M *N*-(methoxycarbonyl)pyrrolidine **1** with 0.1 M allyltrimethylsilane **2** and (ii) 0.1 M *N*-carbomethoxy-L-proline methyl ester **12** with 0.1 M **2** in EMIM BF$_4$ under ultrasonication. Scan rate was 0.1 V s^{-1}. Dashed line indicates the response in the absence of substrates.

From these generality experiments, it can be stated that this new electrolytic system using acoustic emulsification is effective for a wide range of anodic substitution reactions of carbamates except for some substrates such as amino acid derivative **12** whose oxidation potentials are higher than that of the electrolytic medium.

Conclusions

We have developed a novel electrolytic system for anodic substitution reactions using acoustic emulsification. This new methodology has many practical advantages and characteristics: (a) nucleophilic reaction can be achieved by a one-step electrochemical operation in a single reactor; (b) the selective oxidation of substrates without affecting the oxidation of nucleophile; (c) the smooth trapping of carbocations with nanometer size nucleophile droplets formed by ultrasonication; (d) a reduction in the chance for overoxidation of products by the introduction of a "phase tag". It is hoped that this facile and novel electrolytic system will open a new aspect not only of synthetic electrochemistry but also of general synthetic chemistry.

Experimental

Materials

Pt mesh was purchased from The Nilaco Co. 1-Ethyl-3-methylimidazolium tetrafluoroborate (EMIM BF$_4$) was purchased from Kanto Chem. Co. and used after drying under vacuum for 24 h. CH_3CN and Et_2O were purchased from Kanto Chem. Co. and used as received. Allyltrimethylsilane (**2**), *N*-(acetyl)pyrrolidine (**4**) and tetrabutylammonium tetrafluoroborate (n-Bu_4NBF_4) were purchased from Tokyo Kasei Kogyo Co. and used as received. *N*-(methoxycarbonyl)pyrrolidine (**1**), methyl 2-(2-propenyl)pyrrolidinecarboxylate (**3**), 1-(2-allyl-pyrrolidin-1-yl)ethanone (**5**), *N*-(methoxycarbonyl)piperidine (**6**), methyl 2-(2-propenyl)piperidinecarboxylate (**7**), dimethyl-carbamic acid methyl ester (**8**), but-3-enyl-methyl-carbamic acid methyl ester (**9**), diethyl-carbamic acid methyl ester (**10**), ethyl-(1-methyl-but-3-enyl)-carbamic acid methyl ester (**11**), *N*-carbomethoxy-L-proline methyl ester (**12**), and 5-allyl-pyrrolidine-1,2-dicarboxylic acid dimethyl ester (**13**) were prepared according to literature procedures, respectively.[23–25] The ^{1}H NMR and mass spectral data of all of the prepared compounds were consistent with the expected structure.[9,26]

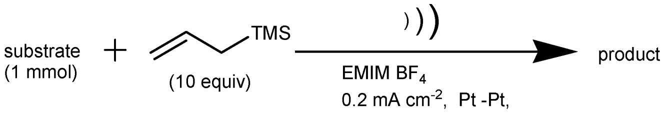
Investigation of suitable electrolytic medium for our electrosynthetic system

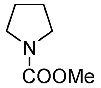
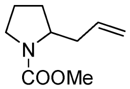
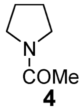
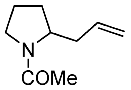
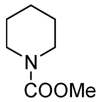
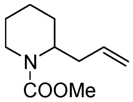
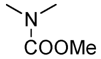
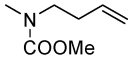
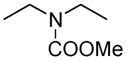
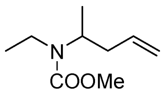
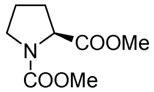
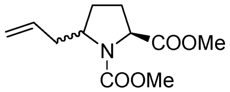
The 0.2 mL of allyltrimethylsilane was added to the 0.8 mL of electrolytic medium including a piece of methylene blue (methylene blue was used as an indicator for the phase separation).

Linear sweep voltammetry of *N*-(methoxycarbonyl)pyrrolidine (1) and allyltrimethylsilane (2)

Linear sweep voltammograms for the oxidation of **1** (1 mmol), **2** (1 mmol) and a mixture of them were measured with a three-electrode system using a platinum plate (1 × 1 cm^2) working electrode, a platinum plate (2 × 2 cm^2) counter electrode, and a saturated calomel electrode (SCE) as a reference electrode in 10 mL of 0.1 M n-Bu_4NBF_4–CH_3CN solution or EMIM BF$_4$ under

Table 2 Anodic substitution reactions of several carbamates with allyltrimethylsilane using acoustic emulsification



Entry	Substrate	Electricity/F mol^{-1}	Product	Yield (%)[a]
1	 **1**	2	 **3**	70
2	 **4**	2	 **5**	43
3	 **6**	3	 **7**	50
4[b,c]	 **8**	4	 **9**	66
5	 **10**	4.5	 **11**	41
6	 **12**	3	 **13**	Trace[d]

[a] Determined by GC. [b] After 2 F mol^{-1} of electricity was passed, 10 equivalent of nucleophile was further added. [c] Current density was 0.08 mA cm^{-2}. [d] Substrate was recovered almost completely.

ultrasonication (ultrasonic stepped horn, 20 kHz, 150 W cm^{-2} intensity) at a solution temperature of 25 ± 1 °C. The linear sweep voltammograms of **3** and **12** were recorded with same system used for measurement of the starting substrate **1**.

General procedure for the anodic substitution reaction

A divided H-type glass cell with a glass frit diaphragm in a cooling bath was equipped with a Pt mesh anode (*ca.* 25 cm^2), a Pt mesh cathode (*ca.* 50 cm^2), and an ultrasonic stepped horn (3.2 mm diameter) connected with a 20 kHz oscillator (SONIFIER-250D, Branson Ultrasonics Co.). A photograph and illustration of the electrochemical cell are shown in Fig. 9.

N-(Methoxycarbonyl)pyrrolidine **1** and the other compounds **4**, **6**, **8**, **10**, and **12** were galvanostatically electrolyzed at 5 mA in 0.1 M *n*-Bu_4NBF_4–CH_3CN solution and EMIM BF_4 (12 cm^3) in the presence of **2** by passing 2 F mol^{-1} of charge under ultrasonication with 150 W cm^{-2} intensity at a solution temperature of 25 ± 1 °C unless otherwise stated. Mechanical stirring at 1500 rpm (Magnestir, MGP-306 Sibata Scientific Technology Ltd.) was also used instead of ultrasonication. After electrolysis, products **3**, **5**, **7**, **9**, **11**, and **13** formed were extracted with Et_2O (10 × 10 mL) and analyzed by gas chromatography (GC-2014 with Tween 80, 3 m column, Shimadzu Co., Japan).

Measurement of supporting electrolyte concentration in nucleophile (allyltrimethylsilane) phase

1 mL of allyltrimethylsilane was added to 5 mL of EMIM BF_4. Next, the solution was left to stand for 12 h at 25 ± 1 °C, and then 0.5 mL of allyltrimethylsilane phase was pipetted into the 25 mL plastic graduated flask and diluted with CH_3CN. Subsequently, the concentration of boron in the sample solution was measured by inductively coupled plasma spectrometry (ICPS-8100, Shimadzu Co.). The detection limit of spectrometer used in this work is 1 ppb.

Measurement of partition ratio

First 0.3 mmol of **1** or **3** was added to the mixture of 3 mL of EMIM BF_4 and 0.5 mL (*ca.* 3 mmol) of allyltrimethylsilane. Next, the solutions were left to stand for 12 h at 25 ± 1 °C, and then 0.1 mL of

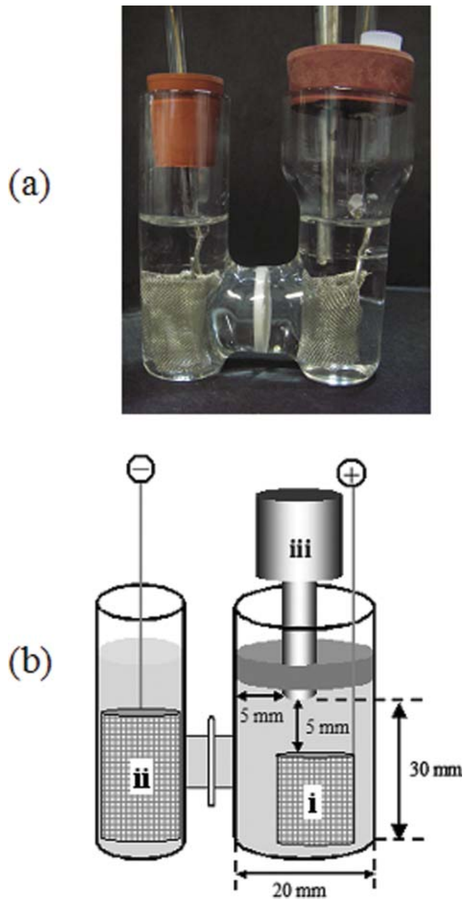


Fig. 9 (a) Photograph and (b) illustration of the electrochemical cell assemblies used for the anodic substitution reaction using acoustic emulsification. i: platinum mesh anode, ii: platinum mesh cathode, c: ultrasonic stepped horn.

allyltrimethylsilane phase was pipetted into 5 mL glass graduated flask and diluted with CH_3CN. Subsequently, the partition ratios of substrate **1** or product **3** between electrolytic medium (EMIM BF_4) and nucleophile phase (allyltrimethylsilane) were determined by gas chromatography (GC-2014 with Tween 80, 3 m column, Shimadzu, Japan).

Measurement of droplet size and distribution

Droplet size and distribution were determined by the dynamic light scattering (DLS) method at 25 °C with a light scattering photometer (DLS-7000, Otsuka Electronics Co.) without diluting the mixture.

Acknowledgements

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