Deprotonation in anodic methoxylation of fluoroethyl phenyl sulfides using site-isolated heterogeneous bases†

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On the basis of the concept of site isolation in electrochemical reactions, we have successfully demonstrated acceleration of the deprotonation step in anodic methoxylation of fluoroethyl phenyl sulfides using silica gel supported bases.

In principle, opposing reagents (*e.g.* acid/base and oxidizing/reducing reagents) cannot be put in a single reactor owing to their mutual destruction. About 30 years ago, Cohen *et al.* demonstrated one-pot multistep reactions with the concept of site isolation, which was defined as that the attachment of opposing reagents to the respective insoluble polymers suppresses their mutual destruction.[1] Since the pioneering work of Cohen *et al.*, sol–gel materials,[2] layered clays,[3] star polymers,[4] magnetic particles,[5] and microcapsules[6] have been applied to site-isolated catalysts toward one-pot multistep reactions.[7]

Electrodes in electrochemical reactions are inherently site-isolated heterogeneous redox reagents. Therefore, an anode and a cathode, which are respectively equivalent to oxidizing and reducing reagents, can be put in a single reactor. On the other hand, site isolation between electrodes and solid-supported reagents would also be achieved. Namely, solid-supported reagents should act as site-isolated heterogeneous reagents in electrochemical reactions without the oxidative and reductive destruction at electrodes. We have recently developed novel electrolytic systems for organic electrosynthesis using solid-supported acids[8] and bases.[9] In a series of studies, it was found that solid-supported acids and bases are electrochemically stable and thus reusable for many times. Breinbauer and Nad also reported that direct electrochemical oxidation of polymer-immobilized furans is difficult because of steric reasons.[10] We can regard their electrochemical stability and reactivity as site isolation in electrochemical reactions.

The concept of site isolation in electrochemical reactions may also be applied to the use of solid-supported reagents in organic electrosynthesis for accelerating the subsequent chemical reactions that typically follow electron transfer at electrodes. For instance, it is generally difficult to accelerate the deprotonation step in anodic oxidation of organic compounds using homogeneous bases owing to the oxidative destruction at the anode. The concept of site isolation in electrochemical reactions would potentially solve the problem. Thus, we herein demonstrate acceleration of the deprotonation step in anodic methoxylation of fluoroethyl phenyl sulfides using site-isolated heterogeneous bases.

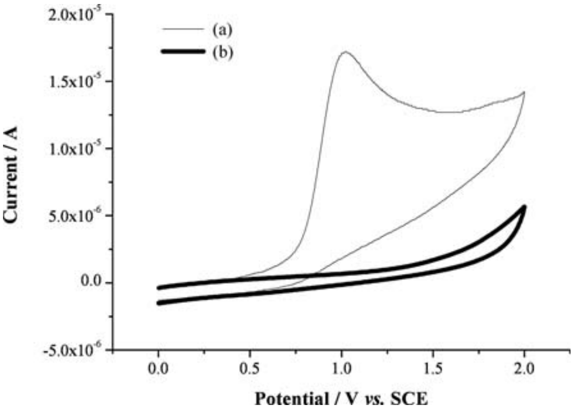

Fig. 1 Cyclic voltammograms of (a) MTBD (0.01 M) and (b) Si-TBD (0.01 M) in 0.1 M $NaClO_4$–MeCN, recorded at a Pt disk electrode (ϕ = 0.8 mm). The scan rate was 100 mV s^{-1}.

First of all, in order to demonstrate the site isolation between the anode and solid-supported bases, we measured the cyclic voltammograms of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), which is a strong base, and silica gel supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (Si-TBD) in MeCN. As shown in Fig. 1, MTBD was easily oxidized at *ca.* 1.0 V *vs.* SCE, while Si-TBD was not oxidized at all in the same potential range. These results support the concept of site isolation in electrochemical reactions.

It has been reported that anodic oxidation of alkyl phenyl sulfides in anhydrous organic solvents generally gives sulfonium ions to form sulfonium salts with anions derived from supporting electrolytes (Scheme 1, path A),[11] while anodic substitution reactions are favored in the presence of bases or nucleophiles, and by the presence of electron-withdrawing groups at the α-position of the sulfur atom (Scheme 1, path B).[12,13] With these facts in mind, we next measured the cyclic voltammograms of 2,2-difluoroethyl phenyl sulfide (**1**) in the absence and presence of Si-TBD in MeCN. As shown in Fig. 2(a), two oxidation waves were observed in the absence of Si-TBD. These waves correspond to the oxidation of **1** and the resulting sulfonium salt, respectively (Scheme 1, path A).[11b] In the presence of Si-TBD, the first oxidation wave was shifted in the negative direction and became larger as shown in Fig. 2(b). These results suggest that Si-TBD accelerates the deprotonation of the radical cation intermediate, which is followed by a rapid loss of the second

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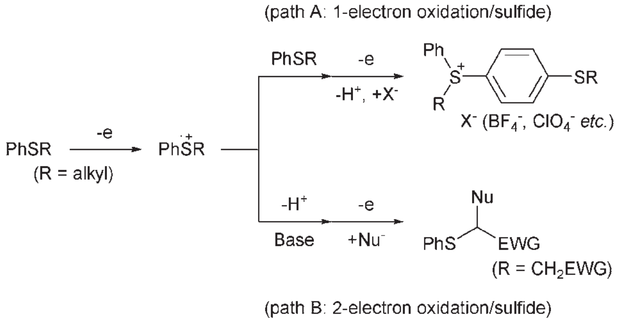


Scheme 1 Anodic oxidation of alkyl phenyl sulfides in anhydrous organic solvents.

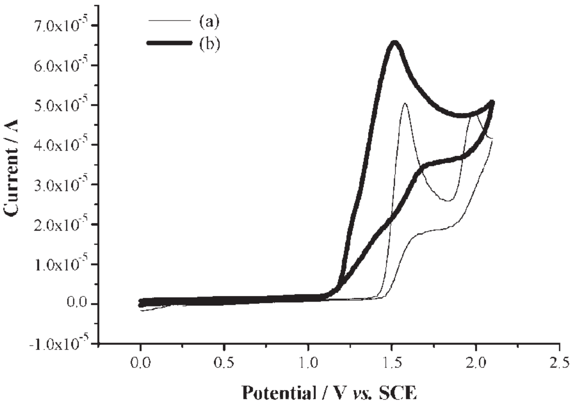
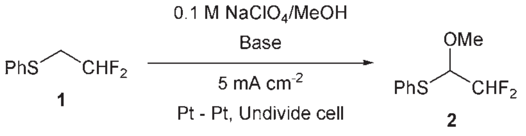


Fig. 2 Cyclic voltammograms of (a) **1** (0.01 M) and (b) **1** (0.01 M) in the presence of 0.2 M Si-TBD in 0.1 M $NaClO_4$–MeCN, recorded at a Pt disk electrode (ϕ = 0.8 mm). The scan rate was 100 mV s^{-1}.

electron (Scheme 1, path B). The second oxidation wave for the sulfonium salt disappeared, which also supports our suggestion.

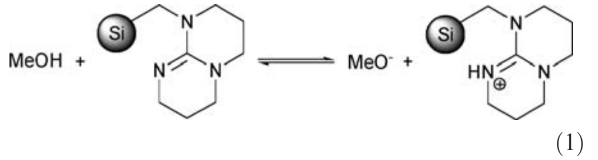
Table 1 Anodic methoxylation of **1** using silica gel supported bases



Entry	Base	Electricity/ Faraday mol^{-1}	Yield[a] (%)
1	—	4	29
2	0.01 M Si-TBD (14.5)[b]	3	32
3	0.1 M Si-TBD	6	54
4	0.2 M Si-TBD	6	67
5	0.2 M Si-pyridine[c] (5.2)	5	31
6	0.2 M Si-pyperidine[d] (11.2)	5	47
7[e]	0.2 M Si-TBD	6	86
8[e]	0.2 M MTBD	6	0 [98][f]

[a] ^{19}F NMR yield based on the CHF_2 group using monofluorobenzene as an internal standard. [b] pK_a value of the conjugate acid in parentheses. [c] Silica gel supported pyridine. [d] Silica gel supported piperidine. [e] Electrolysis was carried out in the absence of $NaClO_4$. [f] Recovery of **1** in brackets.

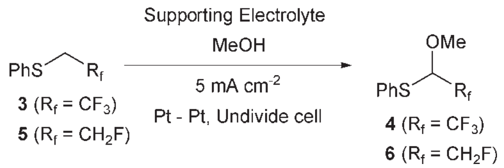
We then investigated anodic methoxylation of **1**[12] as a model reaction using silica gel supported bases as shown in Table 1.‡ In the absence of bases, anodic methoxylation of **1** did not proceed smoothly and the corresponding α-methoxylated product **2** was formed in low yield (Entry 1). In contrast, the yield of **2** increased with increasing amount of Si-TBD (Entries 2–4). These findings indicate that anodic methoxylation of **1** is promoted by Si-TBD, thereby suggesting that the deprotonation of the radical cation intermediate is accelerated by Si-TBD. However, the lifetime of the radical cation intermediate generated at the anode surface seems to be too short for it to be affected directly by the site-isolated Si-TBD. In the presence of Si-TBD, the acid–base reaction between MeOH as a solvent and Si-TBD should occur to generate methoxide ion [eqn (1)]. The methoxide ion might act as a base in the neighborhood of the anode surface to accelerate the deprotonation of the radical cation intermediate. When Si-TBD was used (Entries 3 and 4), a larger amount of electricity was required compared to that in the absence of Si-TBD (Entry 1). This seems to be due to the oxidation of the methoxide ion at the anode. Therefore, these results suggest that the methoxide ion derived from eqn (1) acts as a base in the neighborhood of the anode surface and hence it is oxidized at the anode. On the other hand, the yield of **2** was correlated with the basicity of silica gel supported bases (Entries 4–6). These results indicate that Si-TBD is the most suitable for accelerating the deprotonation step in anodic methoxylation of **1**. The use of Si-TBD as not only a base but also a supporting electrolyte[9a] increased the yield of **2** to 86% (Entry 7). In this case, the methoxide ion derived from eqn (1) must form an electrical double layer at the anode surface, because the electrolysis was carried out in the absence of $NaClO_4$ as a supporting electrolyte. Therefore, the methoxide ion can attack the radical cation intermediate generated at the anode surface to accelerate its deprotonation more effectively. In sharp contrast, when MTBD was used instead of Si-TBD, **1** was completely recovered (Entry 8). In this case, the acid–base reaction between MeOH and MTBD should take place to generate methoxide ion homogeneously in the electrolytic solution. Therefore, the methoxide ion seems to be mainly oxidized at the anode. From the comparison of Entries 7 and 8, it is clear that Si-TBD acts as a site-isolated heterogeneous base in anodic methoxylation of **1**. Furthermore, the methoxide ion derived from eqn (1) seems to be mostly localized on the porous silica gel surface because of the formation of the conjugate acid–base pair. In other words, a methoxide ion concentration gradient seems to form in the presence of Si-TBD (Entry 7). Thus, it is suggested that the methoxide ion as well as the site-isolated Si-TBD is protected within the porous silica gel matrix.



(1)

In order to demonstrate the scope and limitations, we next investigated anodic methoxylation of fluoroethyl phenyl sulfides **3** and **5** in the absence and presence of Si-TBD as shown in Table 2. Although **3** has a strongly electron-withdrawing CF_3 group at the α-position of the sulfur atom, anodic methoxylation of **3** did not proceed smoothly and the corresponding α-methoxylated product **4** was formed in low yield in the

Table 2 Anodic methoxylation of **3** and **5** in the absence and presence of Si-TBD



Entry	R_f	Supporting electrolyte	Electricity/ Faraday mol^{-1}	Yield[a] (%)
1	CF_3	0.1 M $NaClO_4$	3	31
2	CF_3	0.2 M Si-TBD	7	76
3	CH_2F	0.1 M $NaClO_4$	3	Trace
4	CH_2F	0.2 M Si-TBD	3	16

[a] ^{19}F NMR yield based on the R_f group using monofluorobenzene as an internal standard.

absence of Si-TBD (Entry 1). This result suggests that spontaneous deprotonation of the radical cation intermediate is not favored in the absence of Si-TBD. In sharp contrast, **4** was obtained in high yield in the presence of Si-TBD (Entry 2). Anodic methoxylation of **5** did not proceed at all in the absence of Si-TBD, because **5** has the low acidity of the α-proton of the sulfur atom due to the weakly electron-withdrawing CH_2F group (Entry 3). On the other hand, the yield was low, but **6** was certainly formed in the presence of Si-TBD (Entry 4). These findings indicate that the deprotonation step in anodic methoxylation of fluoroethyl phenyl sulfides is accelerated by Si-TBD.

In conclusion, we have successfully demonstrated acceleration of the deprotonation step in anodic methoxylation of fluoroethyl phenyl sulfides using site-isolated heterogeneous bases. It is expected that solid-supported reagents will be applied extensively in organic electrosynthesis to accelerate the subsequent chemical reactions without the oxidative and reductive destruction at electrodes. Furthermore, the concept of site isolation in electrochemical reactions will enable us to create multisolid-phase systems including electrodes toward one-pot multistep reactions.

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Notes and references

‡ General procedure for anodic methoxylation of fluoroethyl phenyl sulfides **1**, **3**, and **5**: anodic methoxylation of a substrate (1 mmol) was carried out with platinum plate electrodes (2×2 cm^2) in 0.2 M Si-TBD (particle size: 40–63 μm, loading: 0.91 mmol g^{-1})/MeOH (based on the concentration of TBD, 10 ml)) using an undivided cell. Constant current electrolysis (5 mA cm^{-2}) was conducted with magnetic stirring at room temperature. After the electrolysis, the yield of the product was calculated by means of ^{19}F NMR using a known amount of monofluourobenzene (1 mmol) as an internal standard. The products **2**,[12b] **4**,[12c] and **6**[13d] were identified by comparison with the literature values using ^1H and ^{19}F NMR and mass spectroscopy.

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