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Direct Oxidative Cyanation Based on the Concept of Site Isolation

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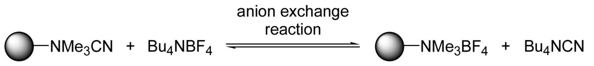
Nucleophilic reactions of carbon nucleophiles with carbocations are one of the most important reactions for carbon−carbon bond formation.[1] The generation of carbocations must be carried out in the presence of carbon nucleophiles owing to their instability. Acid-promoted generation of carbocations is commonly used for carbon−carbon bond formation (Scheme 1, path A). Direct oxidative carbon−carbon bond formation is generally difficult because carbon nucleophiles are easily oxidized to prevent the oxidative generation of carbocations (Scheme 1, path B).[2] In order to achieve direct oxidative carbon−carbon bond formation, Yoshida and Suga et al. have developed the cation pool method which enables the electrochemical generation and accumulation of carbocations at low temperature.[3] However, it requires a stepwise procedure for direct oxidative carbon−carbon bond formation.

About 30 years ago, Cohen and Patchornik et al. demonstrated one-pot multistep reactions with the concept of site isolation, which defined that the attachment of opposing reagents to the respective insoluble polymers suppresses their mutual destruction.[4] This concept may also be applied to the use of polymer-supported carbon nucleophiles in electrochemical generation of carbocations for direct oxidative carbon−carbon bond formation because site isolation between an anode and polymer-supported carbon nucleophiles would be achieved to suppress the oxidation of carbon nucleophiles at the anode. With these facts in mind, we herein demonstrate direct oxidative cyanation based on the concept of site isolation.

In order to demonstrate the site isolation between an anode and a polystyrene-supported quaternary ammonium cyanide (PS-NMe_3CN, Amberlite IRA900 CN^- form), we first measured the cyclic voltammograms of Bu_4NCN as a homogeneous cyanating reagent and PS-NMe_3CN as a heterogeneous cyanating reagent, respectively. As shown in Figure 1a, the oxidation current for CN^- was clearly observed (the onset potential was ca. 1.3 V vs SCE) in the presence of Bu_4NCN. On the other hand, the oxidation current for CN^- remarkably decreased in the presence of PS-NMe_3CN, as shown in Figure 1b. These results support the site isolation between an anode and PS-NMe_3CN. However, the oxidation wave for CN^- was slightly observed in the presence of PS-NMe_3CN. This seems to be due to the oxidation of Bu_4NCN, which is derived from the anion exchange reaction between PS-NMe_3CN and Bu_4NBF_4 as a supporting electrolyte (eq 1).



(1)

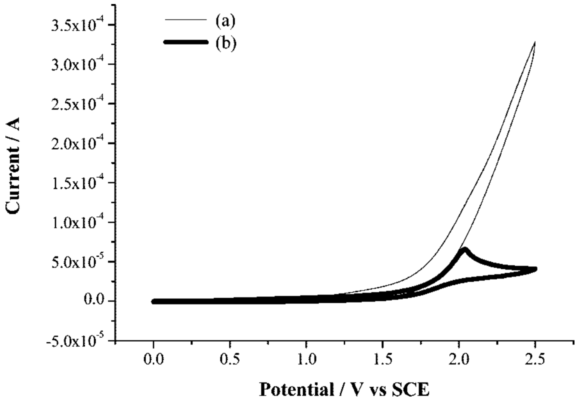


Figure 1. Cyclic voltammograms of (a) 0.2 M Bu_4NCN/MeCN and (b) 0.2 M PS-NMe_3CN in 0.2 M Bu_4NBF_4/MeCN, recorded at a Pt disk electrode (ϕ = 1 mm) at 20 °C. The scan rate was 100 mV s^{-1}.

Scheme 1. Carbon−Carbon Bond Formation via Generation of Carbocations

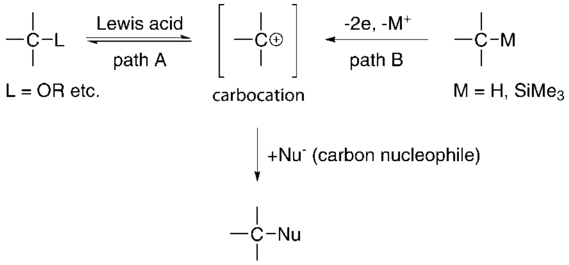
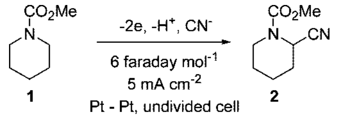


Table 1. Anodic Cyanation of **1** Using PS-NMe_3CN



entry	solvent	supporting electrolyte	cyanating reagent	temp (°C)	yield[a] (%)
1	MeCN	0.1 M Bu_4NBF_4	0.1 M PS-NMe_3CN	20	40[b]
2	MeCN	0.2 M Bu_4NBF_4	0.2 M PS-NMe_3CN	20	80
3	MeCN		0.2 M Bu_4NCN	20	17 (77)[c]
4	MeCN		0.2 M PS-NMe_3CN	20	
5	MeCN	1 M Bu_4NBF_4	0.2 M PS-NMe_3CN	20	31 (53)
6	MeCN	0.2 M Bu_4NBF_4	0.2 M PS-NMe_3CN	0	35[b]
7	MeCN	0.2 M Bu_4NBF_4	0.2 M PS-NMe_3CN	40	40 (39)
8	CH_2Cl_2	0.2 M Bu_4NBF_4	0.2 M PS-NMe_3CN	20	trace[b] (31)

[a] Isolated yield. [b] The corresponding enecarbamate was also formed. [c] Recovery of **1** in parentheses.

While there have been many reports on direct oxidative cyanation of amines,[5] there is no successful example of direct oxidative cyanation of amides owing to their high oxidation potentials. Therefore, as shown in Table 1, we chose anodic cyanation of *N*-(methoxycarbonyl)piperidine (**1**: E_p^{ox} = 2.10 V vs SCE) as a model reaction. Although anodic oxidation of **1** proceeded smoothly in the presence of PS-NMe_3CN, the yield of the cyanated product

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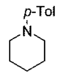
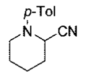
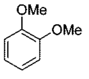
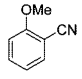
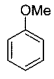
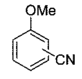
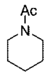
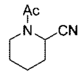
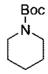
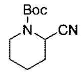
Table 2. Anodic Cyanation of Various Organic Compounds Using PS-NMe$_3$CN and Bu$_4$NCN

$$\text{substrate} \xrightarrow[\substack{5\ \text{mA cm}^{-2} \\ \text{Pt - Pt, undivided cell} \\ 20\ ^{\circ}\text{C}}]{-2e,\ -H^+,\ CN^-} \text{product}$$

entry	substrate	E_p^{ox} (V vs SCE)[a]	method[b]	electricity (faraday mol^{-1})	product	yield[c] (%)
1	 **3**	0.77	A	2	 **4**	72
2			B			77
3	 **5**	1.45	A	2	 **6**	77
4			B			65 (23)[d]
5	 **7**	1.81	A	2.3	 **8**	83 [*o*/*p* = 1/1.2][e]
6			B			38 (58) [*o*/*p* = 1/1.3]
7	 **9**	2.05	A	6	 **10**	80
8			B			37 (46)
9	 **11**	2.09	A	8	 **12**	91
10			B			32 (67)

[a] The oxidation potential was measured in 0.1 M Bu$_4$NBF$_4$/MeCN, recorded at a Pt disk electrode ($\phi = 1$ mm). The scan rate was 100 mV s^{-1}. [b] Method A: 0.2 M PS-NMe$_3$CN in 0.2 M Bu$_4$NBF$_4$/MeCN. Method B: 0.2 M Bu$_4$NCN/MeCN. [c] Isolated yield. [d] Recovery of the substrate in parentheses. [e] Regioisomeric ratio in brackets.

2 was moderate and the corresponding enecarbamate was also formed (entry 1). This finding suggests that the nucleophilicity of CN$^-$ is insufficient in this case. The yield of **2** was increased up to 80% with increasing the amount of PS-NMe$_3$CN (entry 2), which supports our suggestion. In sharp contrast, a large amount of **1** was recovered in the presence of Bu$_4$NCN (entry 3). From comparison of entries 2 and 3, it is clear that the oxidation of CN$^-$ at the anode is suppressed by using PS-NMe$_3$CN because it is a site-isolated heterogeneous cyanating reagent. In the anodic cyanation using PS-NMe$_3$CN, not only the nucleophilicity of CN$^-$ but also its oxidation at the anode would be affected by the anion exchange reaction between PS-NMe$_3$CN and Bu$_4$NBF$_4$ as a supporting electrolyte (eq 1). In order to clarify the role of the anion exchange reaction, we next focused on the concentration of Bu$_4$NBF$_4$, the reaction temperature, and the solvent. In the absence of Bu$_4$NBF$_4$, ionic conductivity was not observed at all (entry 4). This means that the ion pair of the quaternary ammonium cation and CN$^-$ is held together by Coulomb force, which makes it difficult to provide sufficient ionic conductivity to the MeCN solvent. On the other hand, 53% of **1** was recovered in the presence of 1 M Bu$_4$NBF$_4$ (entry 5). In this case, Bu$_4$NCN, which is derived from the anion exchange reaction (eq 1), should be mainly oxidized at the anode because the equilibrium 1 shifts to the right in the presence of a large amount of Bu$_4$NBF$_4$. Although anodic oxidation of **1** proceeded smoothly at 0 °C, **2** was obtained in low yield and the corresponding enecarbamate was also formed (entry 6). This seems to be due to the low nucleophilicity of CN$^-$. In contrast, anodic oxidation of **1** was remarkably suppressed at 40 °C (entry 7). When CH$_2$Cl$_2$ was used as a less polar solvent, **2** was not obtained at all (entry 8). In this case, CN$^-$ should be more strongly associated with the quaternary ammonium cation in CH$_2$Cl$_2$. Therefore, this result suggests that PS-NMe$_3$CN does not act as a cyanating reagent directly. These results indicate that not only the nucleophilicity of CN$^-$ but also its oxidation at the anode depends on the anion exchange reaction between PS-NMe$_3$CN and Bu$_4$NBF$_4$ as a supporting electrolyte (eq 1). Thus, it is possible to control both the nucleophilicity of CN$^-$ and its oxidation at the anode by adjusting the reaction conditions.

In order to demonstrate the scope and limitations, we next investigated anodic cyanation of various organic compounds using PS-NMe$_3$CN and Bu$_4$NCN, respectively. As shown in Table 2, the use of PS-NMe$_3$CN and Bu$_4$NCN gave the almost same yields of **4** in anodic cyanation of a cyclic amine **3** (entries 1 and 2). Anodic cyanation of methoxybenzenes **5** and **7** was carried out to provide **6** and **8** in high yields with the use of PS-NMe$_3$CN (entries 3 and 5), while the use of Bu$_4$NCN resulted in the recovery of considerable amounts of **5** and **7** (entries 4 and 6).[6] In entries 4 and 6, anodic oxidation of **5** and **7** seems to compete with that of Bu$_4$NCN. Although a large amount of electricity was required until the complete consumption of an amide **9**, **10** was obtained in high yield by using PS-NMe$_3$CN (entry 7). On the other hand, the use of Bu$_4$NCN remarkably suppressed the oxidation of **9** (entry 8). Anodic cyanation of a carbamate **11** was successfully achieved in excellent yield by using PS-NMe$_3$CN (entry 9). In sharp contrast, when Bu$_4$NCN was used, a large amount of **11** was recovered (entry 10). These results suggest that the use of PS-NMe$_3$CN allows the oxidation of the substrates to be faster than that of CN$^-$ because the concentration of Bu$_4$NCN derived from eq 1 at the anode surface is much lower than those of the substrates. Thus, it enables us to do anodic cyanation of a wide range of organic compounds, even which have higher oxidation potentials compared to that of CN$^-$.

In conclusion, we have successfully demonstrated the direct oxidative cyanation based on the concept of site isolation, which involves anodic cyanation of amides. The further applications of this new methodology are now under investigation.

Supporting Information Available: Experimental procedures and spectral data for compounds **4** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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