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Article

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Anodic Fluorination and Cathodic Michael Addition of Schiff Bases Bearing Trifluoromethyl and Ester Groups

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ABSTRACT

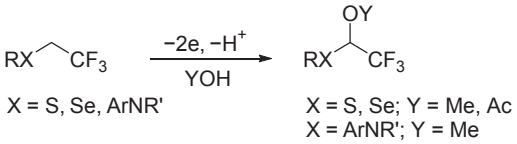
Anodic fluorination of *N*-(diphenylmethyleneamino)-2,2,2-trifluoroethane and *N*-[bis(methylthio)methyleneamino]-2,2,2-triphenylethane in acetonitrile containing poly(HF) salt ionic liquids afforded monofluorinated products in moderate to good yields. On the other hand, anodic fluorination of *N*-[bis(methylthio)methylene]glycine methyl ester provided mono- and difluoroproducts depending on the amount of electricity passed. This is the first successful electrochemical fluorination of open-chain α-amino acid derivatives. Cathodic Michael addition of *N*-(diphenylmethyleneamino)-2,2,2-trifluoroethane to activated olefins such as acrylate and acrylonitrile was also successfully carried out using a titanium cathode.

Keywords : Anodic Fluorination, Cathodic Michael Addition, Schiff Base, α-Fluoroglycine Ester Equivalent

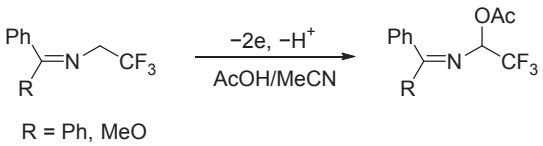
1. Introduction

Organofluorine compounds are highly useful for development of new types of pharamceuticals, agrochemicals, and functional materials.[1–6] In recent years, a large number of organofluorine molecules and macromolecules have been developed. However, their synthesis is not so easy due to the unique nature of a fluorine atom. For example, selective fluorination of organic compounds under safe conditions and selective conversion of organofluorine compounds remain under-developed. Therefore, development of new methodology to solve such problems is highly important in modern synthetic organofluorine chemistry. From these points, we have developed selective electrochemical fluorination of various organic molecules and macromolecules under safe comditions.[7,8] We have also achieved nucleophilic and electrophilic substitutions at α to a CF_3 group by using electrochemical methodology although these substitution reactions have been quite difficult to accomplish by ordinary chemical methods.[9–11] For instance, anodic methoxylation and acetoxylation of trifluoroethyl sulfides, selenides, and anilines have been achieved for the first time as shown in Scheme 1.[12–15] It was demonstrated that the products were versatile building blocks bearing a CF_3 group. We also reported the first examples of anodic α-acetoxylation of CF_3-containing imine and imidate as shown in Scheme 2.[16]

Fluorinated α-amino acids are biologically interesting and highly useful since they have various bio-organic medicinal applications.[17–20] Although synthesis of side chain-fluorinated amino acids and fluorinated β-amino acids has been well established, synthetic methods of α-fluoro-α-amino acids have been underdeveloped so far. Particularly, *N*-unprotected α-fluoro-α-amino acids are unstable because of facile elimination of HF as shown in Scheme 3.[21]



Scheme 1. Anodic methoxylation and acetoxylation of trifluoroethyl sulfides, selenides and anilines.



Scheme 2. Anodic acetoxylation of CF_3-containing imine and imidate.

We have achieved anodic fluorination of *N*-protected thiazolines and 1,3-oxazolines derived from *L*-cysteine and *L*-threonine, respectively, as shown in Scheme 4.[22,23] However, anodic fluorination of *N*-protected open-chain amino acid such as glycine was not successful (Scheme 5).

Quite recently, Molander et al. reported the synthesis of α-fluoro-α-amino acid derivatives via photoredox-catalyzed carbofluorination as shown in Scheme 6.[24]

In consideration to these facts, we anticipate that α-fluoroglycine Schiff base would be stable because there is no proton on the nitrogen atom (Fig. 1).

In fact, quite recently, Mita et al. prepared a stable difluoroglycine derivative using multi components including difluorocarbene precursor followed by esterification as shown in Scheme 7.[25]

As already mentioned, electrophilic substitution at α to a CF_3 group is also problematic. For instance, generation of α-anion to a

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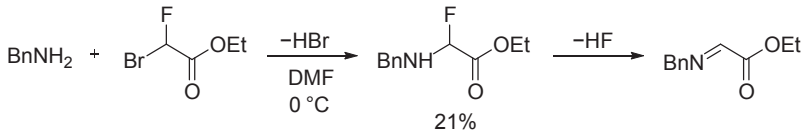
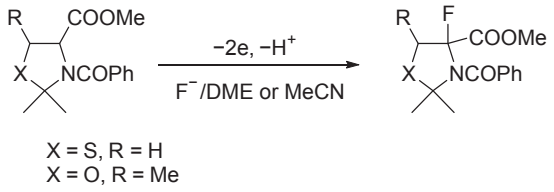
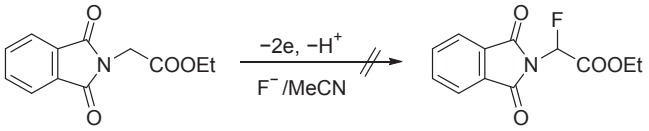


Scheme 3. Synthesis and defluorination of an *N*-unprotected α-fluoro-α-amino acid.



Scheme 4. Anodic fluorination of *N*-protected thiazoline and 1,3-oxazoline.



Scheme 5. An attempt of anodic fluorination of *N*-protected glycine ethyl ester.

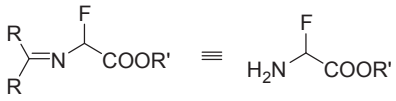


Figure 1. α-Fluoroglycine Schiff base as α-fluoroglycine ester equivalent.

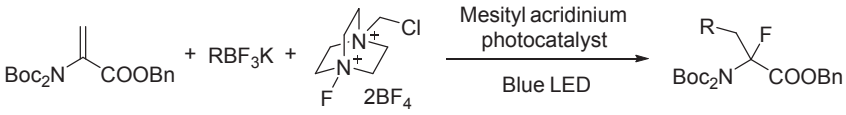
CF_3 group is quite difficult because of facile eliminaton of a fluoride ion.[11,26,27] However, we successfully generated a stable enolate from (trifluoromethyl)malonate ester by using an electrogenerated base such as α-pyrrolidone anion with tetraethylammonium ion, followed by α-alkylation as shown in Scheme 8.[28]

With these facts in mind, we have studied anodic fluorination of Schiff bases of 2,2,2-trifluoroethylamine and glycine methyl ester. Furthermore, we have also studied the cathodic generation of α-anion of 2,2,2-trifluoroethylamine, which can be trapped by activated olefins as a Michael acceptor.

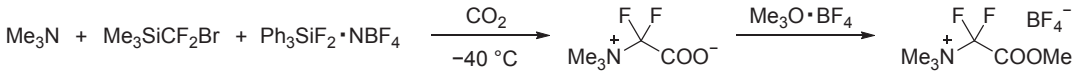
2. Experimental

2.1 General.

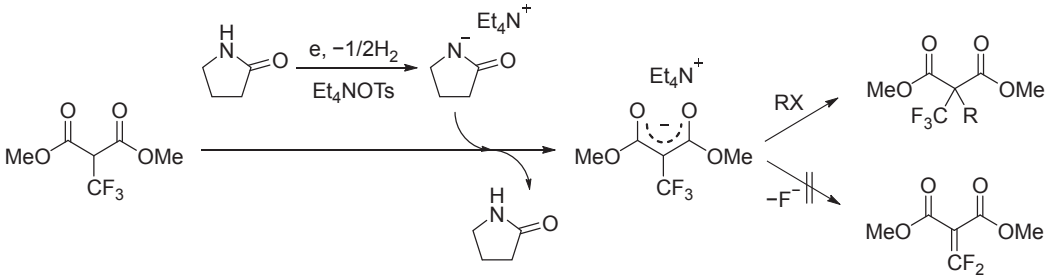
^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL JNM EX-270 (^{1}H: 270 MHz, ^{13}C: 67.8 MHz, ^{19}F: 254.05 MHz) spectrometer in $CDCl_3$. The chemical shifts for ^{1}H and ^{13}C are given in δ (ppm) downfield from internal TMS and $CDCl_3$, respectively. ^{19}F NMR chemical shifts are given in δ (ppm) upfield from external trifluoroacetic acid. All calculations were performed using Gaussian 16 software. Geometry optimizations, frequency calculations, and single point calculations were performed for all compounds at the B3LYP level of theory using 6-31G(d) basis set for all atoms. Oxidation potentials (E_p^{ox}) were measured in 0.1 M Bu_4NBF_4/MeCN at a scan rate of 100 mV/s by cyclic voltammetry using ALS Instruments model 600 A. A platinum disk electrode ($\phi = 1$ mm) and a platinum plate (1 cm × 1 cm) were used as working and counter electrodes, respectively. A saturated calomel electrode (SCE) was used as a reference electrode. Preparative electrolysis



Scheme 6. Synthesis of α-fluoro- α-amino acid derivatives via photoredox-catalyzed carbofluorination.



Scheme 7. Synthesis of a stable difluoroglycine derivative.



Scheme 8. Generation of an anion α to a CF_3 group by using an electrogenerated base and α-alkylation.

experiments were carried out with a Hokuto Denko HABF 501 potentiostat/galvanostat. Mass spectra and high resolution-mass spectra were obtained with a Shimadzu GCMS-QP-2000A or JEOL JMS-700 mass spectrometer. ^{19}F NMR yields were estimated with α,α,α-trifluorotoluene as an internal standard.

2.2 Materials.

Et_3N-nHF (n = 2, 3) and Et_4NF-nHF (n = 3, 4) were kindly supplied by Morita Chemical Industries Co. Ltd. Japan. *N*-(Diphenylmethyleneamino)-2,2,2-trifluoroethane (**1a**) was prepared simlarly according to the literature.[29] *N*-[Bis(methylthio)methylene]-2,2,2-trifluoroethane (**1b**),[30] *N*-[bis(methylthio)methylene]glycne methyl ester (**1c**),[30] and *N*-[bis(phenylthio)methylene]glycine methyl ester (**1d**)[31] were prepared according to the literature methods.

N-(Diphenylmethyleneamino)-2,2,2-trifluoroethane (**1a**) — 87 % yield; ^{1}H NMR: δ = 3.86 (q, *J* = 9.5 Hz, 2H), 7.68–7.15 (m, 10H); ^{19}F NMR: δ = 5.70 (t, *J* = 9.5 Hz, 3F); MS m/z 263 (M^+); HRMS Calcd for $C_{15}H_{12}F_3N$: 263.0922, found: 263.0984.

2.3 General procedure for electrochemical fluorination.

Anodic oxidation of substrate (1 mmol) was carried out at a constant current (10 mA/cm^2) with platinum plate electrodes (2 cm × 2 cm) in a single compartment glass cell containing 10 mL of 1 M Et_3N-nHF (n = 2, 3) or Et_4NF-nHF (n = 3, 4)/DME or MeCN. Comsumption of the starting material was comfirmed by alumina TLC. After the electrolysis, the electrolytic solution was passed through a short column filled with alumina using $CHCl_3$ as an eluent to remove fluoride salts. Since the fluorinated products are readily decomposed by silica gel column chromatography, the products were purified by alumina column chromatography with hexane/ethyl acetate (10:1) as an eluent. However, monofluoro products **2a** and **2b** were not stable enough to be isolated in pure form.

N-(Diphenylmethyleneamino)-1-fluoro-2,2,2-trifluoroethane (**2a**) — ^{19}F NMR: δ = −3.88 (dd, *J* = 12.8, 3.7 Hz, 3F), −81.28 (dq, *J* = 52, 12.8 Hz, 1F); MS m/z 281 (M^+), 212 (M^+-CF_3); HRMS Calcd for $C_{15}H_{11}F_4N$: 281.0827, found: 281.0841.

N-[Bis(methylthio)methyleneamino]-1-fluoro-2,2,2-trifluoroethane (**2b**) — ^{19}F NMR: δ = −5.04 (dd, *J* = 11.1, 3.7 Hz, 3F), −78.80 (dq, *J* = 52, 12.8 Hz, 1F); MS m/z 221 (M^+), 174 (M^+-MeS); HRMS Calcd for $C_5H_7F_4NS_2$: 220.9956, found: 220.9968.

N-[Bis(methylthio)methylene]-1-fluoroglycine methyl ester (**2c**) — ^{19}F NMR: δ = −69.71 (d, *J* = 55 Hz, 1F); MS m/z 211 (M^+), 164 (M^+-MeS), 152 (M^+-CO_2Me); HRMS Calcd for $C_6H_{10}FNO_2S_2$: 211.0137, found: 211.0127.

N-[Bis(methylthio)methylene]-1,1-difluoroglycine methyl ester (**3**) — ^{1}H NMR: δ = 3.88 (s, 3H), 2.60 (s, 3H); 2.55 (s, 3H); ^{19}F NMR: δ = −2.33 (s, 2F); MS m/z 229 (M^+); 182 (M^+-MeS), 170 (M^+-CO_2Me), HRMS Calcd for $C_6H_9F_2NO_2S_2$: 229.0043, found: 229.0032.

2.4 General procedure for cathodic Michael addition.

Cathodic reduction of **1a** (1 mmol) was carried out at a constant current (10 mA/cm^2) with various cathode materials and a titanium anode (2 cm × 2 cm, each) in an H-type divided glass cell with a sintered glass separator containing 10 mL of 1 M Et_4NBF_4/MeCN or DMF including activated olefin (5 mmol). Comsumption of the starting material was comfirmed by silica gel TLC. After the electrolysis, the electrolytic solution was mixed with water. The resulting solution was extracted with ethyl acetate and the extracts were washed with brine, and then were dried over $MgSO_4$. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel using a mixure of hexane/ethyl acetate (7:1) as an eluent to give **4a** or **4b**.

1-[(Diphenylmethylene)amino]-1-trifluoromethyl-3-methoxycarbonylpropane (**4a**) — Colorless oil; ^{1}H NMR: δ = 7.66–7.15 (m, 10H), 3.94–3.85 (m, 1H), 3.55 (s, 3H), 2.37–2.08 (m, 4H); ^{13}C NMR: δ = 173.00, 172.61, 138.58, 135.38, 130.83, 128.85, 128.79, 128.61, 128.03, 127.60, 125.34, 118.48, 62.52, 51.64, 29.68, 24.93, 13.43; ^{19}F NMR: δ = 2.93 (d, *J* = 7 Hz, 3F); MS m/z 349 (M^+), 348, 276 (M^+-CH_2COOMe), 262 (M^+-MeOCOCH$_2$CH$_2$); HRMS Calcd for $C_{19}H_{18}NO_2$: 349.1290, found: 349.1298.

1-[(Diphenylmethylene)amino]-1-trifluoromethyl-3-cyanopropane (**4b**) — Colorless oil; ^{1}H NMR: δ = 7.68–7.16 (m, 10H), 4.02–3.95 (m, 1H), 2.42–2.03 (m, 4H); ^{13}C NMR: δ = 174.37, 138.20, 134.83, 131.15, 129.11, 128.92, 128.83, 128.09, 127.41, 124.85, 118.48, 61.80, 26.14, 13.43; ^{19}F NMR: δ = 3.17 (d, *J* = 7 Hz, 3F); MS m/z 316 (M^+), 315 (M^+-H), 262 (M^+-CH_2CH_2CN); HRMS Calcd for $C_{18}H_{15}F_3N_2$: 316.1187, found: 316.1200.

1-[(Diphenylmethylene)amino]-2,2-difluoroethylene (**5**) — Colorless oil; ^{1}H NMR: δ = 7.78–7.18 (m, 10H), 6.03 (d, *J* = 18 Hz, 1H); ^{13}C NMR: δ = 165.72, 157.99, 135.27, 130.30, 128.92, 128.64, 128.57, 128.25, 128.07, 96.59; ^{19}F NMR: δ = 18.89 (d, *J* = 19 Hz, 1F), 8.93 (dd, *J* = 19, 18 Hz, 1F); MS m/z 243 (M^+), 224 (M^+-F), 166 (M^+-Ph); HRMS Calcd for $C_{15}H_{11}F_2N$: 243.0860, found: 243.0846.

3. Results and Discussion

3.1 Oxidation potentials of Schiff bases of 2,2,2-trifluoroethylamine and glycine methyl ester

At first, the oxidation potentials (E_p^{ox}) of various Schiff bases, **1a**–**1d** were measured by cyclic voltammetry in Et_4NBF_4/MeCN using a platinum (Pt) disk electrode. The oxidation potentials are summarized in Table 1.

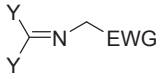
The oxidation potentials of sulfur-containing Schiff base derivatives **1b**–**1d** are much less positive compared to that of imine **1a** devoid of sulfur atoms. Schiff base **1c** having MeS groups is more easily oxidized than that having PhS groups **1d**. Since a CF_3 group is a stronger electron-withdrawing group than an ester group, the oxidation potential of imine **1b** bearing a CF_3 group is more positive compared to that bearing an ester group **1c**.

To theoretically determine the site of electron abstraction of imines **1a**–**1d**, density functional theory (DFT) calculations were carried out (Fig. 2). The highest occupied molecular orbital (HOMO) of **1a** was mainly located on one of the phenyl groups and the C=N bond while that of **1b** and **1c** is mainly located on one of the sulfur atoms and the C=N double bond. The HOMO of **1d** is mainly located on one of the phenylthio groups and the C=N double bond as shown in Fig. 2.

3.2 Anodic fluorination of Schiff bases

At first, anodic fluorination of *N*-(diphenylmethyleneamino)-2,2,2-trifluoroethane (**1a**) was carried out at a Pt anode in DME and MeCN containing Et_3N-nHF (n = 2, 3) or Et_4NF-nHF (n = 3, 4) using an undivided cell. The results are summarized in Table 2.

Table 1. Oxidation potentials of Schiff bases **1a**–**1d**.[a)]



Substrate	Y	EWG	E_p^{ox} (V vs. SCE)
1a	Ph	CF_3	2.30
1b	MeS	CF_3	1.76
1c	MeS	COOMe	1.62
1d	PhS	COOMe	1.82

a) Pt disk electrode (φ = 1 mm), 0.1 M Et_4NBF_4/MeCN, scan rate: 100 mV/s.

As shown in Table 2, electrolysis in Et_4NF-3HF/DME provided the desired α-monofluorinated product **2a**; however, the yield was low (run 1). In this case, even a large excess amount of electricity was passed, the starting material **1** was not completely consumed and a considerable amount of **1** was recovered. When Et_4NF-4HF/DME was used, the conversion of **1** increased, but the yield of **2a** was extremely low (run 2) because of formation of unidentified by-products. Since the oxidation potential of **1a** is rather positive (E_p^{ox} = 2.70 V vs. SCE), DME was more easily oxidized than the substrate **1a** resulting in low current efficiency. Then, anodically stable MeCN was used as an electrolytic solvent. As expected, the yield increased to 18 % when Et_3N-2HF/MeCN was employed (run 3), but a larger excess amount of electricity was necessary to consume **1a** because of readily oxidizable Et_3N-2HF containing free Et_3N. Then, anodically more stable Et_3N-3HF/MeCN was used. In this case, the starting material **1a** was consumed by passing an amount of electricity slightly higher (2.5 F/mol) than the theoretical amount and the yield of **2a** was increased significantly to 45 % (run 4). However, the use of anodically stable Et_4NF-3HF/MeCN was found to be less effective (run 5). Since Et_3N-3HF contains free Et_3N, the deprotonation of **1a** radical cation was presumably promoted to give the better yield in run 4.

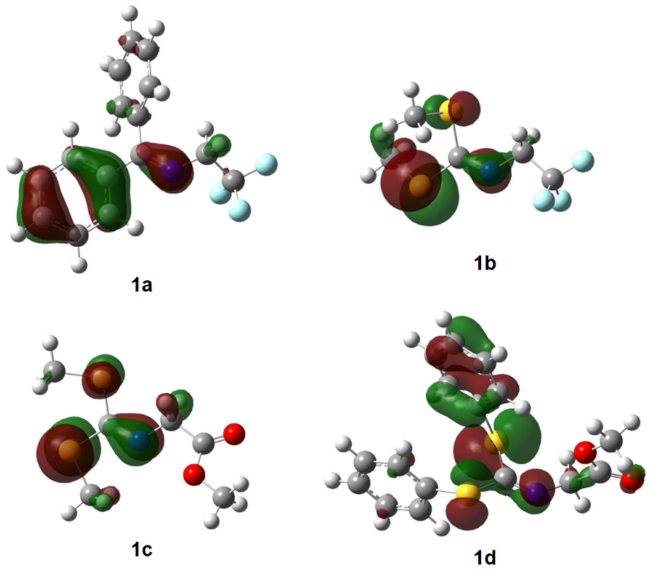
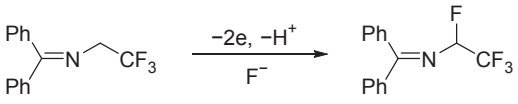


Figure 2. Computationally simulated HOMO diagrams of **1a**, **1b**, **1c** and **1d** with a B3LYP/6-31G(d) level of theory (iso value = 0.04).

Table 2. Anodic fluorination of *N*-(diphenylmethyleneamino)-2,2,2-trifluoroethane (**1a**).



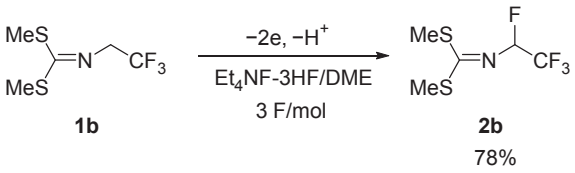
Run	Supporting electrolyte	Solvent	Electricity (F/mol)	Yield of **2a** (%)[a]	Recovery of **1a** (%)[a]
1	Et_4NF-3HF	DME	9.3	11	63
2	Et_4NF-4HF	DME	7.2	2	23
3	Et_3N-2HF	MeCN	10.0	18	0
4	Et_3N-3HF	MeCN	2.5	45	0
5	Et_4NF-3HF	MeCN	5.2	15	0

a) Determined by ^{19}F NMR.

Next, more easily oxidizable 2,2,2-trifluoroethylimine bearing two methylthio groups **1b** was subjected to anodic fluorination. As shown in Scheme 9, anodic fluorination proceeded efficiently even in DME containing Et_4NF-3HF. When 3 F/mol of electricity was passed, starting **1b** was consumed and the desired fluorinated product (**2b**) was formed in good yeild as 78 %.

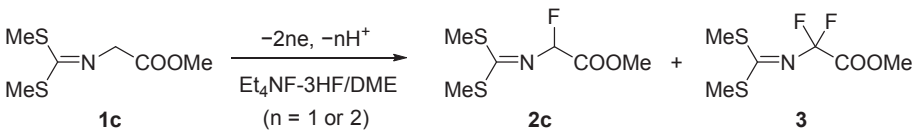
Next, anodic fluorination of *N*-[bis(methylthio)methylene]glycine methyl ester (**1c**) was carried out in Et_4NF-3HF/DME. The results are summarized in Table 3.

When the theoretical electricity (2 F/mol) was passed, the expected monofluoro product **2c** was formed in moderate yield as 50 % (run 1). When the electricity was increased to 3 F/mol, the yield also increased to 77 %. However, the electricity was increased further to 4 F/mol, the yield decreased to 60 %. In this case, difluoro product **3** was formed. The yield of **3** was increased with increasing electricity, and reached 34 % at 8 F/mol. At a larger excess amount of electrcity (10 F/mol), difluoro product **3** was formed predominantly in 35 % yield. The relationship between the yields of **2c** and **3** with electricity passed is shown in Fig. 3.



Scheme 9. Anodic monofluorination of **1b**.

Table 3. Anodic fluorination of *N*-[Bis(methylthio)methylene]glycine methyl ester (**1c**).



Run	Electricity (F/mol)	Yield (%)[a]	
		2c	**3**
1	2	50	0
2	3	77	0
3	4	60	11
4	6	33	17
5	8	5	34
6	10	0	35[b]

a) Determined by ^{19}F NMR. b) Isolated yield.

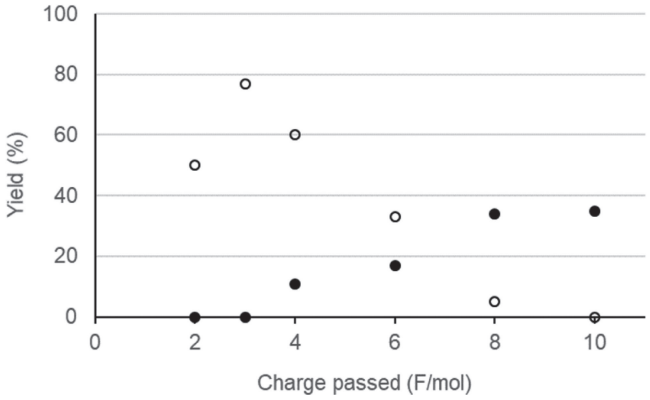
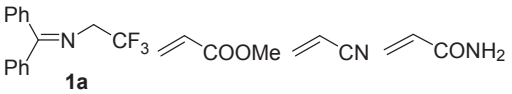


Figure 3. Dependence of yields of **2c** and **3** on charge passed: (○) **2c**, (●) **3**.

Table 4. Reduction potentials of **1a** and activated olefins.[a)]



1a

E_{onset}^{red} (V vs. SCE)	−2.04	−2.15	−2.23	−1.93
E_p^{red} (V vs. SCE)	−2.25	−2.39	−2.36	−2.28

a) CV measurement conditions: 100 mM substrate in Et_4NBF_4/MeCN, Pt disk working electrode ($\phi = 1$ mm), scan rate 100 mV/s.

Next, we attempted anodic fluorination of Schiff base having bis(phenylthio) group **1d**. However, fluorination did not proceed at all. In this case, decomposition of **1d** took place during electrolysis and diphenyl disulfide was formed.

In consideration to the relationship between the yields of **2c** and **3** with electricity passed shown in Fig. 3, anodic fluorination of imines seems to proceed as shown in Scheme 10. As already mentioned, electron transfer takes place from the $(Ph)_2C{=}N$- (**1a**) or the $(RS)_2C{=}N$- (**1b**–**1d**) portion to generate the delocated radical cation **A** followed by deprotonation, and further one electron oxidation to form cation intermediate **B**. The resulting cation reacts with a fluoride ion to give fluorinated products **2b** and **2c**. Product **2c** undergoes two-electron oxidation and deprotonation followed by reaction with a fluoride ion to form *gem*-difluoro product **3**.

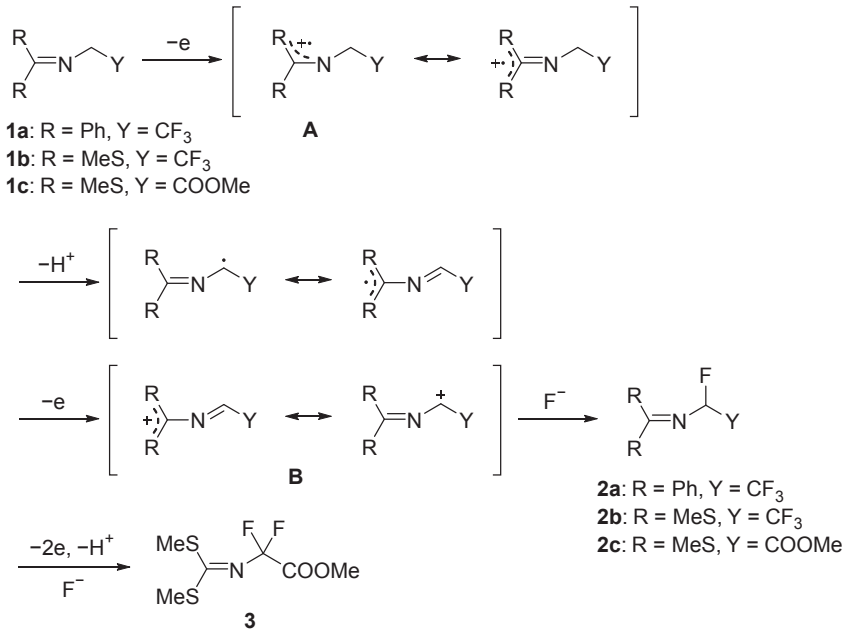
3.3 Cathodic Michael addition of *N*-(diphenylmethyleneamino)-2,2,2-trifluoroethane (1a) to activated olefins

At first, the reduction potentials of **1a** and activated olefins such as methyl acrylate, acryronitrile, and acrylamide were measured by cyclic voltammetry. Their reduction onset and peak potentials (E_{onset}^{red} and E_p^{red}) are summarized in Table 4.

As shown in Table 4, the reduction onset potential (E_{onset}^{red}) and the reduction peak potential (E_p^{red}) of **1a** are less negative than those of methyl acrylate and acryronitrile, while E_{onset}^{red} of **1a** is more negative than that of acrylamide and E_p^{red} of **1a** is almost same as that of acrylamide. Cathodic reduction of **1a** was carried out at a Pt cathode in DMF and MeCN containing Et_4NBF_4 in the presence of methyl acrylate as a Michael acceptor in a divided cell. The results are summarized in Table 5.

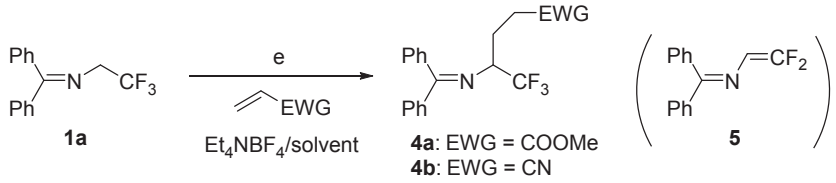
As shown in Table 5, the expected Michael adduct **4a** was formed in 12 % yield (run 1). Use of MeCN instead of DMF resulted in a two-fold increase of the yield (run 2). Then, cathodic reduction **1a** was performed with various cathode materials other than Pt. Glassy carbon (GC) and copper (Cu) cathodes were found to be more efficient than a Pt cathode (runs 3 and 4), while a lead (Pb) cathode was not effective (run 5). In the latter case, a small amount of defluorination by-product **5** was formed. Notably, a titanium (Ti) cathode was found to be the best choice to give **4a** in 64 % yield (run 6). When the amount of activated olefin i.e. Michael acceptor, acrylate was reduced, the yield also decreased (runs 7 and 8).

Next, we investigated cathodic Michael addition of **1a** to other acceptors such as acrylonitrile and acrylamide using a Ti cathode similarly. Cathodic Michael addition to acrylonitrile took place to give the corresponding adduct **4b** in moderate yield (45 %) (Table 5, run 9) while the use of acrylamide resulted in no formation of the expected adduct (run 10). In this case, the coresponding trifluoroethylamine derived from **1a** was detected in the crude product by ^{19}F NMR and MS spectra.



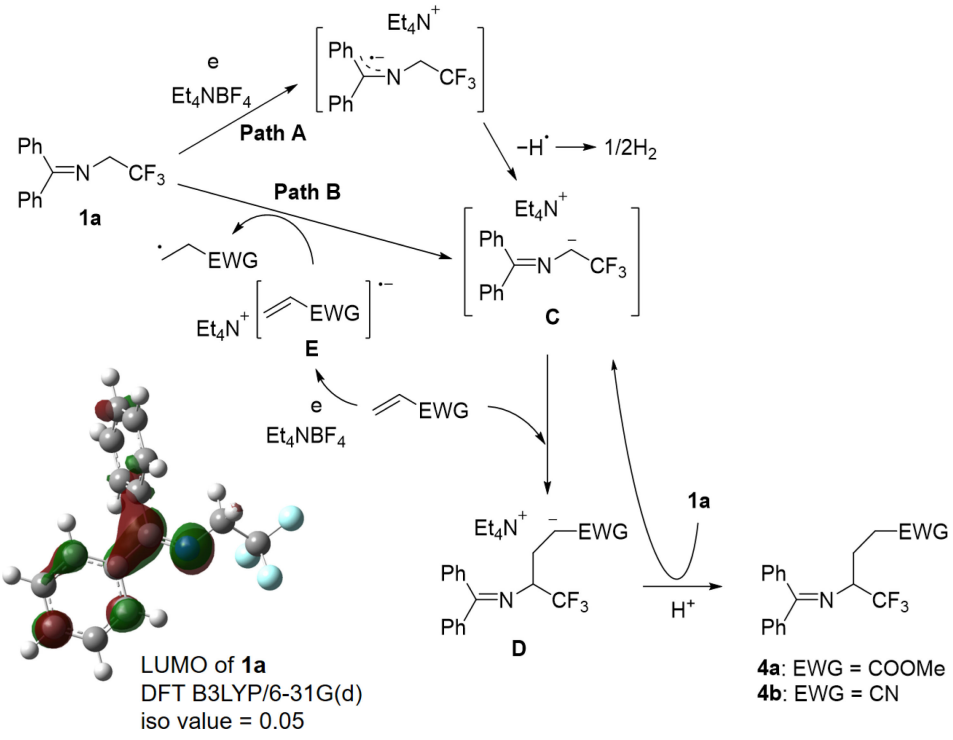
Scheme 10. Plausible mechanism for anodic fluorination of **1a**–**1c**.

Table 5. Cathodic Michael addition of **1a** to activated olefins.



Run	Cathode	Solvent	Activated olefin		Charge passed (F/mol)	Yield of **4** (%)[a]
			EWG	Equiv.		
1	Pt	DMF	COOMe	5	0.9	12
2	Pt	MeCN	COOMe	5	0.8	25
3	GC	MeCN	COOMe	5	1.0	31
4	Cu	MeCN	COOMe	5	1.3	30
5	Pb	MeCN	COOMe	5	1.0	3[b]
6	Ti	MeCN	COOMe	5	0.9	64 (48)[c]
7	Ti	MeCN	COOMe	3	0.8	35
8	Ti	MeCN	COOMe	1	0.9	12
9	Ti	MeCN	CN	5	1.7	45 (28)[c]
10	Ti	MeCN	$CONH_2$	5	2.2	0[d]

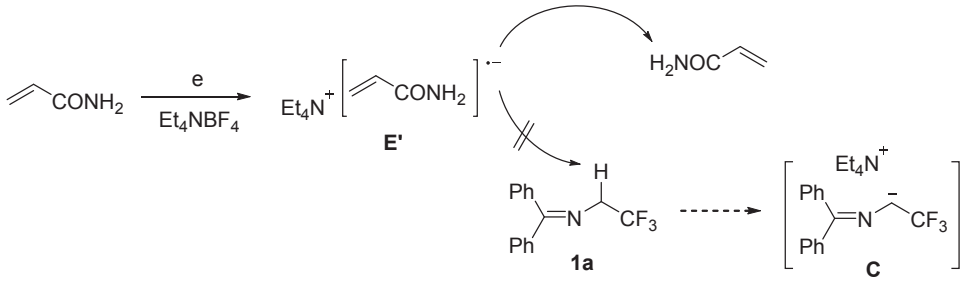
a) Determined by ^{19}F NMR. b) By-product **5** (3 %) was detected by ^{19}F NMR. c) Isolated yield is shown in parentheses. d) $CF_3CH_2NHCHPh_2$ was detected by ^{19}F NMR (5.85 ppm (t, $J = 9$ Hz)) and MS spectra (m/e = 265 [M^+]).



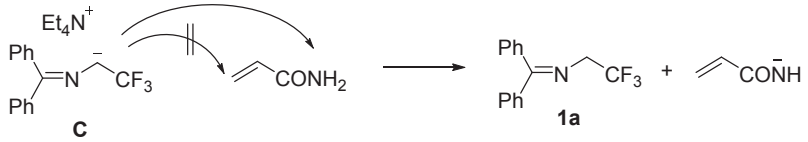
Scheme 11. Plausible mechanism of cathodic Michael addition.

Cathodic Michael addition of imine **1a** seems to proceed as shown in Scheme 11. The calculated LUMO of **1a** is mainly located on the C=N bond. Therefore, one-electron transfur takes place at the C=N bond to generate radical anion followed by elimination of an H atom to generate anion intermediate **C**, which should be stabilzed by a counter quaternary ammonium ion similarly to the reported case (Path A).[28] The resulting anion intermediate **C** reacts with acrylate and acrylonitrile to form anionic intermediate **D**, followed by protonation to give the corresponding Michael adduct **4a** and **4b**, respectively.

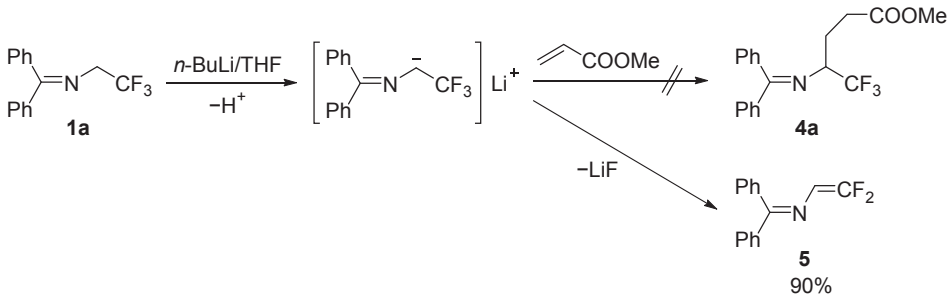
Since a large excess amount of acrylate and acrylonitrile as a Michael acceptor was necessary to form **4a** and **4b**, these activated olefins would be also reduced simultaneously in spite of their more negative reduction potentials comapared to **1a**. The resultant radical anion intermediate **E** abstructs a proton from **1a** to generate **C** (Path **B**). Michael addition of anion **C** to the activated olefin gives anion **D**, which would abstract a proton from **1a** to regenerate **C** and form the Michael adduct **4**. In contrast, acrylamide is more easily reduceable, acrylamide should be reduced at the cathode prior to **1a**. However, the resulting radical anion **E′** seems to abstruct a proton from acrylamide itself prior to from **1a** as shown in Scheme 12. Thus, no formation of the Michael adduct with acrylamide is explained reasonably. Even if anionic intermediate **C** is generated, **C** abstracts a proton from acrylamide prior to addition of **C** to acrylamide (Scheme 13).



Scheme 12. Reactivity of an radical anion **E′** of acrylamide.



Scheme 13. Reactivity of anionic intermediate **C**.



Scheme 14. Reaction of **1a** with n-BuLi in the presence of acrylate.

The desired anion **C** can be generated by the reaction of **1a** with a strong base. However, treatment with *n*-BuLi followed by addition of acrylate did not form **4a** at all. In this case, the elimination of HF proceeded predominantly to form **5** solely in high yield as shown in Scheme 14. Since Li counter cation has a strong affinity for the fluorine atom, the defluorination seems to be accelerated.[26–28]

4. Conclusions

We have disclosed electrochemical properties of Schiff base derivatives of 2,2,2-trifluoroethylamine and glycine ester by cyclic voltammetric studies, and we have achieved their anodic fluorination as well as cathodic Michael addition of 2,2,2-trifluoroethylamine Schiff base to activated olefin using a Ti cathode. Thus, we have illustrated the first successful examples of electrochemical fluorination of open-chain amino acid and cathodic Michael addition.

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