Facile Preparation of Flavinium Organocatalysts

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Abstract: We developed a safe, simple, inexpensive, and environmentally benign method for preparing *N*(5)-ethylated flavinium organocatalysts without using any hazardous reagents or inert conditions as previously required. 5-Ethyl-3-methyllumiflavinium cation was prepared from its reduced form by $NaNO_2$-free aerobic oxidation, which was subsequently extracted onto commercial cation-exchange resins under $NaClO_4$-free conditions. The resulting resin-immobilized flavinium salts were found to be effective organocatalysts for aerobic oxidation reactions.

N(5)-Ethylated flavinium salts (**FlEt$^+$A$^-$**, Figure 1) are proven to be highly active and chemoselective catalysts in various oxidation reactions with hydrogen peroxide or molecular oxygen as terminal oxidants over the past quarter century.[1] Although these are environmentally benign oxidation reactions because they utilize metal-free organocatalysts, nonhazardous terminal oxidants, and produce nontoxic wastes, the use of them for laboratorial as well as industrial synthetic chemistry has been limited compared with traditional metal-based oxidation reactions.[2] One of the reasons for such limitation would be conventional preparation methods for **FlEt$^+$A$^-$**. In general, the perchlorate anion (ClO_4^-) is selected as A^- because of high crystallinity and high catalytic activity of the resulting flavinium salts, and these are prepared from the corresponding *N*(5)-unmodified flavin molecules through *N*(5)-ethylation, *N*(5)-cationization, anion exchange, and then purification as crystals (Figure 1). The most commonly used procedure today was introduced by Mager two decades ago,[3] but has not so far been updated despite its unsatisfactory practicality, which requires careful operation under an inert atmosphere, product purification and analysis with skillful experimental techniques, and, most problematically, a large excess of hazardous reagents such as toxic $NaNO_2$ and explosive $NaClO_4$ (Figure 1a). Only very recently Murahashi and coworkers demonstrated that other non-coordinating anions such as TfO^-, BF_4^-, and PF_6^- are also usable to crystalize **FlEt$^+$A$^-$**, although excess amounts of their sodium salts as well as acid forms, which are much more expensive than conventional perchlorates, are required.[4]

Herein, we present a safe, easy, and inexpensive novel method for preparing **FlEt$^+$A$^-$** (Figure 1b). We have found that molecular oxygen in air can be used as an oxidizing agent for *N*(5)-cationization under suitable reaction conditions. In addition, we show that *N*(5)-ethylated flavinium cations **FlEt$^+$** generated

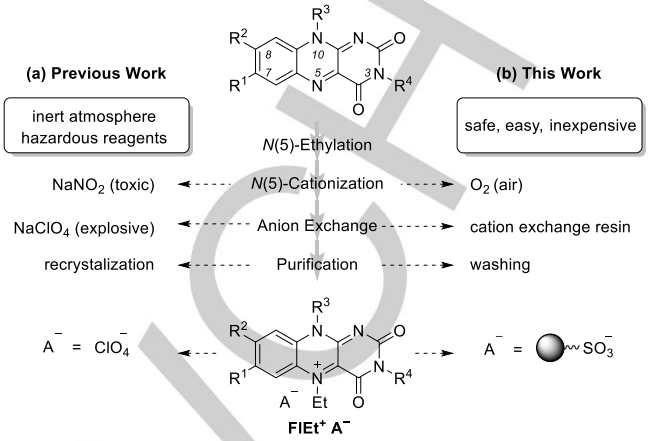

Figure 1. Preparation of *N*(5)-ethylated flavinium salts. (a) previous work, (b) this work.

under such aerobic conditions can be readily extracted onto commercial sulfonic acid-functionalized cation-exchange resins and purified by washing the resulting resins with inexpensive solvents. Finally, we demonstrate that the resin-immobilized *N*(5)-ethylated flavinium salts can be used as efficient organocatalysts for aerobic oxidation reactions.

We have chosen 3-methyllumiflavin (**LFl**) as a model substrate and started our investigation by exploring whether its *N*(5)-ethylated reduced form, 5-ethyl-3-methyl-1,5-dihydrolumiflavin (**LFlHEt**), could be converted into the corresponding two-electron oxidized form, 5-ethyl-3-methyllumiflavinium cation (**LFlEt$^+$**), by aerobic oxidation (Scheme 1).[5] This process previously required the removal of Pd/C by filtration with Celite under an inert atmosphere after reductive *N*(5)-ethylation of **LFl** followed by the oxidation with an excess (6 equiv.) of $NaNO_2$ (Scheme 1a).[4,6] Early studies on the redox chemistry of *N*(5)-alkylated flavin molecules showed that their reduced forms such as **LFlHEt** readily underwent oxidation in water with a range of pH under aerobic conditions to give the corresponding one-electron oxidized forms, such as 5-ethyl-3-methyllumiflavosemiquinone (**LFlEt•**), via an autocatalytic mechanism involving the aerobic formation of **LFlEt$^+$** that readily reacts with **LFlHEt** to give **LFlEt•**.[7a,7b] Therefore, we expected that it must be possible to produce **LFlEt$^+$** by further oxidation of **LFlEt•** with O_2 in air as an oxidant after all of **LFlHEt** is consumed (Scheme 1b).

Although Cibulka and coworkers used such aerobic conditions for the formation of **FlEt$^+$A$^-$** attached to cyclodextrins from their reduced forms, its reaction mechanism was not studied and the products were not isolated.[8]

Reductive *N*(5)-ethylation of **LFl** (24 mM, 674×10^{-3} wt%) was conducted according to well-established protocols using acetaldehyde and hydrogen gas in the presence of Pd/C catalyst under acidic aqueous-alcoholic conditions.[3,4,6] After the completion of the reaction as judged by thin-layer chromatography (TLC) analysis with the disappearance of **LFl**, the subsequent Celite filtration was carried out under air by using water for rinsing to give a reddish brown-colored solution

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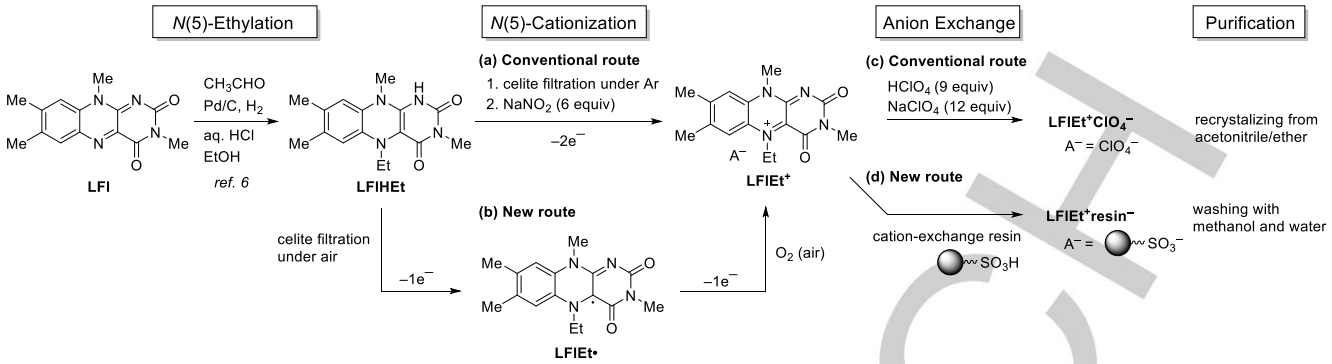


Scheme 1. Preparation of 5-ethyl-3-methyllumiflavinium salt. (a) and (c) conventional route, (b) and (d) new route.

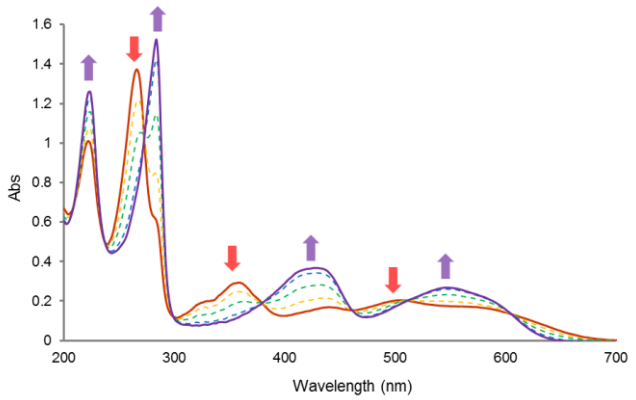


Figure 2. Time variation of absorption spectra in the conversion of **LFIEt·** into **LFIEt⁺** ([**LFIEt·**]+[**LFIEt⁺**]=2.0×10^{-3} wt%) under air. 0 min (red), 6 min (yellow), 17 min (green), 38 min (blue), 60 min (purple).

including **LFI**-related species at 225×10^{-3} wt%.

A small portion of the solution was diluted about 110× with nitrogen-bubbled deionized water to give a 2.0×10^{-3} wt% solution to be analyzed by UV/Vis spectroscopy. An absorption curve assignable to a protonated **LFIEt•** (492 and 358 nm)[7c] was mainly observed together with that assignable to **LFIEt⁺** (545, 430, and 282 nm)[7c] in the ratio of 75:25, which remained unchanged under nitrogen atmosphere for a few hours (Figure 2, red). This observation suggested that **LFIHEt** generated by the *N*(5)-ethylation could be rapidly converted into **LFIEt•** during the Celite filtration, and its further oxidation into **LFIEt⁺** could also proceed with O_2 in air although it is not as fast as the first single electron oxidation (Scheme 1b). To confirm this assumption, the above UV/Vis sample solution was bubbled with air for 1 min and its subsequent changes were pursued on UV/Vis measurements. As expected, the conversion of **LFIEt•** into **LFIEt⁺** was triggered by the addition of air and completed in 60 min without generating any other components (Figure 2, red to purple). It should be noted that distinct isosbestic points were observed in the UV/Vis spectra, showing that the desired oxidation may take place via direct electron-transfer mechanism from **LFIEt•** to O_2 to produce **LFIEt⁺** and $O_2^{\bullet-}$. A similar reaction was also observed in the main part of the filtrate (225×10^{-3} wt%) continuously exposed to air with vigorous stirring at room temperature after the Celite filtration, which could be recognized by a change of the color of solution from reddish brown to deep purple known as the characteristic color of **LFIEt⁺**. However, the ratio of **LFIEt•** to **LFIEt⁺** was 33:67 even after 360 min spectroscopically (Table 1, entry 1), which was much slower than the above reaction at 2.0×10^{-3} wt% (Figure 2 and Table 1, entry 2).

We then attempted to optimize reaction conditions for the conversion of **LFIEt•** into **LFIEt⁺** under aerobic conditions. An approximately 75:25 mixture of **LFIEt•** and **LFIEt⁺** (225×10^{-3} wt%, pH 0.6) was prepared according to the aforementioned procedure prior to use and used as a starting solution for each of the following experiments. Reactions were evaluated by UV/Vis spectroscopy. When the starting solution was exposed to 1 atm of O_2 under vigorous stirring at room temperature the desired reaction proceeded much faster than that conducted in air under otherwise identical conditions (Table 1, entry 1 vs 3), in which absorption peaks for **LFIEt•** completely disappeared in 150 min to give only those for **LFIEt⁺**. This result shows that the reaction is facilitated by increasing the partial pressure of O_2. To enhance the reaction efficiency under air, the effect of pH values was next explored. When the pH of the starting solution was increased from 0.6 to 1.5 by adding sodium bicarbonate, the

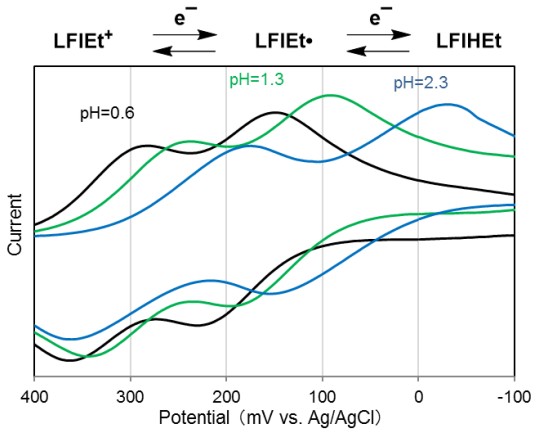
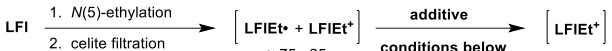


Figure 3. Cyclic voltammograms vs Ag/AgCl of **LFIEt⁺** in HCl aqueous solutions under different pH conditions. pH 0.6 (black), pH 1.3 (green), pH 2.3 (blue).

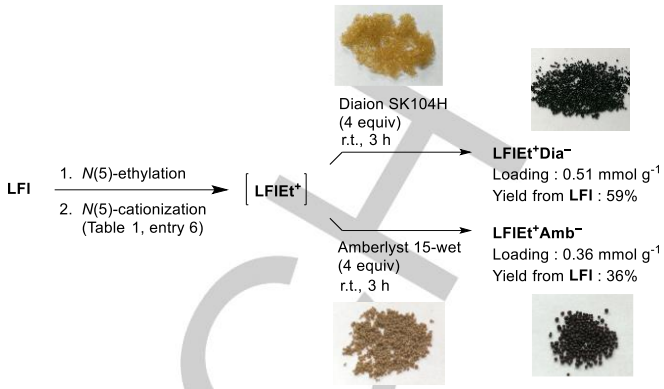
Table 1. Conversion of **LFlEt·** into **LFlEt⁺** under aerobic conditions[a]



Entry	Additive	Conditions			Time (min)[b]
		Conc. ($\times 10^3$ wt%)	pH	Atmo.	
1	-	225	0.6	air	>360[c]
2[d]	H_2O	2.0	2.8	air	60
3	-	225	0.6	O_2 (1 atm)	150
4	$NaHCO_3$	225	1.5	air	105
5	$NaHCO_3$	225	2.7	air	-[e]
6[f]	H_2O	25	1.8	air	120

[a] The starting solution including **LFlEt·** and **LFlEt⁺** in the ratio of ≈75:25 (225×10^{-3} wt%, pH 0.6) was prepared via the *N*(5)-ethylation of **LFl** followed by the Celite filtration under air (Scheme 1) prior to use. Subsequent reactions were performed under vigorous stirring and evaluated by UV/Vis spectroscopy measured in N_2-bubbled 0.5 N HCl_{aq}. unless otherwise noted. [b] Time for full conversion. [c] Evaluated by UV/Vis spectroscopy measured in N_2-bubbled H_2O (**LFlEt·** :**LFlEt⁺** = 33:67 in 360 min). [d] Performed in a UV/Vis cuvette without stirring. [e] Decomposed. [f] The starting solution was poured into H_2O (additive) over 2 min.

reaction performed under air was rapidly completed in 105 min (Table 1, entry 4). To understand this pH dependence of the reaction rate, redox potentials of **LFlEt⁺** under different pH conditions were measured by cyclic voltammetry. Two reversible one-electron reduction peaks were observed under pH 0.6, 1.3, and 2.3 at $E^{0'}$ = 324 and 189 mV (Figure 3, black), 292 and 144 mV (Figure 3, green), and 269 and 62 mV (Figure 3, blue), respectively, clearly indicating that **LFlEt•** is oxidized easier at higher pH level because of its weak Brønsted basicity.[9] This result could also explain why the above reaction at 2.0×10^{-3} wt% (pH 2.8) proceeded smoothly (Figure 2 and Table 1, entry 2). Nevertheless, raising the pH of the starting solution from 0.6 to 2.7 by adding sodium bicarbonate resulted in considerable formation of undesired molecules including **LFl** (Table 1, entry 5), probably because of locally enhanced pH that may cause rapid decompositions of **LFlEt⁺**. This result shows that it is important to adjust a pH in a mild manner. As a result, we concluded that simple dilution of the starting solution with water would be the most efficient way to promote the desired oxidation in terms of both reaction efficiency and synthetic facility. Actually, it was found that diluting the starting solution 9× with deionized water followed by exposing the resulting mixture (25×10^{-3} wt%, pH 1.8) to air with vigorous stirring led to full conversion of **LFlEt•** to **LFlEt⁺** within 120 min (Table 1, entry 6).

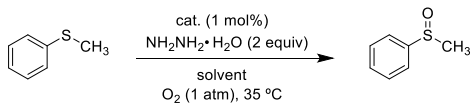


Scheme 2. Preparation of **LFlEt⁺Dia⁻** and **LFlEt⁺Amb⁻**.

N(5)-Ethylated flavinium salts **FlEt⁺A⁻** (Figure 1) are labile under basic and nucleophilic conditions, so that it is difficult to employ ordinary extractions and column chromatographic separations for their purification. Therefore, conventional isolation of **FlEt⁺A⁻** had to rely on recrystallization,[4,6] which significantly limited designable structures. For example, **LFlEt⁺** has been isolated as its perchlorate salt (**LFlEt⁺ClO₄⁻**) via anion exchange by using a large excess of $HClO_4$ (9 equiv.) and $NaClO_4$ (12 equiv.) followed by purification by recrystallization (Scheme 1c).[6] With the aforementioned facile procedure for *N*(5)-cationization in hand, we next examined whether **LFlEt⁺** can be extracted from a crude mixture onto sulfonated resins to give the corresponding anionic resin-countered 5-ethyl-3-methyllumiflavinium cation (Scheme 1d, **LFlEt⁺resin⁻**).[10] To a purple crude solution of **LFlEt⁺** prepared via the *N*(5)-ethylation followed by the aerobic *N*(5)-cationization (Table 1, entry 6) was added 4 equivalents[11] of Diaion SK104H (Mitsubishi) or Amberlyst 15-wet (Organo) and the resulting heterogeneous mixture was shaken at room temperature for 3 h (Scheme 2). In both cases, the solution phase became more transparent and, at the same time, the resin darkened, showing that **LFlEt⁺** was successfully transferred onto the solid-phase. The resulting resins were simply washed with methanol and water and then freeze-dried to obtain the flavinium salt immobilized on Diaion SK104H (**LFlEt⁺Dia⁻**, 59%, 0.51 mmol g^{-1}) and Amberlyst 15-wet (**LFlEt⁺Amb⁻**, 36%, 0.36 mmol g^{-1}), in which the yield and loading were determined through elemental analysis (Scheme 2). Higher yields were obtained by using larger amounts of a resin. For example, the best yield (74%) of **LFlEt⁺Dia⁻** was attained by using 16 equivalents[11] of Diaion SK104H, although its loading was inversely decreased to 0.19 mmol g^{-1} (see the Supporting Information). It should be eventually noted that the sequential synthesis of **LFlEt⁺resin⁻** from **LFl** was demonstrated to be feasible on gram scale.

To demonstrate the usefulness of **LFlEt⁺resin⁻**, their catalytic activity was tested. We previously reported that flavinium perchlorate **FlEt⁺ClO₄⁻** could be efficient organocatalysts for aerobic oxidation of sulfides,[12] amines,[12] ketones,[13] and hydrazine.[14a,14c] At first, we used **LFlEt⁺Dia⁻** (0.51 mmol g^{-1}) and **LFlEt⁺Amb⁻** (0.36 mmol g^{-1}) as a catalyst

Table 2. Catalytic aerobic sulfoxidation with **LFlEt⁺resin⁻**[a]



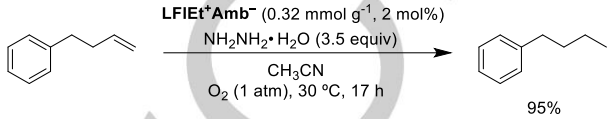
Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	**LFlEt⁺Amb⁻**[c]	CF_3CH_2OH	17	98
2	**LFlEt⁺Dia⁻**[d]	CF_3CH_2OH	17	11
3[e]	**LFlEt⁺Dia⁻**[d]	CH_3CN:CF_3CH_2OH = 1:5.25	23	95
4[e,f]	**LFlEt⁺Dia⁻**[d]	CH_3CN:CF_3CH_2OH = 1:5.25	14	98
5	-	CF_3CH_2OH	17	0

[a] Reactions were performed using 0.1 mmol of thioanisole, 0.2 mmol of hydrazine monohydrate in 0.5 mL of the solvent in the presence of 1 mol% of the catalyst under 1 atm of O_2 at 35 ºC. [b] Determined by GC analysis. [c] 0.36 mmol g^{-1} [d] 0.51 mmol g^{-1} [e] The catalyst was mixed with $NH_2NH_2 \cdot H_2O$ in CH_3CN prior to mixing with CF_3CH_2OH and thioanisole. [f] 3 equivalents of $NH_2NH_2 \cdot H_2O$ was used.

for the aerobic oxidation of thioanisole under conditions that had been previously developed for the reaction with **LFlEt⁺ClO₄⁻**.[12]

To a solution of thioanisole (0.2 M) and hydrazine monohydrate (0.4 M, 2 equiv.) in 2,2,2-trifluoroethanol (TFE) was added 1 mol% of **LFlEt⁺resin⁻** and the resulting mixture was stirred under O_2 (1 atm) at 35 ºC for 17 h (Table 2). The reaction with **LFlEt⁺Amb⁻** catalyst proceeded smoothly to give the corresponding sulfoxide in 98% yield without overoxidation (entry 1), while that with **LFlEt⁺Dia⁻** catalyst resulted in only 11% yield of methyl phenyl sulfoxide (entry 2). This huge difference in catalytic activity between **LFlEt⁺Dia⁻** and **LFlEt⁺Amb⁻** can be explained by the nature of their original resins. Although both Diaion and Amberlyst are a sulfonic acid-functionalized crosslinked polystyrene that is not swollen in TFE, the former has only micropores, while the latter has characteristic macropores capable of accepting molecules even in the nonswollen state. Actually, only in the latter case the solution phase of reaction mixture was colored with dark purple (Supporting Information), which made us recognize that **LFlEt⁺** could be efficiently released from the solid-phase to solution-phase by reacting with hydrazine to start the catalytic cycle. On the other hand, the fact that Diaion is much cheaper than Amberlyst prompted us also to develop the following procedure for utilizing **LFlEt⁺Dia⁻** as a catalyst: (i) **LFlEt⁺Dia⁻** is soaked in a small amount of acetonitrile to swell the resin; (ii) hydrazine monohydrate is added to release the catalyst; (iii) TFE and thioanisole are successively added and the resulting mixture is stirred under O_2 (1 atm) at 35 ºC. According to this procedure, the sulfoxidation reaction was smoothly catalyzed to afford the desired sulfoxide in 95% yield in 23 hours (entry 3), which became more efficient by slightly increasing the amount of hydrazine monohydrate (entry 4). It should be noted that this reaction does not proceed at all without a catalyst (entry 5).

Finally, it was also demonstrated that **LFlEt⁺resin⁻** could be effective organocatalysts for reduction of olefins based on aerobic oxidation of hydrazine, which was previously reported.[14] For example, in the presence of 2 mol% of **LFlEt⁺Amb⁻** (0.32 mmol g^{-1}) and 3.5 equivalent of hydrazine monohydrate under O_2 (1 atm) at 30 ºC, 4-phenyl-1-butene was converted into butylbenzene in 95% yield within 17 h (Scheme 3).



Scheme 3. Aerobic reduction of 4-phenyl-1-butene catalyzed by **LFlEt⁺Amb⁻**.

In conclusion, we developed a facile preparation method of flavinium organocatalysts utilizing safe and inexpensive materials under mild conditions. This is the first example of (i) the synthesis of **LFlEt⁺** from **LFl** via the general *N*(5)-ethylation[6] followed by *N*(5)-cationization that utilizes air as the oxidant and its mechanistic study, (ii) the preparation of **LFlEt⁺resin⁻** by extracting **LFlEt⁺** from its crude mixture onto sulfonated resins such as Diaion and Amberlyst, and (iii) aerobic oxidation reactions catalyzed by **LFlEt⁺resin⁻**. The presented method for preparing flavinium organocatalysts is arguably more attractive than conventional methods because it can be easily performed without using any inert conditions and hazardous or expensive chemicals that were previously required. We believe that this research boosts fundamental as well as practical applications of flavinium organocatalysts, which will become significant tools for the development of future sustainable catalytic oxidation reactions.

Experimental Section

Preparation of **LFlEt⁺resin⁻**: A mixture of **LFl** (81 mg, 0.3 mmol), Pd/C (5%; 128 mg, 0.06 mmol), and acetaldehyde (0.75 mL, 12 mmol) in degassed ethanol (6 mL), HCl (conc.; 0.5 mL) and degassed water (6 mL) was stirred at room temperature for 48 h under hydrogen (1 atm). The mixture was filtered through a pad of Celite (2.3 g) under air by using H_2O for rinsing. The reddish-brown colored filtrate (40 g, 225×10^{-3} wt%) was poured into H_2O (320 mL) over 2 min and vigorously stirred under air for 120 min at room temperature. To the resulting deep purple mixture was added 4 equivalents of a resin (Diaion SK104H: 818 mg, Amberlyst 15-wet: 544 mg) and the heterogeneous mixture was shaken at room temperature for 3 h. The resulting darkened resin was recovered by filtration and washed successively with H_2O (15 mL), CH_3OH (15 mL), and H_2O (15 mL), and freeze-dried under reduced pressure to afford **LFlEt⁺resin⁻**, which was characterized by elemental analysis. **LFlEt⁺Dia⁻** (59% yield, 0.51 mmol/g): Elemental analysis, found: C 51.85; H 4.84; N 2.86. **LFlEt⁺Amb⁻** (36% yield, 0.36 mmol/g): Elemental analysis, found: C 50.94; H 5.36; N 2.00.

Catalytic oxidation of thioanisole with **LFlEt⁺Amb⁻**: A mixture of thioanisole (12 mg, 0.1 mmol), **LFlEt⁺Amb⁻** (3 mg, 0.01 μmol),

and $NH_2NH_2 \cdot H_2O$ (10 mg, 0.2 mmol) in TFE (0.5 mL) was stirred at 35 ºC for 17 h under an atmosphere of oxygen. The reaction yield was determined to be 98% by GC analysis with absolute calibration (no side reactions were observed).

Catalytic oxidation of thioanisole with **LFlEt$^+$Dia$^-$**: **LFlEt$^+$Dia$^-$** (2 mg, 0.01 μmol) was mixed with acetonitrile (80 μL) and then $NH_2NH_2 \cdot H_2O$ (15 mg, 0.3 mmol) was added. To the resulting yellow mixture was successively added TFE (0.42 mL) and thioanisole (12 mg, 0.1 mmol), which was stirred at 35 ºC for 14 h under an atmosphere of oxygen. The reaction yield was determined to be 98% by GC analysis with absolute calibration (no side reactions were observed).

Catalytic reduction of 4-phenyl-1-butene with **LFlEt$^+$Amb$^-$**: To a mixture of 4-phenyl-1-butene (33 mg, 0.25 mmol) and **LFlEt$^+$Amb$^-$** (16 mg, 5 μmol) in acetonitrile (2 mL) was added $NH_2NH_2 \cdot H_2O$ (44 mg, 0.88 mmol) and the resulting mixture was stirred at 30 ºC for 17 h under an atmosphere of oxygen. The reaction yield was determined to be 95% by GC analysis with absolute calibration (no side reactions were observed).

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Keywords: environmentally benign • flavinium salt • ion-exchange resin • organocatalysis • oxidation

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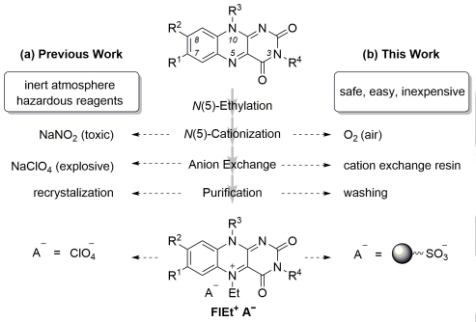
N(5)-Ethylated flavinium organo-catalyst can be readily prepared without using any hazardous chemicals or inert atmosphere as previously required. This work breaks the limited application of flavinium oxidation catalysts in both laboratory and industrial synthesis.



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