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Selectfluor™ on a PolyHIPE Material as Regenerative and Reusable Polymer-Supported Electrophilic Fluorinating Agent

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Abstract: The first recyclable polymer-supported electrophilic fluorinating agent was prepared by reaction of molecular fluorine with the triethylenediamine motif that is grafted onto a poly(4-vinylbenzyl chloride-co-divinylbenzene) polyHIPE material. The resulting polymeric Selectfluor™-type reagent demonstrated high efficiency in the fluorination of naphthol in the course of repeated sequences of fluorination and regeneration. It also reacted with the enol form and the sodium enolate of 1,3-dicarbonyl compounds.

Keywords: fluorination; green chemistry; high internal phase emulsion (HIPE) templating; molecular fluorine; supported reagents

The synthesis of selectively fluorinated new chemical entities is an important challenge in organic chemistry that receives an ever-growing attention due to the wide potential applications in the life science fields and materials science. Indeed, the chemical positioning of a fluorine atom, which possesses a strong electron-withdrawing ability and a relatively small size, often leads to stunning changes in the physical, chemical and biological properties of fluorinated compounds when compared with their non-fluorinated analogues.[1] From a synthetic point of view, the direct and selective electrophilic fluorination of organic compounds was made possible thanks to a collection of various fluorinating agents.[2–4] In the early stages, sources of positive fluorine were designed featuring the O–F moiety (fluoroxyperfluoroalkanes R_fOF, perfluoroacyl hypofluorites R_fCOOF, and sulfonyl hypofluorites R_fSO_2OF) but their explosive nature caused their rapid phase-out.[3] Thereafter, N–F reagents emerged as safer and shelf-stable reagents for electrophilic fluorinations.[4] A wide range of fluorinating powers together with commercial availability secured a widespread use of this class of reagents. Representative reagents include NFSI (*N*-fluorobenzenesulfonimide), *N*-fluoropyridinium salts and Selectfluor™ {1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate) or F-TEDA-BF_4; TEDA = triethylenediamine}. These reagents have been continuously employed in a wide variety of fluorination reactions; however, they suffer from poor atom-economy because of their high molecular weight for the transfer of ^{19}F and no effort was made to recover and regenerate either the benzenesulfonimide, the pyridine moiety or the TEDA residue of the corresponding reagents. In a previous work on enantioselective electrophilic fluorination by means of quinine-based $[N–F]^+$ reagents conducted in ionic liquids, the *Cinchona* alkaloid as well as the solvent were recycled.[5] With a view to ensuring minimization of waste generation toward a greener chemistry, we envisaged the preparation, applications, and the regeneration of *de novo* polymeric architectures as support for electrophilic fluorinating agents. In the context of green chemistry, polymer-supported reagents offer attractive and practical approaches for the clean and efficient synthesis of organic compounds.[6] Polymeric electrophilic fluorinating agents are extremely rare. In 1986,

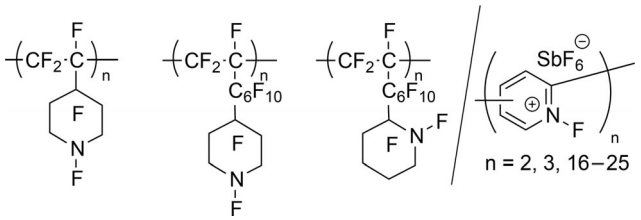


Figure 1. Structures of Banks' and Umemoto's polymeric fluorinating agents.

Banks' group reported polymeric analogues of *N*-fluoroperfluoropiperidines (Figure 1, *left*).[7] The LaMar fluorination process was applied on cross-linked poly(4-vinylpyridine) and two other similar entities to yield perfluoropolymers. However, the fluorination of sodium malonates and 1-(*N*-morpholinyl)cyclohexene by these polymers did not proceed in more than 23% yield and the recycling was not addressed. In 1998, Umemoto et al. synthesized poly(*N*-fluoropyridinium) salts that have increased effective fluorine content (Figure 1, *right*) but only the dimeric ones were studied and demonstrated high fluorination capacity.[8] Herein, we describe the preparation of the first polymeric F-TEDA reagent, its successful application in the fluorination of naphthols, the enol form of dibenzoylmethane, and the sodium enolate of ethyl 3-oxo-3-phenylpropanoate as well as its regeneration and reuse.

Possessing a high electrophilic power, Selectfluor™ is one of the most employed fluorinating agents. With the aim to mimic Selectfluor™, we designed a polymeric analogue by grafting the triethylenediamine motif onto a polymer (Figure 2). We reasoned that a suitable polymeric support for an electrophilic fluorinating agent would have appropriate porosity to facilitate efficient contact with molecular fluorine.[9] We prepared the highly porous polymer from 4-vinylbenzyl chloride (VBC) and divinylbenzene (DVB) in ratio of VBC/DVB = 93:7 by utilizing the high internal phase emulsion (HIPE) templating approach,[10a] which enables the preparation of monolithic polymer supports with interconnected, multi-level porosity thus avoiding the diffusion limitations that are usually problematic with gel-type polymer supports. PolyHIPE supports based on VBC have already been shown as suitable carriers of reagents and catalysts.[10] Our styrene/DVB-based polyHIPE material was powdered and further functionalized by nucleophilic displacement of chloride by triethylenediamine to afford the polyHIPE-TEDA **1** (Scheme 1), which was titrated by anion exchange with a 0.02 M sodium hydroxide solution for measuring the loading of TEDA units at 1.24 mmol g^{-1}.

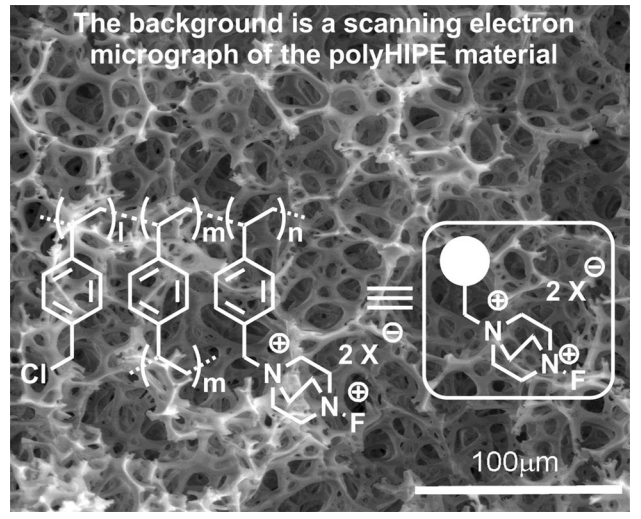
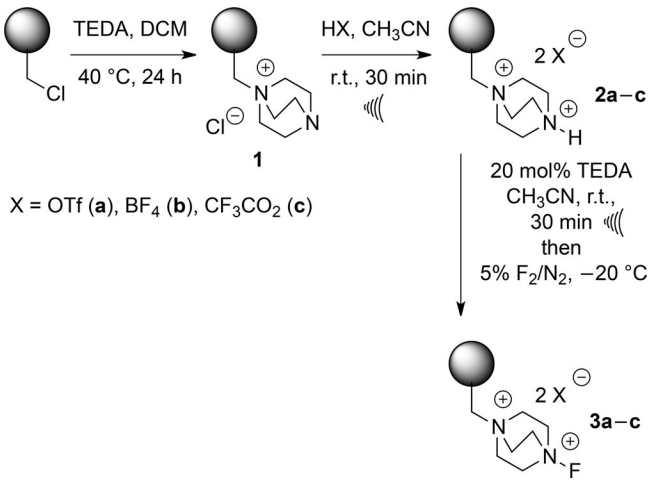


Figure 2. Structure of polyHIPE F-TEDA (chemical composition and schematic representation).



Scheme 1. Synthesis of polyHIPE F-TEDA.

From this polyHIPE-TEDA, four synthetic routes were considered for the preparation of the corresponding polyHIPE F-TEDA **3** by means of molecular fluorine: (i) fluorination of **1** and subsequent anion metathesis, (ii) fluorination of a mixture of **1** and the metal salt of an acid, (iii) fluorination of a preformed ammonium hydrogen salt **2**, (iv) fluorination of an ammonium-Lewis acid complex.[11] We opted for the procedure (iii) in which the anion exchange is done prior to the fluorination in order to avoid possible oxidation of chloride anions by F_2. Furthermore, this procedure allows the control of the counteranion and titration of the intermediate ammonium hydrogen salts **2a–c**. The polyHIPE-TEDA was treated under ultrasound irradiation with a Brønsted acid that include triflic acid, tetrafluoroboric acid solution 48 wt% in water, and trifluoroacetic acid in order to produce the bis-ammonium salts polyHIPE H-TEDA **2a–c** (Scheme 1). At this stage, titration with a 0.01 M sodium hydroxide solution was conducted to determine the loading of protonated TEDA units, i.e., the number of available nitrogen sites for

Table 1. Synthesis and titration of polyHIPE H-TEDA **2a–c**.

Synthesis[a]			Titration by 0.01 M NaOH[b]		
Amount of **1** [mg]	Brønsted acid	Amount of product **2** [mg]	Amount of **2** [mg]	NaOH [mL]	Loading of H-TEDA [mmol/g]
1000	TfOH	1670 (**2a**)	34.1 (**2a**)	5.74	0.84
500	HBF_4	603 (**2b**)	29.1 (**2b**)	6.48	1.11
500	CF_3CO_2H	552 (**2c**)	27.6 (**2c**)	5.84	1.06

[a] *Typical reaction conditions for **2a**:* **1** (1.00 g, 1.24 mmol of TEDA unit), acetonitrile (50 mL), ultrasonic irradiation, room temperature, 30 min, triflic acid (1.36 g, 9.07 mmol).
[b] See the Supporting Information for full details.

fluorination (Table 1). The loading of functional sites in the polyHIPE H-TEDA was calculated to be in the range 0.84–1.11 mmol g^{-1}. Finally, the fluorination was performed by flowing 5% F_2 in N_2 into the teflon reactor containing the polyHIPE H-TEDA.[12] We noticed that the fluorination gave better results when it was conducted in the presence of a catalytic amount of free TEDA. Indeed, the active fluorine content of the polymer declined by nearly 70% when the fluorination was achieved without additional free TEDA. Because F_2 gas itself is almost insoluble in acetonitrile, it is therefore rather difficult to have the F_2 gas in close contact with the polymer. We believe that TEDA can assist the fluorination of polyHIPE through reaction with F_2 generating an F_2 adduct with TEDA that is readily soluble in acetonitrile. TEDA may work as an effective carrier of F_2 gas within the insoluble polymer. Next, the oxidation ability of the polyHIPE F-TEDA **3a–c** was determined by iodometric titration. The active fluorine content was calculated to be 0.52, 0.80, and 0.63 mmol g^{-1} for the triflate, the tetrafluoroborate and the trifluoroacetate, respectively (Table 2). These values are to be compared with Selectfluor™ reagent that has a fluorine loading of 2.82 mmol g^{-1}. To test the general robustness of the fluorination, we demonstrated on eight batches that the optimized fluorination conditions consistently provided the polyHIPE F-TEDA with similar active fluorine contents.

As a model reaction to evaluate the fluorinating power of the polyHIPE F-TEDA **3a–c**, we examined the fluorination of 2-naphthol **4** because it is a relevant structural unit found in many biologically active molecules and it allows a direct comparison of the reactivity of our supported reagent *versus* that of non-supported fluorinating agents.[13] To a suspension of the polyHIPE F-TEDA **3a** in acetonitrile (stoichiometric amount and 2.2 equivalents), 2-naphthol was added at room temperature and the reaction was monitored by gas chromatography (Table 3, entries 1–10). As expected, two fluorinated products were obtained by fluorination at the position 1 only: 1-fluoro-2-naphthol **5** and 1,1-difluoro-2(1*H*)-naphthalenone **6** (Scheme 2, *top*).

With one equivalent of fluorinating agent, the reaction did not go to completion and the monofluorinated product **5** was predominant in a **5**/**6** ratio of 5.1:1 and an overall yield of 73.6% whereas with 2.2 equivalents of **3a** the difluorinated product **6** became the major one with a **5**/**6** ratio of 1:4.3 and an overall yield of 90.6%. These results are in line with those obtained using Selectfluor™. Next, the fluorinating power of polyHIPE F-TEDA-OTf **3a** was compared with those of Selectfluor™, *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate (FP-B800) and *N*-fluoropyridinium triflate (FP-T500). Our polymeric reagent showed slightly weaker activity than Selectfluor™ and FP-B800, but a much stronger reactivity than FP-T500 (Table 3, entries 5–23). This is a very encouraging result for further application of the polyHIPE F-TEDA reagents. For example, the regioisomeric 1-naphthol **7** was fluorinated at the positions 2 and 4 in a ratio 10.1:1 and a yield of 79.2% (Scheme 2). In addition to aromatic substrates, the methylene active dibenzoylmethane **10** reacted smoothly *via* its enol form with the polymer **3a** to give the mono- and difluori-

Table 2. Synthesis and iodometry of polyHIPE F-TEDA **3a–c**.

Synthesis[a]			Iodometric titration[b]		
Amount of **2** [mg]	Amount of TEDA [mg]	Amount of product **3** [mg]	Amount of **3** [mg]	$Na_2S_2O_3$ [mL]	Active fluorine [mmol/g]
252 (**2a**)	5.6	242 (**3a**)	30.5 (**3a**)	1.58	0.52
202 (**2b**)	5.0	205 (**3b**)	28.7 (**3b**)	2.30	0.80
226 (**2c**)	5.4	220 (**3c**)	32.3 (**3c**)	2.24	0.63

[a] *Typical reaction conditions for **3a**:* **2a** (252 mg, 0.212 mmol of TEDA units), TEDA (5.6 mg), acetonitrile (50 mL), ultrasonic irradiation, then −20 °C, 5% F_2/N_2 (2,12 mmol at 10 mL/min).
[b] See the Supporting Information for full details.

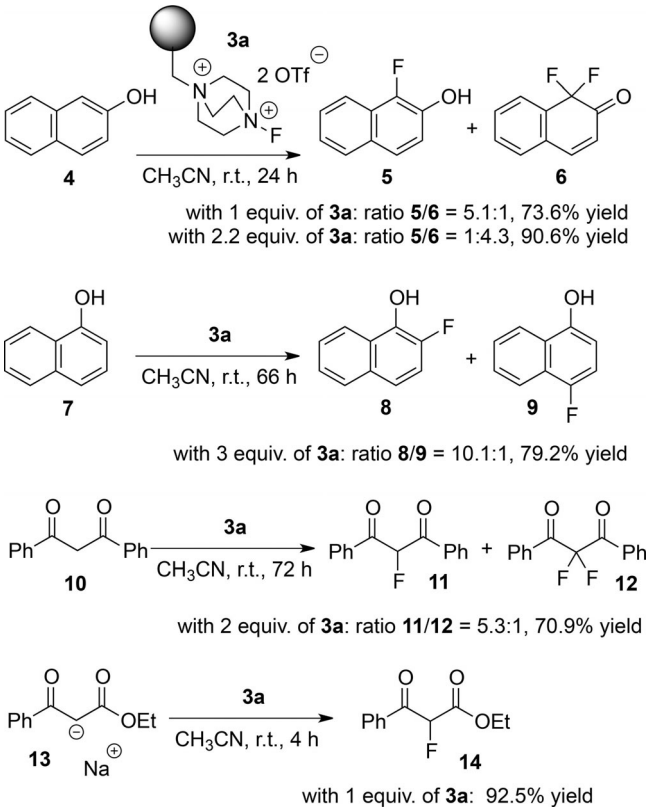
Table 3. Fluorination of 2-naphthol **4**. Comparison of the reactivity of polyHIPE F-TEDA-OTf **3a** with Selectfluor™, FP-B800 and FP-T500.

Entry	Time [h]	**4** [%]	**5** [%]	**6** [%]	Yield [%][b]
Fluorination of 2-naphthol **4** with **3a** [1 equiv.][a]					
1	0	100	0	0	0
2	2	43.8	47.5	8.7	64.9
3	6	40.0	50.9	9.1	69.1
4	24	36.7	53.0	10.3	73.6
Fluorination of 2-naphthol **4** with **3a** [2.2 equiv.]					
5	0	100	0	0	0
6	2	3.9	38.2	57.9	77.0
7	3	0	35.1	64.9	82.5
8	6	0	25.9	74.1	87.1
9	24	0	20.2	79.8	89.9
10	48	0	18.8	81,2	90.6
Fluorination of 2-naphthol **4** with Selectfluor™ [2.2 equiv.]					
11	0	100	0	0	0
12	0.5	0	46.7	53.3	76.7
13	1	0	28.4	71.6	85.8
14	2	0	13.8	86.2	93.1
15	4	0	7.8	92.2	96.1
Fluorination of 2-naphthol **4** with FP-B800 [2.2 equiv.]					
16	0	100	0	0	0
17	0.5	2.5	60.2	37.3	67.4
18	1	0	42.3	57.7	78.9
19	2	0	26.6	73.4	86.7
20	4	0	11.2	88.8	94.4
21	6	0	6.5	93.5	96.7
Fluorination of 2-naphthol **4** with FP-T500 [2.2 equiv.]					
22	0	100	0	0	0
23	48	100	0	0	0

[a] *Reaction conditions:* **3a** (200 mg, 0.104 mmol of active fluorine), **4** (14.4 mg, 0.1 mmol), acetonitrile (5 mL), room temperature, 0–24 h.
[b] Yields were determined by gas chromatography.

nated products **11** and **12** in a ratio 5.3:1 in 70.9% yield (Scheme 2). More efficiently and selectively, the sodium enolate of ethyl 3-oxo-3-phenylpropanoate reacted with the polymer **3a** to give the monofluorinated β-keto ester **14** in 92.5% yield (Scheme 2).

The fluorination of 2-naphthol was next performed with polyHIPE F-TEDA **3b** and **3c** featuring counteranions BF_4^- and $CF_3CO_2^-$ for assessment of their effectiveness. We observed a decreased efficiency with overall reaction yields of 60% and 18% for **3b** and **3c**, respectively. Therefore, although we regenerated the polyHIPE F-TEDA **3a–c**, the recycling studies were conducted only with the most efficient polyHIPE F-TEDA-OTf **3a**. Apart from one case in the literature of reuse of the dimeric *N,N′*-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (MEC-31) by Adachi et al.,[13d]



Scheme 2. Fluorination of 2-naphthol **4**, 1-naphthol **7**, dibenzoylmethane **10**, sodium enolate of ethyl 3-oxo-3-phenylpropanoate **13**.

no polymeric fluorinating agent was recycled. For cost-effective industrial fluorination and to better account for environmental concerns, we herein report the first regeneration and reuse of the polymer-supported electrophilic fluorinating agent polyHIPE F-TEDA. After the reaction with 2-naphthol, the polyHIPE H-TEDA **2a²–c²** were recovered by simple filtration and washing, and then resubmitted to the fluorination step by means of F_2 to give a "second generation" of polyHIPE F-TEDA **3a²–c²**. The regeneration proceeded very well providing polymers with similar or even slightly increased active fluorine contents; this trend was confirmed in a second regeneration giving rise to a "third generation" of polymer **3a³** (Table 4). Subsequently, the fluorinating powers of polyHIPE F-TEDA **3a²** and **3a³** were assessed in the fluorination of a stoichiometric amount of 2-naphthol for comparison with data obtained with polyHIPE F-TEDA **3a** (Table 5 *versus* Table 3, entries 1–4).

Interestingly, the reactivity of the regenerated polyHIPE F-TEDA **3a²** was improved compared to the original polymeric fluorinating agent **3a**; indeed, the overall yield **5**+**6** increased from 73.6 to 88.3%, probably as the result of an increased fluorine content of the regenerated polymer. The regeneration/reuse sequence was repeated one more time affording the third generation polyHIPE F-TEDA-OTf **3a³** and

Table 4. "Second and third generations" of polyHIPE F-TEDA **3** from recovered materials.

Synthesis[a]			Iodometric titration[b]		
Recovered **2** [mg]	Amount of TEDA [mg]	Amount of product **3** [mg]	Amount of **3** [mg]	$Na_2S_2O_3$ [mL]	Active fluorine [mmol/g][c]
146 (**2a²**)	4.1	128 (**3a²**)	30.4 (**3a²**)	1.60	0.53 (0.52)
122 (**2b²**)	3.4	112 (**3b²**)	29.0 (**3b²**)	2.38	0.82 (0.80)
125 (**2c²**)	3.1	118 (**3c²**)	28.6 (**3c²**)	1.78	0.62 (0.63)
213 (**2a³**)	4.5	199 (**3a³**)	33.2 (**3a³**)	1.92	0.58 (0.53)

[a] See the Supporting Information for full details.
[b] See the Supporting Information for full details.
[c] Values in parentheses refer to active fluorine contents measured for the preceding fluorination.

Table 5. Fluorination of 2-naphthol by means of regenerated polyHIPE F-TEDA-OTf **3a²** and **3a³**.

Entry	Time [h]	**4** [%]	**5** [%]	**6** [%]	Yield [%][b]
Fluorination of 2-naphthol **4** with **3a²**[a]					
1	0	100	0	0	0
2	1	45.2	45.7	9.1	63.9
3	6	30.0	57.3	12.7	82.7
4	24	28.4	54.9	16.7	88.3
Fluorination of 2-naphthol with **3a³**[c]					
5	0	100	0	0	0
6	1	43.0	33.7	23.3	80.3
7	6	33.9	47.4	18.7	84.8
8	24	30.8	51.1	18.1	87.3

[a] *Reaction conditions:* **3a²** (320.8 mg, 0.17 mmol of active fluorine), **4** (24.5 mg, 0.17 mmol), acetonitrile (8.5 mL), room temperature, 0–24 h.
[b] Yields were determined by gas chromatography.
[c] *Reaction conditions:* **3a³** (163.8 mg, 0.095 mmol of active fluorine), **4** (13.7 mg, 0.095 mmol), acetonitrile (4.8 mL), room temperature, 0–24 h.

a constant efficiency in the fluorination of 2-naphthol in a high overall yield for **5**+**6** of 87.3% (Table 5, entries 5–8).

In conclusion, a joint research effort by academic laboratories and Tosoh F-Tech chemical company allowed us to investigate the first high-potential polymer-supported electrophilic fluorinating agent. The TEDA motif that is found in Selectfluor™ was anchored on a polyHIPE architecture and the polyHIPE F-TEDA reagent was prepared by fluorination with molecular fluorine. The relatively high active fluorine content of the polyHIPE F-TEDA did impart a high reactivity in the fluorination of the test substrates 1- and 2-naphthol as well as dibenzoylmethane and ethyl 3-oxo-3-phenylpropanoate. Importantly, the material has high mechanical strength and we have demonstrated the regeneration and the reuse of the fluorinating agent as initially planned in our requirement specification. We now have in hand a reagent with unmatched recycling performance that minimizes wastes and has the potential to reduce manufacturing costs in fluorination reactions in batch. This is particularly true on a large scale in the industry while small scale fluorinations in research laboratories may prefer flow mode reactions on regenerable cartridges. Further developments of the block column–flow technique approach and applications with other substrates are ongoing in our laboratories.

Experimental Section

General Information

^{1}H (400 MHz), ^{13}C (100.6 MHz) and ^{19}F (376 MHz) NMR spectra were recorded on a Bruker AVANCE II 400. Chemical shifts in ^{1}H NMR spectra are reported in parts per million from TMS resonance as the internal standard. Chemical shifts in ^{19}F NMR spectra are reported in parts per million from C_6F_6 or CF_3CH_2OH resonance as the internal standard. The conversion and ratio of the products **4**–**14** were determined by gas chromatography on a SHIMAZU GC-2014. Unless otherwise noted, all solvents and reagents were purchased from commercial sources and were used without further purification. **CAUTION:** Molecular fluorine F_2, neat or diluted in N_2, is a highly oxidizing and toxic gas that requires appropriate precautions for its safe handling.

Synthesis of polyHIPE TEDA 1

A 100 mL aqueous phase, consisting of $K_2S_2O_8$ (0.11 g, 0.41 mmol) in deionized water (100 mL), was added dropwise with continuous stirring at 300 rpm to an oil phase, consisting of 4-vinylbenzyl chloride (11.62 g, 76 mmol), divinylbenzene (0.79 g, 1.9 mmol), and the surfactant sorbitan monooleate (Span 80; 2.20 g). The emulsion was stirred for another 30 min after addition of the aqueous phase, then transferred to a mold for curing (24 h at 60 °C). The resulting polyHIPE was purified by Soxhlet extraction (deionized water and acetone, both for 24 h) then dried under vacuum for 24 h. Next, 1 g of powdered VBC/DVB polyHIPE (5.5 mmol of chlorine) was suspended in 4 mL of dichloromethane and 680 mg of 1,4-diazabicyclo[2.2.2]octane (TEDA) were added (1.1 times excess with regards to chloromethyl groups). The mixture was stirred using a magnetic stirrer at 40 °C for 24 hours, filtered, washed with dichloro-

methane and 2-propanol and further purified *via* Sohxlet extraction with 2-propanol for 24 hours and air dried.

Synthesis of polyHIPE H-TEDA-OTf 2a

1.00 g of **1** (1.24 mmol of TEDA unit) was suspended in 50 mL of acetonitrile under ultrasonic irradiation at room temperature for 30 min. To this suspension, 1.36 g of triflic acid (9.07 mmol) was added and the mixture was left at room temperature under ultrasonic irradiation for additional 30 minutes. Then, **2a** was collected by filtration under reduced pressure, and washed with 50 mL of acetonitrile 3 times to give **2a**; yield: 1.67 g.

Synthesis of polyHIPE F-TEDA-OTf 3a

252 mg of **2a** (0.212 mmol of TEDA unit) and 23.5 mol% of TEDA (5.6 mg) were suspended in 50 mL of acetonitrile, under ultrasonication at room temperature for 30 min under 10 mL min^{-1} N_2 flow conditions. This suspension was cooled to −20 °C and 10 equivalents of F_2 gas diluted to 5% concentration by N_2 gas were introduced at a rate of 10 mL min^{-1} into the suspension under vigorous stirring. Then, only N_2 gas was continuously bubbled for 30 min and the temperature of the reaction mixture was raised to room temperature. Product **3a** was collected by filtration under reduced pressure and washed with 10 mL of acetonitrile for 5 times and dried to give **3a**; yield: 242 mg.

Procedure for the Fluorination of 2-Naphthol by polyHIPE F-TEDA-OTf 3a

The polyHIPE F-TEDA-OTf **3a** (200 mg, 0.104 mmol of active fluorine) was suspended in 5 mL of acetonitrile and 2-naphthol (14.4 mg, 0.1 mmol) was added and the mixture stirred for 24 h at room temperature with monitoring of the conversion by gas chromatography. On completion of the reaction, the polymer was filtered out and washed twice with 5 mL of acetonitrile to give recovered **2a**; yield: 197 mg. The acetonitrile layers were combined and concentrated under vacuum to give a crude mixture of 1-fluoro-2-naphthol **5** and 1,1-difluoro-1,2-dihydronaphthalen-2-one **6**; yield: 14.7 mg. The fluorination yield was measured to be 72% by ^{19}F NMR with trifluoroethanol as internal standard. From this mixture, 6.8 mg of **5** and 2.7 mg of **6** were isolated as pure products by HPLC separation.

1-Fluoro-2-naphthol (5): ^{1}H NMR (acetone-d_6): $\delta = 8.87$ (d, $J = 1.6$ Hz, 1H), 7.94 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 7.63 (d, $J = 8.8$ Hz, 1H), 7.53 (t, $J = 7.2$ Hz, 1H), 7.38 (t, $J = 7.2$ Hz, 1H), 7.28 (t, $J = 8.8$ Hz, 1H); ^{19}F NMR (acetone-d_6): $\delta = -152.8$ (d, $J = 7.5$ Hz, 1F).

1,1-Difluoro-2(1*H*)-naphthalenone (6): ^{1}H NMR (acetone-d_6): $\delta = 7.87$ (d, $J = 6.8$ Hz, 1H), 7.78 (d, $J = 10.0$ Hz, 1H), 7.70–7.62 (m, 3H), 6.29 (dt, $J = 10.0$, 2.6 Hz, 1H); ^{19}F NMR (acetone-d_6): $\delta = -101.18$ (s, 2F).

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