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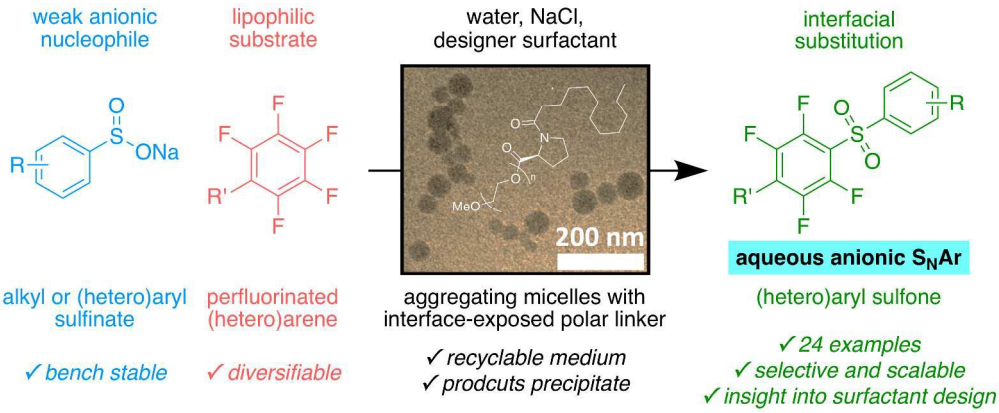

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Green Chemistry

Micelle-Enabled Clean and Selective Sulfonylation of Polyfluoroarenes in Water Under Mild Conditions

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Proline-based designer surfactant FI-750-M has been demonstrated to enable selective nucleophilic aromatic substitution of polyfluoro(hetero)arenes by sulfinate salts in water under mild micellar conditions. Resultant sulfones were obtained from diverse substrates in good yields without side product formation and could usually be purified by simple filtration. The nature of micelles of FI-750-M and the solubility of coupling partners in different micellar regions has been supported by dynamic light scattering, cryo-TEM, and DFT calculations.

With the advent of micellar catalysis, significant headway has been made toward not only replacement of organic solvents but also achievement of transformations with very low catalyst loadings under mild conditions.[1] Recently, the domain of these non-traditional reaction media has broadened, and systems ranging from enzymatic catalysis to nanocatalysis are now possible at an industrial scale under micellar or completely aqueous conditions with perfect reproducibility and low E factor.[2] Work by Kobayashi,[3] Krause,[4] Lipshutz,[5] and Uozumi[6] in this area to address the issues described by Sheldon in his many reviews[7] is highly compelling. Reports of challenging transition-metal-free processes in micellar media have been sparse;[8] however, in 2015 Lipshutz and co-workers reported nucleophilic aromatic substitutions (S_NAr) in water, limited to neutral nucleophiles.[8d] S_NAr is a highly important and useful category of organic transformation offering atom-economy, metal-free conditions, and complementarity of reactivity with cross-coupling reactions.[9] Unfortunately, these reactions are predominantly studied and conducted in organic media with over 50% of cases using highly toxic and problematic solvents such as DMF, DMAc, NMP, etc.[10] These solvents pose serious health risks to the liver, kidney, spleen, thymus, and brain and also impair embryo-fetal development.[11] NMP is also listed under California's Prop 65 as a developmental toxin.[12] Similarly, the health and environmental concerns associated with these solvents have led to increasing restrictions in the EU under the REACH Regulation.[13]

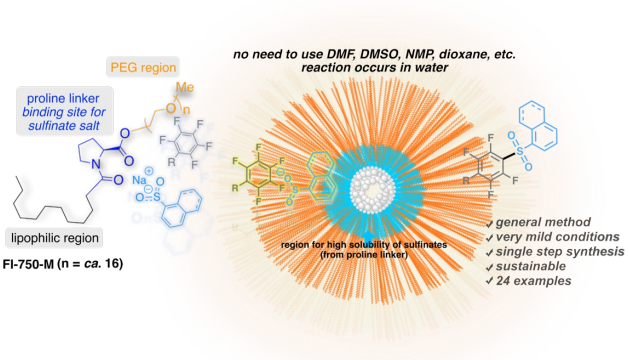

Figure 1 FI-750-M, a designer amphiphile enabeling clean sulfonylation.

The S_NAr chemistry reported by Lipshutz and co-workers involved aromatic chlorides and fluorides with non-ionic nucleophiles in water using TPGS-750-M amphiphiles and achieved low E-factors with mild conditions. However, transformations involving ionic nucleophiles are still considered problematic in micellar media, which may be due to the association of the nucleophilic ion with water, preventing the desired reactivity.[14] Typically, transformations with ionic nucleophiles require polar aprotic solvent and high reaction temperature, as exemplified by the traditional syntheses of (hetero)arylsulfones and polyfluorarylsulfones.[15] Oftentimes, transition metal catalysts are also required.[16]

Along the same lines, (hetero)arylsulfone scaffolds have applications as reaction intermediates in synthesis of medicinal compounds,[17] and dyes.[18] Among this class of compounds, polyfluoroarylsulfone has applications in synthesis of materials for membrane gas separation[19] and also have potential applications in photocatalysis[20] A typical two-step route to synthesis of polyfluoroarylsulfone, first developed by Tatlow, is the S_NAr reaction of highly activated polyfluoroaryl substrates with a hot solution of sodium thiophenoxide in refluxing pyridine followed by oxidation of the resulting sulfide under

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Electronic Supplementary Information (ESI) available: [reaction optimization, physical data of FI-750-M, computational details, analytical data of products]. See DOI: 10.1039/x0xx00000x

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very harsh conditions.[15a] In a separate report by Haszeldine and coworkers, a similar product was synthesized through reaction of the highly activated pentafluoropyridine system with phenysulfinate salt in refluxing DMF.[15c] These methods lack demonstrated substrate scope and suffer from limited functional group tolerance. Under such conditions, many functionalities are incompatible, including esters, carbamates, nitriles, nitro groups, and thiocarbamates. Furthermore, handling thiols is often unpleasant. Therefore, a general, direct, and selective method for sulfonylation of polyfluoroarenes under ambient conditions in a greener medium, i.e., recyclable water, is desirable. We sought to develop such a method by leveraging synergistic local micellar effects of the newly engineered, environmentally benign amphiphile FI-750-M, which can mimic toxic polar organic solvents such as DMF, 1,4-dioxane, NMP, etc.[1d]

We propose that when dissolved in water, FI-750-M forms nanomicelles with different binding sites (Figure 1, see FI-750-M) for polyfluoroarenes and sulfinate salts; i.e., i) the inner lipophilic region (shown in black), ii) the proline linker (shown in blue), and iii) the mPEG region (shown in orange). Such an arrangement could bring nucleophiles, including anionic weak nucleophiles, into very close proximity with polyfluoroarenes during the dynamic exchange process typical of micelles. This effective binding of reactants along with hydrophobic effects can potentially lead to clean conversion to polyfluoroarylsulfones, especially when micellar reactant concentration is high. Notably, the transformation involving sulfinate salts are otherwise not possible in any polar-protic solvents including water. Herein, we disclose a general, efficient, mild, and sustainable method for the synthesis of polyfluoroarlysulfones.

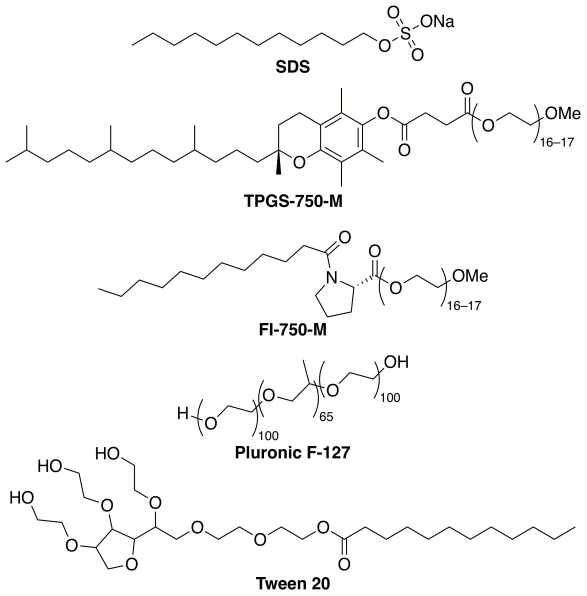


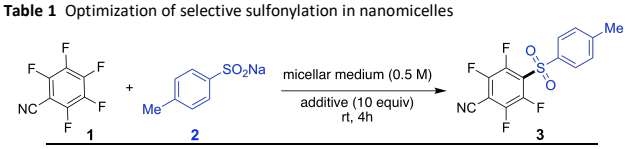
Figure 2 Surfactants evaluated in this study.

Reaction Optimization and Scope

Our investigation began with reaction of polyfluoroarene **1** with bench-stable sodium arylsulfinate **2** in various aqueous micellar solutions (TPGS-750-M, SDS, FI-750-M, tween 20, pluronic F-127, see Figure 2) using additives (NaF, NaCl, NaBr) to afford product **3** (See SI). Optimization studies revealed a dependence of the reaction on several variables; most notably, the presence of aqueous nanomicelles of FI-750-M and sodium chloride as well as acetone as an additive (Table 1). Additives are presumably required to enhance the exchange process between dynamic micelles. Notably, most reactions proceeded cleanly at ambient temperature, i.e., 24–25 °C. No argon atmosphere was required. FI-750-M was found to be superior to any other surfactant. No desired reaction was observed when neat water was used as a solvent. Sodium sulfinate salts afforded clean reactions compared to their lithium counterparts or the corresponding sulfinic acids.

After finding optimal reaction conditions (i.e., 10 equivalents sodium chloride and acetone as additives, sodium sulfinate salt as coupling partner with an exact 1:1 stoichiometry of sulfinate salt to perfluoroarene, 3 wt% aqueous FI-750-M as solvent; for details, see SI) the substrate

Table 1 Optimization of selective sulfonylation in nanomicelles



1 2 3

entry	micellar medium	additive	% yield **3**
1	neat water	–	0
2	neat water	NaCl	0*
3	3 wt% SDS	NaF	1
4	3 wt% SDS	NaCl	1
5	3 wt% TPGS-750-M	NaF	14
6	3 wt% TPGS-750-M	NaCl	48
7	3 wt% FI-750-M	NaF	27
8	**3 wt% FI-750-M**	**NaCl**	**80 (100**)**
9	3 wt% FI-750-M	–[†]	57
10	3 wt% FI-750-M	NaBr	38
11	3 wt% Tween 20	NaCl	52
12	3 wt% Pluronic F-127	NaCl	26

Conditions: **1** (0.5 mmol), **2** (0.6 mmol), additive (5 mmol), aqueous surfactant (0.8 mL), 0.2 mL acetone, rt, 4 h. Unless otherwise noted, yields are isolated. *18% yield when 20% acetone was used as additional additive. **GCMS conversion. Prolonged reaction time did not improve conversions. [†]in the absence of acetone.

scope was further established while paying attention to functional group tolerance, sterics, and electronic parameters. Remarkable generality was found with respect to the nature of the sulfinate salt, which supports systems that are electronically rich (Table 2; **3**, **5**, **6**, **10**, **21**, **22**, **26**) and deficient (**7**, **8**, **11**, **12**, **14**, **15**, **17**, **20**, **25**), containing aryl and heteroaryl combination

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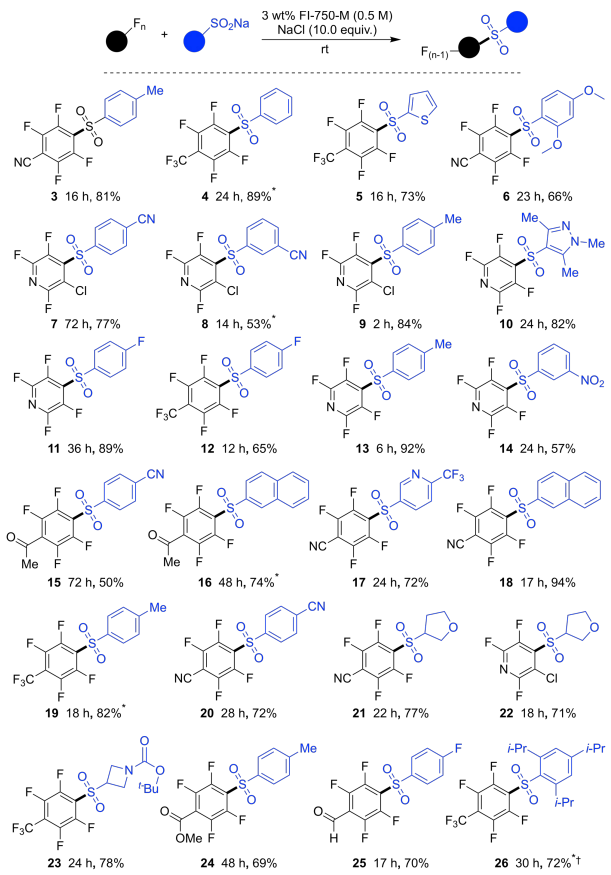
Table 2 Substrate scope of selective sulfonylation of polyfluoraromatics

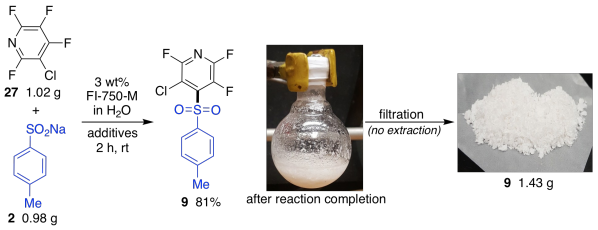


Conditions: polyfluoroaryl (0.25 mmol), sodium arylsulfinate (0.25 mmol), NaCl (10 equiv.), 0.1 mL acetone, 0.4 mL 3 wt% aq. FI-750-M; *yields with reaction temperature 45 °C; †lithium sulfinate salt was used.

(**5**, **7**–**10**, **17**), cycloalkyl (**21**–**23**), and with considerable steric bulk (**26**). Notably, the reactive chloro group on a polyfluoroarene (**7**–**9**, **22**) remained intact and did not show any side reaction. No side reactions were observed at the 2′ and 6′-position of pyridyl rings (**7**-**11**, **13**, **14**, **22**). Residues such as acetyl (**15**, **16**), carbamate (**23**), ester (**24**), nitrile (**3**, **6**, **7**, **8**, **20**, **21**), formyl (**25**), and trifluoromethyl (**4**, **5**, **12**, **17**, **19**, **23**, **26**) are well tolerated. No aldol-type product was observed when an acetyl residue was present on a coupling partner. Good reactivity was observed in substrates with notable steric congestion (**6**, **26**). Heteroaromatic thiophene (**5**) displayed excellent reactivity without formation of any polymerized side products. Percentage conversions to desired products were mostly excellent. However, isolated yields ranged from moderate to excellent depending upon the nature of substrates and products (e.g., whether they are highly volatile or not). Alternatively, reactions yields could be slightly improved by using excess of sulfinate salt (See SI for details). However, in such cases, product purifiation and extraction steps are required.

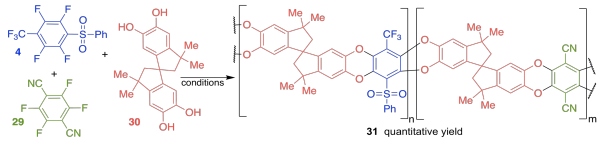
Implementation

Reproducibility and application of our experimental approach was further verified by a gram scale reaction (Scheme 1). A reaction of **27** and **2** in a perfect 1:1 stoichiometry afforded clean product **9** in a quantitative yield within 2 hours. Although micellar catalysis eliminates or drastically reduces organic solvent in the reaction medium, the solvents are still utilized in the process of product extraction and purification; this remaining dependence is the basis for a common criticism of



Scheme 1 Reproducibility at gram-scale with no use of organic solvent for extraction and purification—just simple filtration.

micellar catalysis. Therefore, technology needs to be developed which does not require organic solvents for extraction and product purification. A unique feature of FI-750-M is the presence of optimal hydrophobicity in the micellar cores for crystallization of sulfone products from the reaction mixture, facilitating avoidance of solvent-intensive extraction and purification processes. Accordingly, no organic solvent was required for extraction of the gram-scale product. The product was isolated with simple filtration and washing with water. Notably, ^{1}H NMR showed no residual surfactant in the product. Aqueous nanomicelles recovered from this reaction were further reused for substrate scope. Thus, neither aqueous nor organic waste was generated in this process.



Scheme 2 Synthesis of polymer in micellar media—direct application of this methodology. Conditions: **4** (0.28 mmol, 1.0 equiv.), **29** (0.56 mmol, 2.0 equiv.), **30** (0.84 mmol, 3.0 equiv.), K_2CO_3 (2.8 mmol, 10 equiv.), 10 mL 3 wt% aqueous FI-750-M, reflux.

As previously described, resulting sulfones are highly applicable in material chemistry. One such application of these compounds was demonstrated by a synthesis of polymer **31**, which exhibits microporous properties facilitating separation of trace impurities from gases (Scheme 2).[19] Product **4**, which had been obtained in 90% yield at gram scale, was subsequently introduced into a polymerization reaction with **29** and **30**. Resultant polymer **31** was obtained with high purity quantitatively. Notably, this polymer synthesis was conducted entirely in aqueous FI-750-M; unlike the previously reported method, no organic solvent was used for its synthesis or purification at any stage. Starting with octaflurotoluene and sodium phenylsulfinate, a one-pot synthesis of **31** was also achieved without affecting purity or yield.

For the most part, these micelle-enabled transformations did not display any side reaction or double sulfonylation. Therefore, no extra purification was required. Recycle studies were also performed with a full recovery of additives and FI-

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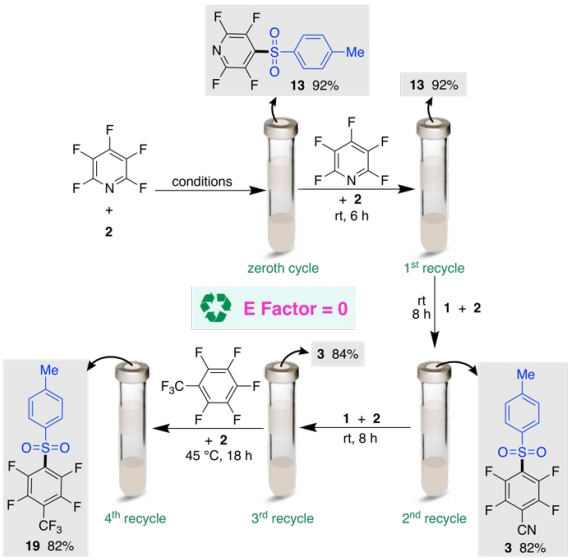

Scheme 1 Demonstration of method greenness by E factor and recycle study. Conditions: perfluoroarene (0.25 mmol), aryl sodium sulfinate (0.25 mmol), NaCl (2.5 mmol, only in zeroth cycle), acetone (0.1 mL, only in zeroth cycle), 3 wt% aqueous FI-750-M (0.4 mL, only in zeroth cycle), rt (unless otherwise noted), 6 h (unless otherwise noted).

750-M between cycles (Scheme 3). Reuse of micellar reaction media did not affect reaction outcomes in terms of yield or reaction time. The polyfluoroarene was also varied in each recycle and the outcome was similar to when a fresh solution of FI-750-M was used. After obtaining **13** from the zeroth cycle by simple filtration, the recovered aqueous solution of nanomicelles and additives was reused for the first recycle to obtain additional **13**. Second, third, and fourth recycles were performed with different substrates to obtain products **3** and **19**. Notably, this is a clean process without generation of any organic waste; i.e., E-factor = 0.[7] Aqueous micellar media can potentially be reused even beyond the fourth recycle.

Analytical and Computational Studies

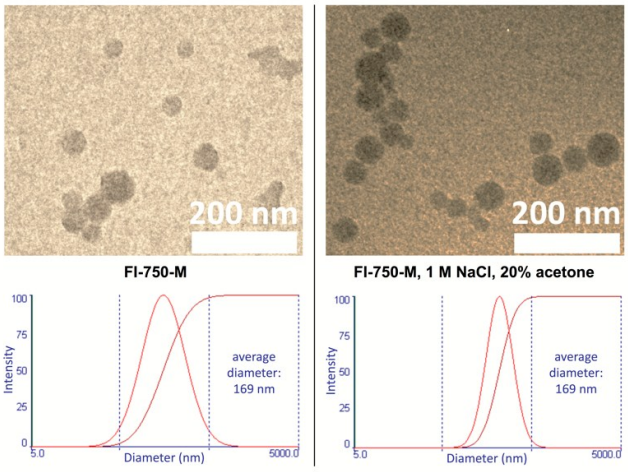

Figure 3 Cryo-TEM and DLS results for 3 wt% FI-750-M with and without additives.

Additional studies were undertaken to corroborate our hypotheses about the nature of our reaction system. To better understand experimental findings suggesting the beneficial influence of additives on micelle size and size distribution, cryo-TEM and dynamic light scattering (DLS) experiments were conducted (Figure 3; for more details, see SI). Cryo-TEM in the absence of any additive revealed the existence of round-shaped nanomicelles of FI-750-M with sizes of 50–150 nm, and very little agreegation of nanomicelles was observed. With 1 M NaCl and 20% acetone as additives, aggregation of nanomicelles was observed in cryo-TEM. Thus, the aggregation of nanomicelles was a key factor that facilitated the exchange process as well as close proximity of coupling partners. Notably, additives did not cause any expansion of micelles. Similar results were obtained in DLS studies. A wider distribution of nanomicelles was detected in the absence of additive. With additives, a slight increase in average diameter and narrowing of particle size distribution was observed. The increase in micellar aggregation along with reduction of peak area supports the hypothesis behind the design of this reaction methodology.

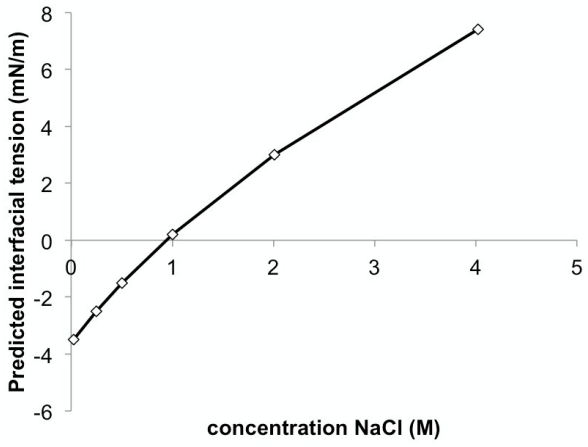

Figure 4 Interfacial tension between water and FI-750-M surfactant as a function of NaCl concentration in the water phase as predicted by DFT calculations.

Calculations using COSMO-RS[21] revealed that the interfacial tension (IFT) between the surfactant and water increased significantly upon adding salt to the water (Figure 4). An increased interfacial tension would lead to aggregation or particle expansion in order to minimize the surface area, which is consistent with Figure 2. Calculations with increasing amounts of acetone showed that very little change in the IFT was observed, which demonstrates that it was the addition of salt that led to the increased aggregation. The IFT was negative for low salt concentration, which is consistent with spontaneous micelle formation for the pure FI-750-M surfactant. The calculations also revealed that the proline linker was the most hydrophilic part of the surfactant and thus responsible for reducing the IFT. The water–surfactant interface would thus be enriched with proline linker parts of the surfactant. The lipophilic region would thus prefer to be located in the interior

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of the micelle according to the calculations while a portion of mPEG and proline linker contribute to micellar interface. However, the calculations do not take into account the full 3D geometry and because the mPEG region is far larger than the proline linker region, the interface between the micelles and the surrounding water phase cannot be made up of only the proline linker. Therefore, the mPEG region will undoubtedly also be in contact with the surrounding water phase, but in such a way as to maximize contact between the proline linker and the water.

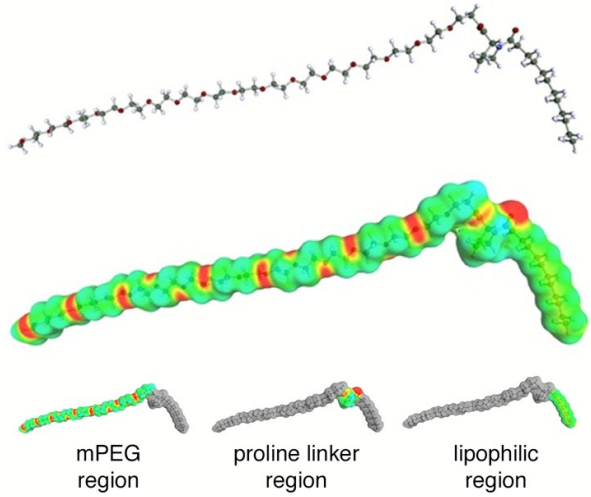

Figure 3 FI-750-M molecular structure (top left), COSMO surface (top right) and the partial COSMO surfaces (bottom row) of the surfactant regions defined in Figure 1.

Experimental findings and proposed hypotheses were further confirmed by gaining information about the local solubility in FI-750-M. COSMO-RS local solubility predictions of reactants **1** and **2** in water and the various parts of the FI-750-M surfactant revealed the importance of FI-750-M for this synthetic methodology (Figure 4 and Table 3). Based on the calculations, perfluoroarene **1** is mainly located in the PEG region. Sulfinate salt **2** prefers to be in either the water phase or the proline linker region. On the logarithmic scale, the sum of the logarithms represents a product of the maximum attainable concentrations. A higher sum of solubilities means an increased combined local concentration of the reactants, which significantly increases the reaction rate. Clearly, in comparison with TPGS-750-M, the maximum value is obtained for FI-750-M, especially in the proline linker location (bold).

Table 3 COSMO-RS predicted solubilities in 2.5 M NaCl solution and local regions of FI-750-M and TPGS-750-M surfactants. All solubilities are written as $\log_{10}$(max mole fraction) and thus represent the maximum attainable concentration in the phase. A value of 0 represents complete solubility.

solution	solubility of **1**	solubility of **2**	solubility of **1**+**2**
2.5 M NaCl	-4.6	-0.3	-4.8
TPGS-750-M			
PEG region	-0.4	-1.2	-1.6
succinic acid linker	-0.7	-1.3	-2.0
lipophilic part	-0.9	-5.7	-6.6
FI-750-M			
PEG region	-0.4	-2.1	-2.5
proline linker	-0.8	-0.2	**-1.0**
lipophilic part	-1.3	-7.0	-8.3

In order to assess the influence of the salt additives, we also calculated the partition coefficients for the sodium arylsulfinate **2** between water and the proline linker region as a function of the salt chemistry (Table 4). The salt effectively pushes the sulfinate into the micelles and increases local concentration in the proline linker. The magnitude of the effect of different salt additives are NaCl = NaBr > NaF > water, which are consistent with the experimental results (see Table 1). These results confirm that the local concentration of sulfinate salt in the micelle plays an important role for the reaction.

Table 4 Partition coefficients, $\log_{10}$(P) for Na-sulfinate (**2**) between salt solutions and the FI-750-M proline linker region, predicted by COSMO-RS calculations. The more positive the log(P) value, the more the Na-sulfinate (**2**) prefers the surfactant phase over the aqueous solution.

solution	$\log_{10}$(P)
pure water	-1.3
2.5 M NaF (aq)	-1.0
2.5 M NaCl (aq)	-0.7
2.5 M NaBr (aq)	-0.7

Therefore, the calculations demonstrate that, based on the local predicted concentrations, FI-750-M is a better surfactant for the reaction than TPGS-750-M as a result of the linker chemistry, which is better at solubilizing the sodium aryl sulfinate in the former case. The preferential location of proline linker at the micelle–water interface could also play a role in the exchange process, with easy access to sodium sulfinate from the water as well as polyfluoroarene from the PEG region of the micelles.

Conclusions

Proline-based surfactant FI-750-M has been shown to enable clean and selective sulfonylation of polyfluoroarene in water under mild conditions. The presented protocol uses easily handled sulfinate salts, allows for recycling of the reaction medium, and isolation of pure product by simple filtration; no organic solvents are required for product extraction and purification. The design concept behind FI-750-M was to mimic polar-aprotic solvents by introducing a greater degree of

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polarity into the micellar core, and the success of this approach was demonstrated through empirical and theoretical comparison with other surfactants. In particular, COSMO-RS calculations indicated that the FI-750-M linker region was best suited for mutual solubility of the polyfluoroarene and the sulfinate anionic nucleophile. Protocol scalability and application were demonstrated with gram-scale and polymer syntheses.

Conflicts of interest

The authors declare the following competing financial interest(s): Patent is pending for surfactant(s) FI-750-M used in the study.

Acknowledgment

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