Difluorination Followed by Hydrodefluorination in Aqueous Micelles Leading to Transition Metal-Free Highly Selective Monofluorination of Unprotected Indoles

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ABSTRACT: Unprecedented aqueous fluorine chemistry has been reported, involving a highly selective monofluorination of unprotected indoles via simultaneous difluorination-hydrodefluorination, all in water. This is achieved through a carefully engineered process, which utilizes a benign proline-based surfactant called PS-750-M in an aqueous micellar environment. In situ formation of the difluorinated indole and the *N*-(phenylsulfonyl)benzenesulfonamide byproduct are vital to the process, and extensive control experiments have indicated the significance of *N*-(phenylsulfonyl)benzenesulfonamide and zinc in the two-electron transfer process, leading to a highly selective transformation. Notably, the unique feature of this technology is the requirement for simultaneous zinc activation and zinc ion sequestering within the reaction medium, which can only be achieved through the use of zinc and a fluorinating source. The resulting synthetic methodology can selectively prepare a broad range of monofluorinated indoles, is easy to execute, and is greener than traditional 3-fluoro indole-forming reactions requiring toxic reaction medium or rare-earth metals.

Introduction. Fluorinated *N*-heterocycles are structurally important to pharmaceuticals.[1–4] Over 75% of recently FDA-approved drug molecules contain *N*-heterocycles, with or without fluorine atoms.[4,5] Fluorine has a significant impact on the activity of agrochemicals and pharmaceuticals. More than 35% of agrochemicals and 25% of pharmaceuticals on the market today are fluorinated molecules.[2,3,6,7] Furthermore, three out of five best-selling pharmaceuticals are fluorinated molecules, and many in clinical trials contain fluorinated substituents.[3,8] This is because adding a single fluorine atom can significantly impact a molecule's bioavailability by enhancing metabolic stability and lipophilicity.[9,10] As a result, there is a growing demand for efficient and environmentally friendly methods for fluorinating *N*-heterocycles.[11] ACS Green Chemistry Institute has emphasized the need for greener approaches in fluorination chemistry, including it in its top 10 key green chemistry research areas.[12-14]

The site-selective monofluorination of unprotected indoles is significantly challenging. However, the compounds resulting from this process have proven incredibly useful as bioactive scaffolds.[15,16] In particular, 2-substituted-3-fluoroindoles have found widespread use in medicinal chemistry, as they play a crucial role in the development of inhibitors for treating cancer, immunoregulatory diseases, and hepatitis C (Figure 1A).[17,18] Unfortunately, the synthesis of these highly desirable compounds is hindered by the lack of available efficient methods, many of which require multiple steps of prefunctionalization, protection-deprotection strategies, or the use of expensive metal catalysts.[19–22] Furthermore, the existing methodologies often result in undesired side products, such as 3,3-difluoro-indole or 3-difluoro-2-hydroxyindoles (Figure 1B). While some progress has been made in achieving selective monofluorination of 3 *N*-protected indoles under aqueous micellar conditions using the environmentally friendly amphiphile PS-750-M, this method

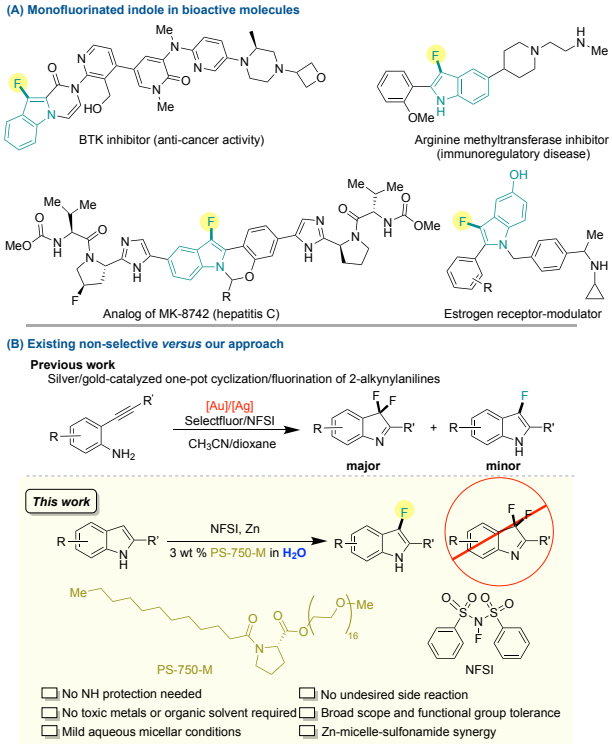
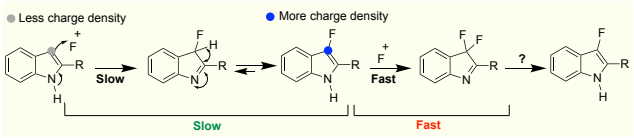


Figure 1. (A) Representative examples of pharmaceutically relevant molecules having fluorinated indoles. (B) Comparison between the existing route to access monofluorinated indoles and our newer selective route in water.

still suffers from low yields due to side reactions and requires specific protecting groups prior to the monofluorination step.[23] Additionally, it is not selective with 2-substituted indoles. To date, no general methods exist for site-selective

monofluorination of unprotected 2-substituted indoles to produce 3-fluoro indoles as the sole product. Overall, the challenges posed by the difluorination in this process make it a particularly difficult transformation.



Scheme 1. A pathway to uncontrolled difluorination.

In the reaction of unprotected indoles, after introducing a first fluorine atom on the C-3 position, π-electron density is more localized at the C-3 due to electron polarization induced by the fluorine atom (Scheme 1).[24] This can lead to uncontrolled electrophilic difluorination at a faster rate compared to monofluorination. To prevent this, the *N* atom can be protected, which restricts the tautomerism that causes the shift in charge density. However, the extra protection-deprotection steps involved in this process can affect the cost, functional group compatibility, and sustainability. To address this issue, we propose that the in situ formed difluorinated species can be simultaneously reduced to the desired monofluorinated product through a redox process, leading to hydrodefluorination. However, this is challenging because the redox process can also quench the fluorinating agent. Moreover, after the hydrodefluorination, the difluorination can occur again, leading to repetitive unproductive difluorination-hydro defluorination. Therefore, optimal control of the hydrodefluorination rate and difluorination is required to achieve the proposed transformation successfully.

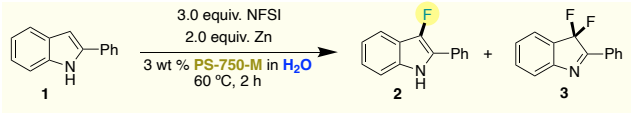
The use of micelles can positively impact the desired reaction pathway if an appropriate micelle-insoluble reductant is present. This is because neutral fluorinating agents and more lipophilic di- and mono-fluorinated indoles tend to have a strong affinity for micelles, which allows them to remain within the micelles. This can prevent the unnecessary quenching of the fluorinating agent. At the same time, the micelle-insoluble reductant provides and allows electrons to slowly diffuse from bulk water to the indole-containing micelles, facilitating selective hydrodefluorination.

Notably, the hydrodefluorination step is challenging and mostly requires the use of toxic transition metal catalysts, such as ligated nickel, palladium, gold, ruthenium, rhodium, and iridium.[25,26] However, due to their anticipated water-sensitivity, these catalysts may not be suitable for our proposed hypothesis. Among most reductants, zinc (Zn) is water- and micelle-insoluble and has an appropriate oxidation potential that can serve the purpose of the proposed hypothesis.[27] Furthermore, its byproduct is water-soluble, allowing for easy product purification. However, the surface oxidation of Zn in water and the formation of zinc oxide (ZnO) layer on the zinc's surface could cause severe issues with in situ deactivation of Zn.[28,29] Simultaneously, we also anticipated that the in situ formed *N*-(phenylsulfonyl)benzenesulfonamide from mild and inexpensive *N*-fluorobenzenesulfonimide (NFSI) could assist in the surface activation of Zn. Nonetheless, if this unprecedented aqueous methodology can be performed in a domino (tandem) fashion where fluorination and hydrodefluorination simultaneously occur without the need to isolate intermediates. The resulting method can provide a better alternative to access monofluorinated unprotected indoles. The use of the benign medium, anticipated high yields, easier product isolation, and high product purity could be the additional features of this technology. The exclusion of toxic reaction medium, more corrosive and stronger oxidizing agent Selectfluor as a fluorinating agent,[30] and expensive transition metals can potentially reduce harmful waste generation from the toxic reaction medium and ligated metals (Figure 1B).

Results and Discussion. According to our hypothesis, we have successfully developed a sustainable and highly selective monofluorination technique for functionalized indoles without the need for transition metals. This process takes place in water and is mild. Our optimization study, which utilized 2-phenyl-1*H*-indole **1** as the benchmark substrate and NFSI as an electrophilic fluorine source (Table 1), revealed that the best conditions were achieved with 3.0 equivalents of NFSI, 2.0 equivalents of Zn powder (100 mesh size), a temperature of 60 °C, 3 wt % aqueous PS-750-M as the reaction medium, and 0.25 M global concentration (entry 1), afforded the 99% of **2** (based on area % determined by HPLC) with 100% selectivity. Reducing the NFSI to one molar equivalent and removing Zn from the reaction afforded only the difluorinated byproduct **3** (entry 2). This suggests that monofluorination proceeds at a much slower rate than difluorination. Replacing the fluorine source with Selectfluor lowered the yield of **2** (72%) and selectivity (82:18 ratio of mono- and di-fluorinated products **2** and **3**, respectively), most likely due to poor solubility of Selectfluor in micelles (entry 3). The yield of **2** was lower when the amount of NFSI was reduced from 3.0 equiv. to 2.0 equiv. (entry 4). As anticipated, no monofluorination was observed in the absence of Zn as the reductant (entry 5). Optimal selectivity and yield were achieved with 2.0 equivalent loading of 100 mesh Zn powder. Reducing the amount to 1.5 equivalents resulted in decreased selectivity and yield (entry 6), with only 37% of **2** and 60% of unwanted **3** being observed. Notably, the mesh size of the Zn powder did not affect the reaction— Zn powders with mesh sizes 40 and 100 provided similar conversions of **1** to **2** as well as selectivity. (See Supporting Information, page S6). A comparative study was also carried out to determine the importance of micelles of PS-750-M in achieving high selectivity. This was done using common organic solvents such as THF, nitromethane, nitrobenzene, and toluene as a reaction medium. The results showed that these solvents only yielded **3,** along with traces of **2** (entry 7). Inferior reactivity was observed in CH_3CN and DMF as reaction medium, and only 51% and 27% of **2** with poor selectivity were observed in these cases, respectively. The reaction in neat water yielded 31% of **2** with a selectivity of mono- and di-fluorinated products 39:61 (entry 10). Thus, the significance of micelles of PS-750-M as a reaction medium for obtaining high selectivity is validated again.[23, 31–36] Lipshutz surfactants Nok and TPGS-750-M were also tested. However, TPGS-750-M was found to be incompatible and produced only 48% of **2** with poor selectivity (entry 11). Other options, such as Nok, Tween-20, Pluronic, and CTAC, have proven inferior to PS-750-M, resulting in lower selectivity and yield of **2** (entry 12; for details, see Supporting Information, page S5). The lower pH of aqueous PS-750-M (pH = 4 to 5) may contribute to maintaining mildly acidic reaction conditions. This could facilitate Zn activation, leading to an efficient reduction of **3** to the desired product **2**. It

was observed that lowering the temperature from 60 °C to 45 °C resulted in a lower conversion to **2** (entry 13).

Table 1. Optimization studies[a]



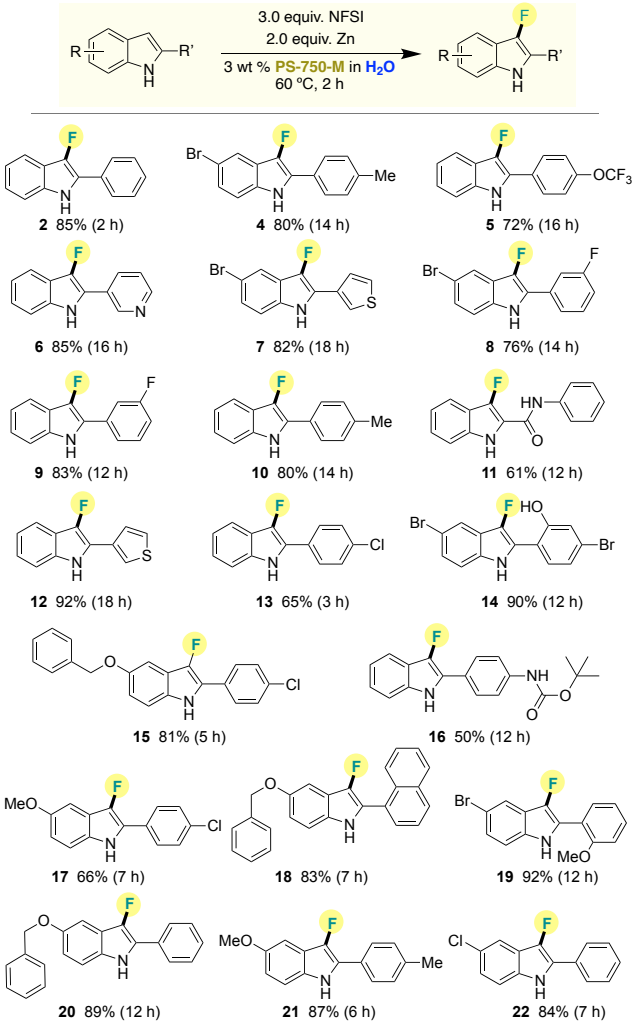
entry	deviation from standard conditions	**2** (%)[b]	Selectivity **2**/**3** (%)
1	none	99	100/n.d.
2	1.0 equiv. NFSI and no Zn	n.d.	n.d./100%
3	Selectfluor instead of NFSI	72	82/18
4	2.0 equiv. of NFSI	74	100/n.d.
5	No Zn	n.d.	n.d./100
6	1.5 equiv. of Zn	37	40/60
7	THF/toluene/nitromethane as a solvent	traces	traces/100
8	CH_3CN as solvent	51	40/60
9	DMF as solvent	27	29/71
10	water as a solvent	31	39/61
11	3 wt % aq. TPGS-750-M as solvent	48	35/65
12	3 wt % aq. Nok as solvent	72	72/32
13	45 °C instead of 60 °C	78	81/19

[a]**Conditions. 1** (0.25 mmol), NFSI (0.75 mmol, 3 equiv.), Zn powder (100 mesh, 0.5 mmol, 2.0 equiv.), 1 mL 3 wt % PS-750-M in H_2O. [b]Area % based on HPLC analysis of the crude reaction mixture.

The optimized conditions for a highly selective tandem transformation were explored using unprotected indoles bearing various functional groups (Table 2). In particular, the study focused on the synthesis of monofluorinated indoles, and it was observed that all 2-substituted indoles displayed excellent reactivity and selectivity in the reaction. The study revealed that monofluorination was achieved in good-to-excellent yields in most cases (**2**, **4**-**22**). The study also included indoles containing heterocycles such as pyridine (**6**) and thiophene (**7**, **12**), and these substrates worked well under standard conditions and the final products were obtained in good yields. Substrates bearing bromo (**4**, **7**, **8**, **14**, **19**), chloro (**13**, **15**, **17**, **22**), fluoro (**8**, **9**), and trifluoromethoxy (**5**) were compatible and reacted well under standard conditions. In addition, the study tested substrates containing amide functional groups (**11**) and protecting groups such as Boc (**16**) and benzyl (**15**, **18**, **20**). The results showed that these functional groups were well-tolerated, and the desired products were obtained in good yields. It is worth noting that in all the substrates, the indole nitrogen was unprotected, indicating that the reaction did not require additional protection of the nitrogen atom. However, this method was not effective for 2-alkyl substituted indoles (see SI, Page S8).

It is worth noting that the monofluorinated intermediate **14** is crucial for finding an analog of Merck's MK-8742, which is used to treat hepatitis C. Our methodology resulted in a 90% isolated yield of **14**, which is significantly higher than the 19% yield achieved using methods previously reported in literature.[37,38] Our synthetic method successfully maintained the phenolic ring without any additional fluorination on it. Additionally, we successfully synthesized various other intermediates of estrogen receptor modulators using our methodology, including **15**, **18**, and **20**.

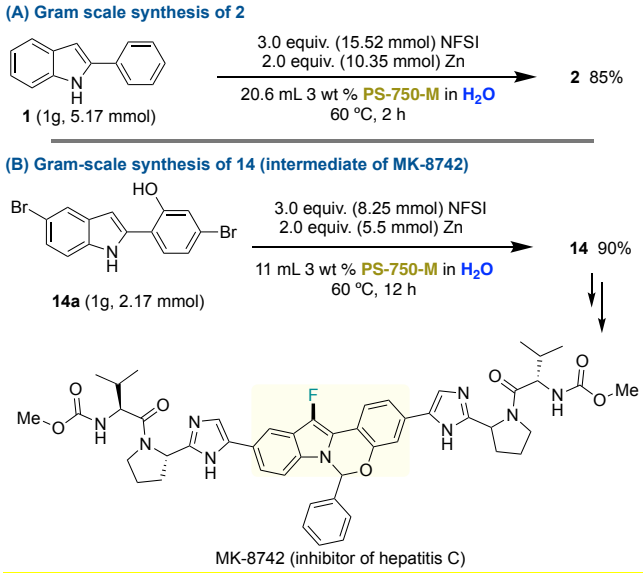
Table 2. Substrate scope[a]



[a]**Conditions:** Indoles (0.25 mmol), NFSI (0.75 mmol, 3 equiv.), Zn (0.5 mmol, 2.0 equiv.), 1 mL 3 wt % PS-750-M, 60 °C. All yields are isolated.

This particular methodology was employed to synthesize an intermediate compound that is used in the production of an inhibitor designed for the treatment of immunoregulatory diseases (**19**). In comparison to the current method,[18] which only yields 40%, our approach achieved an outstanding yield of 92%. The advantage of our method is the absence of a difluoro-byproduct, which makes it easier to isolate the product. As a result, we were able to avoid the need for multiple-column chromatographic separations or re-crystallization. The ease of product isolation contributed to the high yield and reduced the overall time and cost of the process.

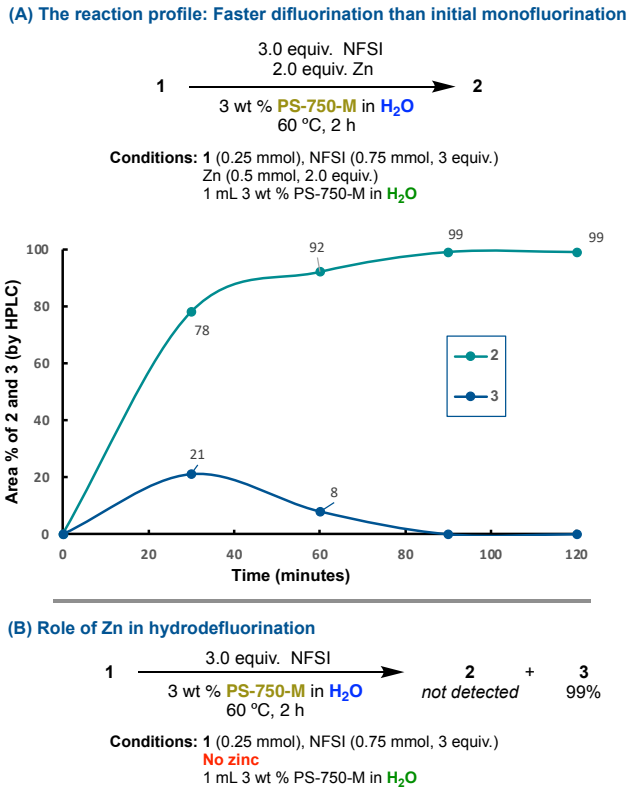
The reaction scale-up was conducted by choosing significant examples for the gram scale reactions (Scheme 2). For instance, the monofluorination of **1** on a gram scale reaction under standard conditions yielded 85% of **2**, which was the same as the small-scale reaction (Scheme 2A). Similarly, the gram-scale synthesis of an intermediate of Merck's MK-8742 (**14**) was carried out, and an excellent yield of 90% was obtained (Scheme 2B). These cases further highlighted the potential of this methodology for multi-gram scale synthesis of industrially relevant bioactive molecules.



Scheme 2. Gram-scale synthesis. (A) Synthesis of 2. (B) Synthesis of 14.

To gain mechanistic insights, a reaction profile was studied where the reaction of **1** was performed under standard conditions (Scheme 3A). The fate of **1** and the formation of monofluorinated **2** and difluorinated **3** were analyzed at 30-minute intervals using high-performance liquid chromatography (HPLC) analysis of the crude reaction mixture. The reaction was found to be rapid as compound **1** was consumed entirely within the first 30 minutes. At this stage, 78% of compound **2** and 21% of compound **3** were observed. After 60 minutes, compound **3** was reduced significantly to 8%, while 92% of compound **2** was formed. Compound **3** was completely consumed in 90 minutes with the complete conversion to compound **2**. These results suggested that the rate of difluorination is faster than the first monofluorination of **1** and hydrodefluorination of **3**, supporting the hypothesis of localization of π-electron density at the C-3 position due to electron polarization induced by the fluorine atom. Additionally, the experiment confirmed that the reaction occurs through the formation of compound **3**, which is then converted into compound **2** by a redox process. Notably, only compound **3** was detected if Zn was not used in the reaction (Scheme 3B).

A control experiment was conducted to better understand the mechanistic process involved in converting **3** to **2** under our tandem reaction conditions. Isolated **3** was reacted with Zn (2.0 equiv.) under aqueous micellar conditions (Scheme 4A; for more details, see the Supporting Information). Surprisingly, after 2 hours, only 13% of the desired product **2** was observed, compared to 99% when the tandem reaction was performed. This result indicates that Zn alone is insufficient to convert **3** to **2** effectively. Other components in situ generated in the reaction mixture must also be crucial to facilitate the hydrodefluorination to form the desired product.

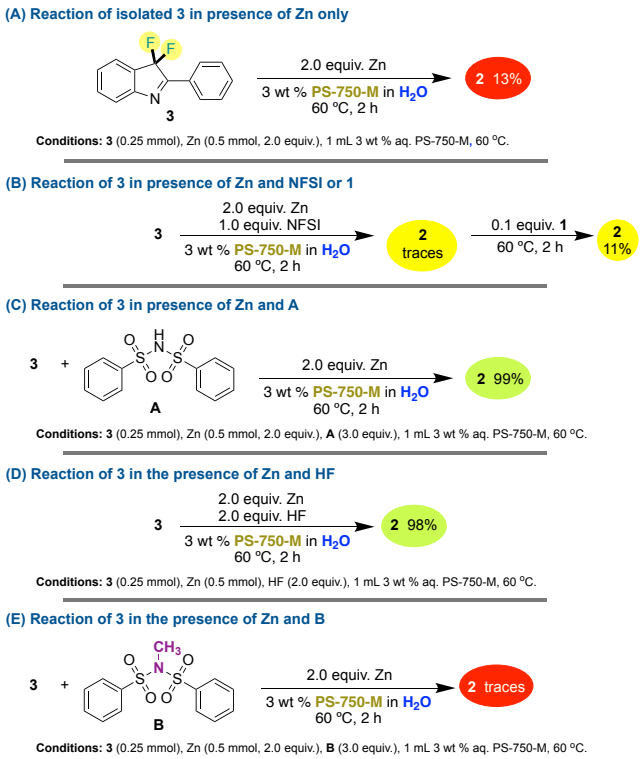


Scheme 3. (A) A reaction profile under standard conditions. (B) Reaction in the absence of Zn.

To investigate the role of NFSI and Zn in the formation of compound **2** from **3**, a control experiment was conducted where isolated compound **3** was reacted in the presence of 1.0 equivalent NFSI and Zn (Scheme 4B). However, only traces of compound **2** were observed in this case. Interestingly, when 0.1 equivalent of compound **1** was added to the same reaction mixture, 11% of the desired product **2** was observed after an additional 2 hours. This suggests that the reaction of NFSI with compound **1** generated *N*-(phenylsulfonyl)benzenesulfonamide **A**, which then facilitated the formation of compound **2**. The reaction stopped after the formation of 11% of **2**, indicating that the stoichiometric byproduct **A** of NFSI is necessary to complete the reaction. This is most likely due to the chelation of **A** with Zn^{2+} ions that drive the redox process.

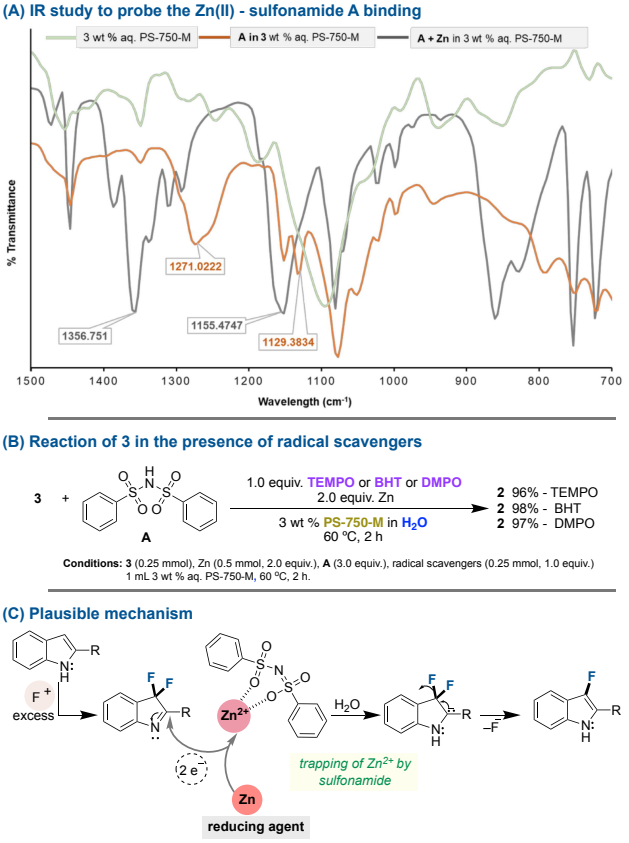
To further verify the role of **A**, a control reaction was performed with **3** in the presence of 2.0 equivalents of Zn and 3.0 equivalents of **A**. It was observed that complete conversion to **2** occurred in 2 hours (Scheme 4C). While it was initially speculated that chelation between Zn^{2+} and **A** could be the cause, it was also possible that the C-F bond of **3** was weakened through intermolecular hydrogen bonding between **3** and **A**. This could have eased C-F bond cleavage and promoted the hydrodefluorination. To test this possibility, control ^{19}F NMR experiments were conducted. However, the ^{19}F NMR analysis of a mixture

of **3** and **A** did not show any significant shift in the ^{19}F signals compared to the signals of **3** alone (for more details, see Supporting Information, page S37). Therefore, it can be concluded that no such mechanism was operative in the pathway.



Scheme 4. Control experiments to establish a plausible reaction pathway. (A) The reaction of 3 in the presence of Zn, (B) Zn or NFSI and 1, (C) Zn and A, (D) Zn and HF, and (E) Zn and B.

Due to its high acidity with a pKa of 1.45, **A** has the ability to activate Zn by removing the in situ generated ZnO that sits on the surface of Zn. Additionally, **A** can sequester the in situ generated Zn^{2+} ion through chelation. This hypothesis was confirmed by conducting a reaction between **3** and Zn under a slightly acidic medium using 2.0 equivalents of HF without **A**. It is likely that HF activates the Zn surface by removing ZnO deposition from the surface.[39] The reaction under these conditions resulted in complete conversion to **2** in 2 hours (Scheme 4D), indicating that the activation of Zn and sequestering of Zn^{2+} ions by fluoride ions are necessary for a smooth reaction. To further demonstrate the activation mechanism, *N*-methyl-*N*-(phenylsulfonyl)benzenesulfonamide **B** was used in place of **A**. Since **B** lacks an acidic proton, Zn activation was not possible. However, chelation was still possible, and traces of **2** were observed, validating the importance of Zn activation (Scheme 4E). In a separate series of experiments, we attempted to hydrodefluorinate compound **3** using freshly activated Zn powder with different mesh sizes. However, without the presence of **A**, only a small amount (5-7%) of compound **2** was observed in these reactions. This confirms that both Zn activation and the Zn^{2+} ions' sequestering are necessary for a successful transformation (for details, see Supporting Information, page S28).



Scheme 5. (A) IR studies to probe the Zn-A binding. (B) Reaction of 3 in the presence of radical scavengers. (C) Plausible reaction mechanism.

The sulfonamides form stable complexes with Zn(II) species.[40–42] Therefore, in addition to promoting the electron transfer process, it is highly probable that **A** trapped the oxidized Zn(II) species from the Zn surface through its complexation and cleaned up the Zn surface, facilitating hydrodefluorination.[34,35] To confirm this possibility, IR experiment was performed to prove the formation of the Zn- *N*-(phenylsulfonyl)benzenesulfonamide complex under the reaction conditions (Scheme 5A). The IR of **A** showed two bands near 1271 cm^{-1} and 1129 cm^{-1}, most likely due to asymmetric and symmetric stretches of the S=O group.[33] In the presence of PS-750-M and excess of Zn, IR of **A** showed the appearance of new bands at higher frequencies at 1357 cm^{-1} and 1156 cm^{-1}. The blue shift of IR bands suggested the involvement of the sulfonamide group's complex formation with Zn^{2+}. A similar peak shift in the IR spectrum was observed when **A** (1 equiv.) was mixed with ZnO (3 equiv.), which supported the binding between Zn(II) and **A** (for details, see Supporting Information, page S35).

The redox process that occurs when Zn transfers either one or two electrons to the difluorinated indole substrate has been confirmed through control experiments using TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl), BHT (butylated hydroxytoluene), and DMPO (5,5-dimethyl-1-pyrroline-*N*-oxide). To verify this, a standard reaction was conducted using Zn and **A** as an activator along with radical scavengers like TEMPO, BHT or DMPO (as shown Scheme 5B). However, it was observed that the conversion to final product **2** was complete in all cases,

thereby ruling out the possibility of a single-electron transfer process.

Based on the aforementioned control experiments, it appears that the likely course of the reaction involves the creation of a difluorinated intermediate **3** and **A**. This intermediate **3** then accepts two electrons from Zn, resulting in hydrodefluorination and the formation of *N*-(phenylsulfonyl)benzenesulfonamide of NFSI, which is captured by Zn^{2+} generated in situ. This complexation facilitates the electron transfer process, ultimately leading to hydrodefluorination (Scheme 5C). At the same time, the NFSI-generated *N*-(phenylsulfonyl)benzenesulfonamide **A** activates the Zn surface by removing any ZnO present on it.

Conclusion. To summarize, our comprehensive study has underscored the pivotal role of Zn and in situ generated *N*-(phenylsulfonyl)benzenesulfonamide in the tandem reaction yielding monofluorinated unprotected functionalized indoles. Zn acts as a facilitator of hydrodefluorination, while *N*-(phenylsulfonyl)benzenesulfonamide sequesters Zn^{2+} ions from the metal surface, thereby catalyzing the redox process. IR spectroscopy studies have corroborated the sequestration of Zn^{2+} ions by *N*-(phenylsulfonyl)benzenesulfonamide in situ produced from NFSI. Control experiments have demonstrated that the micelles of PS-750-M are significant in developing this technology. This method enables the monofluorination of 2-substituted unprotected indoles under mild micellar conditions. It is safer and scalable compared to traditional methods that employ more corrosive Selectfluor and transition metal catalysts; it circumvents the use of toxic or rare-earth metals and problematic reaction mediums while maintaining excellent reaction selectivity. The two-step domino (tandem) reaction is a feature of this aqueous micellar technology, showcasing its potential in synthesizing intermediates of bioactive molecules. Although the methodology leverages the in-situ generated byproduct of NFSI, it still necessitates an excess of NFSI and Zn. While the in situ-generated zinc fluoride (ZnF_2) can be readily separated via membrane filtration to recycle PS-750-M, water-compatible, efficient, and sustainable electrophilic fluorinating agents are still highly desired. Despite certain limitations of our approach, it produces high-yield, high-purity products, employs aqueous micelles as the reaction medium, simplifies product purification by obviating the need to separate mono- and difluorinated products, requires reagents that are more manageable, and thus, contributes to a degree of sustainability.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. It includes details of experimental procedures, compound characterization, and analytical data.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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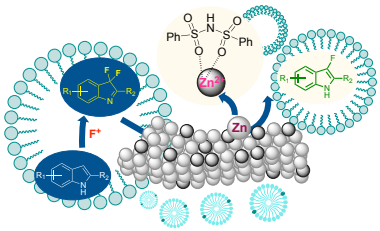

A redox event, surface cleaning of the reductant, and sequestration of the in situ generated zinc ion facilitated concurrent difluorination and hydro-defluorination for cleaner monofluorination of indoles in aqueous micelles.