



A Mechanistic Study of Impurity Formation and Elimination in Selectfluor-Assisted Fluorination of N-Heterocyclic Substrates

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Abstract

The production of side products and the introduction of contaminants make it exceedingly difficult to monofluorinate N-heterocycles using electrophilic fluorinating agents. Identifying, eliminating, and understanding the mechanisms of impurities that develop during Selectfluor monofluorination procedures is the primary focus of this research. Temperature, solvents, chemicals, metal, and silver catalysts were among the many reaction parameters studied in depth to determine the optimal conditions for selective fluorination. The enhanced system demonstrated a significant improvement in product purity and production following the purification of Selectfluor. Meanwhile, a successful amide coupling process in water and a long-lasting aqueous micellar approach for indole monofluorination were developed, which eliminates the requirement for organic solvents, extraction, and chromatography. Nuclide resonance, infrared spectroscopy, mass spectrometry, and high-performance liquid chromatography analyses validated the procedure and its steps. In present synthetic organic chemistry, the emphasis is on both the mechanistic knowledge and the long-term viability.

Keywords: Selectfluor; Fluorination Mechanism; N-Heterocyclic Compounds; Impurity Formation; Reaction Optimization.

1. Introduction

In contemporary organic chemistry, fluorination ranks among the most significant developments. Organic molecules undergo dramatic changes in their physical, chemical, and biological properties when fluorine atoms are added to them. The unique features imparted by the fluorine atom make fluorinated molecules very desirable in the fields of materials science, agrochemicals, and medicine. These properties include increased metabolic stability, lipophilicity, and binding efficiency. This electrophilic fluorinating reagent, Selectfluor (F-TEDA-BF₄; 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2] octane bis(tetrafluoroborate)), is well regarded for its efficacy, relative lack of toxicity, and user-

friendliness. The ability to selectively fluorinate in environmentally safe conditions has contributed to its rise in popularity within synthetic organic chemistry.

While there are numerous potential applications for selectfluor-assisted fluorination processes, one common issue is the formation of contaminants, which can reduce both output and selectivity. Possible causes of these contaminants include incomplete processes, side-chain oxidation, breakdown of the fluorinating agent, or excessive fluorination or rearrangement in competing pathways. Knowing how these contaminants end up in the process is crucial for making it more efficient, making it easier to repeat, and producing purer fluorinated products. Specifically, N-heterocyclic substrates exhibit complex electrical properties and distinct structural features. There may be a plethora of byproducts or unstable intermediates due to their diverse reactions.

Determining the chemical pathways, intermediate species, and kinetic patterns utilized in Selectfluor-mediated reactions is the primary goal of impurity production and removal research. Using state-of-the-art spectroscopic techniques, chemical analyses, and computational models, researchers may determine the primary processes that lead to the formation of contaminants. Because the breakdown products of the reagent might initiate unwanted pathways, cleaning and stabilizing Selectfluor is an important component of preventing adverse effects. Therefore, the fluorination process is accelerated and made more selective by making Selectfluor more pure and simpler to work with. The primary objective of this study is to understand the process of impurity formation and removal in N-heterocyclic substrates that undergo Selectfluor-assisted fluorination. Fluorination procedures may be improved, managed, and made more successful by understanding these technical nuances. This study's findings might have applications in the pharmaceutical and fine chemical sectors, as fluorinated N-heterocycles are fundamental components of physiologically active compounds.

The monofluorination of nitrogen heterocycles has emerged as a significant development in contemporary medicinal chemistry due to the significant impact of fluorine atoms on bioactivity, metabolic stability, and lipophilicity. Because of its stability, lack of toxicity, and electrophilic fluorination potential, Selectfluor [(F-TEDA)BF₄] is a widely used fluorinating chemical. However, the reaction is less successful and more difficult to replicate when using Selectfluor-based techniques since they frequently produce a lot of undesirable by-products and contaminants.

I. The entry of contaminants into Selectfluor-mediated monofluorination of N-heterocycles, (ii) methods for their removal, and (iii) cleaning Selectfluor to increase its reactivity and selectivity are the subjects of this investigation. Sustainable synthetic approaches, in accordance with green chemistry principles, are also investigated; they include amide reactions in water and fluorination in watery micellar medium.

Objectives

1. To purify Selectfluor and enhance its reactivity.
2. To develop sustainable monofluorination and coupling reactions in aqueous systems.
3. To use analytical and spectroscopic methods (NMR, IR, MS, HPLC) for mechanistic elucidation.

Research method

In this study, every reaction was carried out while using argon as the environment. Reaction screens were performed in sealed 4 milliliter microwave vials (Biotage, VWR) using analytical-grade solvents

and reagents obtained from Merck, Fisher Scientific, Sigma-Aldrich, Combi-Block, and Ambeed. The course of the reaction was tracked using both Merck silica gel thin layer chromatography (230–400 mesh) and high-performance liquid chromatography (HPLC). Using indole 2a (0.25 mmol) and Selectfluor (0.375 mmol, 1.5 equiv.) in CH₃CN, optimization tests were performed using a variety of additives, metals, and temperatures. The crude mixes were subjected to high-performance liquid chromatography (HPLC) in order to ascertain the ratios of the products (2a/2b/2c). Following this, the isolated 2b was purified and characterized using nuclear magnetic resonance spectroscopy (400–500 MHz), high-resolution mass spectrometry, and chiral HPLC.

Result And Discussion

Each and every test was carried out in argon, unless otherwise specified. To monitor the reactions, we utilized TLC plates manufactured by Merck as well as standard-grade silica gel with a mesh size ranging from 230 to 400. Fisher Scientific was the source for the acquisition of analytical-grade solvents such as hexanes, diethyl ether, methylene chloride, and CH₂CN. For the purpose of obtaining indoles and several other N-heterocycles, Sigma-Aldrich, CombiBlock, and Ambeed were utilized. Sigma-Aldrich was the retailer from which the Selectfluor was purchased. It was Cambridge Isotope Laboratories that provided the fluids that were used for NMR.

Reactions were carried out in 4 mL argon-filled microwave vials (Biotage, VWR International). NMR spectra were recorded on Varian Unity INOVA spectrometers (400–500 MHz). HRMS spectra were acquired using a Thermo Electron MAT 95XP mass spectrometer (EI or CI mode). Chiral HPLC analyses were conducted using a Shimadzu LG-2030C system.

Reaction Optimization: Monofluorination of 2a

A systematic study examined the effects of solvents, additives, and metal catalysts on monofluorination efficiency and impurity suppression. Optimal results were obtained in acetonitrile with acetic acid and Ag₂SO₄ as an additive at 65 °C for 22 h, yielding 2b with >97% selectivity (48% isolated yield). The role of silver salts in activating Selectfluor and stabilizing radical intermediates was critical to achieving clean monofluorination.

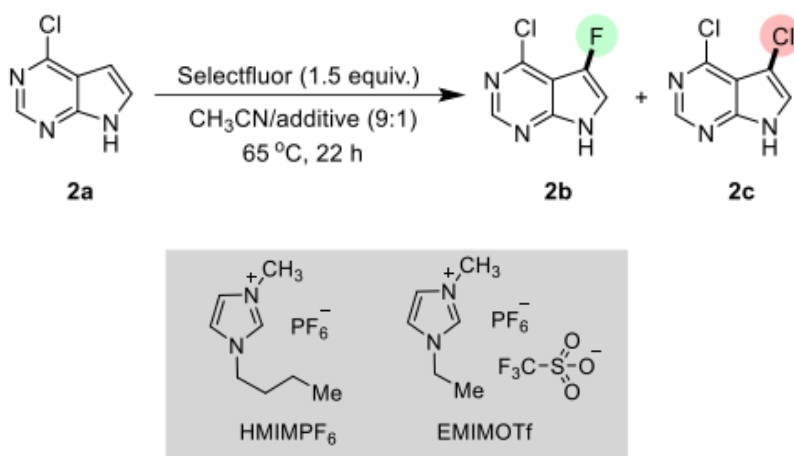


Table 1. Additive effect

Entry	Solvent	Additive	Result (2A/2b/2c %)
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1	CH ₃ CN	AcOH	3/94/4
2	CH ₃ CN	HFIP	29/64/6.7
3	CH ₃ CN	BuOH	31.6/63/5.4
4	DMF	AcOH	20/61/18
5	NO ₂ Me	AcOH	7.3/88/4
6	DMF	-	26/57/16
7	CH ₃ CN	Acetone	30/60/11
8	CH ₃ CN	Ca ₃ PO ₄ (20 mol %)	6/93/1.4 ^b
9	CH ₃ CN	CaCO ₃ (20 mol %)	2/96/3 ^b
10	CH ₃ CN	triethylsilane	30/67/3 ^b
11	CH ₃ CN	triphenylsilane	8/90/3 ^b
12	CH ₃ CN	dimethylethoxysilane	19/77/4 ^b
13	CH ₃ CN	HMIMPF ₆	n.d./90/11 ^b
14	CH ₃ CN	EMIMOTf	n.d./96/3.7 (51%) ^{b,c}
15	CH ₃ CN	NaOAc (20 mol %)	7/89/4 ^b
16	CH ₃ CN	PTSA (10 mol %)	33/60/7
17	CH ₃ CN	Pivalic acid	24.6/70/4.8

There are two conditions that must be met in this scenario: 2a (0.25 m mol) and Selectfluor (0.375 m mol, 1.5 equivalents). With 0.9 ml of CH₃CN and 0.1 ml of additive, heated to 95 degrees Celsius for 22 hours. Based on the results of the HPLC analysis of the crude reaction mixture, the ratio was found to be 2a, 2b, and 2c. We used aqueous hydrochloric acid with a concentration of 0.1%. The isolated yield of 2b is present.

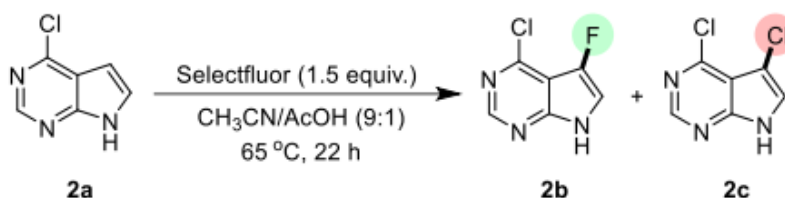


Table 2. Additive effect-2

Entry	Solvent	Additive	Result (2A/2b/2c %)
1	CH ₃ CN	DMAP (10 mol %)	12/76/13
2	CH ₃ CN	Proton-sponge (20 mol %)	11/81/6
3	CH ₃ CN	ZnO ₂ (20 mol %)	31/59/11
4	CH ₃ CN	Al ₂ O ₃ (20 mol %)	28/67/7
5	CH ₃ CN	ZnF ₂ (20 mol %)	17/80/2.5
6	CH ₃ CN	ZnF ₂ (20 mol %) (No AcOH)	92/9/n.d.

There are two conditions that must be met in this scenario: 2a (0.25 m mol) and Selectfluor (0.375 m mol, 1.5 equivalents). The mixture was heated to 65 degrees Celsius for 22 hours, and it contained 1 milliliter of CH₃CN and 20 moles of additive. Based on the results of the HPLC analysis of the crude reaction mixture, the ratio was found to be 2a, 2b, and 2c.

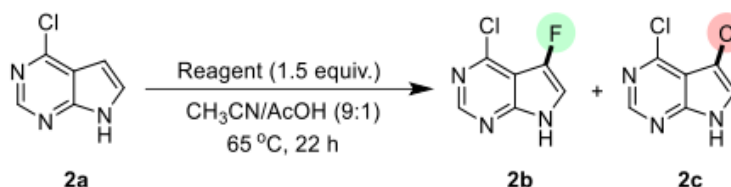


Table 3. Effect of fluorinating Reagents

Entry	Reagent (1.5 equiv.)	Result (2a/2b/2c %)
1	Selectfluor	3/94/4
2	NFSI	n.r
3	N-methyl-Selectfluor	n.r

All of the necessary criteria, including the reagent (0.375 m mol, 1.5 equivalent), 2a (0.25 m mol), and others. Combine 0.9 ml of CH₃CN with 0.1 ml of AcOH and let it sit at 65 degrees Celsius for 22 hours. Based on the results of the HPLC analysis of the crude reaction mixture, the ratio was found to be 2a, 2b, and 2c.

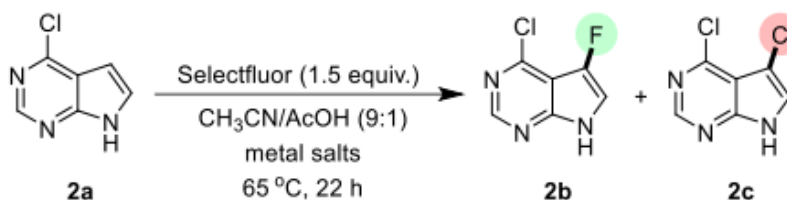


Table 4. Effect of metal catalysts

Entry	Metal salts	Result (2a/2b/2c %)
1	Cu (OAc) ₂ (10 mol %)	67/12/21
2	Fe ₂ O ₃ (10 mol %)	7/89/5
3	FeSO ₄ (10 mol %)	7/90/3
4	Cu (OTf) ₂ (5 mol %)	52/29/18.7
5	CuF ₂ (5 mol %)	47/25/28
6	Cp*Ru(COD)Cl (5 mol %)	72/9/19.7
7	Cp*Ru(COD)Cl (5 mol %) in DMF	21/47/31.7 ^b

8	[Ru(p-cymene)Cl ₂] ₂ (5 mol %)	36/48/14
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There are two conditions that must be met in this scenario: a (0.25 m mol) and Selectfluor (0.375 m mol, 1.5 equivalents). Combine 0.9 ml of CH₃CN with 0.1 ml of AcOH and let it sit at 65 degrees Celsius for 22 hours. Based on the results of the HPLC analysis of the crude reaction mixture, the ratio was found to be a, b, and c. An absence of aqueous acid was made.

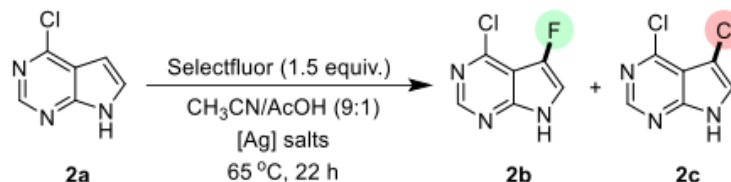


Table 5. Effect of silver salts

Entry	[Ag] salts (10 moles %)	Result (2a/2b/2c %)
1	AgOTs	3/97/0.4
2	AgBF ₄	2/93/6
3	AgF	2/97/0.4% (45) ^b
4	Ag(OAc)	5/93.6/1.3
5	AgNO ₃	traces/98/1.7
6	Ag ₂ O	8.7/91/0.5 (49) ^b
7	Ag ₂ SO ₄	2.5/97/0.3 (48) ^b

There are two conditions that must be met in this scenario: a (0.25 m mol) and Selectfluor (0.375 m mol, 1.5 equivalent). With the use of high-performance liquid chromatography (HPLC), the crude reaction mixture was subjected to the following parameters: pH 7.0, time in hours at 65 degrees Celsius, quantity of silver salts (10 percent), and volume ratio of a to c. a yield of b after it has been isolated.

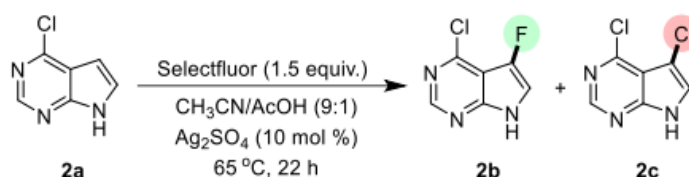


Table 6. Effect of temperature

Entry	Temperature	Result (2a/2b/2c %)
1	rt (50 h)	11/83/4(33) ^b
2	45 °C (30 h)	6/93/2
3	55 °C (26 h)	2/97/2
4	65 °C	2/98/0.3 (48) ^b

There are two conditions that must be met in this scenario: 2a (0.25 mmol) and Selectfluor (0.375 mmol, 1.5 equivalent). A combination consisting of 0.9 milliliters of CH₃CN, 0.1 milliliters of acetic acid, and 10 moles of silver sulfate. Using high-performance liquid chromatography (HPLC), the ratios of 2a, 2b, and 2c were determined by evaluating the crude reaction mixture. a yield of 2b after it has been isolated.

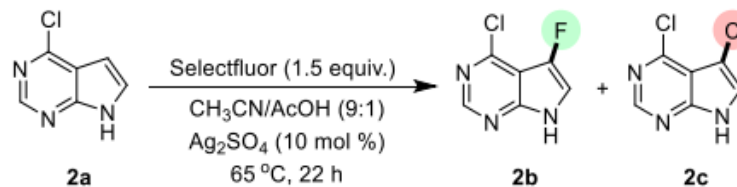


Table 7. Amount of Ag₂SO₄

Entry	Ag ₂ SO ₄ (mol %)	Result (2a/2b/2c%)
1	1 mol%	3/96/2
2	2.5 mol %	2/97/0.4
3	5 mol %	5/95/0.4
4	10 mol %	2/98/0.3 (48) ^b

There are two conditions that must be met in this scenario: 2a (0.25 m mol) and Selectfluor (0.375 m mol, 1.5 equivalents). When the crude reaction mixture was subjected to HPLC analysis, the results showed that the ratio of 2a, 2b, and 2c was obtained. The following conditions were utilized: At a temperature of 65 degrees Celsius and a time of 22 hours, 0.9 milliliters of CH₃CN and 0.1 milliliters of acetic acid were combined. a yield of 2b after it has been isolated.

Sustainable Mon fluorination of Unprotected Indoles Under Aqueous Micellar Conditions

All of the experiments were carried out in an atmosphere of argon, unless one was specifically mentioned otherwise. A UV 254 indicator glass-backed TLC plate with a thickness of 200 mm was purchased from Merck. Other materials that were purchased from Merck include silica gel with a mesh size ranging from 230 to 400. The following chemicals were purchased from Fisher Scientific: hexanes, methylene chloride, CH₃CN, ethyl acetate, diethyl ether, and ethyl ether. We obtained our pure NMR solvents from either Sigma-Aldrich or Cambridge Isotopes Laboratories during our production process. Indoles were among the heterocyclic compounds that were obtained from Sigma-Aldrich, Combi-Block, and Ambeed. Indoles were among the heterocyclic compounds that contained nitrogen. In order to get Selectfluor and NFSI, the sources that were utilized were Chem-Impex and Sigma-Aldrich.

Close-cap microwave vials containing 4 milliliters of liquid were used to carry out the reaction in an atmosphere of argon. Biotage and VWR International were the companies that provided the microwave vials to the company. Moreover, reaction vials were utilized and recycled throughout the process. For the purpose of determining melting points, a MEL-TEMP II melting point instrument was utilized through the utilization of Kimble Kimex 51 capillaries measuring 1.5-1.8 x 90 mm. Unless otherwise specified, Varian Unity INOVA spectrometers (400, 500, and 700 MHz) were used to record any NMR spectra that were not recorded at a temperature of 25 degrees Celsius. As a point of reference for the chemical shifts that have been observed, the remaining solvent peaks are utilized. Either chemical ionization (CI) or electron ionization (EI) was utilized in order to acquire HR-MS spectra. This was

accomplished with the assistance of a Thermo Electron MAT 95XP mass spectrometer. In order to obtain our HPLC results, we made use of a Shimadzu LG2030C HPLC. The chiral column AD was used in conjunction with hexane and IPA as the HPLC solvents for the mechanistic studies and reaction monitoring that were carried out.

Reaction optimization:

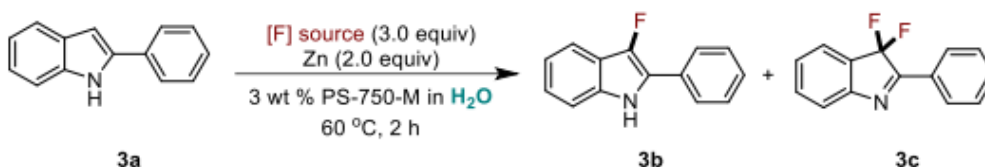


Table 8. Fluorination source

Entry	[F] source (3.0 equiv.)	3b (%) ^a	3b/3c (%) ^a
1	NFSI	99	100/n.d.
2	Selectfluor	72	82/19

The conditions. A total of 1.25 m mol of 3a, 0.75 m mol of F-source, 2.0 equiv. of zinc, and 1 milliliter of 3% PS-750-M in water were used in the experiment. For the purpose of determining the conversions, an HPLC examination of a crude reaction mixture is administered.

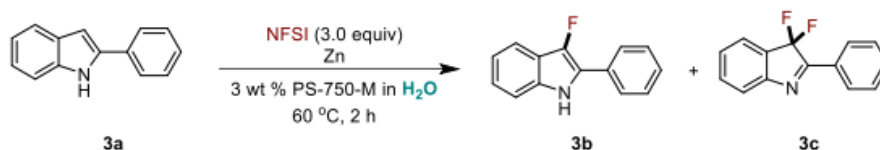


Table 9. Optimal amount of Zn

Entry	Zn (equiv.)	3b (%) ^a	3b/3c (%) ^a
1	-	n.d	n.d./100
2	1.0 equiv. NFSI with no Zn	n.d	n.d./100 ^b
3	0.5	n.d	n.d./100
4	1.0	n.d	n.d./100
5	1.5	37	40/60
6	2.0	99	n.d./100

The conditions. Zn, 3a (0.25% by weight), NFSI (0.75% by weight, 3 equivalents), and one milliliter of 3% PS-750-M in water are the components that come together. The foundation for these conversions is provided by an HPLC examination of a basic reaction mixture. It was observed that 40% 3c and 60% were both present. 3a.

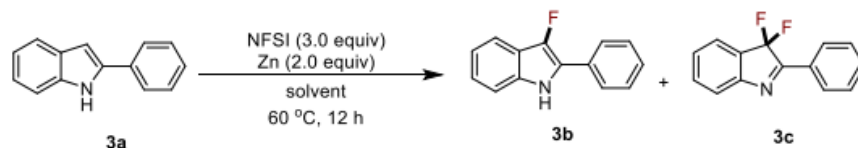
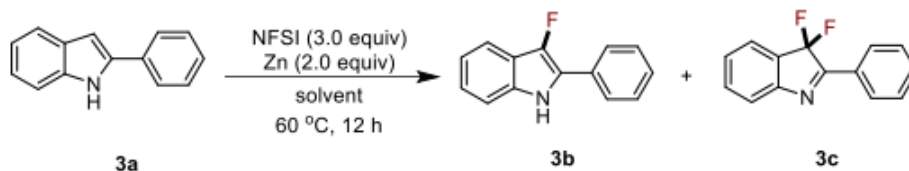


Table 10. Solvent screening

Entry	Solvent (0.25 M global conc.)	3b (%) ^a	3b/3c(%) ^a
1	THF	traces	Traces/99
2	DMF	28	29/72
3	Nitromethane	n.d.	n.d./100
4	CH ₃ CN	53	40/50
5	Dioxane	8	8/93
6	Toluene	3	2/97
7	Nitrobenzene	1.4	1/98
8	3 wt % PS-750-M	98	100 /n.d.

The conditions. 1 milliliter of solvent, 0.5 millimoles of NFSI (three equivalents), zinc, and three parts of 3a are the components that are required. The foundation for these conversions is provided by an HPLC examination of a basic reaction mixture.

**Table 11. Surfactant screening**

Entry	3 wt % surfactant (0.25 M global conc.)	3b (%) ^a	3b/3c(%) ^a
1	NOK	60	72/27
2	CTAC	72	74/25
3	Pluronic	57	65/33
4	TPGS-750-M	47	83/17
5	Neat H ₂ O	24	30/72
6	0.1 wt % HPMC	45	47/52
7	3 wt % PS-750-M	98	100/n.d

The conditions. A total of one milliliter of water, one milliliter of 3% surfactant in water, 0.25 millimoles of 3a, 0.75 millimoles of NFSI (three equivalents), half a millimole of zinc (two equivalents), and one

milliliter of water complete the mixture. For the purpose of determining the conversions, an HPLC examination of a crude reaction mixture is administered.

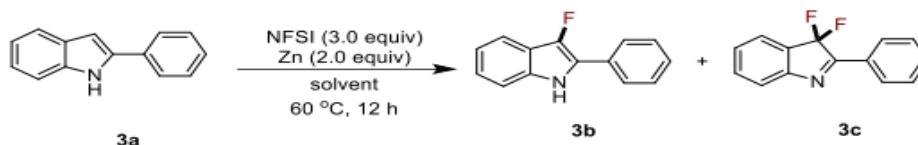


Table 12. Optimal temperature

Entry	Solvent (0.25 M global conc.)	3b (%) ^a	3b/3c(%) ^a
1	rt	54	57/43
2	45°C	75	81/19
3	61°C	97	100/n.d.

3a (0.25 m mol), NFSI (0.75 m mol, 3 equivalents), zinc (0.5 m mol, 2.0 equivalents), and 1 ml of PS750-M in water at a concentration of 3 weight percent are the components utilized in this experiment. For the purpose of determining the conversions, an HPLC examination of a crude reaction mixture is administered.

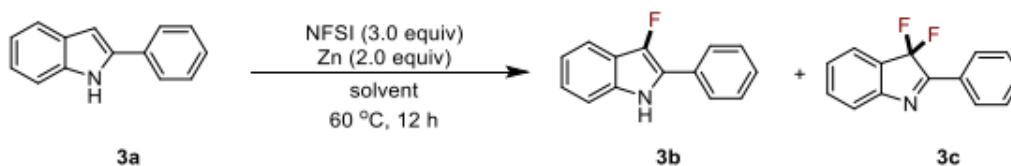


Table 13. Optimal amount of NFSI

Entry	NFSI (equiv.)	3b (%) ^a	3b/3c(%) ^a
1	1.0	72	100/n.d. ^b
2	2.0	83	100/n.d. ^b
3	2.5	94	100/n.d. ^b
4	3.0	97	100/n.d.

The conditions. 1 milliliter of 3% PS-750-M in water, supplemented with 0.25 millimoles of a, 0.5 millimoles of NFSI, and 2.0 millimoles of zinc. In order to perform conversions, an HPLC examination of a crude reaction mixture is utilized. Furthermore, ba was found to be present in addition to b.

Conclusion

In monofluorination chemistry employing Selectfluor, this study presents a unified and systematic technique for discovering impurities, explaining how things operate, and making the method last. Cleaning Selectfluor made it more selective and reactive, eliminating byproducts and ensuring consistent reactions. Zinc and silver ions moved electrons and stabilized radical intermediates during fluorination, according to the study. Mechanistic research indicated radical-driven electrophilic substitution. Micellar encapsulation stabilized intermediates and increased product selectivity. Green fluorination chemistry advanced with sustainable water micellar systems. These procedures enabled

high-yield fluorination and effective amide coupling without organic solvents, extraction, or chromatographic purification. This technique followed green chemistry by using mild, eco-friendly procedures. This reduced environmental impact and commercial costs. In summary, the study provides a repeatable and accurate foundation for chosen monofluorination and coupling operations. This shows how to employ green approaches in sophisticated organic chemistry. It enables long-lasting, high-efficiency fluorination processes that benefit business and the environment.

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