Catalytic, Dearomative 2,3-Difluorination of Indoles

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Abstract

Indolines, characterized by their diverse biological activities and structural significance, have garnered considerable attention in the realms of natural product synthesis and drug discovery. Concurrently, the incorporation of fluorine atoms into organic molecules has emerged as a powerful strategy to enhance their pharmacological properties. Herein, we report a robust and diastereoselective approach for the synthesis of 2,3-difluorinated indolines through the iodine(I/III)-catalyzed dearomatization of readily available indoles. The protocol operates under mild conditions, displaying excellent functional group tolerance and remarkable diastereoselectivity. By employing this developed protocol, vicinal-difluorinated analogues of indole-containing drugs can be efficiently accessed. Theoretical calculations have shed light on the underlying reaction mechanism, proposing the formation of a β-fluorine-substituted carbocation intermediate. It is postulated that the observed high diastereoselectivity can be attributed to the dipole-dipole interactions facilitated by the C-F bond. Crystallographic analysis has revealed the profound impact of fluorine atom introduction on the conformational preferences of the indoline core. Given the unique structural characteristics and pharmacological significance of 2,3-difluorinated indolines, we anticipate their widespread application in medicinal chemistry and drug discovery endeavors.

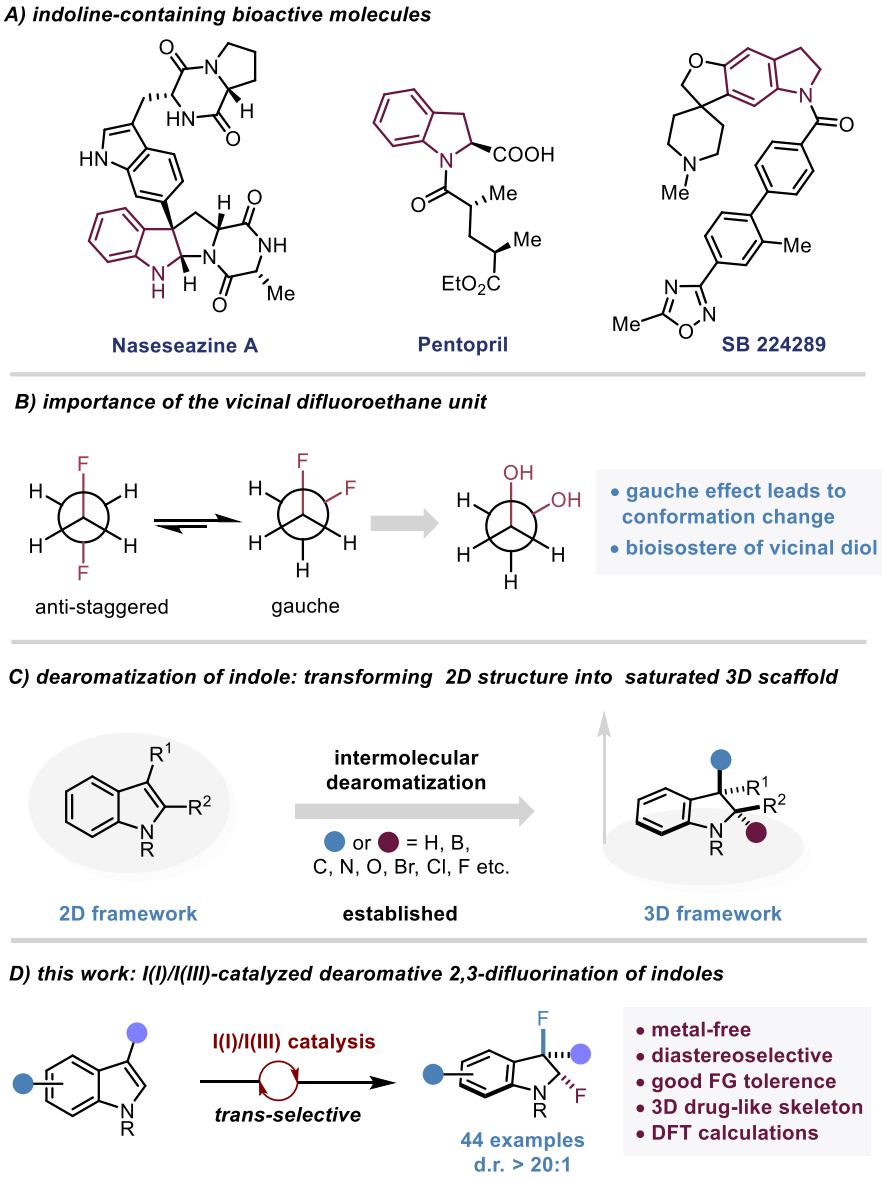
Keywords

Indole; indoline; dearomatization; vicinal difluorination; iodine catalysis.

Introduction

Indolines serve as the predominant frameworks in a diverse range of natural products, pharmaceuticals, and biologically active molecules (**Scheme 1A**).[1-2] Given the ubiquitous nature of this structure, numerous synthetic approaches have been developed for the construction of indolines.[3] Among these, direct dearomative difunctionalizations of indoles have emerged as an appealing and potent synthetic method due to the abundant supply and synthetic accessibility of indoles.[4-6] The intramolecular version of this strategy has been explored in a lot of elegant studies. Furthermore, numerous intermolecular variations that offer enhanced synthetic versatility have also been developed, including metal-mediated,[7-10] photochemical,[11-14] electrochemical,[15-17] as well as nucleophilic[18] or electrophilic[19-22] dearomatization reactions (**Scheme 1C**). These diverse approaches enable the transformation of a planar 2D structure into a saturated 3D scaffold, thereby altering the molecular spatial arrangement. This aspect holds significant importance for achieving clinical success, as the increased 3D complexity has the potential to enhance the binding affinity of small molecules to target proteins.[23-24]

In another context, organofluorine compounds have gained increasing prominence in the field of medicinal and agricultural chemicals.[25] Of particular interest are the vicinal difluoroethane units, which possess distinctive steric and electronic properties. These units serve as bioisosteres of ethyl, vicinal diols, or trifluoromethyl groups,[26] making them attractive for enhancing the bioactivity and pharmacokinetics of target molecules (**Scheme 1B**).[27-28] Notably, the incorporation of the vicinal difluoro motif can significantly influence the conformational properties of parent molecules due to the fluorine gauche effect.[29] Consequently, there has been significant research focus on the synthesis of vicinal difluoroalkanes in recent years.[30] Among the various synthetic methodologies, the direct difluorination of olefins using iodine(I)/(III) catalysis stands out as a particularly appealing approach.[31-37]



Scheme 1. Bioactive indolines and their synthesis.

Taking into account the extensive applications of the indoline skeleton and vicinal difluoroalkanes, we hypothesize that the incorporation of a vicinal difluoro unit into indoline could provide two notable advantages: the desired three-dimensional configuration and improved pharmacokinetic stability.[38-40] To the best of our knowledge, however, only scattered examples for the construction of vininal difluoro-doped indolines have been reported. In 1977, Hesse and co-workers reported the first difluorination of indole derivatives using CF_3OF

in Freon at -78 °C, resulting in *cis*-2,3-difluoro adducts with low yields.[41] Subsequently, more than 30 years later, Fuchigami and co-workers achieved the synthesis of 2,3-difluoro-2,3-dihydroindoles through electrochemical methods. However, drawbacks such as limited substrate scope, harsh reaction conditions, and poor diastereoselectivity were observed.[42] Consequently, there is a pressing need to develop more effective methods for accessing 2,3-difluorinated indolines under mild conditions with high stereoselectivity. In light of recent advancements in fluorination reactions utilizing hypervalent iodine reagents,[43-56] and in line with our ongoing research endeavors in hypervalent iodine-mediated fluorination reactions,[57-60] we postulated that this particular strategy may also be amenable to the difluorination of indoles. Of note, previously, the hypervalent iodine-mediated alkene vicinal difluorination has thus far been restricted to substituted styrene,[31, 33, 36-37] terminal alkenes[31-32, 35, 61] or acrylamide derivatives.[34] Moreover, in the absence of a neighboring participating group, the formation of *cis*-difluorination products has typically been observed.[31] The vicinal difluorination of double bonds within aromatic systems remains unexplored. In this study, we present an iodine(I)/(III)-catalyzed, diastereoselective dearomative difluorination of indoles, leading to the formation of *trans*-2,3-difluorinated indolines (**Scheme 1D**). Significantly, this transformation takes place under mild reaction conditions, displaying a broad substrate scope, excellent functional group tolerance, and remarkable diastereoselectivity.

Experimental Methods

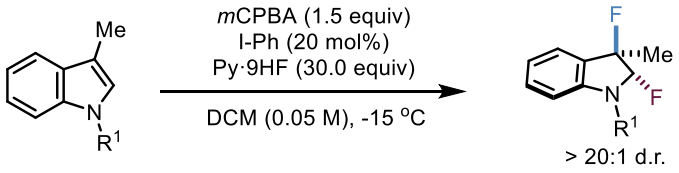
A 10 mL low density polyethylene tube equipped with a stir bar was charged with catalyst Ph-I (8.2 mg, 0.04 mmol, 20.0 mol%), *m*-chloroperbenzoic acid (95% by weight, 54.6 mg, 0.3 mmol, 1.5 equiv) and dichloromethane (2.0 mL). The reaction mixture was cooled to −15 °C. Py·9HF (0.17 mL, 6.0 mmol, 30.0 equiv) was added via plastic syringe, and the resulting mixture was vigorously stirred. A solution of the indole substrate (0.2 mmol, 1.0 equiv) in dichloromethane (2 mL) was added dropwise to the reaction mixture through plastic syringesyringe pump over 2 hours. The reaction mixture was added slowly to 6.0 mL cold saturated aqueous solution of $NaHCO_3$ until the complete consumption of indoles as monitored by TLC analysis. The organic phase was separated and the aqueous layer was extracted with dichloromethane (4 mL) for three times. The

combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography on silica gel with an appropriate solvent as eluent to afford the pure products. (**See Supporting Information).**

Results and Discussion

Optimization of Reaction Conditions. To start, we examined the feasibility of this dearomative difluorination reaction by employing differently protected 3-methylindoles under the conditions of iodobenzene (20 mol%), *m*CPBA (1.5 equiv.), and Py·9HF (30.0 equiv.) in DCM at -15 °C (**Table 1**). In the initial trials, the oxidative fluorination of *N*-H or *N*-Me-3-methylindole did not yield the desired products, and instead, an inseparable mixture was obtained (entries 1-2). However, when *N*-Boc-3-methylindole was used as the substrate, the desired *trans*-2,3-difluorinated indoline was formed with good diastereoselectivity (>20:1), although the yield was low at 15% (entry 3). Encouragingly, the efficiency of the reaction significantly improved with *N*-SO_2Ph-3-methylindole, resulting in the formation of the corresponding *trans*-2,3-difluorinated indoline **1** with excellent diastereoselectivity (>20:1) and a good yield of 66% (entry 4). The structure and stereochemistry of the product were confirmed through X-ray diffraction analysis of products **2** and **18** (see below). Subsequently, *N*-SO_2Ph-3-methylindole was chosen as the model substrate to investigate the impact of various reaction parameters. When 4-iodobenzoate was used instead of iodobenzene as the iodine(I) catalyst, the yield decreased to 20% (entry 5). Changing the solvent to DCE or $CHCl_3$ resulted in slightly lower yields of the desired product (entries 6-7). Lowering the amount of *m*CPBA to 1.2 equivalents led to a moderate yield (entry 8). We also explored different temperatures and found that -15 °C was the optimal choice (entries 9-10). Modifying the equivalent amount of Py·9HF, either by increasing or reducing it, resulted in diminished yields of 51-60% (entries 11-12). Additionally, other anionic fluorine sources were found to be ineffective in this reaction (entry 13). Using Selectfluor as the oxidant provided an acceptable yield, although the diastereomeric ratio decreased to 6:1 (entry 14). As expected, the transformation did not proceed in the absence of the iodine catalyst (entry 15).

Table 1. Optimization of the reaction conditions[a]

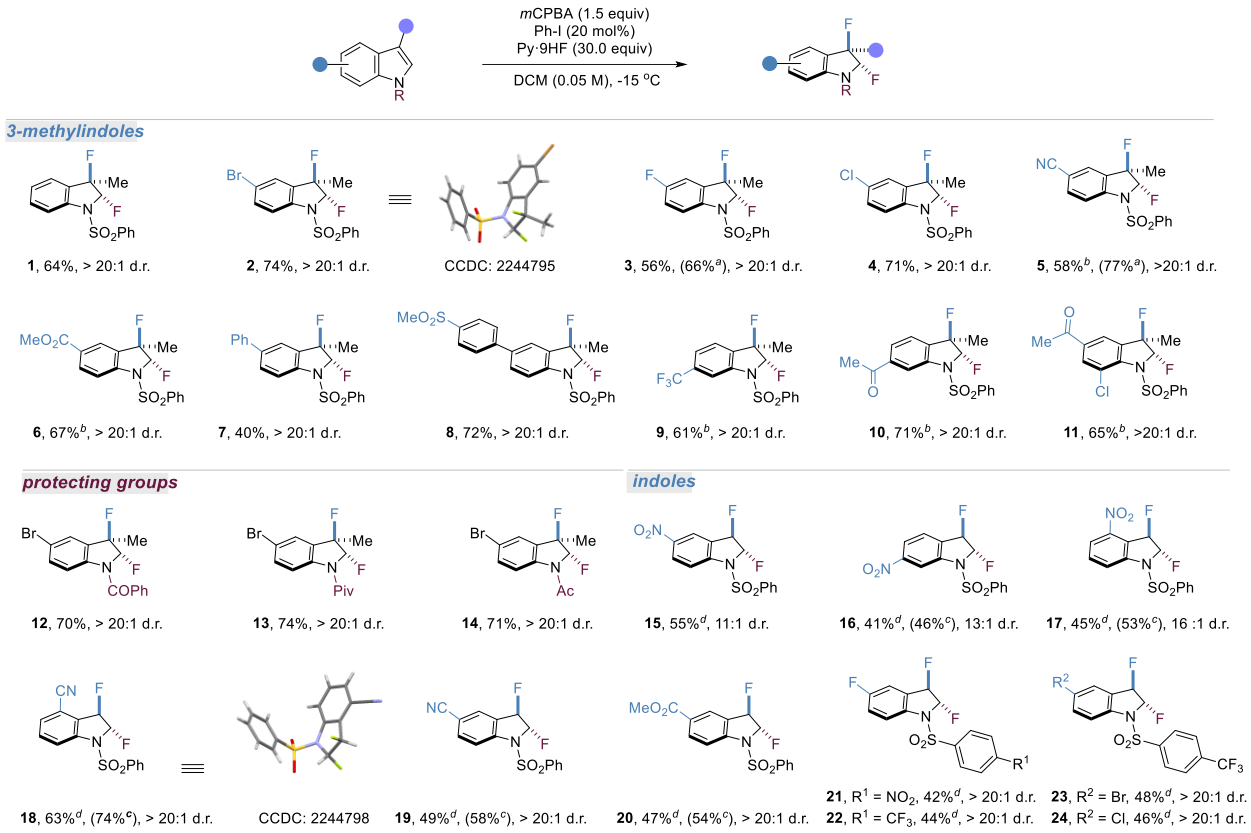


Entry	R^1	Changes from above conditions	Yield [%]
1	-H	none	0
2	-Me	none	0
3	-Boc	none	15
4	-SO_2Ph	none	66 (64%[b])
5	-SO_2Ph	methyl 4-iodobenzoate as catalyst	20
6	-SO_2Ph	DCE	46[c]
7	-SO_2Ph	$CHCl_3$	56[c]
8	-SO_2Ph	1.2 equiv. *m*CPBA	54
9	-SO_2Ph	0 °C	54
10	-SO_2Ph	-20 °C	40
11	-SO_2Ph	20.0 equiv. Py•9HF	60
12	-SO_2Ph	40.0 equiv. Py•9HF	51
13	-SO_2Ph	Et_3N•3HF or AgF or CsF	0
14	-SO_2Ph	Selectfluor as oxidant	49[d]
15	-SO_2Ph	without iodobenzene	0

[a]Reaction conditions: substrate (0.1 mmol, 1.0 equiv), Ph-I (20 mol%), *m*CPBA (1.5 equiv), Py•9HF (30.0 equiv), DCM (2.0 mL), -15 °C. Reactions were conducted with slow addition of substrates over 2 h. Yields were determined by ^{1}H NMR analysis using *p*-iodoanisole as an internal standard. Diastereomeric ratios (d.r.) were determined by ^{19}F NMR of crude reaction mixtures. [b]Isolated yield. [c]Yield was based on recovered starting material. [d]Product was formed in 6:1 d.r.

Scope. Having established the optimized conditions, we proceeded to investigate the substrate scope of the diastereoselective difluorination reactions of indoles. We first examined the compatibility of different functional groups and substitution patterns at the benzene ring. As shown in **Scheme 2**, halides (Br, F, Cl) positioned at the 5-position of the indole were well-tolerated, affording the desired products with good yields (**2**-**4**). Furthermore, *N*-SO_2Ph-3-methylindoles bearing both electron-neutral (**7**) and electron-withdrawing

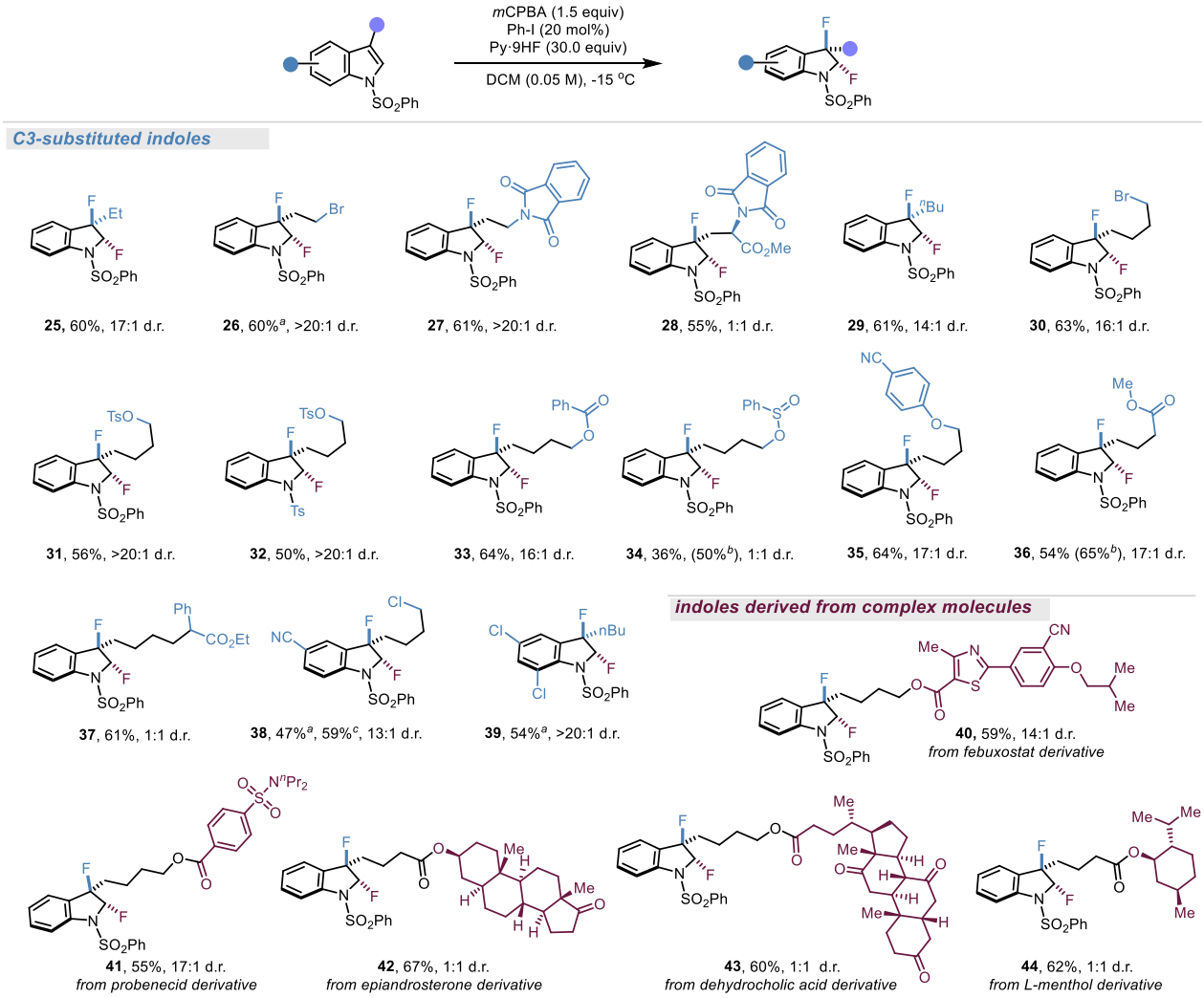
groups (**5**-**6** and **8**) underwent the dearomative difluorination with moderate to good yields ranging from 40% to 72%. 3-Methylindoles carrying a trifluoromethyl or carbonyl substituent at the 6-position were generally compatible with the reaction conditions (**9**-**10**). Disubstituted 3-methylindoles yielded the corresponding products in good yields (**11**). Notably, indoles featuring different *N*-acyl protecting groups such as benzoyl, pivaloyl, or acetyl underwent the reaction smoothly, leading to good yields of the desired products (**12**-**14**).



Scheme 2. Scope of indoles with substituents on aromatic ring. Conditions: substrate (0.2 mmol, 1.0 equiv), Py•9HF (30.0 equiv), *m*CPBA (1.5 equiv), Ph-I (20 mol%), DCM (4.0 mL), -15 °C. Reactions were conducted with slow addition of substrate over 2 h. [a]Yield based on recovered starting material. [b]0 °C, 40.0 equiv. Py•9HF. [c]Yields determined by ^{1}H NMR analysis using *p*-iodoanisole as an internal standard. [d]Py•9HF (60.0 equiv) was used.

Importantly, the protocol was not limited to 3-methylindoles alone. A series of *N*-SO_2Ph-indoles bearing electron-withdrawing substituents, including nitro, ester and cyano at various positions, were also amenable

to the reaction conditions, albeit with slightly reduced yields (**15**-**20**). Encouragingly, by introducing stronger electron-withdrawing *N*-protecting groups, even weakly electron-poor 2,3-dihydroindoles were tolerated, providing moderate yields of the desired products (**21**-**24**).



Scheme 3. Scope of indoles with substituents on 3-position. Conditions: substrate (0.2 mmol, 1.0 equiv), Py•9HF (30.0 equiv), *m*CPBA (1.5 equiv), Ph-I (20 mol%), DCM (4.0 mL), -15 °C. Reactions were conducted with slow addition of substrate over 2 h. [a]0 °C, 40.0 equiv. Py•9HF. [b]Yield determined by ^{1}H NMR analysis using *p*-iodoanisole as an internal standard. [c]Yield based on recovered starting material.

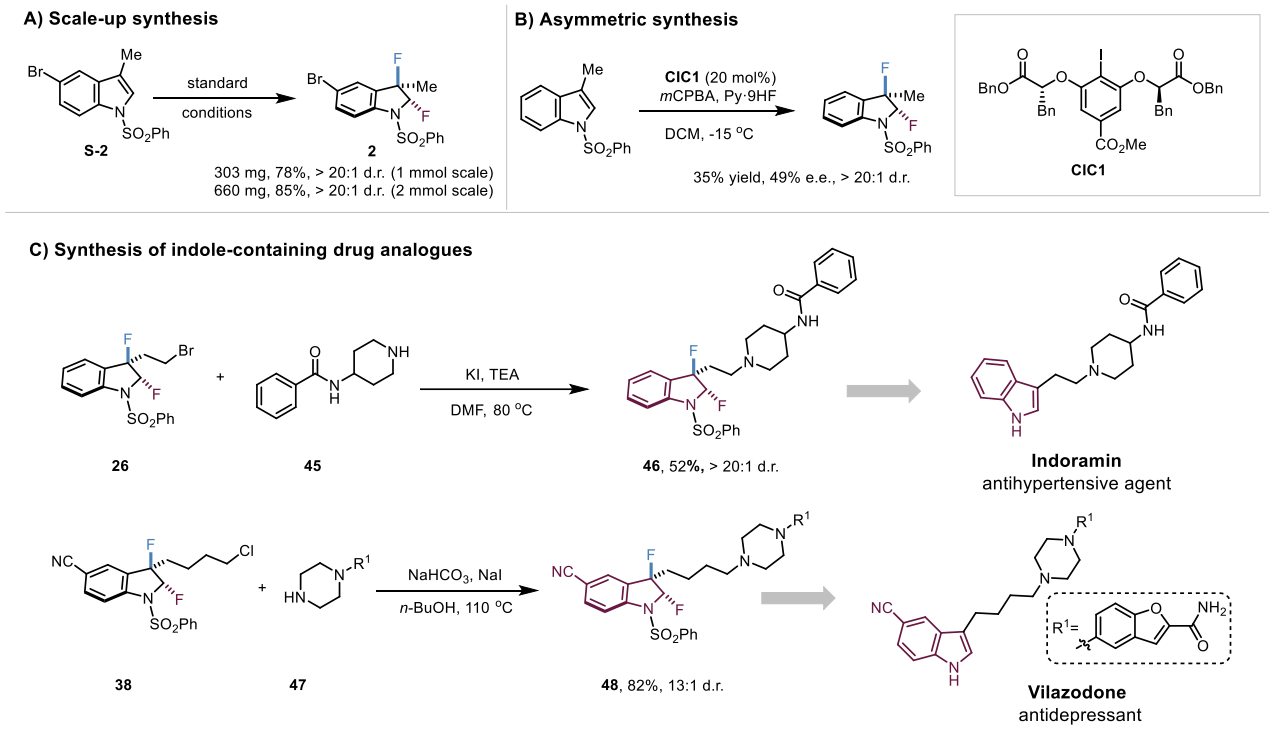
Subsequently, we investigated the applicability of the method to indoles with substituents at the C3 position (**Scheme 3**). The length of the alkyl chain did not significantly affect the reaction efficiency, as demonstrated by

the successful transformation of indoles with varying alkyl chain lengths (**25**, **29**). Furthermore, protected tryptamine and tryptophan were successfully converted into the corresponding dearomative products (**27**, **28**) with moderate yields. Notably, a wide range of functional groups (FGs), including bromo (**26**, **30**), phthalimide (**27**, **28**), sulfonate ester (**31**, **32**), benzoate (**33**), sulfonic ester (**34**), phenyl ether (**35**), methyl ester (**36**), and chloro (**38**) on the alkyl chain, remained unreacted, indicating the high chemoselectivity and mild reaction conditions of the protocol. To further assess the compatibility of this method in more structurally complex contexts, several natural products and biologically active compounds containing indoles were subjected to the reaction. Functionalized indoles derived from febuxostat (**40**), probenecid (**41**), epiandrosterone (**42**), dehydrocholic acid (**43**), and L-menthol (**44**) were all suitable substrates, affording the corresponding *trans*-2,3-difluorinated indolines with good efficiency. These results underscored the robustness and versatility of the method.

Scale-up experiments and asymmetric synthesis. To evaluate the synthetic utility of the developed protocol, scale-up experiments were performed to demonstrate its practical application. As depicted in **Scheme 4A**, the desired *trans*-2,3-difluorinated indoline **2** was obtained with high yields of 78% and 85% when starting from 1.0 and 2.0 mmol scales of **S-2**, respectively. This showcases the scalability and efficiency of the reaction on a larger scale. Additionally, we explored the possibility of catalytic asymmetric synthesis using a chiral iodine(I) catalyst (see supporting information for details). As shown in **Scheme 4B**, the use of **CIC1** as catalyst gave the desired chiral difluorinated indoline **1** with excellent diastereoselectivity (>20:1 d.r.), but with moderate enantioselectivity (49% e.e.) and yield (35%).

Derivatization. To highlight the significance of the developed methodology in drug discovery, two fluorinated drug analogues were synthesized, as depicted in **Scheme 4C**. The transformation of product **26** resulted in the synthesis of an analogue of Indoramin, an antihypertensive agent,[62] through the nucleophilic attack of secondary amine **45**. Similarly, a difluorinated derivative of Vilazodone, an antidepressant,[63] was obtained in an excellent yield of 82% via a simple S_N2 reaction starting from product **38**. These examples demonstrate the

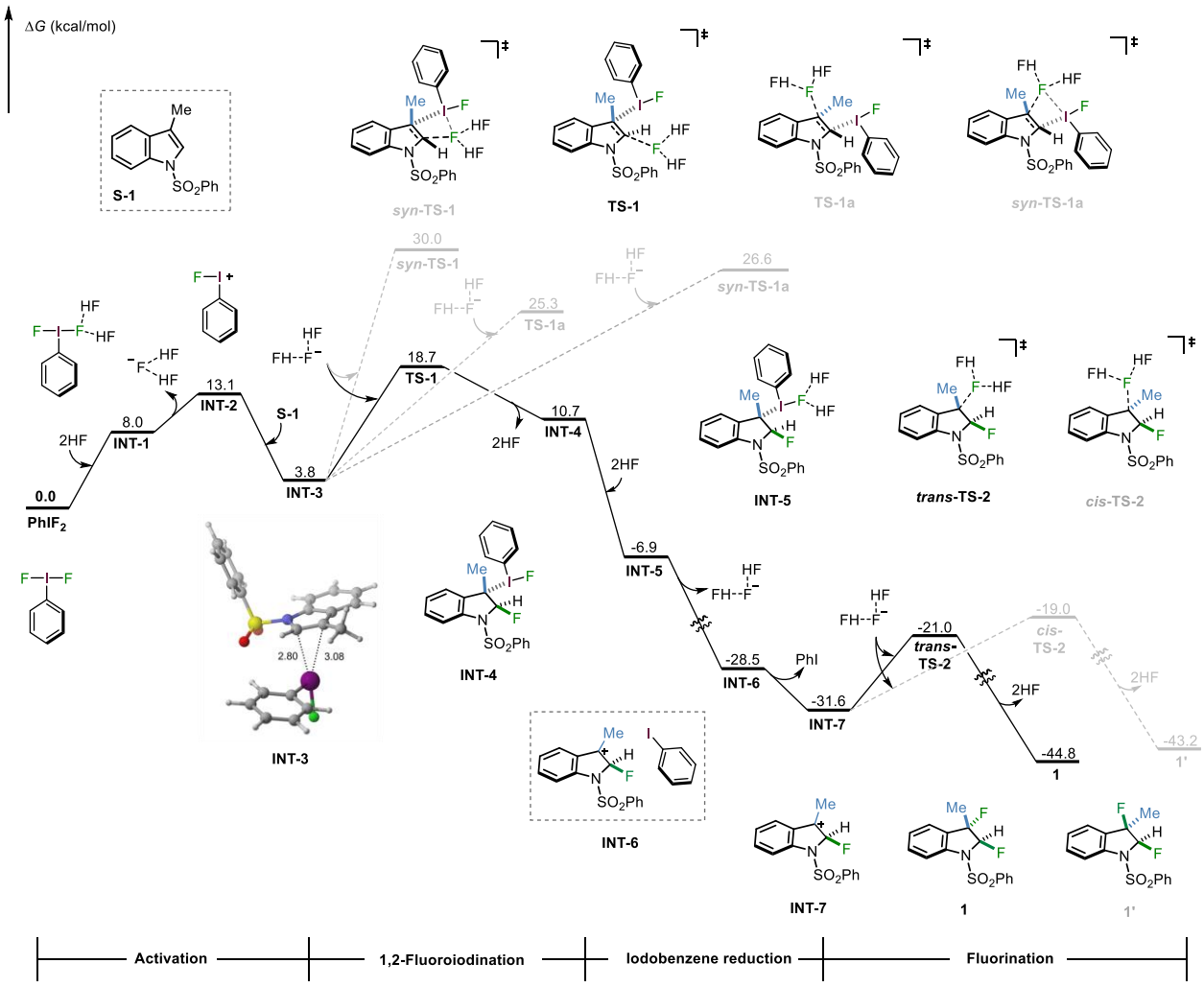
versatility of the methodology in the synthesis of fluorinated drug analogues, which may possess enhanced pharmacological properties.



Scheme 4. Synthetic utility and conformational analysis

Conformational analysis. Furthermore, we investigated the conformational effects of the vicinal-difluoro motif in the indoline core. A non-fluorine-containing indoline **49** was synthesized to compare its conformation with that of *trans*-2,3-difluorinated indoline **2**. X-ray crystallographic analysis revealed that the introduction of two vicinal fluorine atoms led to a significant decrease in the dihedral angle (ϕ_{NCCC}) within the indoline skeleton, from 29.5° to 17.4°. Similarly, the dihedral angle (ϕ_{HCCH}) decreased from 33.6° to 26.6° upon introduction of the

fluorine atoms. These observations highlight the conformational impact of the vicinal-difluoro motif on the indoline core, which may have implications for the design and optimization of new drug candidates.



Scheme 5. DFT calculations study.

DFT calculations. To gain a deeper understanding of the reaction mechanism and the factors contributing to diastereoselectivity, density functional theory (DFT) calculations were performed by selecting $PhIF_2$ formed *in situ* as the starting point in combination with two HF molecules as activators.[64] As depicted in **Scheme 5**, the reaction between HF and $PhIF_2$ generates the active species **INT-2**, which subsequently coordinates with the indole substrate (**S-1**) to form the iodonium ion intermediate **INT-3** (ΔG = 3.8 kcal/mol). Next, nucleophilic attack

of $(HF)_2F^-$ on the C2 position of indole **S-1** via transition state **TS-1** is found to be energetically favorable, with a barrier of 14.9 kcal/mol, compared to nucleophilic attack on the C3 position via **TS-1a**, which has a higher barrier of 21.5 kcal/mol. Energy decomposition analysis[65] reveals that the stability of fluorination at the C2 position in **TS-1** is determined by a lower distortion energy ($\Delta\Delta E_{dist}$ = 3.9 kcal/mol) and a larger interaction energy between $(HF)_2F^-$ and the indole-iodobenzene complex ($\Delta\Delta E_{int}$ = 1.1 kcal/mol) compared to **TS-1a**. In comparison, the *syn* 1,2-fluoroiodination from **INT-3** proceeds through ***syn*-TS-1** with a higher barrier of 26.2 kcal/mol and ***syn*-TS-1a** with a barrier of 22.8 kcal/mol. These barriers are higher than those of the *anti* 1,2-fluoroiodination **TS-1** and **TS-1a**. The formation of the C-I bond in **INT-4** weakens the I-F bond, resulting in elongation from 1.96 Å to 2.11 Å. Consequently, the C-I bond is prone to dissociation under the activation of HF, leading to the formation of a more stable complex **INT-6**, involving a carbenium ion intermediate with iodobenzene. The energy difference from **INT-4** to **INT-6** is highly exergonic, with a release of 39.2 kcal/mol. Upon the departure of iodobenzene, further energy is released, resulting in the formation of the carbenium ion intermediate **INT-7** (ΔG = -31.6 kcal/mol). Subsequent fluoride attack on **INT-7** proceeds through the ***trans*-TS-2** pathway to afford the *trans*-difluorinated indoline product **1** with a barrier of 10.6 kcal/mol. In contrast, the *cis*-difluorinated indoline product **1'** is obtained via the ***cis*-TS-2** pathway, which has a higher energy barrier probably due to dipole-dipole interactions. The difference in activation energy ($\Delta\Delta G^{\neq}$ = 2.0 kcal/mol) corresponds to diastereomeric ratio of 97:3, which is consistent well with our experimental observation that the *trans*-selective products are obtained predominately in good diastereoselectivity.

Conclusion

In conclusion, we have successfully developed a highly efficient and diastereoselective dearomative difluorination method for indoles, facilitated by iodine(I)/(III) catalysis. This methodology offers several notable advantages, including mild reaction conditions, broad substrate scope encompassing diverse functional groups and substitution patterns, and excellent diastereoselectivities. Importantly, the facile derivatization of the *trans*-2,3-difluorinated indolines enables rapid access to vicinal-difluorinated analogues of indole-containing

drugs. Theoretical calculations employing density functional theory (DFT) have provided valuable insights into the reaction mechanism. Additionally, crystal structural analysis has revealed the significant impact of fluorine atom incorporation on the conformation of the indoline core. These findings underscore the potential significance of the novel structural scaffold comprising both vicinal-difluoro and indoline motifs, suggesting promising opportunities for its application in modern drug discovery efforts.

Supporting Information

Supporting Information is available and includes general experimental procedures and characterization spectra. CCDC 2244795, 2244798 and 2263992 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.ca-m.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Conflict of Interest (required)

The authors declare no competing financial interest.

Funding Information (required)

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