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Asymmetric Dearomatizing Fluoroamidation of Indole Derivatives with Dianionic Phase-Transfer Catalyst

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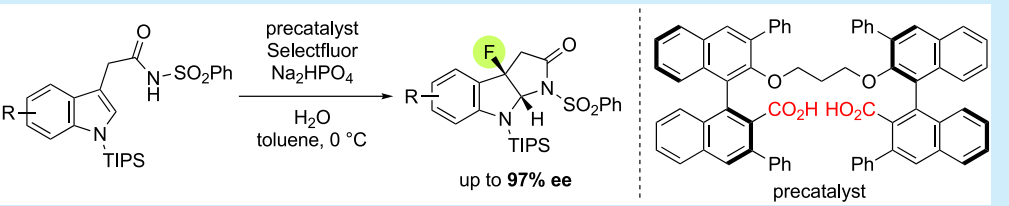

ABSTRACT: Asymmetric dearomatizing fluorocyclization of indole derivatives was investigated using a dicarboxylate phase-transfer catalyst. This reaction proceeds under mild reaction conditions to provide fluoropyrroloindoline derivatives in a highly enantioselective manner. Various substitution patterns on the indole ring are well tolerated. To facilitate the reaction and ensure reproducibility, the addition of water is essential, and its possible role is discussed.

Dearomatizing intramolecular cyclization of indole derivatives with a pendant nucleophile is a representative method for the construction of the pyrroloindoline framework. Because this framework is often found in both natural and unnatural bioactive compounds,[1,2] various dearomatizing reactions for its preparation have been investigated and applied to the total synthesis of indole alkaloids.[3]

Reflecting the utility of the fluorine atom in pharmaceuticals and agrochemicals,[4] fluoropyrroloindolines would be of great interest in drug development. Although tremendous efforts have been devoted to the development of efficient fluorination reactions,[5] dearomatizing fluorination of indole derivatives has been less well studied.[6] In 2001, Shibata and co-workers reported the fluorocyclization of tryptophan-derived diketopiperazines with FP-T300, albeit with moderate diastereoselectivity.[7] The same method was also applied to tryptamine derivatives, but the enantioselective version was not examined.[8] To date, there are only a few reports for enantioselective fluorocyclization of tryptamine derivatives. Gouverneur applied a cinchona alkaloid to develop a catalytic asymmetric variant in 2011 (Scheme 1a),[9a] and Yeung recently achieved excellent enantioselectivity using a fluorinating reagent in situ generated from an amino acid derived phthalazine.[9b] In 2017, You demonstrated a similar reaction using Toste's phosphate phase-transfer catalysis conditions.[10,11] However, these reactions normally require extremely low temperature and/or an appropriate substituent at a specific position of the indole ring to achieve high asymmetric induction, and therefore a more general reaction system with broad substrate scope is still required.

We are interested in the synthesis and applications of fluorine-containing molecules.[12] As part of our continuing research program on asymmetric halogenation reactions,[13] we recently developed chiral dicarboxylic acid precatalyst **1** for asymmetric fluorination reactions.[14] The in situ generated dicarboxylate ion can serve as an anionic phase-transfer catalyst to bring Selectfluor (**2**), which is insoluble in nonpolar organic solvents, into the liquid phase, enabling highly enantioselective fluorofunctionalization of alkenes and dearomative fluorination of 2-naphthols.

Anticipating wide applicability of our dicarboxylate catalyst, we became interested in using it for dearomatizing fluorination of indole derivatives. With reference to previous reports,[9a,10] we initially examined the reaction of an *N*-sulfonyl tryptamine derivative. However, the desired product was obtained in a low yield and the enantioselectivity was quite low (10%).[15] In contrast, promising enantioselectivity was observed when an *N*-sulfonyl indole acetamide was used as a substrate, the fluorination of which has not been examined before (*vide infra*). Here, we present asymmetric dearomatizing fluorocyclization of *N*-sulfonyl indole acetamides, affording easy access to chiral fluoropyrroloindoline derivatives (Scheme 1b).

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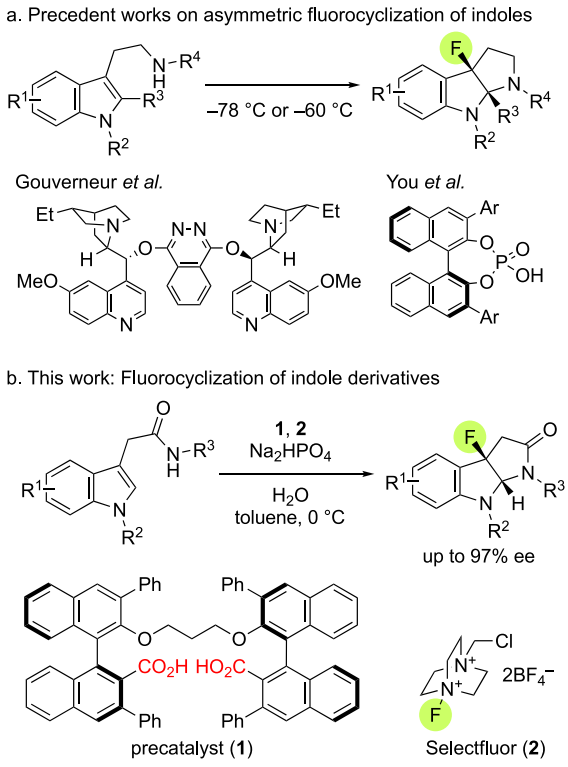
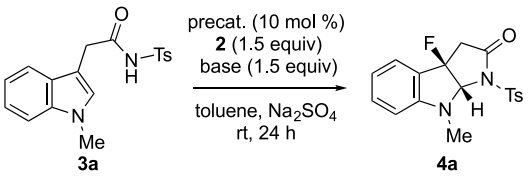
Scheme 1. Asymmetric Fluorocyclizations of Indole Derivatives



To optimize the reaction conditions, *N*-methylindole acetamide derivative **3a** was chosen as a test substrate (Table 1). Encouragingly, the initial experiment using the standard reaction conditions established in the previous report[14a] gave the desired product **4a** in 49% yield with 62% ee (entry 1). In contrast, other carboxylic acid precatalysts such as our hydroxy carboxylic acid **5**[13a] and chiral binaphthyldicarboxylic acid **6** did not work well (entries 2 and 3). Although chiral phosphoric acid **7** could promote the reaction in moderate yield, the ee value was unsatisfactory (entry 4). These results are suggestive of the superiority of the linked dicarboxylic acid precatalyst **1**. Further screening of the reaction conditions revealed the combination of toluene and Na_2HPO_4 to be optimal in terms of the chemical yield and the enantioselectivity (entry 5).[15] Because the use of Selectfluor II instead of **2** afforded **4a** with only 18% ee (entry 6), the structure of the fluorinating reagent is presumed to be important to form a reactive species with a well-defined chiral environment.

We next examined the effect of protective groups and found that protection at the N1 position of the indole ring had a marked impact on the reaction performance (Table 2). For example, an electron-withdrawing *tert*-butoxylcarbonyl (Boc) group was totally ineffective (entry 1), and the nonprotected substrate **3c** gave a low yield and enantioselectivity (entry 2). A benzyl group retarded the reaction, probably due to the lower solubility of **3d**, but a *para*-methoxybenzyl (PMB) group gave comparable results to those observed in the case of *N*-methyl-protected **3a** (entries 3 and 4). When silyl groups were incorporated to examine steric and hydrophobic effects, a great improvement of the asymmetric induction was observed (entries 5 and 6). *N*-Methanesulfonyl amide reduced the reaction efficiency (entry 7), but a benzenesulfonyl group gave a better chemical yield (entry 8). The best enantioselectivity

Table 1. Optimization of the Reaction Conditions[a]



entry	precat.	base	yield (%)[b]	ee (%)
1	**1**	Na_3PO_4	49	62
2	**5**	Na_3PO_4	22	−2
3	**6**	Na_3PO_4	28	−13
4	7	Na_3PO_4	58	5
5	**1**	Na_2HPO_4	56	70
6[c]	**1**	Na_2HPO_4	53	18

[a]The reactions were carried out with precatalyst (10 mol %), base (1.5 equiv), **2** (1.5 equiv), and Na_2SO_4 (50 mg) on a 0.1 mmol scale, unless otherwise mentioned. [b]Determined by ^{1}H NMR analysis using 1,2-dibromoethane as an internal standard. [c]Run with Selectfluor II instead of Selectfluor.

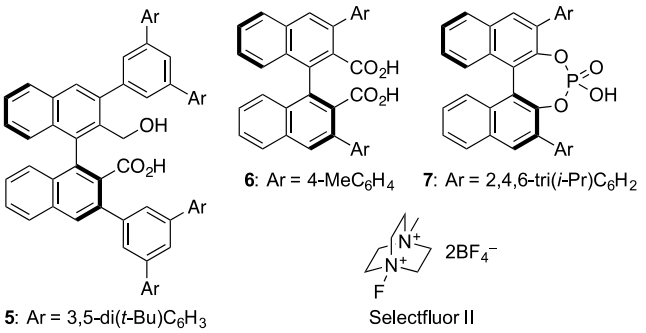
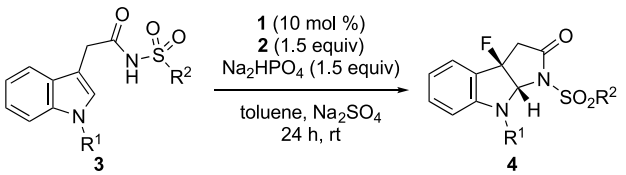


Table 2. Effect of Protective Groups[a]



entry	R^1	R^2	4	yield (%)[b]	ee (%)
1	Boc	4-MeC_6H_4	**b**	N.R.	–
2	H	4-MeC_6H_4	**c**	24	11
3	Bn	4-MeC_6H_4	**d**	20	43
4	PMB	4-MeC_6H_4	**e**	64	73
5	TBS	4-MeC_6H_4	**f**	68	81
6	TIPS	4-MeC_6H_4	**g**	74	86
7	TIPS	Me	**h**	20	43
8	TIPS	Ph	**i**	99	86
9[c]	TIPS	Ph	**i**	quant.	93
10[c,d]	TIPS	Ph	**i**	quant.[e]	94

[a]The reactions were carried out with **1** (10 mol %), Na_2HPO_4 (1.5 equiv), **2** (1.5 equiv), and Na_2SO_4 (50 mg) in toluene (1 mL) at room temperature on a 0.1 mmol scale, unless otherwise mentioned. [b]Determined by ^{1}H NMR analysis using 1,2-dibromoethane as an internal standard. [c]Run at 0 °C. [d]Run with 10 μL of H_2O in the absence of Na_2SO_4. [e]Isolated yield. Boc = *tert*-butoxycarbonyl, Bn = benzyl, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, N.R. = no reaction. quant. = quantitative yield.

(93%) was observed when the reaction was carried out at 0 °C (entry 9). However, we encountered poor reproducibility; the

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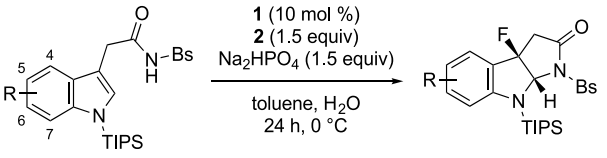
reaction sometimes halted completely under the reaction conditions shown in entry 9. After a series of experiments, we found that the addition of an appropriate amount of H_2O was crucial to ensure reproducibility, and in this case, Na_2SO_4 was no longer necessary for the reaction (entry 10).[15] The reaction could be carried out on a 1 mmol scale, and comparable results (82%, 94% ee) were obtained.[15] The reasons for this will be discussed later. Moreover, when the previously reported methods that worked well for tryptamine derivatives[9a,10] were applied to the present substrate, unsatisfactory results were obtained (Supporting Information, section 3.3),[15] indicating that the present system is the first solution for indole acetic acid derivatives and complementary to those for tryptamine substrates.

Having optimized the reaction conditions, we investigated the generality of the reaction (Table 3). 4-Substituted indole

Table 3. Substrate Scope[a]



3 4

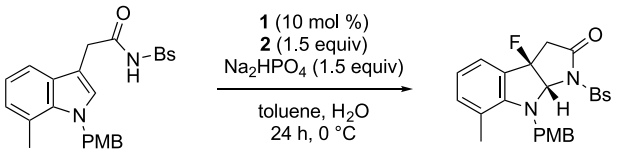
entry	R	4	yield (%)[b]	ee (%)
1	4-Me	**j**	87	93
2	4-F	**k**	90	74
3	4-Cl	**l**	63	96
4	4-Br	**m**	75	97
5[c]	5-Me	**n**	86	81
6	5-MeO	**o**	75	81
7	5-Cl	**p**	76	80
8	5-Br	**q**	90	78
9	5-I	**r**	68	78
10	6-Me	**s**	76	93
11	6-F	**t**	65	92
12[c]	6-Cl	**u**	66	92
13	6-Br	**v**	50	95

[a]The reactions were carried out with **1** (10 mol %), Na_2HPO_4 (1.5 equiv), **2** (1.5 equiv), and H_2O (10 μL) in toluene (1 mL) at 0 °C on a 0.1 mmol scale. [b]Isolated yield. [c]Run for 48 h. Bs = benzenesulfonyl.

derivatives were good substrates irrespective of the electronic properties of the substituent, affording the corresponding products in high yields with up to 97% ee (**4j**–**4m**). Although substituents at the 5 position had some negative influence on the stereoselectivity, the desired products were formed at synthetically useful levels (**4n**–**4r**). As for the substituent at the 6 position, methyl and halogen groups were well tolerated and the desired products were formed in a highly enantioselective manner (**4s**–**4v**). Halogen groups anywhere at the 4–6 positions are expected to be useful handles for further structural modification.

A further example is shown in Scheme 2. Because 7-substituted indole substrate could not be protected with a TIPS group, *N*-PMB-protected indole derivative **3w** was subjected to the reaction. The dearomatizing fluorocyclization proceeded to give **4w** in 50% isolated yield with 90% ee. These results clearly indicate that the present catalytic system is compatible with various substitution patterns on the indole ring, which is still difficult to achieve with other catalytic systems.

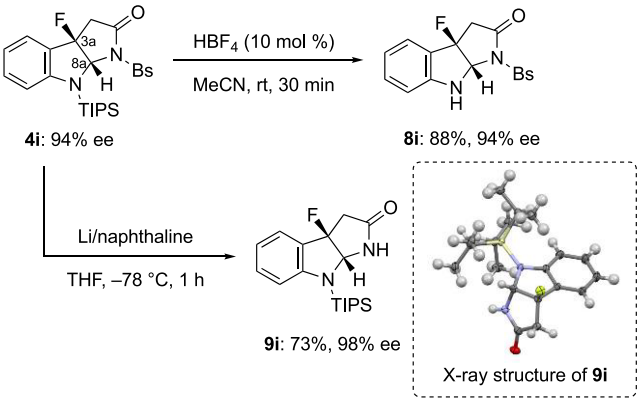
Scheme 2. Asymmetric Dearomatizing Fluoocyclization of 3w



3w **4w**: 50%, 90% ee

Deprotection of the product **4i** with 94% ee was successfully achieved as shown in Scheme 3. The TIPS group could be

Scheme 3. Transformations of Fluorinated Pyrroloindoline 4i



4i: 94% ee **8i**: 88%, 94% ee **9i**: 73%, 98% ee

removed easily under acidic conditions to give **8i** in 88% yield without any loss of optical purity. The *N*-benzenesulfonyl amide could also be deprotected without difficulty when **4i** was treated with Li/naphthalene, affording lactam **9i** in good yield. Interestingly, the ee value of **9i** was found to be 98%, suggesting that self-disproportionation of the enantiomers might occur during purification by silica gel column chromatography.[16] Fortunately, we were able to obtain an enantio-pure single crystal of **9i**, the X-ray structural analysis of which established its absolute and relative stereochemistry.[17] Accordingly, the absolute stereochemistry of **4i** was determined to be 3a*R*, 8a*S*.

While Na_3PO_4 can deprotonate the precatalyst **1** rapidly in toluene, less basic Na_2HPO_4 reacted reluctantly with **1**. However, the ^{1}H NMR spectrum of **1** in toluene-d_8 dramatically changed in the presence of a small amount of water (10 μL of H_2O per 1 mL of toluene).[15] This observation indicated that the precatalyst **1** is quickly converted to its anionic form. Thus, the concentration of the actual phase-transfer catalyst would be increased considerably, facilitating the phase transfer of **2** to give the putative chiral fluorinating reagent. Additionally, the ^{1}H NMR experiment clearly showed that the substrate undergoes facile deprotonation under basic conditions,[15] which is in accord with the expected lower pK_a value of the *N*-sulfonyl amide unit. The high stereoselectivity observed in this reaction can be rationalized in terms of hydrogen bonding between the catalyst and the substrate anion mediated by water molecule(s), resulting in an associative interaction that defines the structure of the transition state, although the details remain to be elucidated.

In summary, we have developed asymmetric dearomatizing fluoroamidation of indole acetamide derivatives using a

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dicarboxylate phase-transfer catalyst. Indole substrates with various substitution patterns were available, and excellent enantioselectivity of up to 97% was achieved. We also found that water efficiently promotes the reaction, which might provide a useful clue to developing other types of reactions. Further study of the present reaction system is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02026.

Optimization of the reaction conditions, NMR experiments concerning H_2O effect, experimental procedure, characterization data (PDF)

Accession Codes

CCDC 1989933 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.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.

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Notes

The authors declare no competing financial interest.

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