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Asymmetric fluorinative dearomatization of tryptamine derivatives†

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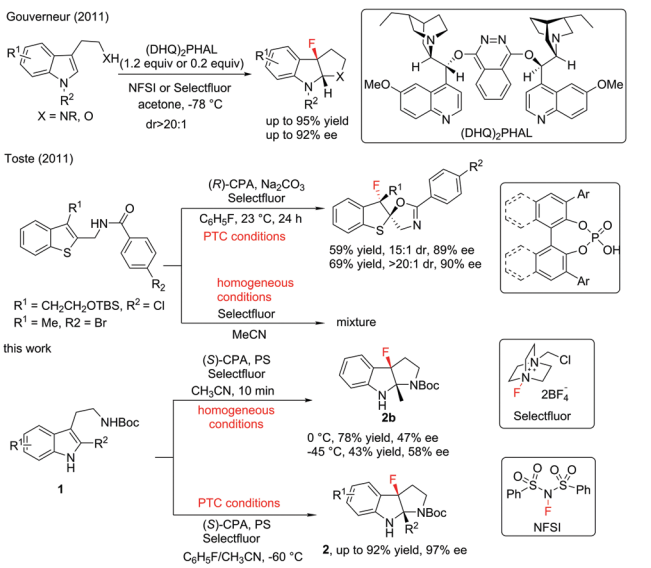
An asymmetric fluorinative dearomatization reaction of tryptamine derivatives was developed by using a chiral anion phase transfer catalyst (PTC) system, and the preliminary results of the reaction mechanistic study were achieved. This method is characterized by a simple operation, facile introduction of a fluorine atom in a highly enantioselective manner and construction of two contiguous quaternary stereogenic centers.

Fluorination reactions have witnessed tremendous development due to the extreme importance of fluorine-containing molecules in medicinal chemistry and materials science.[1] Although catalytic asymmetric fluorination reactions have gained rapid growth accompanied by the emergence of catalytic systems,[2] developing highly efficient stereoselective fluorination reactions is still in great demand. Catalytic asymmetric dearomatization (CADA) reactions have recently attracted enormous research interest due to their powerful ability to construct complex molecules from readily available aromatic compounds.[3] Although CADA reactions through fluorination are undoubtedly attractive in the synthesis of chiral fluorine-containing compounds and highly desirable, successful reports are very limited in number. In 2011, Gouverneur and co-workers reported an elegant enantioselective dearomatization of indole derivatives *via* cascade fluorocyclization. In general, moderate to high levels of enantioselective control are obtained under catalytic conditions (Scheme 1).[4] Almost at the same time, Toste and co-workers reported enantioselective electrophilic fluorination utilizing a chiral anion phase transfer catalyst.[5] The examples of dearomatization of benzothiophenes reported therein elucidated the potential of CADA reactions *via* fluorination. Later, the same group further advanced the asymmetric fluorinative dearomatization reaction using phenols.[6] Due to the great demand for complex chiral fluorinated molecules and our continuous interest in CADA reactions, herein, we report an asymmetric fluorinative dearomatization reaction of tryptamine derivatives, providing fluorine-containing pyrroloindolines bearing two contiguous quaternary stereogenic centers. Ma and co-workers had reported the chiral anion PTC strategy in bromination of tryptamine derivatives. Under the same catalytic conditions, the fluorination of **1a** gave almost racemic results.[7]

We initiated our studies by examining the reaction of the tryptamine derivative **1a** with Selectfluor ((1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane)) (1.1 equiv.), in the presence of (*S*)-TRIP ((*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate) (10 mol%) and sodium carbonate (1.1 equiv.) in fluorobenzene (Table 1, entry 1). The fluorocyclization product **2a** was given in 48% yield and 6% ee.

Encouraged by these results, various chiral phosphoric acids (CPAs) (10 mol%) were evaluated.[8] Although all reactions proceeded



Scheme 1 Enantioselective fluorinative dearomatization reactions of tryptamine derivatives.

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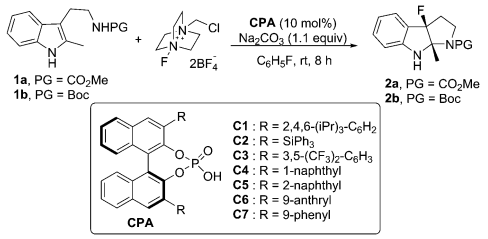
Table 1 Evaluation of chiral phosphoric acids



Entry[a]	CPA	1	Yield[b] (%)	ee[c] (%)
1	C1	**1a**	48	6
2	C2	**1a**	70	4
3	C3	**1a**	52	0
4	C4	**1a**	58	13
5	C5	**1a**	48	3
6	C6	**1a**	67	37
7	C7	**1a**	56	22
8	C6	**1b**	48	55

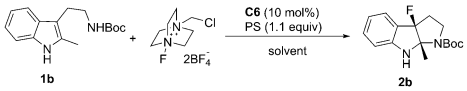
[a] Reactions were performed with **1** (0.2 mmol), Selectfluor (0.22 mmol), Na_2CO_3 (0.22 mmol), **CPA** (0.02 mmol) in C_6H_5F (4 mL) at rt. [b] Isolated yield. [c] Determined by HPLC analysis.

to afford the desired fluorinated 6*H*-pyrroloindole[9] **2a**, only moderate yields could be achieved and the enantioselective control was not satisfactory (Table 1, entries 1 to 7). Among all the CPAs surveyed, **C6** was the optimal one to give **2a** in 67% yield with 37% ee (Table 1, entry 6). To our delight, when the protecting group of tryptamine derivative **1** was switched from CO_2Me (**1a**) to Boc (**1b**), product **2b** was obtained in 55% ee (Table 1, entry 7).

With **1b** as the model substrate, several commonly used non-polar solvents were first screened, and fluorobenzene proved to be the optimal one (48% yield, 55% ee). Due to the importance of a base for the anionic chiral phase-transfer catalysis, both inorganic and organic bases were examined, and proton sponge (PS) was found to be efficient to increase the yield (Table 2, entry 2). When the reaction temperature was decreased from rt to 0 °C, the reaction proceeded smoothly with increased enantioselectivity (56% to 65% ee) but a prolonged reaction time was needed (Table 2, entry 3). However, the addition of 4 Å molecular sieves (MS) led to a complicated reaction mixture with a decreased yield and enantioselective control (Table 2, entry 4).

Different from the phenomena where substrates treated with Selectfluor under homogeneous conditions were converted to a complex mixture in the chiral anion phase-transfer catalytic system,[4,5] screening polar solvents as homogeneous conditions for this reaction afforded positive results (see the ESI† for details). Among those tested, acetonitrile was the most optimal to provide **2b** in 78% yield; however, the enantioselectivity was decreased slightly (Table 2, entry 5). These results encouraged us to test mixed solvents. When mixed solvents of fluorobenzene and acetonitrile (1 : 1) were utilized, the desired product **2b** was obtained in 50% yield and 69% ee within 10 min (Table 2, entry 6). Further decreasing the reaction temperature to −60 °C afforded **2b** in 64% yield with 90% ee (Table 2, entry 7). To our delight, running the reaction in a higher concentration improved the yield to a satisfactory level (87% yield) (Table 2, entry 8). Notably,

Table 2 Evaluation of reaction parameters



Entry[a]	Solvent	Time	Temp. (°C)	Yield[b] (%)	ee[c] (%)
1[d]	C_6H_5F	8 h	rt	48	55
2	C_6H_5F	8 h	rt	72	56
3	C_6H_5F	16 h	0	60	65
4[e]	C_6H_5F	11 h	0	41	5
5	CH_3CN	10 min	0	78	47
6	C_6H_5F/CH_3CN	10 min	0	50	69
7	C_6H_5F/CH_3CN	16 h	−60	64	90
8[f]	C_6H_5F/CH_3CN	16 h	−60	87	90
9[f,g]	C_6H_5F/CH_3CN	18 h	−60	66	90
10[d]	C_6H_5F/CH_3CN	18 h	−60	71	60

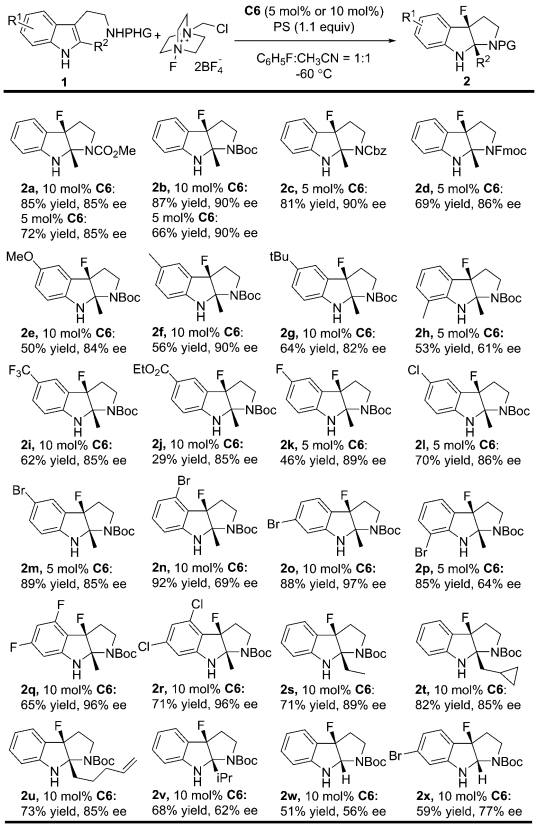
[a] Reaction conditions: **1b** (0.2 mmol), **C6** (0.02 mmol), Selectfluor (0.22 mmol), PS (0.22 mmol) in solvent (4 mL). [b] Isolated yield. [c] Determined by HPLC analysis. [d] Na_2CO_3 instead of PS. [e] 4 Å MS was used. [f] C_6H_5F/CH_3CN (1 : 1, 2 mL). [g] 5 mol% **C6**. PS: proton sponge.

5 mol% catalyst loading gave the same enantioselectivity (90% ee) and 66% yield (Table 2, entry 9).

With the optimal reaction conditions in hand (Table 2, entry 8), the substrate scope was explored to test the generality of this asymmetric fluorinative dearomatization reaction. Firstly, the protecting group of the tryptamine was evaluated. As shown in Table 3, in general, all the substrates with electron-withdrawing protecting groups (CO_2Me, Boc, Fmoc and Cbz) were converted to their corresponding fluorinative dearomatization products with satisfactory enantioselectivity (85–90% ee, **2a** to **2d**) and moderate to good yields. The substituents on the indole moiety were further explored. N-Boc protected tryptamines with varied electron-donating substituents (5-CH_3, 5-MeO, 5-*t*Bu) at the C5 position were well tolerated to provide their corresponding products with good enantioselectivity (82–90% ee) and 50–64% yields (**2e** to **2g**), and a methyl group at the C7 position led to only moderate enantioselectivity (61% ee) due to the steric hindrance effect (**2h**). The electron-withdrawing substituent (5-F, 5-Cl, 5-Br, 5-CF_3 and 5-CO_2Et) at the C5 position of the indole moiety was also well tolerated to provide the target compounds with good enantioselectivity (85–89% ee) and 29–89% yields (**2i** to **2m**). Substrates bearing a Br substituent at the different positions (4, 5, 6, 7) of the indole core underwent dearomatization smoothly (84–92% yields) but with varied enantioselectivity (64–97% ee). Notably, a 6-Br product was obtained in 97% ee (**2o**). Interestingly, the reactions of 4,6-dihalo-substituted substrates proceeded with excellent enantioselectivity (96% ee, **2q**, **2r**). Finally, the 2-substituent of the indole moiety was evaluated, and a good enantioselectivity (85–89% ee) was obtained for substrates bearing simple alkyl (**2s**), cyclopropyl (**2t**), and alkenyl functional groups (**2u**). The reaction conditions were also compatible with substrates bearing more hindered substituents or simple H with slightly dropped enantioselectivity (**2v**, **2w**, **2x**, 51–68% yields, 56–77% ee).

Interestingly, the reaction of 3,5-dimethyl substituted substrate **1y** under the optimal reaction conditions led to the isolation of **2yy** in 72% yield and 93% ee. It is likely that the dearomatized

Table 3 Substrate scope[a]

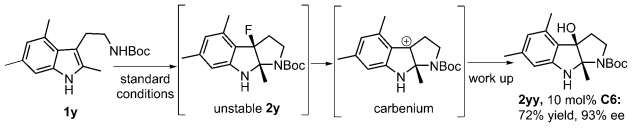


[a] Reaction conditions: **1** (0.2 mmol), **C6** (0.02 mmol), Selectfluor (0.22 mmol), base (0.22 mmol) in $C_6H_5F:CH_3CN$ (1 : 1, 2 mL) at −60 °C. Isolated yield. ee was determined by HPLC analysis.

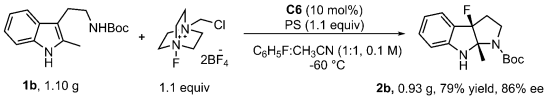
intermediate **2y** is unstable due to the introduction of three methyl groups on the indole ring, which facilitates the C–F bond cleavage to result in the formation of a stable benzyl carbenium (Scheme 2).

The reaction of **1b** in the gram-scale proceeded well affording the dearomative product **2b** in 79% yield and 86% ee (Scheme 3). Furthermore, the protection reaction of N–H in **2b** with trifluoroacetic anhydride was carried out to give **4** in 88% yield, and the Boc group in **3** could be removed by TMSOTf at −78 °C (Scheme 4). X-Ray crystallography analysis of a single crystal of enantiopure **3** revealed its absolute configuration as 3*aR*, 8*aS*. Treatment of **1b** with NBS and 1,3,5-trichloroisocyanuric acid (TCCA) led to the dibromo compound **2bb** (68% yield, 86% ee) together with 32% yield of the monobromo compound **2p**, and the dichloro compound **2bc** (66% yield, 86% ee), respectively.

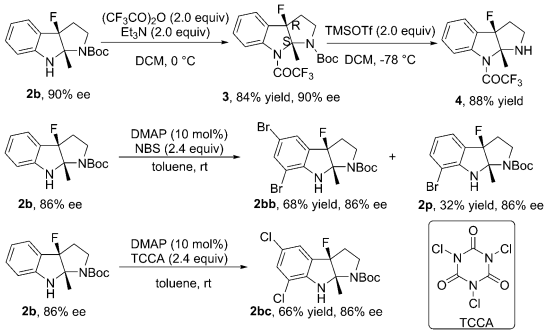
To shed light on the reaction mechanism, control experiments were carried out to examine the effects of acid and base



Scheme 2 The fluorinative dearomatization reaction of **1y** and hydrolysis.



Scheme 3 Gram-scale reaction.



Scheme 4 Transformations of product **2b**.

additives to the reaction outcomes. The correlation between conversion of **1b** with reaction time under varied reaction conditions is shown in Fig. 1. Notably, a strong background reaction was observed. The rate of the reaction of **1b** without a chiral phosphoric acid catalyst or PS was similar to that under the standard conditions (entry 8, Table 2). We envisioned that HBF_4 released from Selectfluor might accelerate the reaction. Indeed, when 1 equiv. of HBF_4 was added, the reaction becomes even faster while the reaction becomes sluggish when 1.2 equiv. of PS was employed. These data imply that the role of PS in this reaction is to neutralize HBF_4 generated *in situ* and hence inhibit the racemic background reaction.

In conclusion, an asymmetric fluorinative dearomatization reaction of tryptamine derivatives was developed based on a chiral anion phase transfer strategy. The preliminary investigations on the reaction mechanism suggested that the reaction proceeds *via* bifunctional activation by a chiral BINOL-derived phosphate anion. This method is characterized by simple operation, facile introduction of a fluorine atom in a highly enantioselective manner and construction of two contiguous quaternary stereogenic centers.

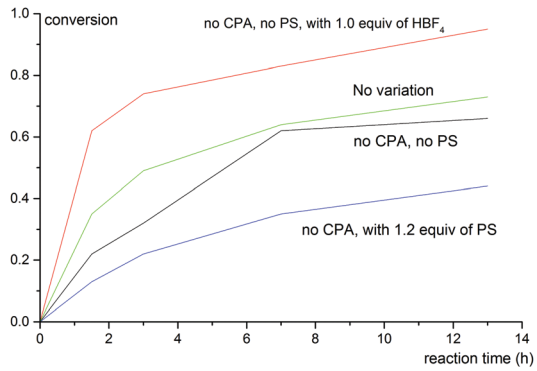


Fig. 1 Correlation between conversion of **1b** with reaction time under varied reaction conditions. The variation from the "standard reaction conditions" (entry 8, Table 2) is denoted for each plot.

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