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Highly Enantioselective Monofluoromethylation of C2-Arylindoles Using FBSM under Chiral Phase-Transfer Catalysis

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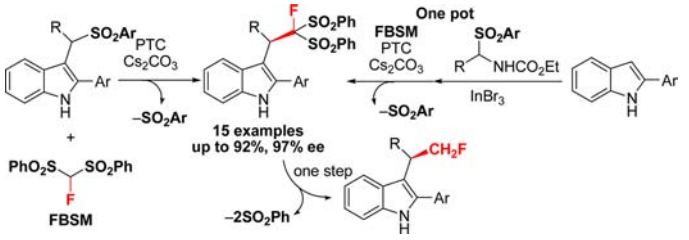
ABSTRACT



The highly enantioselective addition of 1-fluoro-1,1-bis(phenylsulfonyl)methane (FBSM) to vinylogous imines generated in situ from 2-aryl-3-(1-arylsulfonylmethyl)indoles was achieved using chiral ammonium salts derived from cinchona alkaloids. One-pot conversion from 2-arylindoles with FBSM was also adaptable under the same reaction conditions. The key for this transformation is the effective use of the arylsulfonyl group.

Fluorine has become a fundamental tool for drug discovery and material science because of its exceptionally unique properties such as high electron negativity and small size, despite its extremely rare natural occurrence.[1] Nearly 30% of pharmaceuticals and agrochemicals on the market are said to contain at least one fluorine atom somewhere in their structures.[2] Due to the size resemblance of fluorine and hydrogen, fluorine is often used as an isosteric substitution of hydrogen.[3] From the viewpoint of electronegativity, however, fluorine substitution can be recognized as an isosteric substitution of hydroxy group.[3] Therefore, a monofluoromethyl group (CH_2F) is an attractive impersonator of both the corresponding methyl (CH_3) and hydroxymethyl (CH_2OH) groups, which are often encountered in biologically active materials.[4] Therefore, the development of a new strategy to synthesize CH_2F-containing organic compounds has attracted much attention. In particular, the asymmetric introduction of a CH_2F function into target molecules is important due to a recent requirement from the chiral drug industry. In 2006, our group[5] and Hu's group[6] independently developed 1-fluoro-1,1-bis(phenylsulfonyl)methane (FBSM) as a synthetic equivalent of a monofluoromethyl anion species for the direct construction of a C−CH_2F bond. FBSM

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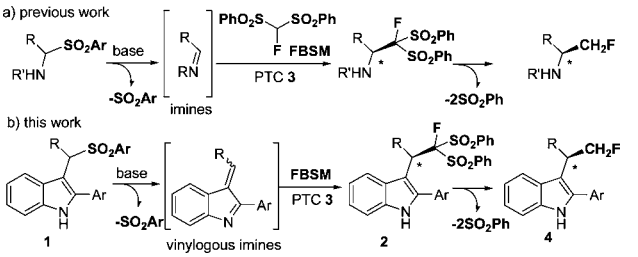
is now commercially available, and the FBSM method has clear advantages over other methods for the synthesis of chiral C*−CH_2F compounds such as dehydroxyfluorination of C*−CH_2OH compounds by DAST, since asymmetric synthesis of chiral C*−CH_2OH compounds followed by racemization-free dehydroxyfluorination should be required. A number of nucleophilic monofluoromethylation reactions using FBSM have emerged,[7,8] and the Mannich-type reaction via in situ generated imines is effective for the asymmetric synthesis of α-monofluoromethylated amines (Scheme 1a).[9] As an extension of this work, herein we disclose an enantioselective monofluoromethylation reaction of C2-arylindoles **1** via vinylogous imines generated in situ with FBSM to provide monofluoromethylated indole derivatives **2** (Scheme 1b). The key for these transformations is the effective use of the arylsulfonyl group for the activation of both the substrates and reagent, FBSM.[10]

Indole and its derivatives are important and common structural motifs in pharmaceuticals and agrochemicals.[11] In particular, C2-arylindoles are ubiquitous substructures indoles.[12] With these background facts, we were interested in the asymmetric synthesis of C2-arylindoles having a CH_2F group on the chiral center. The idea for the generation of vinylogous imines of indoles using an arylsulfonyl group as a leaving group was initially reported by Petrini group. Broad scopes of C3-substituted indoles can be obtained via this method.[13]

Scheme 1. Strategies for Enantioselective Monofluoromethylation via in Situ Generated Imines (a) and Vinylogous Imines (b) Using FBSM



Although some work on enantioselective nucleophilic additions to vinylogous imine intermediates generated from arylsulfonyl indoles **1** under organo or Lewis acid catalysis has been reported,[14] these conditions are not applicable for the monofluoromethylation of **1** by FBSM, since the activation of the CH group of FBSM requires a stronger basic condition. We first tested the monofluoromethylation reaction of arylsulfonyl indoles **1a** with FBSM under the best conditions for our reported asymmetric Mannich-type fluoromethylation reaction using benzylquinidium chloride **3a** as a phase-transfer catalyst in the presence of K_2CO_3 in CH_2Cl_2 at room temperature. However, the initial attempt was quite disappointing, and a racemic product **2a** was afforded in 56% yield (Table 1, entry 1). Similar results were obtained when the reaction was performed in the presence of catalysts QN-**3b** or CD-**3d**, respectively (entries 2 and 4). The enantioselectivity increased slightly to 16% when benzylcinchoninium chloride CN-**3c** was attempted (entry 3). Then we tried to tune the steric hindrance of the catalyst based on CN-**3c** (entries 5−7). In the presence of benzylcinchoninium bromide CN-**3f**, which bears a sterically demanding benzyl substituent, high yield with an acceptable enantioselectivity (70%) was afforded (entry 6). After screening various bases and solvents (Table 1, entries 8−10),[15] a combination of CN-**3f** and Cs_2CO_3 in toluene gave (*R*)-**2a** with high enantioselectivity, up to 74% ee (entry 10). Further optimization of reaction temperature and concentration was studied, and high enantioselectivity (90% ee) was found in toluene (0.040 M) at −10 °C (entry 12). It should be noted that OH-protected derivative CN-**3h** led to high yield but low enantioselectivity (entry 14). The result indicated that the free hydroxy group of the cinchona alkaloid is

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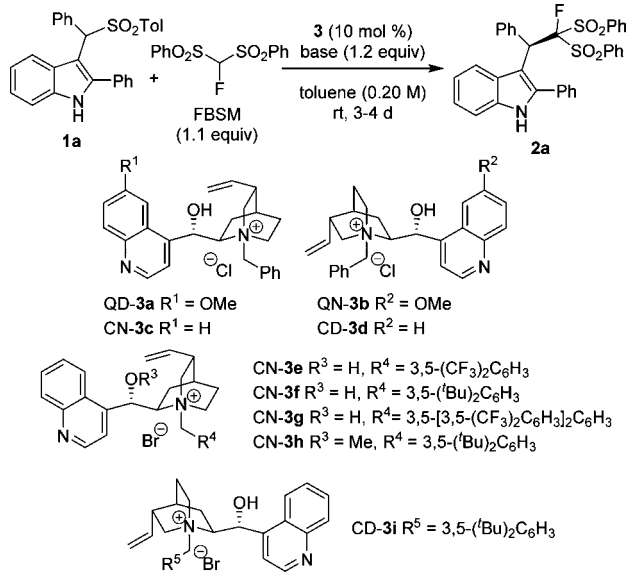
(15) Among the solvents tested, toluene was optimal. Reactions conducted in more polar solvents showed increased background reactivity and decrease in enantiocontrol.

indispensable for achieving high enantiocontrol, presumably by hydrogen bonding.

Table 1. Optimization of the Reaction Conditions[a]

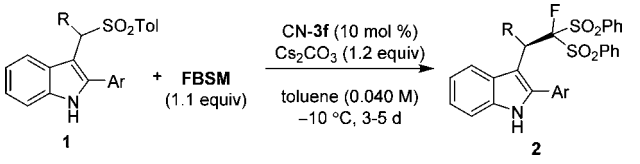


entry	catalyst	base	yield[b] (%)	ee[c] (%)
1	QD-**3a**	K_2CO_3	56	1 (*S*)
2	QN-**3b**	K_2CO_3	56	6 (*S*)
3	CN-**3c**	K_2CO_3	53	16 (*R*)
4	CD-**3d**	K_2CO_3	51	10 (*S*)
5	CN-**3e**	K_2CO_3	34	58 (*R*)
6	CN-**3f**	K_2CO_3	52	70 (*R*)
7	CN-**3g**	K_2CO_3	11	9 (*S*)
8	CN-**3f**	KF/alumina	58	67 (*R*)
9	CN-**3f**	K_3PO_4	92	70 (*R*)
10[d]	CN-**3f**	Cs_2CO_3	99	74 (*R*)
11[e]	CN-**3f**	Cs_2CO_3	99	84 (*R*)
12[e,f]	CN-**3f**	Cs_2CO_3	94	90 (*R*)
13[e,g]	CN-**3f**	Cs_2CO_3	93	76 (*R*)
14[e,f]	CN-**3h**	Cs_2CO_3	94	7 (*R*)

[a] Reactions were carried out using **2a**, FBSM (1.1 equiv), catalyst (10 mol %), and base (1.2 equiv) in toluene (0.20 M) at rt for 3−4 d unless otherwise noted. [b] Isolated yield by silica gel column chromatography. [c] The ee value was determined by HPLC analysis. [d] Reaction time was 1 d. [e] Reaction was carried out at −10 °C. [f] Reaction was carried out in toluene (0.040 M). [g] Reaction was carried out in toluene (0.40 M).

With optimal conditions in hand, the scope of substrate **1** for enantioselective monofluoromethylation with FBSM was investigated (Table 2). By using a catalytic amount of CN-**3f** (10 mol %), all substrates functionalized at R and the Ar position with the aryl group afforded products in moderate to excellent yield and high enantioselectivity (entries 1−11). Notably, using the analogous ammonium bromide derived from cinchonidine (CD-**3i**), a similar ee value was obtained for **2a**, albeit with the opposite (*S*) stereochemistry (entry 2). Both electron-withdrawing and -donating groups at the *para* or *meta* position of the phenyl ring were tolerated (entries 3−11). In the case of substrate **1j**, a smaller amount of toluene was required to complete the reaction and the ee value was excellent (entry 11). When we attempted to react the substrates having an alkyl group at the R position with FBSM, the yields and ee values remained good (entries 12−14). It should be noted that the C2-aryl group of indole derivatives is often crucial for their biological activities;[11,12] it also plays an important role for asymmetric induction in the present reaction. The reactions of substrates possessing either methyl or hydrogen at the C2 position afforded an almost racemic mixture of **2** with high yields (entries 14 and 15). Since it was reported that *E*/*Z* configurations of imino intermediates play an important role on enantioselectivities,[14b−e] we assumed that the phenyl group at the C2 position was the ideal intermediate for this reaction. The absolute stereochemistry of (*R*)-**2a** was determined by X-ray crystallographic analysis (CCDC 937472, see the Supporting Information), and all of the other products are tentatively assigned by analogy to **2a**.

Table 2. Enantioselective Monofluoromethylation of C3-Substituted Indoles with FBSM Catalyzed by Phase-Transfer Catalyst[a]



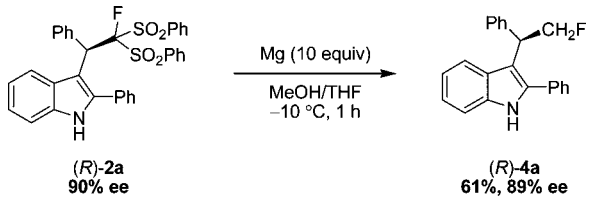
entry	**1**	Ar, R	**2**	yield[b] (%)	ee[c] (%)
1	**1a**	Ph, Ph	(*R*)-**2a**	94	90
2[d]	**1a**	Ph, Ph	(*S*)-**2a**	98	86
3	**1b**	Ph, 4-ClC_6H_4	(*R*)-**2b**	78	80
4	**1c**	Ph, 3-ClC_6H_4	(*R*)-**2c**	77	87
5	**1d**	Ph, 4-FC_6H_4	(*R*)-**2d**	91	85
6	**1e**	Ph, 3-FC_6H_4	(*R*)-**2e**	99	88
7	**1f**	Ph, 3-BrC_6H_4	(*R*)-**2f**	83	88
8	**1g**	Ph, 4-$MeOC_6H_4$	(*R*)-**2g**	80	86
9	**1h**	Ph, 4-MeC_6H_4	(*R*)-**2h**	74	84
10	**1i**	Ph, 4-$^iBuC_6H_4$	(*R*)-**2i**	78	83
11[e]	**1j**	4-MeC_6H_4, Ph	(*R*)-**2j**	92	97
12	**1k**	Ph, Et	(*R*)-**2k**	54	53
13	**1l**	Ph, C_6H_{11}	(*R*)-**2l**	74	57
14	**1m**	Me, Ph	(*R*)-**2m**	93	17
15	**1n**	H, Ph	(*R*)-**2n**	94	1

[a] Reactions were carried out using **1**, FBSM (1.1 equiv), CN-**3f** (10 mol %), and Cs_2CO_3 (1.2 equiv) in toluene (0.040 M) at −10 °C for 3−5 d. [b] Isolated yield by silica gel column chromatography. [c] The ee value was determined by HPLC analysis. [d] CD-**3i** was used instead of CN-**3f**. [e] Reaction was carried out using solvent (0.20 M).

The conjugate addition adduct **2a** could be directly converted into the corresponding monofluoromethylated derivative **4a**. A simple one-step reduction of the two phenylsulfonyl groups was realized under conventional Mg/MeOH conditions to furnish the product in 61% without major loss of enantiopurity of **2a** (Scheme 2).

To further expand the application of this reaction, we were interested in a one-pot process from simple indoles to the asymmetric conjugate addition of FBSM using indium

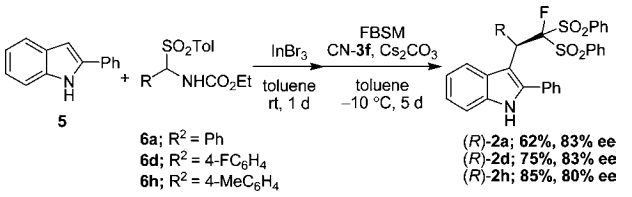
Scheme 2. Reductive Desulfonylation of (*R*)-**2a**



(*R*)-**2a**
90% ee

(*R*)-**4a**
61%, 89% ee

Scheme 3. One-Pot Reaction from **5** to **2**[a]



6a; R^2 = Ph
6d; R^2 = 4-FC_6H_4
6h; R^2 = 4-MeC_6H_4

(*R*)-**2a**; **62%, 83% ee**
(*R*)-**2d**; **75%, 83% ee**
(*R*)-**2h**; **85%, 80% ee**

[a] Reactions were carried out using indoles **5** (1.1 equiv), α-amidosulfones **6**, $InBr_3$ (10 mol %), CN-**3f** (10 mol %), Cs_2CO_3 (2.0 equiv), and FBSM (1.1 equiv) in toluene (0.040 M) at rt to −10 °C for 6 d.

salt as a Lewis acid promoter (Scheme 3). In the first step, $InBr_3$ was used to catalyze the Friedel−Crafts alkylation of indoles **5** with α-amido sulfones **6**,[16] which are readily available from a commercial source.[17] As the result, following the in situ formation of arylsulfonyl indoles, the addition of FBSM, CN-**3f**, and Cs_2CO_3 furnished enantioenriched products **2** in moderate to high yields with high enantioselectivities. Compared with the results shown in Table 2, the ee's (%) of desired products **2** were slightly lower owing to the potential interaction of FBSM with indium salts.[7a] Thus, it is noteworthy that the addition of all reagents in one pot would lead to the formation of a Mannich-type adducts[9] that resulted from α-amidosulfones **6** and FBSM.

In conclusion, the PTC-catalyzed asymmetric monofluoromethylation of indole derivatives with FBSM via in situ generated vinylogous imino intermediates was achieved in high yields with high enantioselectivities for the first time. Both enantiomers of the products (*R*)-**2a** and (*S*)-**2a** with promised ee values can be accessible based on the alterability of the catalysts, CN-**3f** or CD-**3i**. The conjugate addition adducts would be useful building blocks for the synthesis of chiral monofluoromethylated 2-arylindoles. The method developed herein can also be extended into an asymmetric one-pot reaction. Further investigations of this reaction and applications to the synthesis of biologically interesting targets are underway in our laboratory.

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Supporting Information Available. Experimental details, X-ray crystal structure, analytical data (HRMS, HPLC), and copies of ^1H, ^{13}C, and ^{19}F NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.