Difluoromethylenation

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Stereoselective Difluoromethylenation Using Me_3SiCF_2SPh: Synthesis of Chiral 2,4-Disubstituted 3,3-Difluoropyrrolidines**

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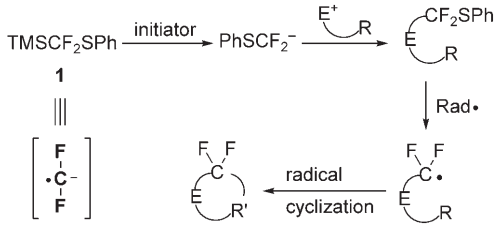
As the most electronegative element, fluorine has attracted enormous attention recently in the fields of agricultural and medicinal chemistry as well as in materials science.[1] Nowadays, the efficient and selective incorporation of fluorine atom(s) or fluorine-containing moieties into organic molecules to modulate their biological properties has become a routine and powerful strategy in drug design. Asymmetric fluorination and fluoroalkylation are two categories of fascinating reactions in organofluorine chemistry, and enantioselective electrophilic fluorinations and enantioselective nucleophilic monofluoromethylation represent the state-of-the-art achievements.[2] Currently, enantioselective trifluoromethylation and difluoromethylation are still very challenging topics with respect to stereoselectivity and generality, while highly diastereoselective trifluoromethylations and difluoromethylations have been achieved by using suitable chiral auxiliaries.[2a,3,4] In 2001 Prakash et al. reported an elegant diastereoselective nucleophilic trifluoromethylation of *N*-(*tert*-butylsulfinyl)imines using the Ruppert–Prakash reagent ($TMSCF_3$),[5] and recently we described highly diastereoselective nucleophilic difluoromethylations and monofluoromethylations using $PhSO_2CF_2H$ and $PhSO_2CH_2F$ as the di- and monofluoromethylating agents, respectively.[4]

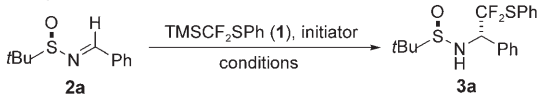
The pyrrolidine unit is ubiquitous in natural products, and recently it was found that the 3,3-difluoropyrrolidine moiety plays very important roles in a variety of enzyme inhibitors such as coagulation factor Xa (or thrombin) inhibitors[6c] and cathepsin inhibitors,[6d] among others.[6e–g] It was rationalized that fluorine substitution on the pyrrolidine moiety can decrease the basicity of the amine functionality and inhibit the enzymatic recognition processes and associated metabolic pathways, resulting in the enhanced biological activity and metabolic stability of a drug candidate.[6] However, we are not aware of any reports of the efficient synthesis of chiral 2,4-disubstituted 3,3-difluoropyrrolidines. As part of our continuing efforts in the development of efficient fluoroalkylation methodologies, herein we report a highly diastereoselective difluoromethylenation method using [difluoro(phenylthio)methyl]trimethylsilane (**1**, $TMSCF_2SPh$)[7] as a difluoromethylene radical anion equivalent. Using this appraoch, we effectively synthesized chiral 2,4-disubstituted 3,3-difluoropyrrolidines **7** from *N*-(*tert*-butylsulfinyl)imines **2** following a selective nucleophilic addition/radical cyclization strategy (Scheme 1).



Scheme 1. Use of $TMSCF_2SPh$ (**1**) as a difluoromethylene radical anion equivalent. TMS = Me_3Si.

First, we carried out the diastereoselective nucleophilic (phenylthio)difluoromethylation of (*R*)-(*tert*-butylsulfinyl)-imines **2** with reagent **1**. Compound **2a** was used as a model compound to study the reaction, and the reaction conditions were carefully tuned as shown in Table 1. We tried LiOAc, CsF, and tetrabutylammonium triphenyldifluorosilicate (TBAT) as the Lewis base initiators for the reaction and found that in all cases excellent diastereoselectivities (d.r. ≥ 99:1) were observed and that the use of 0.3–0.5 equivalents of TBAT in DMF solution gave the best yield of **3a** (Table 1, entries 3 and 5).

Table 1: Optimization of reaction conditions.



Entry	Reaction conditions[a]	d.r.[b]	Yield [%][c]
1	LiOAc (1.1 equiv), DMF	≥99:1	30
2	CsF (1.1 equiv), DMF	≥99:1	67
3	TBAT (0.5 equiv), DMF	≥99:1	75
4	TBAT (0.5 equiv), THF	≥99:1	57
5	TBAT (0.3 equiv), DMF	≥99:1	71
6	TBAT (0.2 equiv), DMF	≥99:1	64

[a] For entries 1 and 2, the reaction mixture was maintained at −40 °C for 2 h then at −20 °C for 4 h; for entries 3–6, the reaction was maintained at −40 °C for 1 h then at −20 °C for 4 h. [b] d.r. = (*Rs*,*S*)/(*Rs*,*R*), determined by ^{19}F NMR spectroscopy on a sample from the crude product mixture. [c] Yield of isolated product. DMF = *N*,*N*-dimethylformamide.

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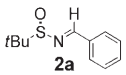
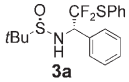
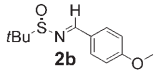
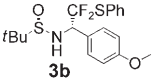
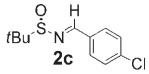
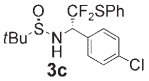
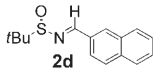
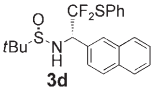
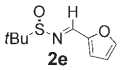
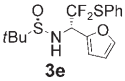
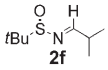
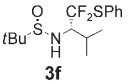
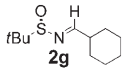
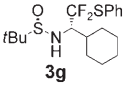
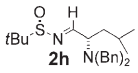
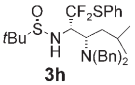
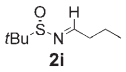
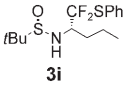
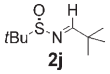
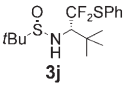
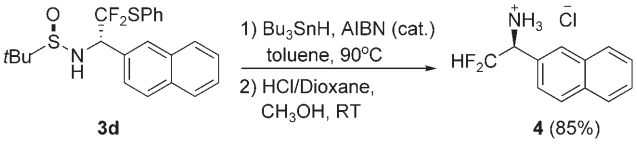
Eventually, we chose the reaction conditions listed under entry 3 (Table 1) as the standard conditions to study the scope of the reaction between imines **2** and **1**. The results are summarized in Table 2. High diastereoselectivity was observed in each case, and good yields were obtained with non-enolizable imines (Table 2, entries 1–5 and 10) and with imines that bear only one α-hydrogen atom (entries 6–8). However, relatively lower yields (30–45%) were obtained in the case of imine **2i**, which bears two α-hydrogen atoms (Table 2, entry 9). Careful TLC analysis revealed that imine **2i** disappeared shortly after the reaction was performed and indicates a labile enolization of **2i** under such basic conditions. Note that products **3** are useful precursors for the preparation of chiral α-difluoromethyl amines. For instance, (phenylthio)difluoromethylated sulfinamide **3d** was treated with Bu_3SnH/AIBN in toluene at 90 °C and the mixture was subjected to acid-catalyzed alcoholysis with HCl/MeOH to afford α-difluoromethyl 2-naphthalenemethanamine **4** (in salt form) in 85% yield (Scheme 2). The specific rotation of **4** was consistent with that of the (*S*)-α-difluoromethyl 2-naphthalenemethanamine salt we reported earlier.[4a] The result demonstrates that the stereochemical outcome of the (phenylthio)difluoromethylation reaction with imines **2** is orientated by a non-chelation-controlled addition mode.[4] Indeed, the present diastereoselective (phenylthio)difluoromethylation of *N*-(*tert*-butylsulfinyl)imines **2** provides an alternative approach for the preparation of homochiral α-difluoromethyl amines, which we previously synthesized by using $PhSO_2CF_2H$.[4a]

Table 2: Stereoselective (phenylthio)difluoromethylation of sulfinylimines **2** with $TMSCF_2SPh$.

Entry	Sulfinylimine **2**	Product **3**	Yield [%][a]	d.r.[b]
1	 **2a**	 **3a**	75	≥99:1
2	 **2b**	 **3b**	85	≥98:2
3	 **2c**	 **3c**	89	≥99:1
4	 **2d**	 **3d**	85	≥98:2
5	 **2e**	 **3e**	72	≥98:2
6	 **2f**	 **3f**	75	≥99:1
7	 **2g**	 **3g**	74	≥99:1
8	 **2h**	 **3h**	58	≥99:1
9	 **2i**	 **3i**	30 (45[c])	≥99:1
10	 **2j**	 **3j**	71	≥99:1

[a] Yields of isolated analytically pure material. [b] Diastereomeric ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture. [c] 1.0 equivalent of TBAT was used. Bn = benzyl.

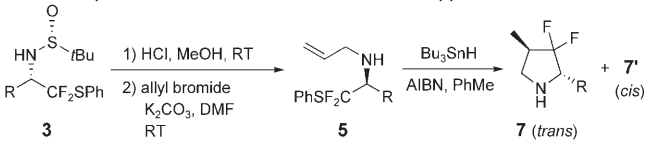
We transformed the above-obtained sulfinamides **3** to the N-allylated products **5** in good yields by acid-catalyzed alcoholysis to remove the *t*BuS(O) group, followed by N-allylation with allyl bromide. The results are summarized in Table 3. With the expectation that the F_2C–S bond could be cleaved homolytically under radical conditions,[8] we carried out the intramolecular radical cyclization reaction of **5** under thermal initiation in the presence of Bu_3SnH and a catalytic amount of AIBN. The cyclization reaction proceeded smoothly, and both *trans* products **7** and *cis* products **7′** were obtained in good yields, with 5-*exo* cyclization being favored exclusively (Table 3). ^{19}F NMR spectroscopic analysis of the crude mixture indicated that the diastereoselectivity (**7**/**7′**) was up to 11:1 (Table 3, entry 5). The absolute configuration of the major *trans* product **7a** (Table 3, entry 1) was confirmed by NOESY experiments (Scheme 3 and Supporting Information) and was consistent with our prediction based on a Beckwith–Houk transition-state model.[9] As shown in Table 3, the radical cyclization reaction gave good product yields and good diastereoselectivity with aryl-substituted substrates (Table 3, entries 1–3). With a 2-furyl group, the yield of **7d** was moderate and the diastereoselectivity dropped (Table 3, entry 4). For the alkyl-substituted substrates, a longer reaction time was required and afforded the cyclization products **7e** and **7f** in reasonable yields and with high diastereoselectivity (Table 3, entries 5 and 6). The present intramolecular cyclization reaction

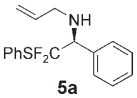
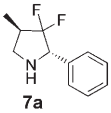
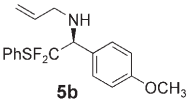
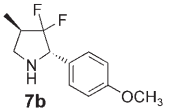
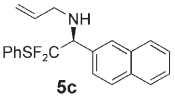
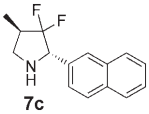
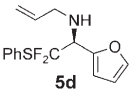
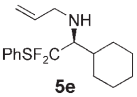
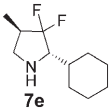
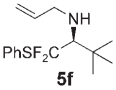
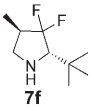


3d **4** (85%)

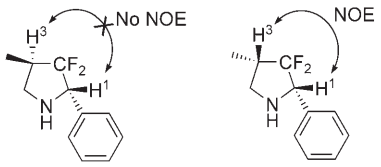
Scheme 2. Preparation of α-difluoromethyl amine salt **4** from **3d**. AIBN = azobis(isobutyronitrile).

Table 3: Stereoselective synthesis of 2,4-substituted 3,3-difluoropyrrolidines **7**.



Entry	Product **5**	Yield (**5**) [%][a]	Product **7**	Yield (**7**) [%][a]	d.r. (**7**/**7'**)[b]
1	 **5a**	78	 **7a**	75	11:1
2	 **5b**	76	 **7b**	71	9:1
3	 **5c**	75	 **7c**	77	10:1
4	 **5d**	72	 **7d**	43	5:1
5	 **5e**	72	 **7e**	52	11:1
6	 **5f**	61	 **7f**	50	10:1

[a] Yield of isolated product. [b] Diastereomeric ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture.



Scheme 3. Determination of configurations of **7a** and **7a'** with NOESY experiments.

provides a new method for the synthesis of pyrrolidines that contain a midchain *gem*-difluoromethylene (CF_2) moiety.

In summary, we have successfully developed a new synthetic application of $TMSCF_2SPh$ as a difluoromethylene radical anion synthon based on the selective ionic cleavage of its F_2C–Si bond and radical cleavage of its F_2C–S bond. Nucleophilic (phenylthio)difluoromethylation of (*R*)-(*N*-*tert*-butylsulfinyl)imines with $TMSCF_2SPh$ affords the corresponding products in good yields and with high diastereoselectivity (d.r. $\geq$ 98:2). The obtained $PhSCF_2$-containing sulfinamides can be further transformed into chiral 2,4-*trans*-disubstituted 3,3-difluoropyrrolidines through an intramolecular radical cyclization methodology.

Experimental Section

Typical procedures for the stereoselective (phenylthio)difluoromethylation of sulfinylimines **2** with $TMSCF_2SPh$ (**1**): TBAT (702 mg, 1.3 mmol) was added under N_2 atmosphere to a 30-mL Schlenk flask containing *N*-(*tert*-butylsulfinyl)aldimine (**2a**; 548 mg, 2.6 mmol) and $PhSCF_2TMS$ (734 mg, 3.0 mmol) in DMF (10 mL) at −40 °C. The reaction mixture was stirred at this temperature for 2 h, and then the temperature was raised to −20 °C and the reaction mixture was stirred for another 4 h. Aqueous saturated NH_4Cl solution (10 mL) was then added to the mixture at this temperature, and the mixture was extracted with EtOAc (25 mL × 3). The combined organic phase was dried over $MgSO_4$, and the volatile solvents were removed under reduced pressure. The crude product was further purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:3 v/v) to give product **3a** as a white solid (721 mg, 75% yield).

Typical procedure for preparation of the N-allylated products **5**: HCl/dioxane (4 N; 0.3 mL) was added under N_2 atmosphere into a 10-mL flask containing **3a** (443 mg, 1.2 mmol) in anhydrous methanol (5 mL). The reaction mixture was stirred at room temperature for 1 h, and then the solvent was removed to give the intermediate product, which was used in the next step without further purification. A mixture of the intermediate product and anhydrous K_2CO_3 (332 mg, 2.4 mmol) in DMF (5 mL) was stirred at room temperature until the intermediate product was consumed. Then H_2O (10 mL) was added, and the mixture was extracted with Et_2O. The combined organic phase was dried over $MgSO_4$, and the solvent was removed to give the crude product, which was further purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:30 v/v) to give product **5a** as an oil (286 mg, 78% yield).

Typical procedure for the intramolecular radical cyclization reaction of N-allylated compounds **5**: Bu_3SnH (0.38 mmol, 0.10 mL) and catalytic AIBN (2.0 mg) were added under N_2 atmosphere to a 10-mL Schlenk flask containing **5a** (76 mg, 0.25 mmol) in toluene (2 mL) at 90 °C, and the reaction mixture was then stirred at this temperature for 2 h. Then, another portion of AIBN (2.0 mg) was added and the reaction mixture was stirred for another 3 h. Aqueous saturated KF solution (10 mL) was then added to the mixture at room temperature, and the solution mixture was extracted with Et_2O (25 mL × 3). The combined organic phase was dried over $MgSO_4$, and the volatile solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:5 v/v) to give product **7a** as an oil (37 mg, 75% yield).

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