JOC *Note*

Trifluoromethylation of Salicyl Aldimines[†]

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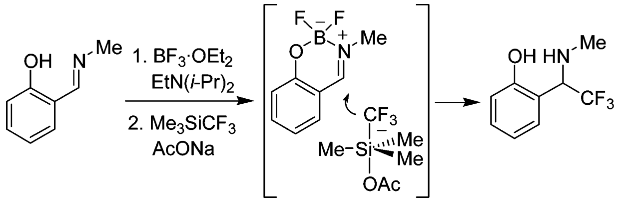

A method for the nucleophilic trifluoromethylation of salicyl aldimines, which do not contain an activating group at the nitrogen atom, has been described. The reaction proceeds through the initial generation of intramolecular boron complex followed by interaction with Me_3SiCF_3 activated by sodium acetate.

Organofluorine compounds have gained considerable attention due to their importance for the pharmaceutical and agrochemical industries.[1] In particular, substances with trifluoromethyl group, as well as methods for their preparation, have become a subject of intense investigations in recent years.[2−4]

Trifluoromethyltrimethylsilane, Me_3SiCF_3, turned out to be an especially useful reagent as an equivalent of trifluoromethyl carbanion for the direct introduction of the CF_3 group.[4a−c,5] The reactions using Me_3SiCF_3 are usually performed in the presence of Lewis base, and processes of this type are very well established for the trifluoromethylation of carbonyl compounds.[4a−c,6] At the same time, analogous addition of CF_3-carbanion to imines has a number of limitations associated mainly with low reactivity of C,N double bond.

Thus, while strongly biased substrates such as azirines,[7] imines of perfluorinated ketones,[8] or *N*-tosylated or sulfinylated[6b,9] imines can be successfully trifluoromethylated using Me_3SiCF_3, imines having an aryl group at nitrogen are markedly less reactive. In the latter case, the reaction requires employment of fluoride ion for the activation of Me_3SiCF_3 and proceeds with moderate yield.[10,11] Reactions of imines bearing an *N*-alkyl fragment with Me_3SiCF_3 are expected to be even more difficult and, to the best of our knowledge, are not described.

The studies performed by our group have demonstrated that the iminium cations serve as good electrophiles for the interaction with fluorinated silanes in the presence of weak Lewis bases, though these investigations mainly focused on the transfer of C_6F_5 group.[12,13]

In this respect, it seemed reasonable to propose that the electrophilicity of imines can be increased by complexation with Lewis acids.[14] However, the major problem in this case is that to activate Me_3SiCF_3 rather strong Lewis bases such as fluoride, alkoxide, carbonate, or acetate anions are required (Scheme 1, path a).[15] As a result, given that the activation of both imine and the silane constitute an equilibrium processes, the Lewis

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[†] This paper is dedicated to Professor Herbert Mayr on the occasion of his 60th birthday.

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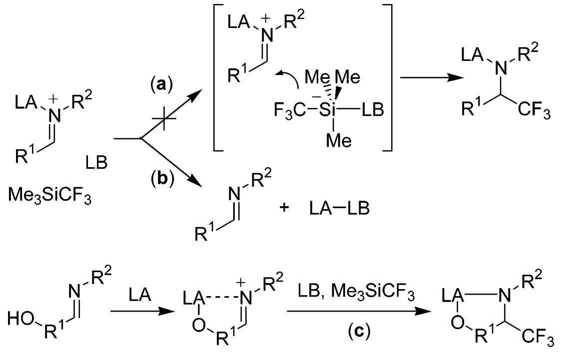
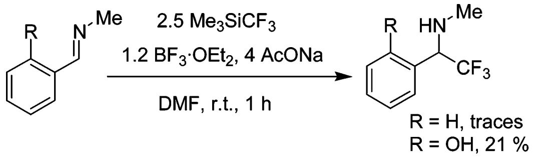
SCHEME 1. Trifluoromethylation of Imines

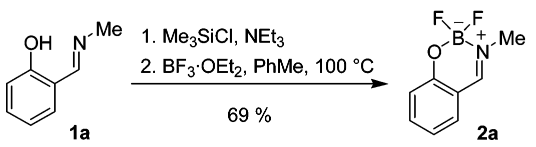


acid and base will quench each other (path b). Herein we report another approach, where the activation of the imine occurs intramolecularly through the chelation with adjacent hydroxyl group, thereby allowing for the favorable Lewis acid/Lewis base combination (path c).

We began our studies from the interaction of *N*-methylimines of benzaldehyde and salicyl aldehyde with Me$_3$SiCF$_3$. Boron trifluoride etherate and sodium acetate[6b] were used for the activation of imines and silane, respectively, performing the reaction in DMF at room temperature (eq 1).



(1)



(2)

While only traces of product were observed with benzaldimine, the reaction of salicyl aldimine provided the corresponding trifluromethylated amine in 21% isolated yield. The presence of *o*-hydroxy group clearly suggested the possibility of intermediate formation of difluoroboron ether capable of chelation with the imine nitrogen. The boron chelate **2a** was synthesized from *N*-methylsalicylaldimine by means of silylation with subsequent silicon/boron exchange (eq 2).

Complex **2a** was isolated in individual form as stable and moisture insensitive compound, and its structure was established by NMR spectroscopy and X-ray diffraction analysis (Figure 1).[16]

It was rewarding to find that complex **2a** smoothly reacted with Me$_3$SiCF$_3$ in the presence of sodium acetate providing amine **3a** in 88% yield after workup with aq Na$_2$CO$_3$[17] (Table 1, entry 1). Dimethylformamide was found to be the best solvent, with tetrahydrofuran and acetonitrile being completely inefficient.[18] Trifluoromethylation can be performed even with catalytic amount of AcONa, but longer reaction time is needed (entry 5).

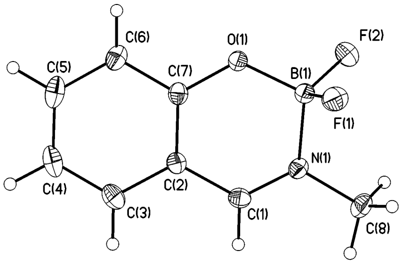
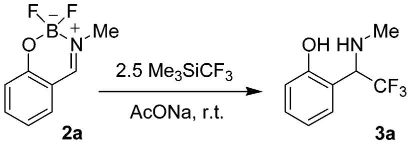


FIGURE 1. X-ray structure of chelate **2a** presented in thermal ellipsoids at 50% probability (except hydrogen atoms).

TABLE 1. Reaction of Complex 2a with Me$_3$SiCF$_3$



entry	solvent	AcONa (equiv)	time	yield of **3a**,[a] %
1	DMF	4	1 h	88
2	DMF	4	15 min	85
3	THF	4	15 min	-
4	MeCN	4	15 min	<5[b]
5	DMF	0.1	6 h	73
6	DMF	-	6 h	11[b]

[a] Isolated yield. [b] Yield determined by NMR with internal standard.

Though the boron chelate **2a** can be trifluoromethylated quite cleanly, its isolation in individual form is inconvenient, and a more practical one-step protocol is desired. A series of experiments was performed to optimize trifluoromethylation procedure involving quantitative generation of complex **2a** (Table 2).

Treatment of imine **2a** with 1.2 equiv of potassium *tert*-butoxide followed by addition of 2.5 equiv of boron trifluoride presumably gave a solution of complex **2a** together with KBF$_4$. Subsequent addition of Me$_3$SiCF$_3$ (2.5 equiv) and sodium acetate (4 equiv) provided amine **3a** in 58% yield (entry 1). The yield of the final product could be increased when the generation of boron chelate and trifluoromethylation are performed in different solvents (entry 2). After further optimization, it was found that employment of Hünig's base in dichloromethane for 2 h, evaporation of solvent, and addition of DMF, Me$_3$SiCF$_3$, and sodium acetate furnished the target product in 86% isolated yield (entry 4).

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(14) (a) For example, BF$_3$ efficiently promotes addition of organometallic reagents to imines. Ma, Y.; Lobkovsky, E.; Collum, D. B. *J. Org. Chem.* **2005**, *70*, 2335. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (c) For BF$_3$-mediated addition of perfluoroalkyllithiums to imines see: Uno, H.; Okada, S.; Shiraishi, Y.; Shimokawa, K.; Suzuki, H. *Chem. Lett.* **1988**, *7*, 1165. However, trifluoromethyllithium and magnesium reagents are highly unstable and cannot be used.

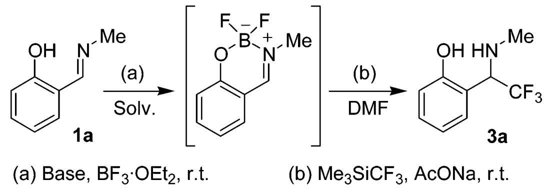
(15) The reactions of Me$_3$SiCF$_3$ are believed to proceed through the five-coordinate siliconate species. For mechanistic discussions, see ref 6 and: (a) Maggiarosa, N.; Tyrra, W.; Naumann, D.; Kirij, N. V.; Yagupolskii, Y. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2252. (b) Kolomeitsev, A.; Bissky, G.; Lork, E.; Movchun, V.; Rusanov, E.; Kirsch, P.; Röschenthaler, G.-V. *Chem. Commun.* **1999**, 1017.

(16) For chelate boron complexes derived from salicyl aldimines, see: (a) Keizer, T. S.; De Pue, L. J.; Parkin, S.; Atwood, D. A. *J. Organomet. Chem.* **2003**, *666*, 103. (b) Mitra, A.; DePue, L. J.; Struss, J. E.; Patel, B. P.; Parkin, S.; Atwood, D. A. *Inorg. Chem.* **2006**, *45*, 9213. (c) Vedejs, E.; Chapman, R. W.; Lin, S.; Müller, M.; Powell, D. R. *J. Am. Chem. Soc.* **2000**, *122*, 3047.

(17) Special experiments demonstrated that no trifluoromethylation of **2a** with Me$_3$SiCF$_3$ occurs on workup with saturated aqueous Na$_2$CO$_3$.

(18) It was demonstrated by Mukaiyama that for successful activation of Me$_3$SiCF$_3$ by acetate anion it is necessary to employ sodium or potassium acetate in DMF or tetrabutylammonium acetate in any other solvent, thereby suggesting that the role of DMF is merely to solvate the alkali metal cation; see ref 6b.

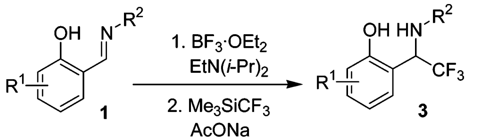
TABLE 2. One-Pot Procedure for the Synthesis of 3a

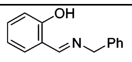
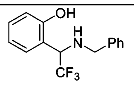
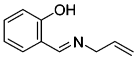
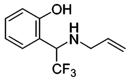
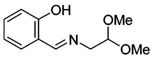
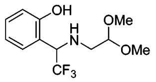
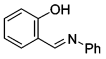
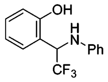
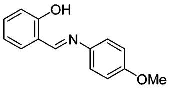
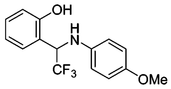
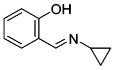
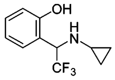
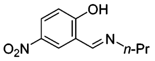
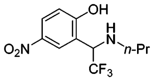
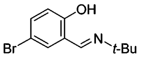
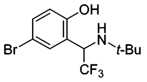
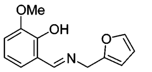
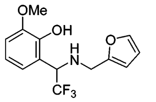
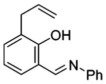
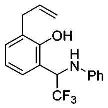


entry	base	solvent	time, h step (a)	time, h step (b)	yield of **3a**,[a] %
1	*t*-BuOK	DMF	1	1	58
2	*t*-BuOK	THF	1	1	79
3	EtN(*i*-Pr)$_2$	DMF	1	1	70
4	EtN(*i*-Pr)$_2$	CH_2Cl_2	2	3	86

[a] Isolated yield.

TABLE 3. Trifluoromethylation of Salicyl Aldimines[a]



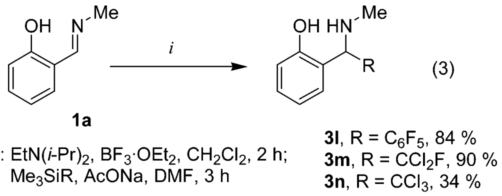
entry	imine	product		yield of **3**, %[b]
1		**1b**		96
2		**1c**		87
3		**1d**		90
4		**1e**		90
5		**1f**		89
6		**1g**		82
7		**1h**		80
8		**1i**		85
9		**1j**		92
10		**1k**		88

[a] First step: 1.2 equiv of EtN(*i*-Pr)$_2$, 2.5 equiv of $BF_3{\cdot}OEt_2$, 0.5 M CH_2Cl_2, rt, 2 h. Second step: 2.5 equiv of Me_3SiCF_3, 4 equiv of AcONa, 0.5 M DMF, rt, 3 h. [b] Isolated yield.

Under the optimized conditions, a variety of imines entered into reaction with boron trifluoride and Me_3SiCF_3 affording products of trifluoromethylation in excellent yields (Table 3). The nitrogen atom of the substrate may have aliphatic and aromatic substituents, cyclopropyl and allyl groups, as well as acid-sensitive acetal fragment and furyl ring (entries 3 and 9). However, imine derived from 2-hydroxynaphtaline-1-carbaldehyde and *p*-methoxyaniline turned out to be completely unreactive. The reason for this failure is not clear at present. Unfortunately, other types of imines bearing adjacent hydroxyl function such as imines obtained from benzaldehyde and *o*-aminophenol, aminoethanol, or 3-amino-1-propanol also did not give the products of trifluoromethylation.

It should be pointed out that the presented method for the synthesis of compounds **3a**−**k** is advantageous over that mentioned in the literature. Thus, the Lewis acid mediated interaction of phenol with imines of trifluoroacetaldehyde was reported, but in all cases mixtures of ortho- and para-substituted products were obtained with the yields of ortho isomers not exceeding 25%.[19]

Besides the trifluoromethyl group, pentafluorophenyl-, dichlorofluromethyl-, and trichloromethyl groups can be transferred from corresponding silanes using the above-described procedure (eq 3). However, allyltrimylsilane did not afford the allylation product.



In summary, a new approach for the trifluoromethylation of unreactive C=N double bond using Me_3SiCF_3 furnishing amines with α-CF_3-group has been described. The intramolecular activation of the imines through the formation of difluoroboron chelates constitutes the key feature of the described reaction. Our future studies will be devoted to the employment of the chelation-induced activation of C=N double bond in the trifluoromethylation processes.

Experimental Section

Trifluromethylation of Salicyl Aldimines. General Procedure. $BF_3{\cdot}OEt_2$ (317 μL, 2.5 mmol) was added dropwise to a solution of imine **1** (1.0 mmol) and EtN(*i*-Pr)$_2$ (198 μL, 1.2 mmol) in CH_2Cl_2 (2 mL) at 0 °C, and the mixture was stirred for 2 h at room temperature. The solvent was evaporated in a vacuum followed by successive addition of DMF (2 mL), Me_3SiCF_3 (370 μL, 2.5 mmol), and AcONa (328 mg, 4 mmol), and the resulting mixture was stirred for 3 h at room temperature. For the workup, saturated aqueous Na_2CO_3 (1 mL) was added dropwise, and the mixture was diluted with water (10 mL), extracted with ether/hexanes (1 : 1, 4 × 5 mL), and dried (Na_2SO_4). Evaporation of the solvent afforded crude product, which was chromatographed on silica gel eluting with hexanes/ethyl acetate.

2-[2,2,2-Trifluoro-1-(methylamino)ethyl]phenol (3a). Chromatography: hexanes/EtOAc, from 10:1 to 3:1, $R_f = 0.37$ (hexanes/EtOAc, 4:1). Mp: 58−59 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 2.30 (br s, $\Delta\nu_{1/2} = 200$ Hz, 1H), 2.49 (s, 3H), 4.20 (q, 1H, $J = 7.7$), 6.82−6.93 (m, 2H), 7.07 (d, 1H, $J = 7.2$), 7.28 (t, 1H, $J = 7.2$), 10.72 (br s, $\Delta\nu_{1/2} = 160$ Hz, 1H). ^{13}C NMR ($CDCl_3$): 33.6, 66.8 (q, $J = 29.3$), 114.0, 117.1, 119.2, 124.9 (q, $J = 282$), 130.5, 131.0, 158.2. ^{19}F NMR ($CDCl_3$): −76.0 (d, $J = 7.7$). Anal. Calcd for

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[19] (a) Gong, Y.; Kato, K.; Kimoto, H. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2637. (b) Gong, Y.; Kato, K.; Kimoto, H. *Synlett* **2000**, 1058.

$C_9H_{10}F_3NO$ (205.18): C, 52.68; H, 4.91; N, 6.83. Found: C, 52.54; H, 4.92; N, 6.84.

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Supporting Information Available: Experimental procedures; spectroscopic, analytical, and X-ray data (CIF) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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