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N-Fluoro-Bis[(trifluoromethyl)sulfonyl]Imide: Electrophilic Fluorination of Imines and Some Methyl-Substituted Pyridines

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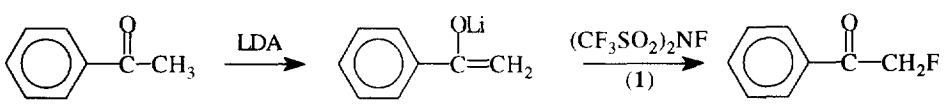
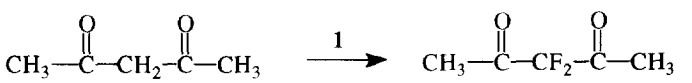
Abstract: Direct fluorination of imines with *N*-fluoro-bis[(trifluoromethyl)sulfonyl]imide **1** afforded mono and/or difluoroketones without the need of a strong base to first generate the imine anions. Structurally related 2- and 4- methyl-substituted pyridines gave the respective fluoromethyl pyridines with **1**. Our results suggest that an enamine intermediate plays a key role in these reactions.

INTRODUCTION

Selective fluorination of organic compounds continues to be an active area of research. A variety of fluorinating reagents and methodologies have been introduced to fulfill the increasing demand for site selective fluorinated organic compounds.[1] Recently, *N*-fluoro compounds have appeared as one of the most attractive reagents for fluorination. The fluorination of enolates and related derivatives by these *N*-fluoro compounds (e.g. *N*-fluorobenzenesulfonimide, *N*-fluoroquinuclidinium fluorides, *N*-fluoropyridinium salts, *N*-fluorosultams, *N*-fluoro-*n*-alkanesulfonamides...) has become one of the most widely-used methods for selective carbon-fluorine bond formation.[2]

Since the first synthesis of *N*-fluoro-bis[(trifluoromethyl)sulfonyl]imide **1** in 1987,[3] we have successfully employed this reagent in the fluorination of several types of carbonyl compounds.[4] The lithium enolates of monocarbonyl substrates were selectively fluorinated when treated with the *N*-fluoro imide **1**. For





β-diketones, the fluorination can be accomplished by simple addition of **1** to the substrate solution in chloroform. In order to further explore the synthetic utility of *N*-fluoro imide **1**, we have investigated the fluorination of several imines and methyl-substituted pyridines.

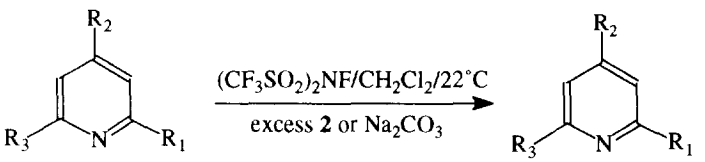
RESULTS AND DISCUSSION

As the nitrogen analogs of enols and enolates, enamines and imine anions have proven to be quite useful alternatives as reactive intermediates for the introduction of an electrophile on the α-carbon of a carbonyl group. This reactivity was demonstrated in fluorination of enamines with *N*-fluoro compounds to give corresponding fluoroketones,[5] but the use of imines directly has not been reported. It is well-known that imines are easily

prepared from primary alkyl amines and ketones or aldehydes, and the products obtained after an electrophilic substitution reaction can be easily converted back to the carbonyl compounds using mild aqueous hydrolysis. Generally, the direct electrophilic substitution of imines will not take place and in most cases the imine anions are required.

Straightforward methods for the preparation of 2- or 4- fluoromethyl pyridines are not available. 2-Fluoro-4-methylpyridine was the main product when direct fluorination was performed on 4-picoline by F_2/N_2.[6] Anders, et. al. reported that 4-fluoromethylpyridine was prepared from 4-chloromethylpyridine using activated tetrabutylammonium fluoride (TBAF).[7] In a study of the fluorination of alkyl-substituted pyridines with **1**,[8] we found that fluoromethyl derivatives could be obtained in moderate yield.

Scheme 1



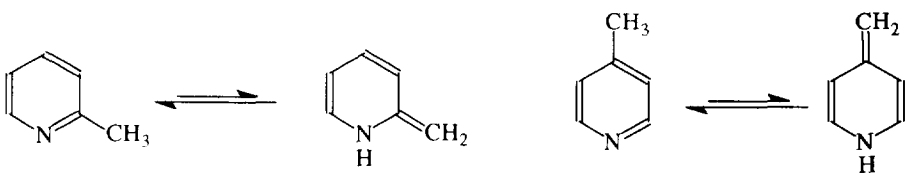
2 a-c **3 a-c**

Entry	Substrate	Product	Yield (%)[a]
1	**2a**. $R_1=R_2=R_3=CH_3$	**3a**. $R_1=CH_2F$, $R_2=R_3=CH_3$	52
2	**2b**. $R_1=CH_3$, $R_2=R_3=H$	**3b**. $R_1=CH_2F$, $R_2=R_3=H$	20[b]
3	**2c**. $R_1=R_3=H$, $R_2=CH_3$	**3c**. $R_2=CH_2F$, $R_1=R_2=H$	72

a. isolated yield after purification by chromatography; b. ^{19}F NMR yield.

Along with the fluorinated products,bis[(trifluoromethyl)sulfonyl]imide **4** was produced as a coproduct. Previous work[9] has shown that **4** is a very strong acid which reacts with pyridines readily to form pyridinium salts. We prepared the corresponding pyridinium bis[(trifluoromethyl)sulfonyl]imides from picolines and **4**. We observed no fluorination of these pyridinium salts under the same reaction conditions. Therefore, removal of **4** as it is formed is necessary to increase the yield of the fluorinated products. This can be accomplished by using an excess of the pyridine or by adding sodium carbonate. A trace amount of 4-difluoromethylpyridine was found in the reaction of 4-picoline.[10] Besides the fluoromethyl products, some fluoropyridines were also obtained , such as 3-fluoro-2,4,6-collidine in 21% yield starting from 2,4,6-collidine.[11]For 2- or 4- methyl substituted pyridines, there are equilibria between the two tautomers **2** and **5** even though the methyl forms are greatly favored.[12] The pK_T values of these equilibria are 13.3 and 13.4 respectively.Tautomers have an

Scheme 2



2b **5b** **2c** **5c**

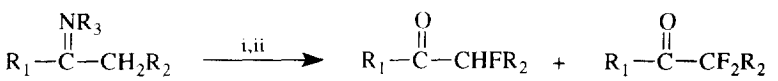
enamine-like structure, and the fluorination of enamines by electrophilic fluorinating reagents is an established reaction.[5] We suggest that fluorination takes place on the methylene site of the enamine and one proton is removed to yield the fluoromethylpyridine. When 2- or 4- methyl substituted pyridines were first converted to corresponding pyridinium salts, no fluoromethyl derivatives were observed due to the absence of required tautomer **5**. Also, under the same reaction conditions, no fluorination of 3,5-lutidine was observed.

So far, no synthetically useful direct fluorination of monocarbonyl compounds by electrophilic reagents has been reported. In most cases, the fluorinated compounds were only obtained by first derivatizing the carbonyl substrates. Fluorination of lithium enolates has proven to be an effective method for α-fluorination, but there are some monocarbonyl substrates (e.g. bromo-substituted compounds) which can not survive the metallation step. Both enamines and imines provide important alternatives to overcome this problem. Practically, imines are much easier to prepare than enamines, and chiral imines are very useful intermediates in asymmetric synthesis.[13] From the reaction of 2- and 4- methyl substituted pyridines with **1**, we assumed that imines might react with **1** directly without using a strong base to generate the imine anions. This assumption proved to be correct.

As in the fluorination of pyridine derivatives, bis[(trifluoromethyl)sulfonyl]imide **4** will form as a coproduct. Sodium carbonate was added to neutralize **4** as it was generated. The reactions were carried out at room temperature and were slightly exothermic. After the fluorination, the imines were hydrolyzed to give the corresponding fluorinated ketone products which were then isolated. The presence of small amounts of H_2O was not very critical to the success of the reaction, but higher yields were obtained using anhydrous solvents. In most cases, the reaction was complete within 5 hours at 22 °C.

When one equivalent of **1** was used, both monofluoro and difluoro products were formed. Unfortunately, the reaction could not be stopped at the monofluoro stage. By varying the ratio between the imines **6** and *N*-fluoro imide **1**, the amount of one of the products could be increased. Monofluoroketones **7** were obtained in 20 to 30% yield (based on the imines) when 0.67 equivalent of **1** was used. Difluoro products **8** were obtained exclusively by using more than two equivalents of *N*-fluoro imide **1**. These fluorinations are summarized in Scheme 3 and Table 1. When free amine was present in the reaction mixture, the formation of (trifluoromethyl)sulfonyl fluoride and other products were detected and as a result, yields of the fluoroketones dramatically decreased.[14] Imines containing an α-hydrogen are capable of imine-enamine tautomerism.[13a]

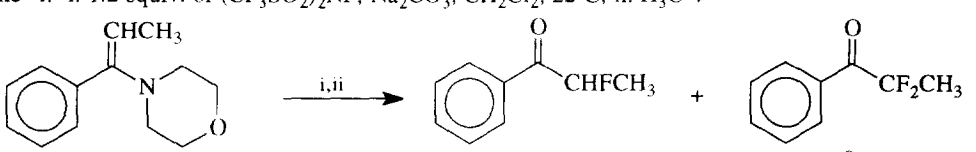
Scheme 3: i. 0.67 or 2.4 equiv. of $(CF_3SO_2)_2NF$, CH_2Cl_2, Na_2CO_3, 22 °C; ii. H_3O^+



6 **7** **8**

Compared with the keto-enol tautomerism, the imines are more easily tautomerized to give the enamines. In the preparation of imines of ethyl 2-oxocyclopentylacetate, we found that the enamines were formed rather than the imines. *N*-Fluoro imide **1** reacted with 1-morpholino-1-phenylpropene **9** to give mainly α-

Scheme 4: i. 1.2 equiv. of $(CF_3SO_2)_2NF$, Na_2CO_3, CH_2Cl_2, 22°C; ii. H_3O^+.

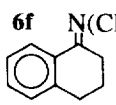
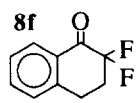
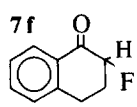
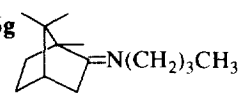


9 **7c** 54% **8c** 6%

fluoropropiophenone **7c** after hydrolysis. In the fluorination of imines **6**, we attribute the predominate formation of the difluoro product to the apparent more facile formation of the enamine from the monofluorinated imine. This same effect was observed in the fluorination of a variety of β-dicarbonyl compounds with **1**.[4b] A possible explanation may be that monofluorination increases the acidity of remaining hydrogen, but this is highly speculative. After adding an aqueous HCl solution, both monofluoro imines and difluoro imines were hydrolyzed to the corresponding ketones. So far, no trifluoro products have been found. We used imine **6e** as an example to demonstrate the merit of this method for a substrate which cannot be

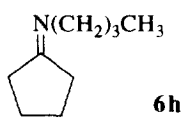
converted to the imine anion by metallation. A proposal summarizing these results for **6a** is shown in Scheme 5.

Table 1. Reaction of imines and *N*-fluoro imide **1**

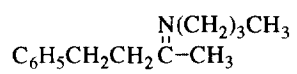
Entry	Imine	Ratio (**1**/**6**)	Product	Yield (%)[a]	
				7	**8**
1	**6a** R_1=C_6H_5, R_2=H,	2.4	**8a** $C_6H_5COCF_2H$	---	82
	R_3=*n*-Pr	0.67	**7a** $C_6H_5COCFH_2$ + **8a**	33[b]	15[b]
2	**6b** R_1=4'-$CH_3C_6H_4$,	2.4	**8b** 4'-$CH_3C_6H_4COCF_2H$	---	83
	R_2=H, R_3=*n*-Pr	0.67	**7b** 4'-$CH_3C_6H_4COCFH_2$ + **8b**	36[b]	16[b]
3	**6c** R_1=C_6H_5, R_2=CH_3,	2.4	**8c** $C_6H_5COCF_2CH_3$	---	58
	R_3=*n*-Pr	0.67	**7c** $C_6H_5COCFHCH_3$ + **8c**	38[b]	17[b]
4	**6d** R_1=4'-$CH_3OC_6H_4$,	2.4	**8d** 4'-$CH_3OC_6H_4COCF_2H$	---	70
	R_2=H, R_3=*n*-Bu	0.67	**7d** 4'-$CH_3OC_6H_4COCFH_2$ + **8d**	26	17
5	**6e** R_1=4'-BrC_6H_4,	2.4	**8e** 4'-$BrC_6H_4COCF_2H$	---	78
	R_2=H, R_3=*n*-Bu	0.67	**7e** 4'-$BrC_6H_4COCFH_2$ + **8e**	30	16
6	**6f** 	2.4	**8f** 	---	65
		0.67	**7f**  + **8f**	22	12
7	**6g** 	2.4	—	0	0

a. isolated yield based on imine; b. ^{19}F NMR yield, not isolated as pure compound.

Fluorination of the *N*-butyl imines of cyclopentanone and *n*-phenyl-2-butanone, **6h** and **6i**, respectively by **1** was successful, but more than two fluorination products were observed in both reactions. This can be explained by the presence of more than one site capable of undergoing fluorination in **6h**, C-2 and C-5 and **6i**, C-1 and C-3. These results indicate an obvious limitation to this methodology.



6h



6i

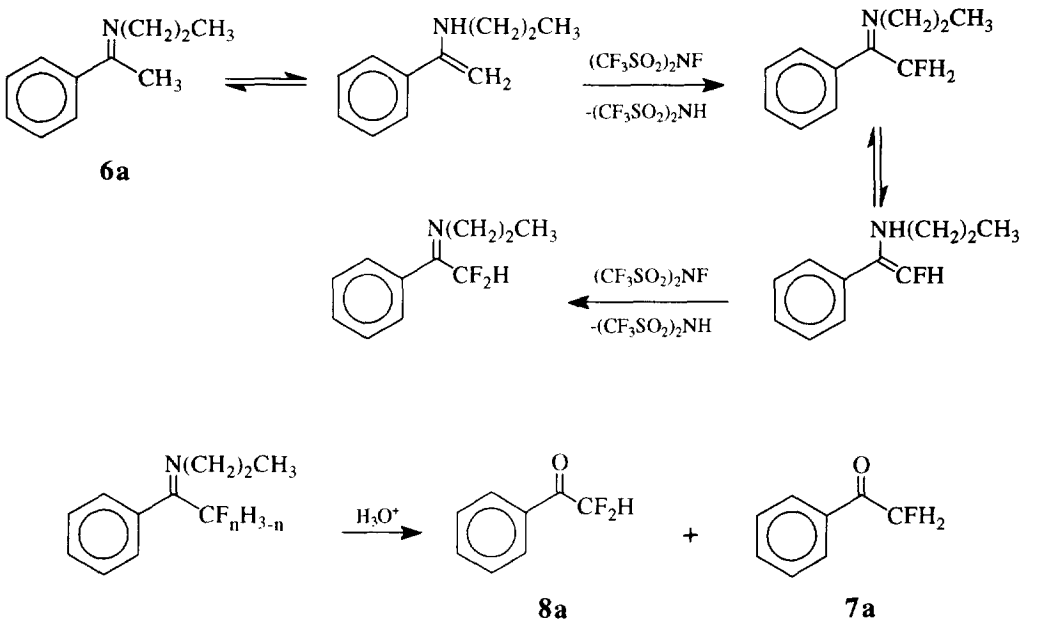
It is noteworthy that no fluorination was observed with imine **6g**. This is probably due to the lack of isomerization caused by the rigid skeleton of imine **6g**.

CONCLUSION

Fluorination of imines by *N*-fluoro-bis[(trifluoromethyl)sulfonyl]imide **1** is a synthetically useful alternative to the preparation of α–fluorinated ketones *via* the corresponding enolates. The mild reaction conditions and good yields of this reaction are promising features for applications in the synthesis of highly functionalized molecules. Because of the availability of various chiral primary amines, this method should provide an attractive approach to asymmetric synthesis of organofluorine compounds. We are currently extending our studies to asymmetric variants of this protocol.

The fluorination of methyl-substituted pyridines, which contain imine-like structures, suggests that these molecular arrays commonly present in many natural products may also be fluorinated with **1**. Thus the use of **1** in site selective fluorination of organic compounds continues to show great promise in organic synthesis.

Scheme 5



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EXPERIMENTAL SECTION

All reactions were performed in glass apparatus. Dichloromethane was dried over 3Å molecular sieves before use. Other commercially available reagent grade solvents were employed without purification. Pyridines, ketones and amines were obtained from Aldrich and Lancaster. **1** was prepared by the literature method.[3a,3b] Caution! **1** is a strong oxidizer and must be handled with care. Neat **1** should not be allowed to contact strong bases or easily oxidized substrates. Flash column chromatography on silica gel was performed as described in the original paper[15]. ^{19}F (188 MHz) and ^{1}H (200 MHz) NMR were recorded on an IBM NR 200AF instrument and ^{13}C (75 MHz) NMR on a Bruker AC 300 using $CFCl_3$ and TMS as internal references. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer. Mass spectra were recorded using a Fisons Trios 1000 GC-MS system.

Fluorination of Methyl-Substituted Pyridines. In a typical reaction, a solution of the *N*-fluoro imide **1** (160 mg, 0.53 mmol) in anhydrous CH_2Cl_2 (2 mL) was stirred with anhydrous Na_2CO_3 (50 mg) for 15 minutes and a solution of 4-picoline **2c** (40 mg, 0.43 mmol) in the same solvent (2 mL) was added dropwise. After stirring overnight, a saturated aqueous $NaHCO_3$ solution (5 mL) was added and the mixture was heated to 50 °C for one hour. After cooling to 22 °C, the solution was poured into a saturated NaCl solution (30 mL) and extracted with ether (20 mL × 3). The combined ether extracts were washed with brine, then dried (Na_2SO_4), and concentrated in vacuum. Pure 4-fluoromethylpyridine **3c** was isolated in 72% yield after flash chromatography (*n*-pentane/diethyl ether (2:1)).

4,6-Dimethyl-2-fluoromethylpyridine (3a). Two equivalents of 2,4,6-collidines **2a** were used. A pure sample of **3a** was obtained by preparative TLC with ether as the eluant. ^{1}H NMR (C_6D_6) δ 1.66 (3H, s), 2.33 (3H, s), 5.30 (2H, d, *J*=47.3Hz), 6.43 (1H, s); ^{19}F NMR (C_6D_6) δ -220.6 (t, *J*=47.4Hz).

2-Fluoromethylpyridine (3b). A pure sample of **3b** was obtained by flash chromatography (*n*-pentane/diethyl ether (2:1)). ^{1}H NMR ($CDCl_3$) δ 5.42 (2H, d, *J*=46.9Hz), 7.15 (1H, m), 7.39 (1H, d, *J*=7.7Hz), 7.68 (1H, t-d, *J*=7.6, 1.3Hz), 8.51 (1H, d, *J*=4.6Hz,); ^{19}F NMR ($CDCl_3$) δ -221.6 (t, *J*=46.8Hz), Mass spectrum m/e (EI) 111 (M^+).

4-Fluoromethylpyridine (3c). A pure sample of **3c** was obtained by flash chromatography (*n*-pentane/diethyl ether (2:1)). ^{1}H NMR ($CDCl_3$) δ 8.6 (2H, br.), 7.0-7.1 (2H, m), 5.36 (2H, d, *J*=46.4Hz); ^{19}F NMR ($CDCl_3$) δ -221.8 (t, *J*=46.2Hz); Mass spectrum m/e (EI) 111 (M^+).

Preparation of Imines and Enamines. In a typical reaction, *n*-butyl amine (10 mL, 100 mmol) and 4'-methoxyacetophenone (12.0 g, 80 mmol) were dissolved in 100 mL of benzene or toluene in a 250-mL flask attached a Dean-Stark trap arranged for azeotropic removal of water, and heated to reflux until the theoretical amount of water was collected in the trap. Zinc chloride (0.1g) was added as catalyst. Removal of the solvent and distillation of the oil residue gave 14.5 g (91%) of a clear liquid **6d** (90-93 °C/4 torr).

In a similar fashion, the other ketones were converted to their imines and/or enamines by using *n*-propyl or *n*-butyl amines and morpholines. ^{1}H NMR and IR spectra were those expected for all imines and enamines.

Fluorination of Imines and Enamines. In a typical reaction, a solution of *N*-fluoro imide **1** (360 mg, 1.2 mmol) in anhydrous CH_2Cl_2 (5mL) was stirred with anhydrous Na_2CO_3 (0.1g) for 15 minutes. A solution of *N*-(1-4'-bromophenylethylidene)-*n*-butylamines **6e** (130 mg, 0.5 mmol) in the same solvent (5mL) was then added dropwise with stirring at room temperature. The resulting solution was stirred for five hours and a 1N aqueous HCl (20 mL) was poured into the reaction mixture. The organic layer was separated and the aqueous phase was extracted with diethyl ether (3 × 20mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed at a rotary evaporator. The residue was flash-chromatographed (*n*-pentane/diethyl ether (30:1)) to give the pure fluorination product **8e** in 78% yield (90 mg). When imine **6e** reacted with 0.67 equivalents of *N*-fluoro imide **1**, monofluorinated ketone **7e** was obtained in about 30% yield in addition to difluorinated ketone **8e**. In the latter reaction, the imine solution has to be added to the *N*-fluoro imide **1** solution in one portion to increase the amount of monofluorinated product. **7a**, **7b** and **7c** were characterized from a mixture with unfluorinated ketones. The spectral data are in agreement with the literature values.[16] The fluorination of enamine **9** was carried out following the same procedure as imines. The enamine solution was added to 1.2 equivalents of *N*-fluoro imide **1** in CH_2Cl_2. Both α-fluoropropiophenone (54% yield) and α,α−difluopropiophenone (6% yield) were isolated by chromatography.

2,2-Difluoroacetophenone (8a). ^{1}H NMR ($CDCl_3$) δ 6.30 (1H, t, *J*=53.5Hz), 7.5-8.1 (5H, m); ^{19}F NMR ($CDCl_3$) δ -121.1 (d, *J*=53.5Hz); IR (neat) 1713 cm^{-1}; Mass spectrum (EI) m/e 156 (1, M^+), 105 (100, M-CF_2H).

2-Fluoroacetophenone (7a). ^{1}H NMR ($CDCl_3$) δ 5.58 (2H, d, *J*=46.9Hz), 7.4-7.9 (5H, m); ^{19}F NMR($CDCl_3$) δ –220.2(t, *J*= 47.1Hz).

2,2-Difluoro-4'-methylacetophenone (8b). ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 6.21 (1H, t, *J*=53.6Hz), 6.93, 8.22 (4H, AB *J*=8.1Hz); ^{19}F NMR ($CDCl_3$) δ -122.4 (d-t, *J*=53.6, 1.0Hz); ^{13}C NMR ($CDCl_3$) δ 187.1, 146.1, 129.6,128.9, 111.1 (t, *J*=252.7Hz), 21.8; IR (nujol) 1706cm^{-1}; Mass spectrum (EI) m/e 170 (4, M^+), 119 (100, M^+-CF_2H).

2-Fluoro-4'-methylacetophenone (7b). ^{1}H NMR ($CDCl_3$) δ 2.34 (3H, s), 5.42 (2H, d, *J*=47.0Hz), 7.00, 7.93 (4H, AB, *J*=7.8Hz); ^{19}F NMR ($CDCl_3$) δ -218.5 (t, *J*=47.4Hz).

2,2-difluoropropiophenone (8c). ^{1}H NMR ($CDCl_3$) δ 1.90 (3H, t, *J*=19.5Hz), 7.4-8.2 (5H, m); ^{19}F NMR ($CDCl_3$) δ -93.3 (q, *J*=19.5Hz); IR (neat) 1700cm^{-1}; Mass spectrum (EI) m/e 170 (2, M^+), 105 (100, M^+-CF_2CH_3).

2-Fluoropropiophenone (7c). ^{1}H NMR ($CDCl_3$) δ 1.60 (3H, d-d, *J*=6.8, 24.0Hz), 5.70 (1H, *J*=6.8, 48.6Hz), 7.4-7.9 (5H, M); ^{19}F NMR ($CDCl_3$) δ -183.3 (d-q, *J*=24.1, 48.6Hz); Mass spectrum (EI) m/e 152

(2, M^+), 105 (100, M^+-$CFHCH_3$).

2,2-Difluoro-4'-methoxyacetophenone (**8d**). ^1H NMR ($CDCl_3$) δ 3.90 (3H, s), 6.25 (1H, t, *J*=53.7Hz), 6.46, 8.60 (4H, AB, *J*=9.0Hz); ^{19}F NMR ($CDCl_3$) δ -121.8 (d, *J*=53.7Hz); IR (nujol) 1701cm^{-1}; Mass spectrum (EI) m/e 186 (14, M^+), 135 (100, M^+-CF_2H), 107 (19, M^+-$COCF_2H$).

2-Fluoro-4'-methoxyacetophenone (**7d**). ^1H NMR ($CDCl_3$) δ 3.90 (3H, s), 5.50 (2H, d, *J*=47.0Hz), 6.51, 8.37 (4H, AB, *J*=8.9Hz); ^{19}F NMR ($CDCl_3$) δ -230.5 (t, *J*=47.0Hz); IR (nujol) 1702cm^{-1}; Mass spectrum (EI) m/e 168(12, M^+), 135(100, M^+-CFH_2), 107(14, M^+-$COCFH_2$).

2,2-Difluoro-4'-bromoacetophenone (**8e**). ^1H NMR ($CDCl_3$) δ 6.24 (1H, t, *J*=53.4Hz), 7.55, 8.07 (4H, AB, *J*=8.3Hz); ^{19}F NMR ($CDCl_3$) δ -122.0 (d, *J*=53.4Hz); IR (nujol) 1698cm^{-1}; Mass spectrum (EI) m/e 234, 236 (4, 4, M^+), 183, 185 (100, 97, M^+-CF_2H), 155, 157 (56, 52, M^+-$COCF_2H$).

2-Fluoro-4'-bromoacetophenone (**7e**). ^1H NMR ($CDCl_3$) δ 5.45 (2H, t, *J*=46.9Hz), 7.56, 7.81 (4H, AB, *J*=8.6Hz); ^{19}F NMR ($CDCl_3$) δ -230.3 (t, *J*=46.8Hz); IR (neat) 1697cm^{-1}; Mass spectrum (EI) m/e 216, 218 (7, 7, M^+), 183, 185 (100, 100, M^+-CF_2H), 155, 157 (35, 34, M^+-$COCF_2H$).

2,2-Difluoro-α-tetralone (**8f**). ^1H NMR ($CDCl_3$) δ 2.58 (2H, t-t, *J*=6.4, 14.6Hz), 3.19 (2H, t, *J*=6.2Hz), 7.3-8.1 (4H, m); ^{19}F NMR ($CDCl_3$) δ -111.7 (t, *J*=14.6Hz); ^{13}C NMR ($CDCl_3$) δ 25.5, 29.6, 113.6 (t, *J*=250.0Hz), 142.7, 134.9, 128.8, 128.7, 127.4, 180.3; IR (neat) 1719 cm^{-1}; Mass spectrum (EI) m/e 182 (67, M^+), 154 (7, M^+-CH_2CH_2), 118 (100, M^+-CF_2CH_2).

2-Fluoro-α-tetralone (**7f**). ^1H NMR ($CDCl_3$) δ 2.48 (2H, m), 3.14 (2H, d-d, *J*=9.5, 3.9Hz), 5.15 (1H, d-d-d, *J*=47.9, 12.7, 5.3Hz), 7.3-8.1 (4H, m); ^{19}F NMR ($CDCl_3$) δ -190.8 (m); ^{13}C NMR ($CDCl_3$) δ 26.9, 30.0, 91.1 (d, *J*=187.1Hz), 127.1,127.8, 134.1, 143.0, 193.5; IR (neat) 1703 cm^{-1}; Mass spectrum (EI) m/e 164 (66, M^+), 118 (100, M^+-$CFHCH_2$).

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