Efficient Synthesis of α,α-Difluoro Ketones Using Selectfluor™ F-TEDA-BF₄

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Abstract: Selective and efficient synthesis of α,α-difluoro ketones was achieved following a protocol which includes the transformation of α-methylene ketones to the corresponding n-butylimine derivatives and their further treatment with Selectfluor™ F-TEDA-BF₄ in acetonitrile solution at 80 °C.

Key words: halogenation, fluorination, imines, ketones, α,α-difluoro ketones, Selectfluor F-TEDA-BF₄

The introduction of a fluorine atom or fluorine-containing groups into organic molecules often dramatically perturbs their physical, chemical and biological properties and affects their application in comprehensive areas covered by the material and life sciences. Site-selective synthesis of fluorine-substituted organic compounds is therefore of wide interest to the research community.

The carbonyl site in α-fluorinated ketones is a much better electrophile than in the corresponding nonfluorinated ketones since fluorine, as the most electronegative atom, is a better electrophile than in the corresponding nonfluorinated ketones. This causes not only changes in reactivity but in biological activity as well. As long as twenty years ago it has been shown that α,α-difluoro ketones are good inhibitors of hydrolytic enzymes and by a range of 10³–10⁵-fold better inhibitors than the corresponding nonfluorinated ketones, as established in the case of acetyl cholinesterase, pepsin and renin.

Increased inhibition of difluoro ketone derivatives was later established for many other enzymes including renin, chymotripsin, porcine pancreatic elastase, interleukin-1β converting enzyme, HIV protease, Alzheimer’s γ-secretase, matrix metalloproteases and others. It is known that α,α-difluoro ketones tend to exist in hydrated form and thus mimic closely the tetrahedral transition state involved in enzyme inhibition.

Efficient synthetic methods for the preparation of α,α-difluoro ketones starting from alkyne or phenols have been developed using various electrophilic fluorinating reagents, while selective fluorination of carbonyl compounds remains troublesome in those cases when the α-methylene carbon atom is not activated. As some 1,3-dicarbonyl compounds (α-diketones, α-keto esters, malonates) could be smoothly difluorinated using various protocols of electrophilic fluorination, mono-carbonyl compounds are usually monofluorinated whenever fluorination proceeds directly from ketones, as well as indirectly via enol acetates, silyl enol ethers or metal enolates. Transformations of ketones with N-fluoro-1,4-diazoniabicyclo[2.2.2]octane dication salts were found to be solvent dependent while further fluorination of thus obtained α-fluoro ketones to α,α-difluoro derivatives was unsuccessful using this methodology. To our knowledge three methods for the transformation of the α-methylene to the α,α-difluoro carbonyl functionality have been reported. Nakano’s procedure follows low temperature reaction of N-fluorobenzensulfonylimide (AccuFlour NFSi) in the presence of a large excess of MnBr₂ with the corresponding enolate anions, obtained by treatment of ketones with an excess of the strong base N,N-bis(tri-methylsilyl)amide. According to DesMarteau the fluorination of imines with N-fluorobis[(trifluoromethyl)sulfonyl]imide followed by an acidic work-up resulted in the formation of α,α-difluoro ketones, while very recently, Shreve reported low-temperature transformation of enamines to α,α-difluoro ketones using Selectfluor in the presence of weak base or molecular sieves.

In our continuing interest in selective fluorination of organic compounds we now report a method for efficient synthesis of α,α-difluoro ketones by fluorination of imines with some commercially available N-F reagents: Selectfluor™ F-TEDA-BF₄ (1) and AccuFlour™ NFTn (2) as representatives of N-fluoro-1,4-diazoniabicyclo[2.2.2]octane dication salts, AccuFlour™ NFSi (3) as one of the N-fluoroamines, and N-fluoro-2,6-dichloropyridinium tetrafluoroborate FB₈00 (4) as the most seldom-used N-F reagent from the N-fluoroypyridinium salt family.

Synthesis of imines from ketones and primary amines using catalytic amounts of trifluoroacetic acid and azeotropic removal of water is a known and routine procedure, but the ordinarily applied corresponding protocols include the use of very toxic solvents such as benzene or toluene. We found that cyclohexane could be used as solvent for efficient synthesis of imines.

We first tested this modification in order to synthesize tetralone imines (Scheme 1) from tetralone (6) and n-butyramine or (±)-phenylethylamine. We were very successful in both cases as the crude reaction mixtures were pure enough to continue with fluorination without further purification. According to the literature the orientation of N-alkyl group is expected to be anti to the aromatic ring.
In order to determine optimal reaction conditions for highly selective and efficient synthesis of \( \alpha,\alpha \)-difluoro ketones using electrophilic fluorination reagents, we selected imines 7 as test compounds. Since according to our previous work \(^{28}\) methanol was the best choice of solvent for fluorination of ketones with N-F reagents, we first tried reactions in methanol at reflux temperature, but as evident from the results collected in Table 1 (entries 1, 5, 10), selectivity of the transformation was poor. Fluorination with 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (1, Selectfluor\textsuperscript{TM} F-TEDA-BF\textsubscript{4}), 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (2, Accufluor\textsuperscript{TM} NFTh) and N-fluorobenzenesulfonimide (3, Accufluor\textsuperscript{TM} NFSi) followed by a hydrolysis with aqueous HCl resulted in the formation of a mixture of monofluoro 8 and difluoro 9 derivatives.

### Table 1 Fluorination of Derivatives of Tetralone Imine 7 with Electrophilic Fluorination Reagents\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>R (^b)</th>
<th>Solvent (^c)</th>
<th>8, 9 (^b)</th>
<th>Yield (%) (^d)</th>
</tr>
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<tr>
<td>1</td>
<td>1</td>
<td>CHMePh</td>
<td>MeOH</td>
<td>73:27</td>
<td>88</td>
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<tr>
<td>2</td>
<td>1</td>
<td>CHMePh</td>
<td>MeCN</td>
<td>25:75</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>CHMePh</td>
<td>MeCN(^d)</td>
<td>0:100</td>
<td>93</td>
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<tr>
<td>4</td>
<td>1</td>
<td>(n)-Bu</td>
<td>MeCN(^d)</td>
<td>0:100</td>
<td>95</td>
</tr>
<tr>
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<td>2</td>
<td>CHMePh</td>
<td>MeOH</td>
<td>56:44</td>
<td>87</td>
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<tr>
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<td>2</td>
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<td>58:42</td>
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<tr>
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<td>MeOH</td>
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<tr>
<td>16</td>
<td>4</td>
<td>CHMePh</td>
<td>MeCN(^d)</td>
<td>79:21</td>
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<tr>
<td>5</td>
<td>5</td>
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</table>

\(^a\) Reaction conditions: 1) imine (1 mmol), fluorinating reagent (2 mmol), solvent (10 mL), reflux temperature; 2) hydrolysis with 37% aq HCl solution (0.5 mL).

\(^b\) Relative distribution in % determined from \(^{19}\)F NMR spectra of isolated reaction mixtures.

\(^c\) Total yield of fluorinated products was determined from \(^{19}\)F NMR spectra of isolated reaction mixtures using octafluoronaphthalene as internal standard.

\(^d\) Anhyd MeCN in dry atmosphere was used.

\(^e\) Pure NFTh 2 was used (not in mixture with Al\(_2\)O\(_3\) as commercially available).
The use of acetonitrile as reaction solvent improved the selectivity of the reaction considerably (entries 2,6,11). Imines are very sensitive to the presence of nucleophiles and therefore acetonitrile is expected to be a better reaction medium than methanol, while moisture in the reaction components would also lower the selectivity of the transformation. Freshly distilled acetonitrile, additionally dried by reaction with anhydrous Na₂SO₄, seems to be the best choice for selective transformation of imines to α,α-difluoro ketones, and among the reagents tested Selectfluor™ F-TEDA-BF₄ (1) gave the best results (entries 3 and 4, Table 1). Accufluor™ NFSi (3) also gave good results (entries 12,13), while Accufluor™ NFTH (2) was less successful (entries 7–9). The use of N-fluoro-2,6-dichloropyridinium tetrafluoroborate FP-B800 (4) was inefficient because the transformation stopped at the stage of α-fluoro ketone 8 (entries 14,15). Cesium fluoroxysulfate (5) was also found to be unsuitable reagent for the transformation of imines to α,α-difluoro ketones (entry 16). The alkyl group R had a very low influence on the selectivity of the reaction as the results were very similar for n-butyl (7a) and phenethyl (7b) derivatives.

In order to determine the limitations of the method, we further studied the effect of the structure of the ketone on the selectivity and efficiency of its transformation to α,α-difluoro derivatives with F-TEDA-BF₄ (1) and the results are collected in Table 2. Following the optimal reaction protocol established after the experiments shown in Table 1, acetophenone (10a, entry 1, Table 2) was readily transformed to 2,2-difluorophenylethan-1-one (11a), as well as 4-methoxyacetophenone (12, entry 5) to its α,α-difluoro substituted derivative 13. Since no ring fluorinated products were observed, evidently the selectivity of the transformation was not interfered by the strong activation of the aromatic ring, which was also confirmed in the case of reaction of the imine prepared from 5-methoxy-1-tetralone (18, entry 9) which was also fluorinated only at the α to carbonyl position, thus yielding 19. The corresponding imines obtained from some derivatives of acetophenone functionalized with alkyl (10b), phenyl (10c) or benzyl (10d) substituent at the methylene carbon atom were readily transformed to the corresponding α,α-difluoro ketones 11b–d, as well as imines from 1-Indanone (16a, entry 7) or benzosuberone (16b, entry 8) to 2,2-difluoro-1-indanone (17a) or 6,6-difluoro-6,7,8,9-tetrahydrobenzocyclohepten-5-one (17b), respectively. The presence of a sulfur atom in the target ketone did not interfere with the selectivity or the efficiency of the fluorination process, although one would expect some interference due to the considerable oxidation power of F-TEDA-BF₄. 3,3-Acetylthiophene (20, entry 10) was thus selectively transformed to 2,2-difluoro-1-thiophen-3-yl-ethanone (21) in high yield.

The fluorination protocol was also tested on some dialkyl ketones and unfortunately complete loss of selectivity was observed in the case of substrates containing two α-methylene groups. Treatment of imines derived from 5-nonanone or 1-phenylacetone under the mentioned reaction conditions resulted in the formation of a complex reaction mixture of products among which at least two different α,α-difluoro carbonyl derivatives could be detected. On the other hand, 1-acetyladamantane (22, entry 11) was via its imine selectively fluorinated to 1-adamantan-1-yl-2,2-difluoroethanone (23) in acceptable yield.

In conclusion, we can claim that Selectfluor™ F-TEDA-BF₄ (1), otherwise one of the most versatile reagents for selective fluorination38 and many other functionalizations39 of organic compounds, is an excellent choice as the mediator for the transformation of ketones to α,α-difluoromethylene ketones after prior activation of the starting material by imine formation. Regioselective transformation could be achieved in the case of aryl alkyl ketones, benzocycloalkanes and alkyl tert-alkyl ketones, while poor regioselectivity was observed in the case of dialkyl ketones.

Imines 7a,b (and Table 1); General Procedure
A modified literature procedure was used.44 To a solution of ketone (10 mmol) in cyclohexane (20 mL), were added amine (12 mmol) and CF₃CO₂H (5 drops). The mixture was refluxed with azeotropic removal of H₂O using a Dean–Stark apparatus until the expected amount of H₂O was eliminated, but not longer than 24 h. The solvent was removed under reduced pressure and the crude mixture was distilled in tert-butyl methyl ether. The organic solution was washed with a sat. aq solution of NaHCO₃ and with 10% aq NaCl solution, dried (Na₂SO₄) and the solvent evaporated. Crude imines were pure enough to continue with fluorination without previous purification. Some imines, on which we tested this procedure, were analyzed and compared with literature data.
Table 2  Synthesis of α,α-Difluoro Ketones from Ketones by Reaction of Imines with Selectfluor F-TEDA-BF$_4$ (1)$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Reaction time (h)</th>
<th>α,α-Difluoro ketone</th>
<th>Yield (%)$^b$</th>
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<td>77</td>
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<tr>
<td>2</td>
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<td><img src="image2" alt="Image" /></td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>c: R$^1$ = Ph</td>
<td>4</td>
<td><img src="image3" alt="Image" /></td>
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<td>d: R$^1$ = CH$_2$Ph</td>
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$^a$ Reaction conditions: 1) imine (1 mmol), Selectfluor$^\text{TM}$ F-TEDA-BF$_4$ (1; 2 mmol), anhyd MeCN (10 mL), reflux temperature, 4–12 h; 2) hydrolysis with 37% aq HCl solution (0.5 mL).

$^b$ Refer to pure products and calculated on the basis of the starting imine.

**Butyl-(3,4-dihydro-2H-naphthalen-1-ylidene)amine (7a)$^{35}$**

Yield: 95%; brown oil.

IR (neat): 1670, 1610, 1580, 1435, 1285, 755, 720 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): δ = 0.97 (t, J = 7.3 Hz, 3 H, CH$_3$), 1.46 (m, 2 H, CH$_2$), 1.73 (m, 2 H, CH$_2$), 1.93 (m, 2 H, CH$_2$), 2.56 (t, J = 6.6 Hz, 2 H, CH$_2$), 2.80 (t, J = 6.1 Hz, 2 H, CH$_2$), 3.44 (t, J = 7.1 Hz, 2 H, CH$_2$), 7.11 (m, 1 H, ArH), 7.18–7.29 (m, 2 H, ArH), 8.17 (m, 1 H, ArH).

$^{13}$C NMR (76 MHz, CDCl$_3$): δ = 14.0, 20.8, 22.6, 27.6, 29.8, 33.2, 50.7, 125.6 (ArCH), 126.3 (ArCH), 128.2 (ArCH), 129.4 (ArCH), 135.0 (ArC), 140.2 (ArC), 163.9 (C=N).

MS (EI, 70 eV): m/z (%) = 201 (10, M$^+$), 158 (35), 135 (99), 105 (100), 77 (76).

**(±)-(3,4-Dihydro-2H-naphthalen-1-ylidene)(1-phenylethyl)amine (7b)$^{34,36}$**

Yield after crystallization from n-hexane: 71%; pale yellow crystals; mp 51 °C.

IR (KBr): 3050, 3005, 2960, 2870, 1620, 1590, 1490, 1450, 1360, 1295, 1230, 1295, 1190, 1065, 1025, 760, 730, 695 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): δ = 1.52 (d, J = 6.5 Hz, 3 H, CH$_3$), 1.90 (m, 2 H, CH$_2$), 2.56 (2 H, CH$_2$), 2.79 (t, J = 6.0 Hz, 2 H,
2,2-Difluoro-1-(4-methoxyphenyl)ethanone (13)33

Yield: 70%; colorless liquid.

IR (neat): 3015, 2995, 1680, 1570, 1430, 1240, 1180, 1030, 990, 875 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 3.89 (s, 3 H, CH₃), 6.26 (t, J = 6.8 Hz, 1 H, ArH), 8.08 (d, J = 8.2 Hz, 2 H, ArH).

19F NMR (56.4 MHz, CDCl₃): δ = −124.2 (d, J = 53.5 Hz, CHF₂).

MS (EI, 70 eV): m/z (%) = 156 (1, M⁺), 105 (100), 84 (13), 77 (92).

2,2-Difluoro-1-phenyldecan-1-one (11b)20

Yield: 91%; yellow crystals; mp 31 °C.

IR (neat): 3060, 2920, 2850, 1700, 1600, 1450, 1175, 710 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.89 (t, J = 7.0 Hz, 3 H, CH₃), 1.30 (m, 10 H, 5 CH₃), 1.50 (m, 2 H, CH₂), 2.18 (m, 2 H, CH₂CF₂), 7.50 (m, 2 H, ArH), 7.63 (t, J = 7.4, 2.0 Hz, 1 H, ArH), 8.11 (dd, J = 7.4, 1.0 Hz, 2 H, ArH).

13C NMR (76 MHz, CDCl₃): δ = 141.1 (CH₃), 21.4 (t, J = 4.0 Hz, CH₃), 22.7 (CH₃), 29.1 (CH₃), 29.3 (CH₃), 29.4 (CH₃), 31.8 (CH₃), 34.1 (t, J = 22.8 Hz, CH₂CF₂), 119.9 (t, J = 252.4 Hz, CH₂), 128.7 (ArCH), 130.1 (ArCH), 132.2 (ArC), 134.2 (ArCH), 189.7 (t, J = 31.0 Hz, C=O).

19F NMR (56.4 MHz, CDCl₃): δ = −101.0 (t, J = 18.1 Hz, CF₂).

MS (EI, 70 eV): m/z = 268 (2, M⁺), 156 (2), 105 (100), 77 (40).


2,2-Difluoro-1,2-diphenylethanone (11d)19

Yield: 70%; colorless liquid.

IR (neat): 3015, 2995, 1680, 1570, 1430, 1240, 1115, 980, 875 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.4–7.5 (m, 5 H, ArH), 7.58 (m, 1 H, ArH), 7.60 (m, 2 H, ArH), 8.06 (d, J = 7.5 Hz, 2 H, ArH).

13C NMR (76 MHz, CDCl₃): δ = 116.9 (t, J = 252.9 Hz, C=O), 125.6 (t, J = 5.8 Hz, ArCH), 128.6 (ArCH), 128.8 (ArCH), 130.2 (ArCH), 130.9 (ArCH), 131.2 (ArC), 133.1 (ArC), 134.2 (ArCH), 188.9 (C=O).

19F NMR (56.4 MHz, CDCl₃): δ = −99.3 (s, CF₂).

MS (EI, 70 eV): m/z = 232 (15, M⁺), 213 (20), 183 (45), 165 (50), 127 (15), 105 (100), 77 (63).

2,2-Difluoro-1,3-diphenylpropan-1-one (11d)33

Yield: 85%; colorless highly hygroscopic crystals; mp 47 °C.

IR (KBr): 3010, 2995, 1680, 1570, 1430, 1240, 1180, 1030, 900 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 3.50 (t, J = 17.8 Hz, 2 H, CH₂), 7.29 (m, 5 H, ArH), 7.43 (m, 2 H, ArH), 7.58 (t, J = 7.4 Hz, 1 H, ArH), 8.01 (dd, J = 7.4 Hz, 1.0 Hz, 2 H, ArH).

19F NMR (56.4 MHz, CDCl₃): δ = −268 (2, M⁺), 156.7 (100), 105 (40), 77 (27).

Anal. Calcd for C₁₆H₁₅F₂O: C, 72.10; H, 5.03.

2,2-Difluoro-1-naphthalen-2-ylethanone (15)33

Yield: 88%; colorless liquid.

IR (neat): 1700, 1600, 1450, 1280, 1180, 1030, 900 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.96 (d, J = 8.8 Hz, 2 H, ArH).

13C NMR (76 MHz, CDCl₃): δ = 31.2 Hz, C=O).

J = 253.7 Hz, CHF₂), 124.7 (ArCH), 128.9 (ArCH), 130.9 (ArCH), 131.2 (ArC), 132.1 (ArC), 134.2 (ArCH), 189.5 (t, J = 31.2 Hz, C=O).

19F NMR (56.4 MHz, CDCl₃): δ = −99.0 (t, J = 17.8 Hz, CF₂).

MS (EI, 70 eV): m/z (%) = 246 (1, M⁺), 105 (100), 77 (42).

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**19F NMR (56.4 MHz, CDCl3):** \( \delta = -122.0 \) (d, \( J = 53.6 \) Hz, CHF2).

MS (El, 70 eV): \( m/z \) (%) = 206 (35, M+), 155 (100), 127 (90), 84 (25).


**1H NMR (300 MHz, CDCl3):** \( \delta = 6.15 \) (t, \( J = 53.7 \) Hz, 1 H, CHF2), 7.40 (dd, \( J = 2.8 \) Hz, \( J = 5.2 \) Hz, 1 H), 7.65 (m, 1 H, ArH), 8.37 (m, 1 H, ArH).

**13C NMR (76 MHz, CDCl3):** \( \delta = 111.1 \) (t, \( J = 253.5 \) Hz, CF2), 126.8 (ArCH), 127.4 (ArCH), 135.5 (t, \( J = 2.0 \) Hz, ArC), 136.1 (t, \( J = 4.3 \) Hz, ArCH), 182.1 (t, \( J = 26.0 \) Hz, C=O).

**IR (KBr):** 1770, 1640, 1350, 1270, 1100, 970, 780 cm\(^{-1}\). Yield: 89%; yellow highly hygroscopic crystals; mp 26–27 \(^{\circ}\)C.

**2,2-Difluoro-1-indanone (17a)**

Yield: 81%; colorless highly hygroscopic liquid.

IR (KBr): 1770, 1640, 1350, 1270, 1100, 970, 780 cm\(^{-1}\). Yield: 76%; colorless liquid.

**4.88.**

**19F NMR (56.4 MHz, CDCl3):** \( \delta = -122.0 \) (d, \( J = 53.7 \) Hz, CHF2).

MS (El, 70 eV): \( m/z \) (%) = 20 (23, M+), 111 (100), 83 (40).

Anal. Calcd for C9H8F2O·1/10H2O: C, 63.48; H, 2.68. Found: C, 63.53; H, 2.68.

**1-Adamantan-1-yl-2,2-difluoroethanone (23)**

Yield: 61%; colorless liquid.

IR (neat): 1690, 1510, 1420, 1250, 1135, 1060, 850 cm\(^{-1}\).

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