Metal - Fluorine Interactions in Organic Synthesis

MARCH 27, 2001

THYMIDINE A

VS.

4,6-DIFLUORO-M-Xylene B

TADDOL C

VS.

F-TADDOL D

\[ \text{M} \times 0.6 = \text{M} \times \text{assoc} B \]
Short Sighted Dismissal of Metal-Fluorine Interactions

0. If one considers what makes oxygen a good donor ligand for metals (high electronegativity, low polarizability), fluorine would seem a logical, if not superior, alternative.

Atomic Properties:

<table>
<thead>
<tr>
<th>Element</th>
<th>1p Ionization Potential (eV)</th>
<th>EA, Electron Affinity (eV)</th>
<th>EN, Electronegativity</th>
<th>( \delta^+ ) (Pauling)</th>
<th>( \delta^- ) (Pauling)</th>
<th>BE, Bond Energy (eV)</th>
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</thead>
<tbody>
<tr>
<td>H</td>
<td>13.6</td>
<td>2.1</td>
<td>2.1</td>
<td>1.20</td>
<td>99</td>
<td>2.3</td>
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<tr>
<td>C</td>
<td>25.8</td>
<td>3.3</td>
<td>4.0</td>
<td>1.35</td>
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<td>2.8</td>
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<tr>
<td>N</td>
<td>15.7</td>
<td>3.4</td>
<td>3.0</td>
<td>1.40</td>
<td>11.6</td>
<td>3.0</td>
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<tr>
<td>O</td>
<td>25.5</td>
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<td>4.0</td>
<td>1.43</td>
<td>11.9</td>
<td>3.5</td>
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<tr>
<td>F</td>
<td>25.8</td>
<td>3.3</td>
<td>4.0</td>
<td>1.35</td>
<td>7.1</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Steric Considerations:

E. Steric parameters suggested by K. W. Taft.
F. E. Steric parameters suggested later by J. E. Dubois.

From: Hipman, T. "Metallic Fluorine Compounds." Pg. 2

Also:

\( H \) (I = 1/2) + 100% NAT. ABUNDANCE

\( H \) (I = 1/2) < 1% NAT. ABUNDANCE

\( H \) (I = 1) < 1% NAT. ABUNDANCE

\( H \) (I = 1) = 100% NAT. ABUNDANCE

\( H \) (I = 1) = 100% NAT. ABUNDANCE

\( H \) (I = 1) = 100% NAT. ABUNDANCE

\( H \) (I = 1) = 100% NAT. ABUNDANCE
X-ray structure search reveals patterns in C-F-M

Analyses of the Cambridge Structure Data Base revealed regularities in C-F-M bond lengths.

A number of metals across the periodic table have unknown M-F contacts:

Li, Na, K, Rb, Cs, Ca, Sr, Ba, Sc, Eu, Y, Zr, Cd, Ag, La, U, Al, Ga, In, Tl, Ge, Sn, Pb and Bi


There may be way more C-F-M bonds than we think.
**Electrophilic Fluorinating Reagents:**

(1) \[ \text{R}^1 \overset{\text{OAc}}{\to} \text{CH}_3\text{CO}_2\text{F} \rightarrow \text{R}^1 \overset{\text{F}}{\to} \]

(2) \[ \text{CH}_2\text{Cl}_2 \overset{\text{Cu}^2\text{Cl}_2}{\to} \text{20}^\circ \rightarrow \text{81\% yield.} \]

(3) \[ \text{LDA} \rightarrow \text{81\% yield.} \]

(4) \[ \text{Su} \text{Me} \overset{\text{MeCN}}{\to} \text{NT.} \]

**Nucleophilic Fluorinating Reagents:**

(1) \[ \text{Et}_2\text{NSiMe}_3 + \text{SF}_4 \rightarrow \text{Et}_2\text{NSF}_3 + \text{necO} \text{O}_{\text{Hone}} \overset{0^\circ}{\to} \text{meO} \overset{\text{F}}{\to} \text{O}_\text{Cuc} \]

N-F and O-F compounds hold the key to easy installation of fluorine.

---

**WHERE DO FLUORINES COME FROM NOW?**
Effects of Fluorine Substitution on Reactive Centers

- Fluorine: F

Fluorine Tends to Destabilize Cations (Predominance of +I) and Destabilize More Remote Cations.

\[ \frac{\text{C}}{\text{C}^+} = \frac{\text{C}}{\text{C}^+} \]

\[ +I \text{ effect} \]

- Iodine: I

Fluorine Tends to Destabilize Anions (Predominance of -M) and Stabilize More Remote Anions.

\[ \frac{\text{C}^-}{\text{C}^+} = \frac{\text{C}^-}{\text{C}^+} \]

\[ -M \text{ effect} \]
EFFECTS OF FLUORINE SUBSTITUTION ON REACTIVE CENTERS.

OTrifluoromethyl:

\[ \because \quad \because \quad \because \quad \because \]

- I\textsuperscript{3} EFFECT

\[ \begin{array}{c}
\text{No Condonitory}\text{ In Effect:}\\
\sigma_{\text{m}}(\text{CF}_3) = 0.43 \quad \delta_{\text{p}}(\text{CF}_3) = 0.54
\end{array} \]

NEUTRAL HYPERCONJUGATION.

\[ \begin{array}{c}
\text{Structural Effects:}\\
\begin{array}{c}
\text{cut:}\\
\text{gelatin:}
\end{array}
\end{array} \]

\[ \quad \begin{array}{c}
\text{due to the high electronegativity of fluorine, stabilization through hyperconjugation outweighs dipole-dipole stabilization in the and: form.}
\end{array} \]

O'HAGAN, D.J.; PAPPA, U.S. JCS CHEM COMM (1977) 645.
The trifluoromethyl group acts as a syn-orienting effect. This is evidenced by the following reactions:


(1) Reflux, EtOH

(2) Toluene, FeCl₃

(3) Toluene, 10% HCl (aqueous)

Chemical reactions demonstrate the syn-orienting effect of the trifluoromethyl group. This is an important aspect of trifluoromethyl chemistry.
Evidence for the Role of the Fluorines.

This material is hygroscopic + volatile. Purification by vac. sublimation is straightforward.

\[
\begin{align*}
\text{HOC(CF}_3)_2\text{PN} & \xrightarrow{\text{LiAlH}_4} \text{LiAl(OCCF}_3)_2\text{PN}_4 \\
\text{The Li}_2\text{O}_2\text{F}_4 \text{ fragment is twist prismatic.} \\
\text{C-F-Li bond lengths} & \ 1.98 - 2.35\text{Å}. \\
\text{This is the shortest Li-F contact on record. The values are equal within} & \ \pm 0.35. \\
\text{Coordinated C-F bonds are lengthened ca. 0.5 Å relative to uncoordinated bonds.}
\end{align*}
\]

\(^{19}\text{F spectroscopy shows a complex pattern at} -75.9 \text{ ppm. It is a 1:1:1:1 quartet superimposed on a broad singlet. This is as expected for coordination of 4 equiv. fluorines to 1 lithium atom \((F^2 = 3/2 \text{ for } \text{^7Li (92.8 \% Na)}\) and I = 1 for \text{^6Li (7.5 \% Na)}\).}

Fluorines atoms serve to release the naked Li\(^+\) into solution.
Figure 2: Crystal structure of K C1 (H atoms are omitted for clarity).

Figure 1: Distribution profile of D% of metal precursors. D%= (PCl4+)×100/(PCl4+ + CoCl2). The metal precursors were formed from a 0.1 M solution of metal chloride or nitrate (AgCl) and 1.0 M LiCl in water.

NMR is a good tool for identifying fluorine interactions.

NMR is a good tool for identifying fluorine interactions.
Effect of Fluorination on Chiral Amine Bases in Desymmetrization.

\[ \begin{array}{c}
& \text{Lithium amide} & \text{HMPA} & \text{Temp.} & \text{Product} \\
\hline
1 & \text{CH}_2\text{Cl}_2 & 0 & -78 & 4a, 86, 52 \\
2 & \text{CH}_3\text{CH}_3 & 1.2 & -78 & 4a, 93, 78 \\
5 & \text{CH}(\text{CH}_3)_2 & 0 & -78 & 4a, 87, 65 \\
6 & \text{CH}_3\text{CH}_2 & 1.2 & -78 & 4a, 73, 75 \\
7 & \text{CH}_3\text{Bu}^t & 0 & -78 & 4a, 93, 86 \\
8 & \text{CH}_3\text{Bu}^t & 1.2 & -78 & 4a, 94, 84 \\
9 & \text{CH}_3\text{CH}_2\text{F} & 0 & -78 & 4a, 85, 69 \\
10 & \text{CH}_3\text{CH}_2\text{F} & 1.2 & -78 & 4a, 67, 85 \\
11 & \text{CH}_3\text{CHF}_2 & 0 & -78 & 4a, 93, 77 \\
12 & \text{CH}_3\text{CHF}_2 & 1.2 & -78 & 4a, 92, 89 \\
13 & \text{CH}_3\text{CF}_3 & 0 & -78 & 4a, 88, 84 \\
14 & \text{CH}_3\text{CF}_3 & 1.2 & -78 & 4a, 74, 87 \\
21 & \text{Ph} & 1.2 & -100 & 4b, 95, 93 \\
22 & \text{Ph} & 1.2 & -100 & 4c, 92, 95 \\
23 & \text{Me} & 1.2 & -100 & 4d, 76, 94 \\
\end{array} \]

- Enantioselectivity increases with both the steric demand and degree of fluorine substitution in R.
- HMPA does not seriously affect the highly selective cases.
- NN2 (\text{N}_2\text{O}, \text{Li}, \text{+} \text{F}) do not indicate any Li-F bonding.
- "It is conceivable that electrostatic interaction between S^- of the fluorine and S^+ of the lithium fixes the conformation of the chelated monomeric form of 2e-h."

R = H. reflux for 11 h.

BY NMR with PDC as an internal standard (cyclohexane) these yields were determined. The yields were obtained in the absence of a Pd(I) catalyst. In the presence of a Pd(I) catalyst these yields were reduced by ca. 50%.

<table>
<thead>
<tr>
<th>9</th>
<th>11</th>
<th>13</th>
<th>15</th>
<th>17</th>
<th>19</th>
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<tbody>
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<td>0</td>
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<td>90</td>
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<td>90</td>
<td>0</td>
<td>90</td>
<td>0</td>
<td>90</td>
</tr>
</tbody>
</table>

The Heck reaction was carried out at reflux.

The Heck-Umemoto (Umemoto's Heck reaction) was carried out at reflux.

In a manner similar to the above, we have carried out reactions with CF₃ as a leaving group.

The Heck-Umemoto reaction proceeded with a good yield.
STERELECTRONIC EFFECTS IN THE URELAND CLAISEN DEARRANGEMENT

0 BETTER σ* → σ C-C DONATION
FAVORS THE SYN MANIFOLD
SUGGESTING THE IMPORTANCE
OF STERELECTRONICS
RATHER THAN STERICS.

SYN  71:0  YIELD
     82:18  SYN:ANTI
**FLUORINE CONTAINING CIRCULAR AUXILIARIES**

\[
\begin{align*}
\text{CF}_2 \quad \text{(1a)} & \quad 67 \quad [90] & 79 \quad [80] & 82 \quad [68] & -1.16 & -0.78 \\
\text{CHF}_2 \quad \text{(1b)} & \quad 58 \quad [88] & 45 \quad [84] & 61 \quad [72] & -0.67 & -0.32 \\
\text{CH}_2\text{F} \quad \text{(1c)} & \quad 50 \quad [82] & 41 \quad [84] & 49 \quad [62] & -0.24 & -0.20 \\
\text{i-Pr} \quad \text{(1d)} & \quad 50 \quad [56] & 31 \quad [48] & 77 \quad [28] & -0.47 & -0.48
\end{align*}
\]

*Es: Taft steric constant with reference to a methyl group (Me: 0.00), Es: revised Taft steric constant by Dubois and co-workers. Me: 0.00, Ph: -2.31.

**YAMAZAKI, T; et al. Org. Lett. (1999) 1, 90.**

OMERS IN DIASTEREOMER SELECTIVITY DO NOT TRACK WELL WITH TAFT ES PARAMETERS SUGGESTING SIMPLE STEYEN DIFFERENTIATION IS NOT ENOUGH.

**PSYNO AXIAL METHYL GROUP PROVIDES STEYEN BIAS.**

AE BETWEEN THE 2 LOWEST ENERGY CONFORMERS IS 0.81 MEWH WHICH CORRELATES TO A SELECTIVITY OF 94.6:5.4 @ -78°C.

**ENDURE GEOMETRY FIXED BY F-K INTERACTION**
SUBSTRATE DIRECTED REDUCTION OF KETONES BY METAL HYDRIDES.

\[
\begin{align*}
\text{Ru} & \quad \text{O} \quad \text{O} \quad \text{Cl}_3 \\
\text{DIBALH} & \quad -78^\circ \\
\text{Ru} & \quad \text{O} \quad \text{O} \quad \text{Cl}_3 + \quad \text{Ru} & \quad \text{O} \quad \text{O} \quad \text{Cl}_3 \\
\text{N} & \quad \text{C} \quad \text{C} \quad \text{N} & \quad \text{DIBALH} & \quad -78^\circ \\
\text{R} & \quad \text{F} \quad \text{F} \quad \text{N} & \quad \text{R} & \quad \text{F} \quad \text{F} \quad \text{N} \\
\text{YIELD} & \quad \text{SYN} \quad \text{ANTI} \\
99\% & \quad 0 \quad 100 \\
95\% & \quad 25 \quad 75 \\
\end{align*}
\]
Fluorinated Lignans in Asymmetric Epoxidations.
PROPOSED CATALYSTS + INTERACTIONS

1. Sharpless Transition State

2. Nitrogen Coordination

3. Fluorine Bidentate Coordination

SYSTEM IS UNDERDEFINED TO DRAW REASONABLE STRUCTURES.
Fluorinated Ligands in Asymmetric Sulfoxide Oxidations.

Ti(IV)Cl4, 1 equiv

(4R,5R)-1

R = H (1a)
R = OMe (1b)
R = CF3 (1c)

Av-S-2

Table. Enantioselective oxidations employing diols (R,R)-1a-c as ligands.

<table>
<thead>
<tr>
<th>entry</th>
<th>diol</th>
<th>sulfide</th>
<th>ee (%)</th>
<th>Abs. conf.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2b</td>
<td>62</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2b</td>
<td>94</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>2a</td>
<td>60</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>2b</td>
<td>65</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>2a</td>
<td>70</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>2b</td>
<td>80</td>
<td>R</td>
</tr>
</tbody>
</table>

*Conditions: 2-bromo-2-methylpropanoic acid (1.0 equiv); 0.1 M in CH2Cl2 at 0°C under N2; ammoxidation time 2 h; 2 equivalents of 7% TBHP in water at 40°C. *Isolated yield; amount of sulfone < 10%. *Determined by comparison of [o]-opt. with literature values, see ref. 5. *Determined by HPLC on a Daicel Chiral OD column. *Determined by HPLC on a Daicel Chiral OD column.
Favored ligands in Pd(II)-catalyzed allylic acylation.

```
Ph Ph + NaCu(CO₂Et)₂ → [Pd]₂Cu(CO₂Et)₂
```

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>&lt;sup&gt;31&lt;/sup&gt;P NMR, ppm&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee, %&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Config&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>118.6, 113.9</td>
<td>-0</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>121.7, 115.4</td>
<td>-0</td>
<td>—</td>
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<tr>
<td>3</td>
<td>Ph</td>
<td>122.1, 115.3</td>
<td>16</td>
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<tr>
<td>4</td>
<td>Ph</td>
<td>127.4, 124.5</td>
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<td>(R)</td>
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<tr>
<td>5</td>
<td>Ph</td>
<td>110.6, 108.8</td>
<td>39</td>
<td>(R)</td>
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<table>
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<tr>
<th>Entry</th>
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<th>&lt;sup&gt;31&lt;/sup&gt;P NMR, ppm&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee, %&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Config&lt;sup&gt;d&lt;/sup&gt;</th>
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<td>151.9, 148.1</td>
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<td>(R)</td>
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</table>

<sup>a</sup> Ar of 4 was phenyl except entry 1 in which 2-naphthyl was applied.
<sup>b</sup> Chemical shifts of the ligands in CDCl₃, 85% H₃PO₄ was a reference standard.
<sup>c</sup> Determined by HPLC analysis with a chiral column (Daicel OD).<br> <sup>d</sup> Determined by the major peak of HPLC analysis from an authentic (R) major sample by the reaction with (S,S)-CHIRAPHCS.

Again, system is undefined from these experiments.

The end

- Systematic Analysis (cross-section) needs to be used to
- Some kind of subtle or strong economic effect
- Some kind of linear and mis-interpreted, as
- Some kind of linear and mis-interpreted, as
- Normalized in terms of C-F interaction
- A number of interactions have been performed with only
- Fluorine substitution generally affects reactivity and screening.

Conclusions.
REFERENCES OF NOTE
