CATALYTIC FLUORINATION & TRIFLUOROMETHYLATION

Speaker: Tao Xu
Wednesday seminar
March 6th, 2013
Outlines

Introduction
- Importance of F & CF₃ compounds
- Traditional ways to introduce F & CF₃
- How nature introduce F & CF₃

TM-Med./Cat. Fluorination
- Cu-mediated C-F formation
- Pd-catalyzed C-F formation
- Ag-catalyzed C-F formation

TM-Med./Cat. CF₃lation
- Cu-mediated C-F formation
- Pd-catalyzed C-F formation

Why are fluorination & trifluoromethylation important

2011 top prescription drugs

# 5 Lipitor $5.55 billion
blood cholesterol lowering

# 10 Crestor $6.65 billion
high cholesterol & cardiovascular disease

# 30 Seretide $8 billion
asthma & chronic obstructive pulmonary disease

# 65 Lilly Prozac
depressant

# 74 Pfizer Celebrex
anti-inflammatory & joint pain

# 103 Januvia
type II diabetes inhibitor

Increased i) Lipophilicity ii) Metabolically stablity
iii) Bioavailability iv) Low friction coefficient v) H-bonding vi) Interaction with target protein

Increased i) Lipophilicity ii) Metabolically stablity
iii) Bioavailability iv) Low friction coefficient v) H-bonding vi) Interaction with target protein
Application of F-containing in material and bio-imaging

Positron Emission Tomography (PET)

Millions of PET scans
Half Life of $^{18}\text{F}=109.771$ mins/1.8 hrs

**Taditional ways to form C-F bond**

**Nucleophilic Fluorination----Halex process**

\[
\begin{align*}
\text{Cl-Cl} & \xrightarrow{\text{KF, CNC, sulfolane}} \text{F-F} \\
\text{Cl} & \text{N} & \text{Cl} & \text{N} & \text{Cl} & \text{N} & \text{Cl} & \text{N} & \text{Cl} & \text{N} & \text{Cl} & \text{N} & \text{Cl} & \text{N}
\end{align*}
\]


**Electrophilic Fluorination**

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{PhO}_2S\text{N}_2\text{SO}_2\text{Ph}} \text{Ph}
\end{align*}
\]


**Balz-Schiemann reaction**

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{HBF}_4, \text{NaNO}_2} \text{Ph}
\end{align*}
\]


**Summary**

i) still important for industry  
ii) harsh conditions (pyrolysis)  
iii) limited substrates  
iv) early stage introduction
Traditional ways to form C-CF$_3$ bond

Swarts reaction (1892)

Electrophilic Fluorination

Nature’s way to introduce Cl vs. F

How haloperoxidase function

Nature’s way to introduce F

How fluoperoxidase function

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TM-Med./Cat. CF₃lation

- Cu-mediated C-F formation
- Pd-catalyzed C-F formation

The strongest single C-F bond is thermodynamically favored, while reductive elimination is kinetically slow. A thermodynamically feasible but kinetically challenging reaction can be addressed ideally by catalysis.

Summary

i) C-F bond is the strongest single bond.

ii) F is the most electron negative.

iii) M-F bond is highly polarised & strong.

iv) F forms H-bonding with OH, NH & amide.
First catalytic C-F bond formation (2002)

\[ \text{M-F}_x + \text{C-H} \rightarrow \text{M-F}_{x-2} + \text{C-F} + \text{HF} \quad \text{Eq. 1} \]

**Hypothesis**

\[ \text{M-F}_{x-2} + 0.5 \text{O}_2 + 2\text{HF} \rightarrow \text{M-F}_x + \text{H}_2\text{O} \quad \text{Eq. 2} \]

**Which metal fluoride salts**

Table 1. Oxidation-reduction potential for metals in various oxidation states. In the group with reduction potential \( E^o > 1 \), the fluorides are strong oxidants and can be recycled with elemental fluorine. For the group with \( E^o \) in the range \( 1 > E^o > 0 \), the fluorides are moderate oxidants and can be recycled with HF and \( \text{O}_2 \). For the group with \( E^o < 0 \), the fluorides are inert toward C–H bonds. \( (E^o, \text{reduction potential} = 0.0 \text{ for } 2\text{H}^+ + 2\text{e}^- \leftrightarrow \text{H}_2) \)

<table>
<thead>
<tr>
<th>( E^o &gt; 1 )</th>
<th>( 1 &gt; E^o &gt; 0 )</th>
<th>( E^o &lt; 0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Co}^{3+} + \text{e}^- \leftrightarrow \text{Co}^{2+} )</td>
<td>( \text{Cu}^{2+} + 2\text{e}^- \leftrightarrow \text{Cu}^0 )</td>
<td>( \text{Zn}^{2+} + 2\text{e}^- \leftrightarrow \text{Zn}^0 )</td>
</tr>
<tr>
<td>( \text{Ag}^{2+} + \text{e}^- \leftrightarrow \text{Ag}^{1+} )</td>
<td>( \text{Ag}^{1+} + \text{e}^- \leftrightarrow \text{Ag}^0 )</td>
<td>( \text{Mg}^{2+} + 2\text{e}^- \leftrightarrow \text{Mg}^0 )</td>
</tr>
<tr>
<td>( \text{Pb}^{4+} + 2\text{e}^- \leftrightarrow \text{Pb}^{2+} )</td>
<td>( \text{Te}^{4+} + 4\text{e}^- \leftrightarrow \text{Te}^0 )</td>
<td>( \text{Al}^{3+} + 3\text{e}^- \leftrightarrow \text{Al}^0 )</td>
</tr>
<tr>
<td>( \text{Ce}^{4+} + \text{e}^- \leftrightarrow \text{Ce}^{2+} )</td>
<td>( \text{Hg}^{2+} + 2\text{e}^- \leftrightarrow \text{Hg}^0 )</td>
<td>( \text{Co}^{2+} + 2\text{e}^- \leftrightarrow \text{Co}^0 )</td>
</tr>
</tbody>
</table>

**Catalytic process**

\[ \text{CuF}_2 + \text{C-C} \rightarrow \text{CuF}_2 + \text{HF} + \text{H}_2\text{O} \]

**Summary**

i) Limited substrate scope: PhF, TolF.
ii) Low regioselectivity.
iii) High temperature.

First Pd catalyzed C-F bond formation (Sanford, 2006)

\[
\text{Scheme 28}
\]

\[\begin{align*}
\text{Product} & \quad \text{Yield (%) Product} & \quad \text{Yield (%)}
\hline
\text{CF}_3 & \quad 75 & \quad \text{F} & \quad 33\text{–}75\%
\text{CO}_2\text{Et} & \quad 67 & \quad \text{MeO} & \quad 33
\end{align*}\]

Summary

i) the first Pd-catalyzed C-F bond formation.
ii) harsh conditions still needed. (Microwave)
iii) blocking groups to avoid difluorination.

The fluorination of arylpalladium(IV) fluoride complexes is a promising approach for the formation of aryl fluorides. This process is particularly appealing due to the mild reaction conditions and the broad scope of functional groups that can be tolerated. A variety of fluorinating reagents, such as XeF$_2$, have been utilized in these transformations, and the use of oxidants like NBS and FN(SO$_2$Ph)$_2$ further enhances the reaction efficiency.

For example, in 2006, our group demonstrated that 2,2'-substituted aryl groups can be fluorinated with high efficiency using the XeF$_2$-catalyzed ligand-directed fluorination of arylpalladium(II) complexes. This method has since been extended to a wide range of substrates, leading to the preparation of fluorinated products with yields comparable to those obtained with electrophilic fluorinating reagents.

Mechanistic studies have suggested that the reaction proceeds through the formation of an unsymmetrical square planar Pd(II) intermediate, which undergoes a C–F bond formation upon oxidation. The mechanism of C–F bond formation has been proposed to involve the oxidative addition of XeF$_2$ to the Pd(II) complex, followed by the oxidative addition of a fluorinating reagent to the resulting Pd(IV) complex, leading to the formation of the aryl fluoride product.

While a variety of synthetic approaches are available for the fluorination of arylpalladium complexes, the development of more efficient and practical methods for the formation of aryl fluorides is still a significant challenge. An attractive approach to address this challenge would be the use of catalytic systems for the fluorination of arylpalladium complexes, which could potentially provide a more versatile and environmentally friendly method for the synthesis of aryl fluorides.
Follow up work by Yu group (2009)

**Product Yield (%)**

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Nucleophilic fluorination" /></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summary**

1. **NMP is essential for the fluorination.**
2. **blocking groups still remained.**
3. **derivatization of DG is versatile.**

Pd-catalyzed fluorination of ArB(OH)₂ by Ritter (2008)

12 examples, 65–91%

Pd-catalyzed fluorination of ArB(OH)$_2$ by Ritter (2008)

Mechanism study

Summary

i) A Pd(IV) might be involved.

ii) couldn’t observed by NMR.

iii) reversible color change--yellow to orange.


$^{19}$F NMR: $-169$, $-278$ ppm; $^3$J$_C$-$F$ = 113 Hz; $^3$J$_C$-$F$ = 63 Hz
Ag-catalyzed C-F bond formation of ArB(OH)$_2$ (Ritter 2009)

Yields are given for isolated and purified compounds. If boiling points were too low to report accurate yields, the yield was determined by $^{19}$F NMR (internal standard, see Supporting Information). Isolated yields and yields determined by $^{19}$F NMR differed by less than 5%. $^a$ 1.2 equiv of NaOH and 3.0 equiv of AgOTf were used.

Ag-catalyzed C-F bond formation of Aryl Stannanes (Ritter 2009)

Application in NP substrate

- deoxy-fluoro-δ-tocopherol (16), 69% yield
- fluorocamptothecin (17), 70% yield
- demethoxy-fluoroquinine (18), 73% yield

First Pd-catalyzed C-F formation back in 2007 (Yandulov)

**Proposed mechanism (Grushin 2007)**

Grushin, V. V.; Marshall, W. J. *Organometallics* 2007, 26, 4997.

First Pd-catalyzed C-F formation from ArOTf (Buckwald 2009)

\[
\text{R} - \overset{\text{OC}}{\text{OTf}} + \text{CsF} \rightarrow \text{R} - \overset{\text{F}}{\text{F}}
\]

L = 2. \( ^a \) 5 equiv. AgF, CH$_2$Cl$_2$, 25 °C, exclusion of light, 12 to 24 h. 

\( ^b \) toluene, 100 °C, 2 h, yields determined by $^{19}$F NMR spectroscopy.
Cul-mediated fluorination of Aryl iodide & Aryl boron ester (Hartwig 2012)

Proposed mechanism

\[
\begin{align*}
\text{Cu}_2\text{O} + \text{HX} \xrightarrow{\text{RCN}} (\text{RCN})_4\text{CuX} \\
(\text{BuCN})_n\text{Cu} - \text{OTf} + \text{AgF} \xrightarrow{\text{F}^-} (\text{BuCN})_n\text{Cu} - \text{F} \xrightarrow{\text{ArF}} \text{Ar} - \text{F} + (\text{BuCN})_n\text{Cu} - \text{OTf}
\end{align*}
\]

Boron ester substrate

Catalyst preparation

\[\text{Cu}_2\text{O} + \text{HX} \xrightarrow{\text{RCN}} (\text{RCN})_4\text{CuX}\]

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- Cu-catalyzed C-CF$_3$ formation

Pd-mediated/catalyzed trifluoromethylation

**CF₃ source**

a) polyfluorinated methanes (CF₃I, CF₃Br, CF₂Br₂, CF₃H)
b) derivatives of CF₃CO₂H & FSO₂CF₂CO₂H.
c) *in situ* generated CF₃Cu from transmetallation.
d) TMSCF₃, TESCF₃

**Difficulty of reductive elimination**

\[
\begin{align*}
\text{Ph} & \quad \text{Pd} & \quad \text{CF}_3 & \quad \text{o-tol} & \quad 130 \, ^\circ\text{C}, \text{days} & \quad \text{no reaction} \\
\text{Ph} & \quad \text{Pd} & \quad \text{CF}_3 & \quad \text{CH}_2\text{CF}_3 & \quad 110 \, ^\circ\text{C}, 36 \, \text{h} & \quad 96\% \\
\text{Ph} & \quad \text{Pd} & \quad \text{CH}_3 & \quad \text{CH}_2\text{CF}_3 & \quad 40 \, ^\circ\text{C}, 4 \, \text{h} & \quad 99\%
\end{align*}
\]


**Large bite angle**

\[
\begin{align*}
\text{Ph} & \quad \text{Pd} & \quad \text{CF}_3 & \quad \text{Xantphos} & \quad 80 \, ^\circ\text{C} & \quad \text{PhCF}_3 + [(\text{Xantphos})_2\text{Pd}] \\
\text{Ph} & \quad \text{Pd} & \quad \text{CF}_3 & \quad \text{Xantphos} & \quad 80 \, ^\circ\text{C} & \quad \text{PhCF}_3 + [(\text{Xantphos})_2\text{Pd}]
\end{align*}
\]


First example CF₃ RE on Pd(II) center
Cu-mediated Ar-CF₃ bond forming reaction

I

CF₃I (0.7 equiv), Cu (3.8 equiv), DMF, 150 °C, 12 h

CF₃

The first Ar-CF₃ forming cross-coupling reaction

First Cu-catalyzed reaction (2009)

I

R₁

R₂

R₃

TESCF₃, KF 10 mol% Cul 10 mol% 1,10-phenanthroline 60 °C

CF₃

R = NO₂, CN, CO₂Et, Cl 63–90%

69%

99%

63%
Pd-mediated/catalyzed trifluoromethylation

**Scheme A**

\[
\begin{align*}
&\text{R} \quad \text{L-Pd-Cl} \\
&12a: \text{R=CO}_2\text{Me} \quad 12b: \text{R=OMe} \\
\quad \text{TESCF}_3 (5 \text{ equiv}) \\
&\quad \text{CsF} (2 \text{ equiv}) \\
&\quad \text{THF}, 24 \text{ h, rt} \\
\quad \text{Dioxane, 80 °C} \\
&\quad \text{L-Pd-CF}_3 \\
&13a: 38\% \\
&13b: 37\% \\
&14a: t_{1/2} = 22 \text{ min} \\
&14b: t_{1/2} = 24 \text{ min}
\end{align*}
\]

**Difficulty of reductive elimination**

**Scheme B**

**Recent results**

\[
\begin{align*}
&\text{R} \quad \text{X} \\
&\quad \text{TMSCF}_3 \\
&\quad \text{TESCF}_3 \\
&\quad \text{Pd(dbq)}_2/t-\text{BuXPhos} \\
&\quad \text{KF or RbF} \\
&\quad \text{Dioxane, 110 °C, 3 ~ 10 h} \\
&\quad \text{CF}_3
\end{align*}
\]

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Pd-mediated/catalyzed trifluoromethylation (Sanford 2010)


Yu’s work


Incorporation of fluorine into organic molecules represents an increasingly important strategy to synthesize bioisosteric compounds with improved properties such as solubility, metabolic stability, and bioactivity, which are prerequisite for many pharmaceuticals. As a consequence, catalytic transformation of aromatic and aliphatic compounds has been extensively studied. Among catalytic reactions, palladium-catalyzed oxidative aryltrifluoromethylation has been made by using a catalytic palladium complex, which was generated from the oxidative cycloaromatization of aryl C–H bond. However, for the arylation of simple aromatic compounds, reactions such as aminooxygenation, fluoroamination, and phosphonamidation have been shown to involve a C–H activation process. For less reactive aryl chlorides, the Pd-catalyzed trifluoromethylation requires expensive CF$_3$ reagents, such as trimethylsilyl triflate (TMSCF$_3$) or (Me$_3$Si)$_2$CF. For instance, Buchwald and co-workers reported a Pd-catalyzed oxidative aryltrifluoromethylation with TMSCF$_3$ as a reagent and CsF as an oxidant (Scheme 1A). Herein, we report a novel Pd-catalyzed oxidative arylation of indoles at room temperature, in which the catalytic system is more practical (Scheme 1B).

**Scheme 1. Pd-catalyzed trifluoromethylation of aromatic compounds.**

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Cu-mediated/catalyzed trifluoromethylation

1/4 [CuOBu-t]₄ → [(phen)CuCF₃]

(1) 1,10-phenanthroline (1.0 equiv.) benzene, r.t., 0.5 h
(2) Me₃SiCF₃ (1.1 equiv.) RT, 18 h

[(phen)CuCF₃] + R\(\text{I}\) → R\(\text{CF₃}\)


R¹ \(\text{R²}\)

(1) 0.75 equiv. B₂pin₂
cat. [[Ir(cod)(OMe)]₂], dtbpy
THF, 80 °C

(2) remove volatiles
(3) 1.2 equiv. [(phen)CuCF₃]
1.0 equiv. KF
Air, DMF, 50 °C


R¹ \(\text{R²}\)

CF₃SiEt₃, KF
Cat. Cul, Cat. Phen
NMP-DMF (V:V = 1:1)
60 °C, 24 h


CuF₂•3H₂O + PPh₃ → (phen)CuCF₃

(1) MeOH, reflux
(2) Evaporation, drying
(3) Me₃SiCF₃ in THF

[Ph₃P]₂Cu(CF₃) + R\(\text{I}\) → R\(\text{CF₃}\)

t-Bu-bpy toluene, 80 °C

Grushin, V. V. etc. Angew. Chem., Int. Ed. 2011, 50, 7655.

F₃C-SiMe₃ + B(OMe)₃ → [K⁺, MeO⁻]⁻ F₃C⁻ B⁻ OMe⁻ OMe⁻

KF
THF, r.t., 24 h

F₃C⁻SiMe₃ + B(OMe)₃ → [K⁺, MeO⁻]⁻ F₃C⁻ B⁻ OMe⁻ OMe⁻

Cul (cat.), phen (cat.)
DMSO, 60 °C, 16 h

R¹ \(\text{R²}\)

R¹ \(\text{R²}\)

Cu-mediated/catalyzed trifluoromethylation

R\(\ce{CH=CH} \) + \(\text{CF}_3\text{OTf}^+\) \(\text{Cu}(\text{OAc})_2\text{ (20 mol\%)}\) \(\text{DMAc, 40 °C}\) \(\text{CF}_3\) 
27 examples up to 78%

R\(\ce{CH=CH} \) + \(\text{CF}_3\) \(\text{CuCl} \text{ (10 mol\%)}\) \(\text{MeOH, 70 °C or 90 °C, 10 min or 1 h}\) \(\text{CF}_3\) 
15 examples 44% ~ 97%

\(\text{Cu(OAc})_2\text{ (40 mol\%)}\) \(\text{phen (40 mol\%)}\) \(\text{CF}_3\text{SiMe}_3, \text{tf-BuONa, NaOAc, air, DCE, 80 °C}\) 

\(\text{Cu(OAc})_2\text{ (40 mol\%)}\) \(\text{phen (40 mol\%)}\) \(\text{CF}_3\text{SiMe}_3, \text{NaOAc, tf-BuONa} \text{ (CH}_3\text{)}_2\text{COOC(CH}_3\text{)}_3 \text{DCE, N}_2, 80 °C\) 

Path I

\(\text{R}^3\text{CuL}_n\text{ + base}\) \(\text{L}_n\text{Cu(I)}\) \(\text{Ar-CF}_3\) \(\text{Ar-CuL}_n\text{ + base}\) 

\(\text{Ar-H}\) \(\text{oxidant}\) \(\text{CF}_3\text{SiMe}_3\) + base 

Path II


In regard to the reaction mechanism, we first excluded the involvement of an allylic radical intermediate. This mechanism was proposed for Cu-catalyzed allylic oxidation or alkylation, but it cannot explain why 6a was never observed in the reaction. The formation of 5a is also difficult to explain using an allylic radical mechanism. Furthermore, the radical allylic H-abstraction mechanism cannot explain why the reaction does not favor internal alkenes. We next tested the Cu/C0 allyl mechanism (Scheme 3). First, 1a was treated with CuTc and L1 in the absence of 2a. Through 1H NMR analysis of the recovered materials, we found no incorporation of deuterium at position i of 1a. We did not observe the isomerization of 1a to 11 either. We subsequently performed trifluoromethylation in CD3OD. We were surprised to find that although 3a was produced, the major product became 4a. Nonetheless, we did not observe any incorporation of deuterium at positions iii or iv in the products or at position i of the recovered reactant 1a. Finally, a trace amount of 5a was also detected. These results argue against a Cu/C0 allyl mechanism.

Finally, we considered another mechanism that was recently proposed for Cu-catalyzed C/C0H functionalization in which the Cu/C0 C bond is generated via a Heck-like four-membered-ring transition state. As shown in Figure 1, in the proposed catalytic cycle, the reaction starts with complex IN0, which reacts with 2a to produce the Cu(III) complex IN1. The olefin substrate replaces OTf/C0 in IN1 to generate IN2 and IN3. From IN3, the critical Heck-like four-membered-ring transition state (TS1a) is identified. Through TS1a the CF3 group is transferred to the terminal carbon atom, whereas the formation of its isomer requires TS1a-iso, which is much less stable. This theoretical prediction explains why 6a is not observed and also indicates that the functionalization of internal alkenes is more difficult than for terminal alkenes. The immediate product of TS1a is IN4. After OTf/C0 coordinates to Cu, an elimination reaction takes place at IN5. Our calculations indicate that the generation of 3a is more favorable than that of 4a. This prediction is consistent with the regioselectivity observed in DMAc. It is also expected that IN5 may be directly protonated at the Cu/C0 C bond, generating compound 4a.
Thank you!
$^{18}\text{F}-\text{FDG}$ synthesis

$$\text{1} + [(\text{crypt-222})\text{K}]^{^{18}\text{F}^-} \rightarrow \text{3}$$

Ac = CH$_3$CO
Tf = CF$_3$SO$_2$

1. NaOH
2. HCl

$$\text{4}$$
Mechanism of DBH

\[
\begin{align*}
\text{Ar-S-CH}_2\text{-CH}_2\text{-R} & \quad \xrightarrow{\text{DBH}} \quad \text{I} \\
\text{CHF}_2\text{-CH}_2\text{-R} & \quad \xrightarrow{a} \quad \text{4} \\
\text{CHBrF-CH}_2\text{-R} & \quad \xrightarrow{b} \quad \text{9} \\
\text{R} &= \text{C}_9\text{H}_{19}
\end{align*}
\]
Electrophilic fluorinating reagents have been achieved by Differding and Lang using the chiral imide this type, such as fluoropyridinium salts were first developed in the 1980s as a new class of broadly applicable fluorinating reagents of -alkylsulfonamides with dilute elemental fluorine. Fluoropyridinium salts were first developed in the 1980s as a new class of broadly applicable fluorinating reagents of -alkylsulfonamides with dilute elemental fluorine. In 1984, Barnette reported the use of milder reaction conditions for the preparation of fluorinated products. The reaction reported by Yu employed milder reaction conditions for the preparation of fluorinated products. A single electron transfer process as shown in Figure 3 as a new class of broadly applicable fluorinating reagents of -alkylsulfonamides with dilute elemental fluorine.

### Scheme 30

![Scheme 30](image)

**Substrate Scope of the Palladium-Catalyzed Directed Electrophilic Fluorination**

Electrophilic fluorination reaction was a significant advance in this area. Challenges that remain are the harsh reaction conditions and the need for blocking groups in the reaction. The reaction reported by Yu employed milder reaction conditions for the preparation of fluorinated products. A single electron transfer process as shown in Figure 3 as a new class of broadly applicable fluorinating reagents of -alkylsulfonamides with dilute elemental fluorine.

### Table 8

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
<th>Product</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td>toluene 130 °C, 12 h 48%</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td>MeOH, 0 °C ~ rt, 24 h 54%~87% yield</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td>CHCl₃ / rt 51%</td>
</tr>
</tbody>
</table>

### General Scheme of Pd-mediated Directed Electrophilic Fluorination

![General Scheme](image)
transformation because the reaction produced group at the allylic position exhibited moderate reactivity in this linear and branched isomers and also showed relatively low.

Allyl substrates bearing an aromatic moiety yielded a mixture of

Scheme 2. Mechanistic Rationale

Scheme 1. Capture of CF

chanism, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well-
to previous reports.

reasonable to conceive a pathway in

cyclohexane derivative
elevated temperature, giving the corresponding CF

at the cyclohexyl ring could also be tri

is noteworthy that a substrate featuring an exocyclic double bond

also react with

ester isomers of the substrate with a shift of the double bond

in the presence of stoichiometric CuCl under the

a

/u0210/C0

order the corresponding tri

s bearing an ester

α,β-

unsaturated

fluoromethylated at slightly

fluoromethylation, it is

fns bearing an ester

C(sp

methylation reaction has been developed. In this transformation,

not clear at the present stage.

n substrate

CuCl catalytically

mechanism. A mechanistic rationale involving several possible

pathways is outlined in Scheme 2. Initially, CuCl catalytically

ing allyl radical

the hypervalent iodine(III) reagent to generate the correspond-

path (a).

\[ \text{path b} \]

\[ \text{path c} \]

\[ \text{path a, c} \]

These experimental results provided supportive evidence that

hypervalent iodine(III) reagent as both the oxidant and the CF

These experimental results provided supportive evidence that

ACKNOWLEDGMENT

AUTHOR INFORMATION

ASSOCIATED CONTENT

REFERENCES