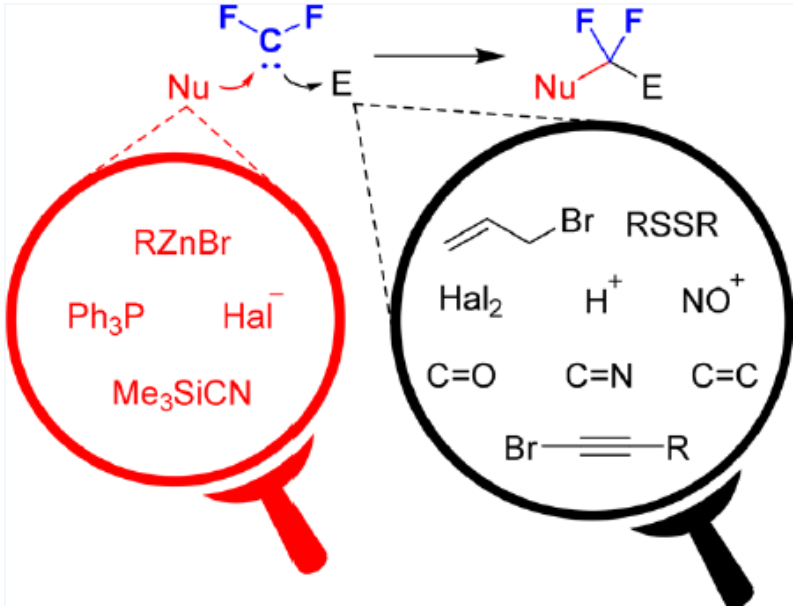
Difluorocarbene as a Building Block for Consecutive Bond-Forming Reactions



Reporter: Jingwei Xu

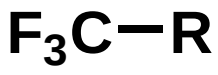
Supervisor: Prof. Yong Huang

2018-05-21

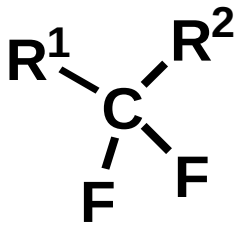
Acc. Chem. Res. **2018**, *51*, 1272−1280

Introduction

Typically, in these molecules, the fluorine is present either in the form of a CF_3-group or as a substituent, whereas compounds with a difluoromethyl group or a difluoromethylene fragment are encountered less frequently.

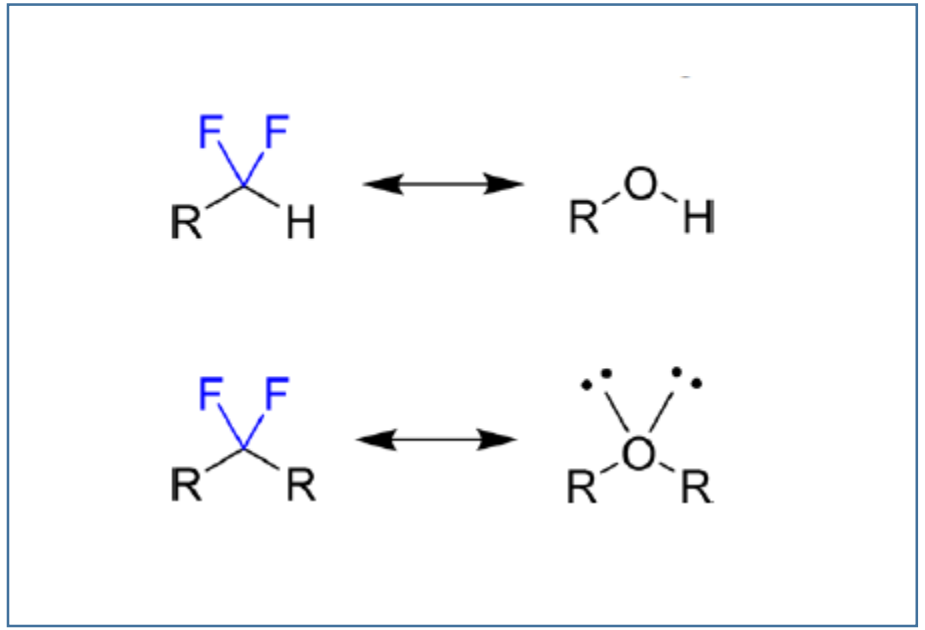


Frequent



Rare

Bioisosterism of the CF_2 Fragment



J. Am. Chem. Soc. **2017**, *139*, 9325−9332
J. Med. Chem. **2005**, *48*, 3319−3327

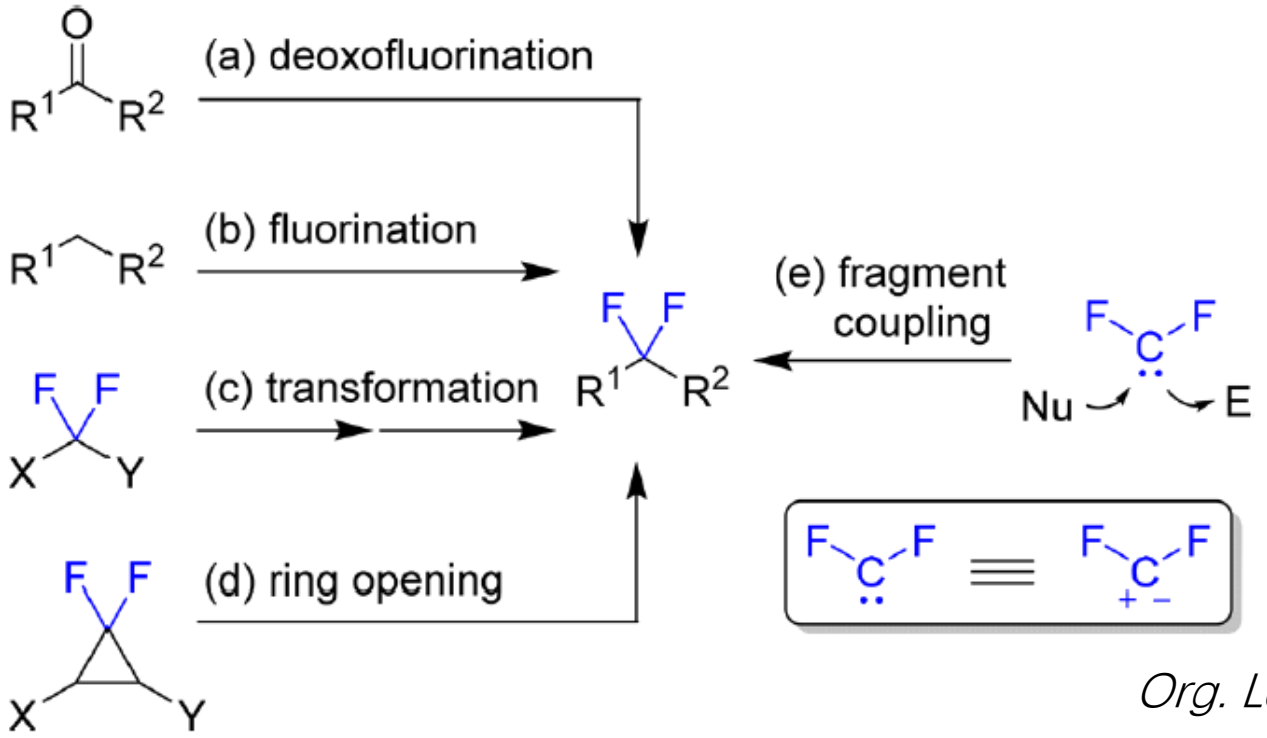
Introduction

Harsh condition and hazardous

remains to be elaborated

long synthetic sequence

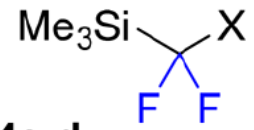
Scope limited



Org. Lett. **2013**, *15*, 917−919

(a) *Aldrichimica Acta* **2011**, *44*, 65−75
(b) *Org. Lett.* **2018**, *20*, 1042−1045
Science **2016**, *353*, 51−54
(c) *Synlett* **2011**, *2011*, 1052−1072
(d) *Chem. Rev.* **2003**, *103*, 1071−1098
J. Org. Chem. **2015**, *80*, 5870−5876
Tetrahedron Lett. **2017**, *58*, 1806−1816

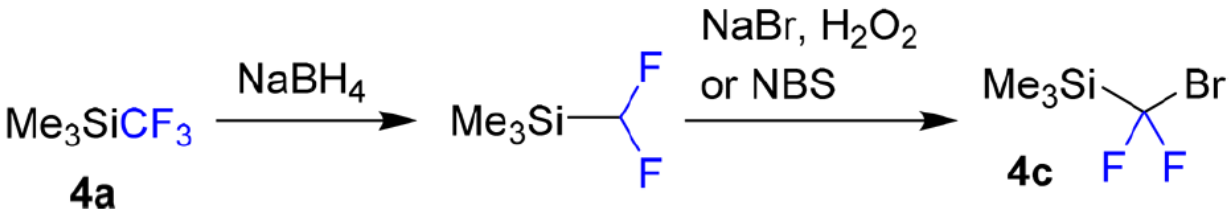
Introduction



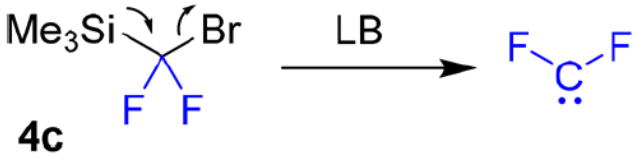
4a-d

	X	reactivity	availability
a	F	*	****
b	Cl	**	**
c	Br	***	***
d	I	****	*

J. Org. Chem. **2014**, *79*, 7831−7835
J. Org. Chem. **2014**, *10*, 344−351
Mendeleev Commun. **2015**, *25*, 239−244
Synthesis **2017**, *49*, 3394−3406



4a **4c**



4c

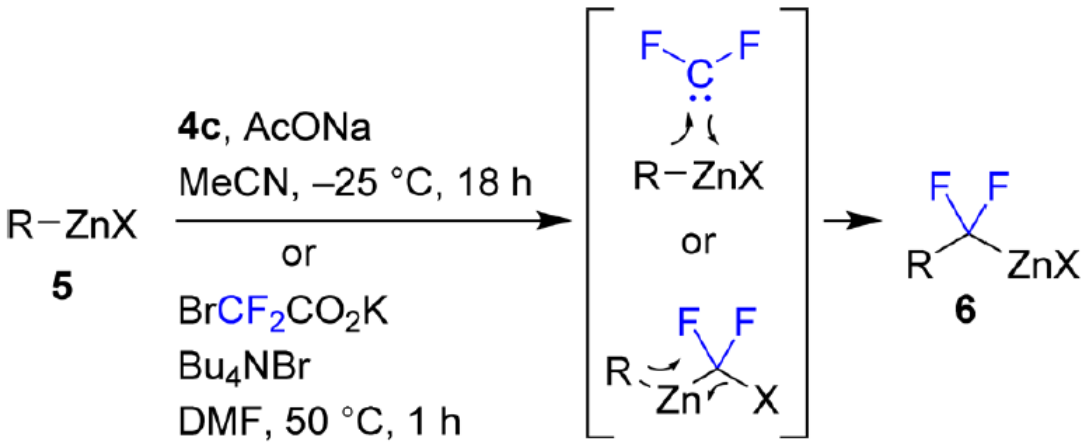
LB= Lewis Base

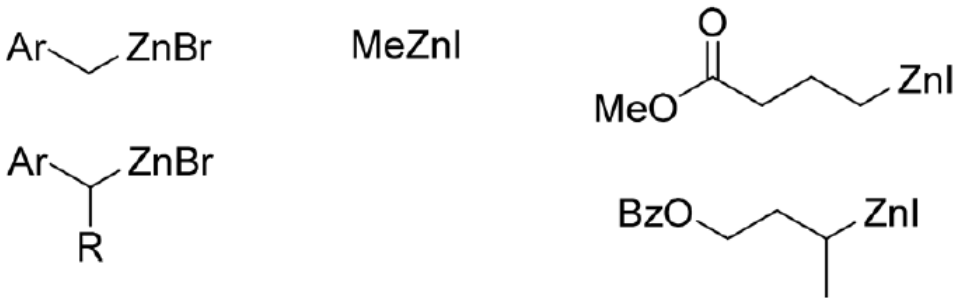
LB	T, °C
Br^-	80–110
HMPA, DMPU	0–rt
AcO^-	–25 °C

Chem. Commun. **2011**, *47*, 2411−2413

ORGANOMETALLIC REAGENTS AS NUCLEOPHILES

Organometallic



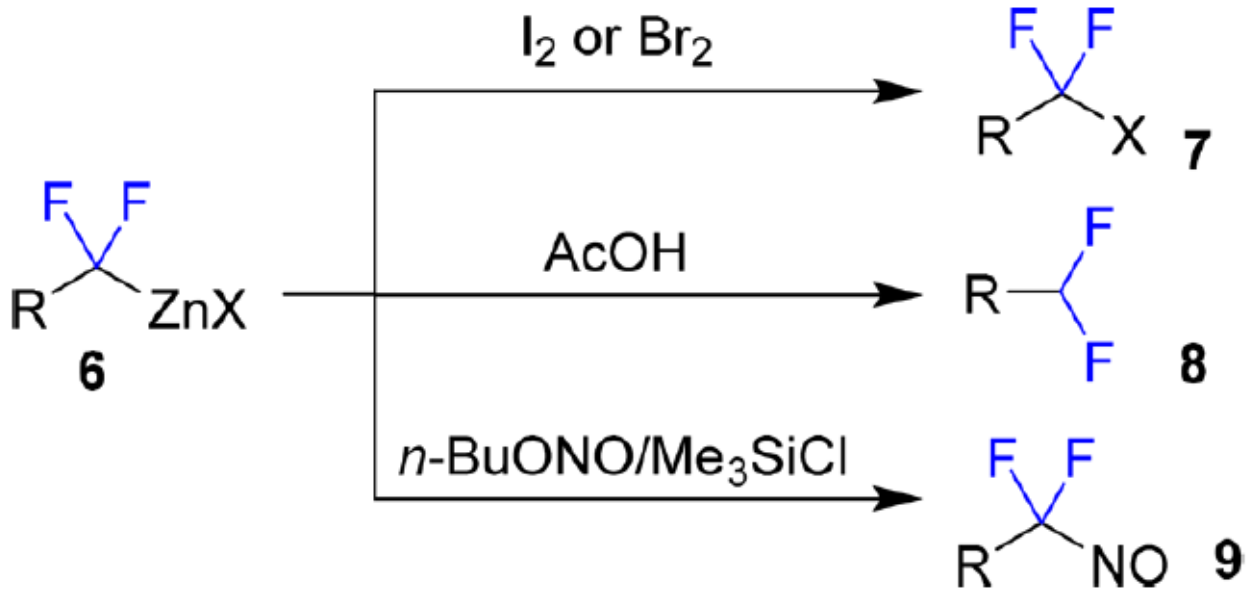


M= Li or Mg

UNSTABLE

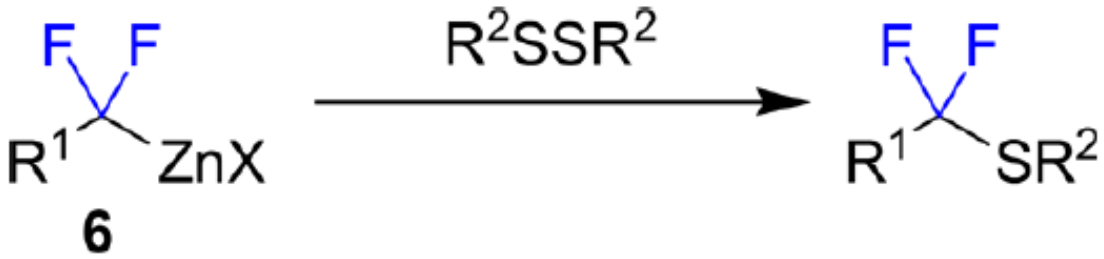
J. Fluorine Chem. **2015**, *171*, 97–101

Organometallic



J. Org. Chem. **2014**,*79*, 11819−11823
Russ. Chem. Bull. **2014**, *63*, 2564−2566
J.Fluorine Chem. **2015**, *171*, 97−101

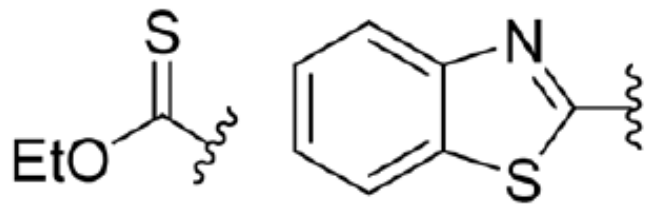
Organometallic



6

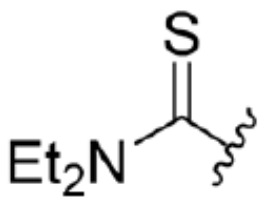
$CuCl \cdot 1.5PPh_3$ (5%)
–25 °C to rt

for R^2 =



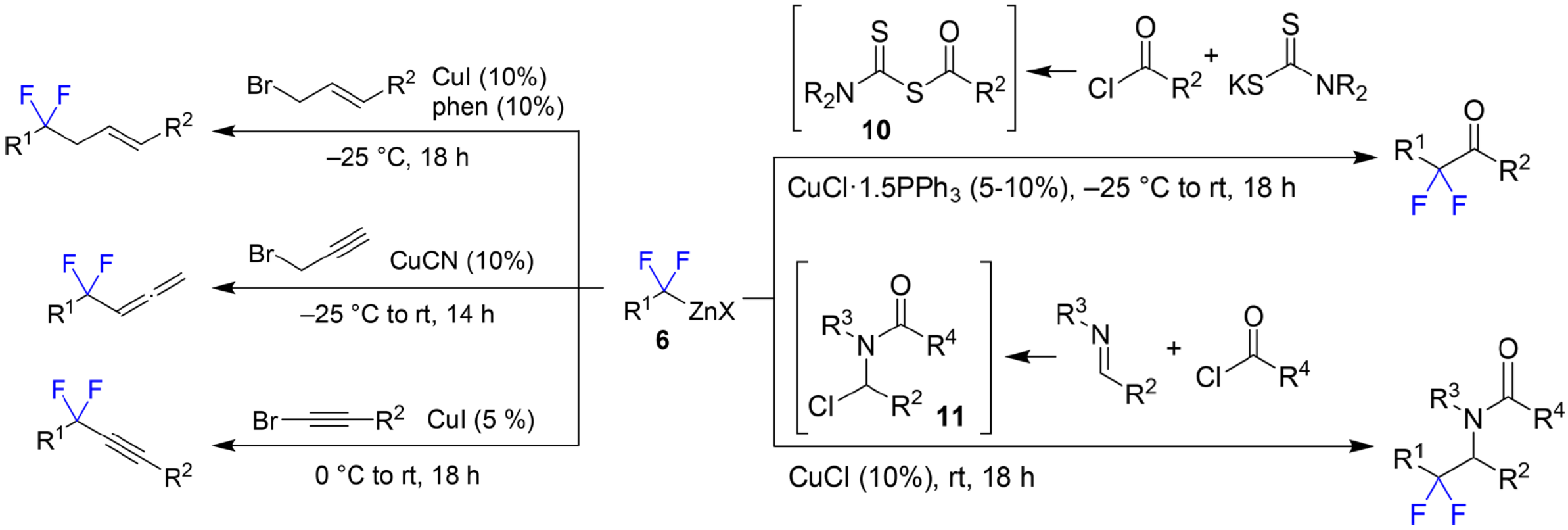
Eosin Y-Na_2 (2%)
blue LED, rt

for R^2 = Ph



J. Fluorine Chem. **2016**, *191*, 143–148

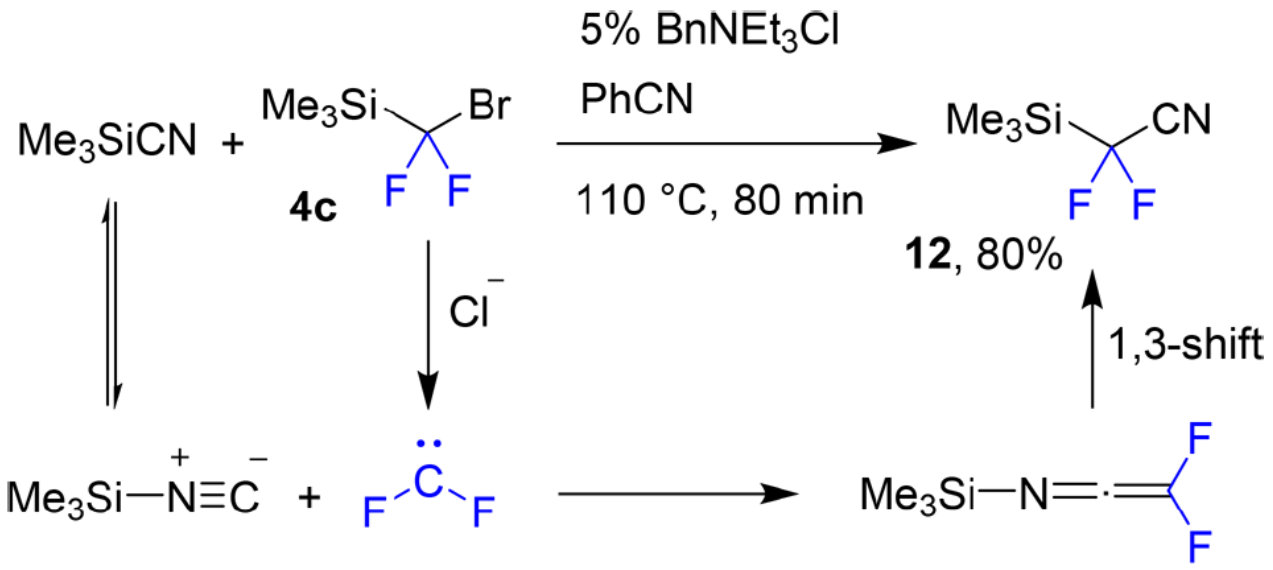
Organometallic

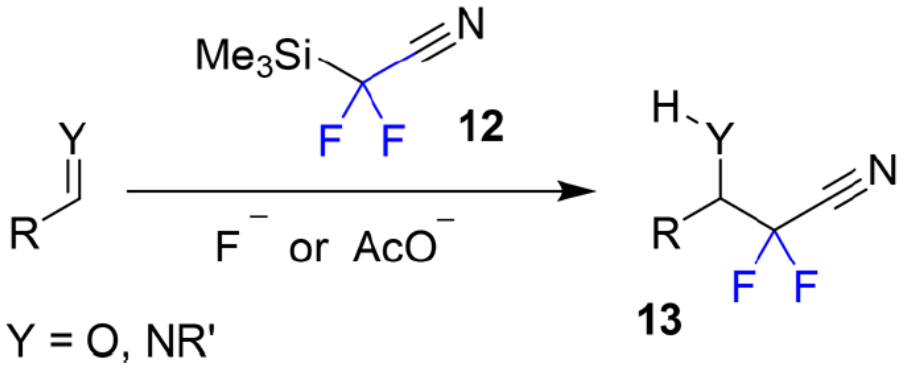


J. Org. Chem. **2014**, *79*, 818−822
J. Org. Chem. **2015**, *11*,2145−2149.
Russ. Chem. Bull. **2016**, *65*, 2760−2762

J. Org. Chem. **2018**, *83*, 478−483
Mendeleev Commun. **2017**, *27*, 139−140

Organometallic



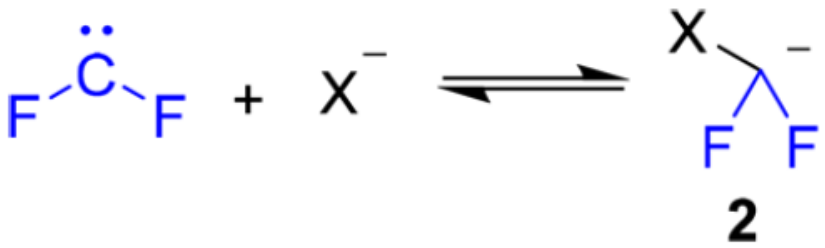


J. Org. Chem. **2012**, *77*, 5850−5855

HALIDE IONS AS NUCLEOPHILES

Halide Ions

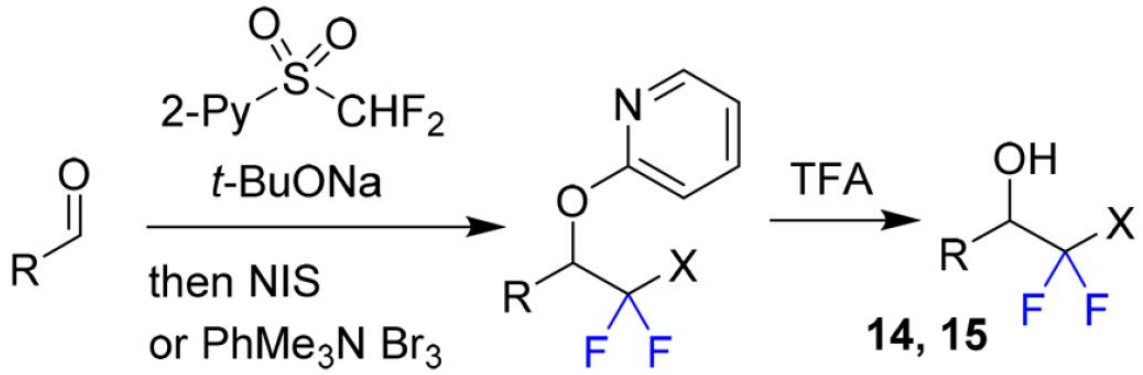
Generation of Halodifluoromethyl Carbanion



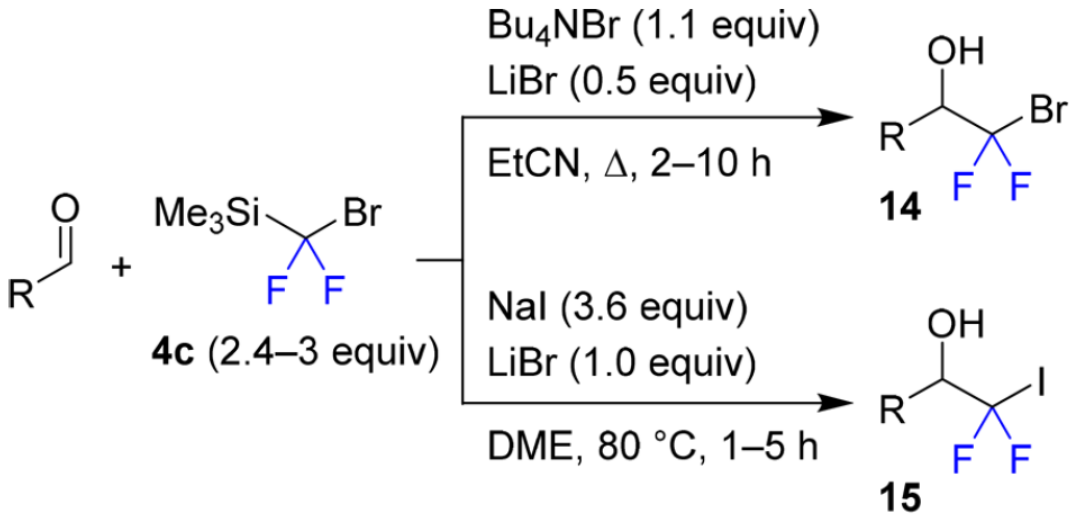
X = F, **2** can be observed
X = Cl, theory, C-Cl 2.56 Å
X = Br, I ?

Angew. Chem., Int. Ed. **2014**, *53*, 11575−11578

Halide Ions



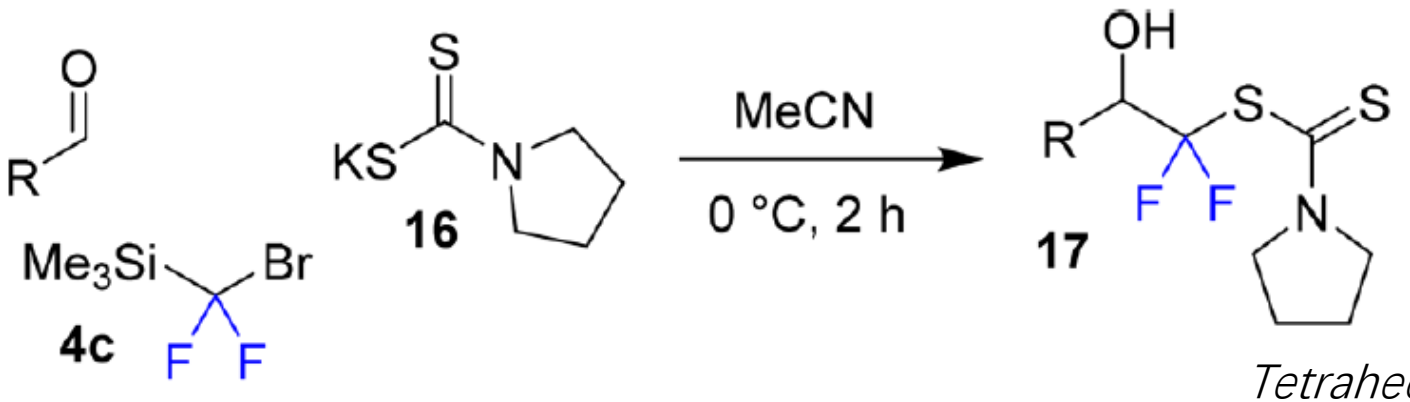
J. Am. Chem. Soc. **2012**, *134*, 5790−5793



Org. Lett. **2014**, *16*, 3784−3787.

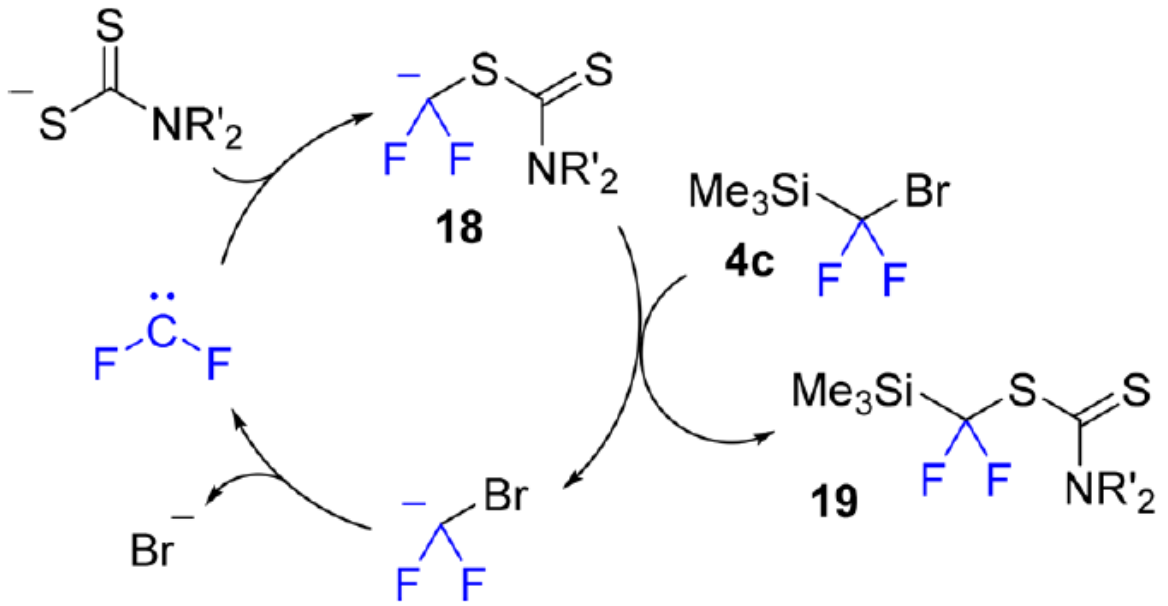
J. Org. Chem. **2015**, *80*, 9349−9353

Halide Ions



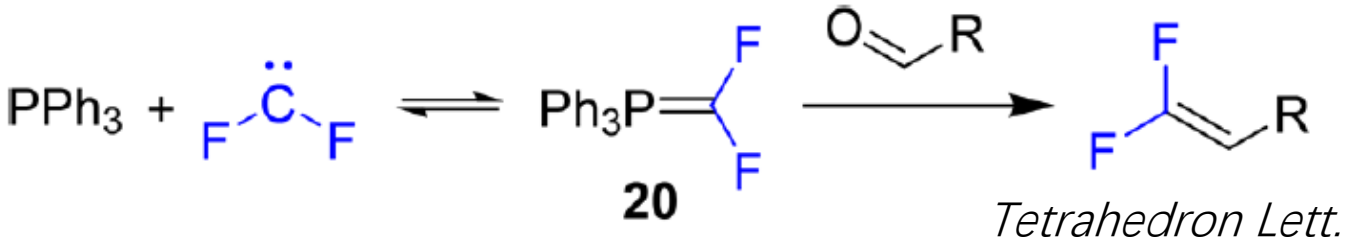
Tetrahedron Lett. **2015**, *56*, 5048−5050

Mechanism



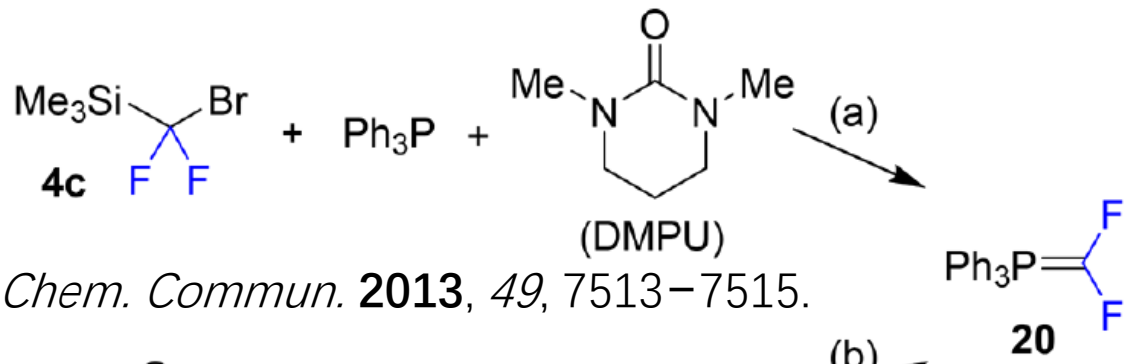
TRIPHENYLPHOSPHINE AS A NUCLEOPHILE

Tripenylphosphine

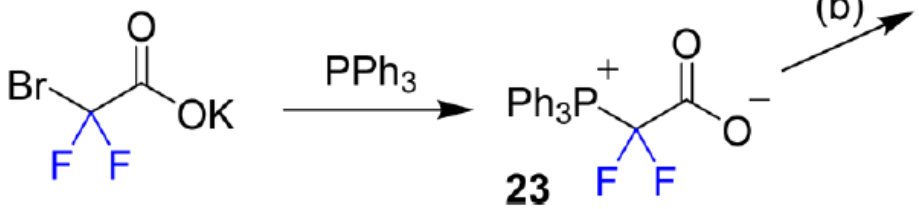


Tetrahedron Lett. **1964**, *5*, 1461−1463

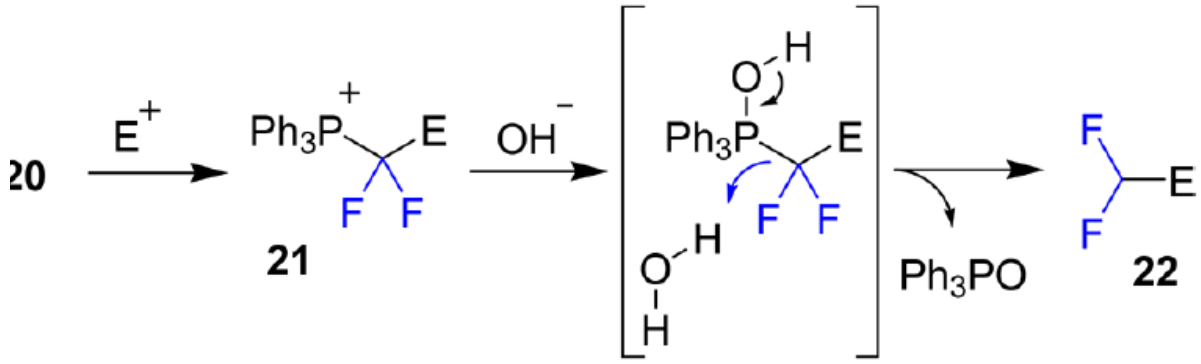
Chem. Rev. **1996**, *96*, 1641−1716



Chem. Commun. **2013**, *49*, 7513−7515.

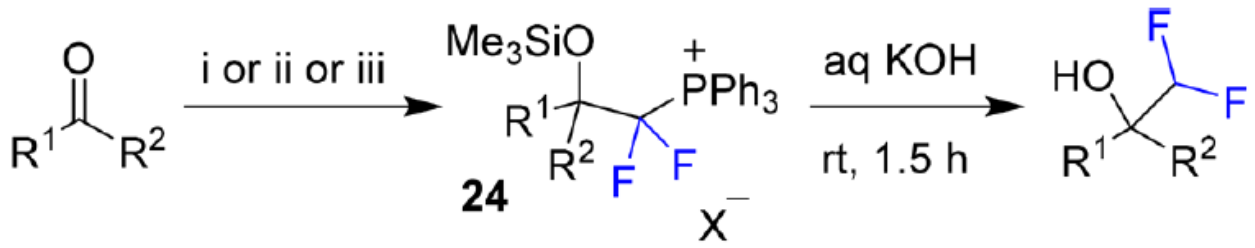


Chem. - Eur. J. **2013**, *19*, 15261−15266.



Org. Lett. **2016**, *18*, 3458−3461

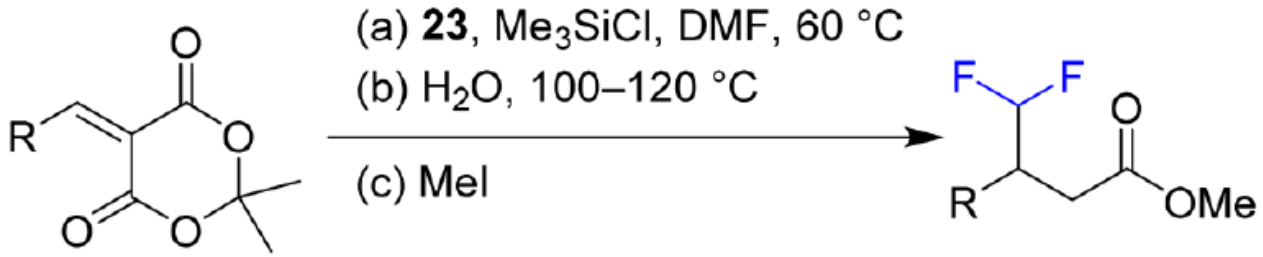
Tripenylphosphine

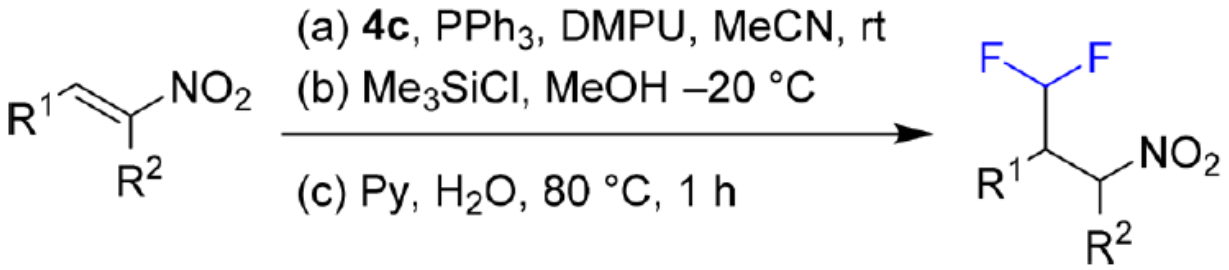


i: **4c**, PPh_3, DMPU, MeCN, rt
ii: **23**, Me_3SiCl, DMF, 50 °C
iii: Me_3SiCF_3 (**4a**) , PPh_3, LiI, $LiBF_4$, DMPU/MeCN, 85 °C

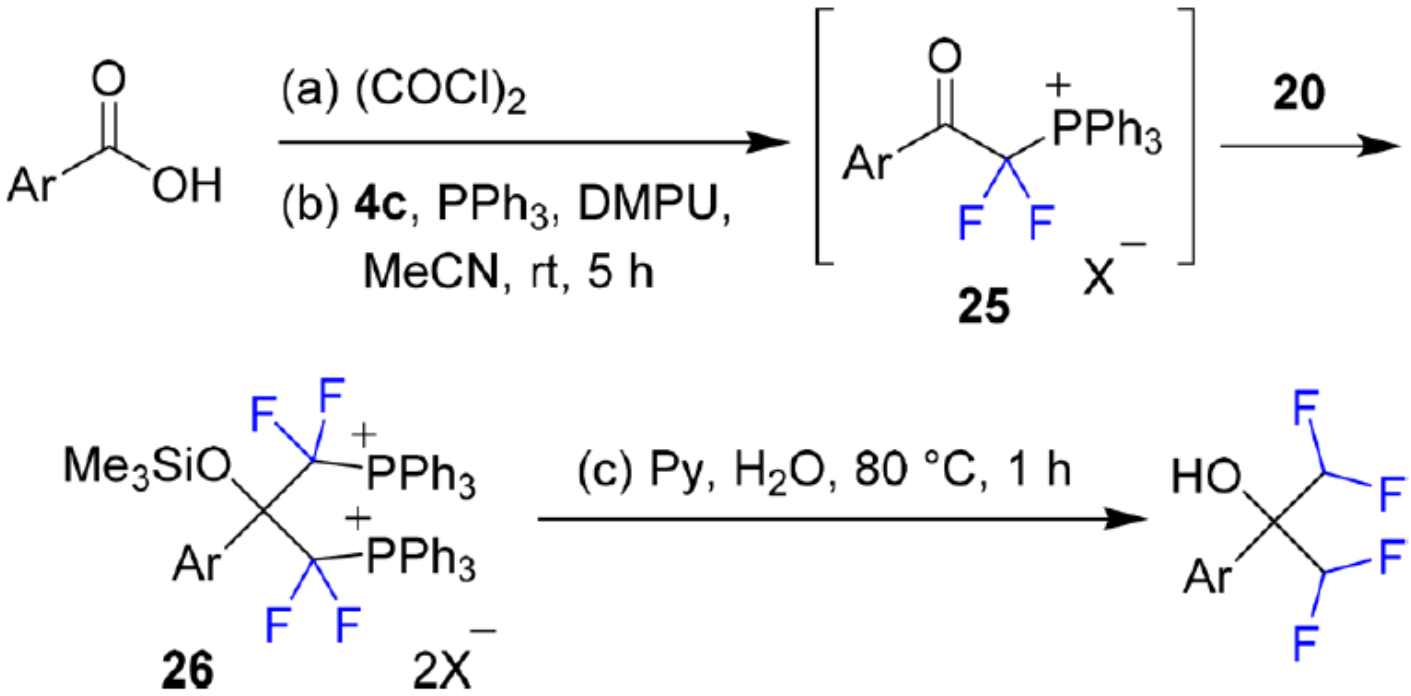
Org. Lett. **2014**, *16*, 6256−6259

J. Fluorine Chem. **2018**, *208*, 10−14





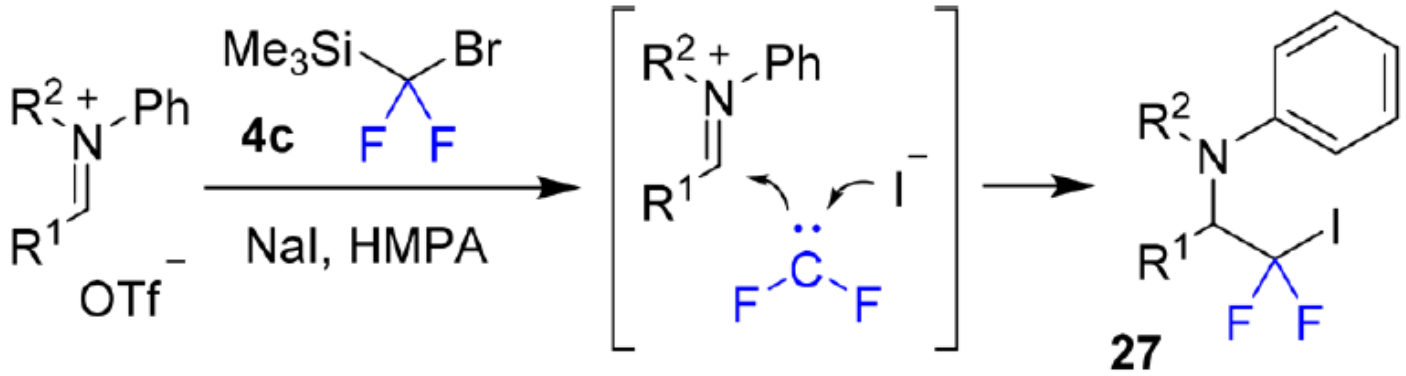
Tripenylphosphine

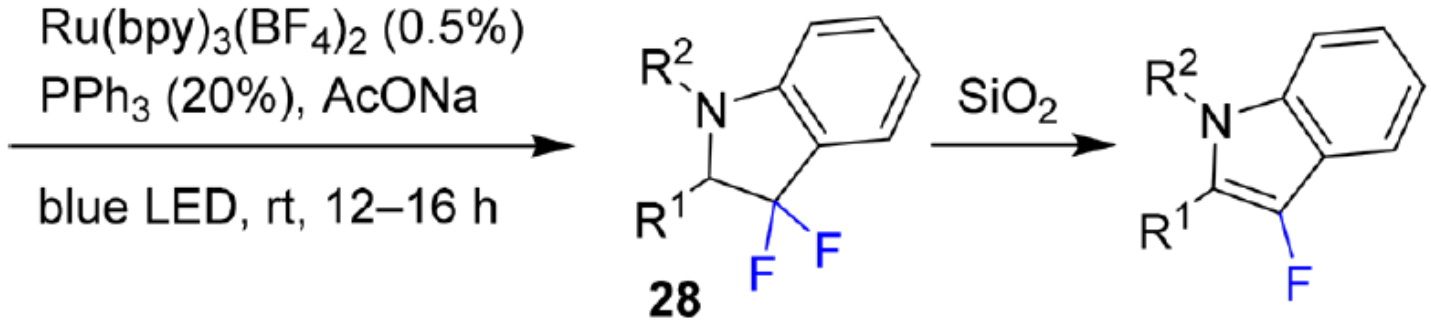


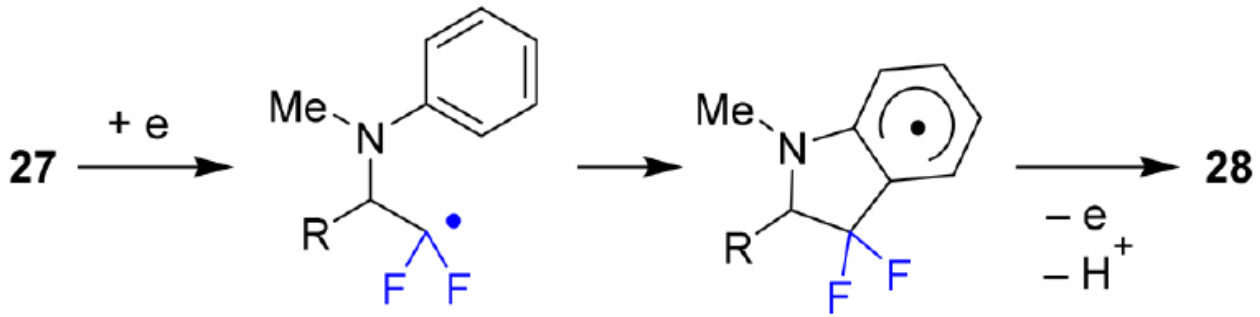
Org. Lett. **2017**, *19*, 5304−5307

LIGHT-PROMOTED REACTIONS

Light-promoted Reaction

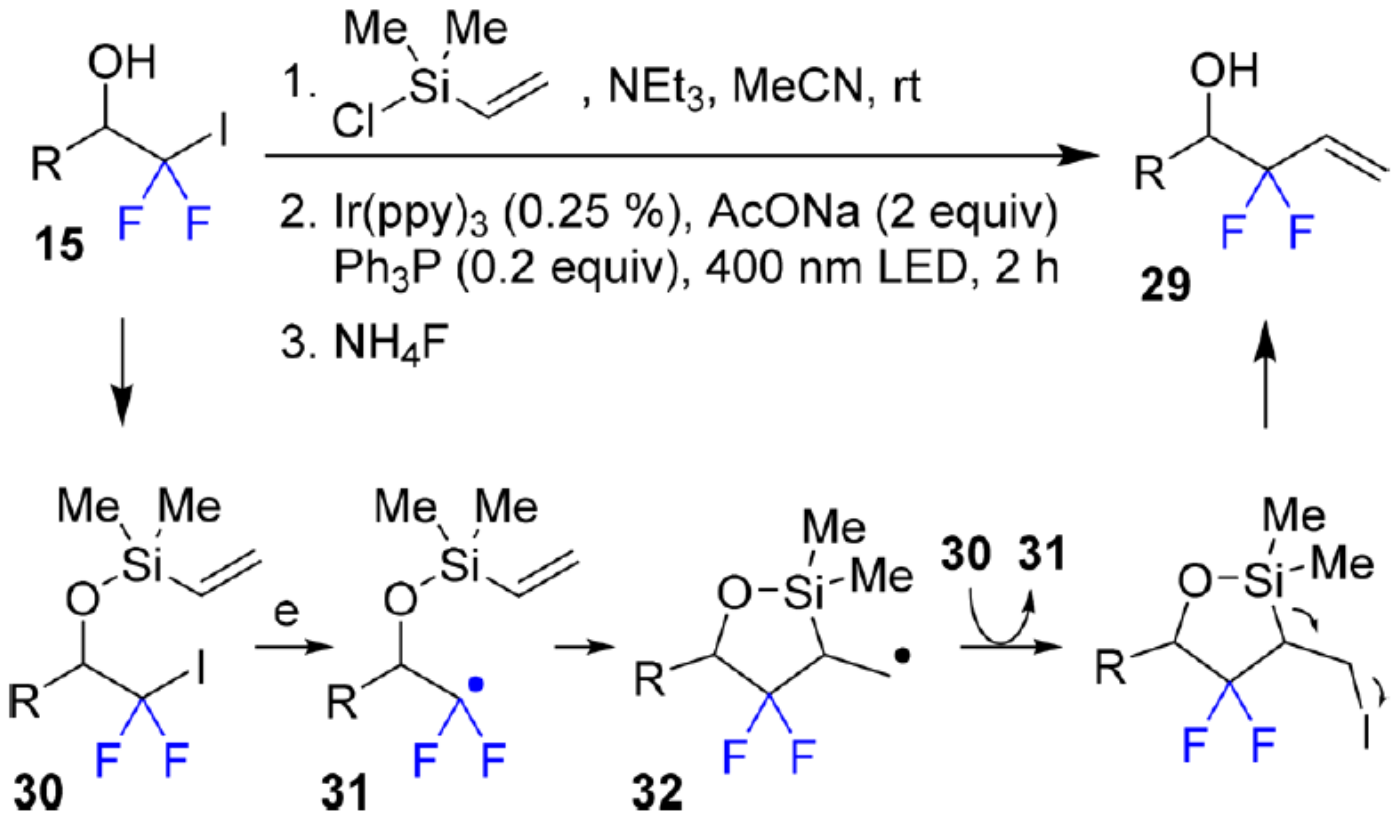






J. Org. Chem. **2017**, *82*, 745−753

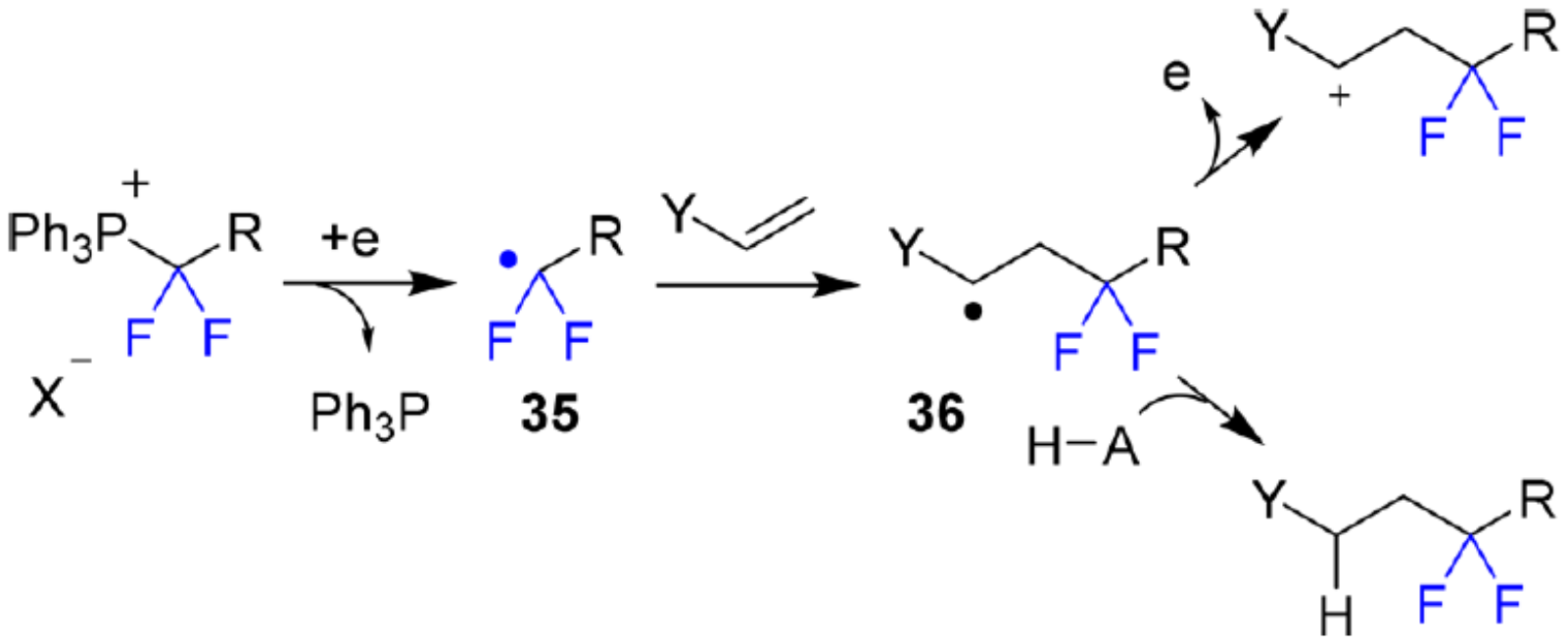
Light-promoted Reaction



Synthesis **2017**, *49*, 4124–4132

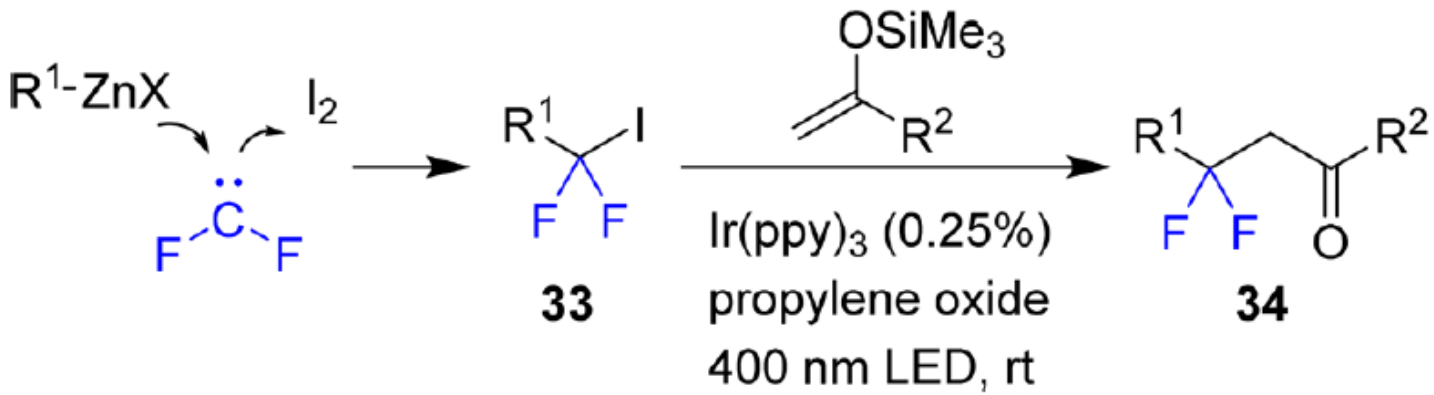
Light-promoted Reaction

Activation of the C-P bond



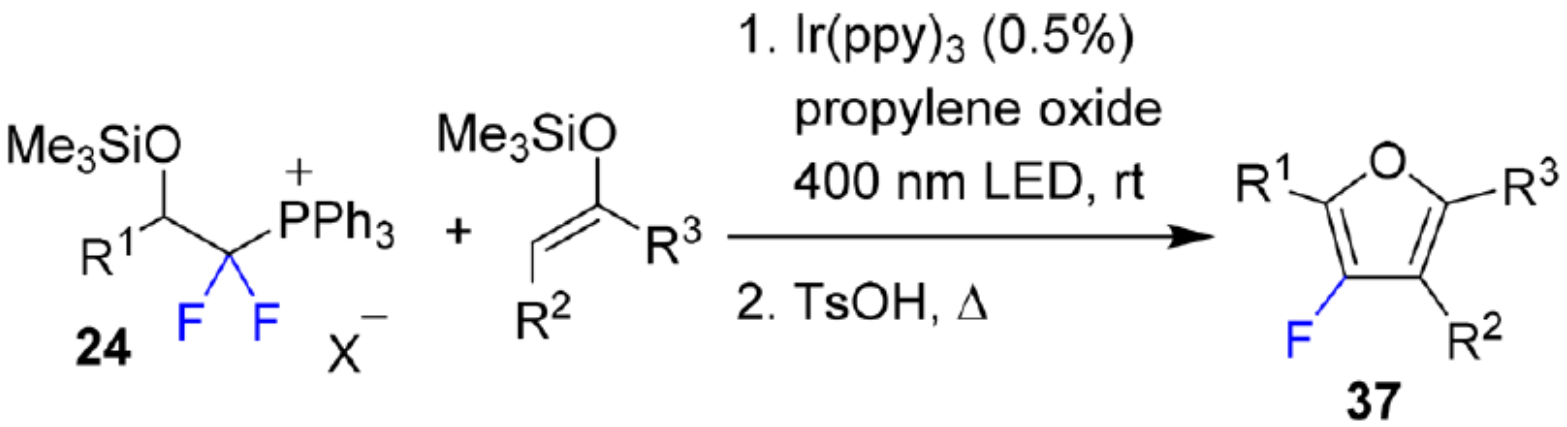
Org. Lett. **2016**, *18*, 996−999

Light-promoted Reaction



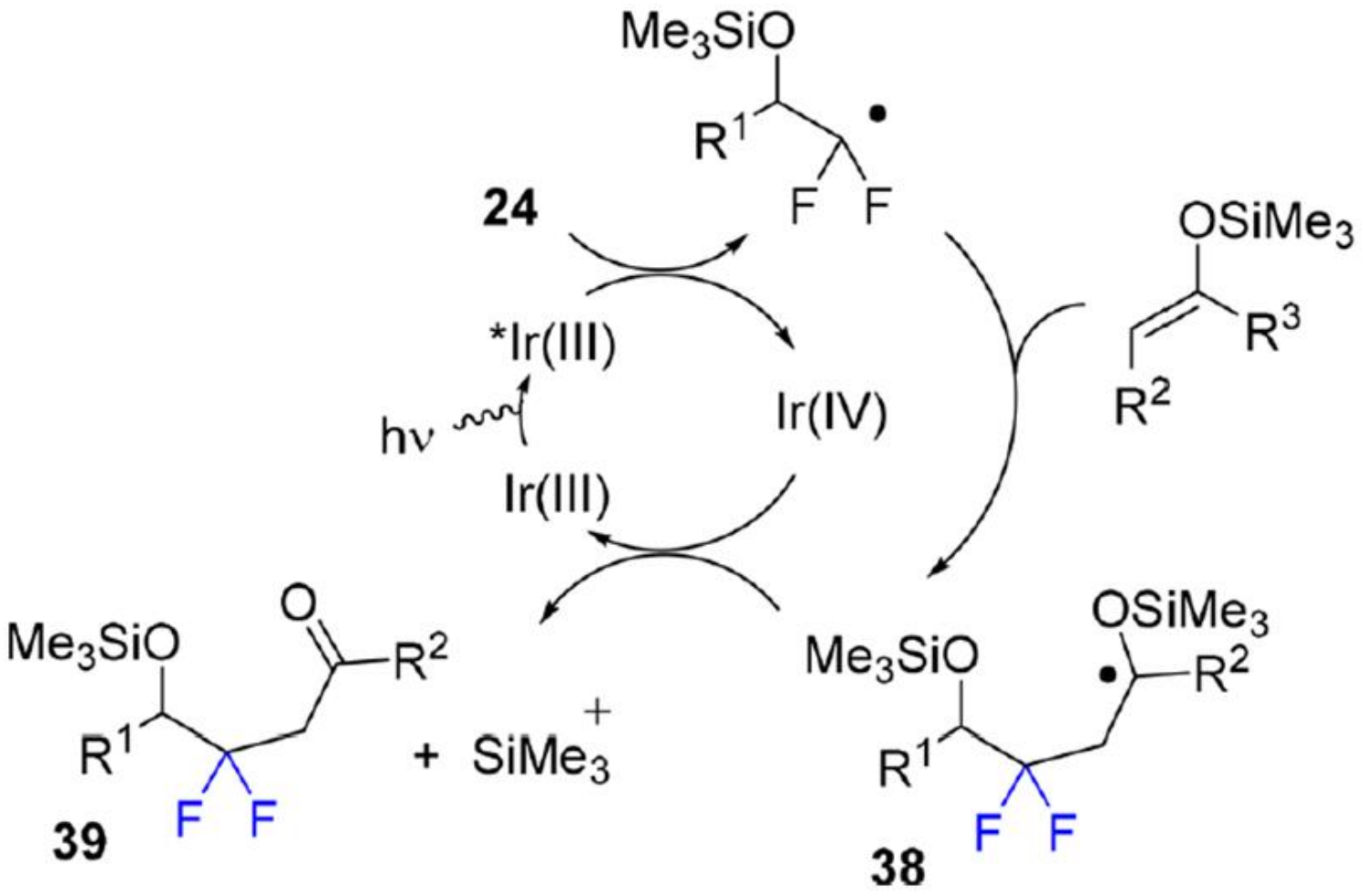
J. Org. Chem. **2016**, *81*, 7001−7007

Light-promoted Reaction

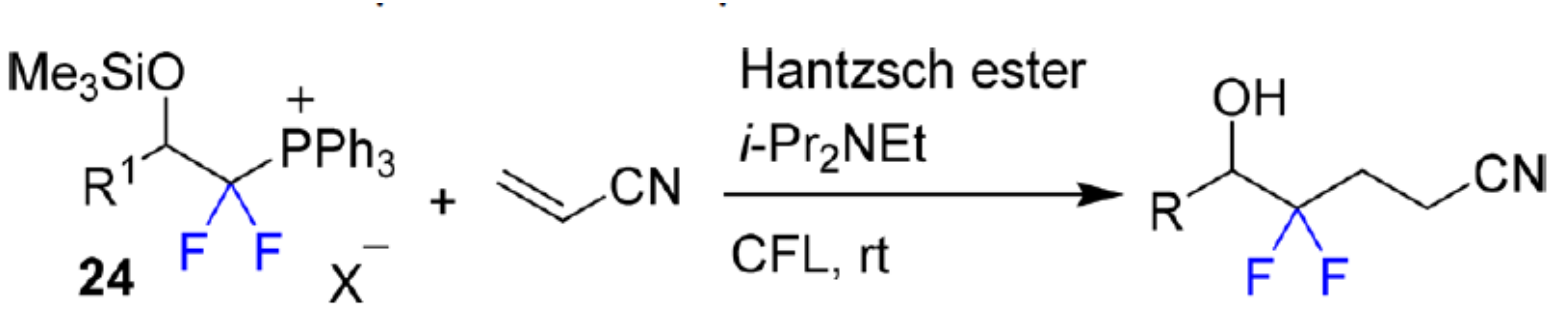


Angew. Chem., Int. Ed. **2016**, *55*, 1479−1483

Light-promoted Reaction



Light-promoted Reaction



CFL= Household flourescent bulbs

Adv. Synth. Catal. **2017**, *359*, 372−383

Conclusion

1) Despite being a short-lived intermediate, difluorocarbene is a useful building block for the synthesis of compounds bearing the difluoromethylene fragment.

2) Many challenges in the practical application of this difluorocarbene methodology still remain.

3) There is still a need for further development on how to construct difluoro-compounds

THANKS