Seminar

Mono C-F Bond Activation in Aromatic and Carbonyl CF_3 Compounds

Reporter: Yuan Yin (袁茵)

Supervisor: Prof. Zhang Junliang

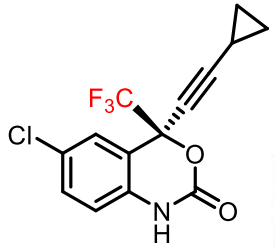
Dr. Yang Junfeng

2022-05-13

Contents

Contents

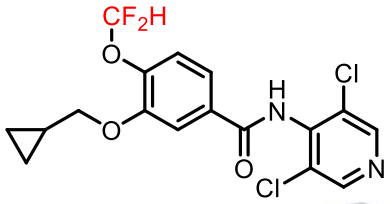
1. Introduction —— **Fluorine in Life**



Efavirenz

依法韦仑

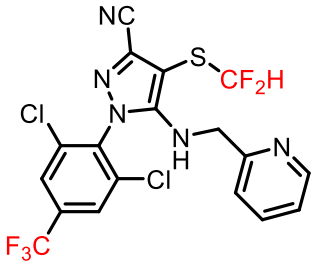
抵抗艾滋病毒的特效药物



Roflumilast

罗氟司特

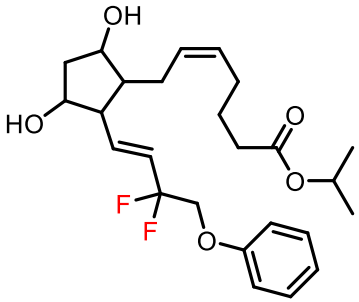
慢性阻塞性肺病



Pyriprole

吡虫啉

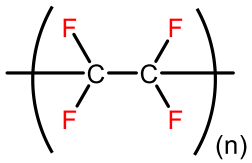
杀虫剂



Tafluprost

他氟前列素

抗青光眼，降低眼压



Polytetrafluoroethylene

聚四氟乙烯

“塑料王”

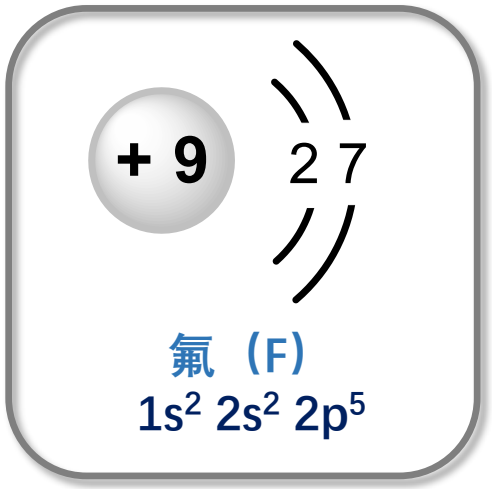
医药、农药、材料

引入氟原子/含氟基团

提高

渗透性、代谢稳定性、选择性

1. Introduction —— **Fluorine**



X	H	F	O	Cl	Br	I	N
Electronegativity (Pauling Scale)	2.1	**4.0**	3.5	3.2	2.8	2.5	2.5
Van der Waals Radius (Å)	1.20	**1.47**	1.52	1.75	1.85	1.98	1.98
C-X bond Length (Å)	1.09	**1.35**	1.43	1.77	1.90	2.10	2.10
C-X bond Dissociation Energy (kJ/mol)	420	**490**	351	328	301	218	356

电负性大

原子半径小

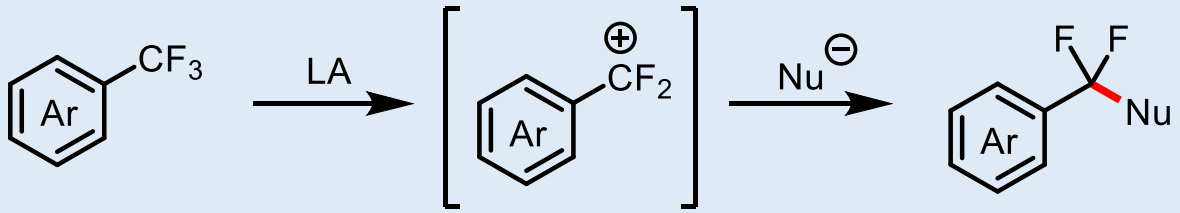
C-F键能大

	H_3C-F	FH_2C-F	F_2HC-F	F_3C-F
C-F bond Dissociation Energy (kcal/mol)	110	120	128	138

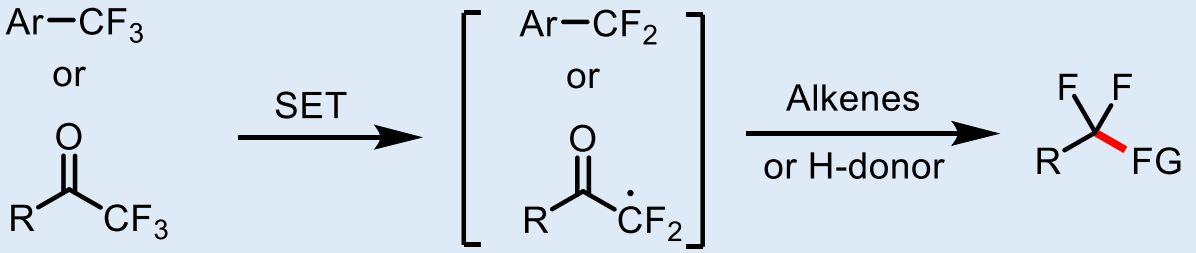
Q. Liu, et al. *Chem. Rev*. **2015**, *115*, 683.

1. Introduction —— Construction of CF_2R

C-F Activation via Lewis Acid/Frustrated Lewis Pair

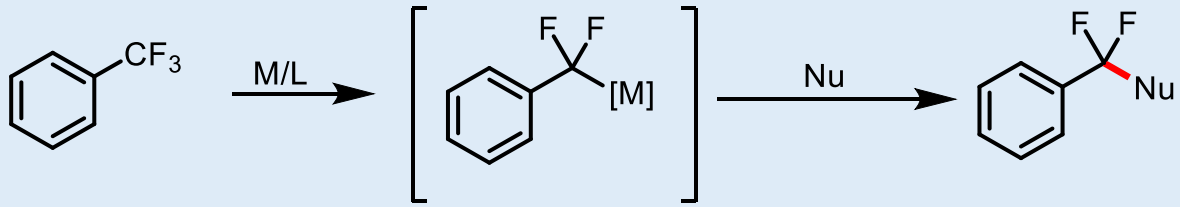


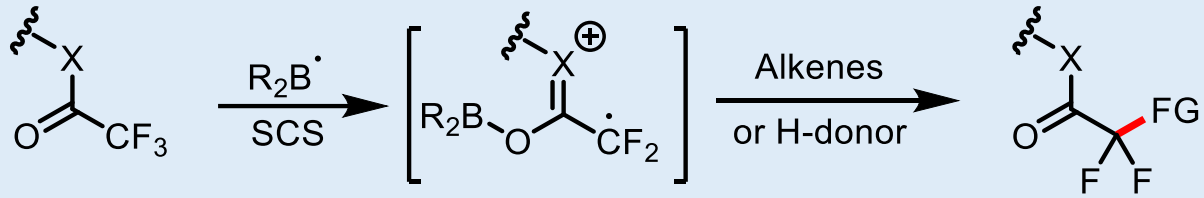
C-F Activation via SET Induced Process



$CF_3 \longrightarrow CF_2R$

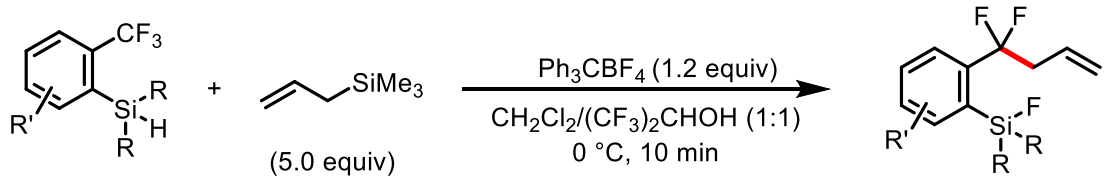
C-F Activation via Transition Metal Induced Process



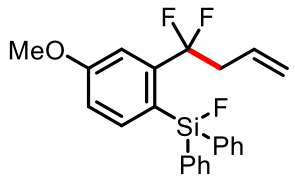


Contents

2.1 C-F Activation via Lewis Acid/Frustrated Lewis Pair



Selected examples



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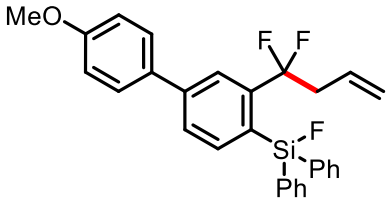

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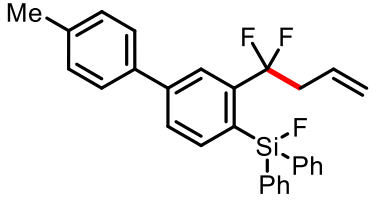

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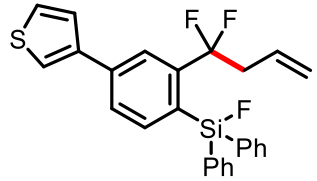

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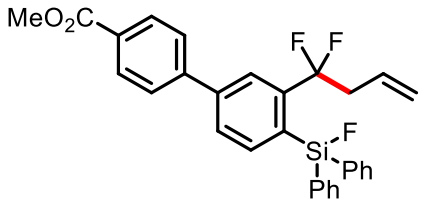

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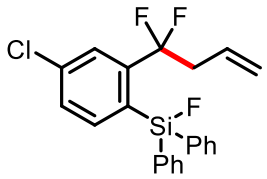

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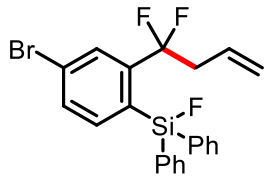

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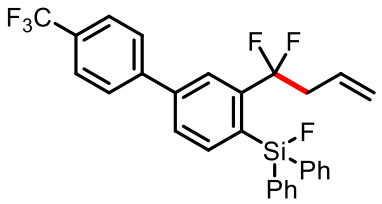

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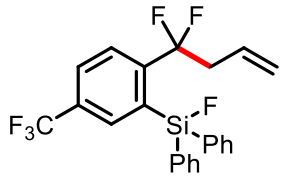

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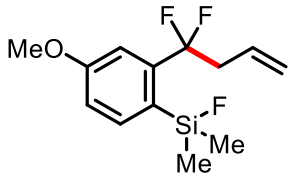

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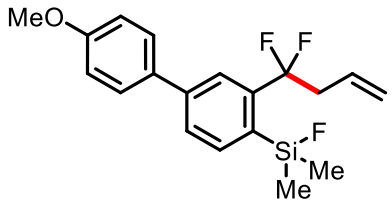

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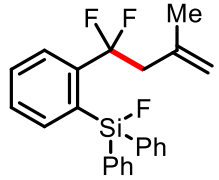

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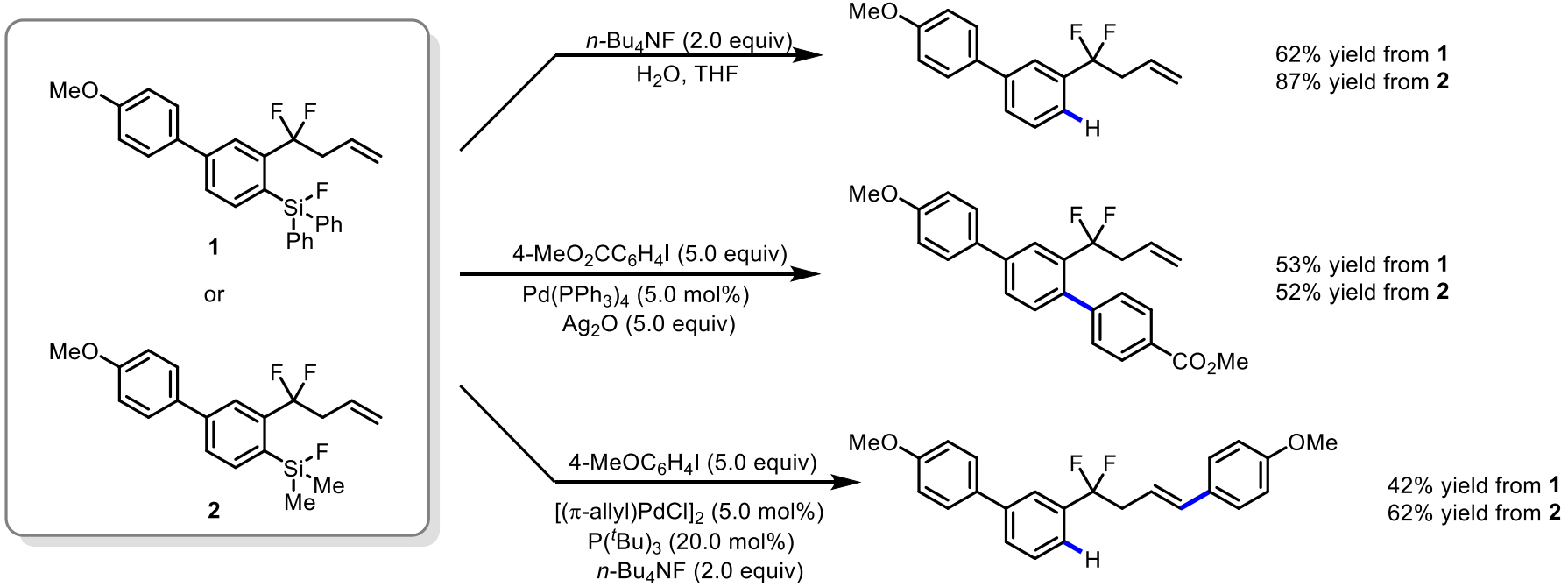
T. Hosoya, et al. *Angew. Chem. Int. Ed*. **2016**, *55*, 10406.

2.1 C-F Activation via Lewis Acid/Frustrated Lewis Pair



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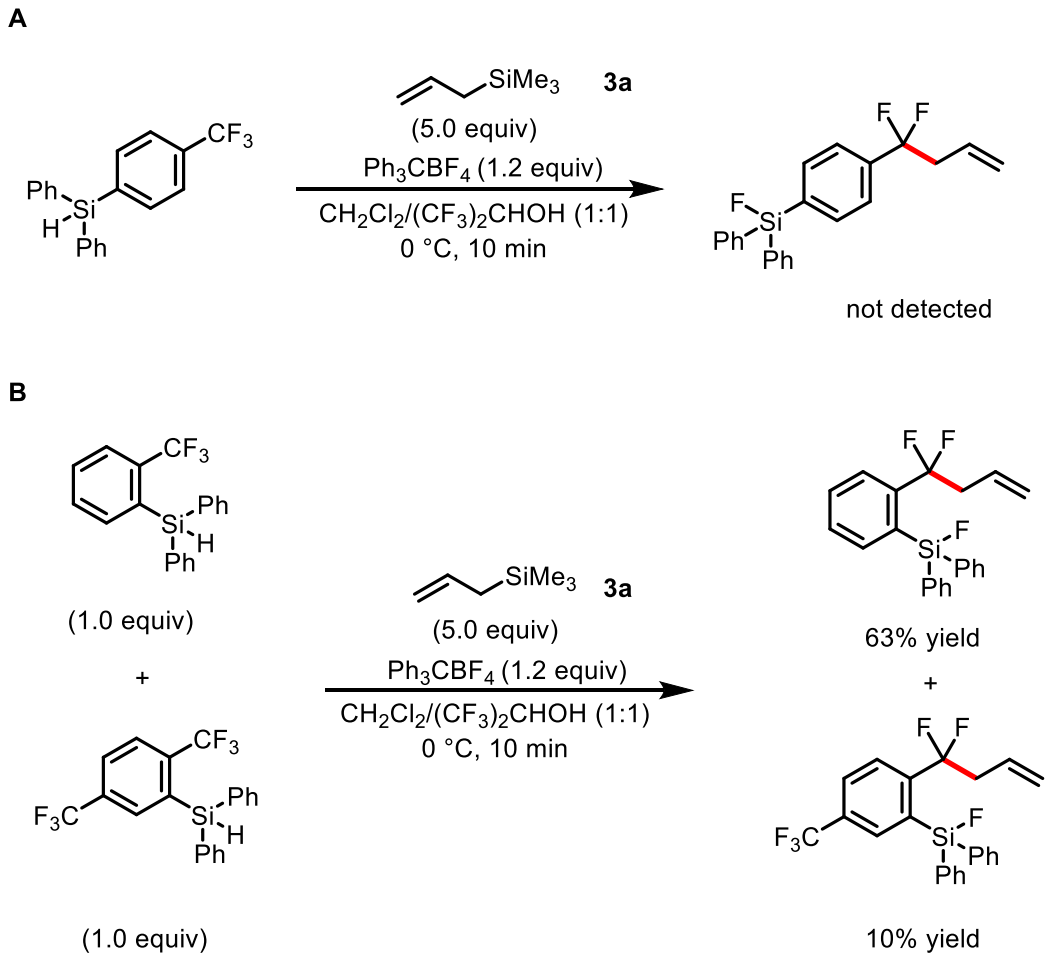

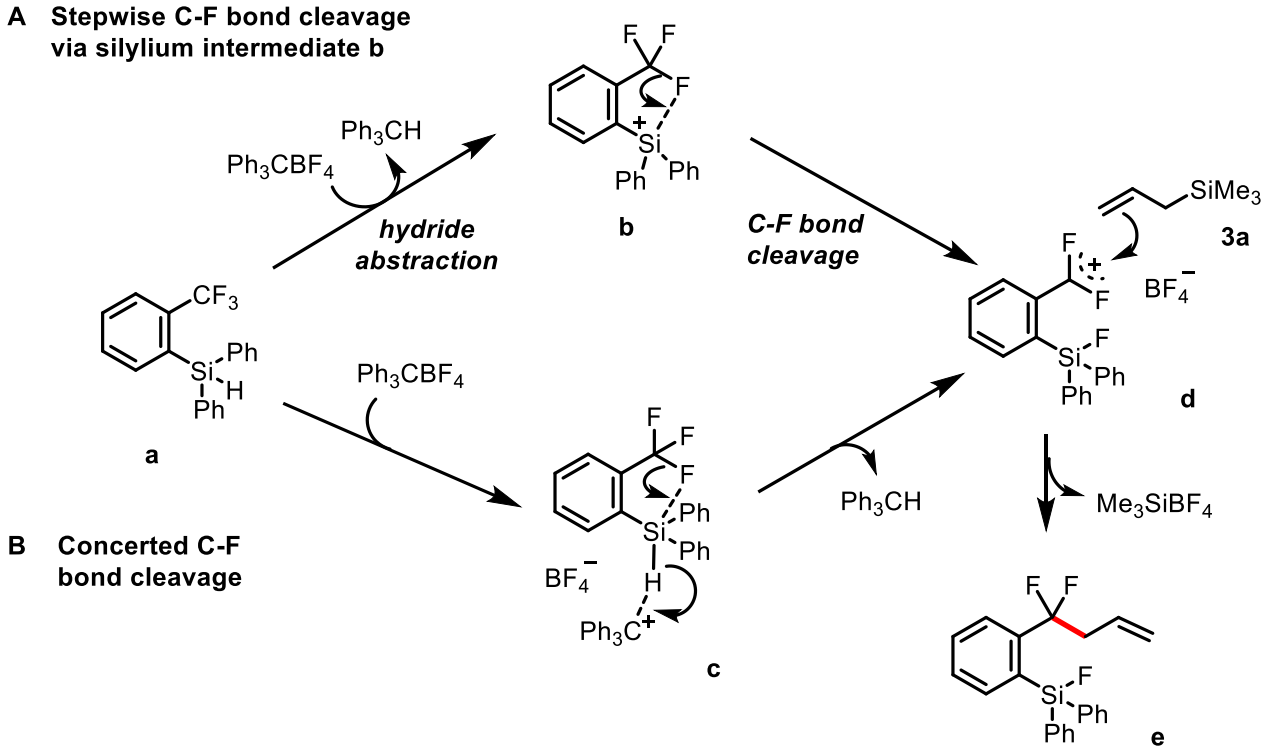

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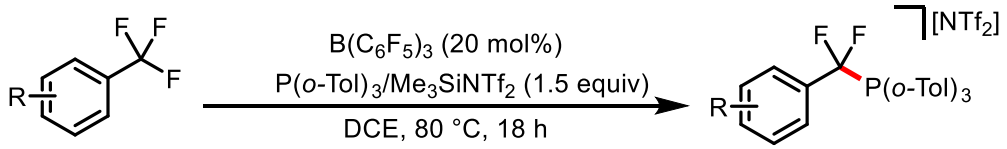

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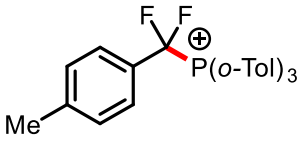

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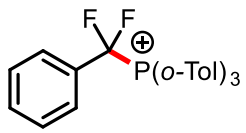

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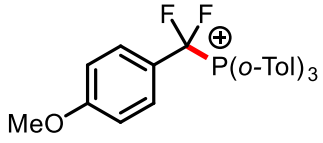

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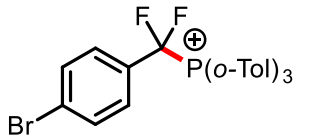

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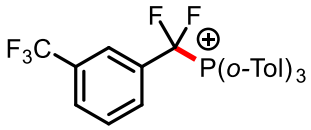

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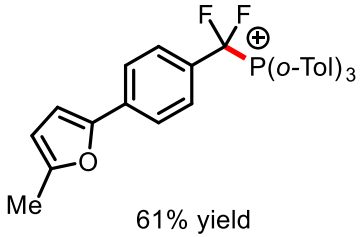

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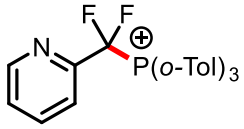

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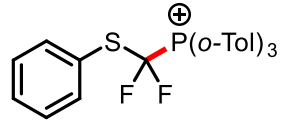

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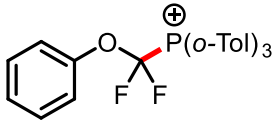

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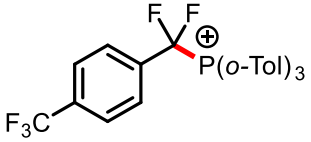

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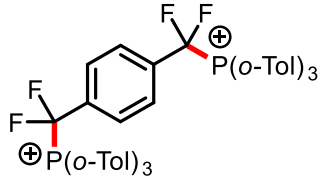
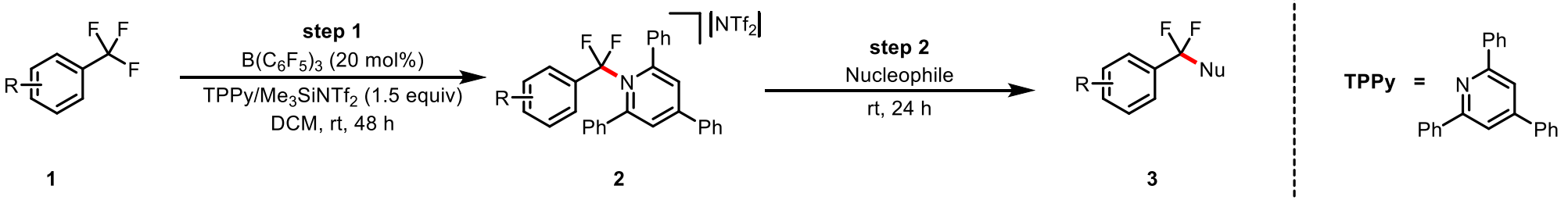


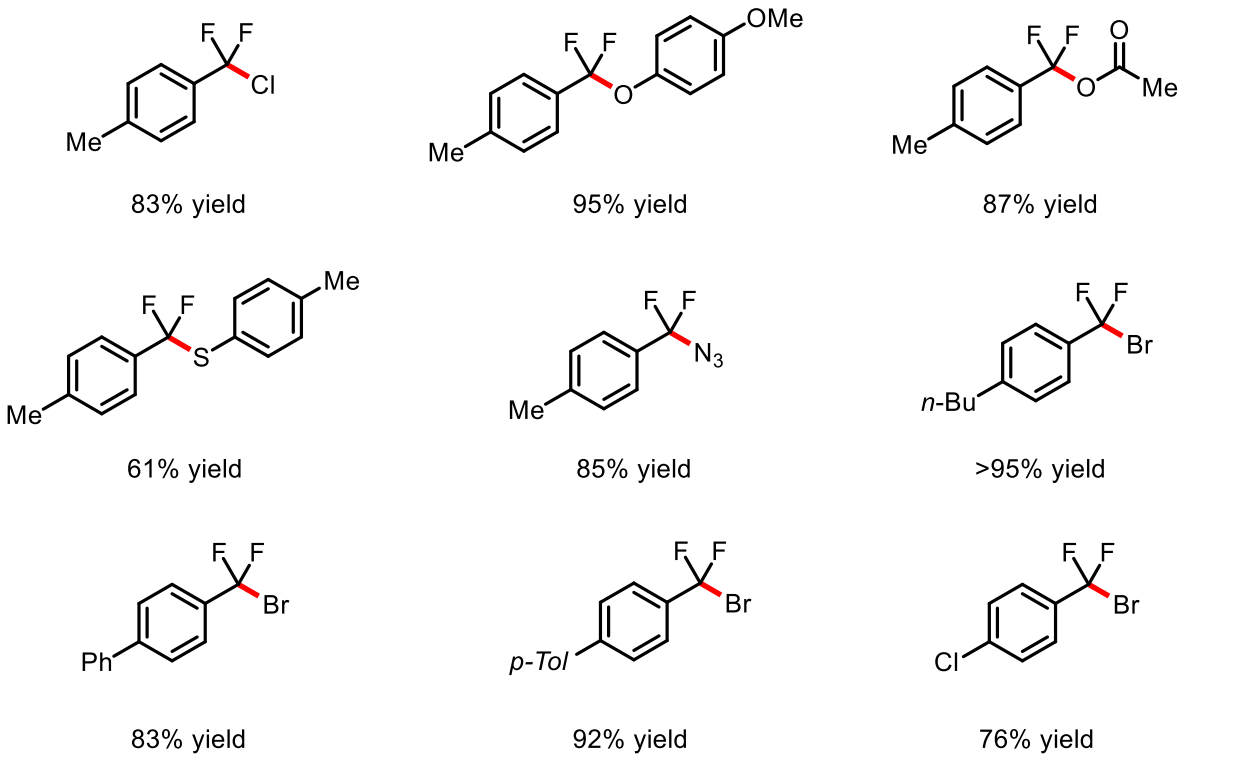
71% yield

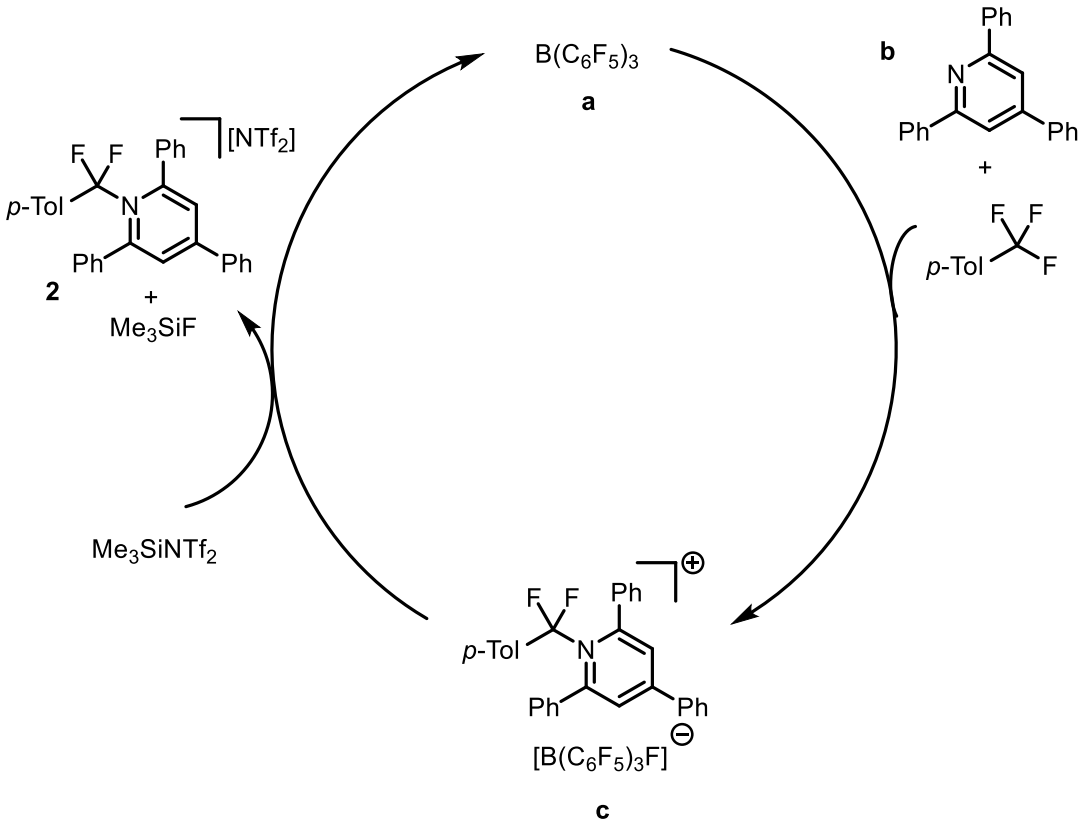
R. D. Young, et al. *J. Am. Chem. Soc*. **2020**, *142*, 2572.

2.1 C-F Activation via Lewis Acid/Frustrated Lewis Pair



Selected examples

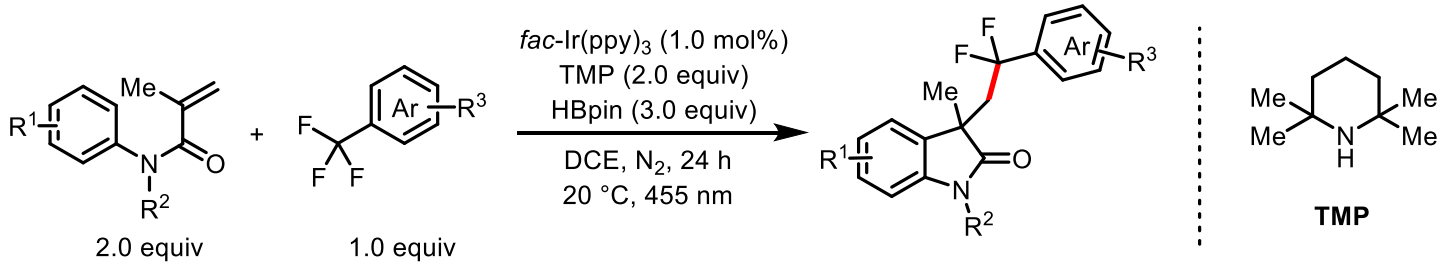




R. D. Young, et al. *J. Am. Chem. Soc*. **2020**, *142*, 2572.

Contents

2.2 C-F Activation via SET Induced Process



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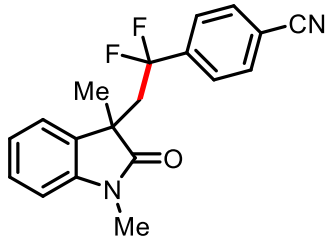

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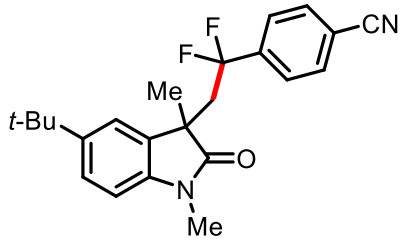

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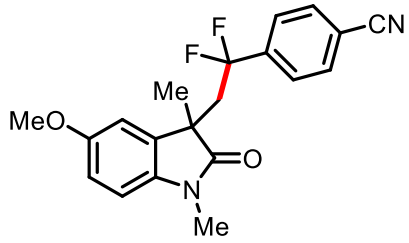

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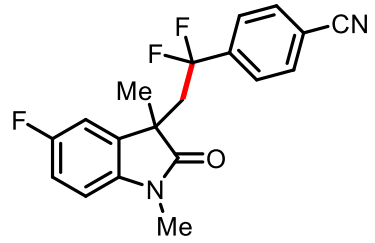
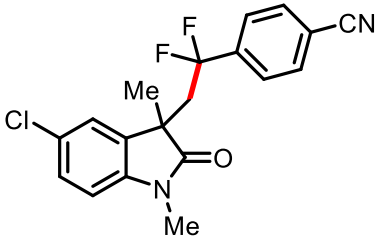
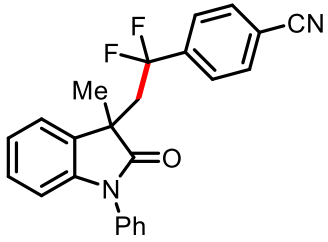


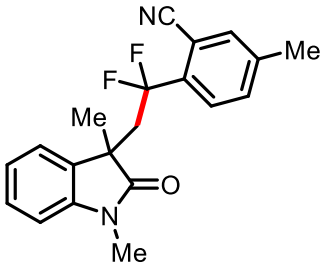
58% yield



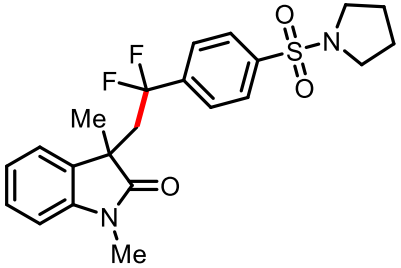
59% yield



66% yield



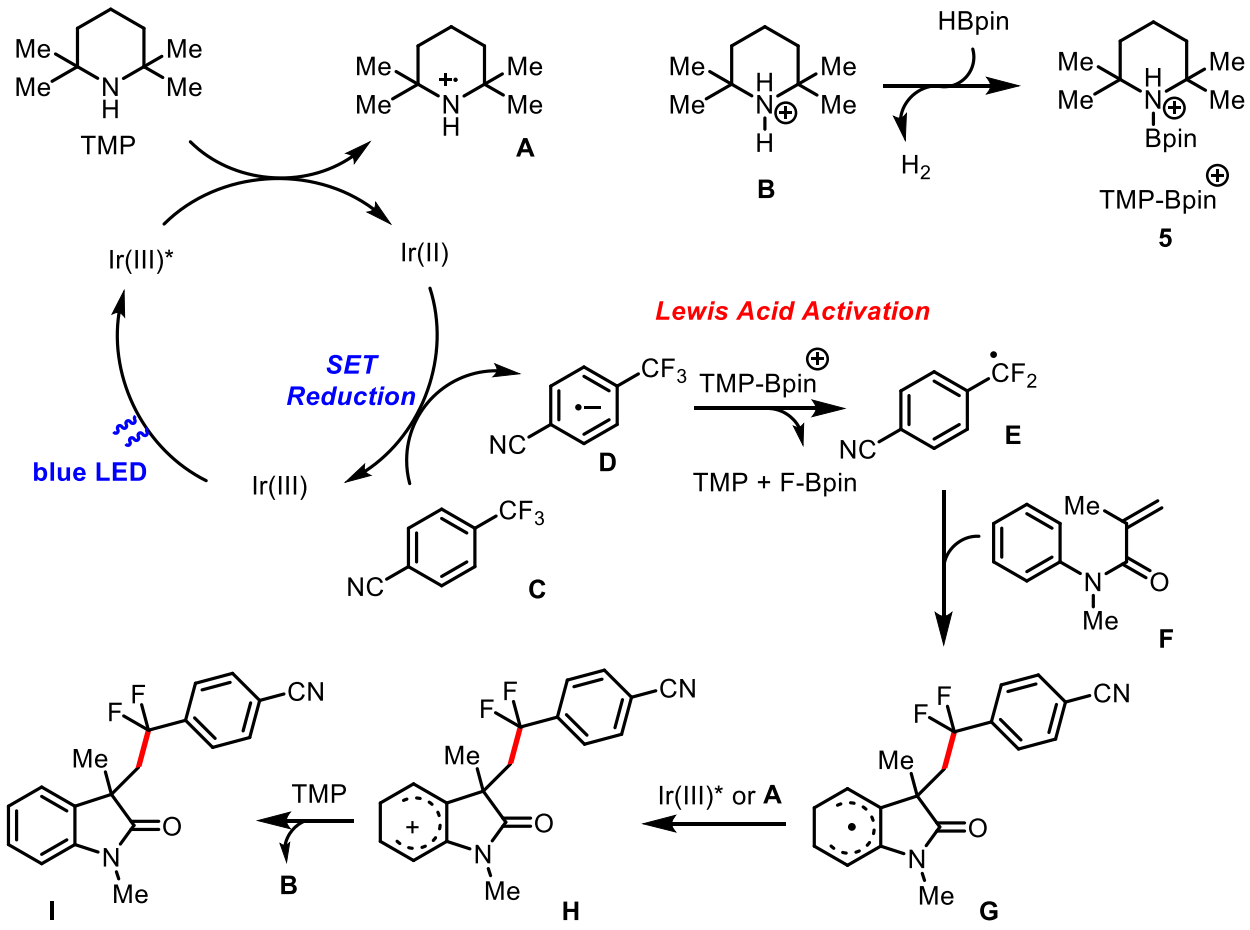
57% yield

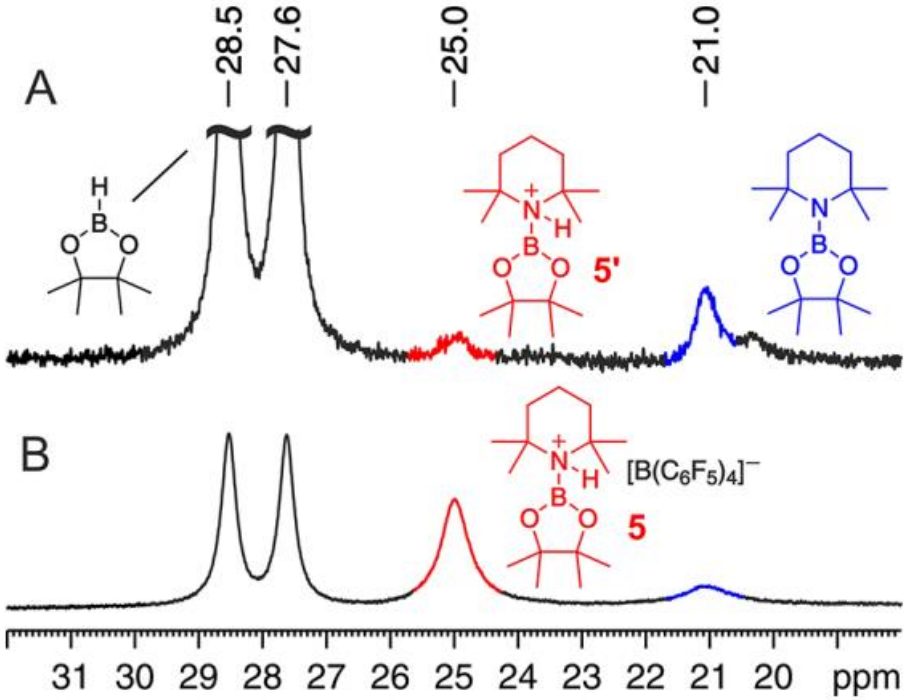


57% yield

B. König, et. al. *J. Am. Chem. Soc.* **2017**, *139*, 18444.

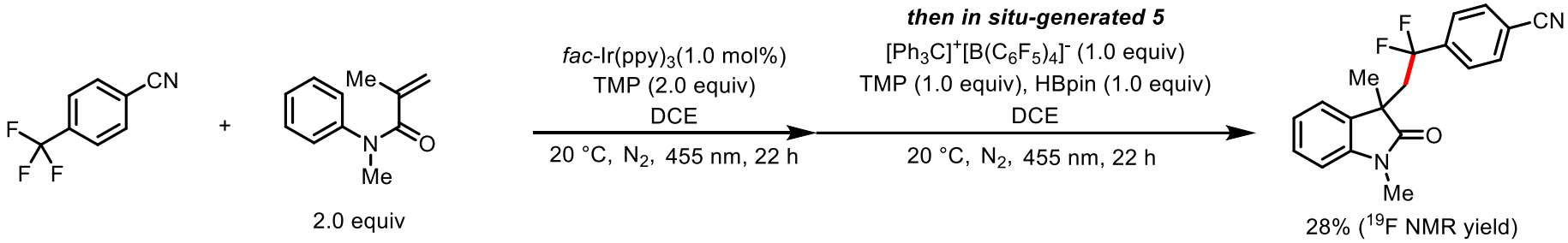
2.2 C-F Activation via SET Induced Process

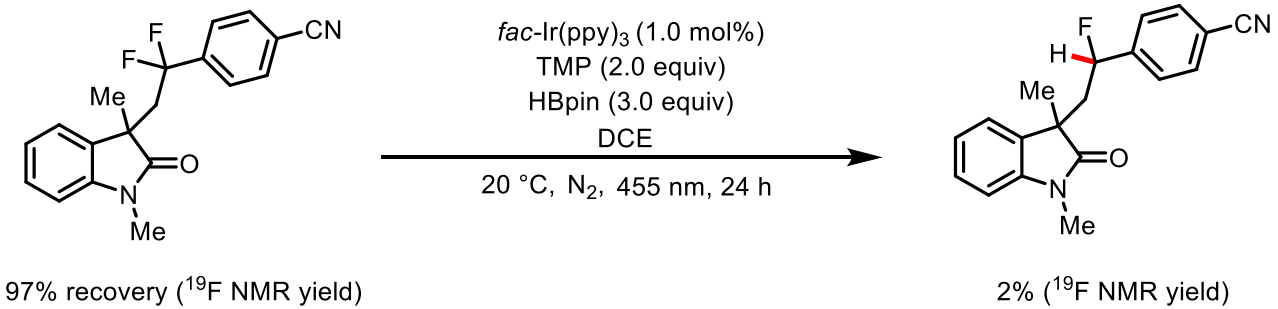




B. König, et. al. *J. Am. Chem. Soc.* **2017**, *139*, 18444.

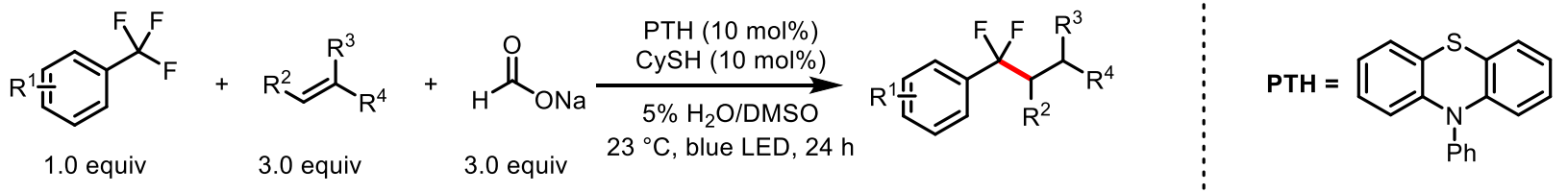
2.2 C-F Activation via SET Induced Process



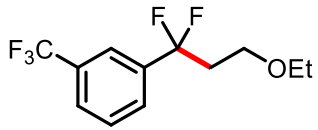


B. König, et. al. *J. Am. Chem. Soc.* **2017**, *139*, 18444.

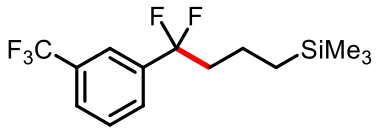
2.2 C-F Activation via SET Induced Process



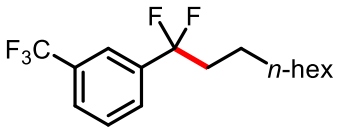
Selected examples



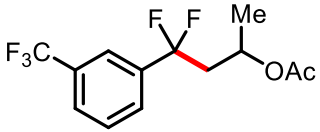
86% yield



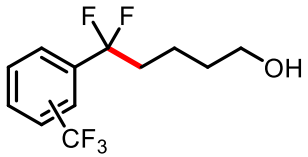
79% yield



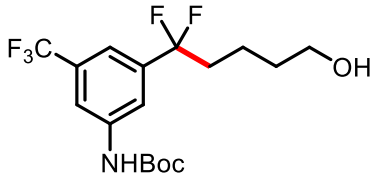
85% yield



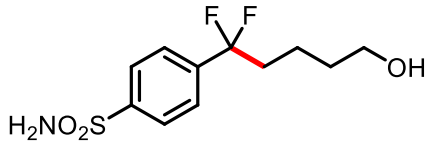
59% yield



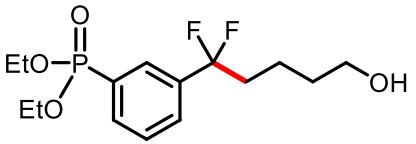
ortho: 80% yield
meta: 87% yield
para: 80% yield



89% yield



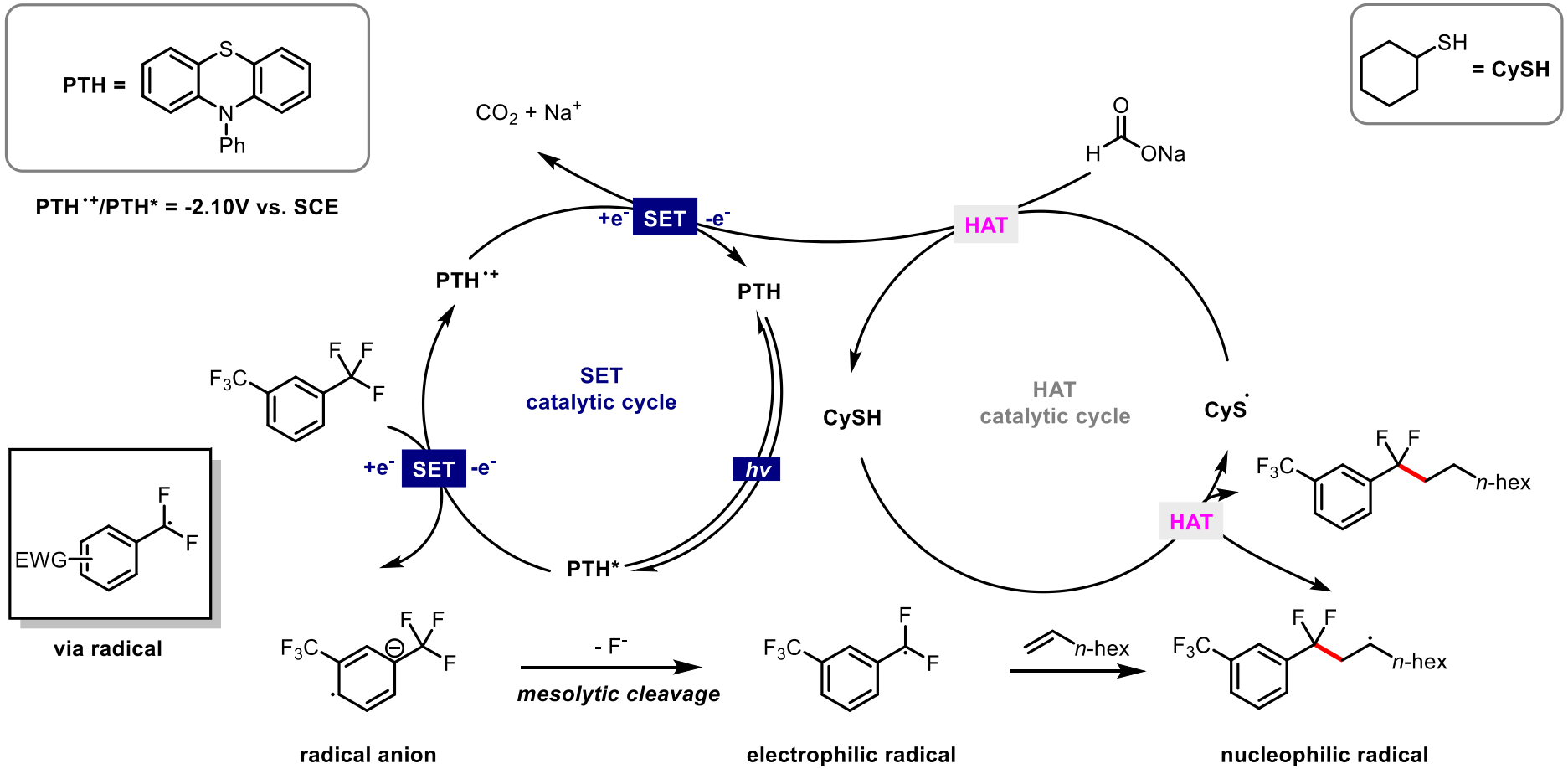
83% yield



56% yield

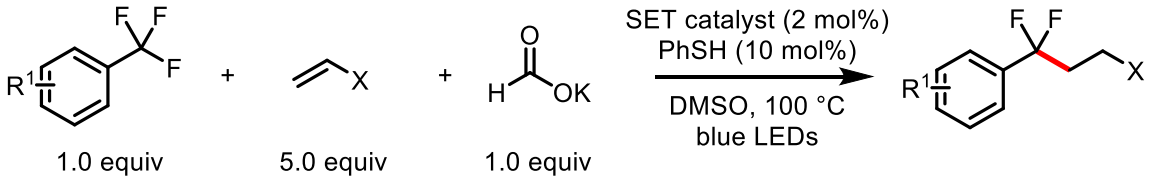
N. T. Jui, et. al. *J. Am. Chem. Soc.* **2018**, *140*, 163.

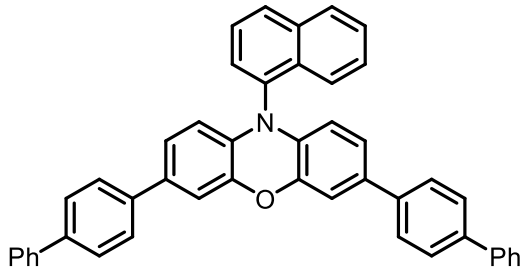
2.2 C-F Activation via SET Induced Process



N. T. Jui, et. al. *J. Am. Chem. Soc.* **2018**, *140*, 163.

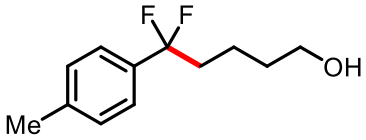
2.2 C-F Activation via SET Induced Process



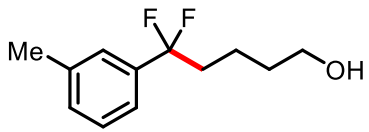


SET catalyst (**S**)

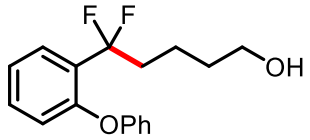
Selected examples



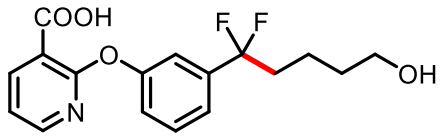
58% yield



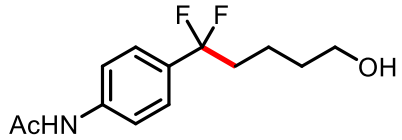
84% yield



44% yield



54% yield



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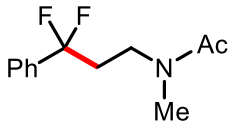
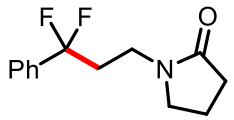
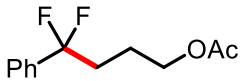


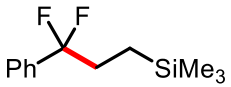
95% yield



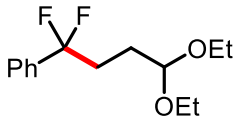
89% yield



64% yield



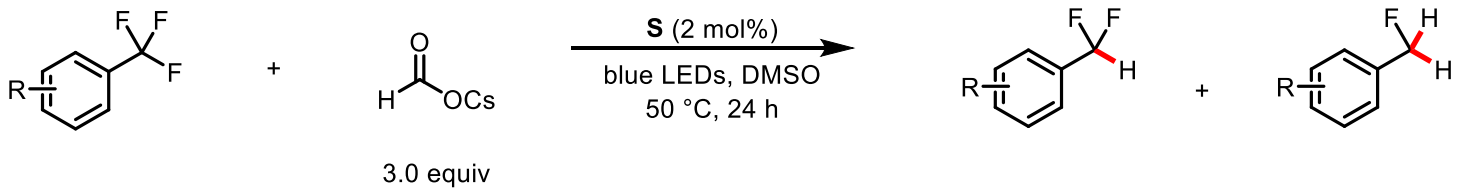
88% yield



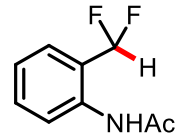
75% yield

N. T. Jui. et. al. *J. Am. Chem. Soc*. **2019**, *141*, 13203.

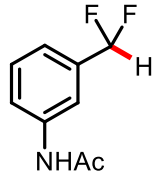
2.2 C-F Activation via SET Induced Process



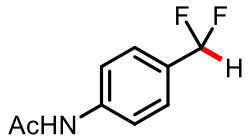
Selected examples



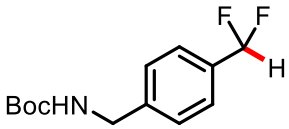
75% yield (>99:1)



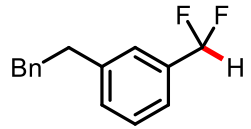
55% yield (>99:1)



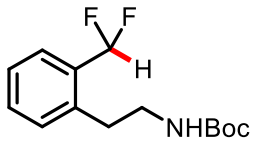
70% yield (>99:1)



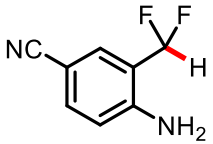
64% yield (13:1)



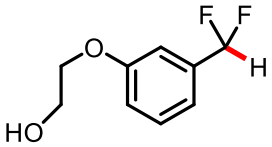
48% yield (3:1)



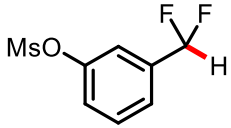
50% yield (7:1)



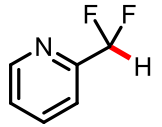
65% yield (4:1)



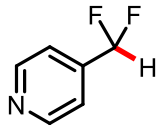
53% yield (>99:1)



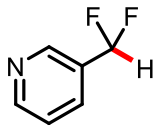
45% yield (>99:1)



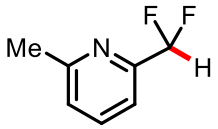
50% yield (9:1)



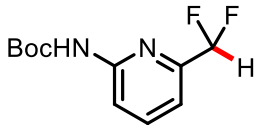
44% yield (4:1)



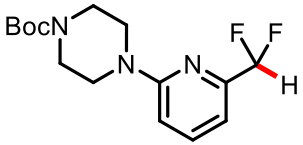
42% yield (4:1)



64% yield (9:1)



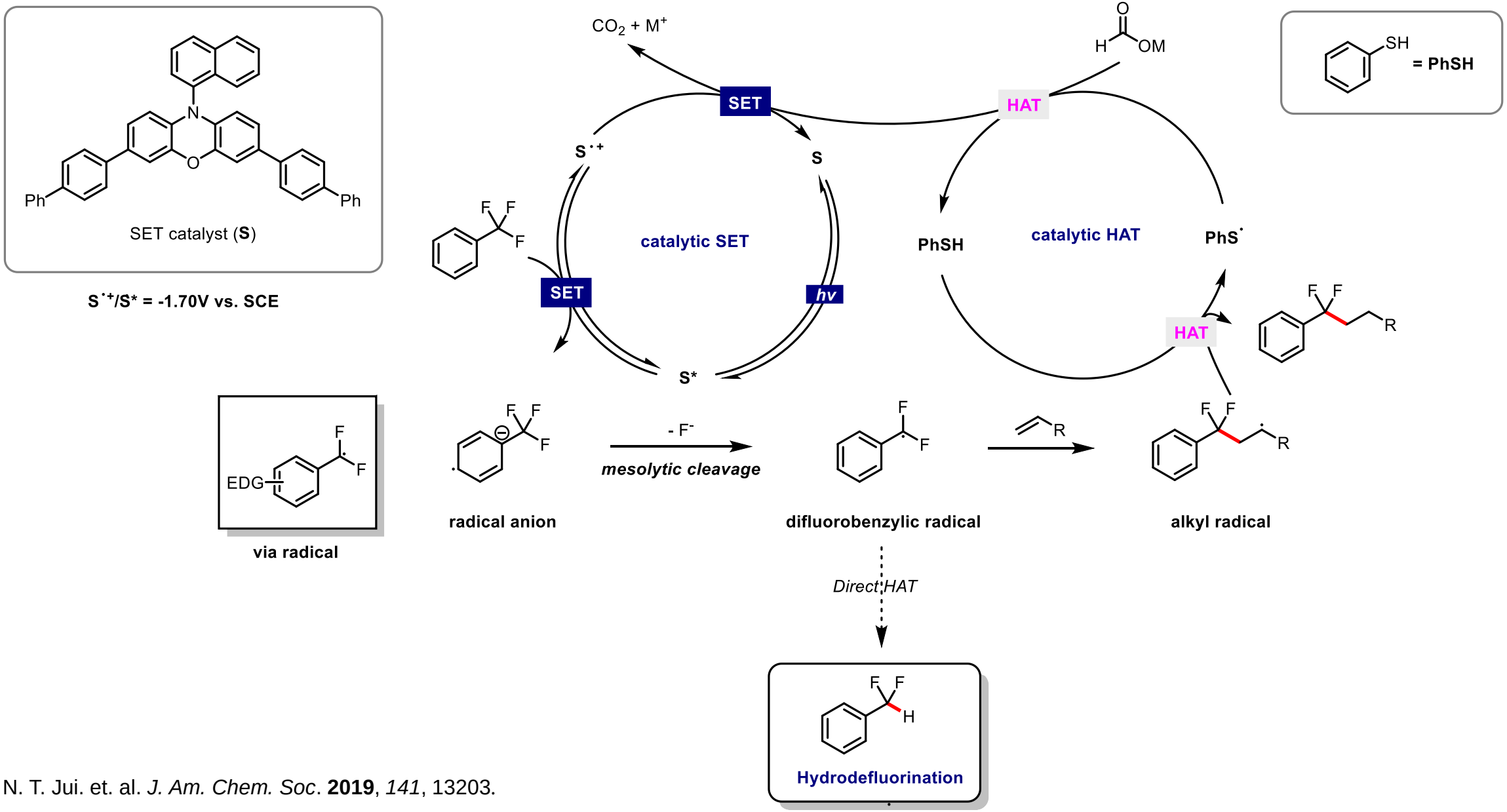
57% yield (5:1)



58% yield (7:1)

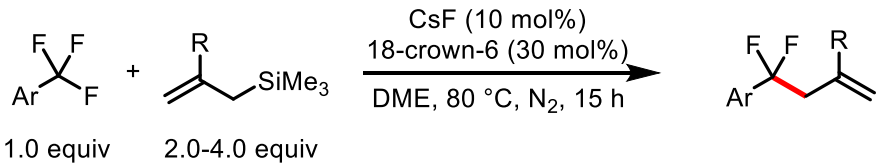
N. T. Jui. et. al. *J. Am. Chem. Soc*. **2019**, *141*, 13203.

2.2 C-F Activation via SET Induced Process



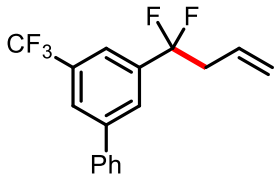
N. T. Jui. et. al. *J. Am. Chem. Soc*. **2019**, *141*, 13203.

2.2 C-F Activation via SET Induced Process

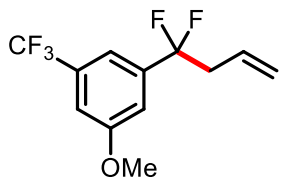


1.0 equiv 2.0-4.0 equiv

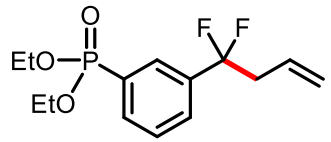
Selected examples



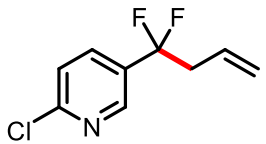
87% yield



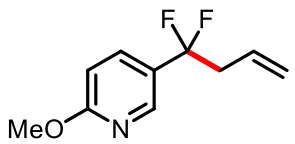
85% yield



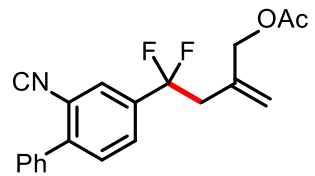
71% yield



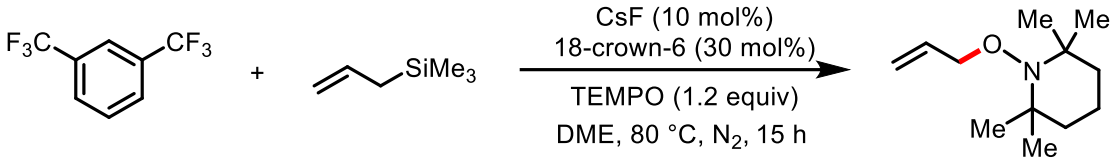
44% yield



64% yield

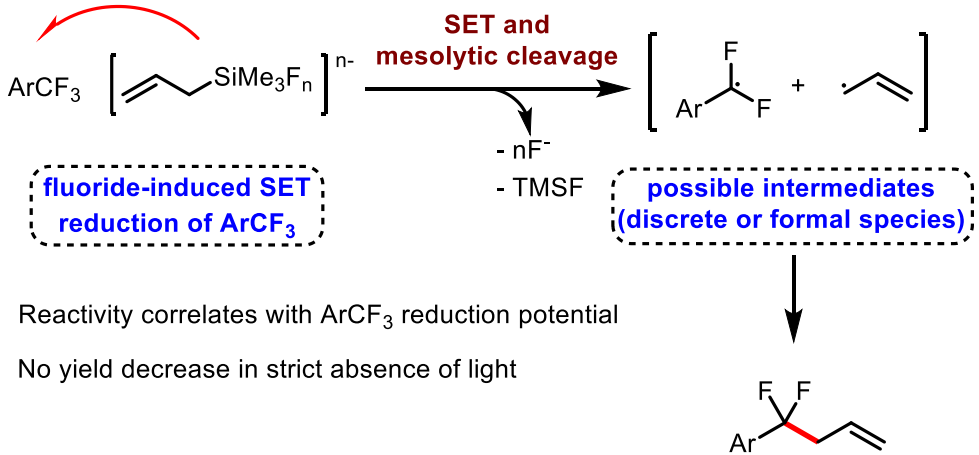


74% yield



1.0 equiv 2.0 equiv 23% yield

No adduct observed in absence of $ArCF_3$ from standard conditions, or if $PhCF_3$ used

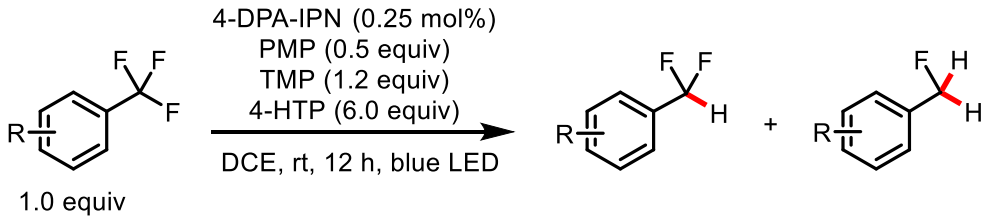


Reactivity correlates with $ArCF_3$ reduction potential

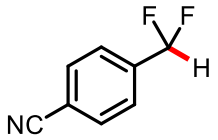
No yield decrease in strict absence of light

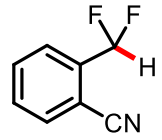
J. S. Bandar, et. al. *J. Am. Chem. Soc*. **2019**, *141*, 14120.

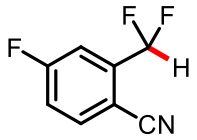
2.2 C-F Activation via SET Induced Process

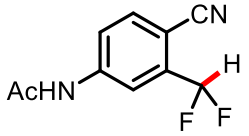


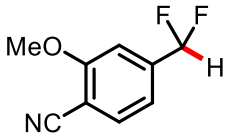
Selected examples

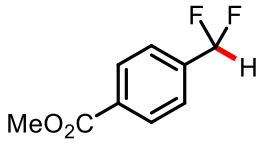

65% yield (5:1)

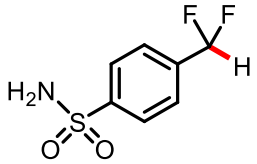

72% yield (>20:1)

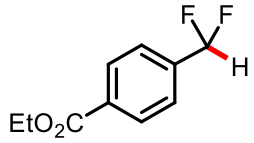

93% yield (>20:1)

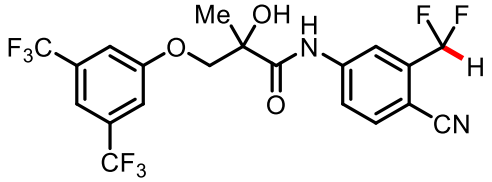

69% yield (10:1)

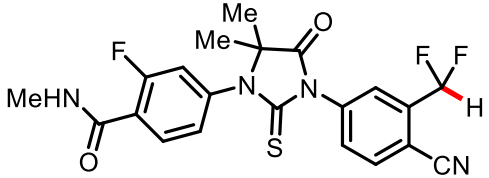

48% yield (>20:1)

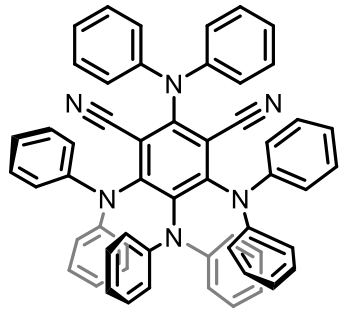

40% yield (3:1)

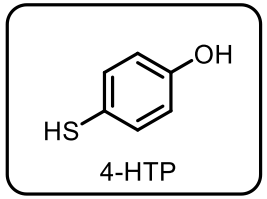

34% yield (>20:1)

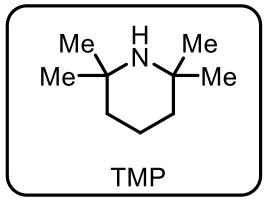

49% yield (3:1)

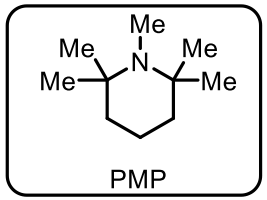

from Enobosarm analogue
(Androgen receptor modulator)
60% yield (>20:1)


from Enzalutamide
(Treats prostate cancer)
45% yield (>20:1)


4-DPA-IPN

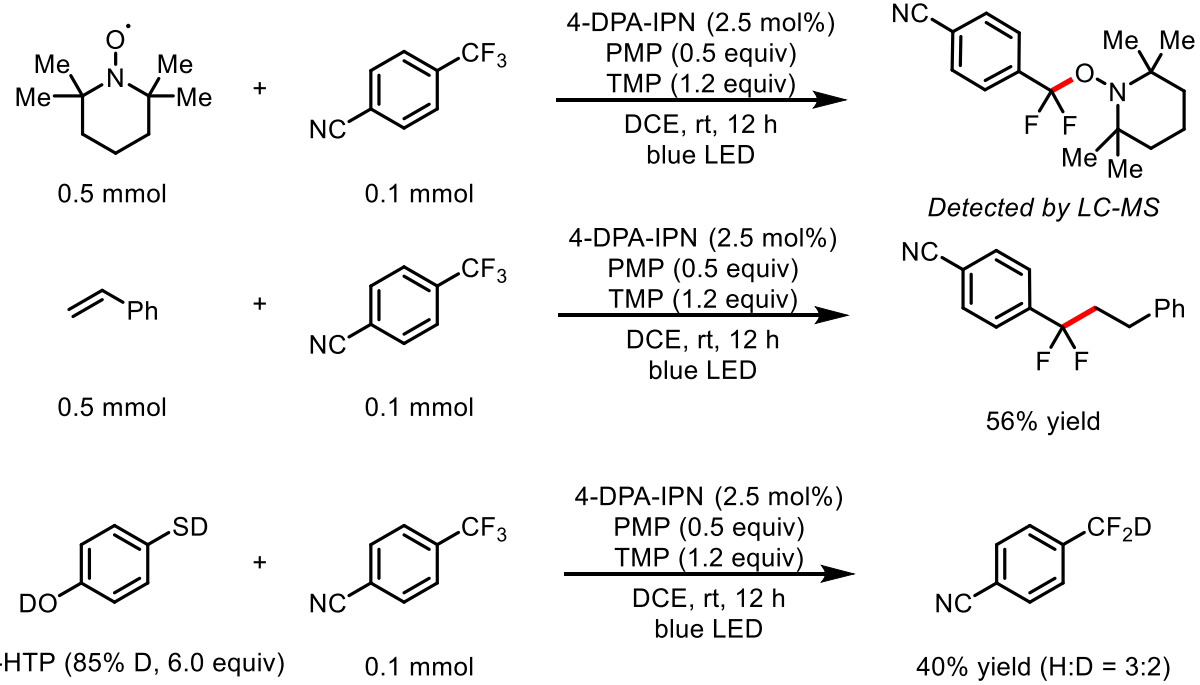


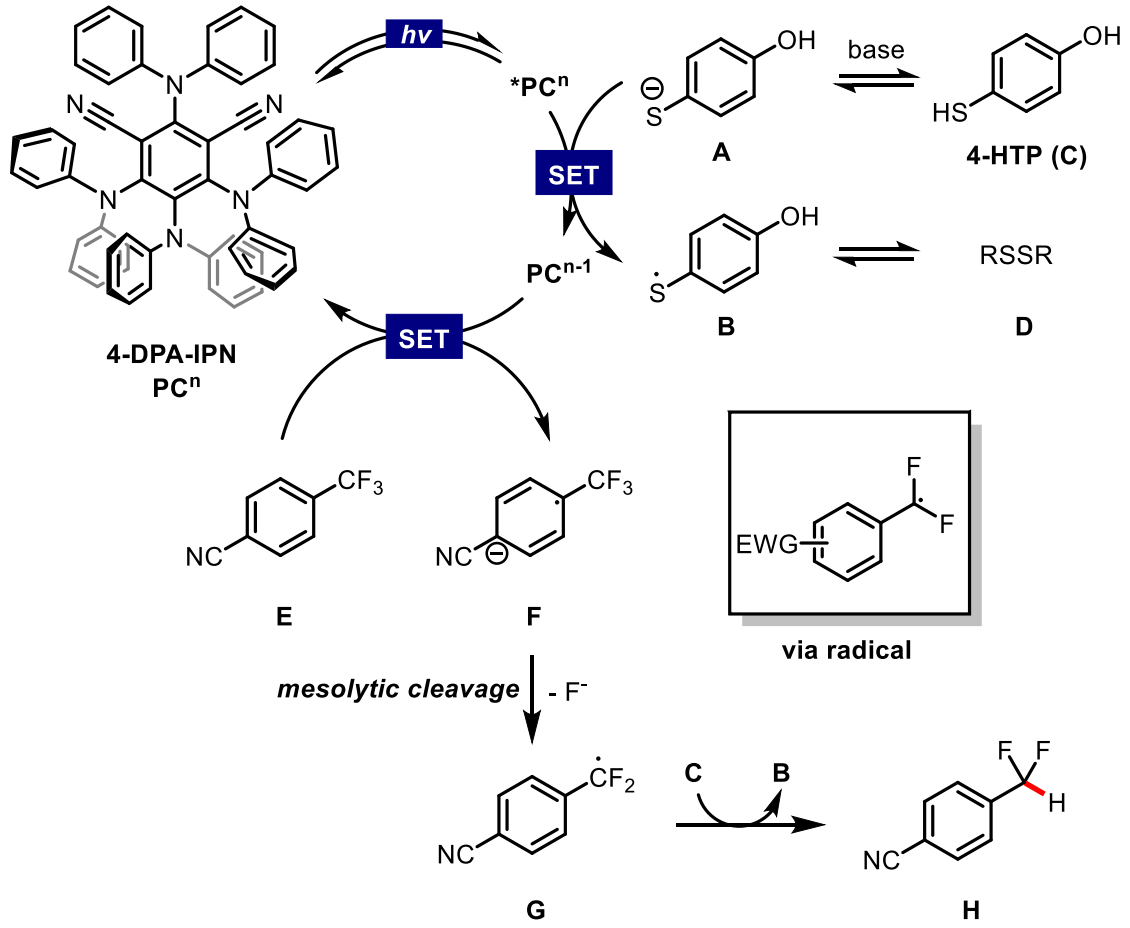




V. Gouverneur´, et. al. *J. Am. Chem. Soc.* **2020**, *142*, 9181.

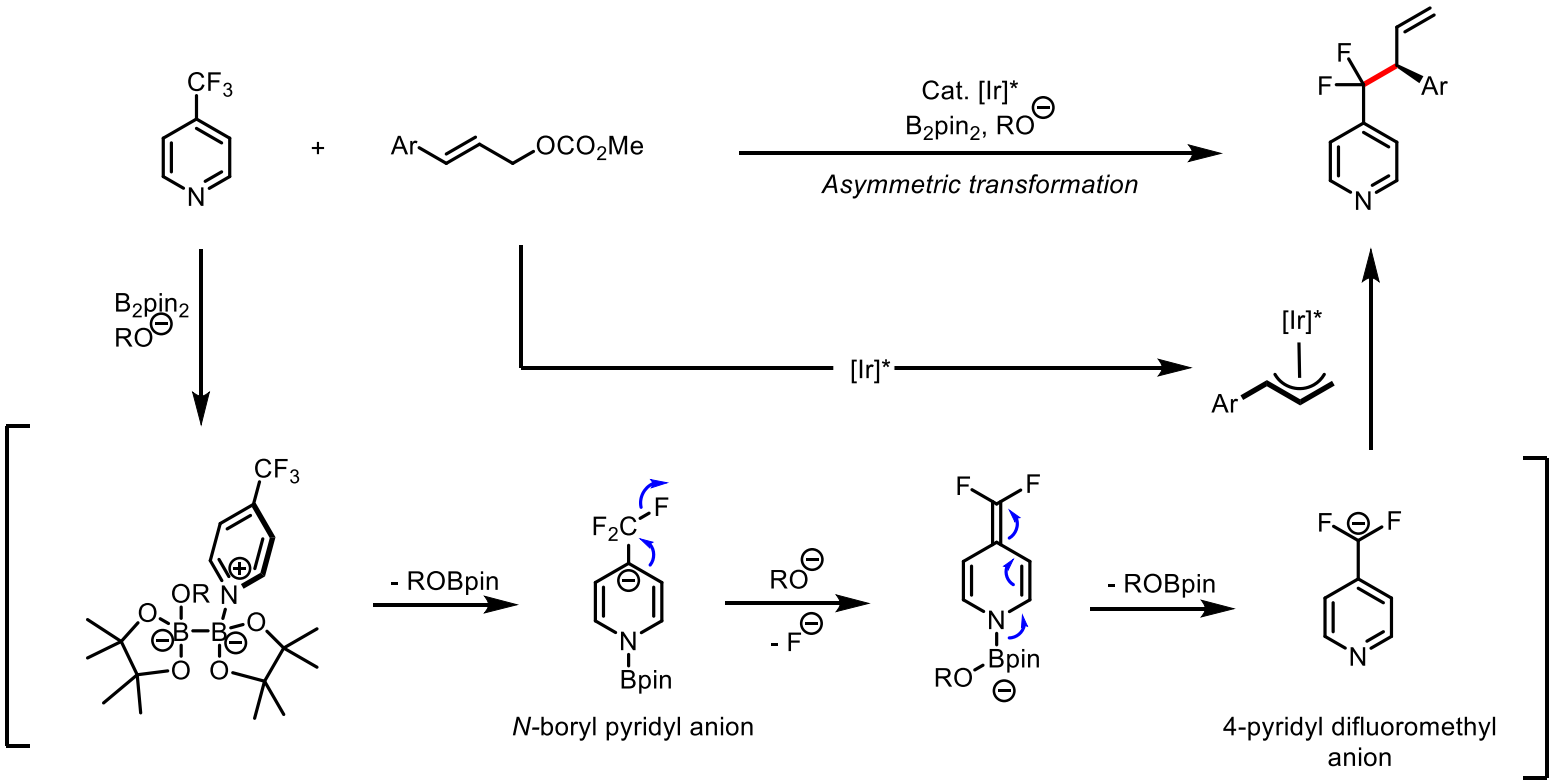
2.2 C-F Activation via SET Induced Process

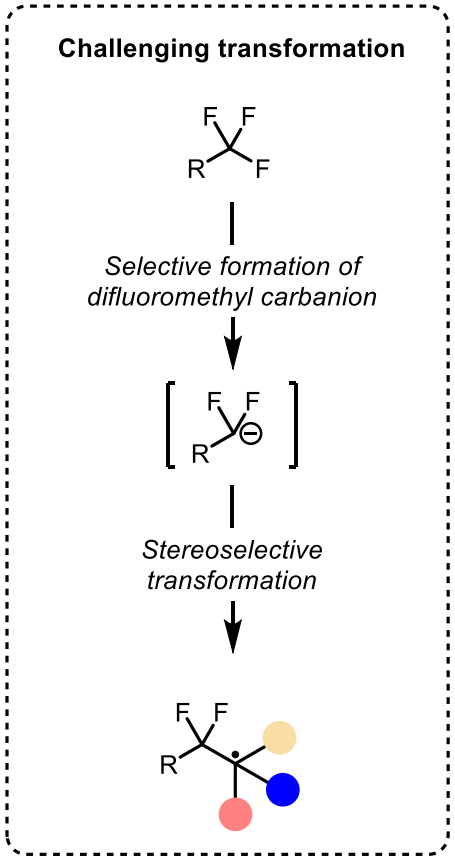




V. Gouverneur´, et. al. *J. Am. Chem. Soc.* **2020**, *142*, 9181.

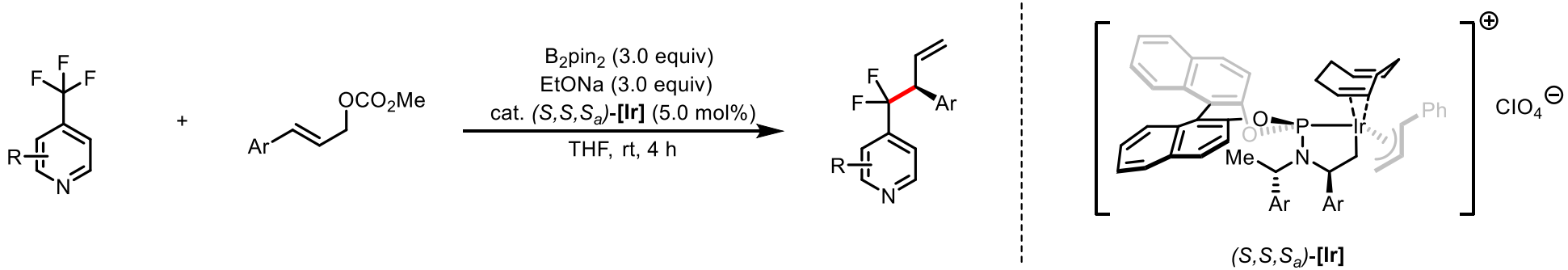
2.2 C-F Activation via SET Induced Process



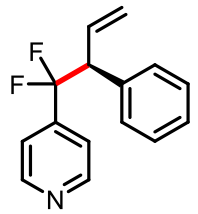


L. Jiao, et. al. *Angew. Chem. Int. Ed*. **2022**, e202201102.

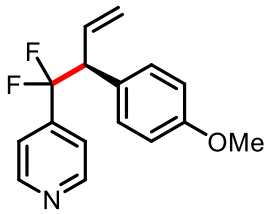
2.2 C-F Activation via SET Induced Process



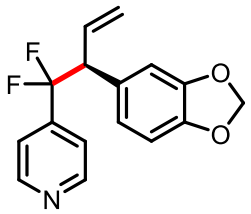
Selected examples



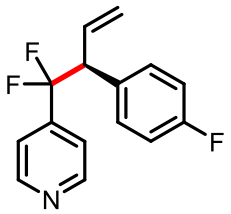
59% yield, 97% ee



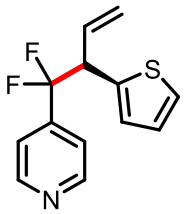
81% yield, 99% ee



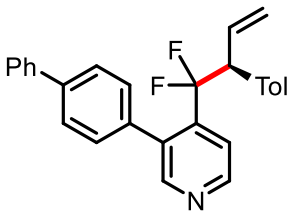
77% yield, 97% ee



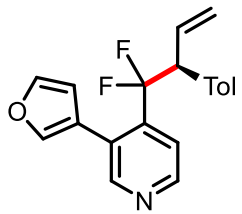
57% yield, 97% ee



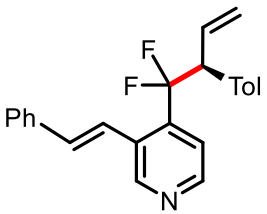
57% yield, >99% ee



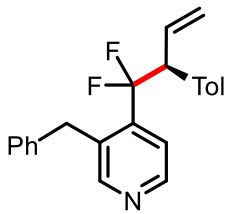
79% yield, 98% ee



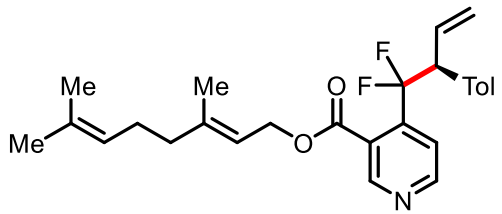
80% yield, 98% ee



84% yield, 96% ee



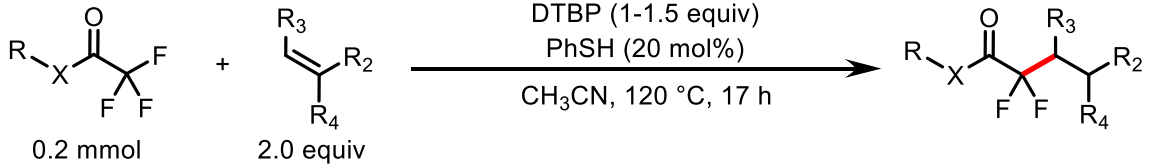
78% yield, 94% ee

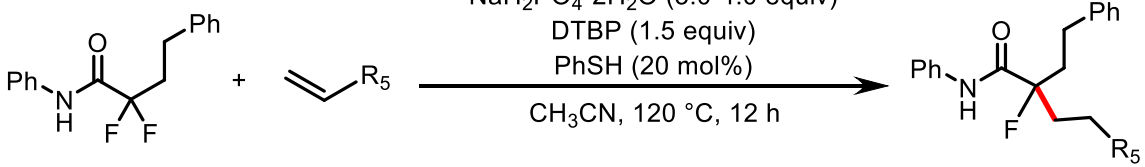


71% yield, 97% ee

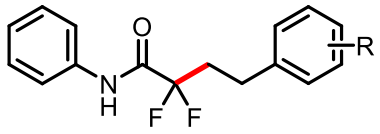
L. Jiao, et. al. *Angew. Chem. Int. Ed*. **2022**, e202201102.

2.2 C-F Activation via SET Induced Process

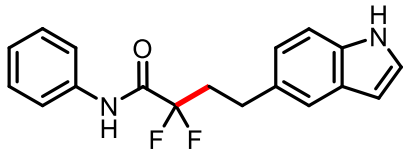




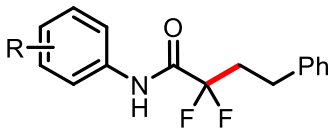
Selected examples



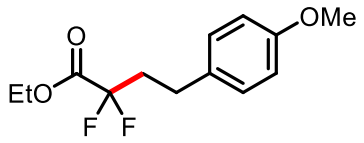
R = H, 75% yield
(gram scale, 59% yield)
R = 4-OMe, 84% yield
R = 4-Cl, 60% yield
R = 3-Me, 80% yield



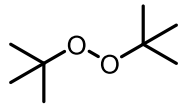
83% yield



R = 4-Me, 67% yield
R = 4-OMe, 74% yield
R = 2-Et, 71% yield
R = 3-Cl, 65% yield
R = 3-OH, 80% yield
R = 4-CH_2CO_2Et, 75% yield

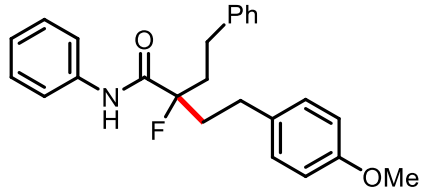


48% yield

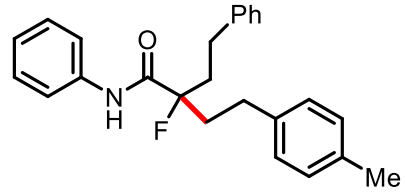


DTBP

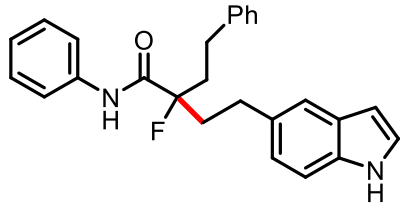
Selected examples



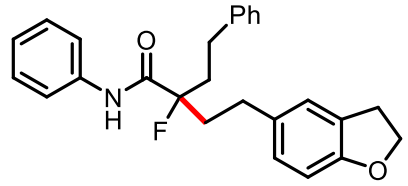
60% yield



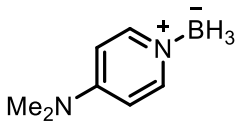
62% yield



55% yield



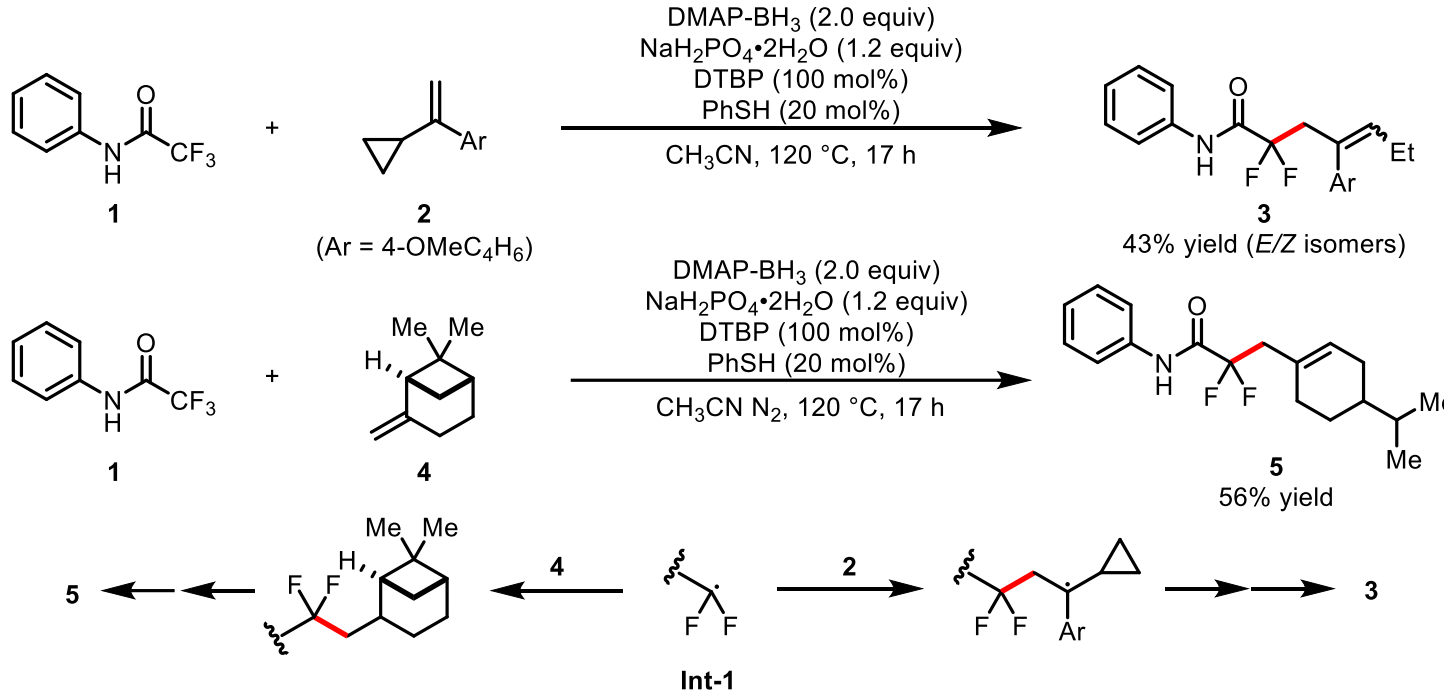
42% yield

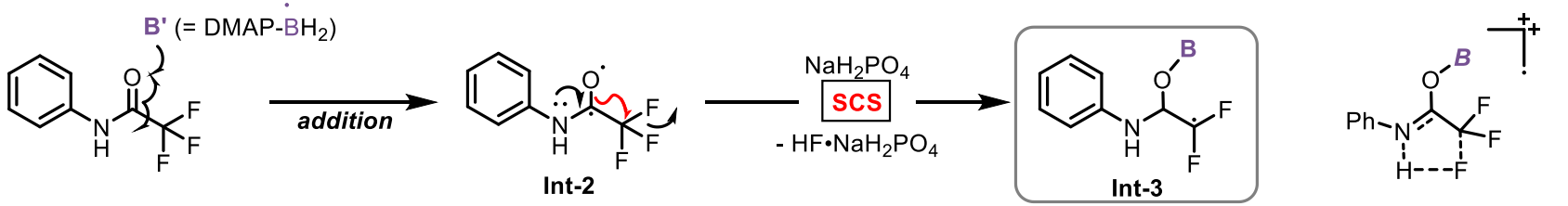


DMAP-BH_3

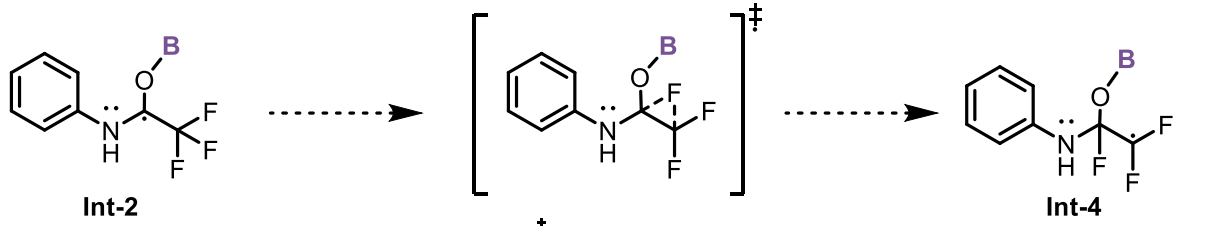
Y. Wang, et al. *Science*. **2021**, *371*, 1232.

2.2 C-F Activation via SET Induced Process



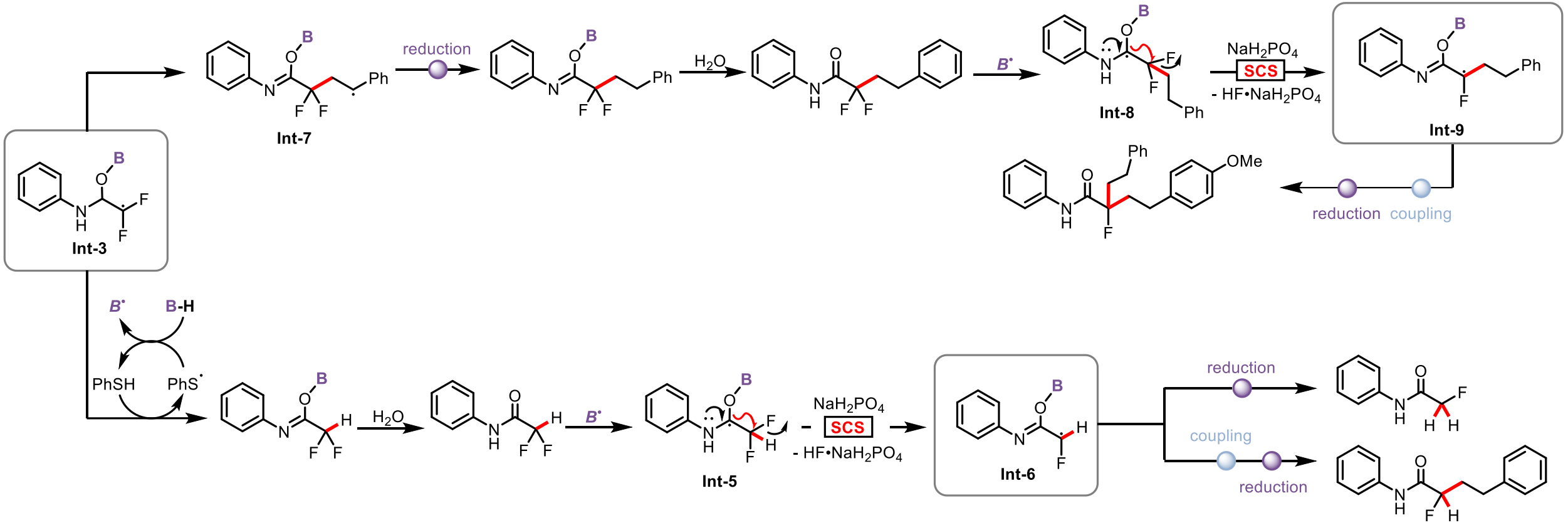


An energetically unfavorable 1,2-F migration pathway:



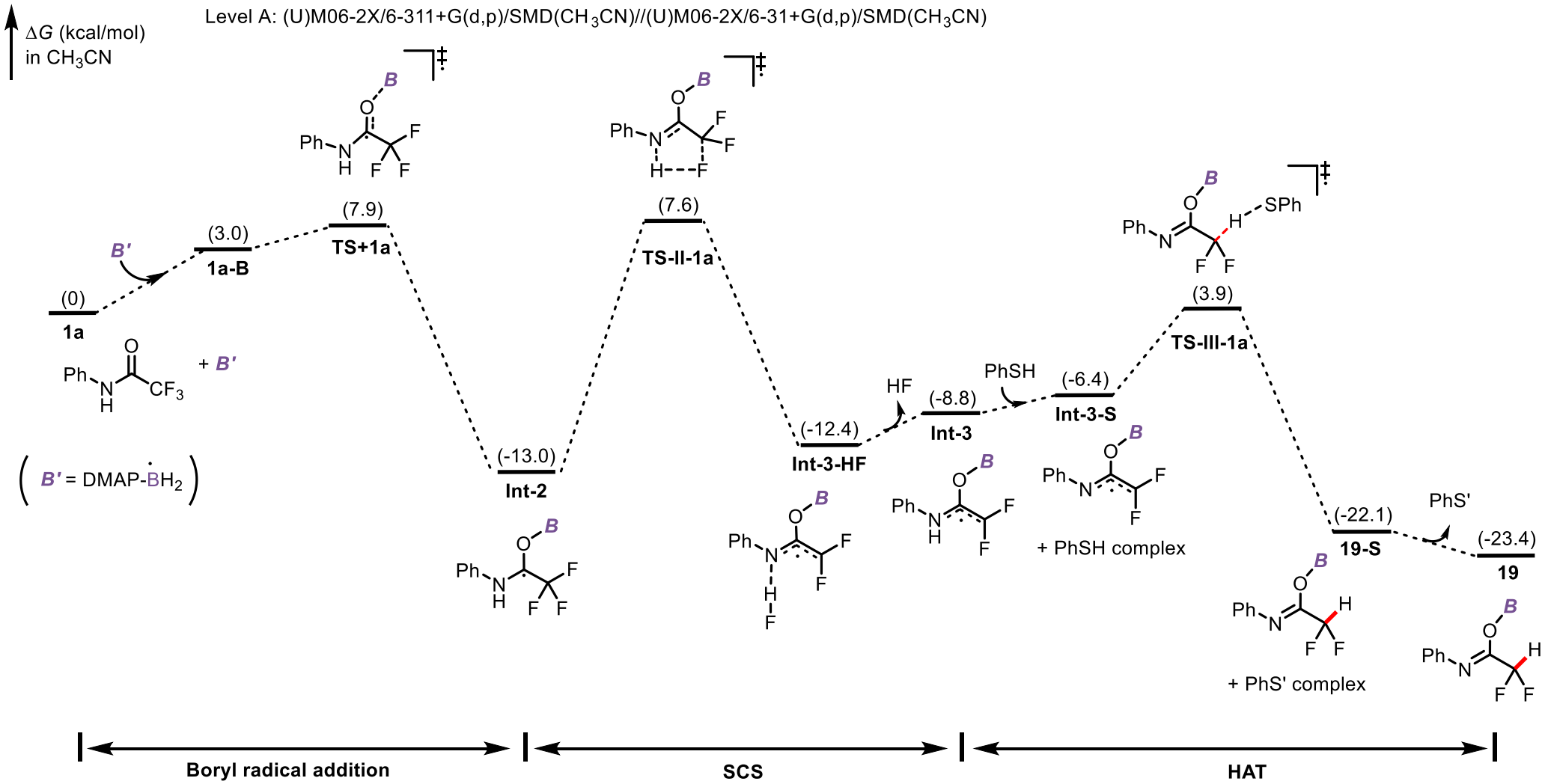
Y. Wang, et al. *Science*. **2021**, *371*, 1232.

2.2 C-F Activation via SET Induced Process



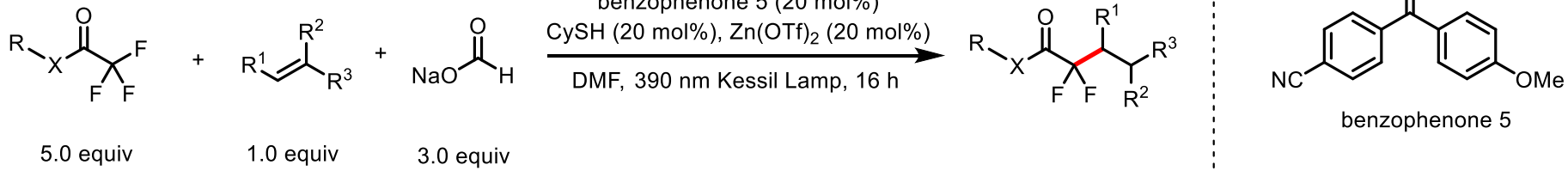
Y. Wang, et al. *Science*. **2021**, *371*, 1232.

2.2 C-F Activation via SET Induced Process

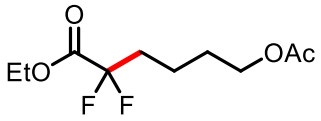


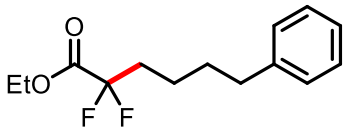
Y. Wang, et al. *Science*. **2021**, *371*, 1232.

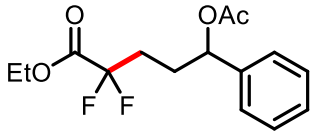
2.2 C-F Activation via SET Induced Process

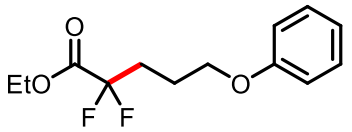


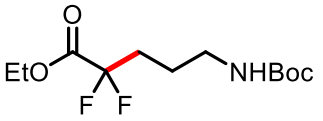
Selected examples

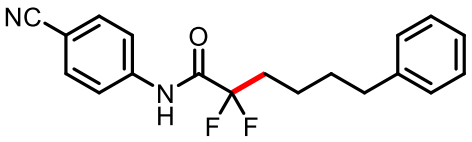

98% yield

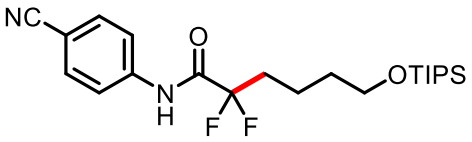

80% yield

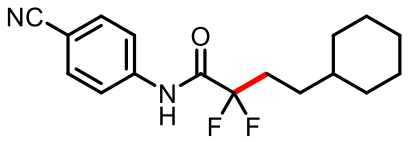

87% yield

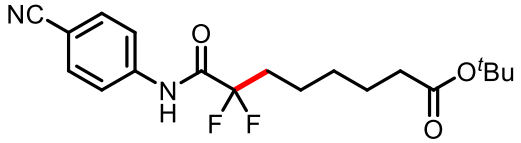

60% yield

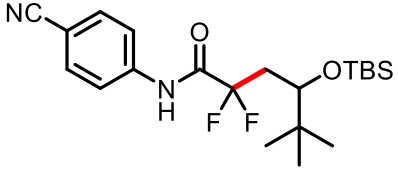

80% yield


70% yield


76% yield

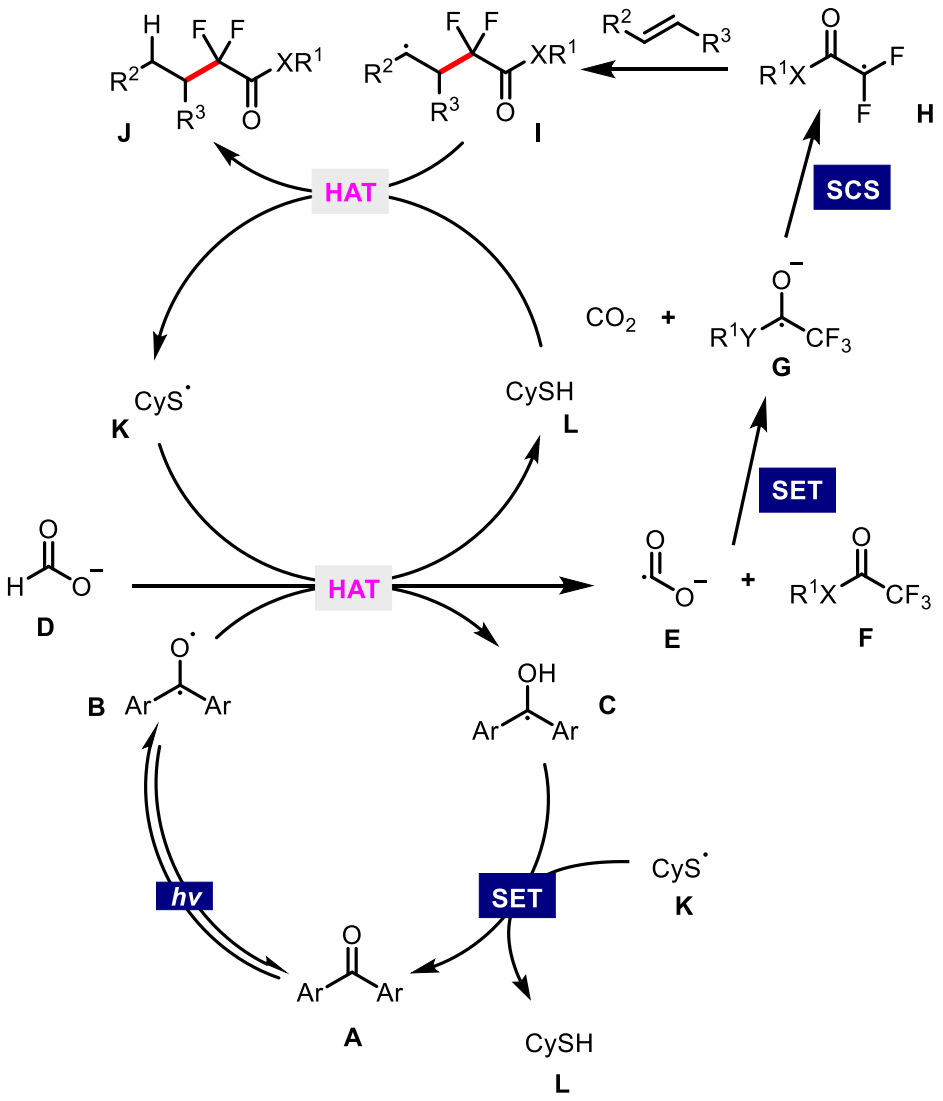

58% yield

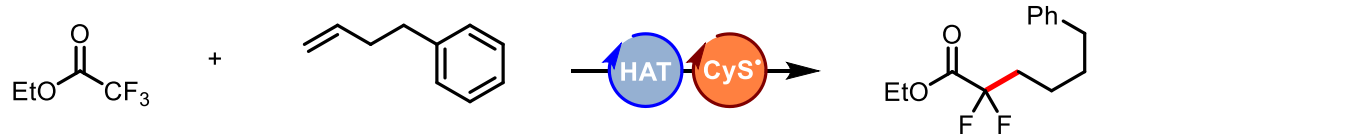

83% yield


88% yield

G. A. Molander, et. al. *J. Am. Chem. Soc.* **2021**, *143*, 19648.

2.2 C-F Activation via SET Induced Process

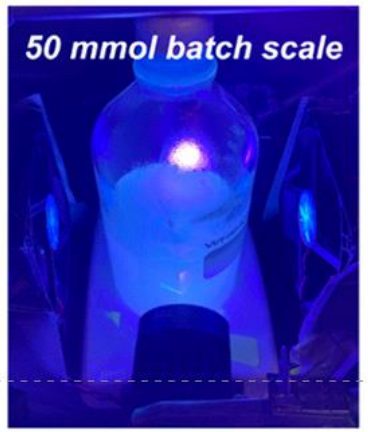


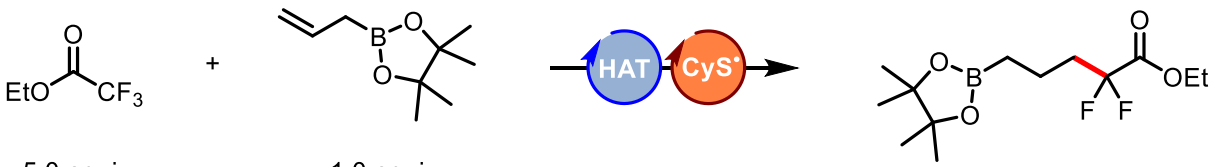


5.0 equiv

1.0 equiv

0.5 mmol scale, 20 mol% benzophenone = 80% yield
20 mmol scale, 10 mol% benzophenone = 85% yield
50 mmol scale, 1 mol% benzophenone = 70% yield





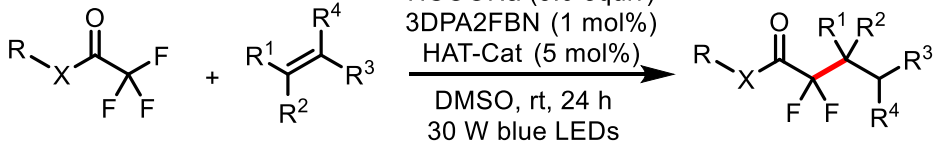
5.0 equiv

1.0 equiv

25 mmol scale, 5 mol% benzophenone = 50% yield
unstable to SiO_2 chromatography
isolated by vacuum distillation

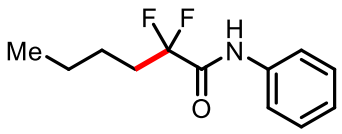
G. A. Molander, et. al. *J. Am. Chem. Soc.* **2021**, *143*, 19648.

2.2 C-F Activation via SET Induced Process

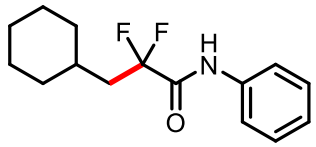


1.0 equiv 0.5-3.0 equiv

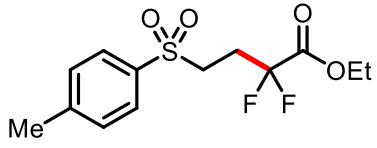
Selected examples



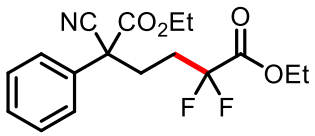
87% yield



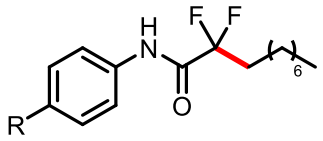
94% yield



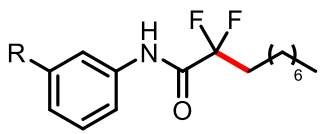
88% yield



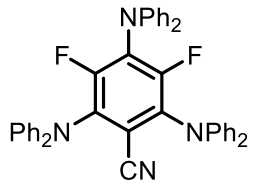
88% yield



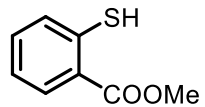
R = Me, 76% yield
R = Cl, 82% yield
R = OMe, 78% yield



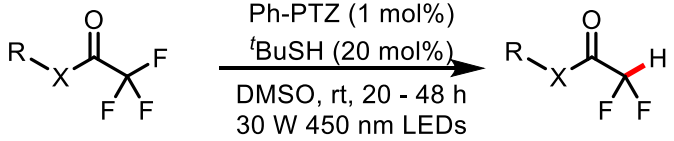
R = OH, 60% yield
R = F, 83% yield
R = OCF_3, 72% yield



3DPA2FBN

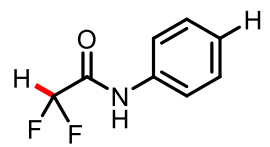


HAT-Cat

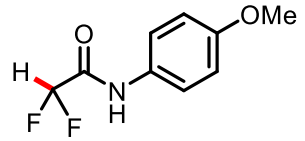


1.0 equiv

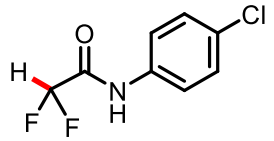
Selected examples



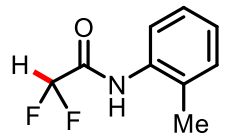
82% yield



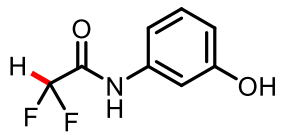
72% yield



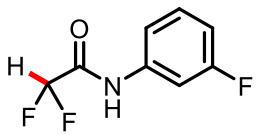
80% yield



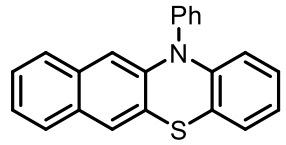
65% yield



72% yield



90% yield

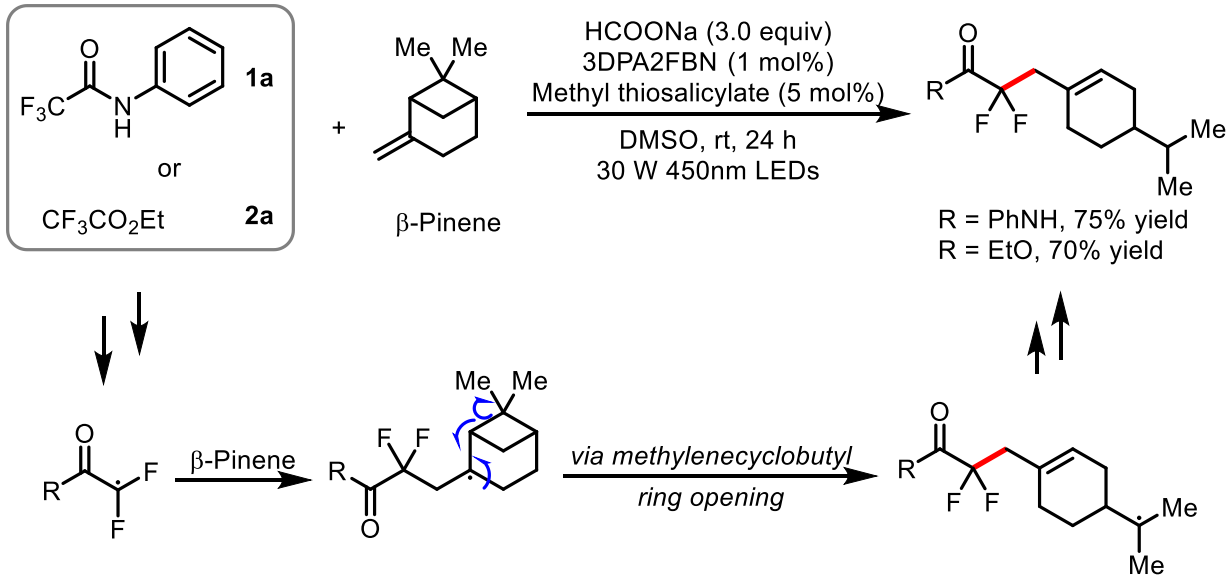


Ph-PTZ

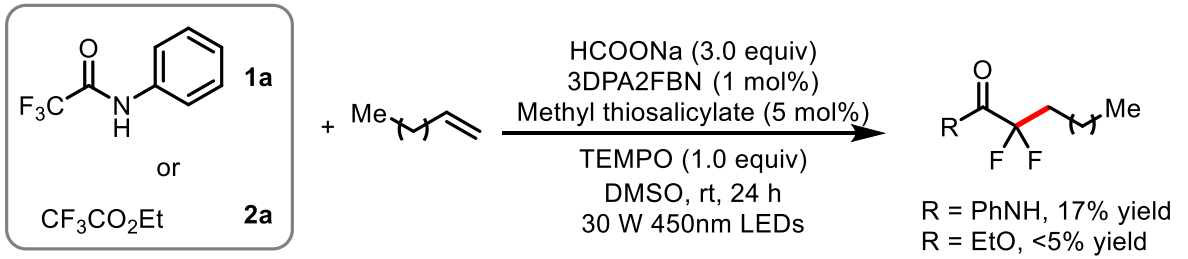
F. Glorius, et. al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202115456.

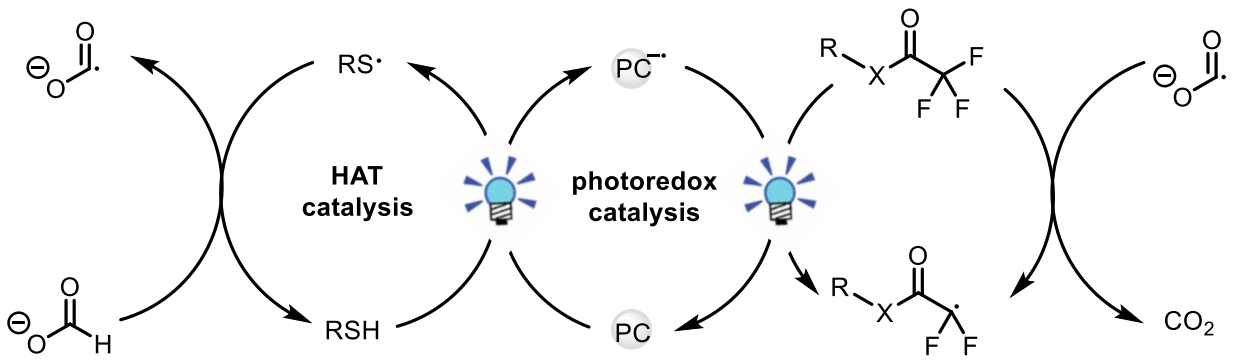
2.2 C-F Activation via SET Induced Process

Radical probe



TEMPO trapping

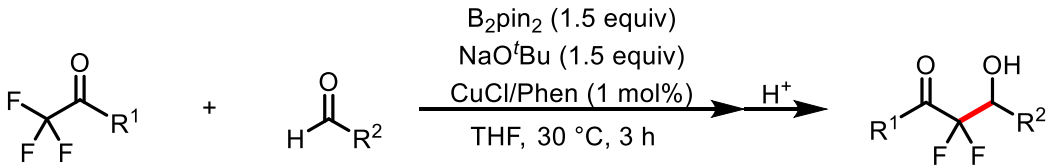




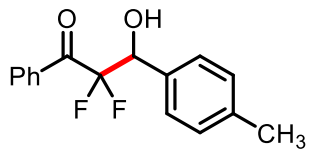
F. Glorius, et. al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202115456.

Contents

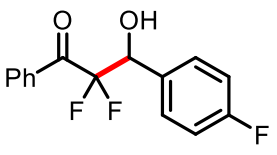
2.3 C-F Activation via Transition Metal Induced Process



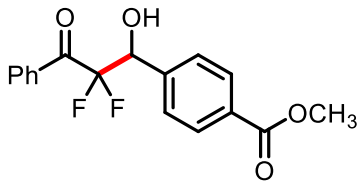
Selected examples



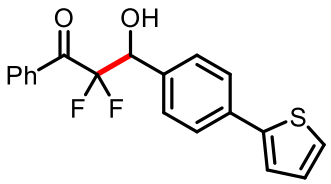
82% yield



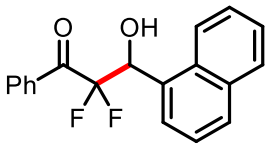
73% yield



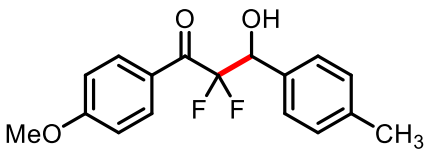
54% yield



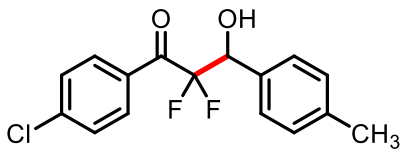
40% yield



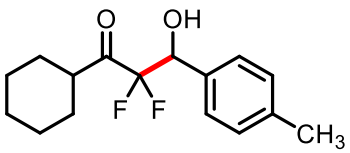
27% yield



55% yield



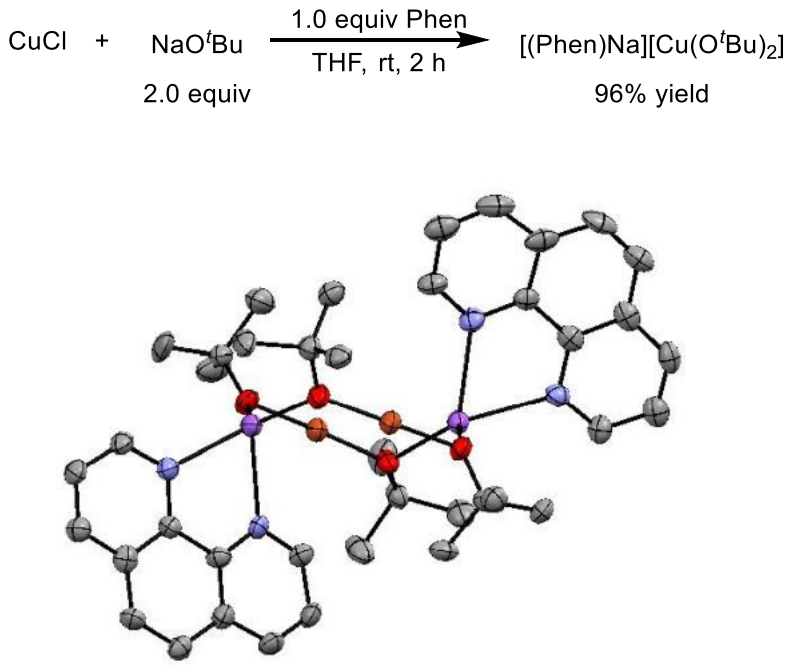
65% yield

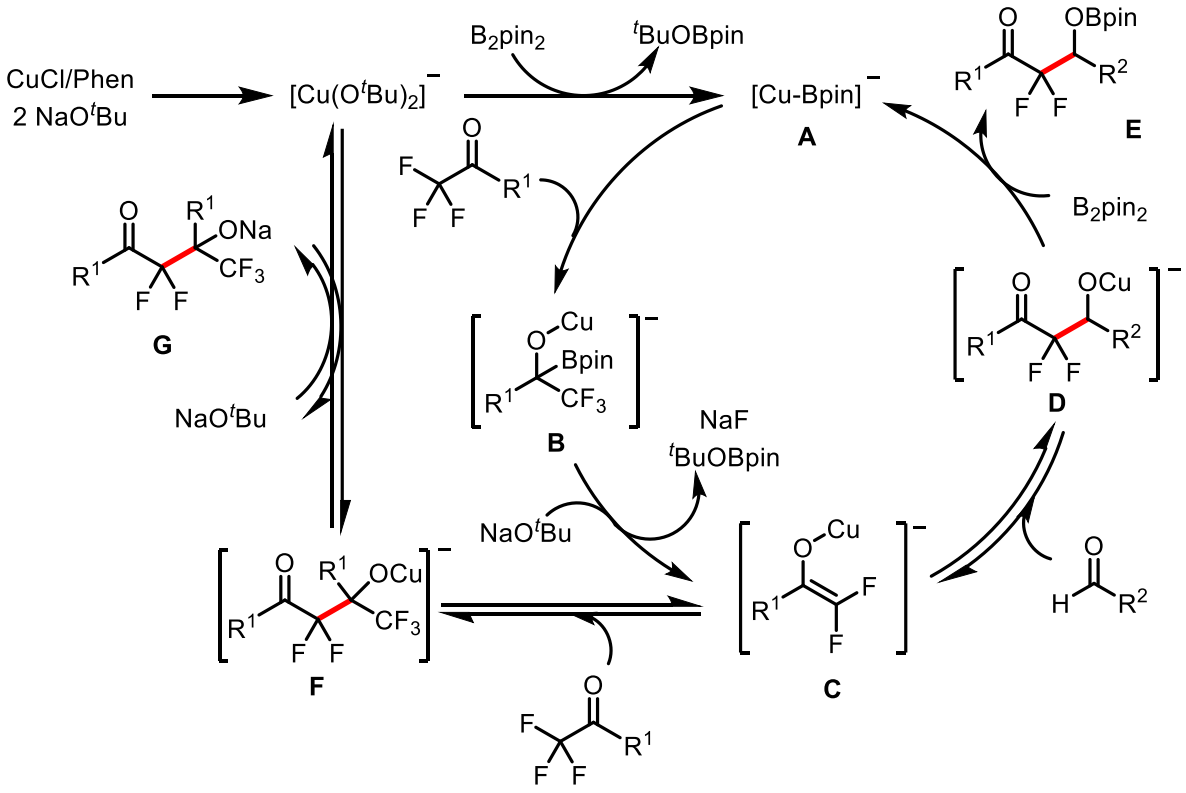


85% yield

S. Ogoshi, et al. *Angew. Chem. Int. Ed*. **2016**, *55*, 341.

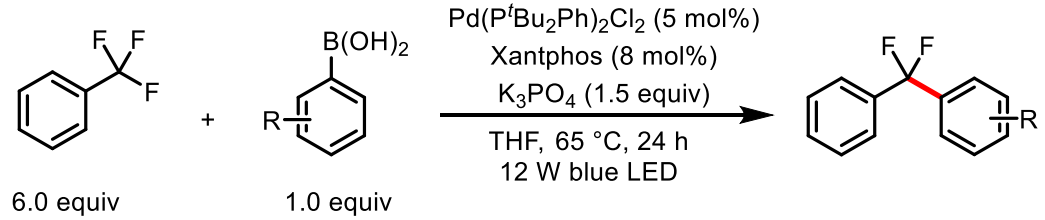
2.3 C-F Activation via Transition Metal Induced Process



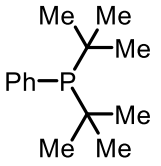


S. Ogoshi, et al. *Angew. Chem. Int. Ed*. **2016**, *55*, 341.

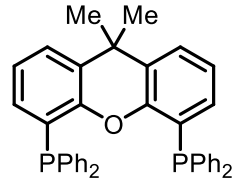
2.3 C-F Activation via Transition Metal Induced Process



6.0 equiv 1.0 equiv

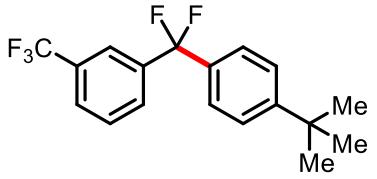


P^tBu_2Ph

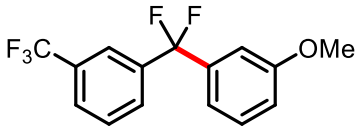


Xantphos

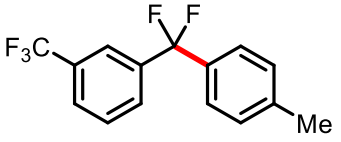
Selected examples



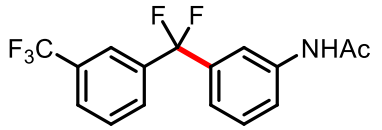
69% yield



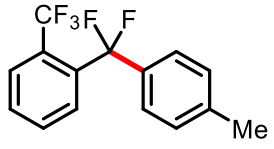
57% yield



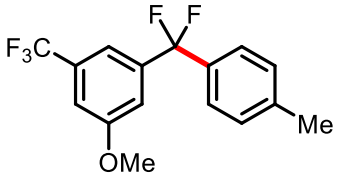
64% yield



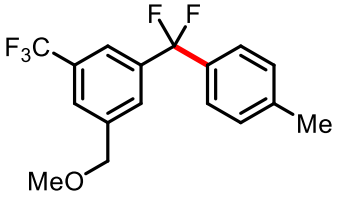
41% yield



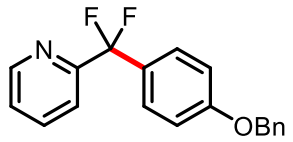
58% yield



49% yield



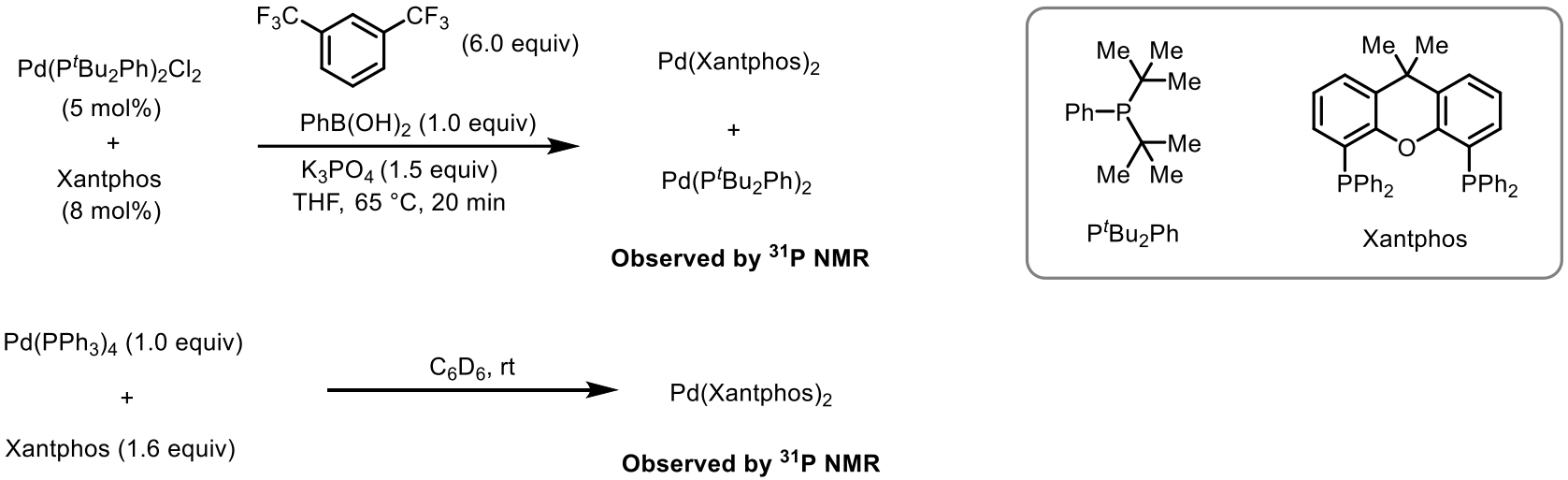
64% yield

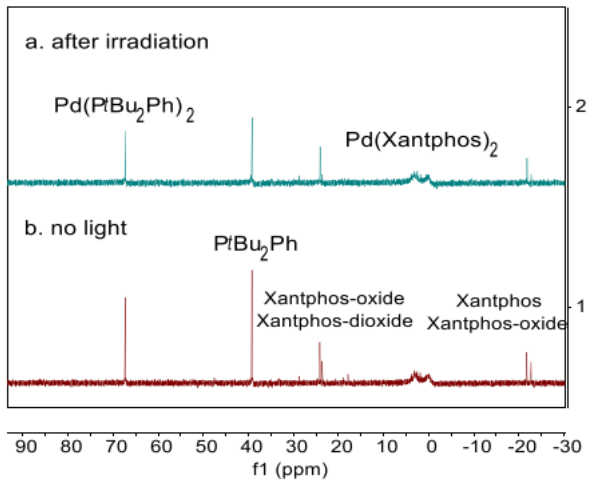


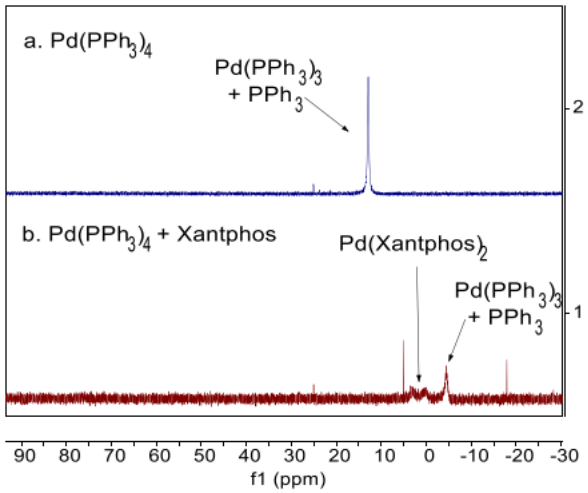
56% yield

X. Zhang, et. al. *J. Am. Chem. Soc*. **2021**, *143*, 13971.

2.3 C-F Activation via Transition Metal Induced Process

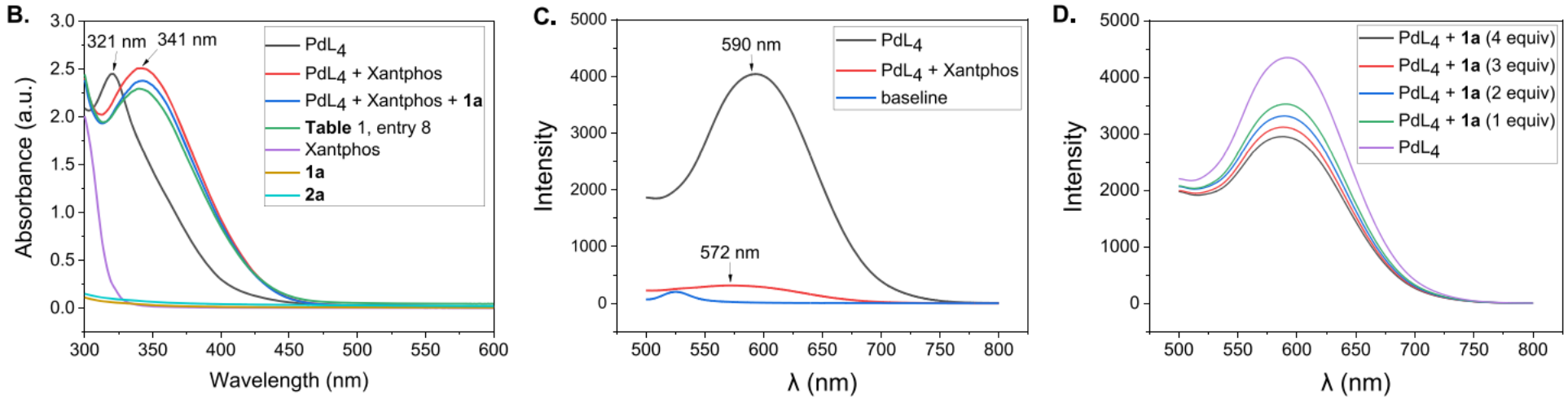


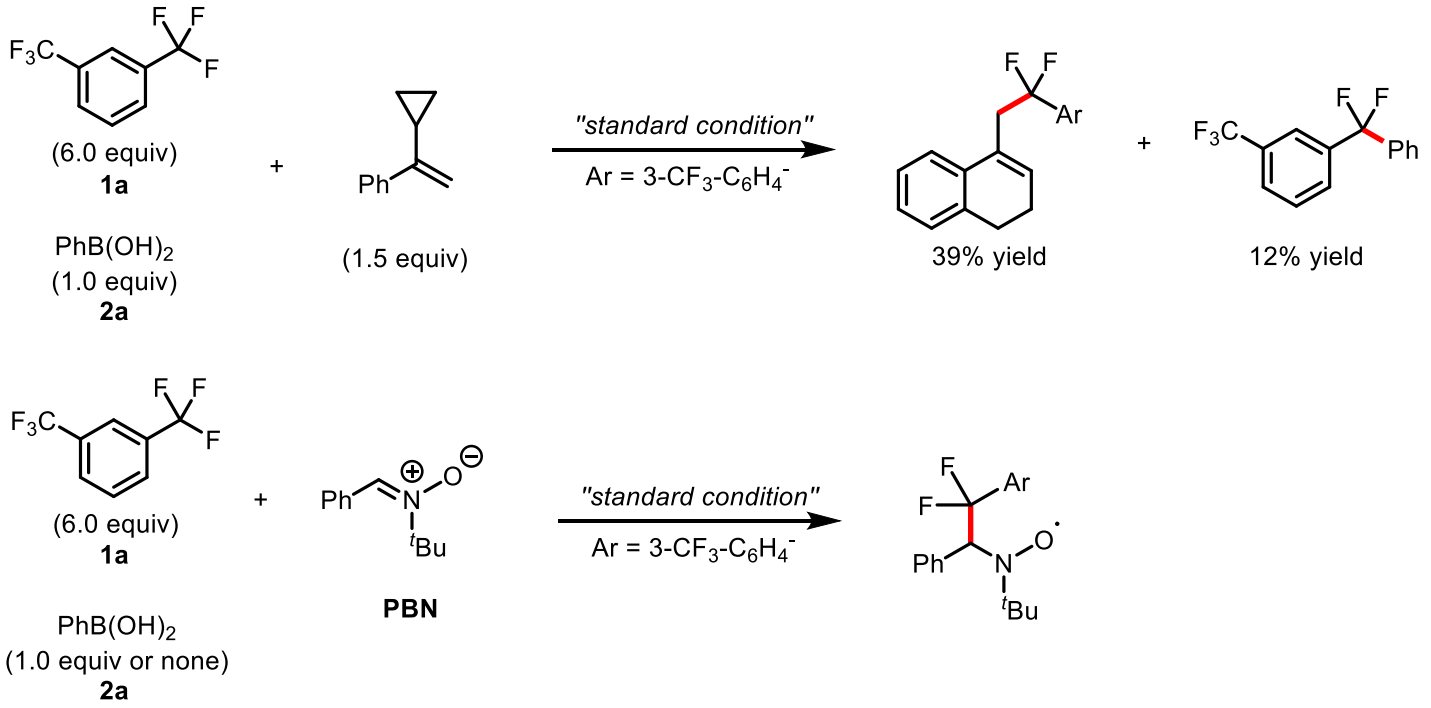




X. Zhang, et. al. *J. Am. Chem. Soc*. **2021**, *143*, 13971.

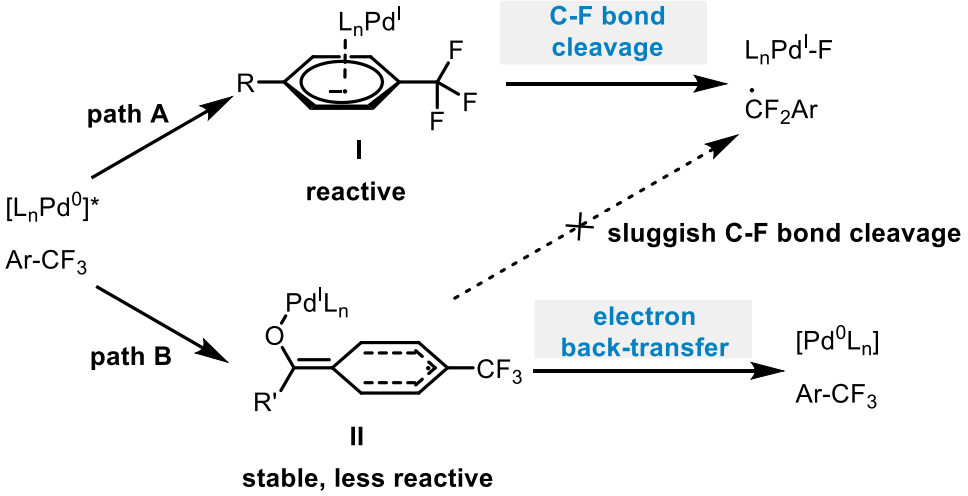
2.3 C-F Activation via Transition Metal Induced Process

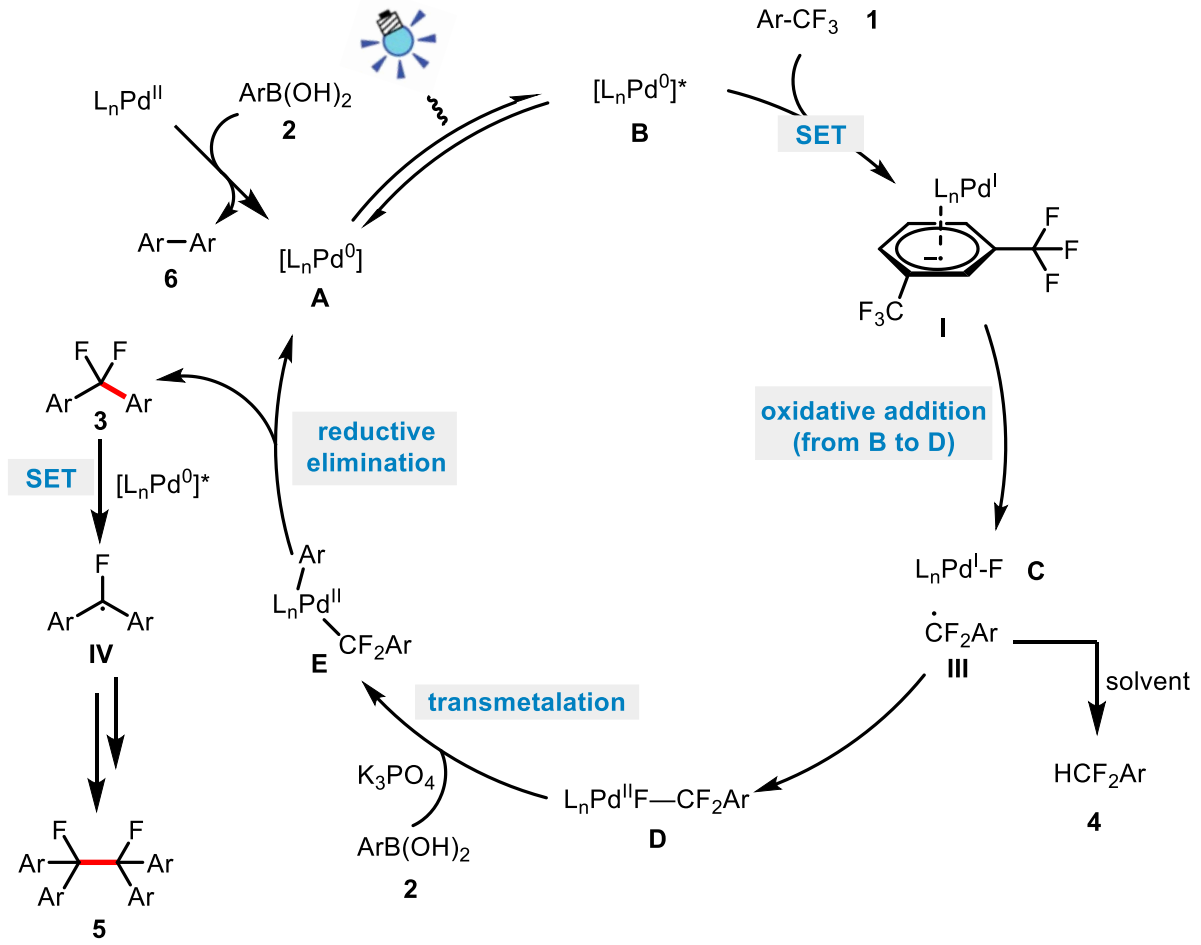




X. Zhang, et. al. *J. Am. Chem. Soc*. **2021**, *143*, 13971.

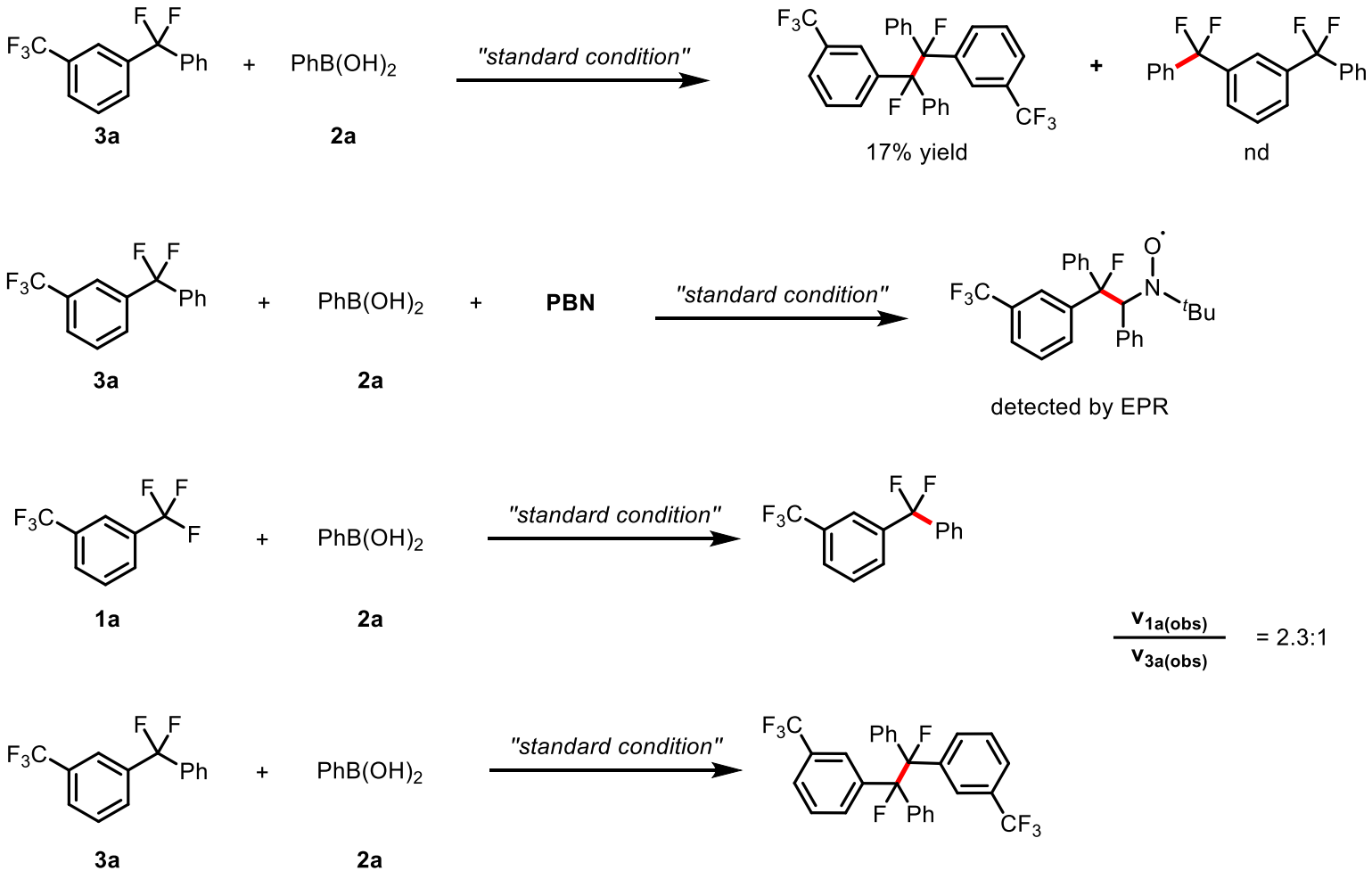
2.3 C-F Activation via Transition Metal Induced Process

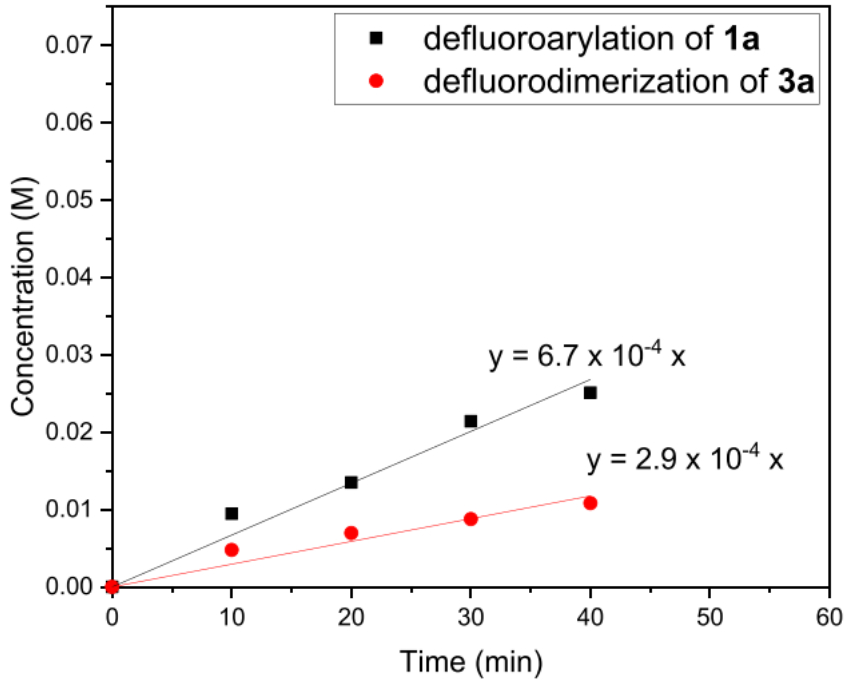




X. Zhang, et. al. *J. Am. Chem. Soc*. **2021**, *143*, 13971.

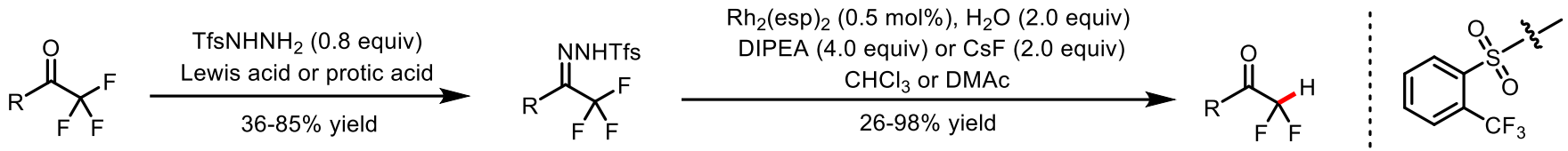
2.3 C-F Activation via Transition Metal Induced Process



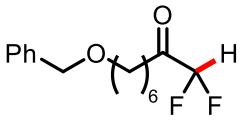


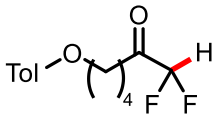
X. Zhang, et. al. *J. Am. Chem. Soc*. **2021**, *143*, 13971.

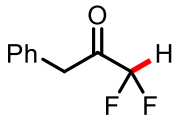
2.3 C-F Activation via Transition Metal Induced Process

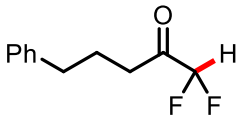


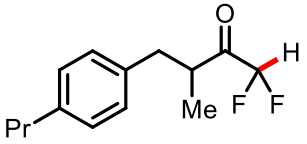
Selected examples

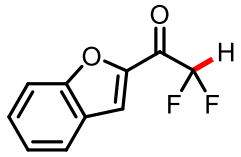

80% yield

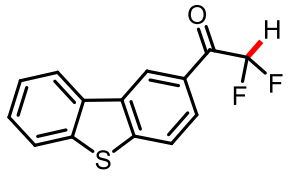

98% yield

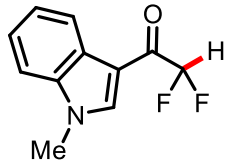

96% yield

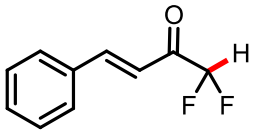

92% yield

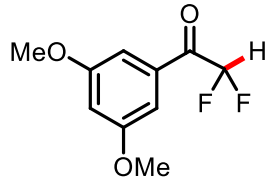

69% yield

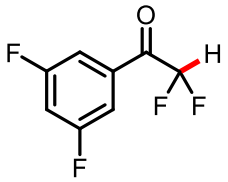

83% yield

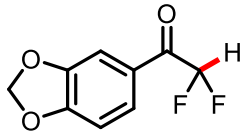

94% yield

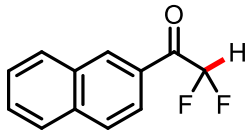

94% yield

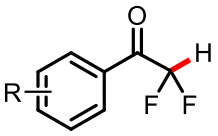

94% yield


72% yield


67% yield


97% yield

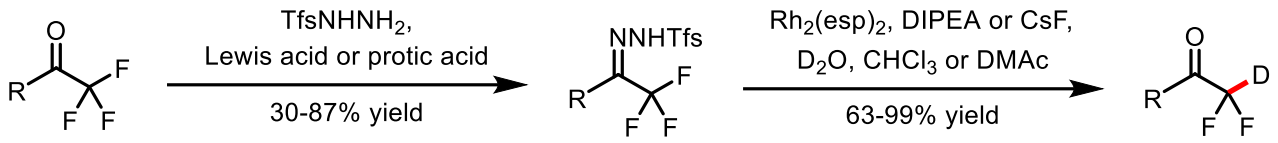

63% yield



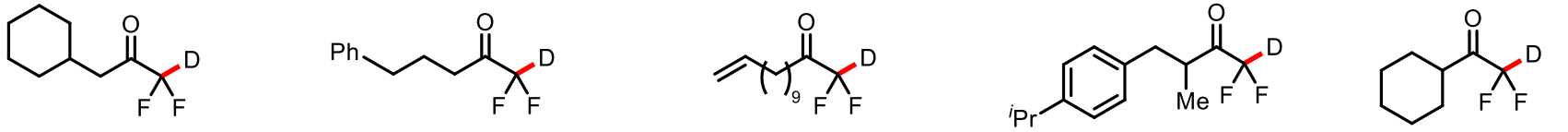
R = 4-Me, 98% yield
R = 4-^{t}Bu, 98% yield
R = 4-NMe_2, 88% yield
R = 4-Cl, 98% yield
R = 4-OCF_3, 80% yield
R = 4-Ph, 97% yield
R = 3-CN, 66% yield
R = 3-NO_2, 62% yield
R = 4-CF_3, 91% yield
R = 4-COOEt, 88% yield
R = 4-Vinyl, 74% yield

X. Bi, et. al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116190.

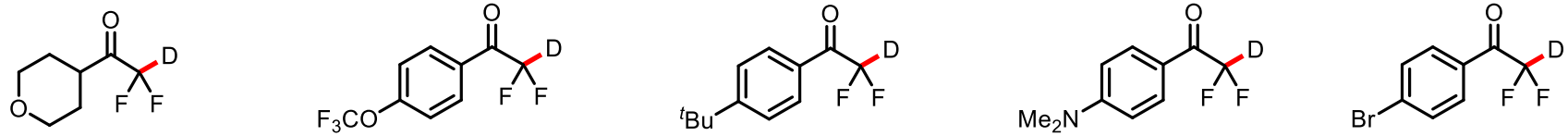
2.3 C-F Activation via Transition Metal Induced Process



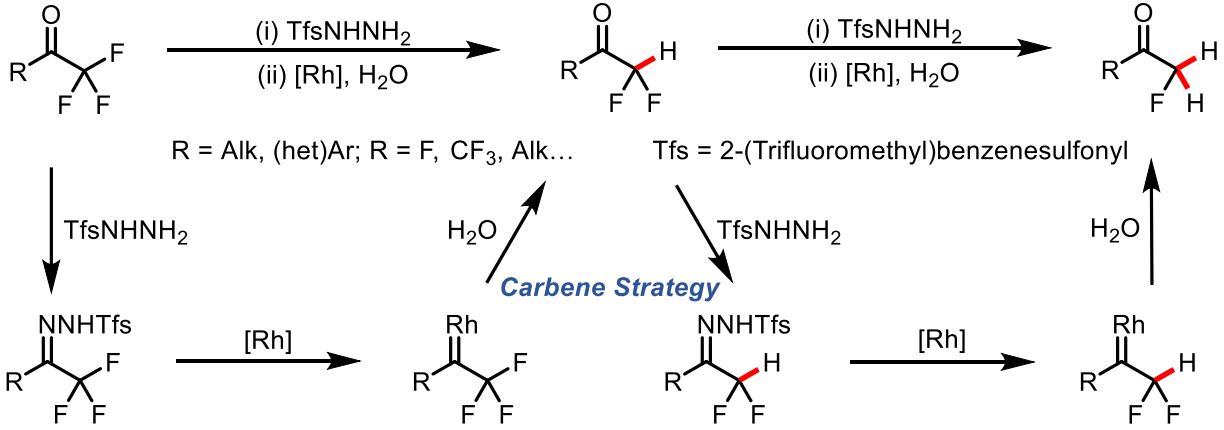
Selected examples



90% (99% D) yield | 87% (97% D) yield | 89% (94% D) yield | 78% (99% D) yield | 86% (99% D) yield

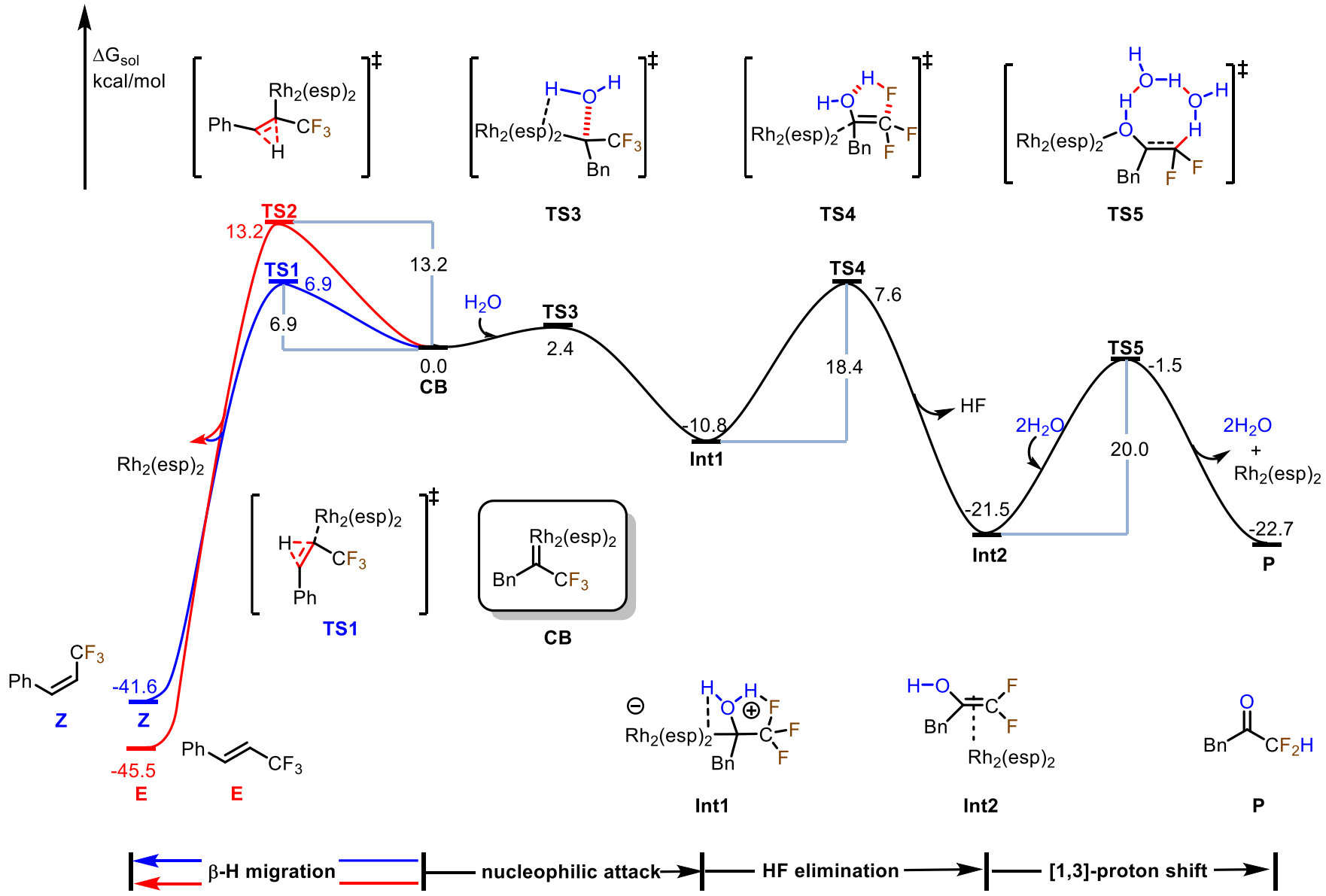


95% (97% D) yield | 85% (95% D) yield | 94% (100% D) yield | 90% (97% D) yield | 92% (95% D) yield



X. Bi, et. al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116190.

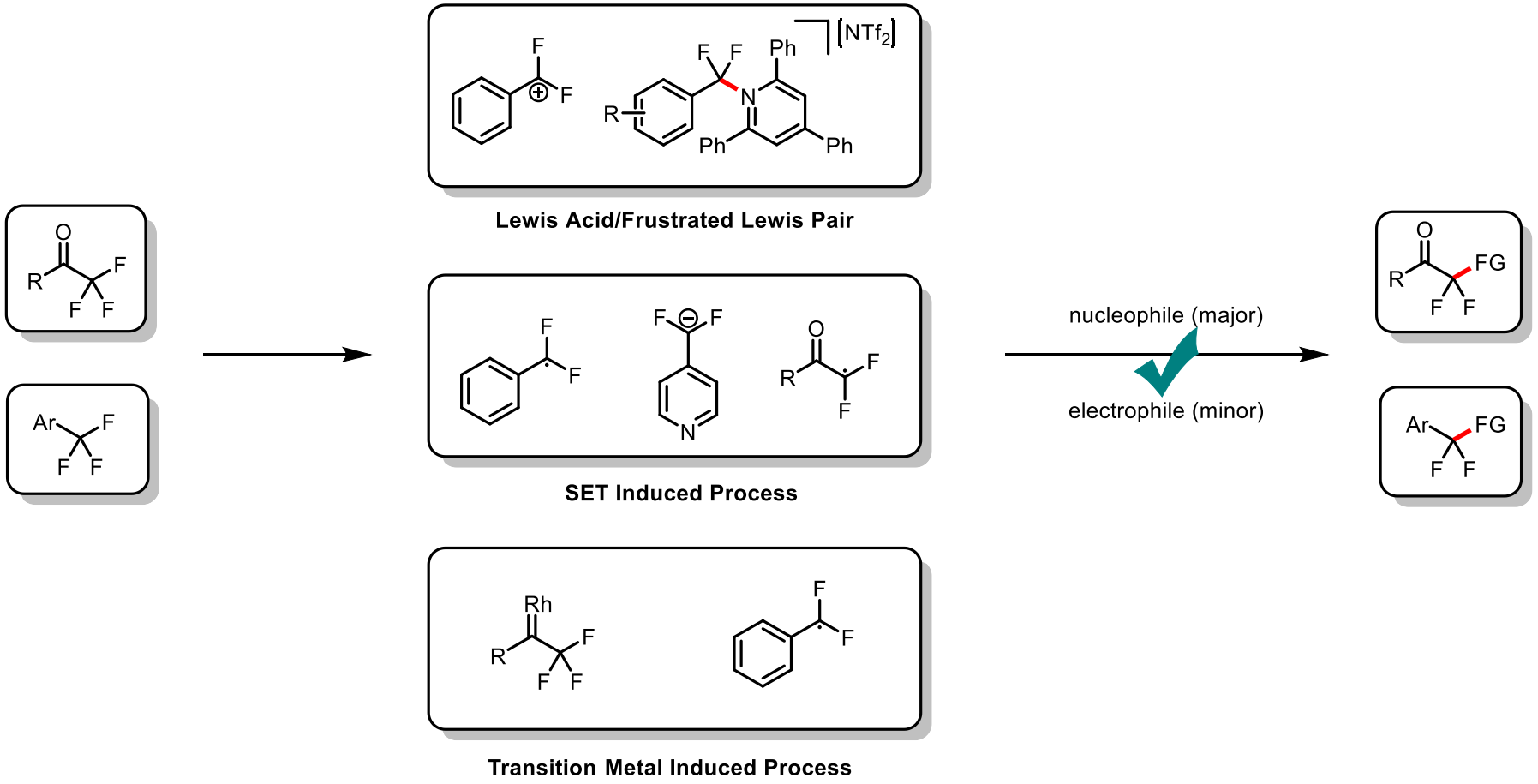
2.3 C-F Activation via Transition Metal Induced Process



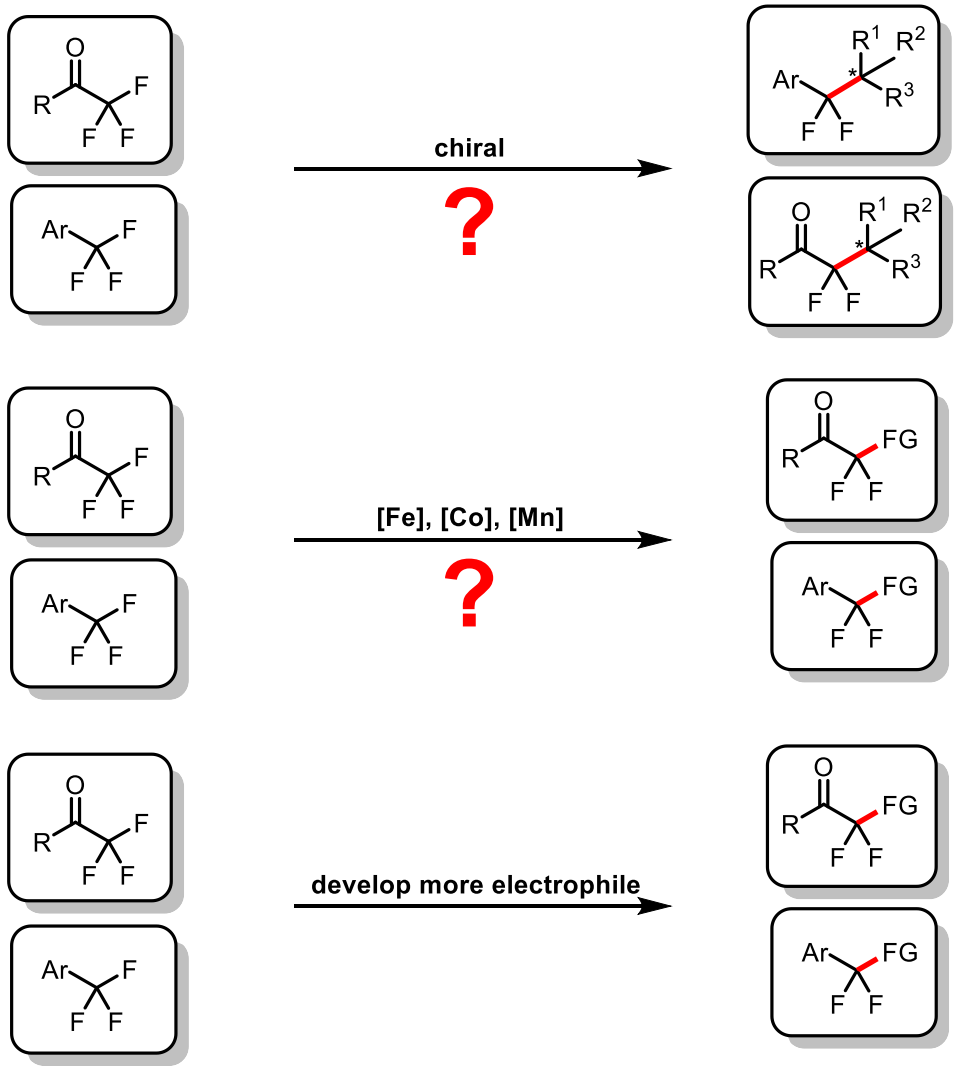
X. Bi, et. al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116190.

Contents

3. Summary and Prospection



3. Summary and Prospection



Thanks For Your Attention