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Pd(II)-Catalyzed ortho-Trifluoromethylation of Arenes Using TFA as a Promoter

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Pd(II)-Catalyzed *ortho*-Trifluoromethylation of Arenes Using TFA as a Promoter

Yu, J.-Q. * *et al*
J. Am. Chem. Soc. **2010**, 132, 3648-3649.

Pd(II)-Catalyzed C-H Trifluoromethylation

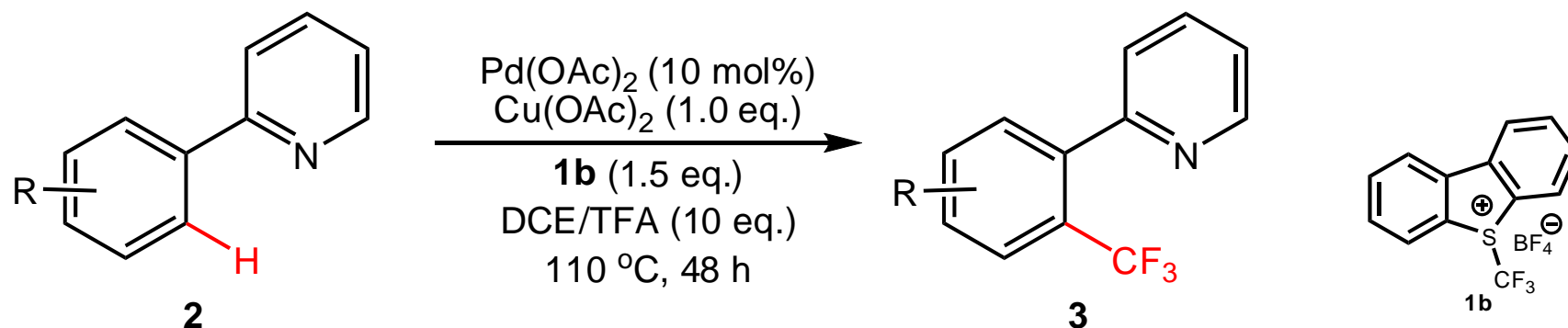
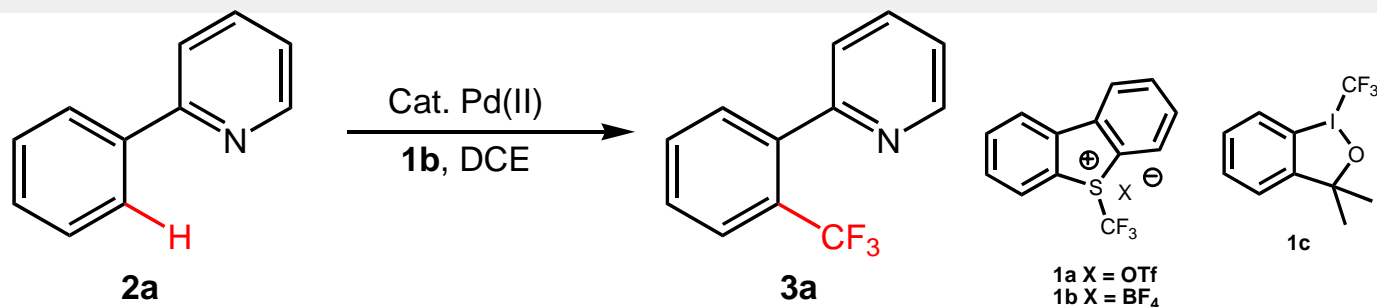


Table 1. Pd(II)-Catalyzed C-H Trifluoromethylation^a



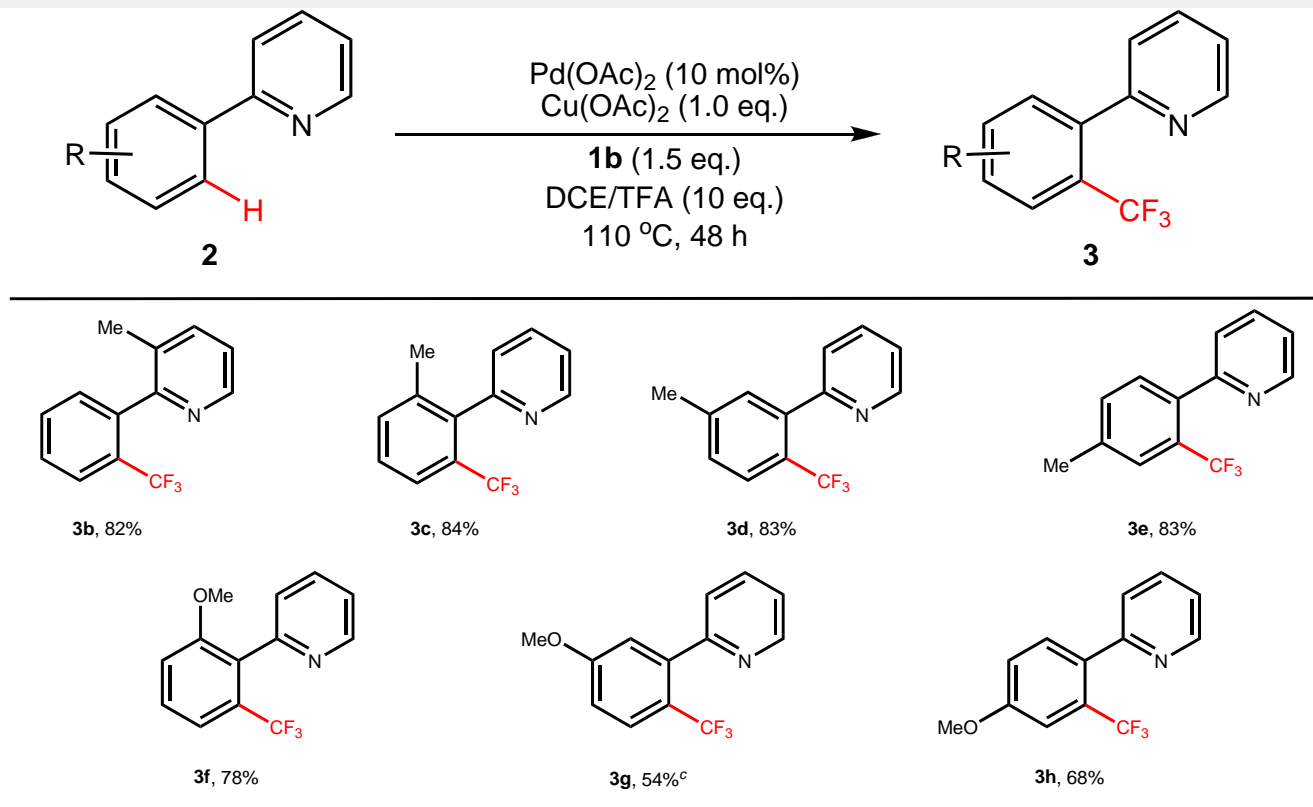
Entry	Catalyst	Additive (eq.)	Oxidant (eq.)	Yield (%) ^b
1	Pd(OAc) ₂	—	—	0
2	Pd(OAc)₂	TFA (10)	—	50
3	Pd(OTFA) ₂	—	—	0
4	Pd(OTFA)₂	TFA (10)	—	52
5	Pd(OAc) ₂	AcOH (10)	—	5
6	Pd(OAc) ₂	TsOH (10)	—	0
7	Pd(OAc) ₂	TfOH(10)	—	0

^a Unless otherwise noted, the reaction conditions were as follows: **2a** (0.2 mmol), Pd(II) catalyst (0.02 mmol, 10 mol%), **1a** (0.3 mmol, 1.5 eq.), DCE (1 mL), 110 °C, 48 h. ^b Isolated yield.

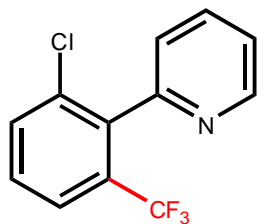
Entry	Catalyst	Additive (eq.)	Oxidant (eq.)	Yield (%) ^b
8	Pd(OAc) ₂	TFA (10)	Cu(OAc) ₂ (1)	70
9	Pd(OAc) ₂	TFA (10)	Cu(OTFA) ₂ (1)	71
10	Pd(OAc) ₂	TFA (10)	Cu(OTf) ₂ (1)	47
11	Pd(OAc) ₂	TFA (10)	AgOAc (2)	43
12	Pd(OAc) ₂	TFA (10)	Ag ₂ CO ₃ (1)	45
13	Pd(OAc) ₂	TFA (10)	Ag ₂ O (1)	44
14	Pd(OAc) ₂	TFA (10)	BQ (1)	30
15 ^c	—	TFA (10)	Cu(OAc) ₂ (1)	0
16^d	Pd(OAc)₂	TFA (10)	Cu(OAc)₂ (1)	86
17 ^e	Pd(OAc) ₂	TFA (10)	Cu(OAc) ₂ (1)	11

^a Unless otherwise noted, the reaction conditions were as follows: **2a** (0.2 mmol), Pd(II) catalyst (0.02 mmol, 10 mol%), **1a** (0.3 mmol, 1.5 eq.), DCE (1 mL), 110 °C, 48 h. ^b Isolated yield. ^c No Pd(OAc)₂ was added. ^d **1b** was used instead of **1a**. ^e **1c** was used instead of **1a**.

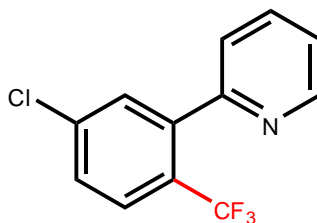
Table 2. C-H Trifluoromethylation of Pyridine Derivatives^{a,b}



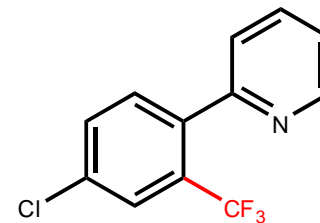
^a Unless otherwise noted, the reaction conditions were as follows: substrate (0.2 mmol), $\text{Pd}(\text{OAc})_2$ (0.02 mmol, 10 mol%), $\text{Cu}(\text{OAc})_2$ (0.2 mmol, 1.0 eq.), **1b** (0.3 mmol, 1.5 eq.), TFA (2 mmol, 10 equiv), DCE (1 mL), 110 °C, 48 h. ^b Isolated yield. ^c $\text{Pd}(\text{OAc})_2$ (15 mol%) was used.



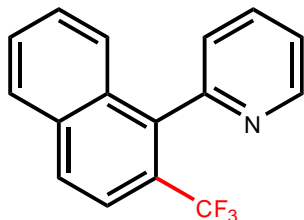
3i, 55%^d



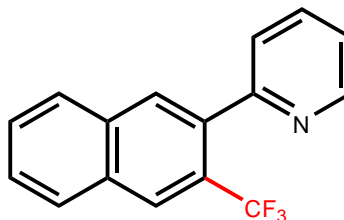
3j, 75%^d



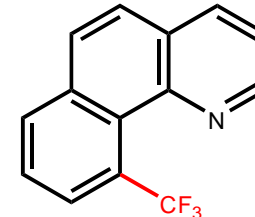
3k, 72%^d



3l, 78%^c

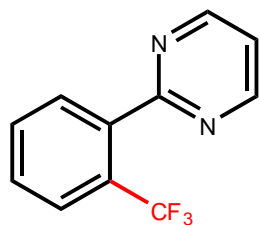


3m, 87%^c

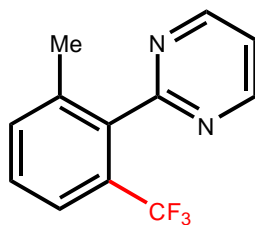


3n, 88%

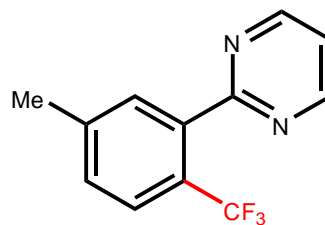
^a Unless otherwise noted, the reaction conditions were as follows: substrate (0.2 mmol), Pd(OAc)₂ (0.02 mmol, 10mol%), Cu(OAc)₂ (0.2 mmol, 1.0 eq.), **1b** (0.3 mmol, 1.5 equiv), TFA (2 mmol, 10 eq.), DCE (1 mL), 110 °C, 48 h. ^b Isolated yield. ^c Pd(OAc)₂ (15 mol%) was used. ^d Pd(OAc)₂ (20 mol%) was used.



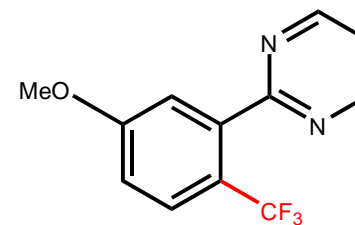
4a, 0%^d



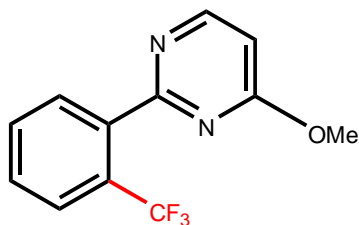
4b, 88%^c



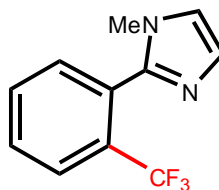
4c, 75%



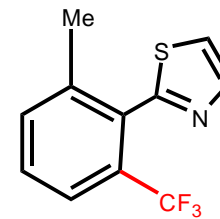
4d, 58%



4e, 62%



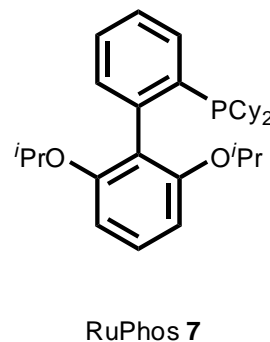
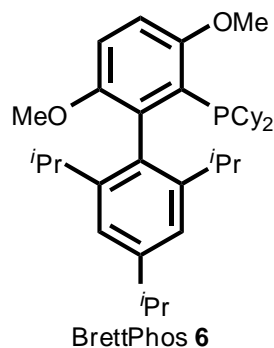
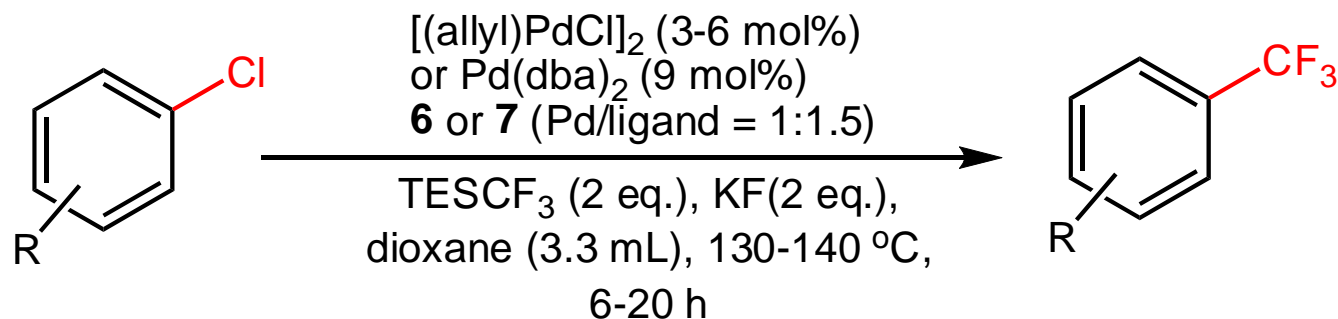
5, 53%



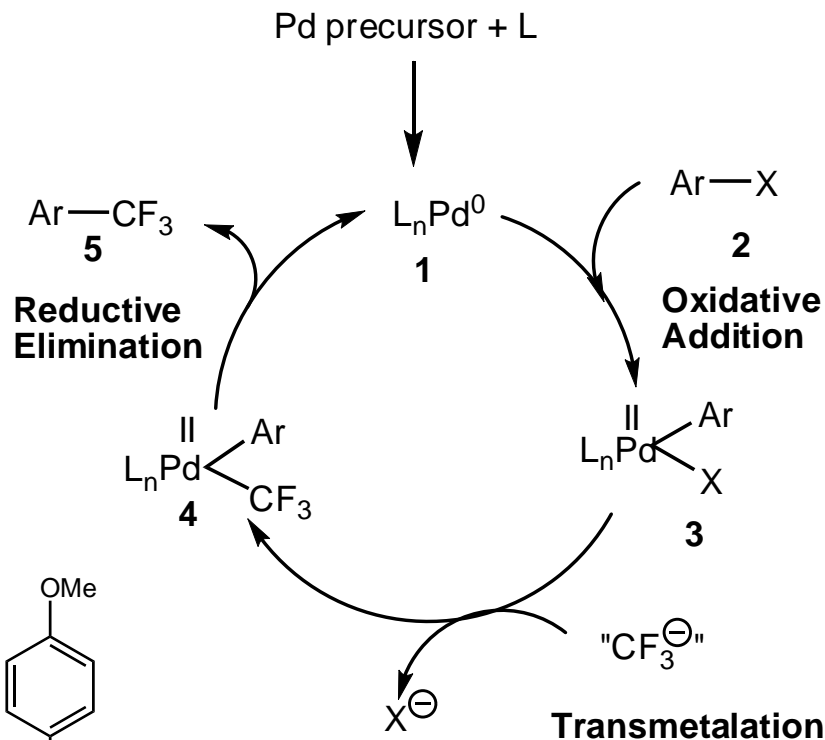
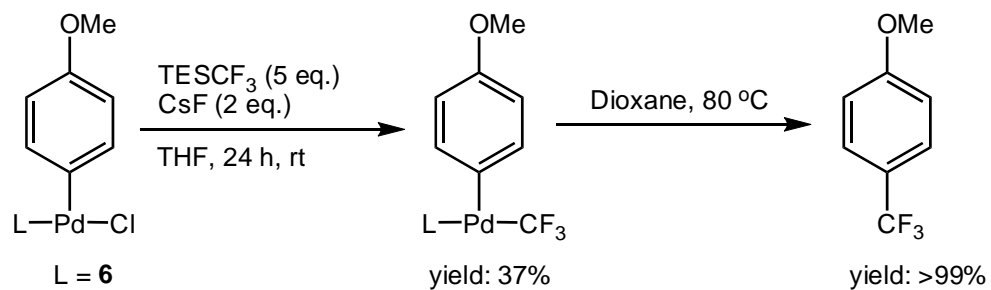
6, 74%^c

^a Unless otherwise noted, the reaction conditions were as follows: substrate (0.2 mmol), Pd(OAc)₂ (0.04 mmol, 20 mol%), Cu(OAc)₂ (0.2 mmol, 1.0 eq.), **1b** (0.3 mmol, 1.5 eq.), TFA (2 mmol, 10 eq.), DCE (1 mL), 110 °C, 48 h. ^b Isolated yield. ^c Pd(OAc)₂ (10 mol%) was used.

The Palladium-Catalyzed Trifluoromethylation of Aryl Chlorides

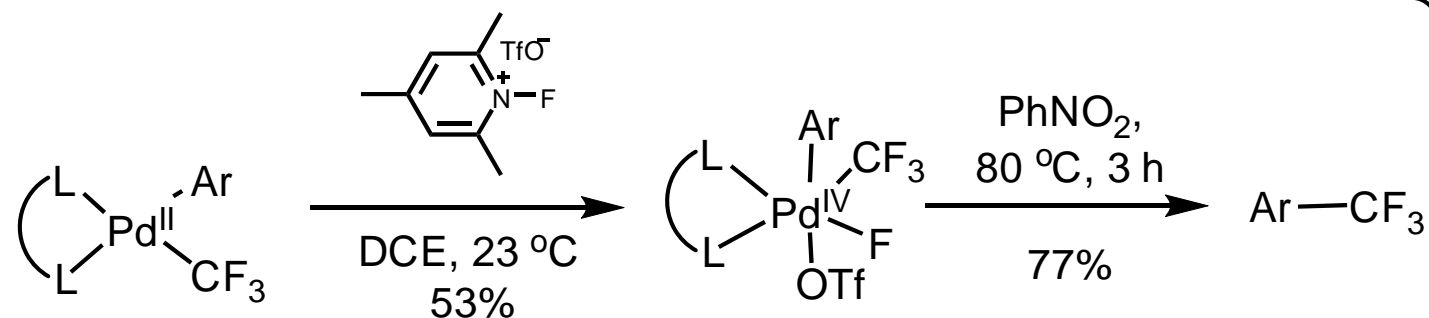
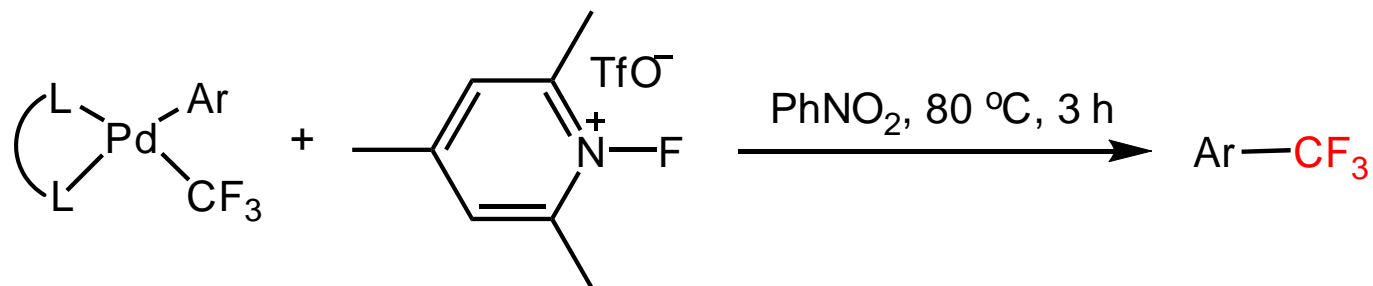


Buchwald, S. L. *et al Science* **2010**, 328, 1679-1681.



Buchwald, S. L. *et al Science* **2010**, 328, 1679-1681.

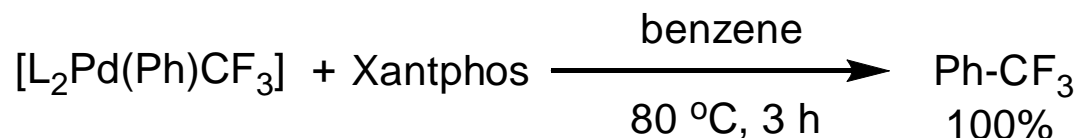
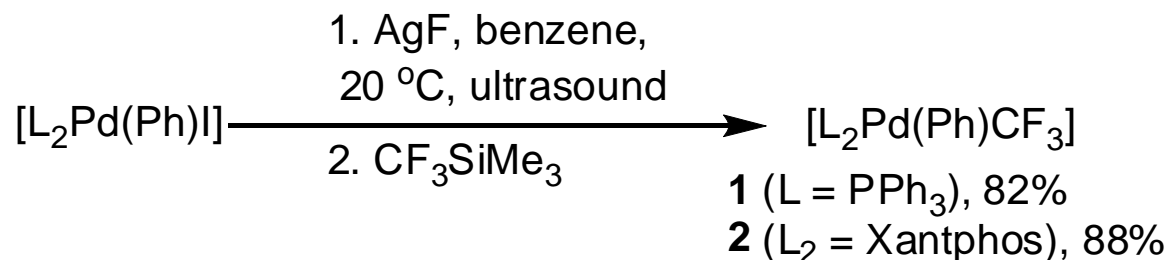
Aryl-CF₃ Bond-Forming Reductive Elimination from Palladium(IV)



N-N = ^tBu-bby
Ar = *p*-FC₆H₄

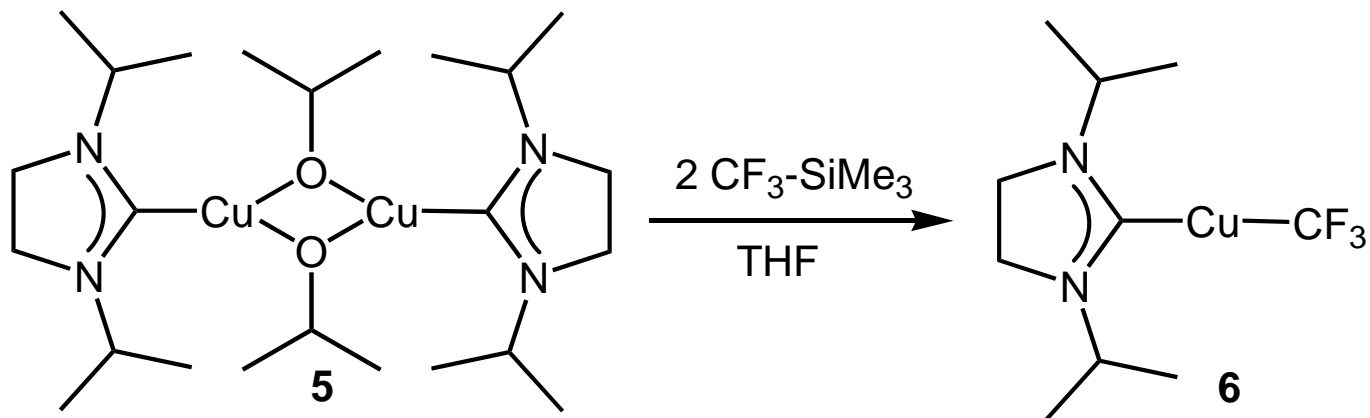
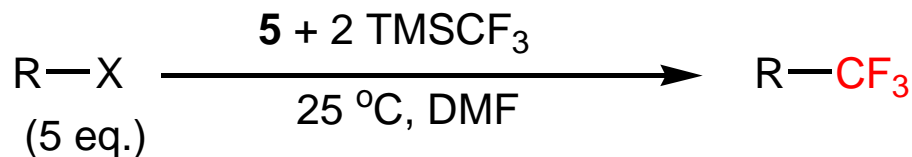
Sanford, M. S. *et al J. Am. Chem. Soc.* **2010**, 132, 2878-2879.

Facile Ar-CF₃ Bond Formation at Pd. Strikingly Different Outcomes of Reductive Elimination from [(Ph₃P)₂Pd(CF₃)Ph] and [(Xantphos)Pd(CF₃)Ph]



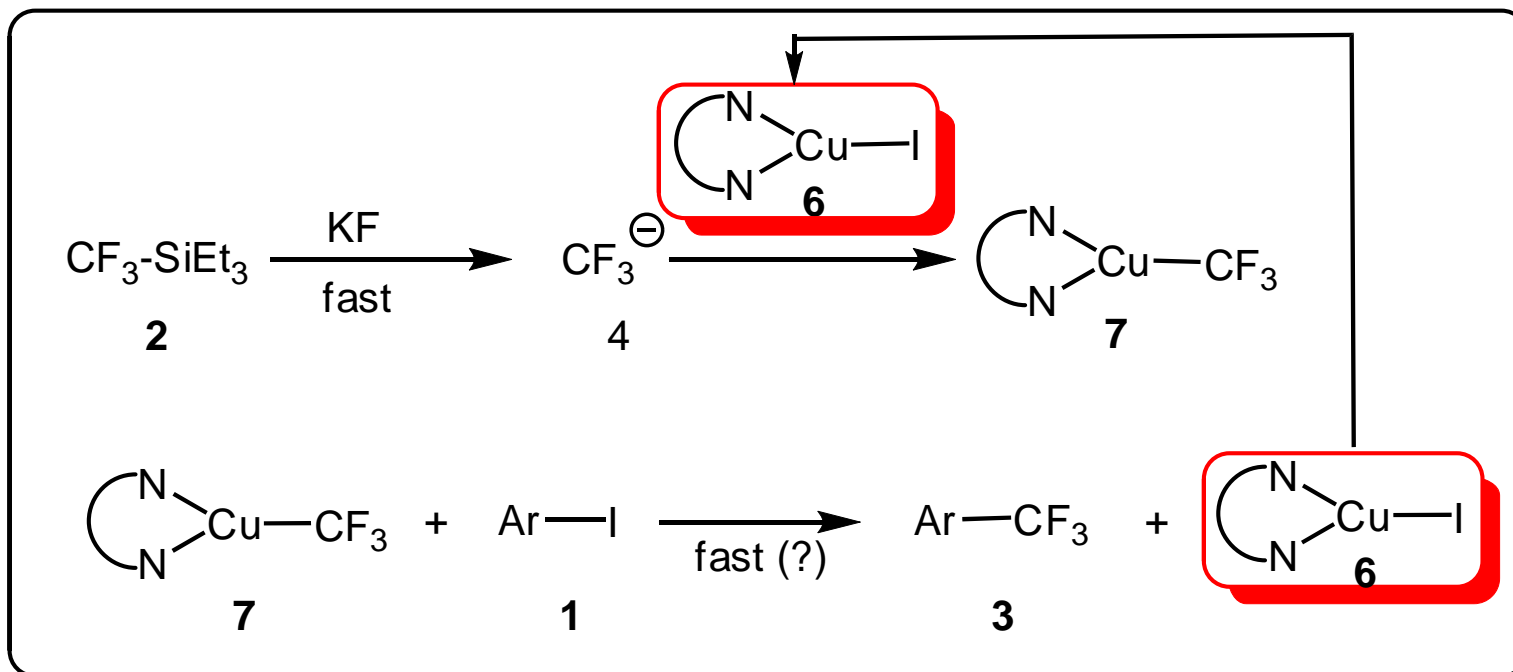
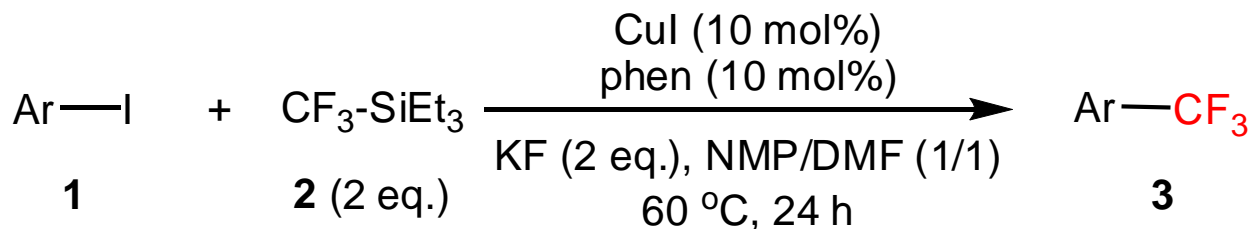
Grushin, V. V. *et al J. Am. Chem. Soc.* **2006**, 128, 12644-12645.

Active trifluoromethylating Agents from Well-Defined Copper(I)-CF₃ Complexes



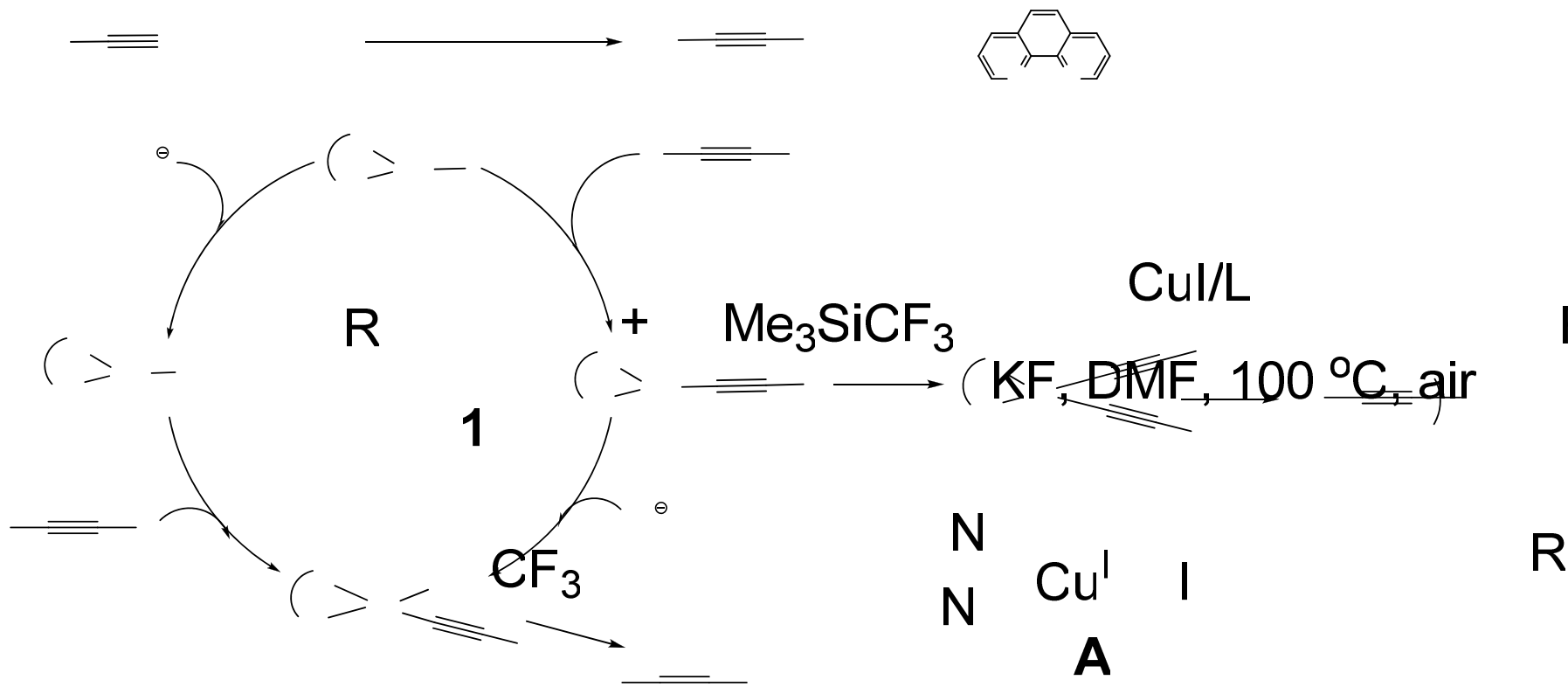
Vicic, D. A. *et al J. Am. Chem. Soc.* **2008**, 130, 8600-8601;
Organometallic **2008**, 27, 6233-6235.

Aromatic Trifluoromethylation Catalytic in Copper



Amii, H. *et al Chem. Commun.* **2009**, 1909-1911.

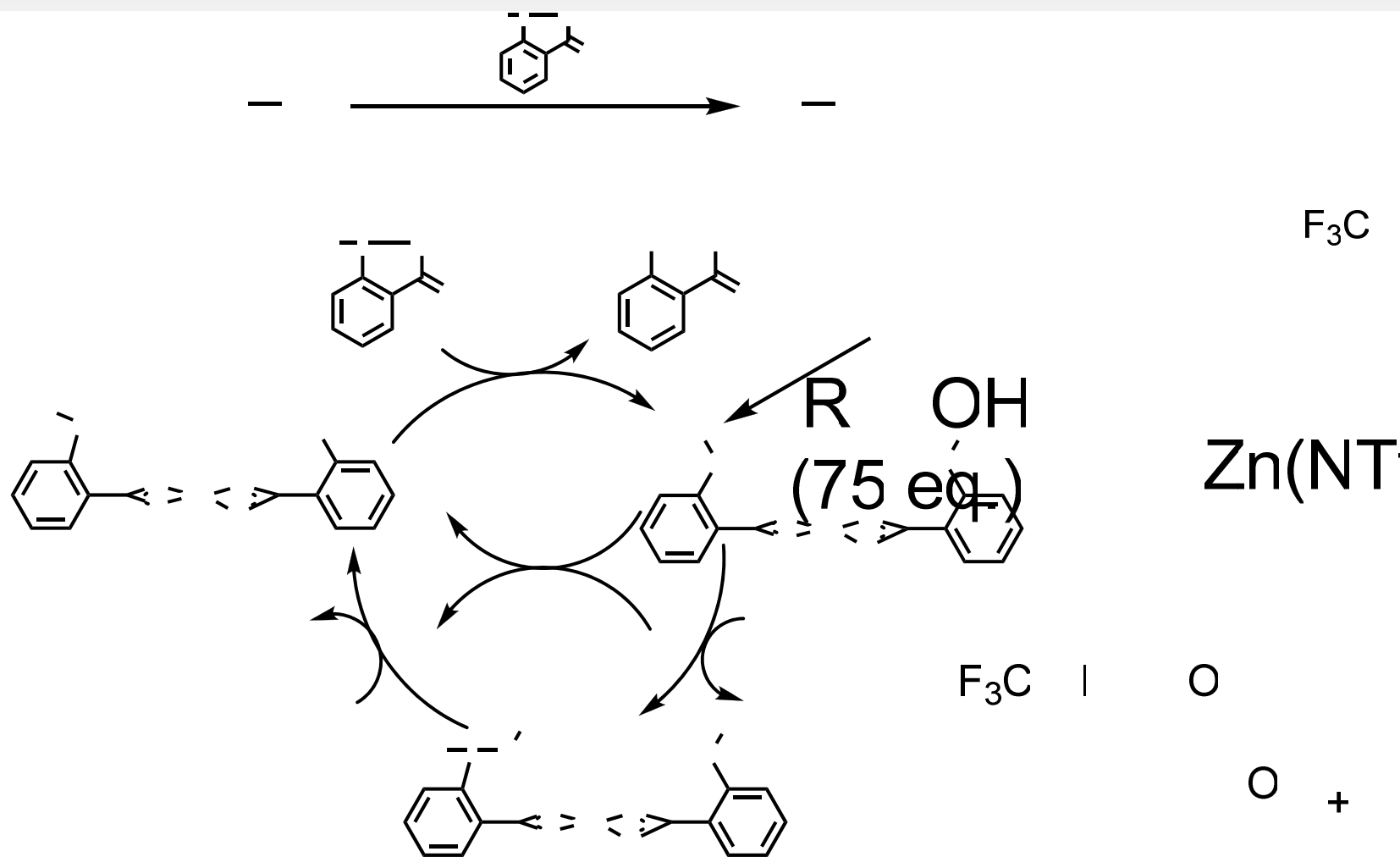
Copper-Mediated Aerobic Trifluoromethylation of Terminal Alkynes with Me_3SiCF_3



Qing, F.-L. *et al J. Am. Chem. Soc.* **2010**, 132, 7262-7263.



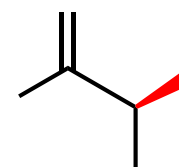
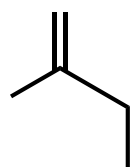
Zinc-Mediated Formation of Trifluoromethyl Ethers from Alcohols and Hypervalent Iodine Trifluoromethylation Reagent



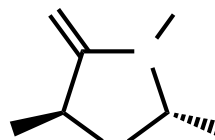
Togni, A. *et al Angew. Chem. Int. Ed.* **2009**, 48, 4332-4336.1



Enantioselective α -Trifluoromethylation of Aldehydes via Photoredox organocatalysis



O



+ CF_3I + 26 W hous

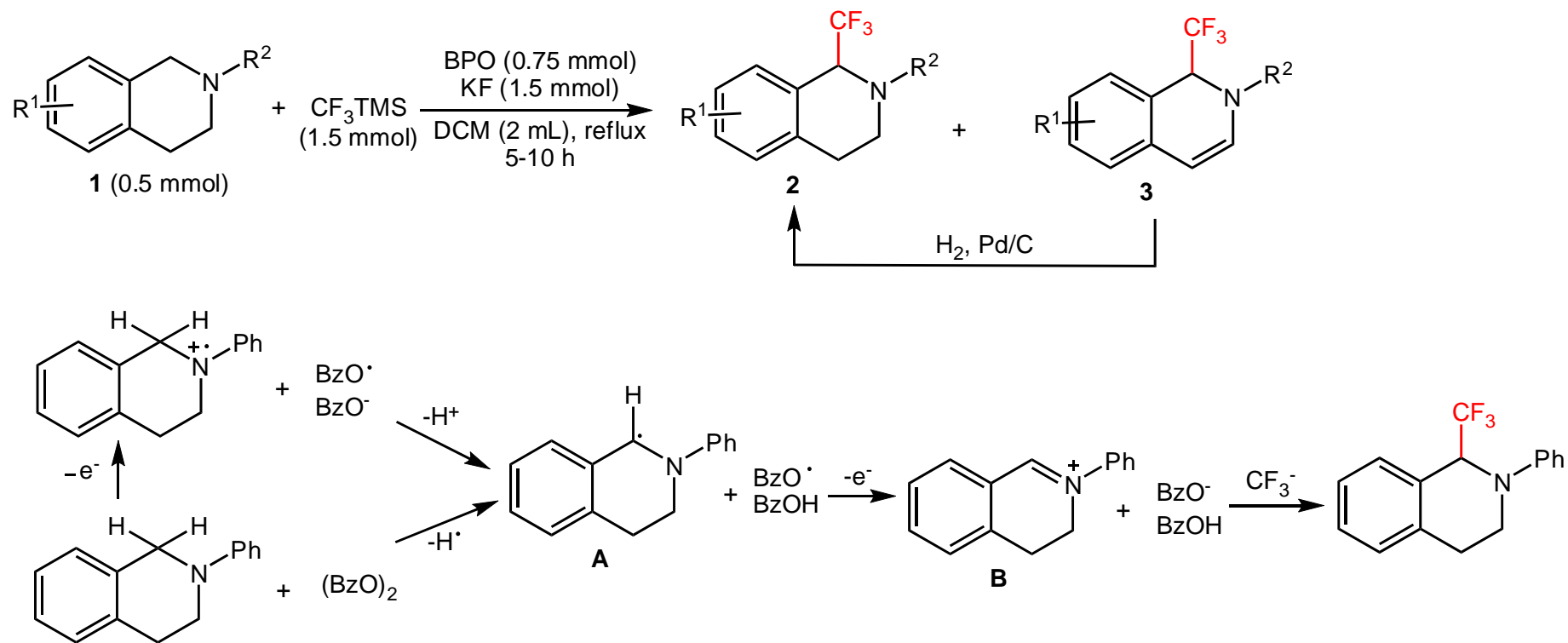
H

R

MacMillan, D. W. C. *et al J. Am. Chem. Soc.* **2009**, 131, 10877-10875.

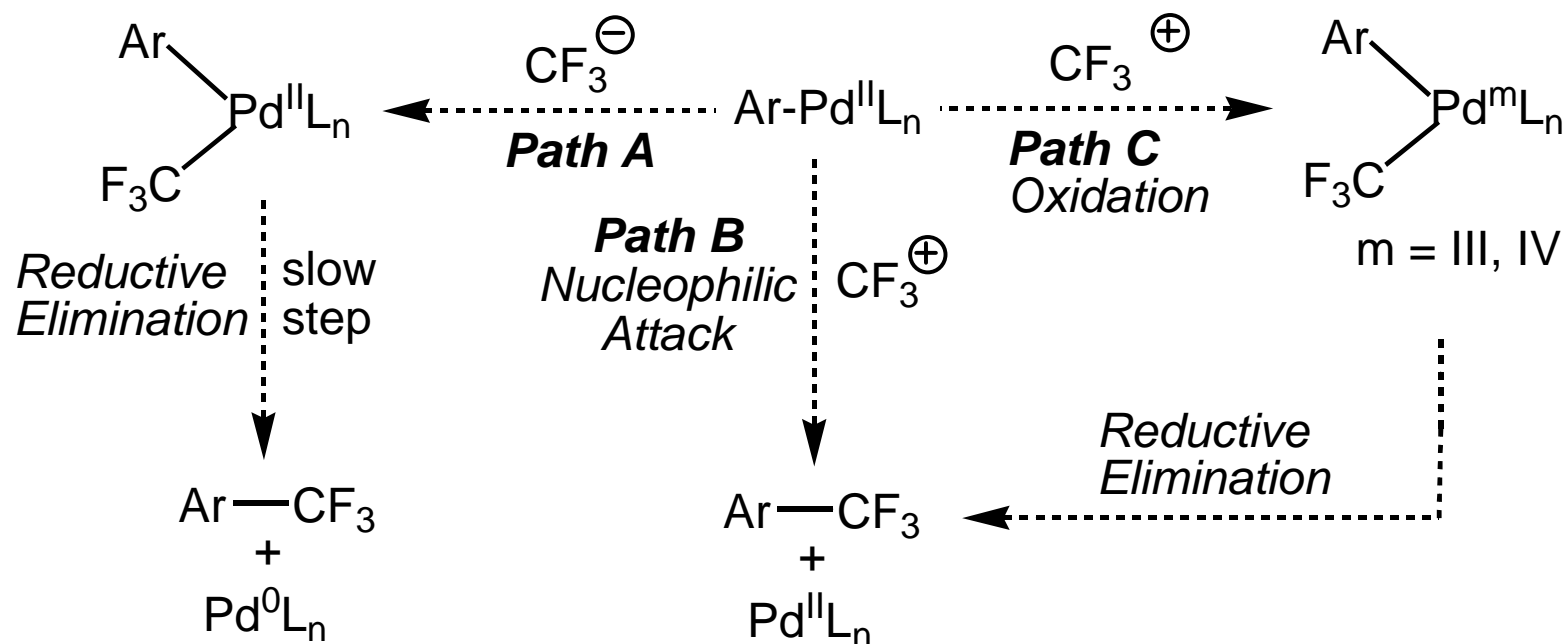
$\text{Ir}(\text{ppy})_3$ (dth bpy) PF_6

Benzoyl peroxide (BPO)-promoted oxidative trifluoromethylation of tertiary with trimethyl(trifluoromethyl)silane



Qing, F.-L. *et al Chem. Commun.* **2010**, ASAP

Summary:



Fluorinated compounds possess unique physical properties that make them indispensable for application as pharmaceuticals, agrochemicals, and organic materials. In medicinal chemistry, for example, the incorporation of CF_3 groups into drug candidates often improves their binding selectivity, lipophilicity, and metabolic stability. Notably, many biologically active aromatics, including the commercially successful antidepressant Prozac and the herbicide Fusilade, contain CF_3 groups as the essential motif. As a consequence, the development of new methods for the introduction of trifluoromethyl groups onto aromatic rings has received intensive attention. Recent findings concerning the stoichiometric and catalytic coupling of ArI with in situ-generated CuCF_3 provides an alternative to the century-old Swarts reaction. Moreover, a single example of $\text{Pd}(0)$ -catalyzed coupling of ArI with CF_3I using Zn powder and a $\text{Pd}(0)$ catalyst under ultrasonic irradiation has also been reported. Generally speaking, the challenge of developing cross-coupling reactions to forge carbon- CF_3 bonds is largely rooted in the inert nature of the metal- CF_3 species. Herein we report a $\text{Pd}(\text{II})$ -catalyzed arene trifluoromethylation reaction via C-H activation.

In summary, we have developed a new Pd(II)-catalyzed trifluoromethylation reaction of arenes through C-H functionalization. The use of TFA was found to be crucial for the success of this Ar-CF₃ bond-forming protocol, and Cu(OAc)₂ was found to be effective for enhancing the catalytic turnover. Subsequent studies to apply this catalytic transformation to other broadly useful classes of substrates are currently underway in our laboratory.