Radical Carbofluorination of Unactivated Alkenes with Fluoride Ions

Zhonglin Liu, He Chen, Ying Lv, Xinqiang Tan, Haigen Shen, Hai-Zhu Yu, and Chaozhong Li

J. Am. Chem. Soc. 2018, *140*, 6169-6175

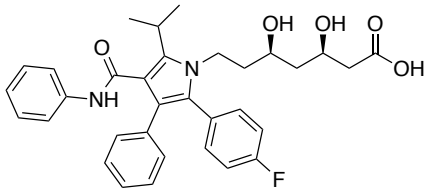
Nikhil Tasker

Wipf Group Current Literature

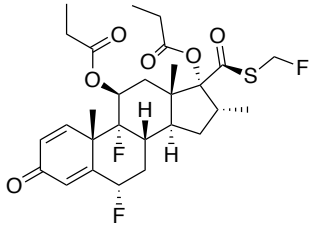
May 26, 2018

Why fluorine?

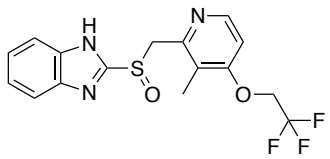
- About 1/3 of drugs approved by the FDA contain fluorine
- Reduce basicity of nearby functional groups
- Increase stability and slow down hydrolytic metabolism
- Introducing fluorine on aliphatics remains a problem



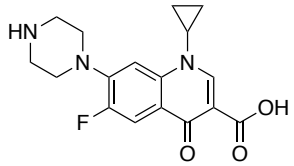
Atorvastatin
(Lipitor)
Cholesterol and triglyceride levels



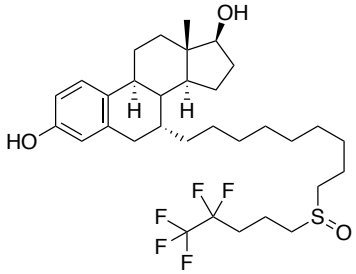
Fluticasone propionate
Anti-inflammatory



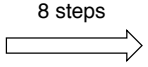
Lanzoprazole
(Prevacid)
Gastric acid

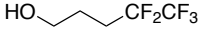


Ciprofloxacin
(Ciprobay)
Antibacterial



Fulvestrant
Estrogen receptor antagonist





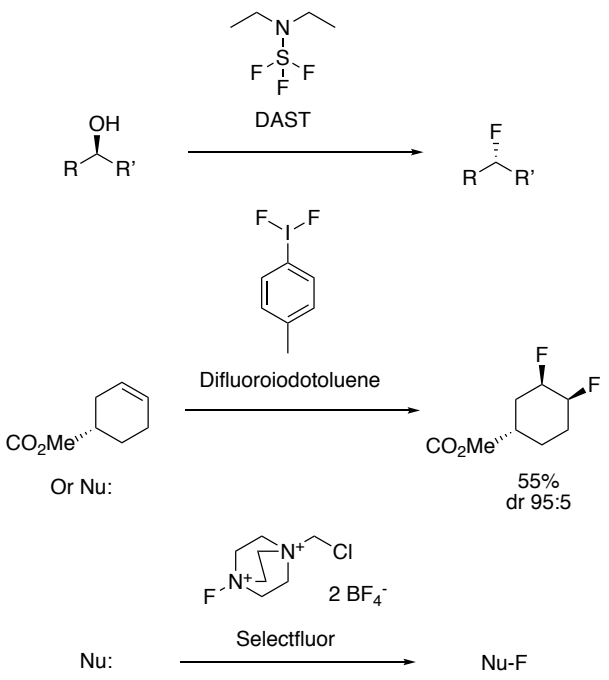
Fluorinated building block

Org. Biomol. Chem., **2016**, *14*, 8398–8427
Chem. Rev., **2014**, *114*, 2432−2506

Some current methods

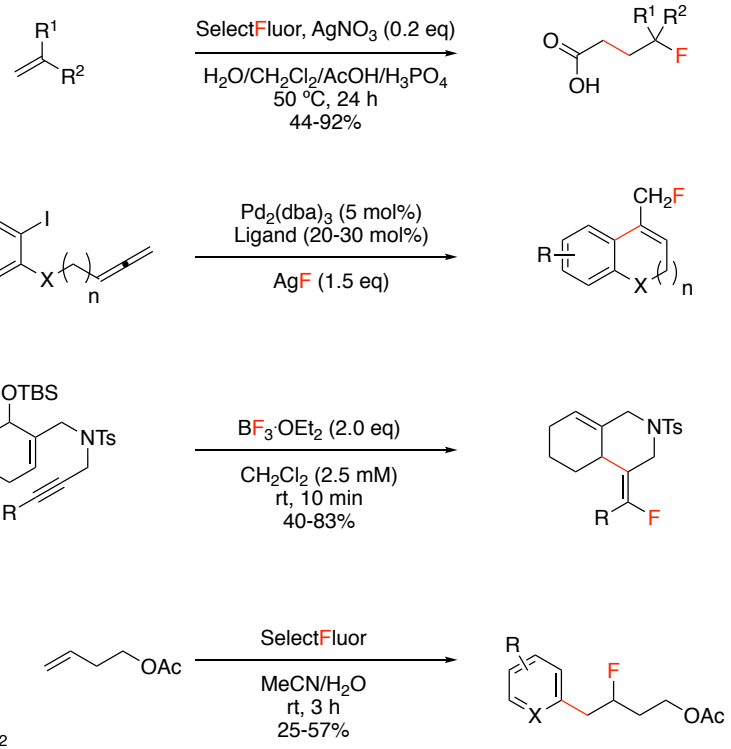
- Nucleophilic fluorination (HF/pyridine, TBAF)
  - Dual reactivity: base and nucleophile
  - Deoxyfluorination (DAST, Deoxofluor)
    - Requires an alcohol
- Hypervalent halogen-based fluorination (IPy_2BF_4, *p*-Tol-IF_2)
- Electrophilic fluorination ("F^+")
  - N-F, O-F, Xe-F, F-F bonds
    - Low selectivity, difficult preparation, high toxicity

- Catalytic methods improve selectivity and yields, but usually still implement these reagents



Chem. Rev., **2015**, *115*, 9073−9174
Chem. Soc. Rev., **2016**, *45*, 6270-6288

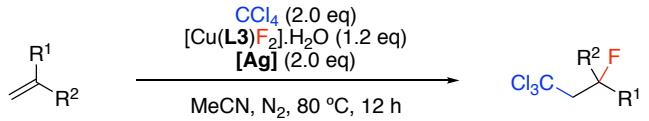
Carbofluorination



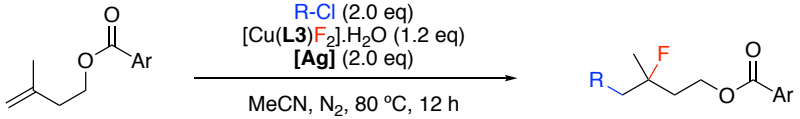
Org. Chem. Front., **2017**, *4*, 565–568
Chem. Sci., **2013**, *4*, 1216–1220
J. Org. Chem., **2013**, *78*, 5521–5529
Chem. Eur. J., **2014**, *20*, 15344 – 15348

Title Paper

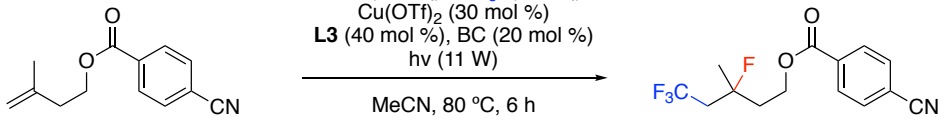
- Fluorotrichloromethylation



- Carbofluorination with alkyl chlorides
  - Inter/intramolecular

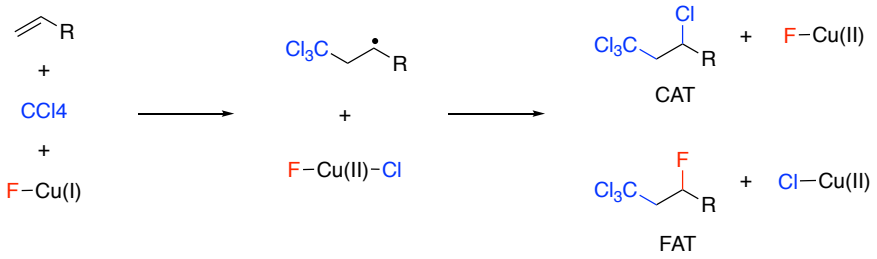


- Fluorotrifluoromethylation



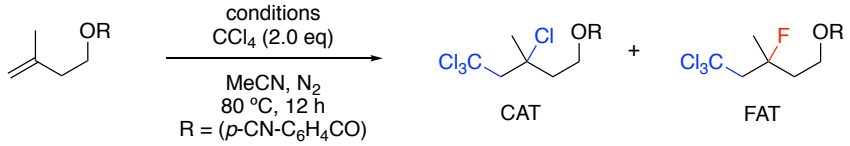
- Mechanistic studies studies

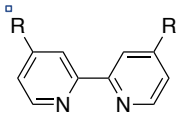
Chlorine vs. Fluorine Atom Transfer



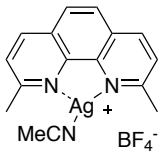
- CAT is a faster process than FAT

Fluorotrichloromethylation Optimization





L1 (R = H)
L2 (R = OMe)
L3 (R = CO_2Me)

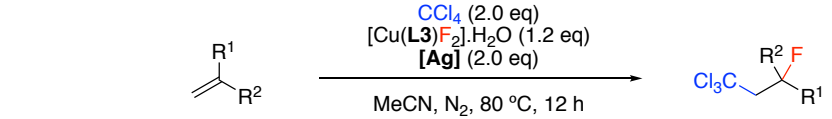


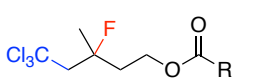
[Ag]

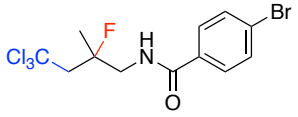
entry	reagents (equiv)	yield (%) CAT	FAT
1	$Cu(OTf)_2$ (0.3), **L1** (0.3), CsF (2.0)	<5	0
2	CuF_2 (0.7), **L1** (0.7)	5	0
3	$Cu(OTf)_2$ (0.7), **L1** (0.7), AgF (2.0)	7	1
4	$Cu(OTf)_2$ (0.7), **L1** (2.7), AgF (2.0)	4	20
5	$Cu(OTf)_2$ (0.7), **L1** (0.7), CsF (2.0), [**Ag**]	27	52
6	$Cu(OTf)_2$ (0.7), **L2** (0.7), CsF (2.0), [**Ag**]	15	8
7	$Cu(OTf)_2$ (0.7), **L3** (0.7), CsF (2.0), [**Ag**]	24	63
8	$Cu(OTf)_2$ (1.0), **L3** (1.0), CsF (2.0), [**Ag**]	30	57
9	[Cu(**L3**)F_2].H_2O (1.0), [**Ag**] (2.0)	10	71
10	[Cu(**L3**)F_2].H_2O (1.2), [**Ag**] (2.0)	<5	77
11	[Cu(**L3**)F_2].H_2O (1.0)	55	0
12	[Cu(**L3**)F_2].H_2O (1.2), $AgBF_4$ (2.0)	7	14
13	[**Ag**] (2.0)	0	0

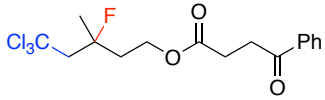
Fluorotrichloromethylation Scope

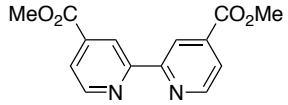
- Negligible CAT for 1,1′-disubstituted alkenes
- CAT predominated for monosubstituted



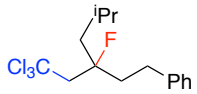

R = *p*-CN-C6H4, 77%
R = o-CO2Me-C6H4, 80%
R = furan-2-yl, 71%

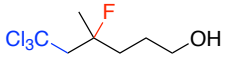

73%


66%


L3


65%


58%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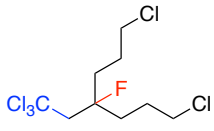
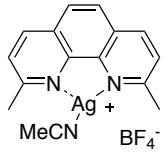
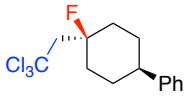
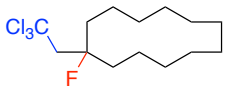

81%


[Ag]


73%, dr 95:5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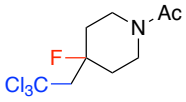
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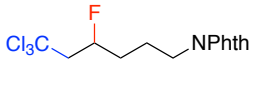
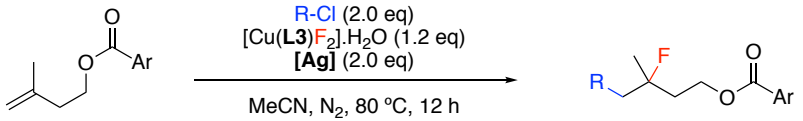
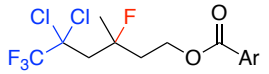
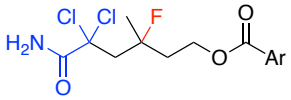

11%

Carbofluorination with Alkyl Chlorides

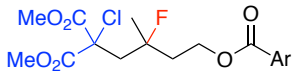




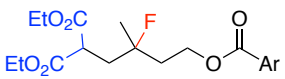
71%



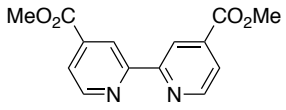
36%



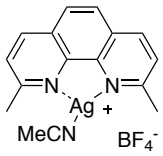
60%



56%



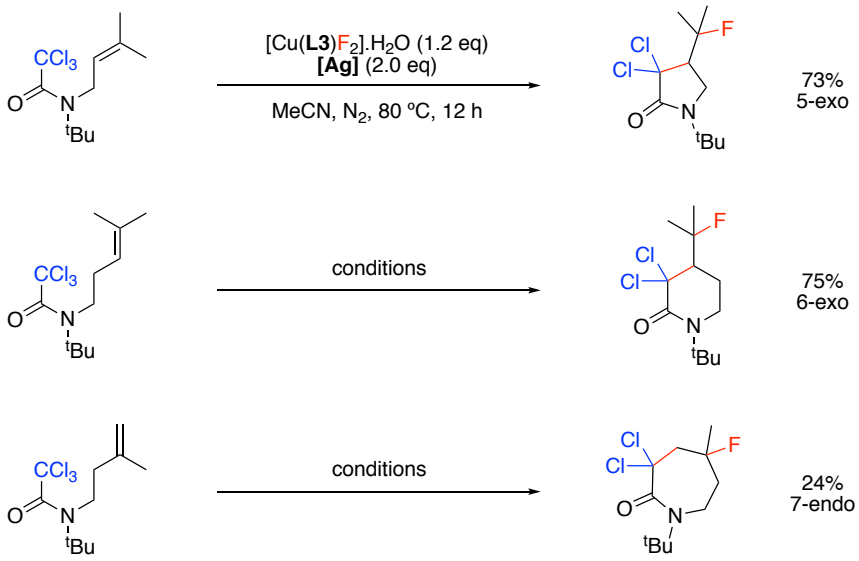
L3

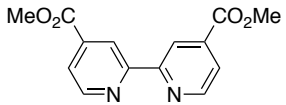


[Ag]

- These substrates are inaccessible by other carbofluorination methods

Intramolecular Carbofluorination





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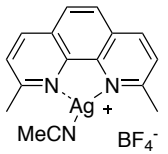
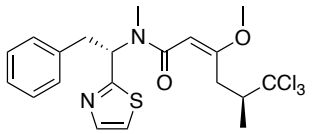


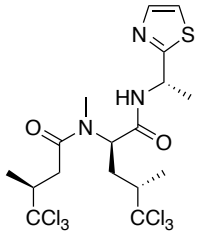
[Ag]

Why fluorotrichloromethylation?

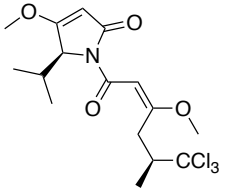
- Although the authors mention no specific reason…
- Some natural products contain trichloromethyl groups
- Pharmaceuticals (uncommon)
- Proof of concept
- Show it can work for alkyl chlorides (which is more useful)



Barbamide



Dysidenin

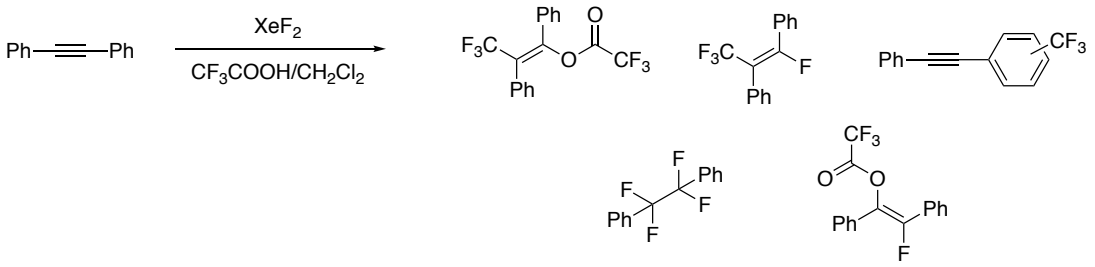


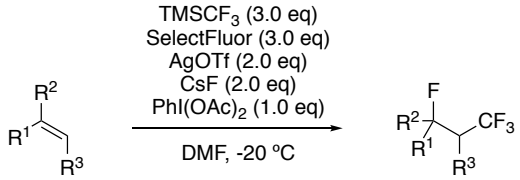
Dysidin

Chem. Asian J., **2011**, *6*, 2260 – 2263

Improvements?

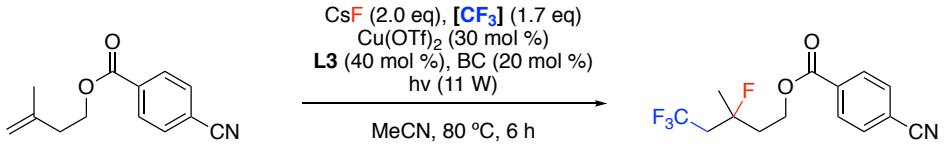
- Stoichiometric copper
- Tri/dichloro substituents are uncommon
  - CF_3 groups are more common
- Pursued fluorotrifluoromethylation

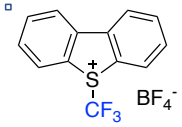




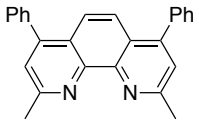
J. Org. Chem., **1979**, *44*, 4120-4122
Adv. Synth. Catal., **2015**, *357*, 2039 – 2044

Fluorotrifluoromethylation

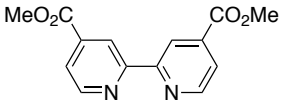




[CF_3]
Umemoto's reagent



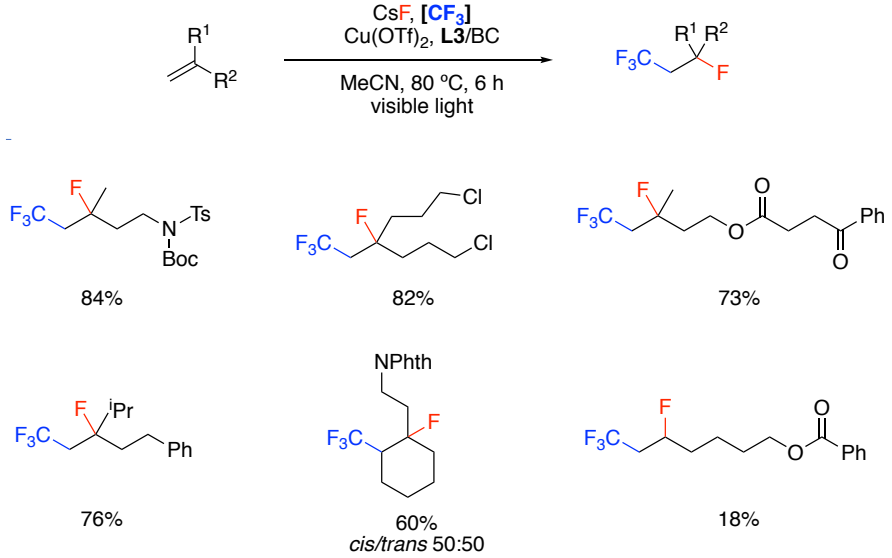
BC

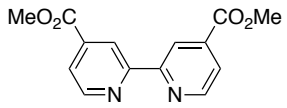


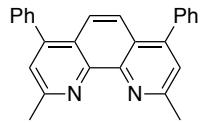
L3

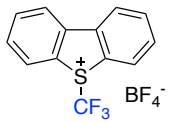
entry	variation	yield (%)
1	none	81
2	dark (no hv)	31
3	**L3** in place of BC	28
4	BC in place of **L3**	45
5	without BC	21
6	without **L3**	37
7	without visible light and BC	0
8	without visible light and **L3**	10
9	without $Cu(OTf)_2$	0

Fluorotrifluoromethylation Scope

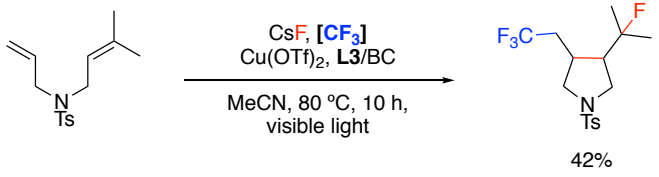


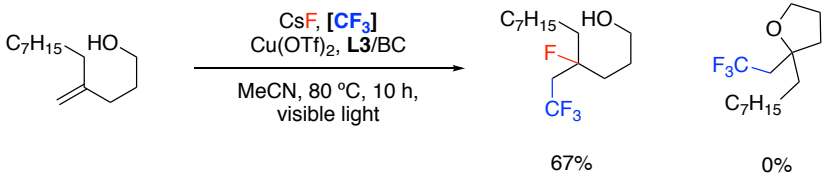


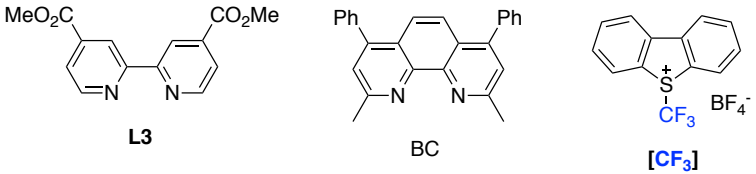


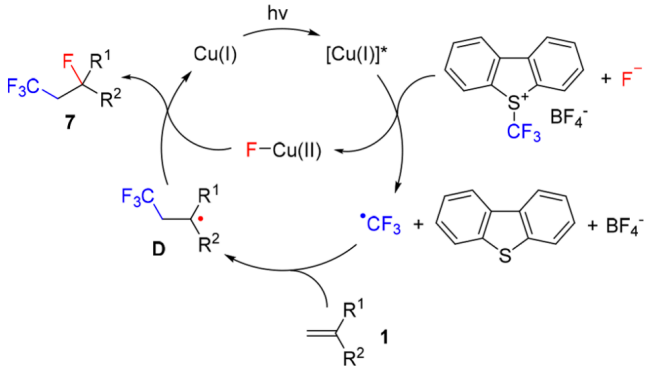


Proposed Mechanism

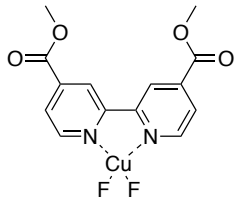


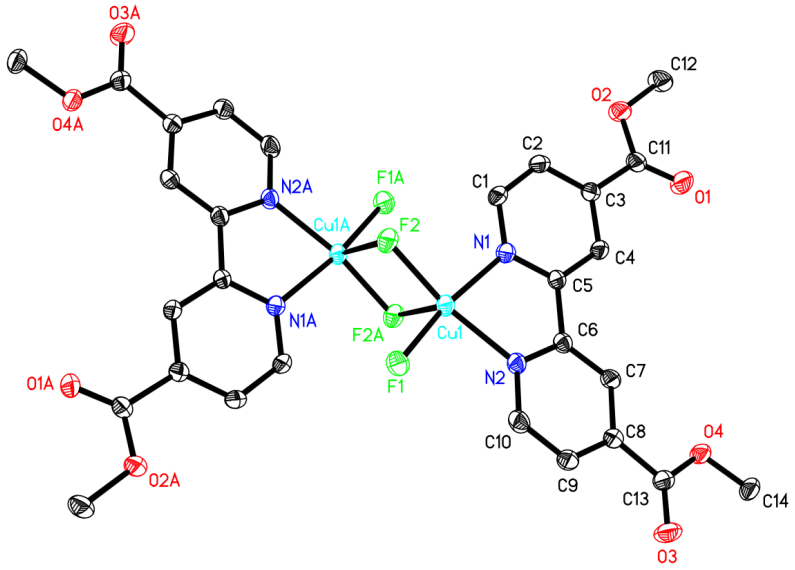


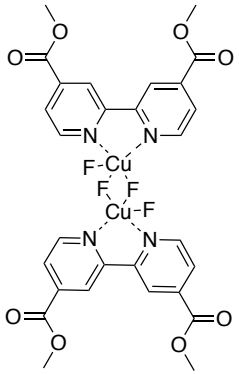




Isolated Catalyst

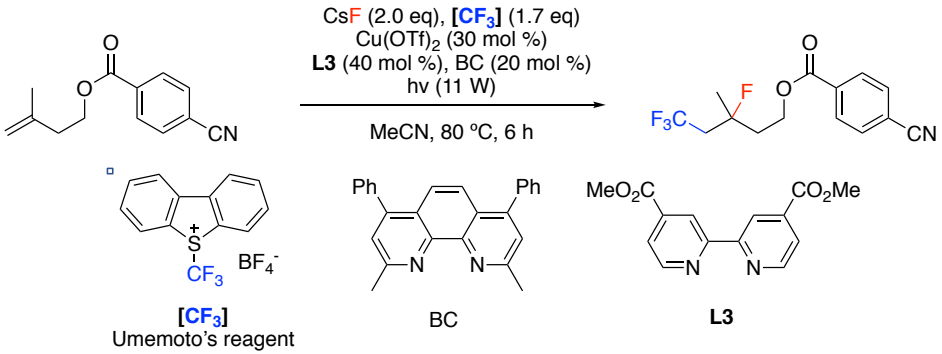




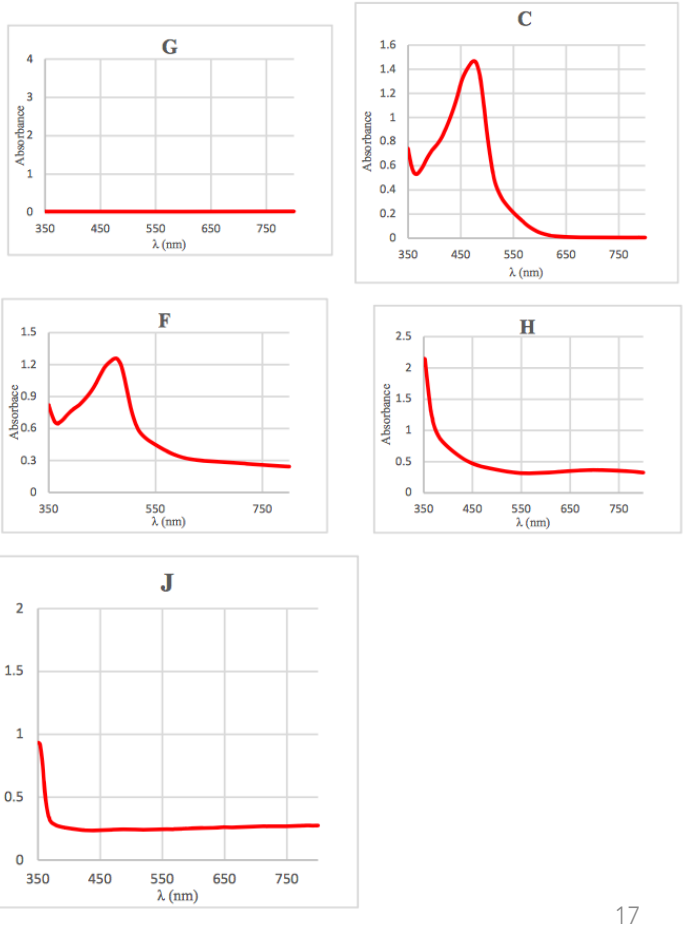


- Computational studies suggest perpendicular approach to plane of dimer results in insensitivity to steric factors

UV/Vis Studies



- G – $Cu(OTf)_2$, CsF
- C – $Cu(OTf)_2$, CsF, L3, BC
- F – $Cu(OTf)_2$, CsF, BC
- H – $[Cu(L3)F2]\cdot H_2O$
- J – BC
- Conclusion: BC helps to excite electron to initiate reaction. L3 increases rate of FAT.



Summary

- Mild and practical
- Broad scope and functional group tolerant
- Moderate to good yields

- **L3**, [**Ag**], Umemoto's reagent = $$$
- Not stereoselective – substrate control
- Racemic mixtures (mostly) and best suited for achiral substrates/products
- Tri-substituted alkenes?