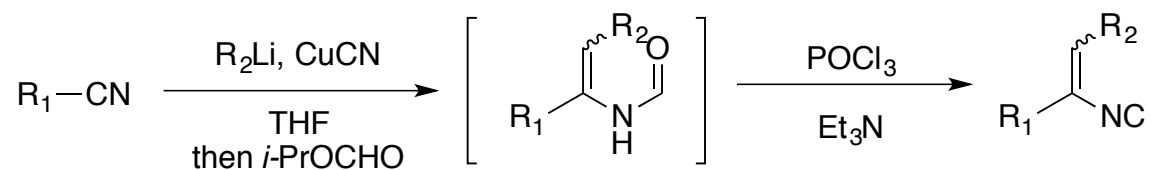


# Direct Conversion of Nitriles into Alkene Isonitriles

Y. Li and F. F. Fleming, *Angew. Chem. Int. Ed.*  
2016, **55**, 14770-14773.

11/19/16

Mike Frasso

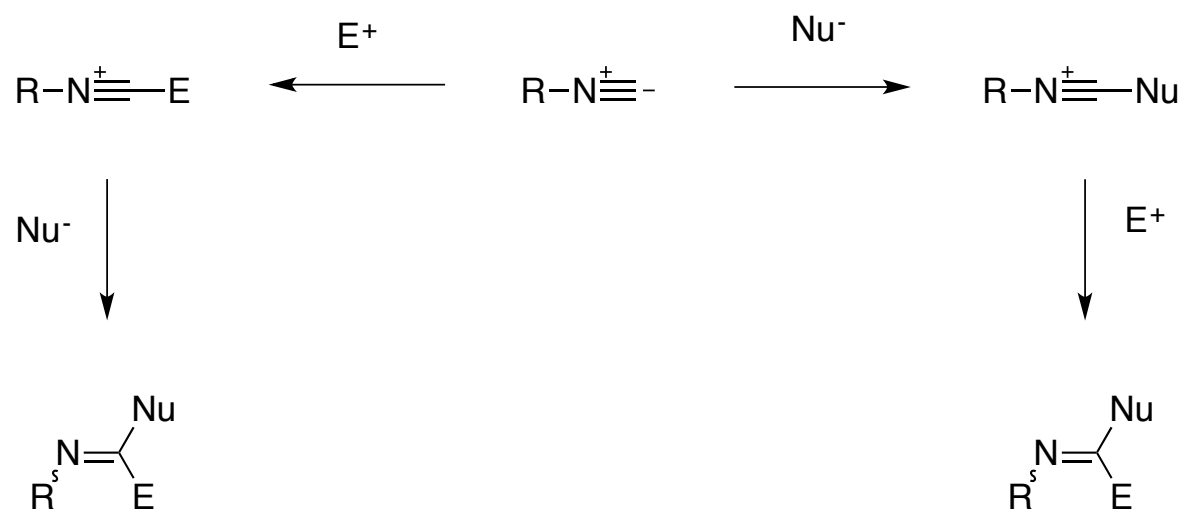


## Most Prominent Physical Characteristic...Stench

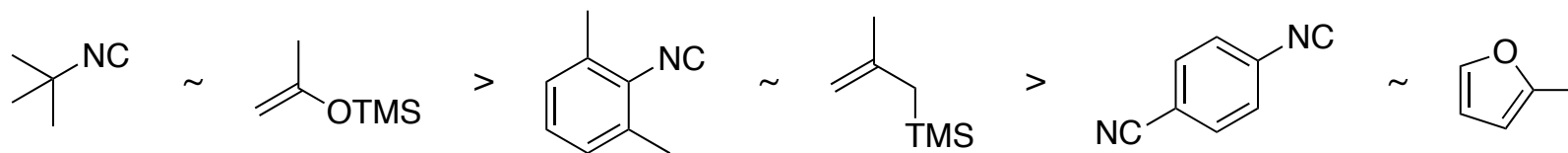
- ‘highly specific, almost overpowering’, ‘horrible’, and ‘extremely distressing’
- To quote odor theorist Luca Turin, “isonitriles” are just the Godzilla of smells, you can’t believe how awful they smell, they make you vomit your guts out instantly.”
- Have been used in nonlethal weaponry
  - “The containment vessel may be comprised of a "paint ball", grenade, non-lethal land mine, spray bottle, rubber bullet, a modified shotgun shell, or other like vessel.”

Burr, C. *The Emperor of Scent: A Story of Perfume, Obsession, and the Last Mystery of the Senses*; Random House: New York, 2002.  
US Pat. 6 352 032, March 5, 2002  
*J. Org. Chem.* **2009**, 74, 4110–4117

# Two General Reaction Pathways



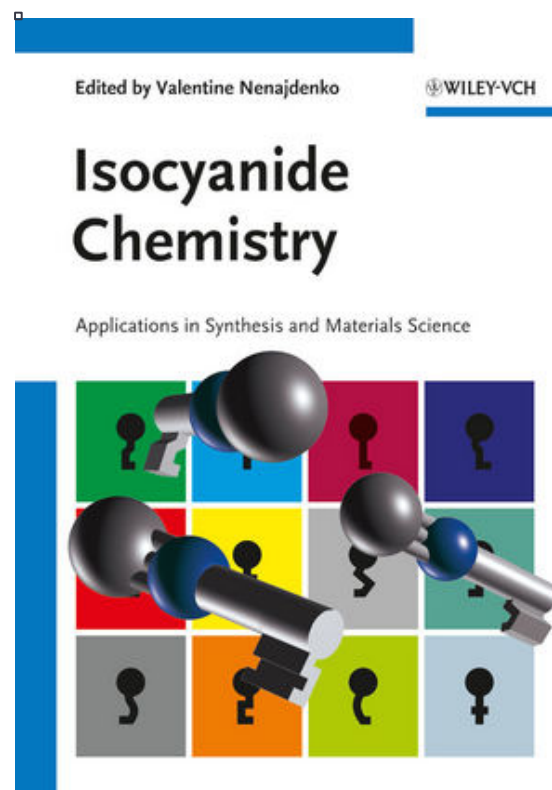
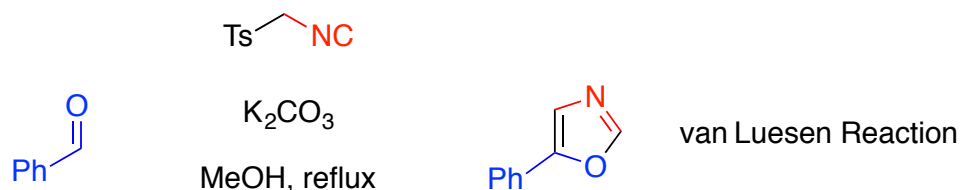
Isonitrile Nucleophilicity



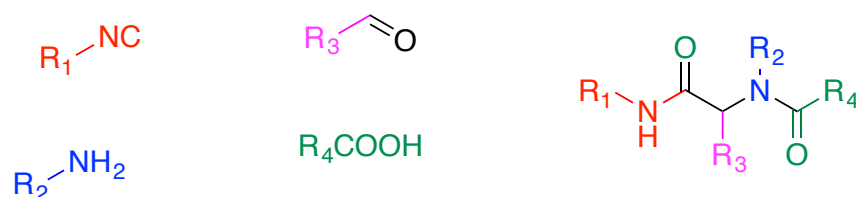
*Angew. Chem. Int. Ed.* **2007**, *46*, 3563-3566.

# Some Characteristic Reactions of Isonitriles

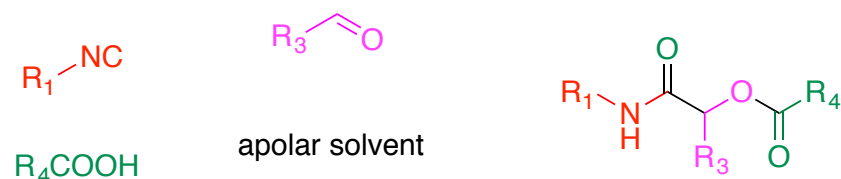
- Heterocycle synthesis: furans, pyrroles, oxazoles, etc.



- Ugi

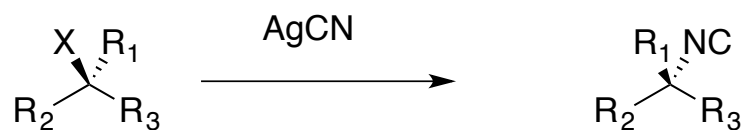


- Passerini

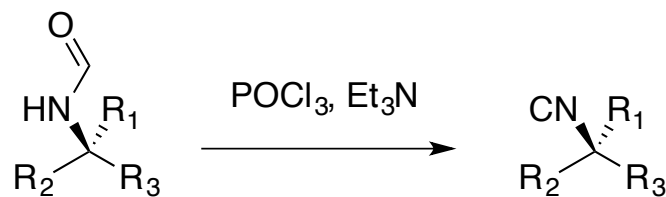


# Preparation of Isonitriles

- Most Common Methods:
  - Substitution: X = halide, activated ester, O-PR<sub>3</sub>; various CN sources possible

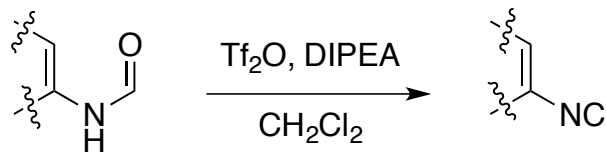


- Dehydration



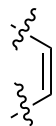
# Preparation of Alkene Isonitriles

*Synlett* 1990,  
603-604.



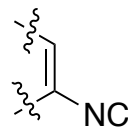
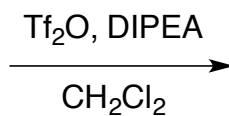
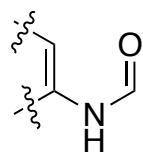
# Preparation of Alkene Isonitriles

*Tetrahedron Lett.* **1989**,  
30, 3335-3338.

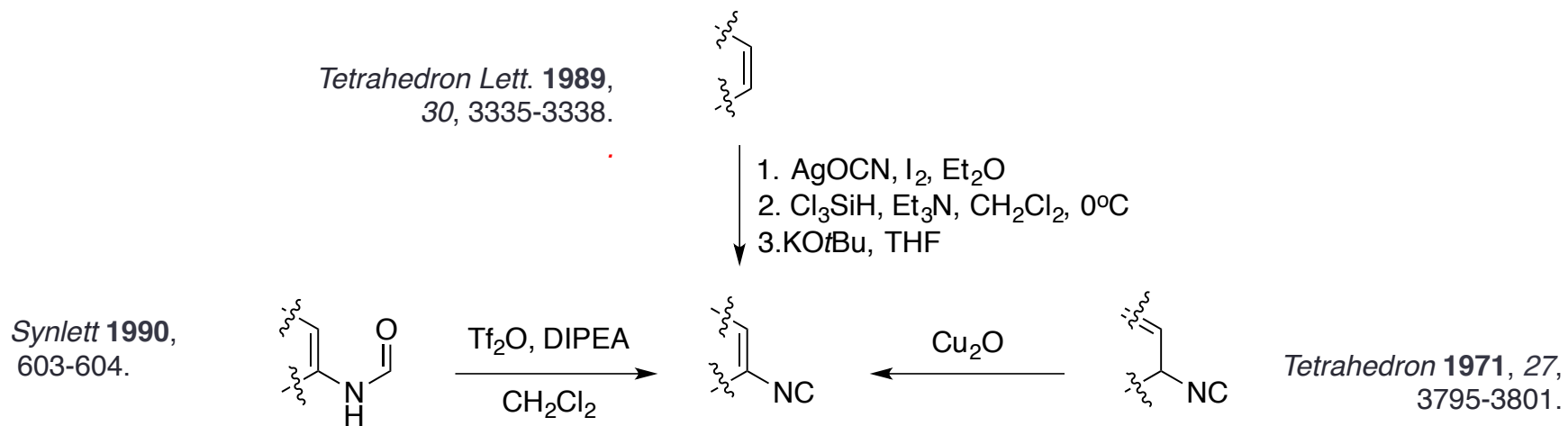


1. AgOCN, I<sub>2</sub>, Et<sub>2</sub>O
2. Cl<sub>3</sub>SiH, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0°C
3. KO<sup>t</sup>Bu, THF

*Synlett* **1990**,  
603-604.

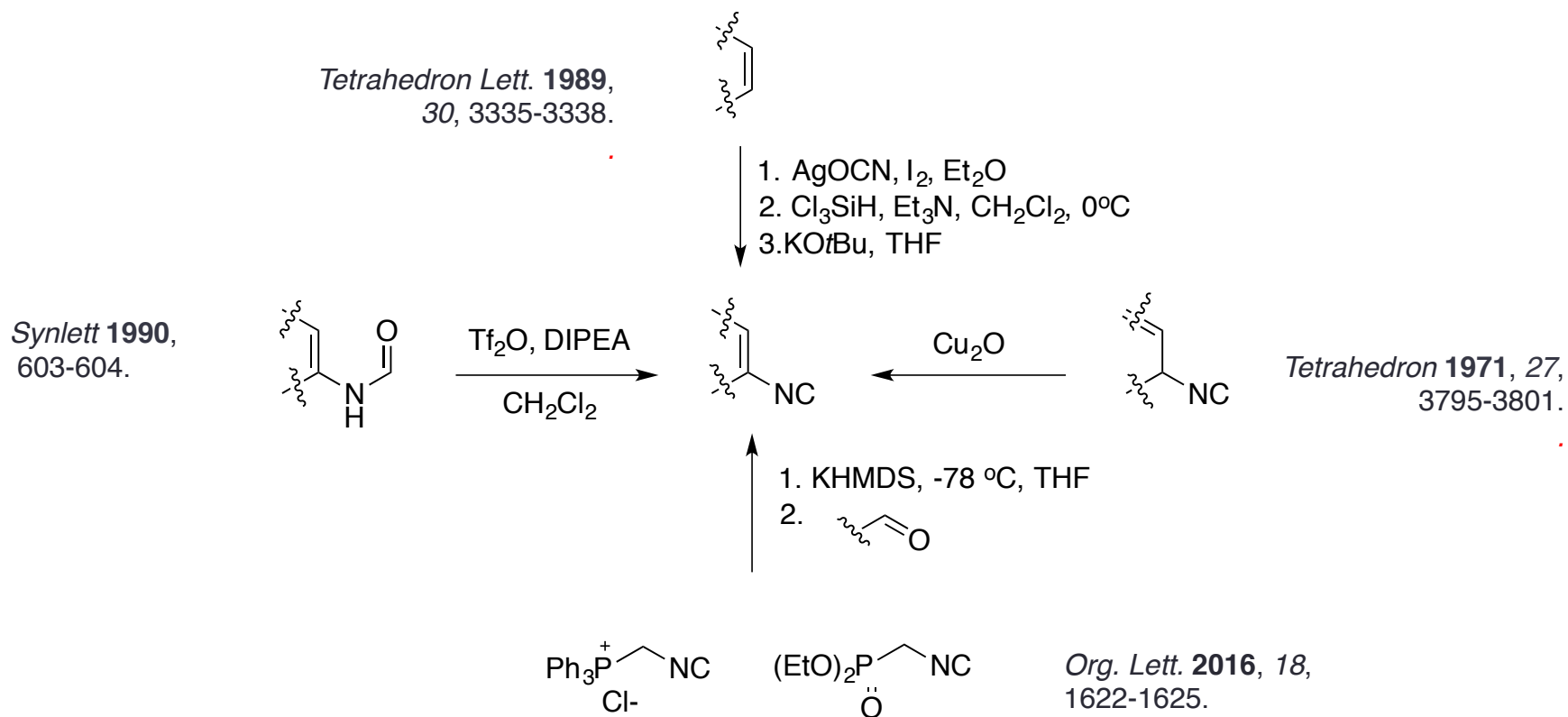


# Preparation of Alkene Isonitriles

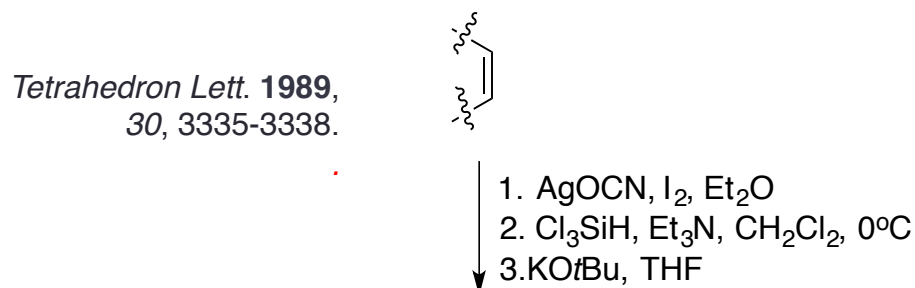




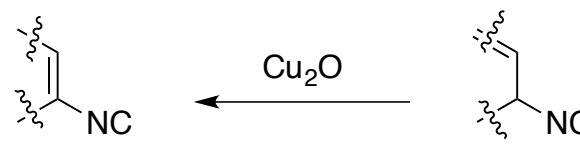
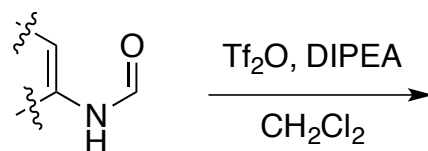
# Preparation of Alkene Isonitriles



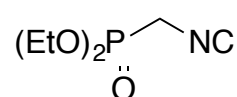
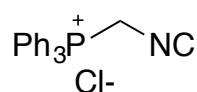
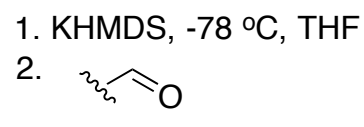
# Preparation of Alkene Isonitriles



*Synlett* **1990**,  
603-604.

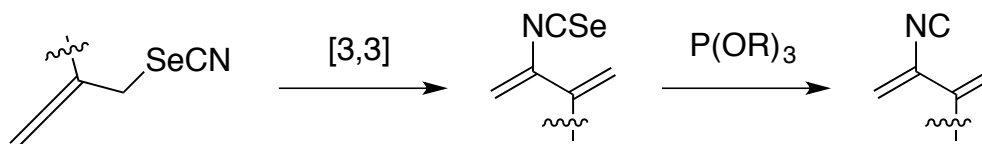


*Tetrahedron* **1971**, 27,  
3795-3801.

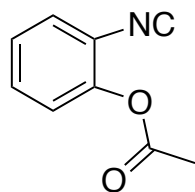
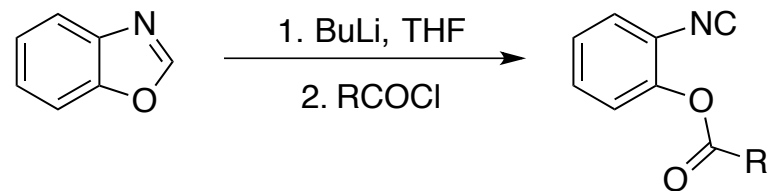


*Org. Lett.* **2016**, 18,  
1622-1625.

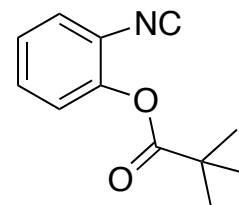
*Angew. Chem. Int. Ed.*  
**1995**, 34, 1627-1629.



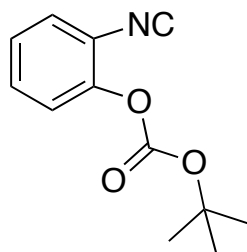
# Isonitriles from Benzoxazoles



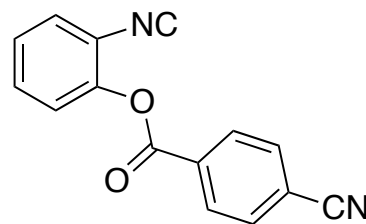
85%  
"malt"



92%  
"natural rubber"



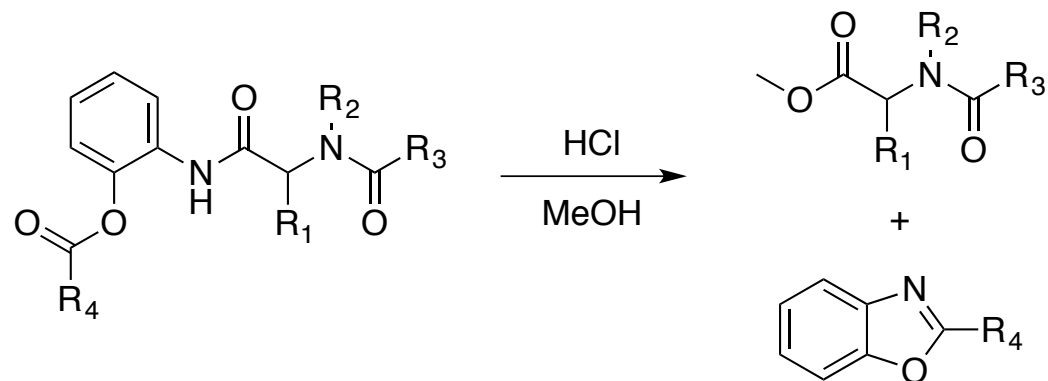
83%  
"taffy"



90%  
"old wood"

*J. Org. Chem.* **2009**, *74*, 4110–4117 .

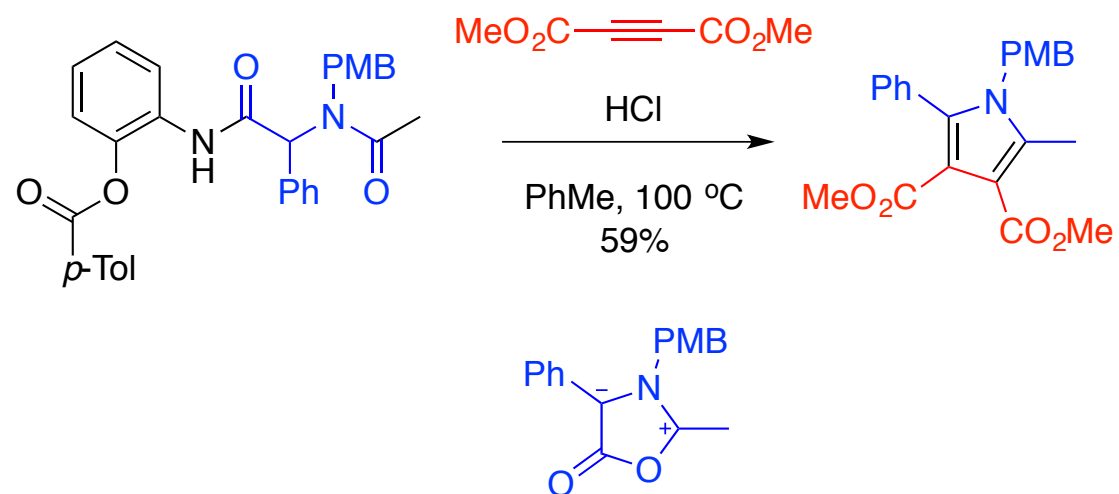
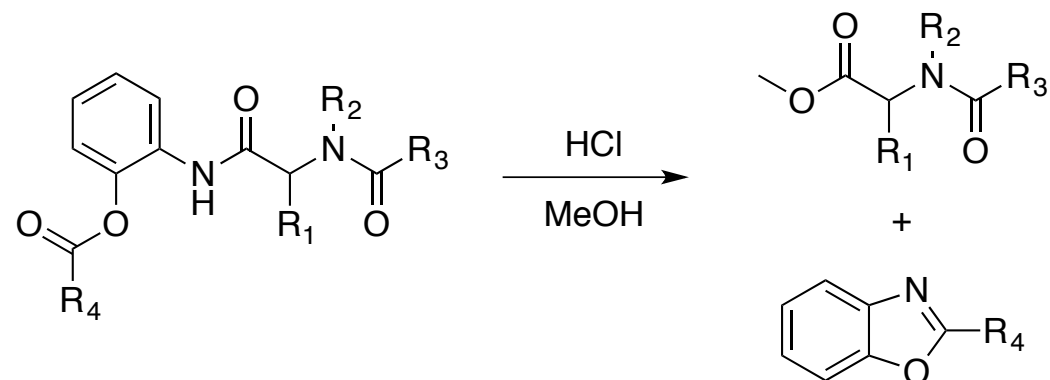
# “Convertible” Isonitriles



- Definition: Resulting amide from Ugi reaction can be readily activated for further transformations

*J. Org. Chem.* **2009**, *74*, 4110–4117 .

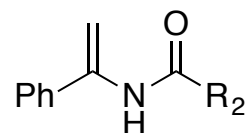
# “Convertible” Isonitriles



*J. Org. Chem.* **2009**, *74*, 4110–4117 .

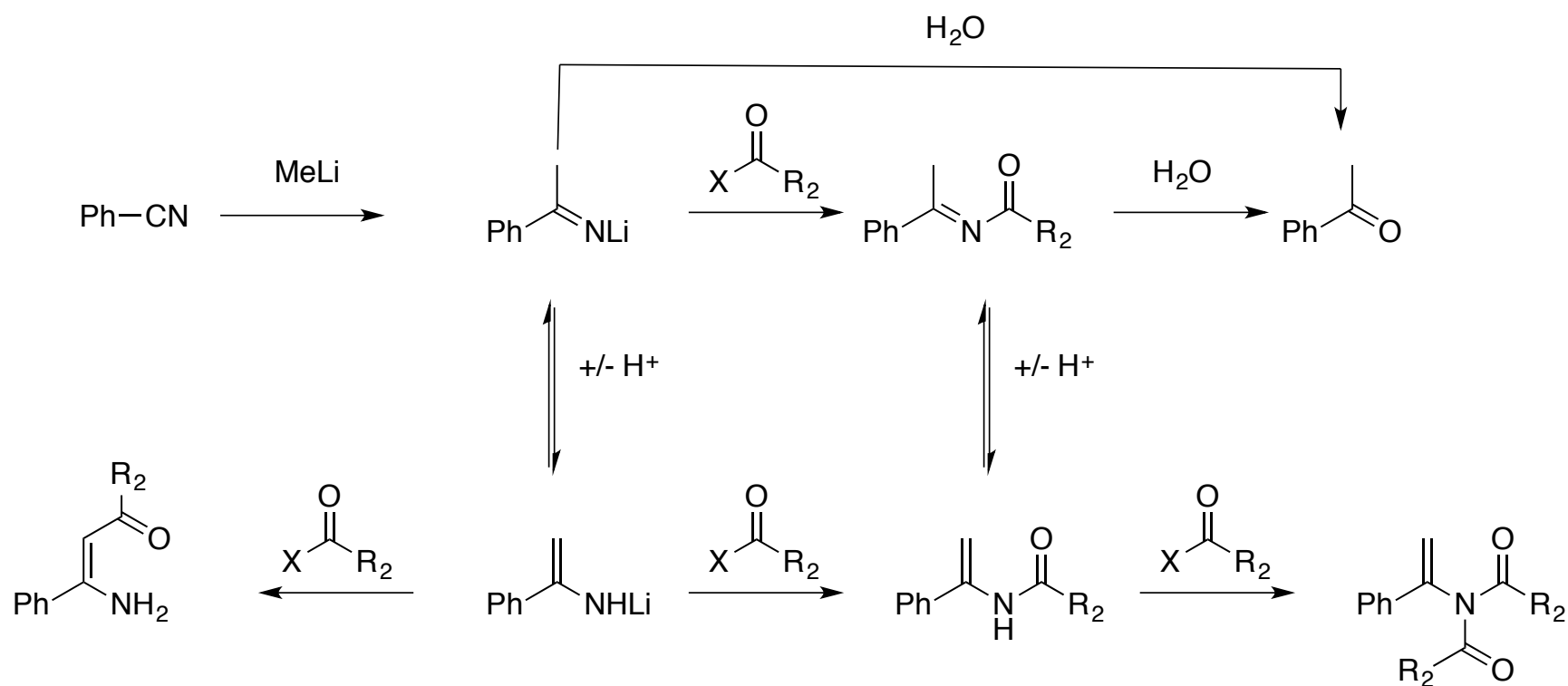
# A Few Possibilities...

Ph-CN



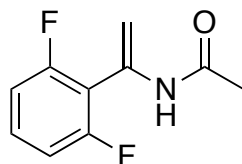
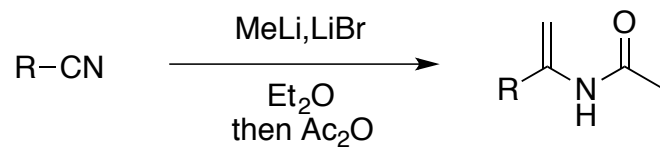
*Angew. Chem. Int. Ed.* **2016**, *55*, 14770-14773.

# A Few Possibilities...

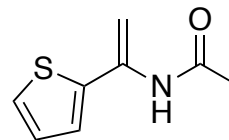


*Angew. Chem. Int. Ed.* **2016**, *55*, 14770-14773.

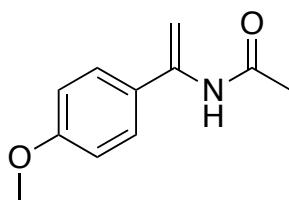
# Foundation of this Work



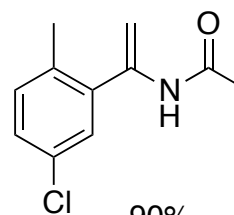
85%



60%



62%

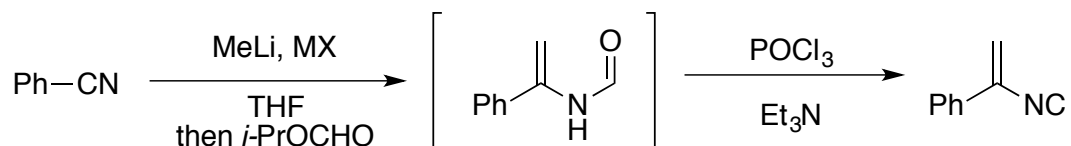


90%

*Org. Lett.* **2006**, *8*, 3903-3906.

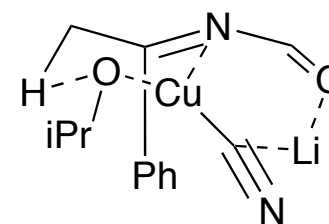


# Screen of Conditions



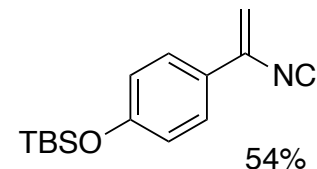
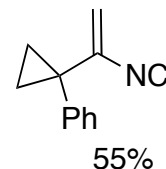
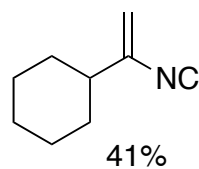
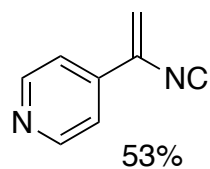
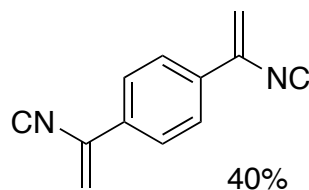
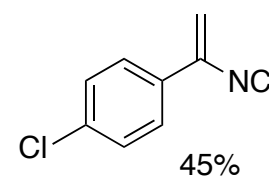
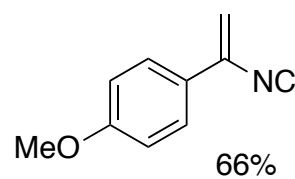
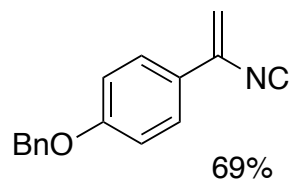
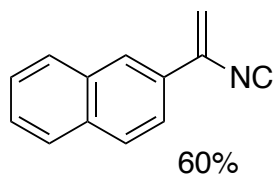
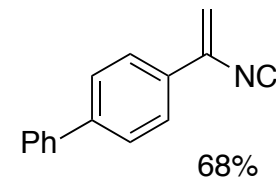
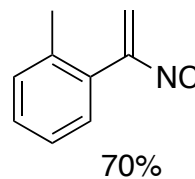
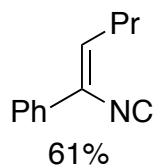
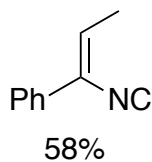
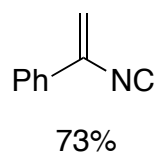
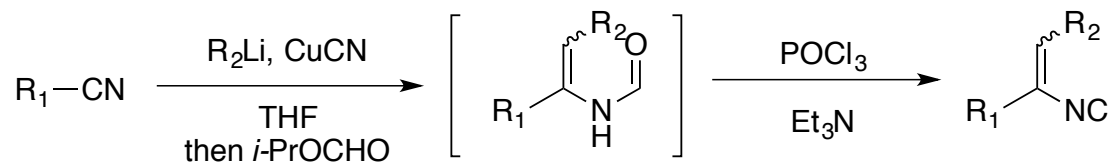
<u>Entry</u>	<u>Metal Salt (mol%)</u>	<u>Yield (%)</u>
1	----	39
2	LiBr (120)	30
3	CuCN (10)	43
4	CuI (10)	40
5	CuBr·SMe <sub>2</sub> (10)	38
6	4-MePhSCu (10)	34
7	CuCN (5)	58
8	CuCN (2)	73

- Using methyl formate favored formyl imine
- Grignard reagents gave complex mixtures



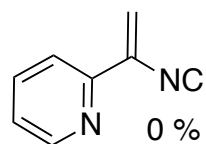
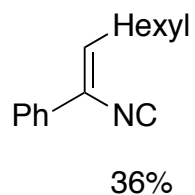
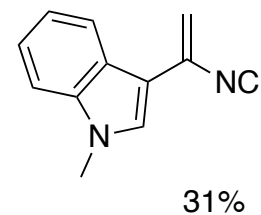
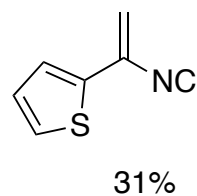
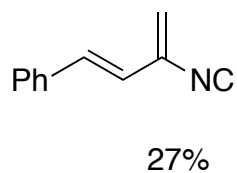
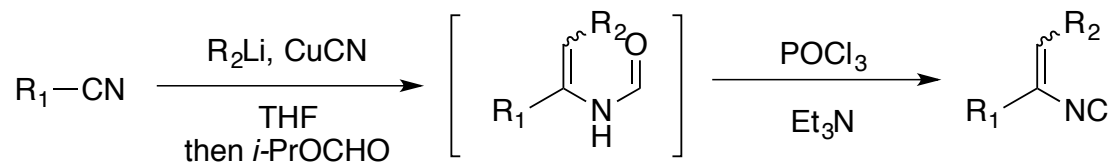
*Angew. Chem. Int. Ed.* **2016**, *55*, 14770-14773.

# Substrate Scope



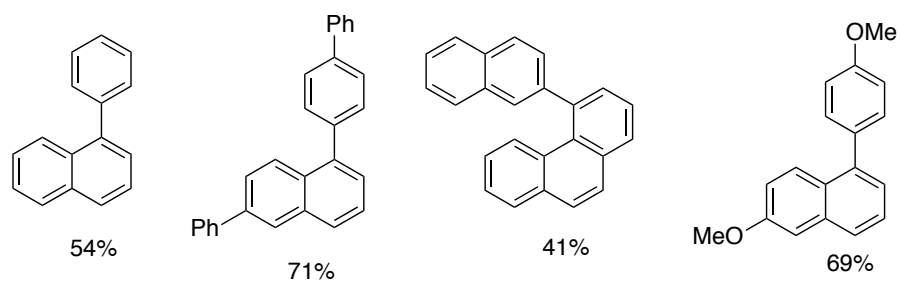
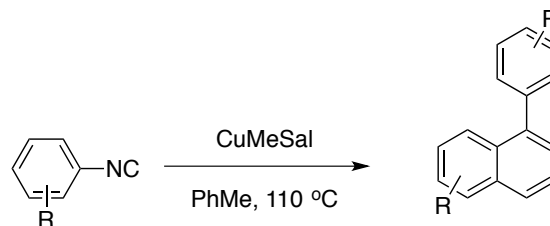
*Angew. Chem. Int. Ed.* **2016**, *55*, 14770-14773.

# Less Successful Substrate Scope

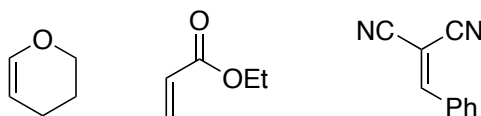


*Angew. Chem. Int. Ed.* **2016**, *55*, 14770-14773.

# [4+2] Cycloaddition

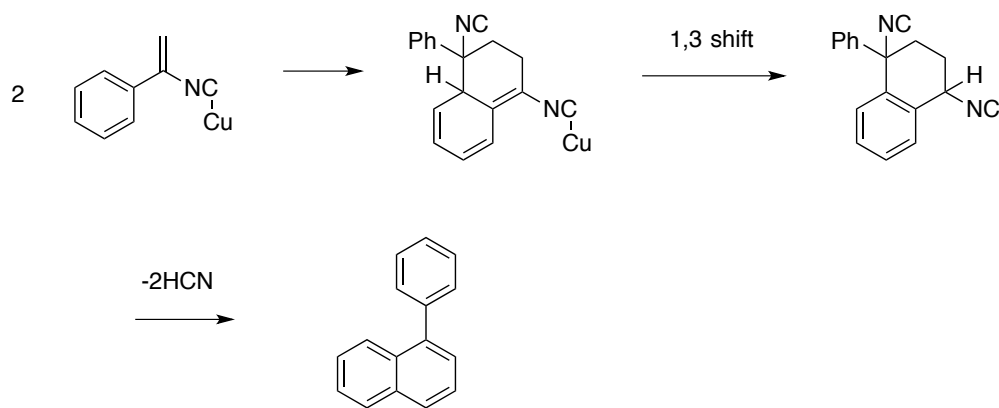
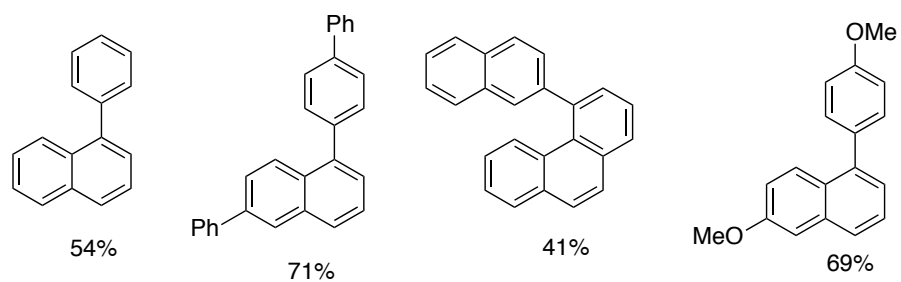
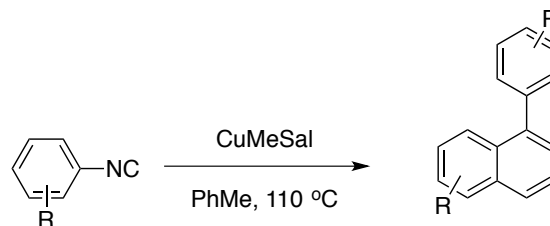


Unreactive with the following in catalyst free reaction



*Angew. Chem. Int. Ed.* **2016**, *55*, 14770-14773.

# [4+2] Cycloaddition



*Angew. Chem. Int. Ed.* **2016**, *55*, 14770-14773.

# Conclusion

- A new preparation of vinyl isonitriles was developed
  - Advantages: one-pot process, fairly simple to perform, no *E/Z* mixtures
  - Disadvantages: only primary alkyl lithium reagent are effective, typical functional group/moisture sensitivity