

**Outline:**

1. Historical perspective
2. Synthesis of isonitriles
3. General reactivity
4. Insertions
5. Chemistry of  $\alpha$ -acidic isonitriles
6. Trapping of zwitterionic intermediates
7. Multicomponent reactions (MCR)
8. Miscellaneous transformations

**Not covered:**

- Isonitrile polymers
- Transformations of isonitriles as ligands



Ivar Karl Ugi

**Book:**

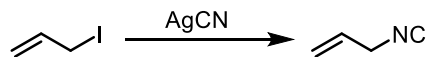
Nenajdenko, *Isocyanide Chemistry: Applications in Synthesis and Material Science*, Wiley **2012**

**Reviews:**

- Ugi, *Angew. Chem. Int. Ed.* **1965**, 4, 472  
 Walborsky, *Organic preparations and procedures*, **1979**, 11, 293  
 Ugi, *Angew. Chem. Int. Ed.* **2000**, 39, 3168  
 Ugi, *Molecules*, **2003**, 8, 53  
 Wu, *Chem. Soc. Rev.* **2013**, 42, 5257  
 Haravi, *RSC Adv.* **2016**, 6, 53203  
 Zhu, *Chem. Soc. Rev.* **2017**, 46, 1295

**1. Historical perspective**

-In 1859 Lieke synthesized allyl isocyanide from allyl iodide and silver cyanide:



Lieke, *Justus Liebigs Ann. Chem.* **1859**, 112, 316

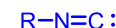
-Gautier (1867) and Hoffmann (1867) have developed conditions for isonitrile synthesis that gave synthetically useful yields (*more in part 2*).

-For almost a century, the chemistry of isonitriles was left unexplored, which is commonly attributed to their very unpleasant smell:

*The development of the chemistry of isonitriles has probably suffered only little delay through the characteristic odor of volatile isonitriles, which has been described by Hofmann and Gautier as "highly specific, almost overpowering", "horrible" and "extremely distressing". - Ugi*

The most notable reactions discovered in this period are Alagna's tetrazole synthesis (1917) and the Passerini reaction (1921).

-In 1892 Nef has proposed the "carbene" representation of isonitriles:



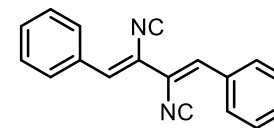
Nef, *Justus Liebigs Ann. Chem.* **1892**, 270, 267

-In 1930 Lindemann and Wiegrebé proposed a zwitterionic structure which is more consistent with the IR C-N stretching band at 2130  $\text{cm}^{-1}$ :



Wiegrebé, *Chem. Ber.* **1930**, 63, 1650

-The first naturally occurring isonitrile, xanthocillin was isolated in 1950:



Rothe, *Pharmazie*, **1950**, 5, 190

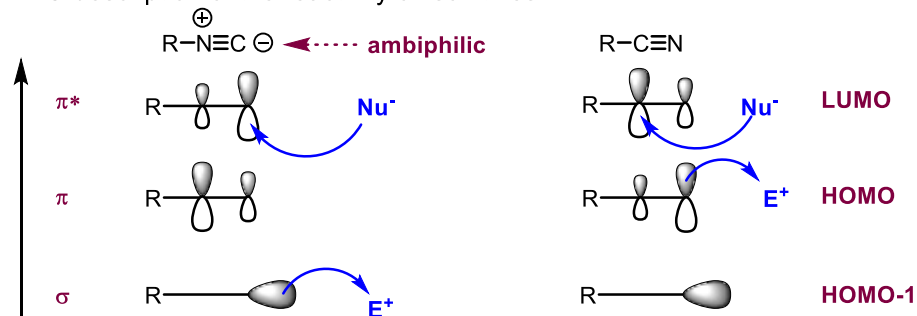
-In the 1950s, new ways to synthesize isonitriles have been discovered which together with the discovery of the Ugi reaction (1959) and reactivity of TosMIC in 1970s, sparked a new era for the chemistry of isonitriles.

-Breathing Orbital Valence Bond (BOVB) analysis supports a carbenic structure (resonance structure weights are given in percentages):

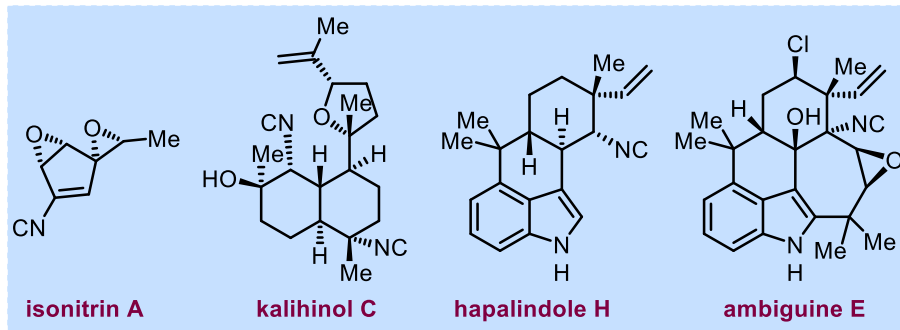


Lessard, *New J. Chem.* **2012**, 36, 1137

-MO description of the reactivity of isonitriles:



-Examples of isonitrile-containing natural products:

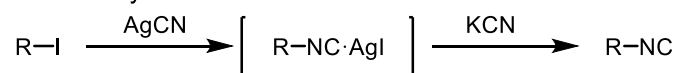


Labelling studies have revealed that the isonitrile functionality is biosynthetically incorporated by the addition of cyanide.

Opatz, *Mar. Drugs*, **2016**, 14, 16

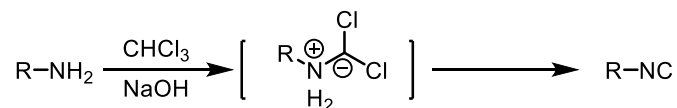
## 2. Synthesis of isonitriles

-Gautier synthesis of isonitriles:



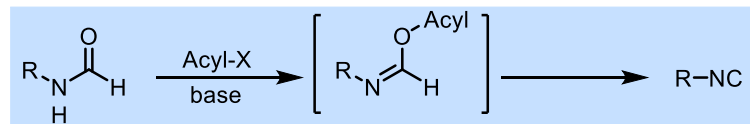
Gautier, *Justus Liebigs Ann. Chem.* **1867**, 142, 289

-Hofmann synthesis of isonitriles (carbylamine reaction):



Hofmann, *Justus Liebigs Ann. Chem.* **1867**, 144, 114

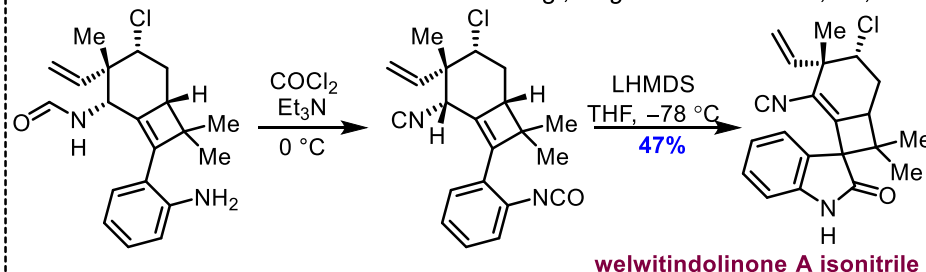
-Dehydration of monosubstituted formamides (the most common method):



Acyl-X = COCl<sub>2</sub>, POCl<sub>3</sub>, SOCl<sub>2</sub>, cyanuric chloride, PhSO<sub>2</sub>Cl, PBr<sub>3</sub>, ClCO<sub>2</sub>CCl<sub>3</sub>  
 base = Et<sub>3</sub>N, pyridine, quinoline, *t*-BuOK, NaOH, K<sub>2</sub>CO<sub>3</sub>

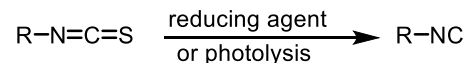
The reaction was first reported by Wegler in 1938. By treating formamides with SOCl<sub>2</sub> (no base), he was able to produce trace amounts of isonitriles. Hogedorn and Tonjes improved the reaction by using PhSO<sub>2</sub>Cl in the presence of pyridine. Ugi made it synthetically useful.

Ugi, *Angew. Chem.* **1965**, 77, 492



Wood, *J. Am. Chem. Soc.* **2006**, 128, 1448

-Desulfurization of isothiocyanates:

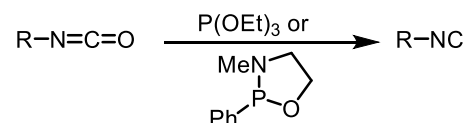


Reducing agent = PEt<sub>3</sub>, Cu, Ph<sub>3</sub>SnH, Bu<sub>3</sub>SnH...

Weith, *Chem. Ber.* **1873**, 6, 210

Witezak, *Tet. Lett.* **1986**, 27, 156

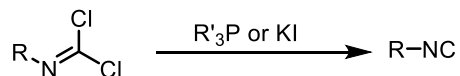
-Deoxygenation of isocyanates:



Mukaiyama, *J. Org. Chem.* **1962**, 27, 3651

Mukaiyama, *Bull. of the Chem. Soc. Jpn.* **1965**, 27, 3651

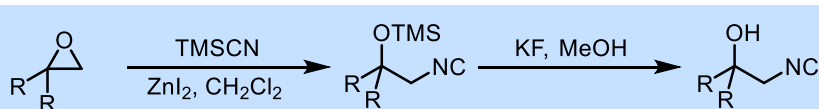
-Dehalogenation of isocyanide dichlorides:



(can be made by chlorination of isothiocyanates)

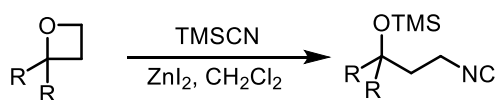
Petrov, *Zh. Obshch. Khim.* **1959**, 29, 2165

-Opening of epoxides with TMSCN:



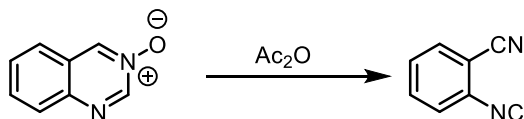
Gassman, *J. Am. Chem. Soc.* **1982**, 104, 5849

-Opening of oxetanes with TMSCN:



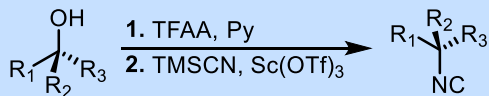
Gassman, *Tet. Lett.* **1985**, 26, 4971

-Fragmentation of quinazoline-3-oxide:



Higashino, *Chem. Pharm. Bull.* **1961**, 9, 635

-Substitution of tertiary alcohols with TMSCN:



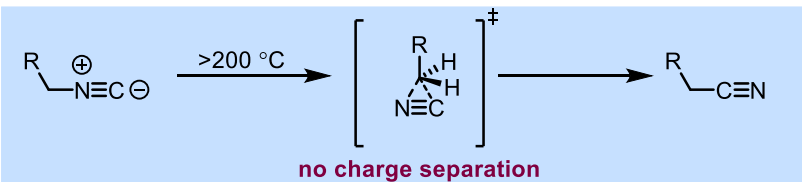
Classical conditions employed  
ZnBr<sub>2</sub>: Tada, *Tet. Lett.*  
**1998**, 39, 1911

Shenvi, *Nature*, **2013**, 501, 195

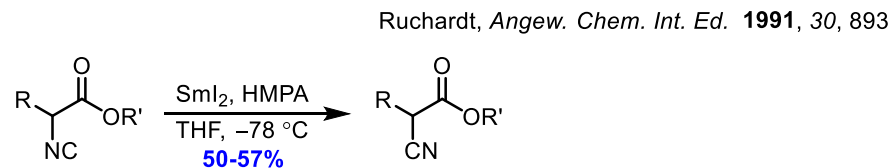
Application in total synthesis: Shenvi, *J. Am. Chem. Soc.* **2017**, 139, 3647

### 3. General reactivity

-Thermal rearrangement of isonitriles to nitriles was discovered by Weith in 1873. Majority of isonitriles isomerize quantitatively at 200-250 °C after several hours with retention of configuration:

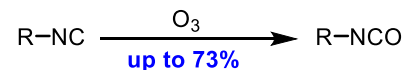


-At higher concentrations of the isonitrile, a free radical chain mechanism becomes competent which can lead to side reactions. Radical inhibitors can shut down this pathway.

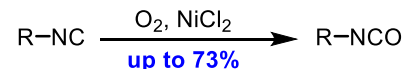


Kang, *Chem. Commun.* **1997**, 821

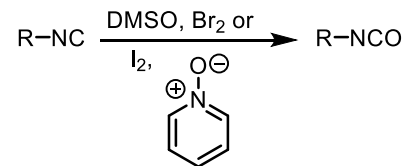
### Oxidations



Feuer, *J. Org. Chem.* **1958**, 23, 1107

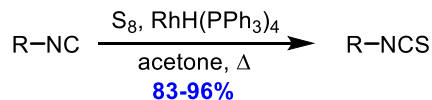


Nakamura, *Chem. Commun.* **1967**, 16, 836

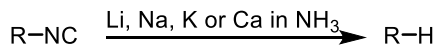
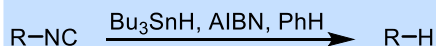


Johnson, *J. Org. Chem.* **1964**, 99, 246

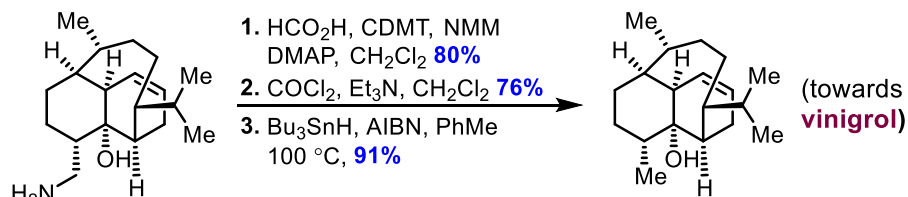
Johnson, *J. Org. Chem.* **1967**, 32, 1939

Yamaguchi, *Tet. Lett.* **2005**, 46, 1727

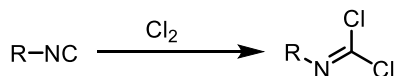
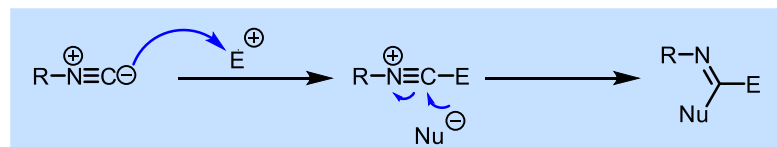
## Reductions

Ugi, *Chem. Ber.* **1961**, 94, 1157Saegusa, *J. Am. Chem. Soc.* **1968**, 90, 4182

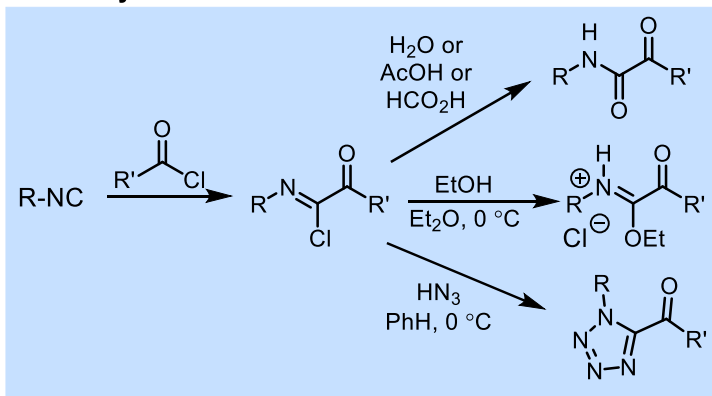
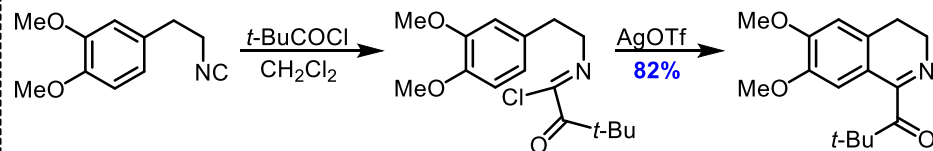
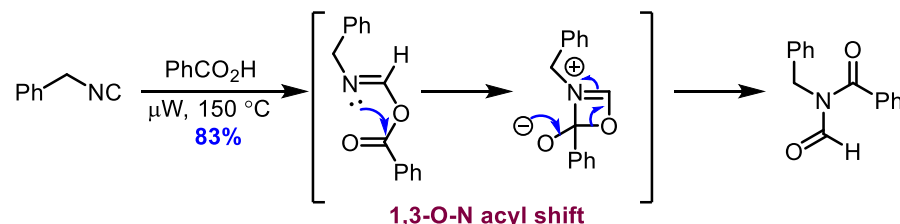
-Indirect way to do deaminations:

Baran, *J. Am. Chem. Soc.* **2009**, 131, 17066

## Reactions with electrophiles

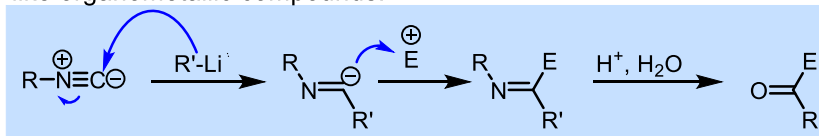
Nef, *Liebigs Ann. Chem.* **1982**, 270, 267

## -Nef-isocyanide reaction:

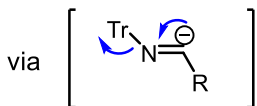
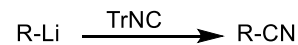
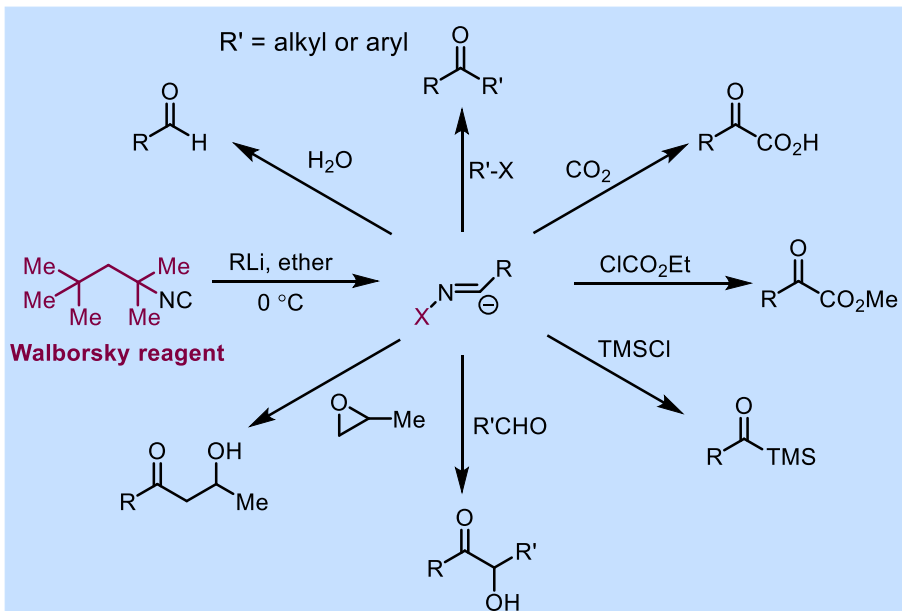
Ugi, *Chem. Ber.* **1961**, 94, 1116Livinghouse, *Tetrahedron*, **1999**, 55, 9947Danishefsky, *J. Am. Chem. Soc.* **2008**, 130, 5446

## Reactions with nucleophiles

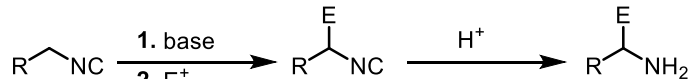
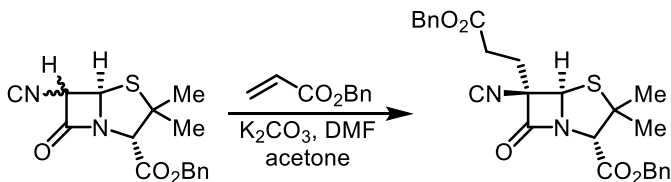
-Isonitriles are weak electrophiles and usually react with strong nucleophiles like organometallic compounds:



-Reactions of the Walborsky reagent (masked acyl anion):

Walborsky, *J. Org. Chem.* **1974**, 39, 600Walborsky, *J. Org. Chem.* **1974**, 39, 611Walborsky, *J. Org. Chem.* **1982**, 47, 52

$\alpha$ -Deprotonation

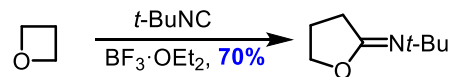
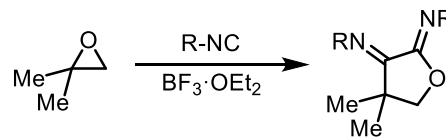
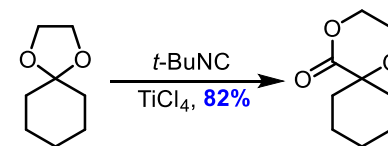
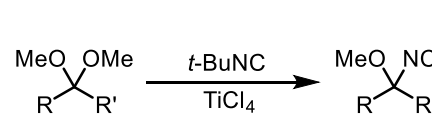
R = aryl or CO<sub>2</sub>EtSchoellkopf, *Ang. Chem. Int. Ed.* **1968**, 7, 85

(more in part 9)

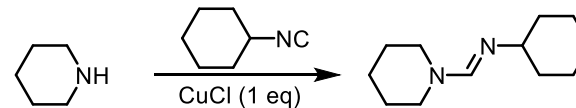
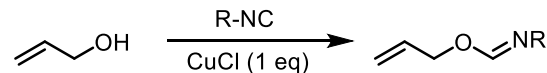
Clayton, *J. Chem. Soc. Chem. Commun.* **1974**, 278

#### 4. Insertions

-Lewis acid promoted insertions:

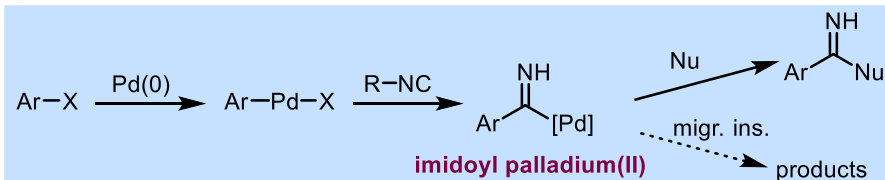
Saegusa, *Synthesis* **1970**, 475Saegusa, *Synth. Commun.* **1971**, 1, 99Saegusa, *Chem. Lett.* **1984**, 937

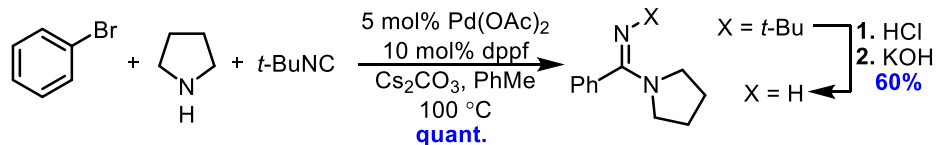
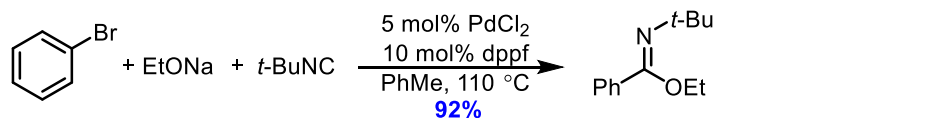
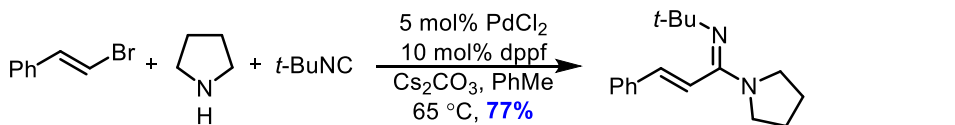
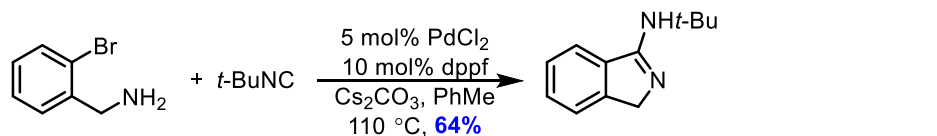
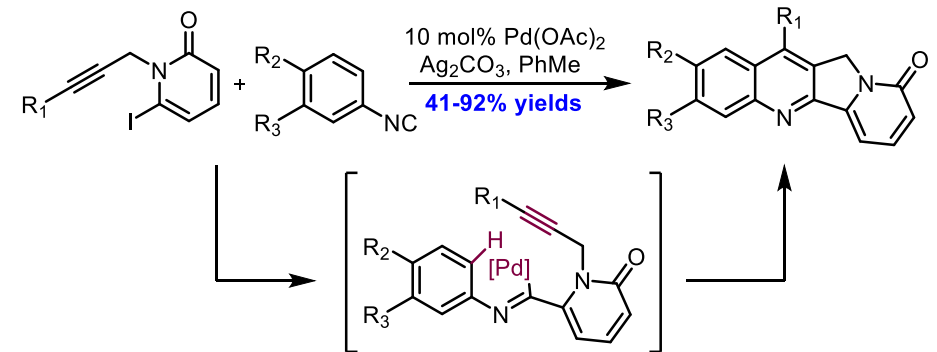
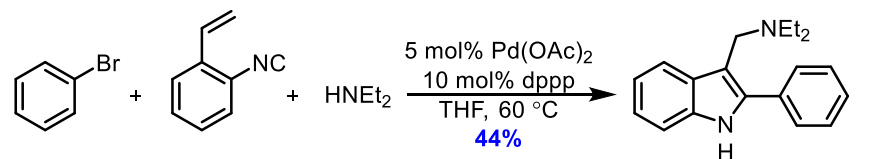
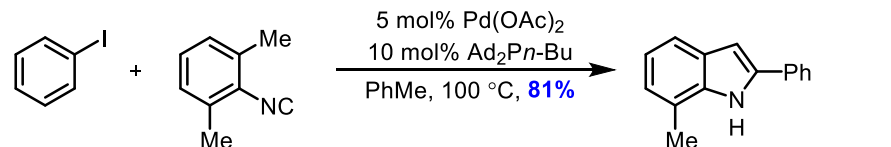
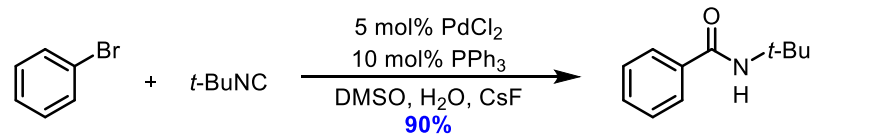
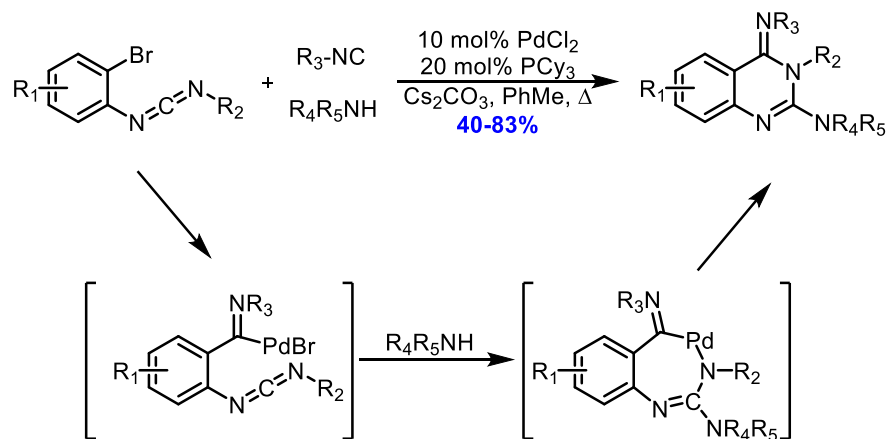
-Transition metal mediated insertions into X-H bonds:

Saegusa, *Tet. Lett.* **1966**, 49Saegusa, *Tet. Lett.* **1967**, 521

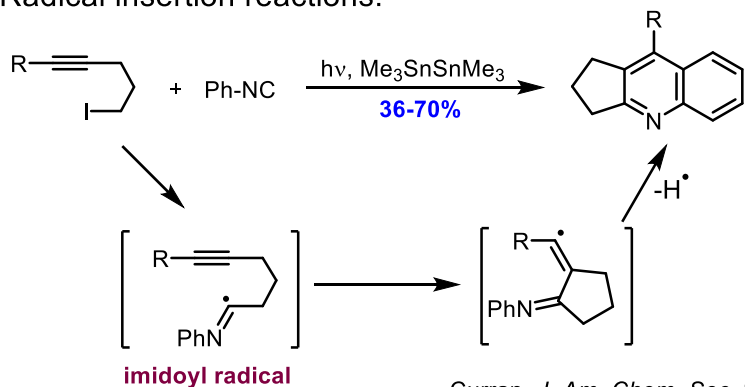
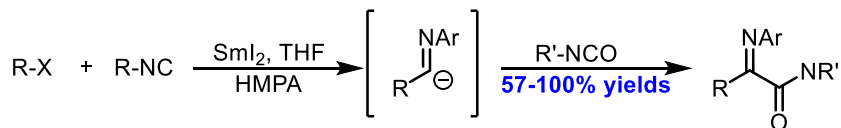
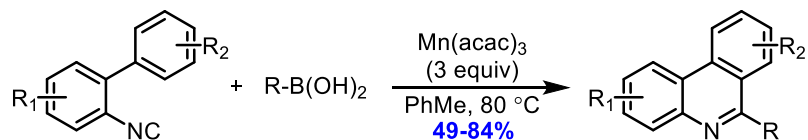
Insertions into S-H, Si-H, P-H have also been reported by Saegusa. Cobalt and nickel work, too.

Palladium catalyzed insertions into C-X and C-H bonds

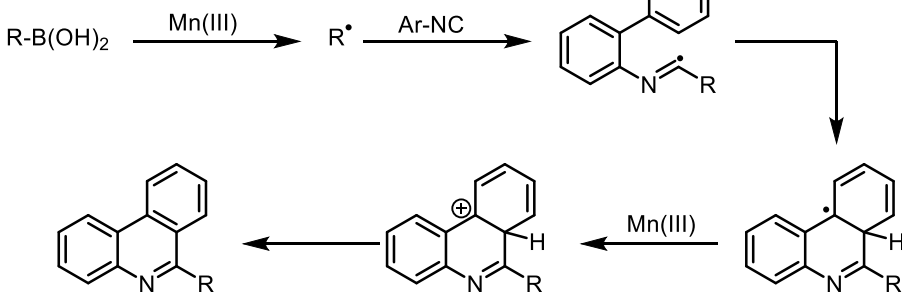


Whitby, *Angew. Chem., Int. Ed.* **2000**, 39, 4156Whitby, *Tet. Lett.* **2001**, 42, 6191Whitby, *Tet. Lett.* **2004**, 45, 6991Whitby, *Tet. Lett.* **2004**, 45, 6995Curran, *Org. Lett.* **2002**, 4, 3215Takahashi, *Tet. Lett.* **2002**, 43, 6197Takemoto, *Org. Lett.* **2012**, 14, 4270Jiang, *Org. Lett.* **2011**, 13, 1028Wu, *Chem. Commun.* **2012**, 48, 2903

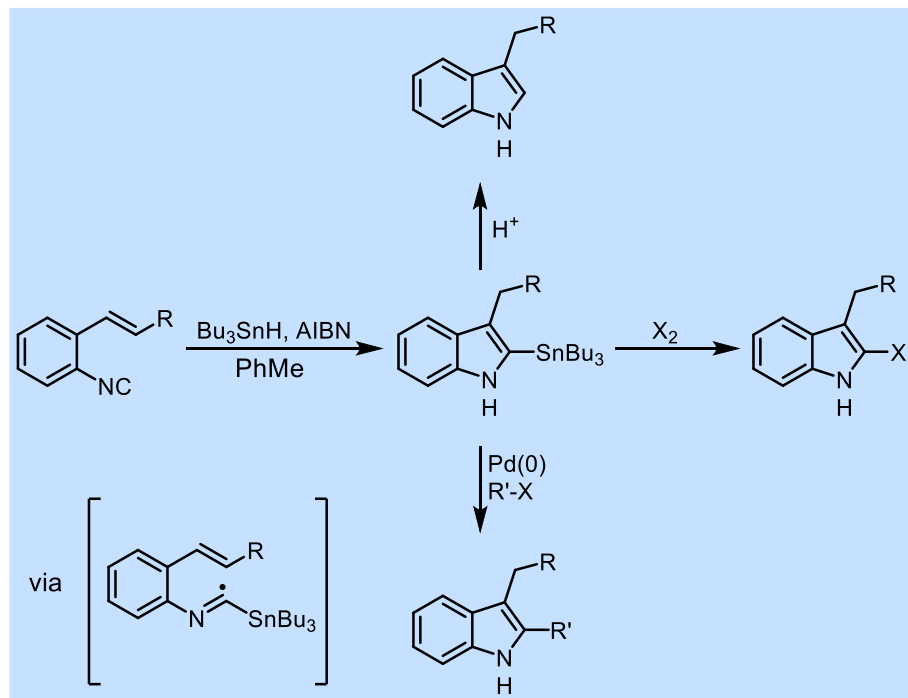
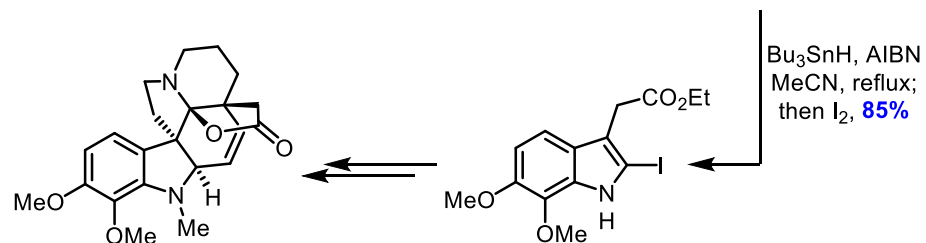
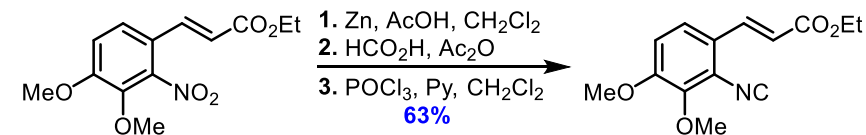
## Radical insertion reactions:

Curran, *J. Am. Chem. Soc.* **1991**, *113*, 2127Takahashi, *Org. Lett.* **2012**, *14*, 4090

Mechanism:

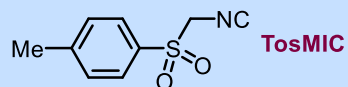
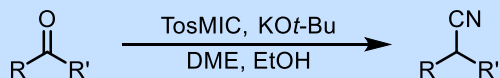
Tobisu, *Angew. Chem. Int. Ed.* **2012**, *51*, 11363

## -Fukuyama indole synthesis:

Fukuyama, *J. Am. Chem. Soc.* **1999**, *121*, 3791**aspidophytine**Fukuyama, *Org Lett.* **2003**, *5*, 1891

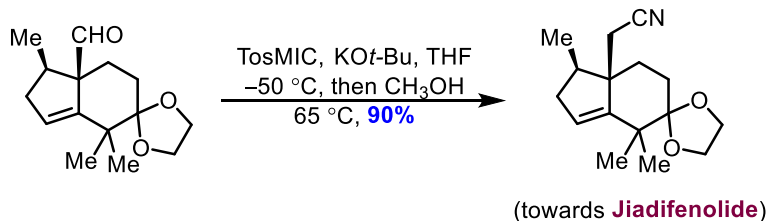
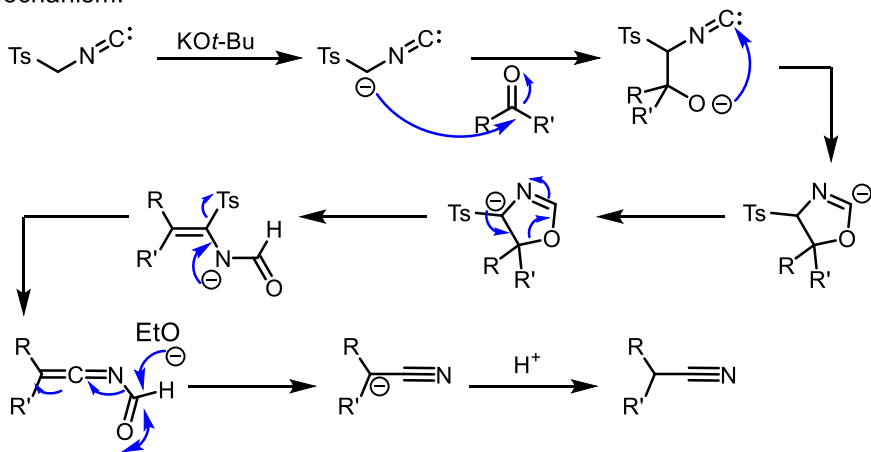
5. Chemistry of  $\alpha$ -acidic isonitriles

Tosylmethyl isocyanide is one of the most versatile isonitrile-based reagents whose chemistry was developed by the van Leusens.

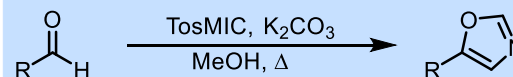
**-Van Leusen reductive cyanation:**

van Leusen, *J. Org. Chem.* **1977**, 42, 3114

## Mechanism:

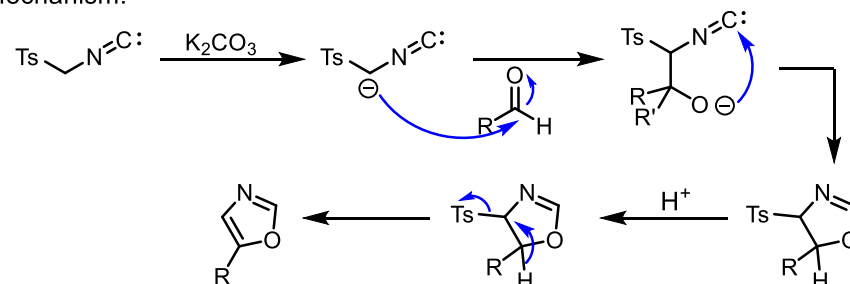
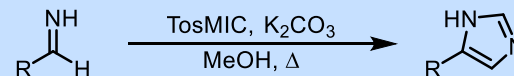


Sorensen, *Angew. Chem. Int. Ed.* **2014**, 53, 5332

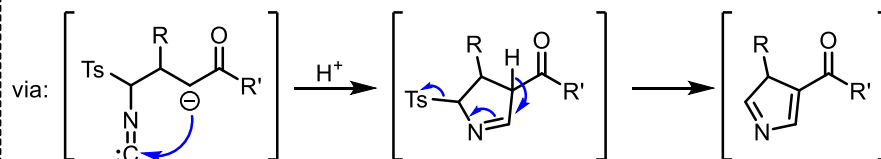
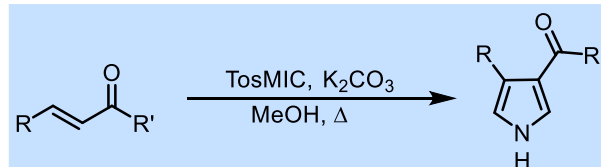
**-Van Leusen oxazole synthesis:**

van Leusen, *Tet. Lett.* **1972**, 13, 2369

## Mechanism:

**-Van Leusen imidazole synthesis:**

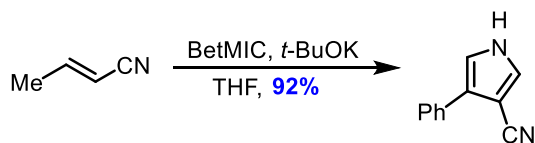
van Leusen, *J. Org. Chem.* **1977**, 42, 1153

**-Van Leusen pyrrole synthesis:**

van Leusen, *Tet. Lett.* **1972**, 52, 5337



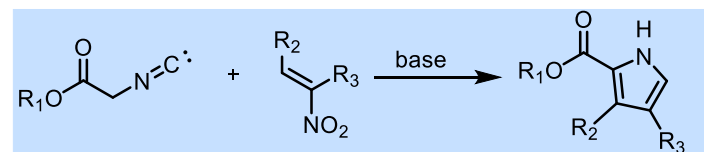
-Benzotriazolymethyl isocyanide is a more reactive version of TosMIC:



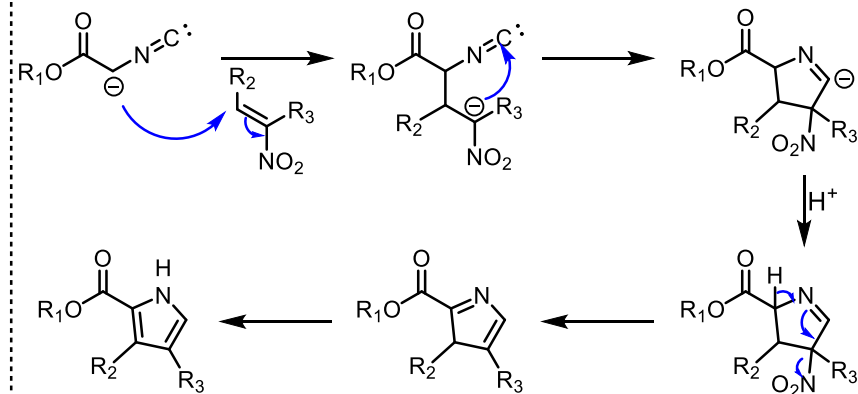
Katritzky, *Heterocycles*, **1997**, 44, 67

-Isocyanooesters are commonly used in the synthesis of heterocycles.

**-Barton-Zard pyrrole synthesis:**

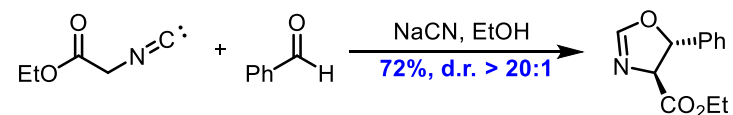


Mechanism:

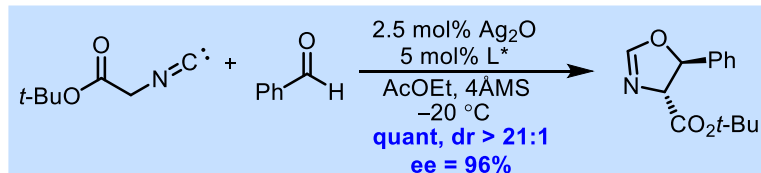


Barton, *J. Chem. Soc. Chem. Commun.* **1985**, 1098

-Oxazoline synthesis:

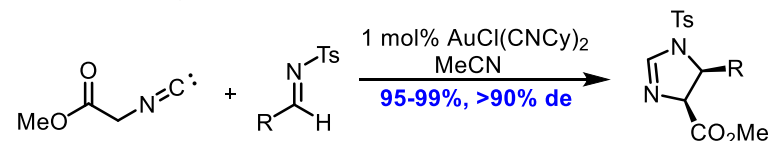


Schoellkopf, *Ang. Chem. Int. Ed.* **1970**, 9, 300



L\*=cinchona-derived amino phosphine  
Dixon, *J. Am. Chem. Soc.* **2011**, 133, 1710

-Imidazoline synthesis:

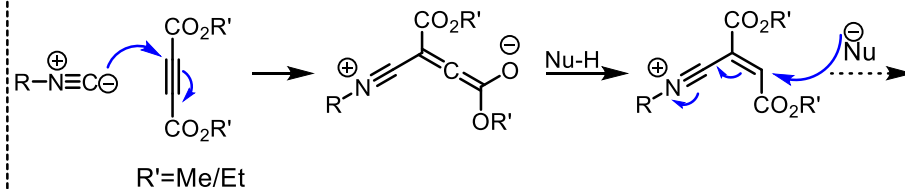


Hayashi, *Tet. Lett.* **1996**, 37, 4969

Cis isomers are obtained commonly, but can be epimerized to trans with base.

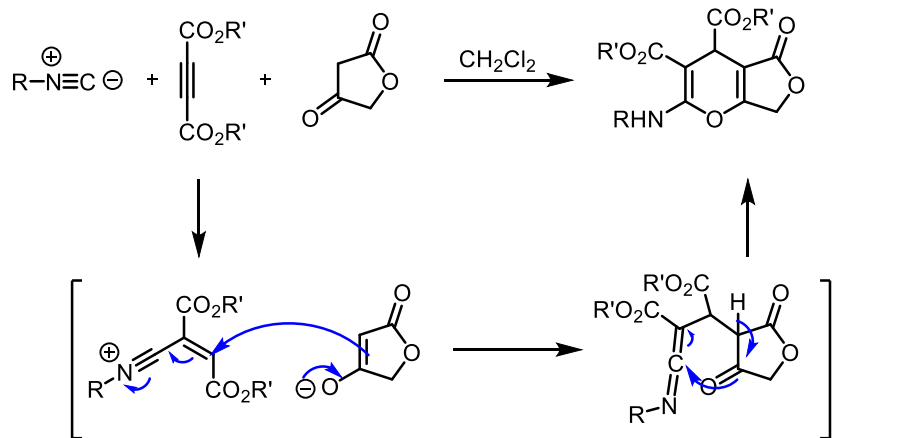
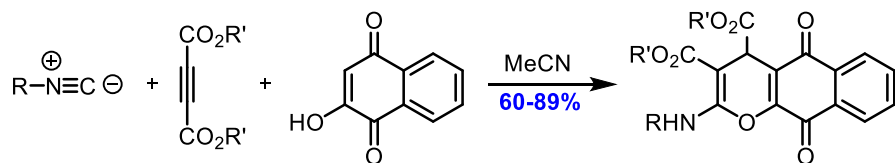
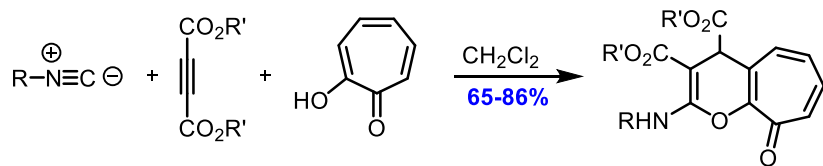
## 6. Trapping of zwitterionic intermediates

-Addition of isocyaniles to activated alkynes gives zwitterionic intermediates which can be trapped by a variety of nucleophiles:

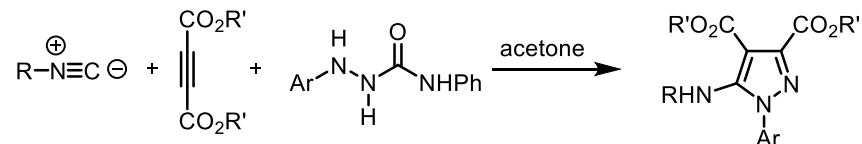


R'=Me/Et

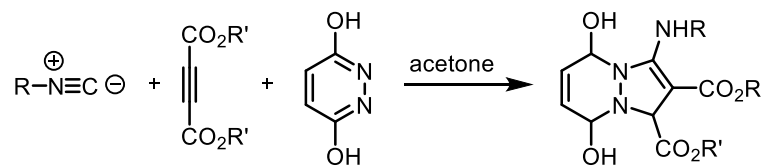
-C-H acids as trapping reagents:

Shaabani, *Bioorg. Med. Chem. Lett.* **2008**, 18, 3968Shaabani, *J. Org. Chem.* **2009**, 74, 4372Ramazani, *Helv. Chim. Acta*, **2011**, 94, 371

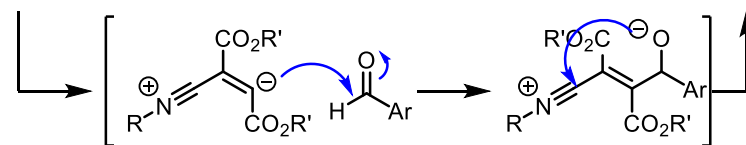
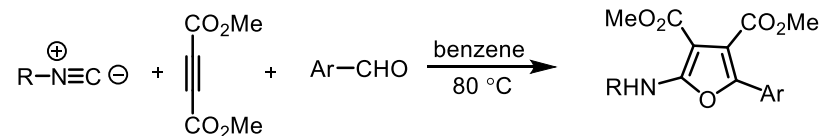
-N-H acids as trapping reagents:

Adib, *Synlett*, **2008**, 3180

-O-H acids as trapping reagents:

Tiemouri, *Tetrahedron*, **2010**, 66, 259

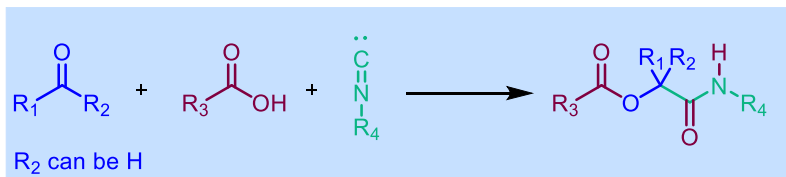
-Carbonyl compounds as trapping reagents:

Nair, *Tetrahedron*, **2003**, 59, 10279

## 7. Multicomponent reactions (MCR)

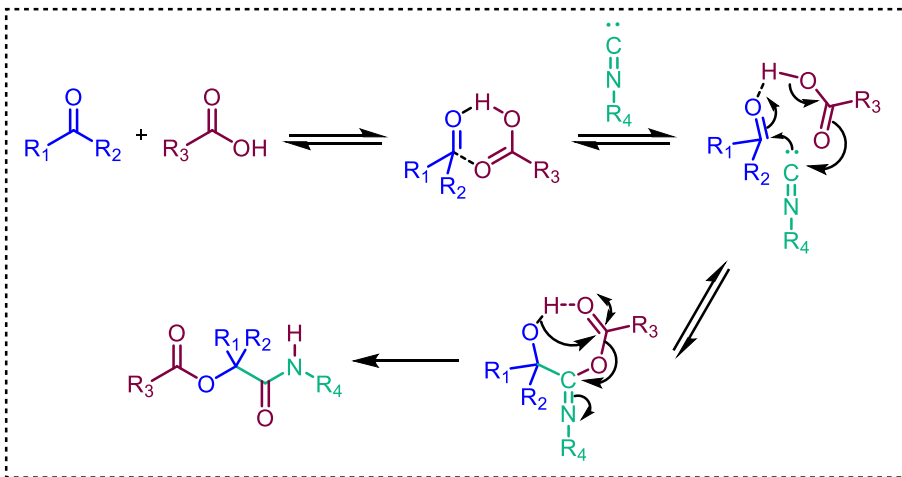
Many of the previously shown transformations are multicomponent, but the focus of this part are Passerini and Ugi reactions.

## -Passerini reaction (P-3CR):

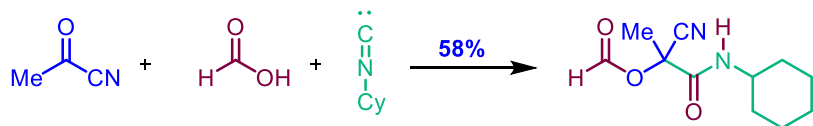


Passerini, *Gazz. Chim. Ital.* **1921**, 51, 126

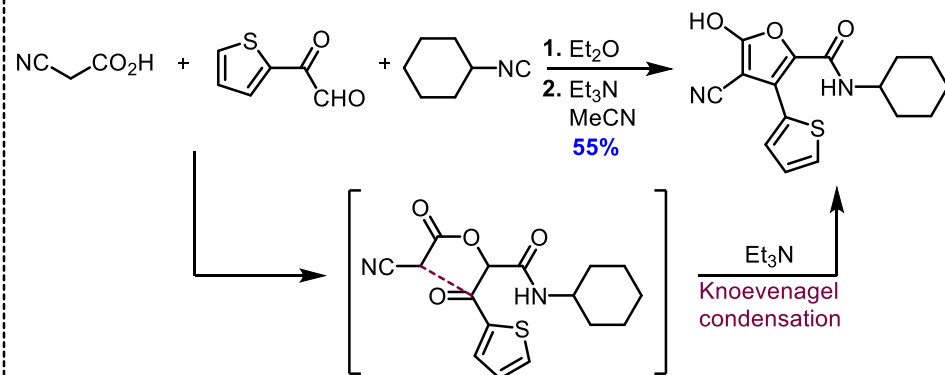
## Mechanism:



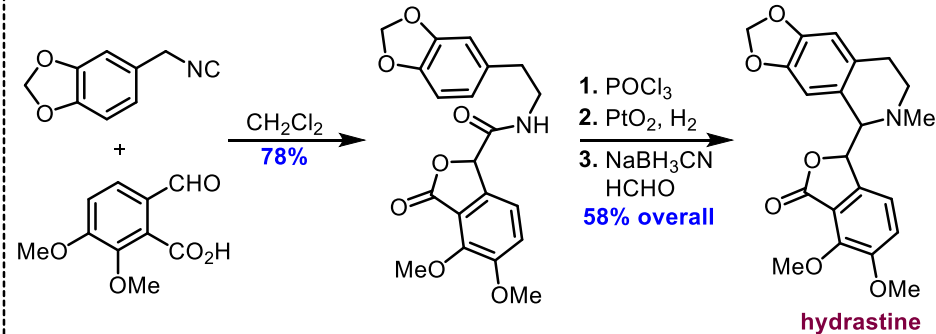
## Examples:



Neidlein, *Arch. Pharm.* **1966**, 299, 603

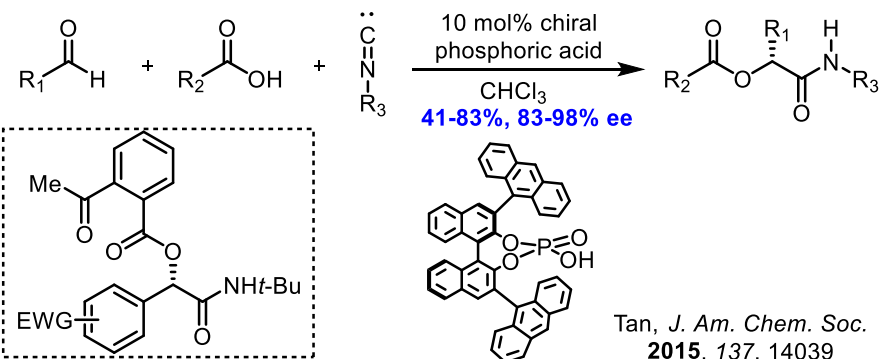


Marcaccini, *Synthesis*, **1993**, 7831

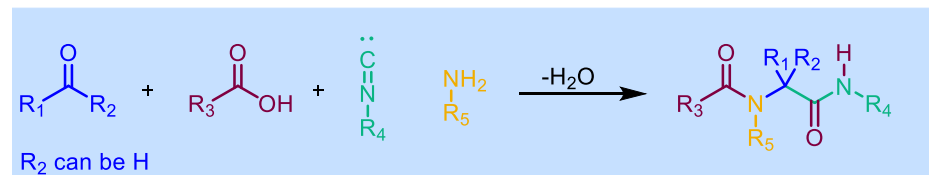
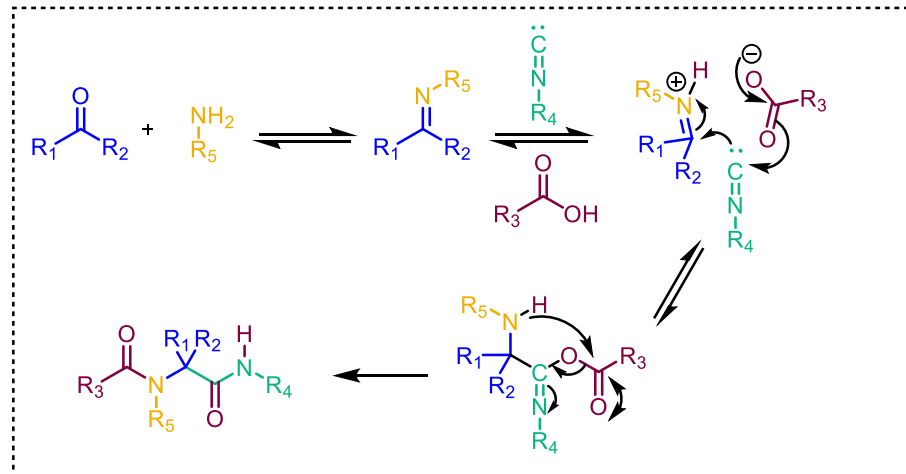


Falck, *Tet. Lett.* **1981**, 22, 619

Enantioselective versions still suffer from narrow substrate scopes:

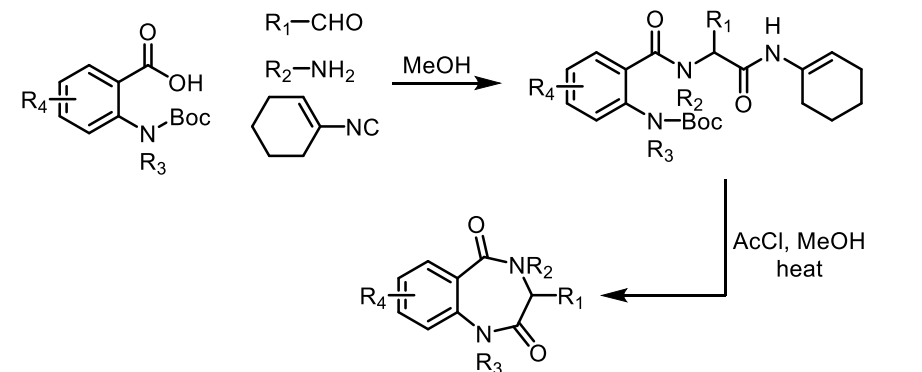
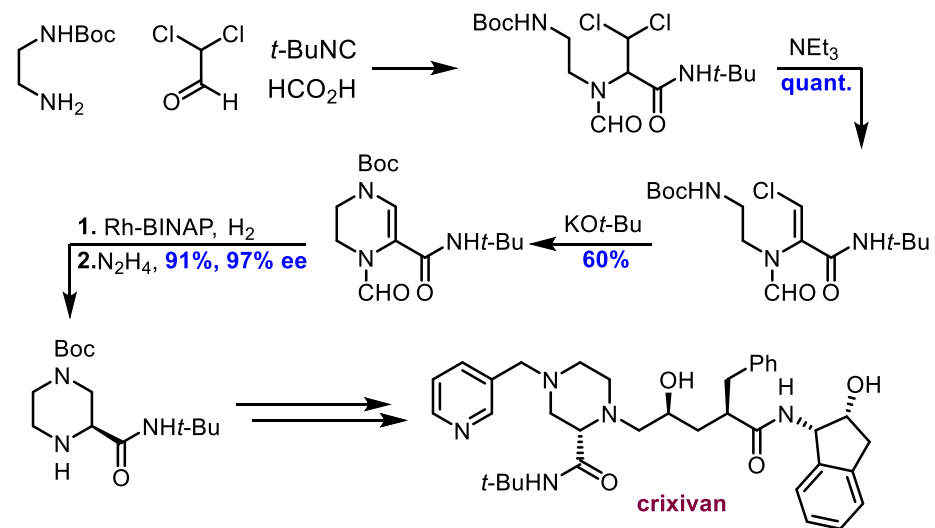
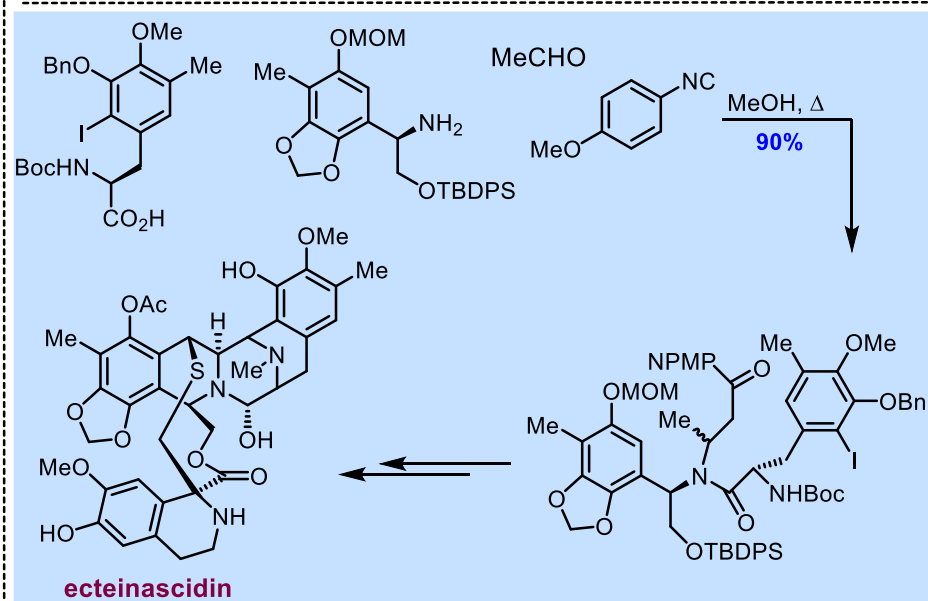


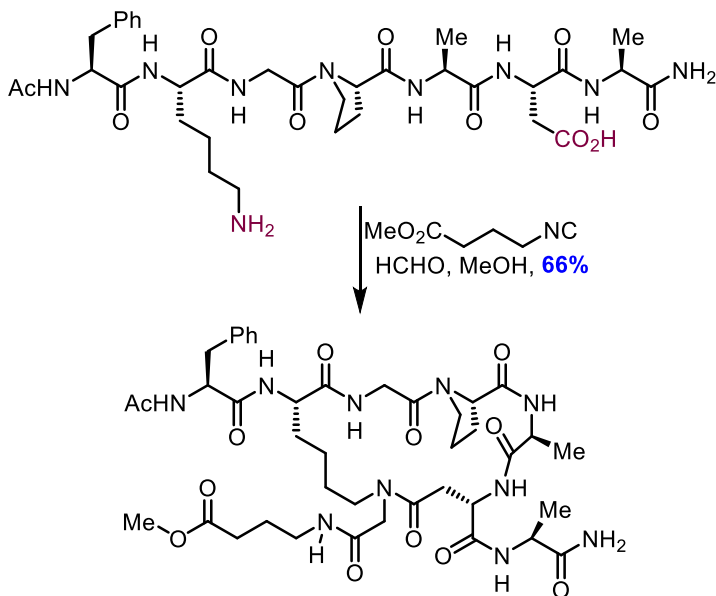
Tan, *J. Am. Chem. Soc.* **2015**, 137, 14039

**-Ugi reaction (U-4CR):**Ugi, *Angew. Chem.* **1959**, 71, 386**Mechanism:**

Extensively used in the synthesis of peptides, drugs, chemical libraries etc.

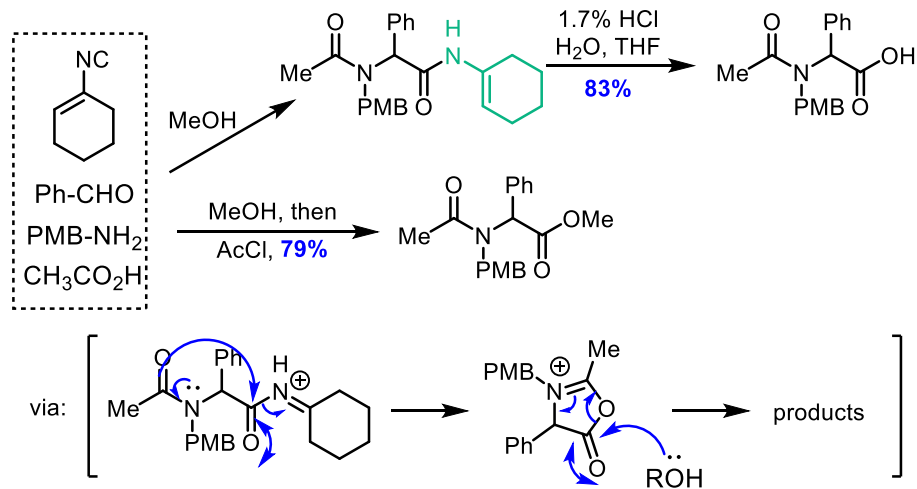
Examples:

Hulme, *J. Org. Chem.* **1998**, 63, 8021Rossen, *Tet. Lett.* **1998**, 39, 6823Fukuyama, *J. Am. Chem. Soc.* **2002**, 124, 6552



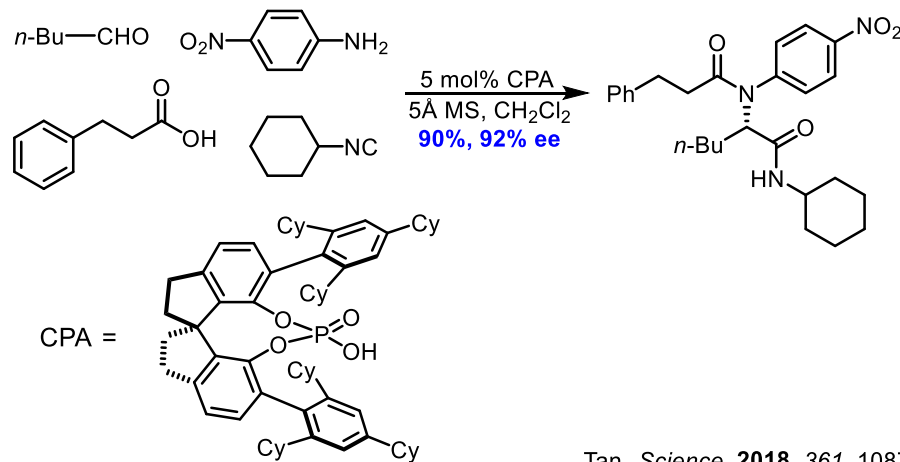
Rivera, *J. Org. Chem.* **2015**, *80*, 6697

- "Convertible" isocyanides lead to Ugi reaction products that can be easily modified at the amide moiety derived from that isocyanide:



Armstrong, *J. Am. Chem. Soc.* **1995**, *117*, 7842

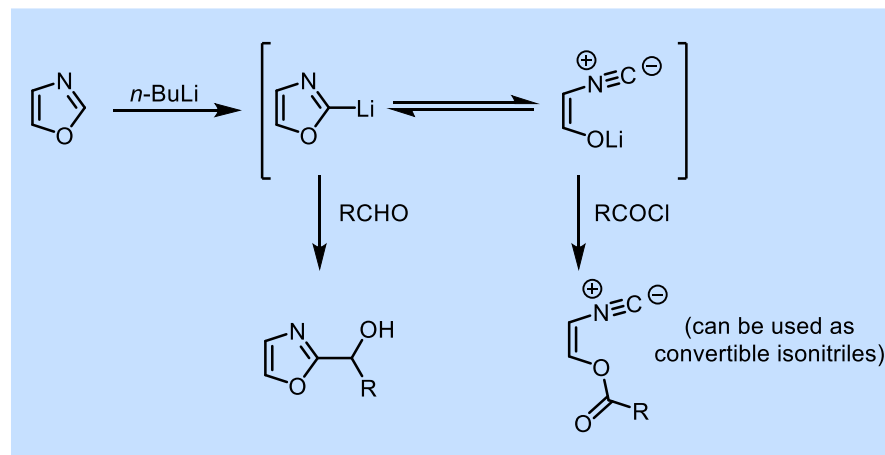
- A major breakthrough in enantioselective Ugi reaction was reported in 2018. The reaction had a much broader substrate scope than previous reports:



Tan, *Science*, **2018**, *361*, 1087

## 9. Miscellaneous transformations

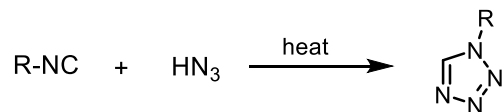
- Lithiated oxazoles and benzoxazoles are in equilibrium with isocyanides which can be trapped with a variety of electrophiles:



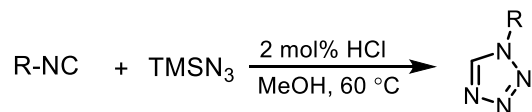
Hodges, *J. Org. Chem.* **1991**, *56*, 449

Pirrung, *J. Am. Chem. Soc.* **2006**, *128*, 11772

-[3+2] cycloadditions:

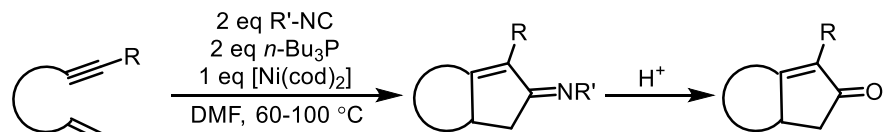


Alagna, *Gazz. Chim. Ital.* **1910**, 40, 442

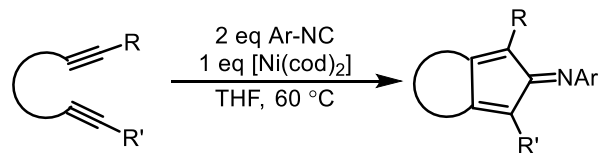


Yamamoto, *Tet. Lett.* **2004**, 45, 9435

-Aza-Pauson-Khand reaction:

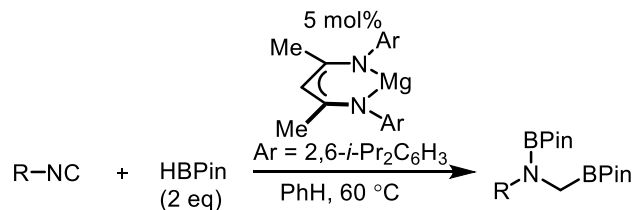


Kobayashi, *J. Am. Chem. Soc.* **1988**, 110, 1286



Kobayashi, *J. Org. Chem.* **1989**, 54, 3517

-Hydroborations are underexplored:



Hill, *Chem. Commun.* **2015**, 51, 14477