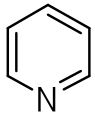
DE NOVO SYNTHESIS OF SUBSTITUTED PYRIDINES

David Kornfilt 07/15/2014

Outline

- Historical Background on pyridines, importance in natural products
- Slicing up the pie: How to disconnect the ring
- Electrocyclizations
- Two Component Reactions
- Three Component Reactions (with ammonia equivalents)
- Four Component Reactions
- Discussion

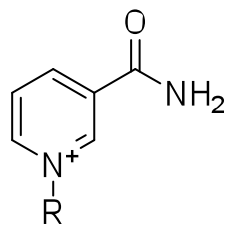
Pyridine



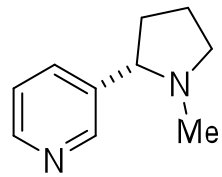
- Simplest 6-membered aromatic azacycle.
- Originally isolated from bone oil (1846).
- Up until the 1930s, research quantities were available from coal tar.
- High bioactivity led to increasing demands for large quantities of pyridines.
- Substitution patterns matter: ability to form the ring with fully functionalized core is important
- Availability of starting materials dictates which synthetic method is most advantageous

Henry G. D., *Tetrahedron*, 2004, 6043

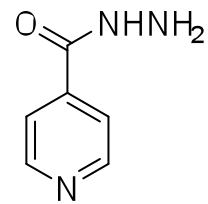
Pyridine Drugs/NPs



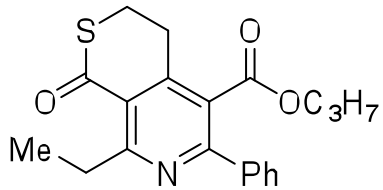
NAD+
R= Ribose-PP-Adenine



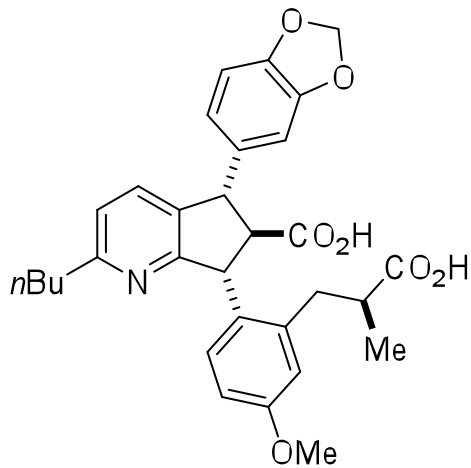
Nicotine



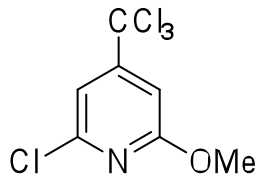
Isoniazide



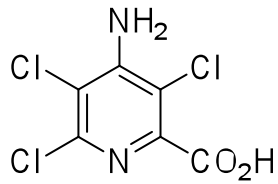
A_3 Adenosine Receptor Antagonist



Endothelin receptor agonist



pyroxychlor

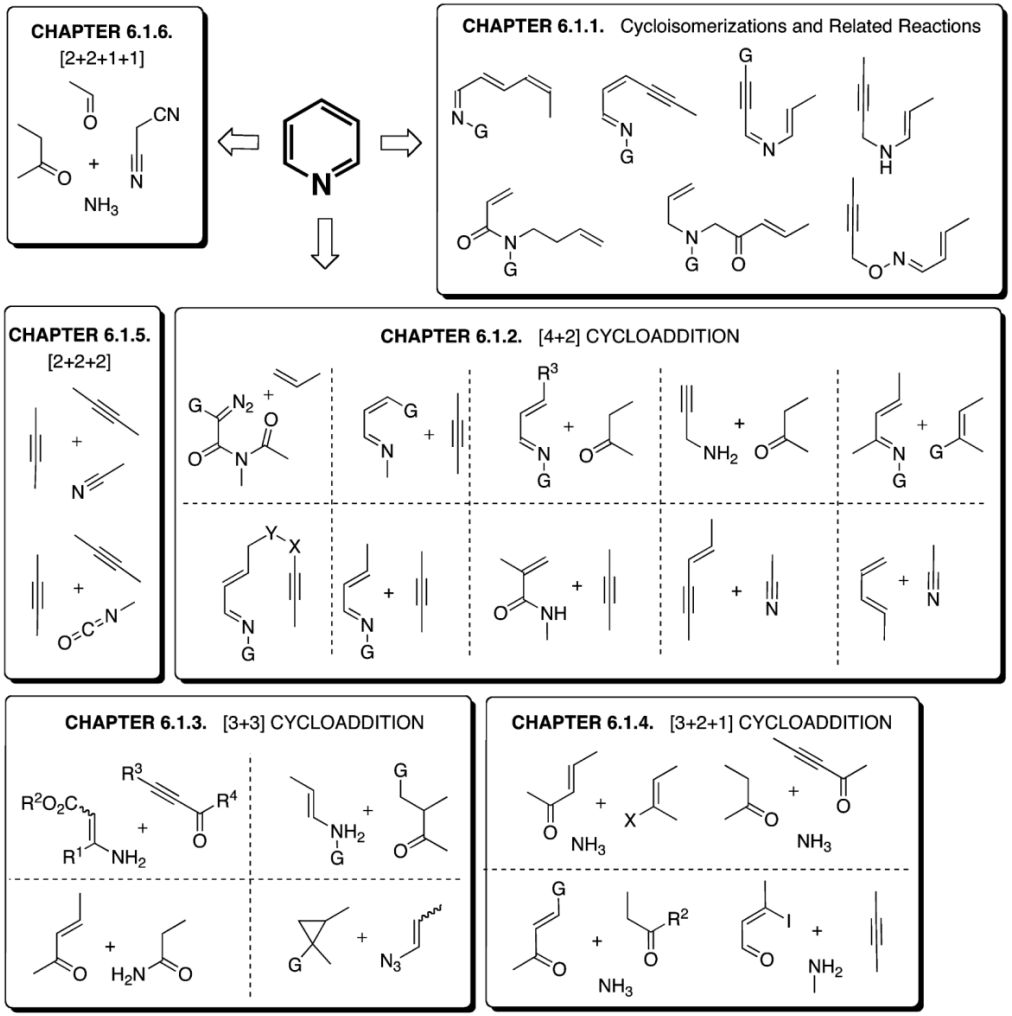


picloram

Over 7000 bioactive compounds containing pyridine moieties in use.

Hill, M.D., *Chem. Eur. J.*, 2010, 12052
Henry G. D., *Tetrahedron*, 2004, 6043

A Generalized Pyridine Synthesis Schema

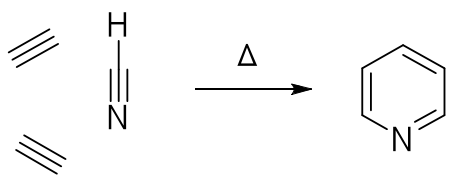


Clearly there is no shortage of different approaches to pyridine synthesis.

Choice of methodology depends on many factors: availability of starting materials, compatibility with functional groups, desired substitution pattern

Gevorgyan, V. et .al. *Chem. Rev.*, 2013, 3084

Ramsay's Synthesis of Pyridine



First performed in 1876 (correct structure was proposed in 1869/71)

Passed acetylene gas (from silver acetylide) through HCN capsule and then heated in an iron tube.

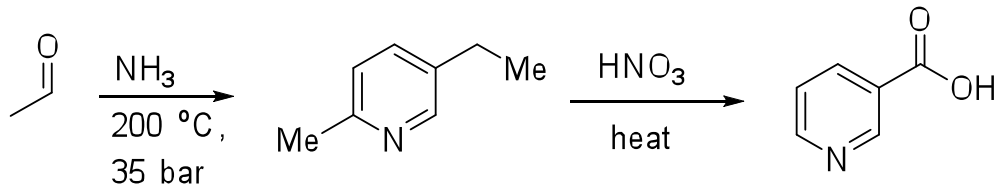
Ramsay reports : Less then 2 cm^3 of liquid was formed along with benzene contamination

In the original report, identified by "smell."

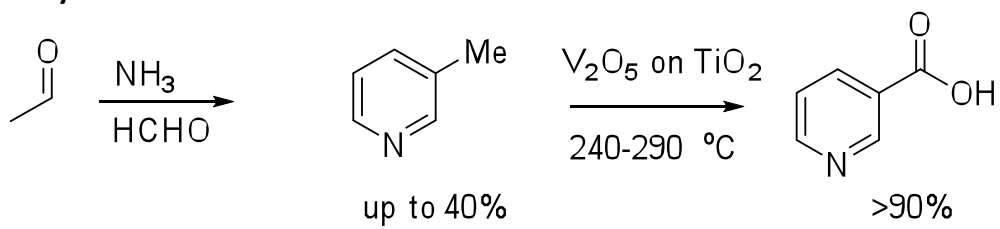
Ramsay , W. *Philos. Mag.*, 1876, 2, 269

Industrial Synthesis of Nicotinic Acid

Original Synthesis:



Modern Synthesis:



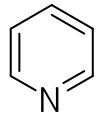
One of the essential human dietary ingredients (Vitamin B3, Nicotinamide)

Widely sold as a supplement.

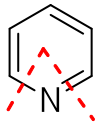
Manufactured on >10,000 t per year scale

Henry G. D., *Tetrahedron*, 2004, 6043
Baxendale et. al., *Beilstein J. Org. Chem.* 2013, 9, 2265

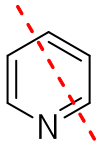
Conceptual Disconnections



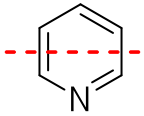
Cycloisomerization



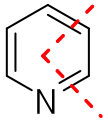
Dicarbonyl [5+1]



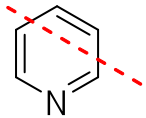
Type A [3+3]



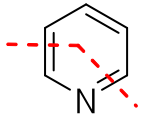
Type B [3+3]



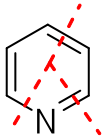
Type A [4+2]



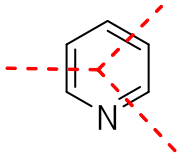
Type B [4+2]



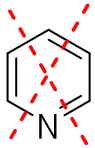
Type C [4+2]



[3+2+1]



[2+2+2]

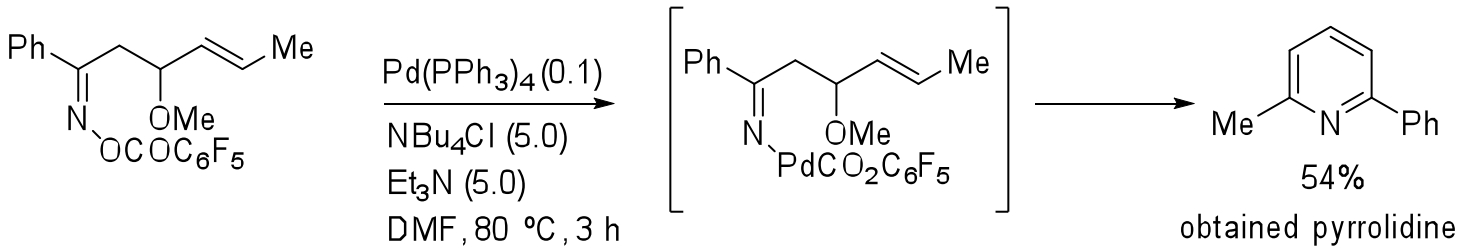


Hantzsch
[2+2+1+1]

While entire books about pyridine synthesis have been written, most major disconnections fall into one of these families.

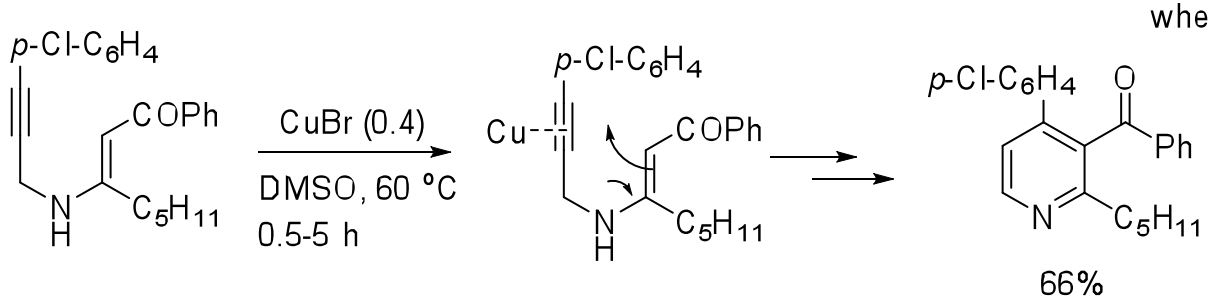
Cycloisomerizations

Single Step, Mild conditions, high degree of regiocontrol possible
High synthetic overhead, generally low degrees of substitution

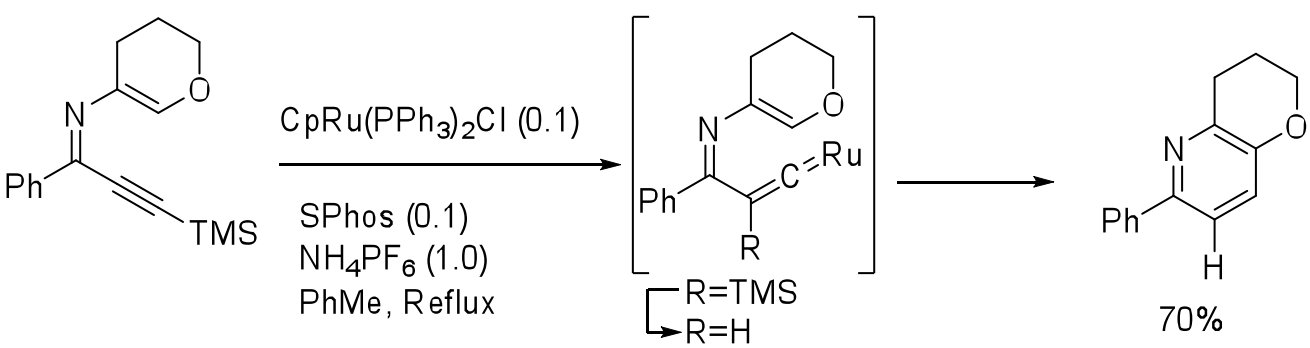


obtained pyrrolidines when dialkyl oximes were tested

Narasaka et. al. *Chem. Lett.* 2001, 526

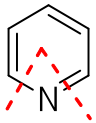


Filisti et. Al. *Org. Lett.*, 2008, 2629

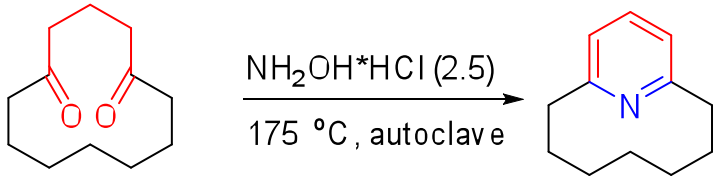


Movassaghi et. Al. *J. Am. Chem. Soc.* 2006, 4592

Condensation of 1,5-dicarbonyls



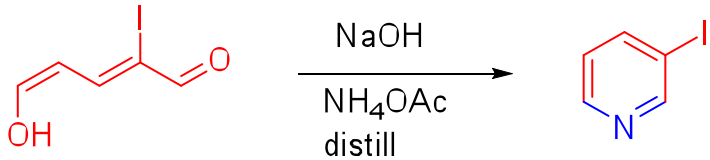
High degree of regiocontrol possible, ammonia equivalents are used
However, starting materials are not readily available, limited substitution patterns, side reactions possible



44%

First synthesis of a pyridocyclophane

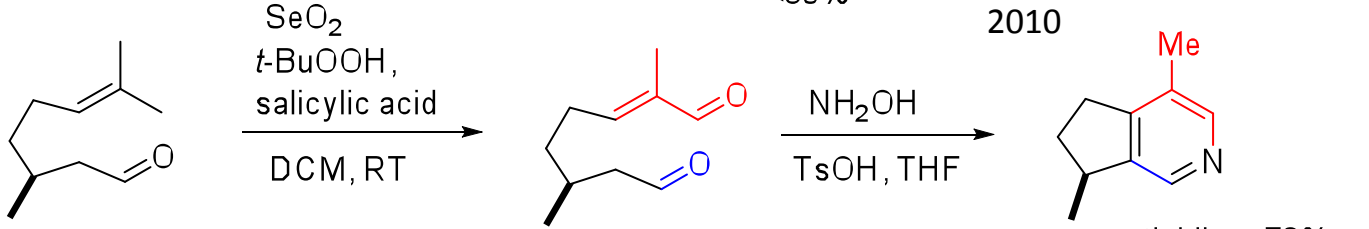
Nozaki et. al. *Bull. Chem. Soc. Jap.*, 1969, 1163



<30%

Starting material is unstable

Baumgarten et. al., Chem. Ber., 1925, 2010



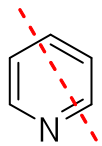
citronellal

40-50%

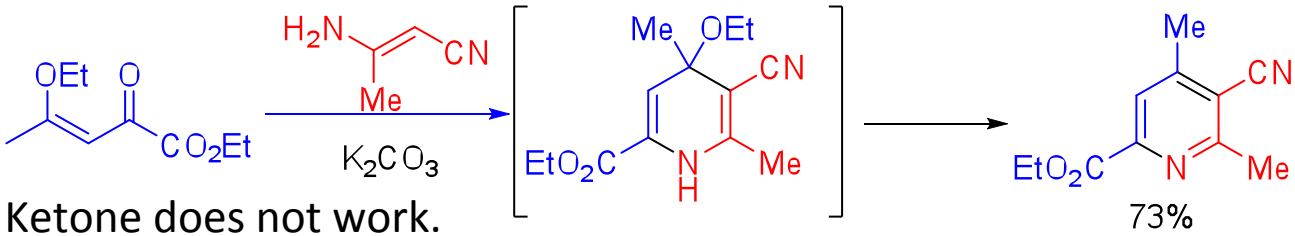
actinidine, 70%
pest control agent

Hofferberth et. al., *Org. Lett.* , 2010, 1408

[3+3] Condensations of enamines and enones



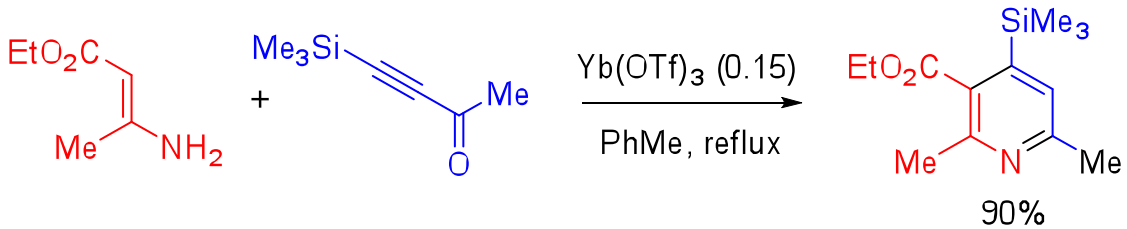
Generally uses preformed enamines.
Either alkynes or β-heteroatomic enones (especially β-amino)
Easy access to tetrasubstituted pyridines.
Workhorse reactions for pyridine synthesis



Ketone does not work.

Guareschi Synthesis

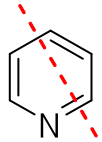
Henecke et. al., *Chem. Ber.* 1949, 36



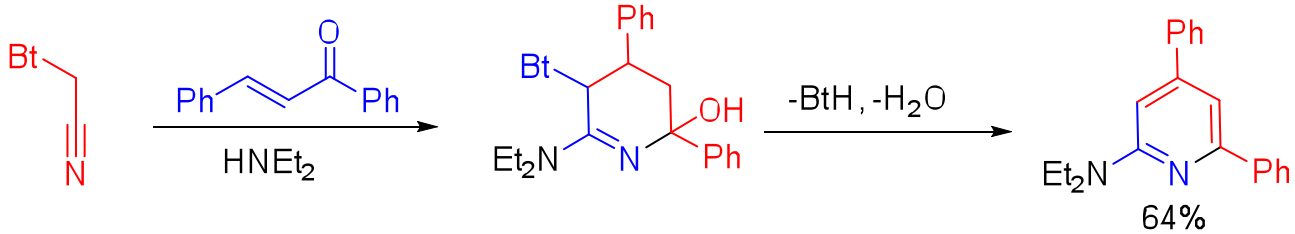
Bohlmann-Rahtz Synthesis

Bagley et. Al. *J. Chem. Soc. Perkin Trans. 1,* 2002, 1663

Alternative C3 Synthons

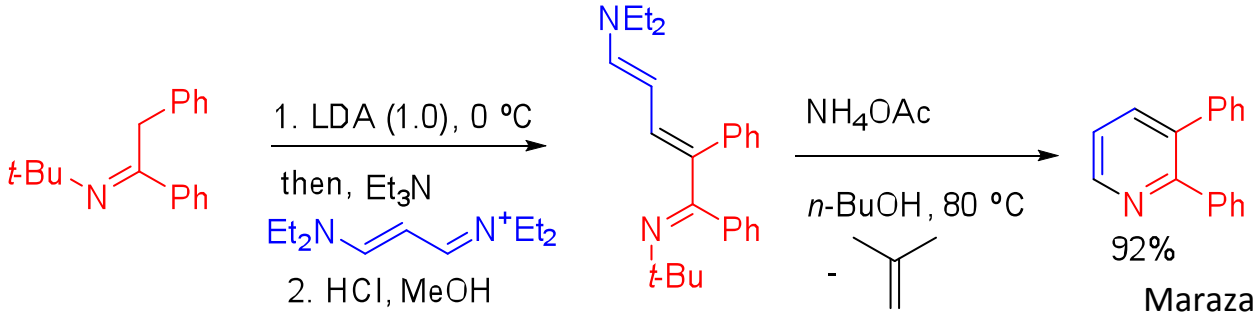


Addition-Elimination to incorporate exogenous amines:
Primarily affords 2,4,6-trisubstituted pyridines



Katritzky et. al., *J. Org. Chem.*, 1997, 6210

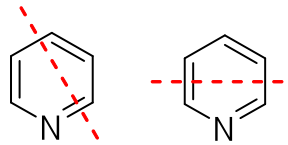
Vinamidine as a C3 synthon for pyridines:



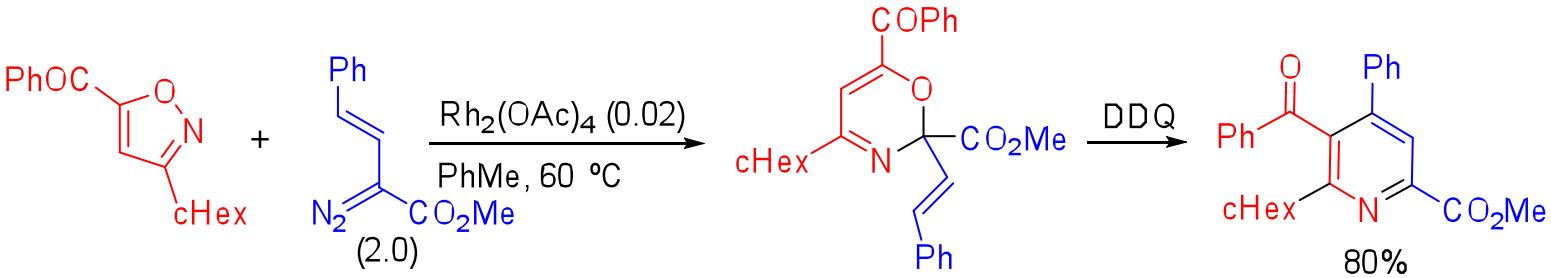
Marazano et. al., *J. Org. Chem.*, 2008, 1169

C3 annulation onto α,α' dihydroimines (ketones) can be accomplished.

[3+3] Reactions that are not condensations

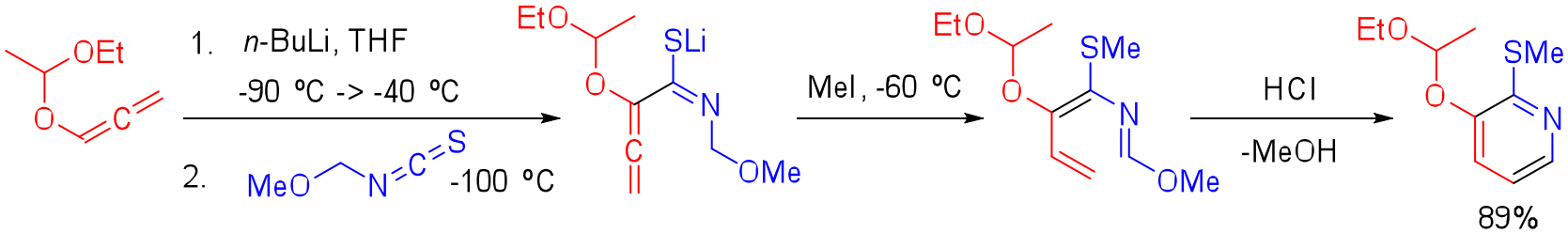


Rhodium-Catalyzed C-H insertion to access 3-carbonyl pyridines



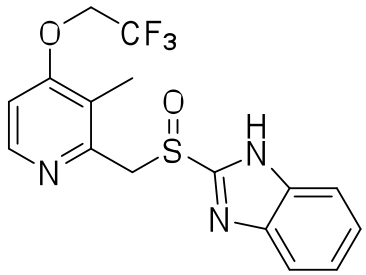
Davies et. al. , *J. Am. Chem. Soc.,* 2008, 8602

Only example of Type B [3+3]:

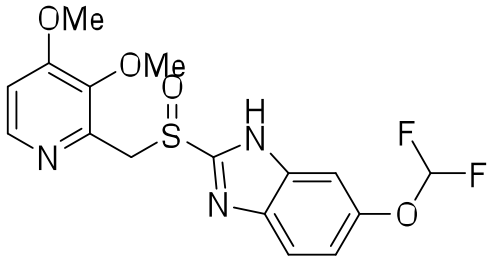


Brandsma et. al. *Tetrahedron Lett.,* 43, 9679

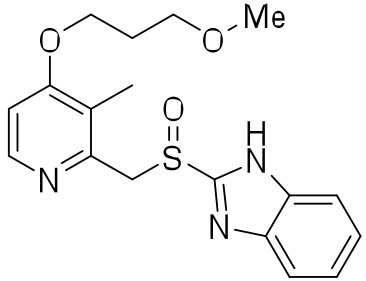
The Synthesis of Lansoprazole (PPI)



lansoprazole

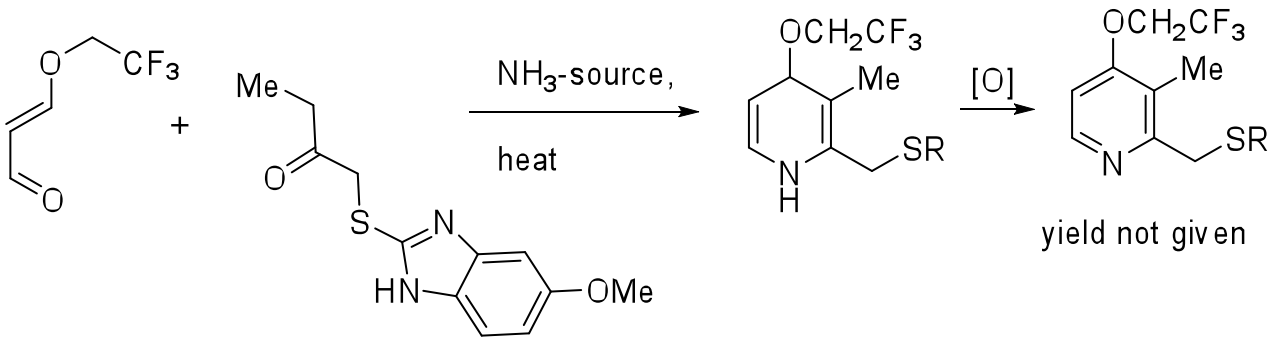


pantoprazole



rabeprazole

Proton-pump inhibitors:
Reduce gastric acid production, prevent heartburn.
One of the top-selling classes of pharmaceuticals
Synthesis:

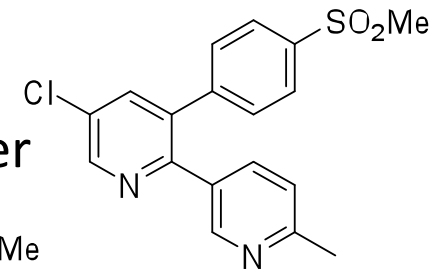


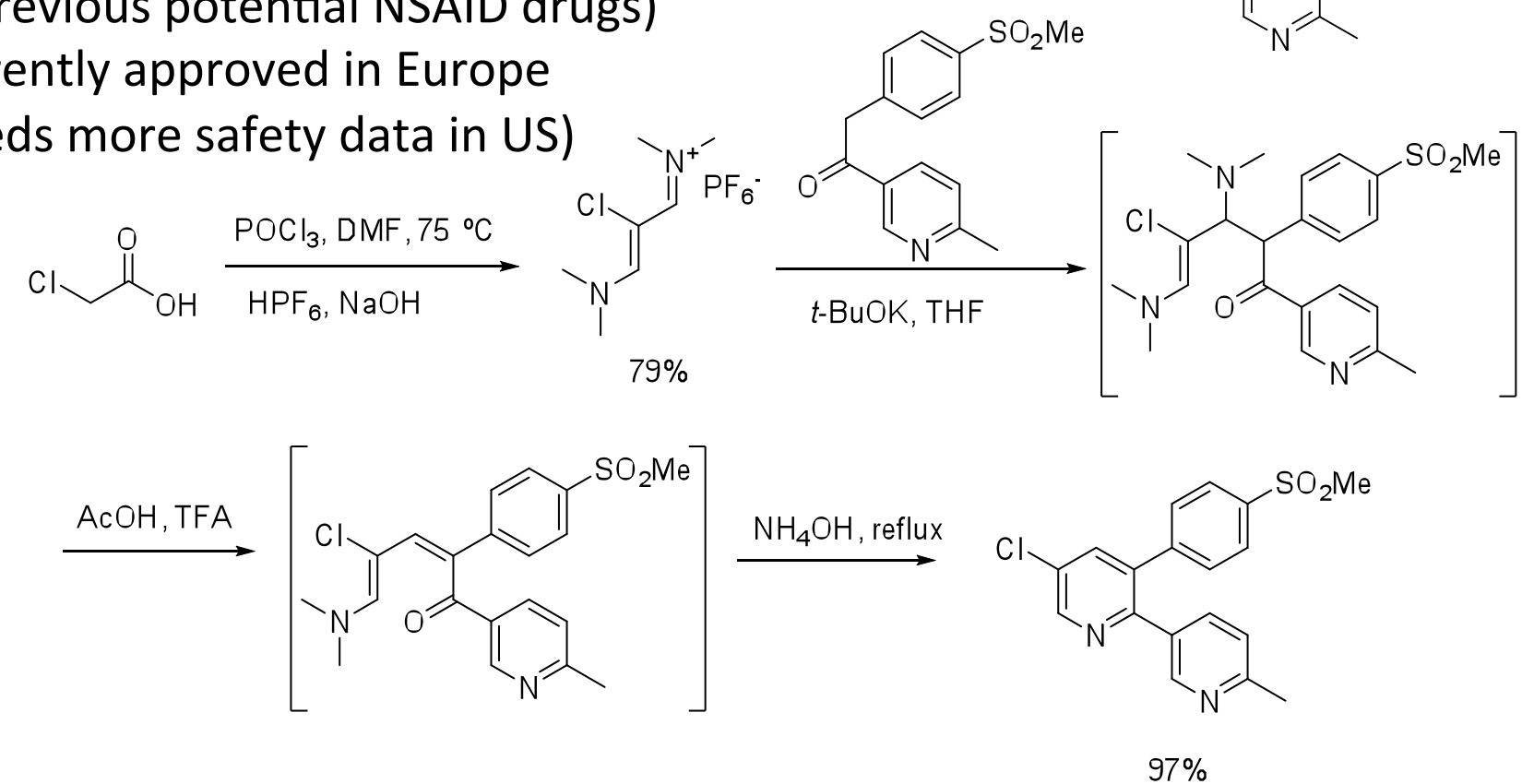
yield not given

Baxendale et. al., *Beilstein J. Org. Chem.* 2013, 9, 2265

Synthesis of Etoricoxib

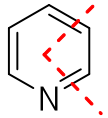
NSAID
Highly selective for COX-2 over COX-1 (sunk a number of previous potential NSAID drugs)
Currently approved in Europe
(needs more safety data in US)



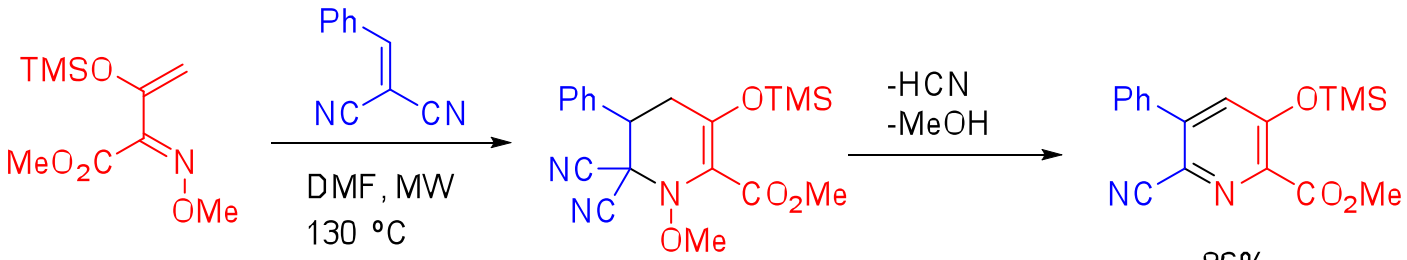


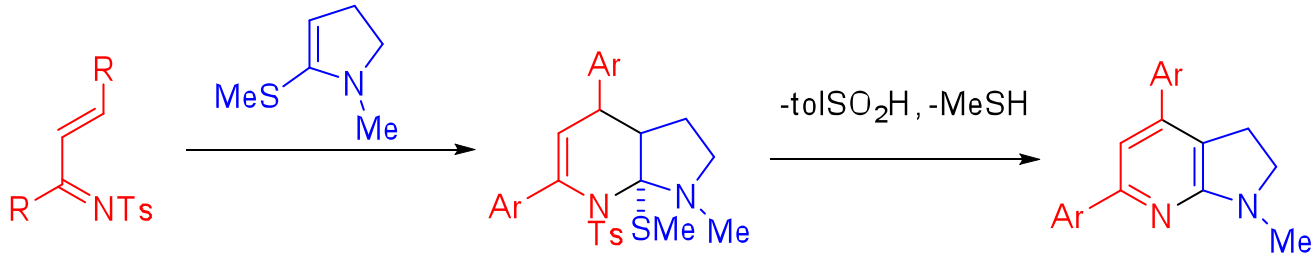
Baxendale et. al., *Beilstein J. Org. Chem.* 2013, 9, 2265

4+2 Type A



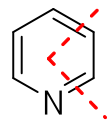
Diels-Alder-like Reactions
Starting materials easy to make from enones.
Thermodynamics does not favor the formation of tetrahydropyridines, therefore a driving force is necessary.

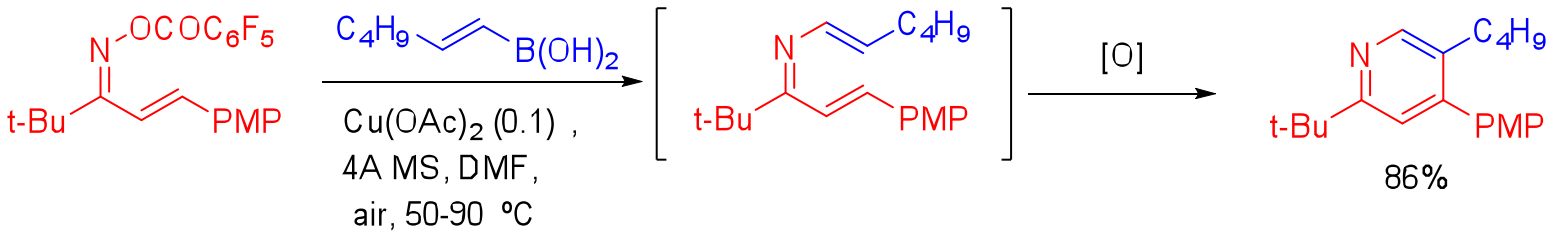




Lu et. al. *J. Am. Chem. Soc.*, 130, 13219
Muller et. Al. *Eur. J. Org. Chem.* 2005, 1834

4+2 Type A – CC/ Electrocyclization



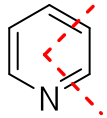


Oximes can be coupled to vinylboranes to afford 3-azatrienes.

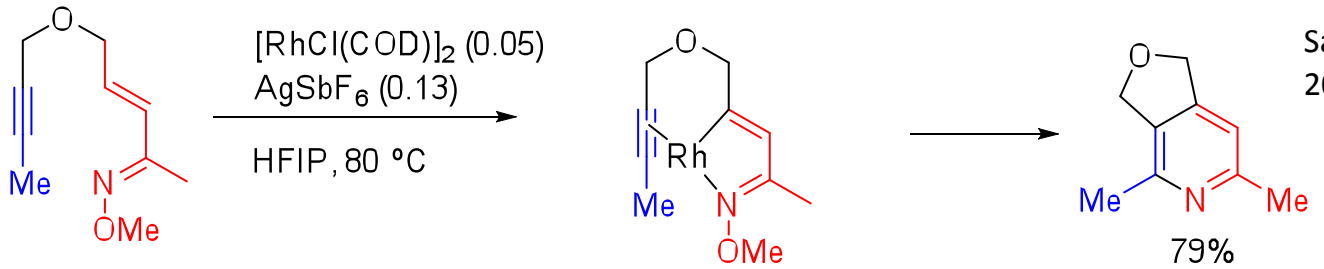
Electrocyclization followed by oxidation leads to the desired pyridines.

Liebeskind et. Al., *J. Am. Chem. Soc.* 2008, 130, 6918

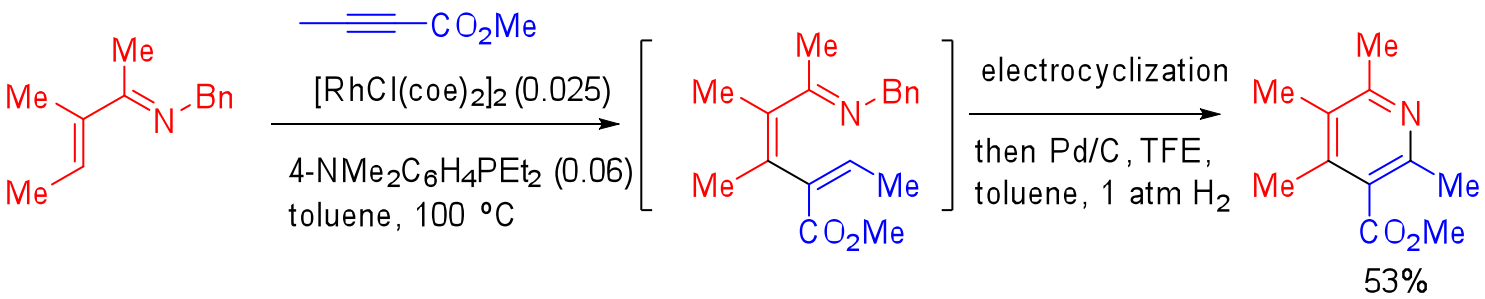
Electrocyclizations for [4+2]



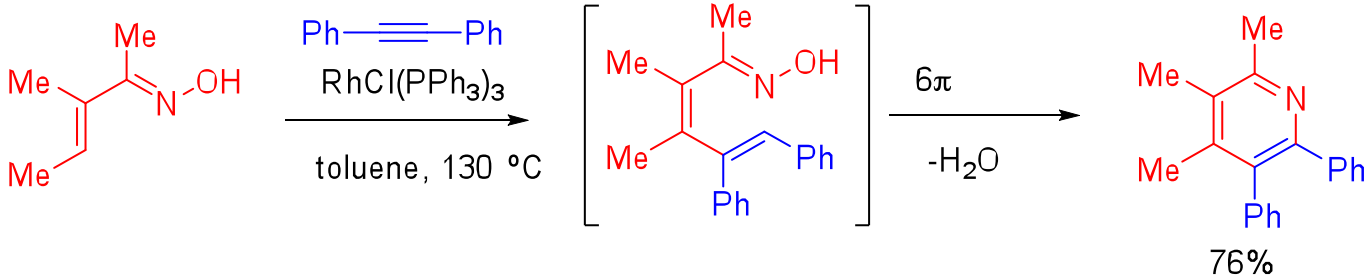
C-H activation followed by electrocyclization
Easy formation of highly substituted pyridine cores.
Simple acetylenes can be used, but regioselectivity can be a problem.



Saito et. al. *Tetrahedron Lett.*, 2007, 48, 6852

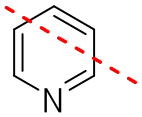


Ellman et. al. , *J. Am. Chem. Soc.*, 2008, 3645

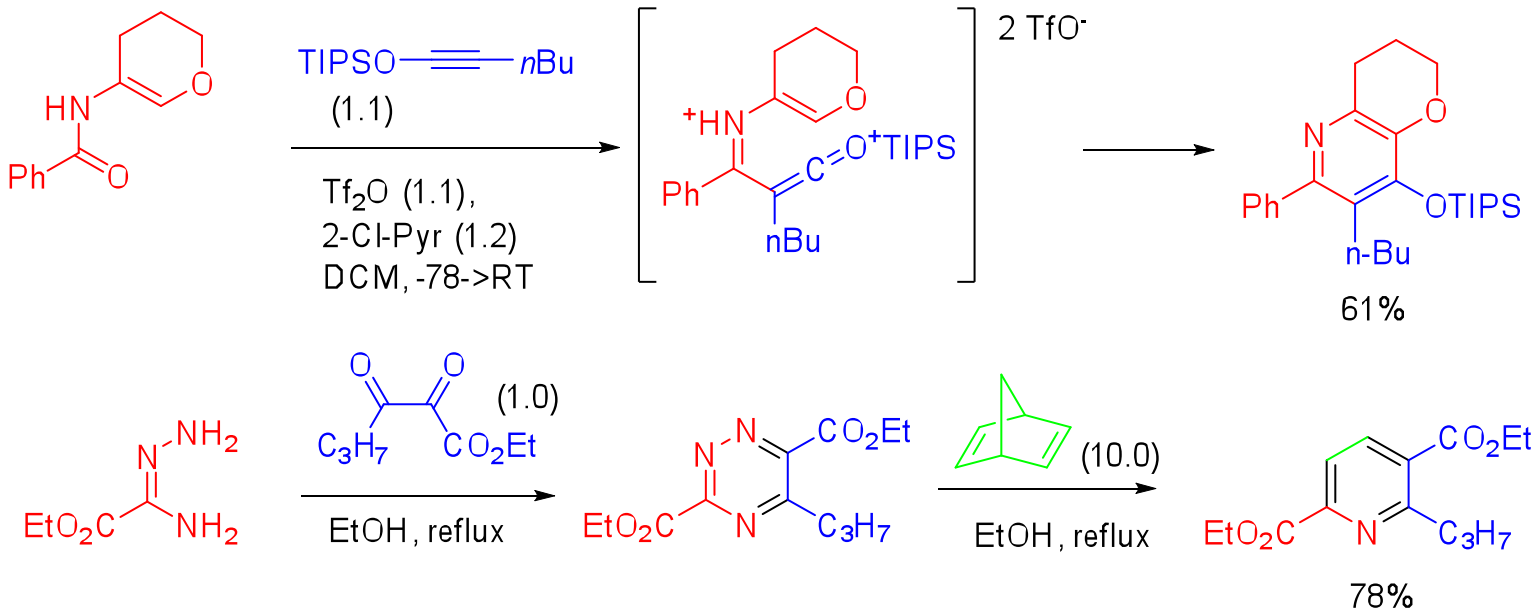


Cheng et. al. *J. Org. Chem.*, 2009, 9359

4+2 Type B – Vinylimine synthons

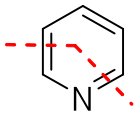


Less prevalent, but garnering more interest.
High degrees of substitution can be achieved.
Fairly mild conditions.

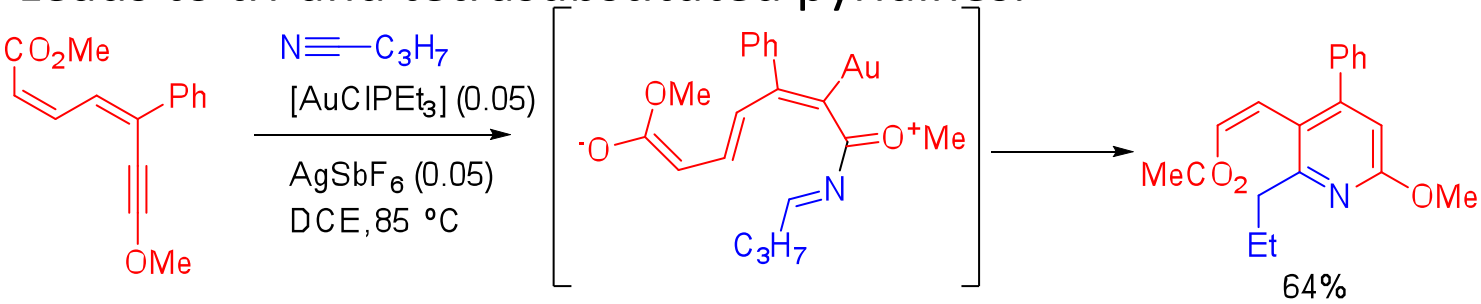


Movassaghi et. al. *J. Am. Chem. Soc.,* 2007, 10096
Stanforth et. al., *Tetrahedron*, 2004, 8893

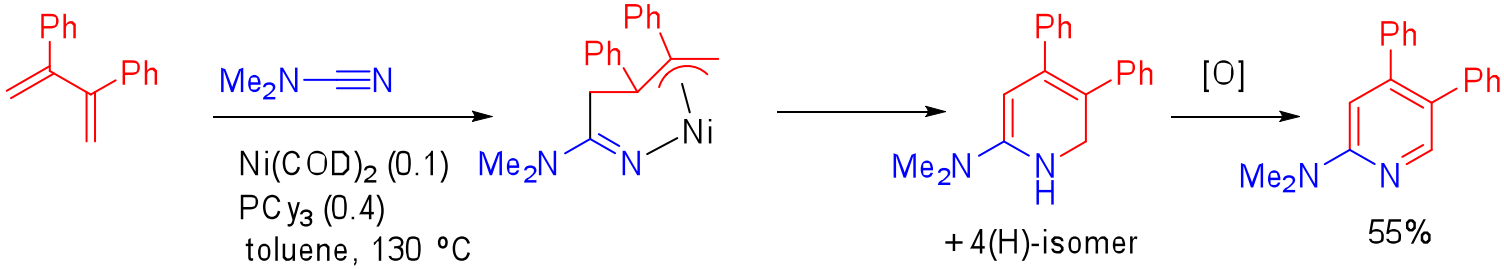
4+2 Type C : Nitriles as dienophiles



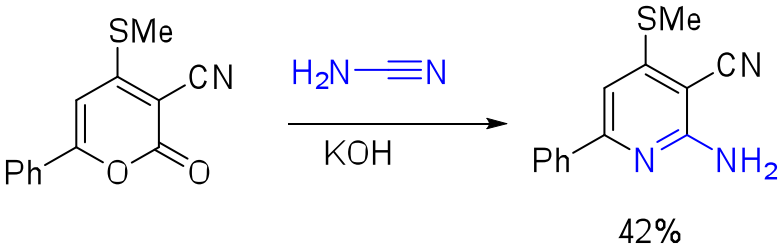
Reaction of a diene or an enyne with a nitrile.
Generally uses a TM catalyst.
Leads to tri-and tetrasubstituted pyridines.



Barluenga et. al., *J. Am. Chem. Soc.* 2008, 2764

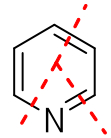


Ogoshi et. al., *J. Am. Chem. Soc.* 2011, 18018



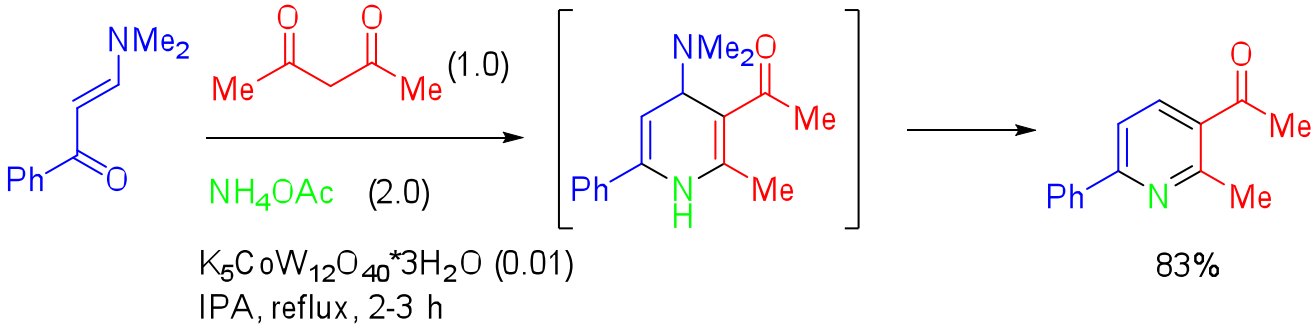
Goel et. al., *J. Org. Chem.*, 2003, 2983

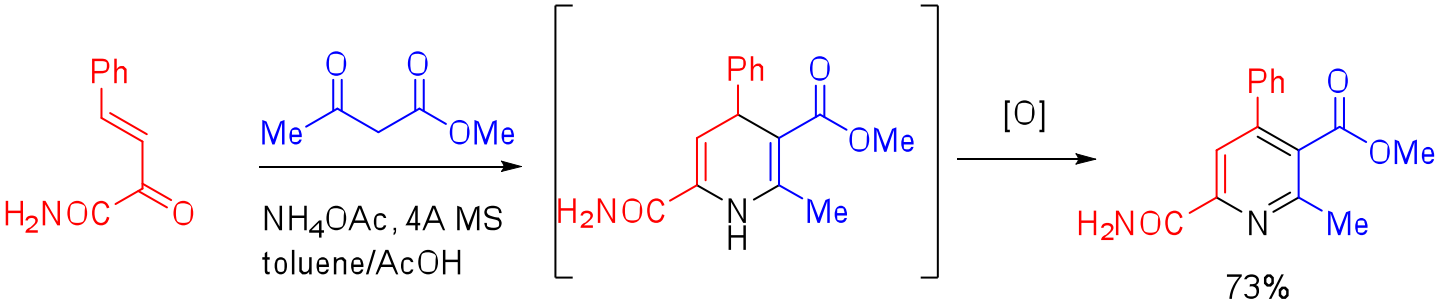
[3+2+1] Cycloadditions



[3+2+1]

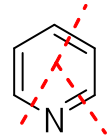
Extremely versatile reaction.
Combination of enones and ketones with ammonium acetate.
Catalyzed by Lewis acids.
Disadvantage: Difficult to get 3,5-substitution.



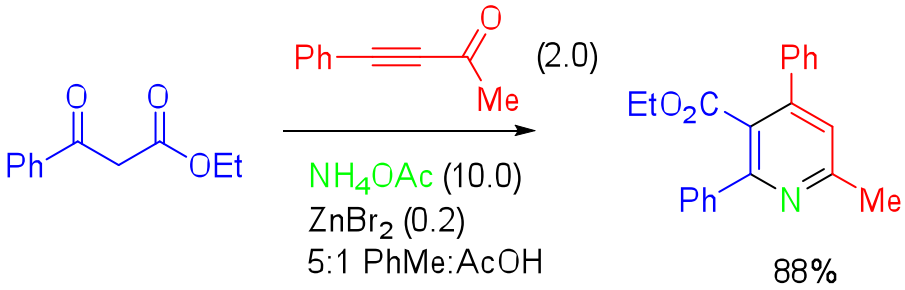


Kantevari et. al. T*etrahedron*, 2007, 13024
Rodriguez et. al. *Chem. Eur. J.*, 2009, 12945

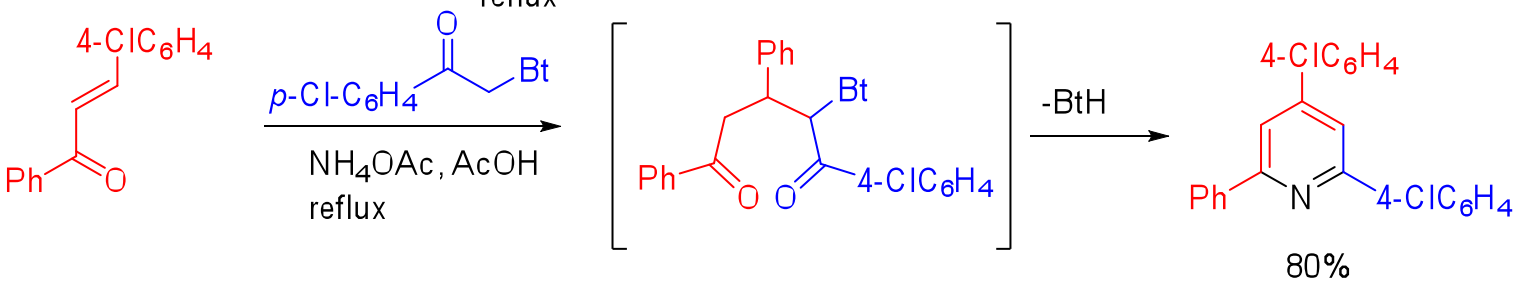
[3+2+1] Cycloadditions



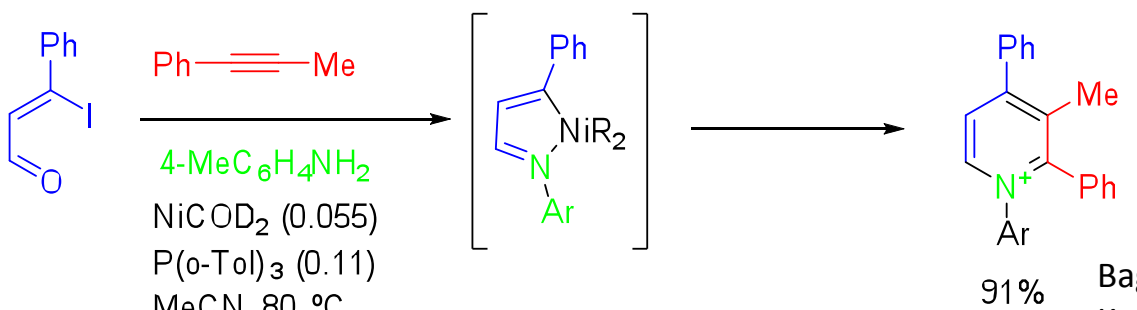
[3+2+1]



Alkynes can also be used (3-component Bohlmann-Rahtz)



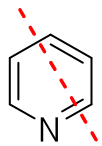
Bt serves as a LG during the final condensation

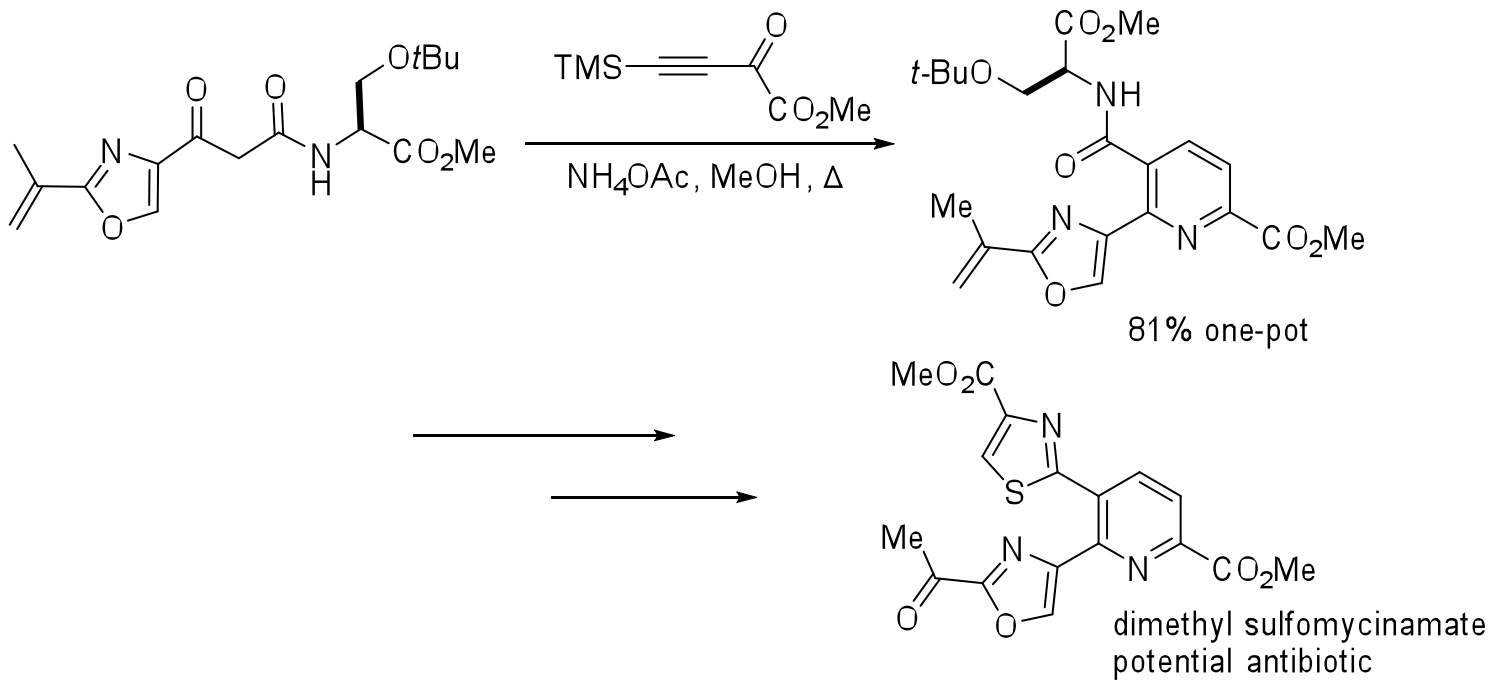


Arylated pyridines can be obtained from anilines

Bagley et. al. *C hem. Comm.* 2002, 1682
Katritzky et. al. *Synthesis* 1999, 2118
Cheng et. al. *Chem. Eur. J.* , 2009, 10727

Applications of the Bohlmann Rahtz Reaction

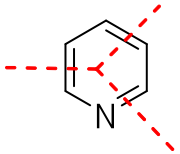




Large class of antibiotics with thiazole-pyridine-oxazole ring system
Bohlmann-Rahtz type reaction was used to access core
Optimization allowed enamine formation to be done in situ.

Bagley et. al. *J. Org. Chem.*, 2005, 70, 1389

2+2+2 Cycloadditions



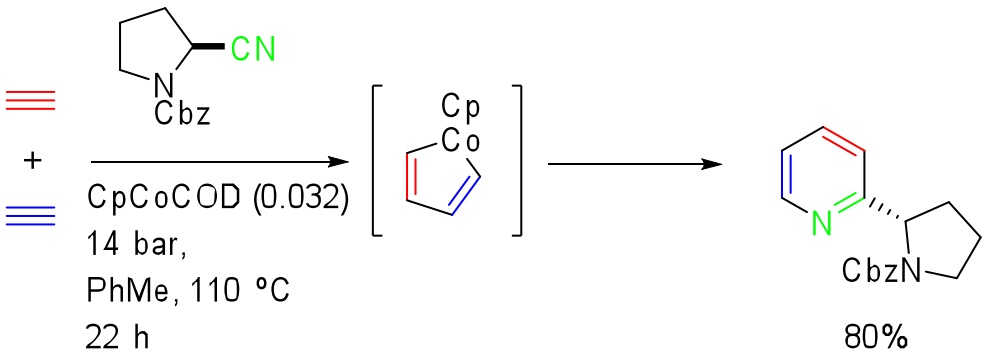
Extremely simple starting materials

Rapid increase in complexity

Suitable for automation/high throughput synthesis

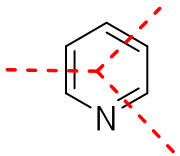
Another workhorse reaction

Disadvantage: Poor regioselectivity, problematic purification

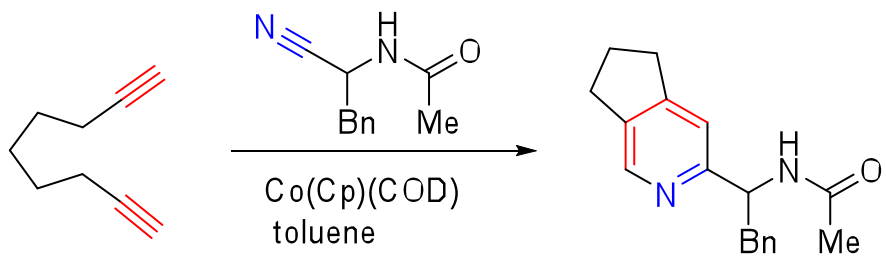


Chelucci et. al. *Synthesis,* 1990, 1121

Tethered [2+2+2]

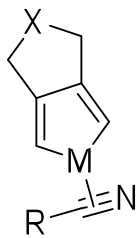


Attempts to solve regioselectivity issue.
Complexity is built into starting material.
Affords fused, semi-saturated ring systems, which can be further functionalized.

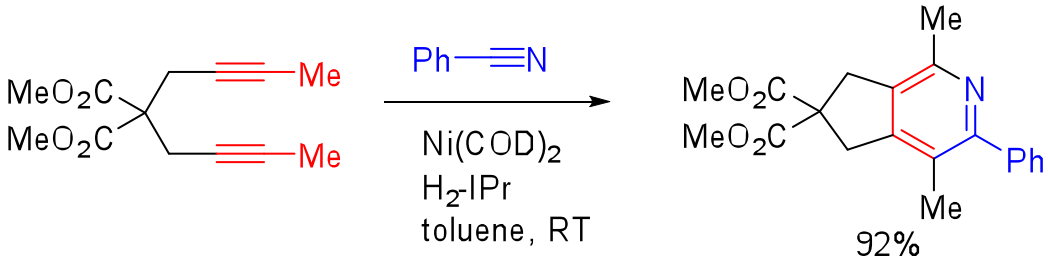


64%

Heller et. al. *J. Org. Chem.,* 2003, 9221



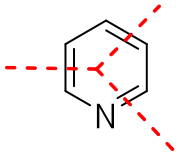
Common intermediate



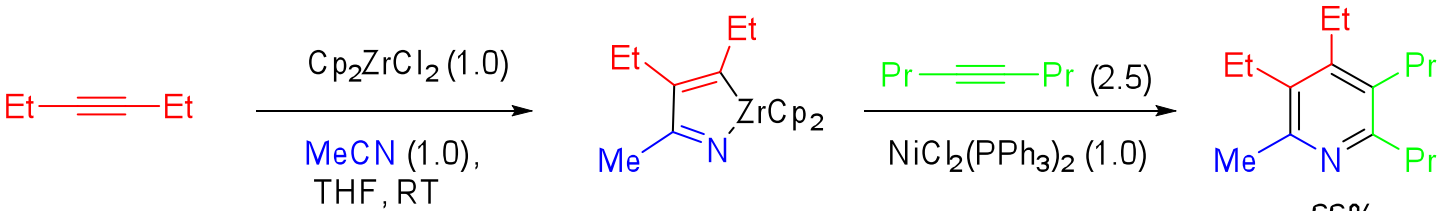
92%

Louie et. al. *J. Am. Chem. Soc.*, 2005, 5030

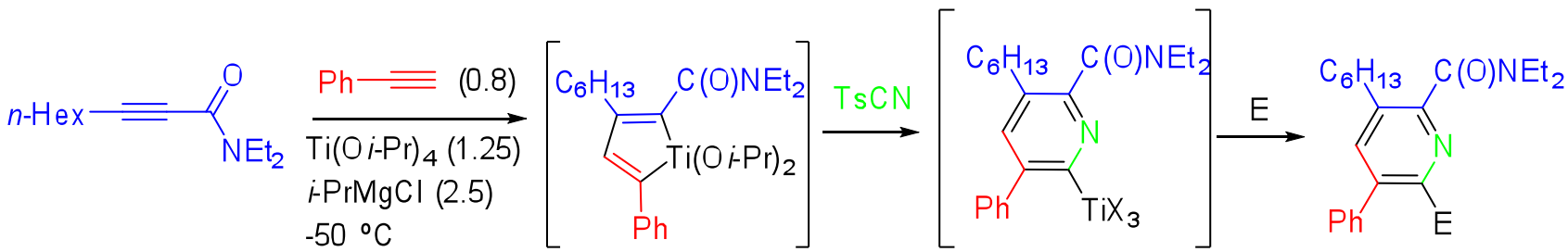
Directed [2+2+2]



Stoichiometric transition metals used.
Strong bias possible. Can prepare highly functionalized pyridines
Organometallic reagents suggest less FG tolerance.



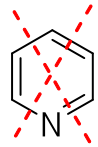
66%



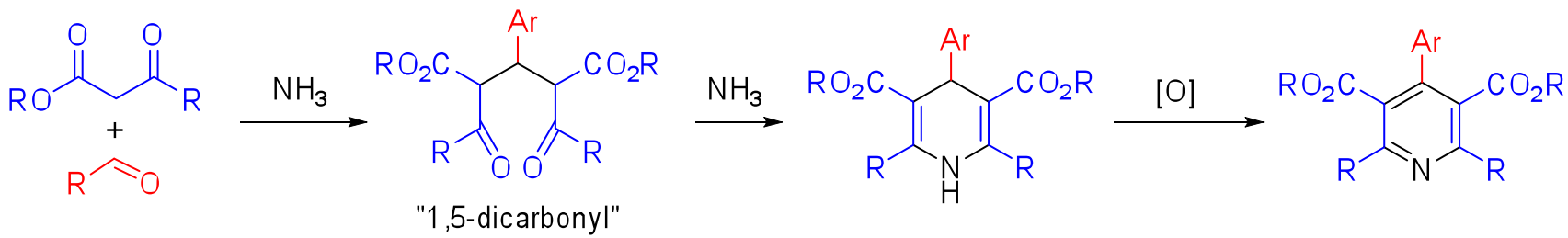
E= H, 70%
E= I, 70%
E= allyl, 52%
(using $Li_2CuCNCl_2$)

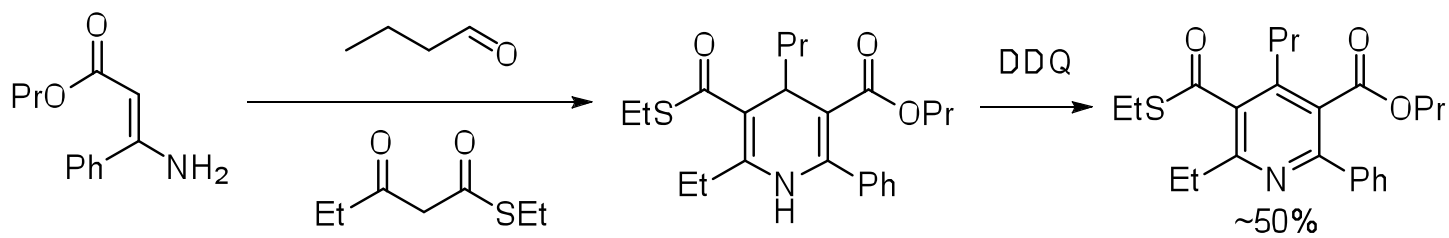
Takahashi et. al. *J. Am. Chem. Soc.* 2000, 4994
Urabe et. al. *J. Am. Chem. Soc.* 2005, 7774

Hantzsch Pyridine Synthesis



Classical method of pyridine synthesis
Easy access to highly substituted pyridines.
3,5-EWG-4-aryl motif is common. 4-alkyl is also possible, but rarer.

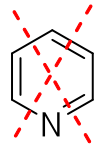


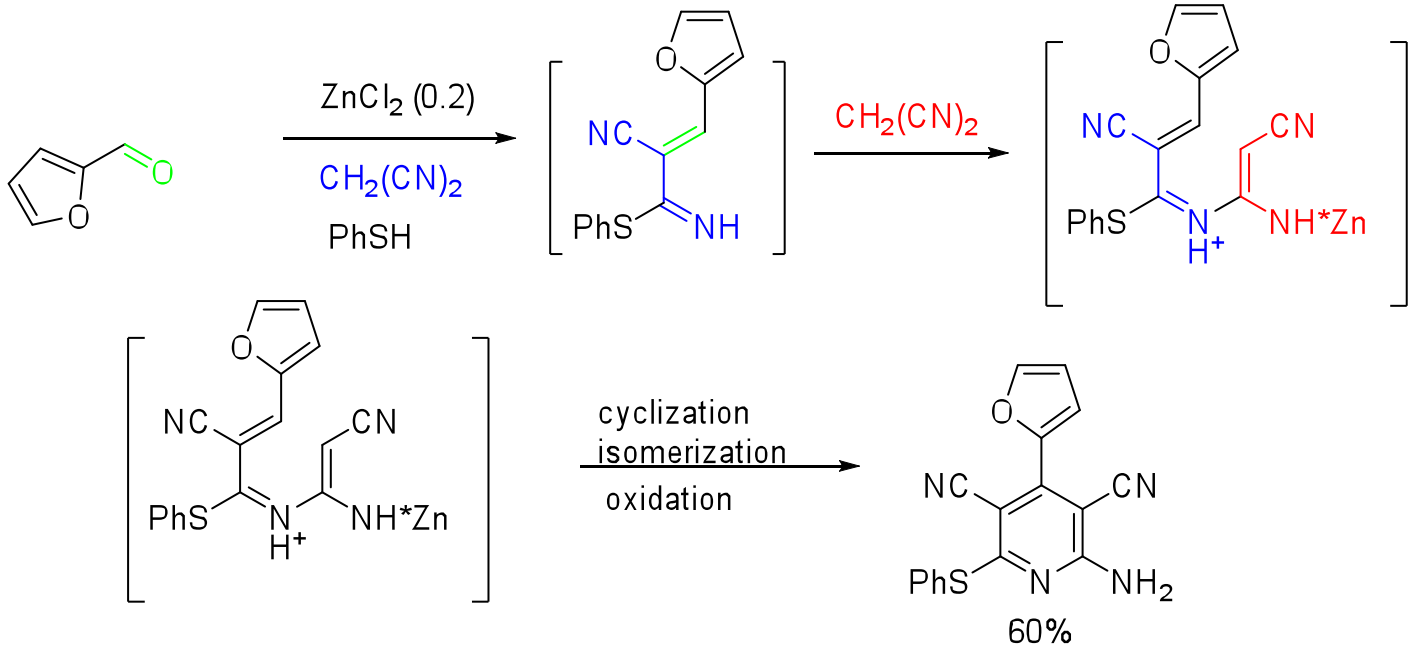


Human A_3 agonist
7400x selective over A_1/A_2

Jacobson et. al. *J. Med. Chem.,* 1999, 706

Four-Component Pyridine Synthesis



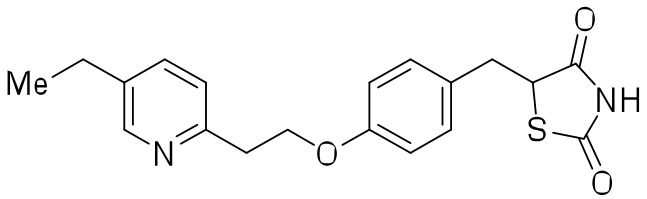


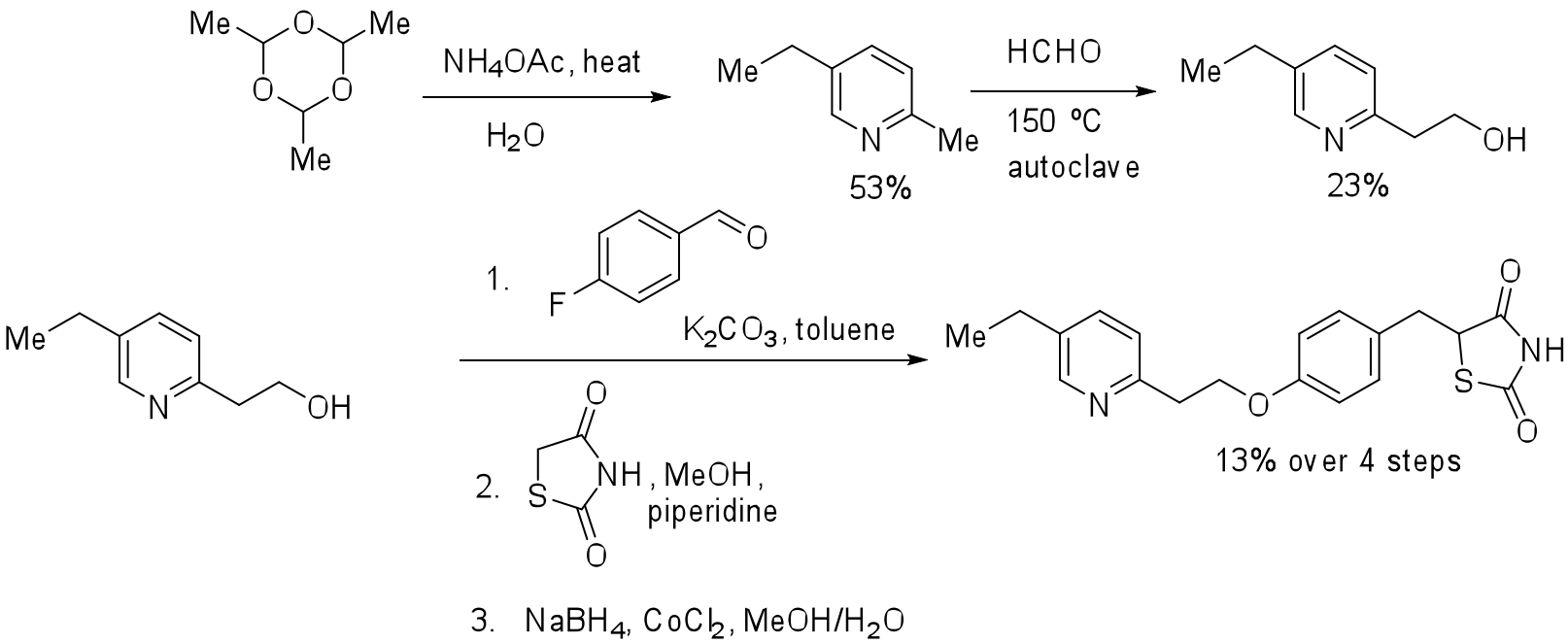
Entire pyridine core is constructed around an aldehyde.
Enolizable aldehydes work.
Very similar to Hantzsch methodology.
Malononitrile/PhSH can be replaced by ketone/ammonium acetate.

Sridhar et. al. *Tetrahedron Lett.,* 2009, 3897
Wang et. al. *Tetrahedron Lett.* 2011, 509

PPAR-Gamma Receptors

Type-2 Diabetes Drug
Activate PPAR-gamma receptor
Controls metabolism of carbohydrates and fatty acids

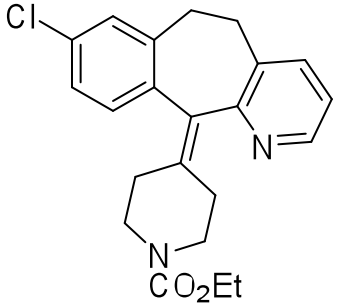




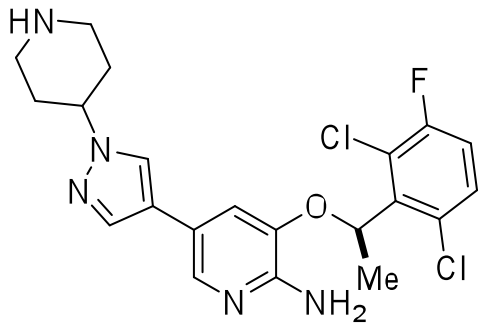
Pyridine core is ultimately derived from acetaldehyde and ammonium acetate.

Baxendale et. al., *Beilstein J. Org. Chem.* 2013, 9, 2265

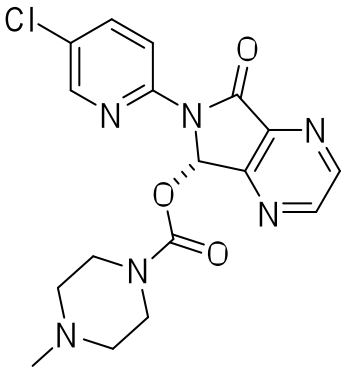
Group Discussion



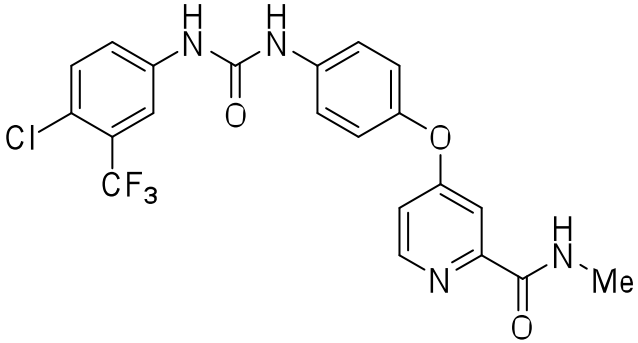
Loratidine
(Claritin, Allergy)



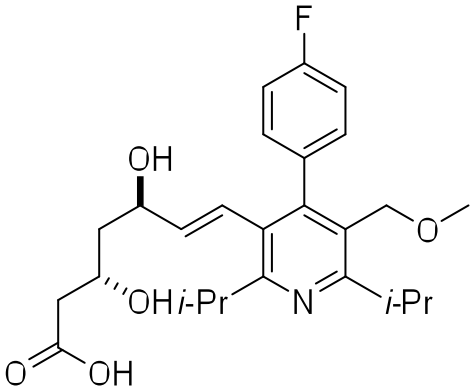
Crizotinib
(Xalkori, Lung Cancer)



Eszopiclone
(Lunesta, Insomnia)



Sorafenib
(Nevaxar, Renal Cell carcinoma)



Cerivastatin
(Baycol, withdrawn statin)

How would you synthesize these?

Conclusions

- Pyridines are one of the most common heterocycles in bioactive compounds
- De novo methods generally rely on condensation or electrocyclization chemistry
- “Best” procedure usually depends on desired substitution pattern. Multiple disconnections of the same molecule are possible.
- Novel methodologies are still being developed to address FG compatibilities, milder reaction conditions

Main Reviews

- Henry G. D., *Tetrahedron*, 2004, 6043
- Hill, M.D., *Chem. Eur. J.*, 2010, 12052
- Baxendale et. al., *Beilstein J. Org. Chem.* 2013, 9, 2265
- Gevorgyan, V. et .al. *Chem. Rev.*, 2013, 3084