One-Pot Synthesis of Highly Functionalized Pyridines via a Rhodium Carbenoid Induced Ring Expansion of Isoxazoles

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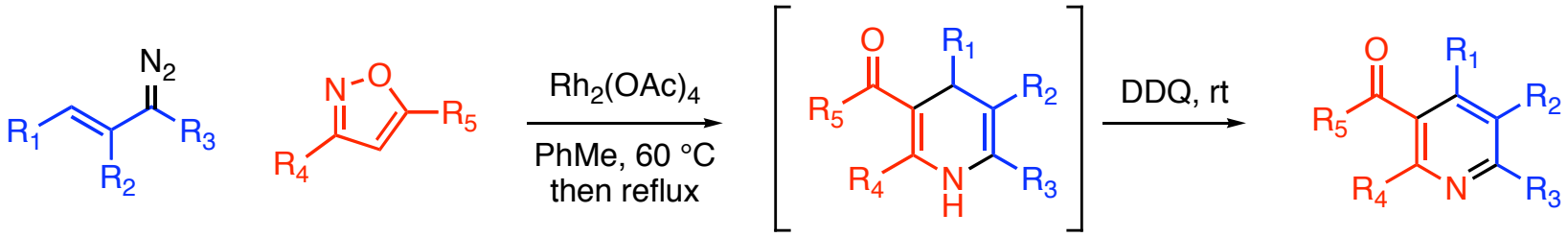
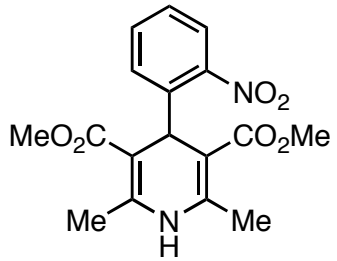


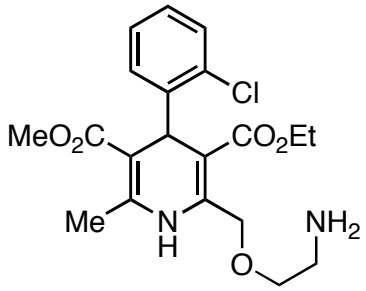
Christopher Rosenker
Wipf Group - Current Literature
June 28, 2008

Biological Importance

1,4-dihydropyridines have been used as calcium channel modulators

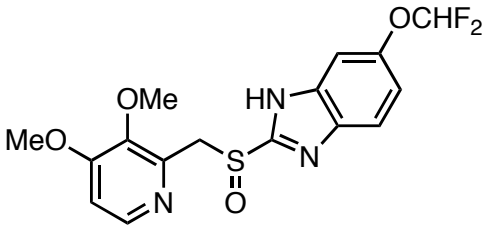


Nifedipine (generic)
calcium channel blocker used
to treat hypertension

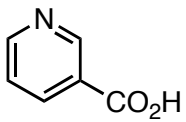


Norvasc (Pfizer)
calcium channel blocker used
to treat hypertension

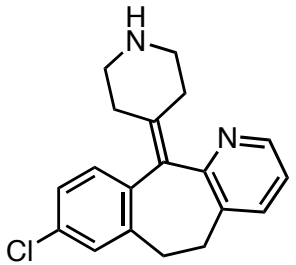
The pyridine nucleus is found in over 7000 drugs and many agrochemicals



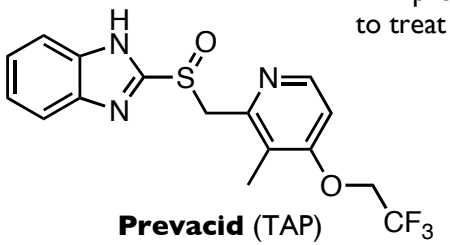
Protonix (Wyeth)
proton pump inhibitor
to treat esophagus inflammation
and erosion



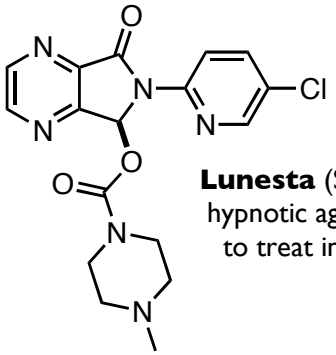
Niacin
nicotinic acid or vitamin B3



Clarinex (Schering-Plough)
antihistamine used to
treat allergies



Prevacid (TAP)
proton pump inhibitor
gastric reflux disease



Lunesta (Sepracor)
hypnotic agent used
to treat insomnia

Top 200 Brand name and Generic drugs in 2006
Cornell University Njardarson Group

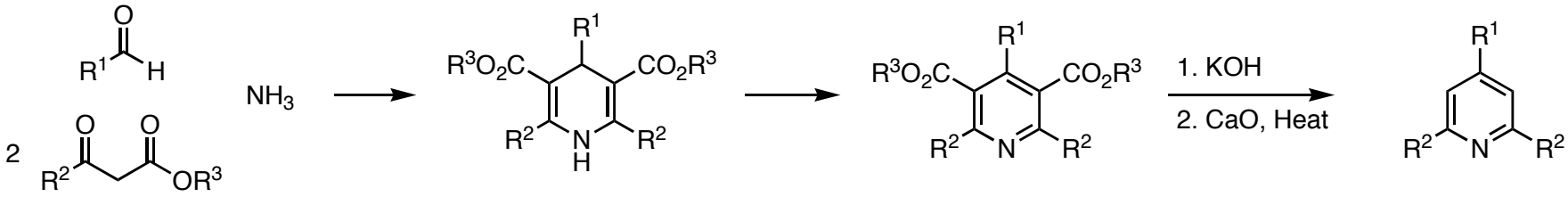
Henry, G. D. *Tetrahedron*. *60*. **2004**. 6043.

Pyridines

Körner (1869) and Dewar (1871) independently proposed the correct structure of pyridine

First synthesis by Ramsay in 1876 from [2+2+2] cycloaddition of acetylene and hydrogen cyanide

In 1882, Hantzsch published the most significant approach for the synthesis of pyridines

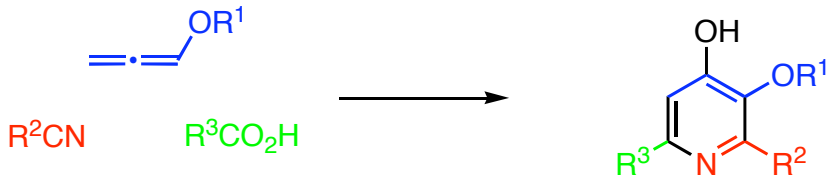


The challenge lies in synthesis of non-symmetrically substituted systems

Henry, G. D. *Tetrahedron*. *60*. **2004**. 6043.

Non-transition metal syntheses of pyridines

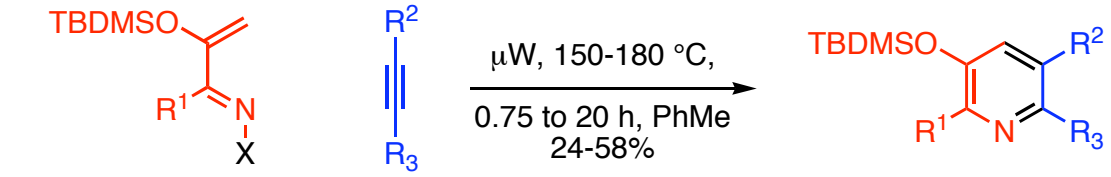
Reissig: three-component synthesis



R1: Bn, $(CH_2)_2$TMS, *p*-OMe Bn
R2: R3: alkyl, aryl

Reissig, H. *et al. Organic Letters*. *9*. **2007**. 5541.

Moody: hetero-Diels-Alder cycloaddion



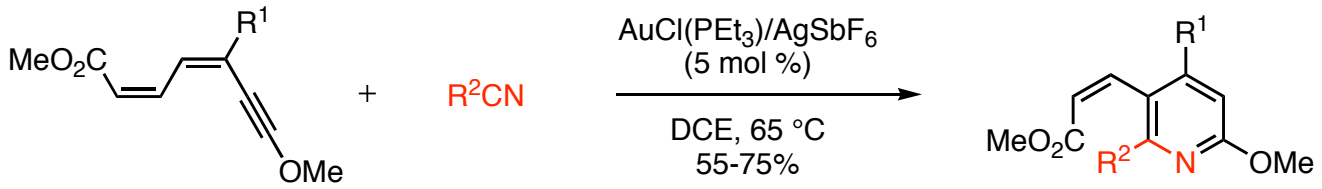
X: OTBDMS, NMe_2 piperidinyl, NMeCbz, phthalimido

R1: Me, CO_2Me
R2: H, CO_2Me
R3: CO_2Me

Moody, C. J. *et al. Tetrahedron*. *62*. **2006**. 5454.

Synthesis via transition metal catalyzed cycloaddition reactions

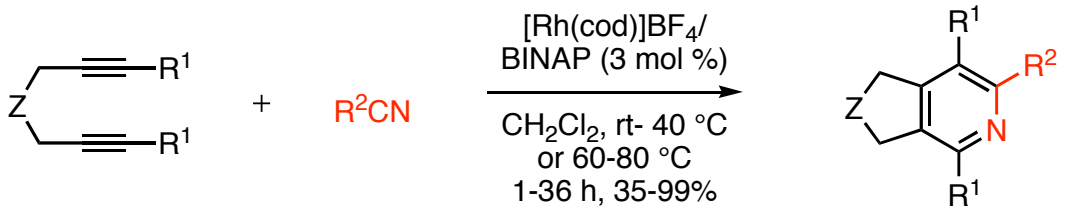
Barluenga: gold catalyzed hetero-dehdro-Diels-Alder cycloaddition



R^1:R^2: alkyl, vinyl, aryl

Barluenga, J. *et al. Journal of the American Chemical Society*. *130*. **2008**. 2764.

Tanaka: cationic rhodium catalyzed alkyne-nitrile [2+2+2] cycloaddition

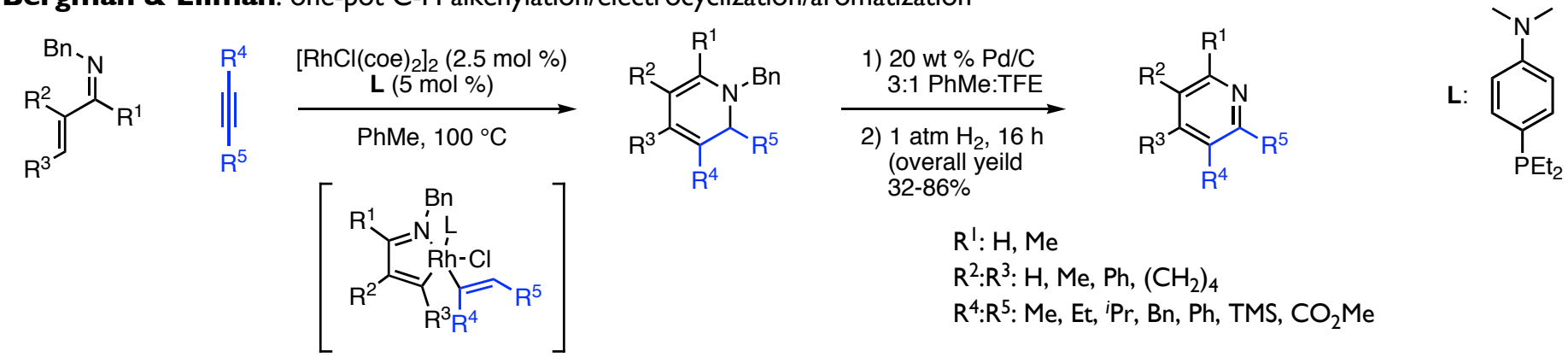


R^1: Me, Et, H
Z: $C(CO_2Me)_2$, $C(CH_2OMe)_2$, NTs, $O,(CH_2)_2$, $(CH_2)_3$
R^2: CO_2Et, COPh, Ac, Ph, Me, Ts, SMe, morpholine

Tanaka, K. *et al.* *European Journal of Organic Chemistry*. **2006**. 3917.

Pyridine syntheses by electrocyclizations of azatrienes

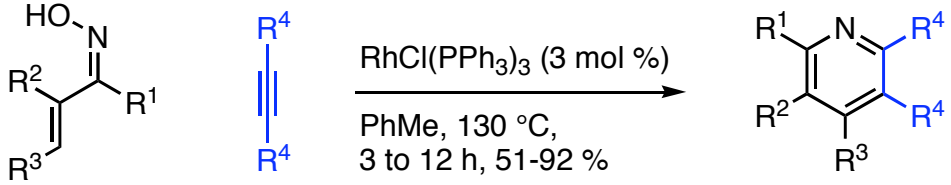
Bergman & Ellman: one-pot C-H alkenylation/electrocyclization/aromatization



R^1: H, Me
R^2:R^3: H, Me, Ph, $(CH_2)_4$
R^4:R^5: Me, Et, ^{i}Pr, Bn, Ph, TMS, CO_2Me

Bergman, R. G. *et al. Journal of the American Chemical Society. 130.* **2008**. 3645

Cheng: C-H activation of α,β-unsaturated ketoxime

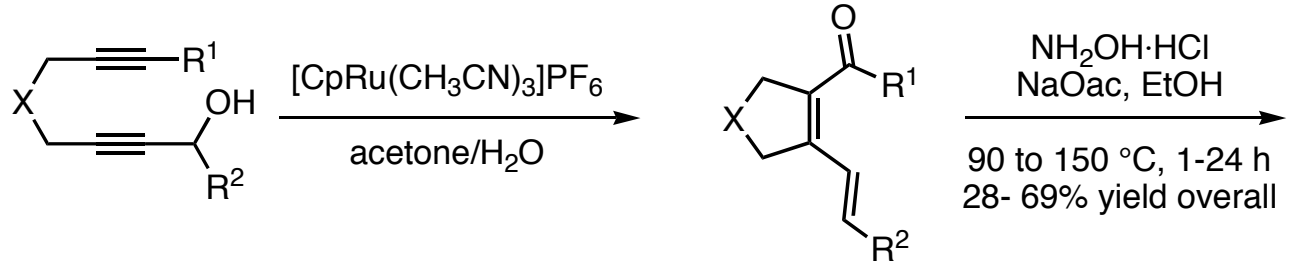


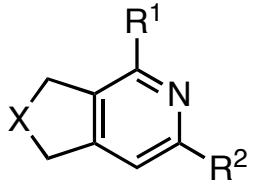
R^1: alkyl
R^2:R^3: alkyl, aryl, or ring
R^4: Ph, Th, Alkyl, TMS, H

Cheng, C. *et al. Organic Letters. 10.* **2008**. 325.

Pyridine syntheses by electrocyclizations of azatrienes

Trost: cycloisomerization then azatriene formation





R^1: H, Me

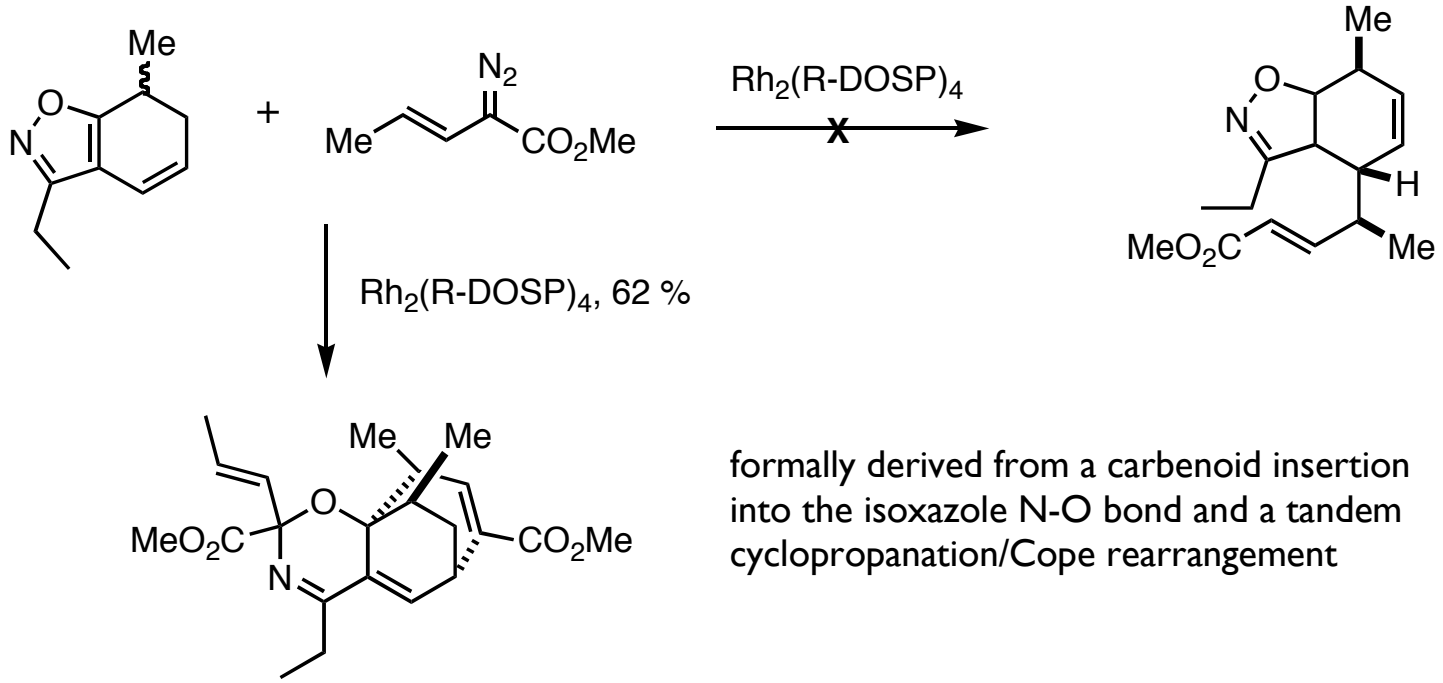
R^2: ^{i}Pr, Ph, Et, Me

X: $C(CO_2Me)_2$, NTs, O, $(CH_2)_2$
$C(CH_2OBn)_2$, $C(CH_2OMe)_2$

Trost, B. M. *et al. Organic Letters*. *9*. **2007**. 1473.

Isoxazole ring expansion

Discovered by Davies during the synthesis of elisabethin C, utilizing their enantiodivergent combined C-H activation/Cope rearrangement methodology

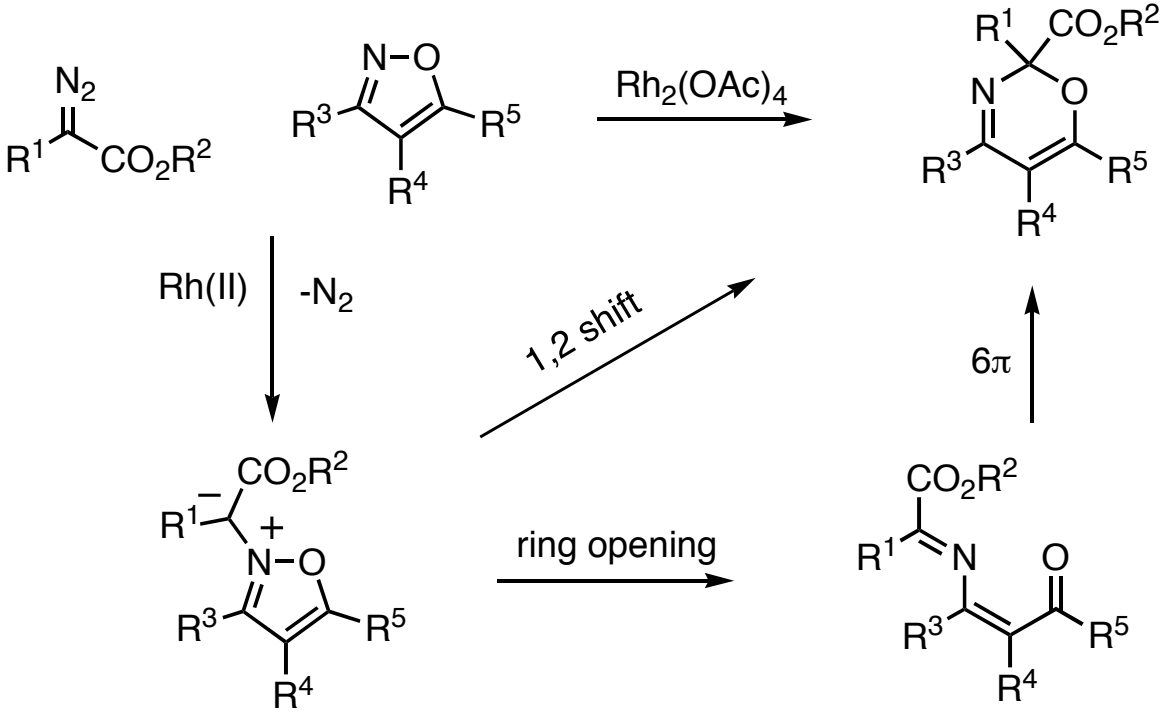


formally derived from a carbenoid insertion into the isoxazole N-O bond and a tandem cyclopropanation/Cope rearrangement

Manning, J. R.; Davies H. M. L. *Tetrahedron*. *64*. **2008**. 6901.

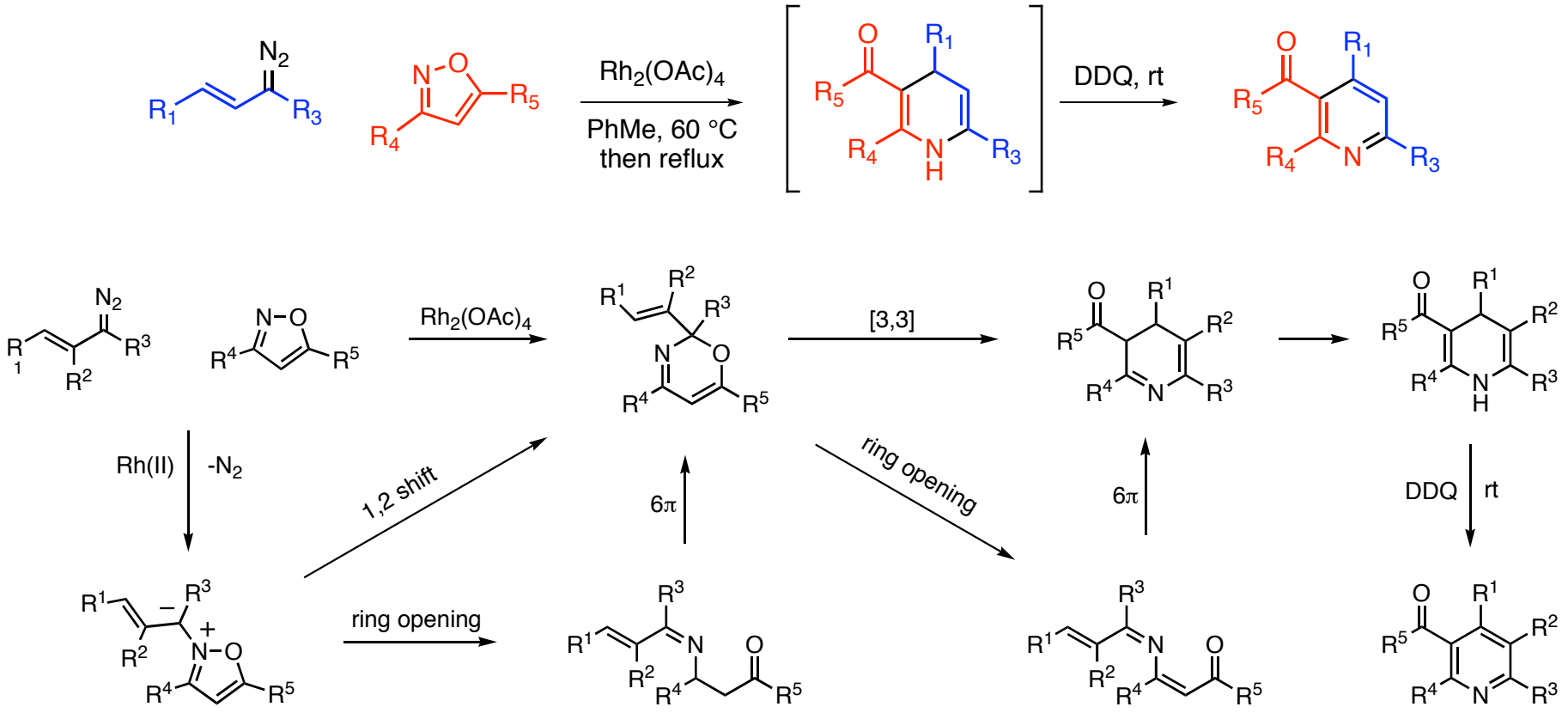
Mechanism of isoxazole ring expansion

Proposed to go through an isoxazolium ylide intermediate then process though either a 1,2 shift or open and undergo a 6π-electrocyclization



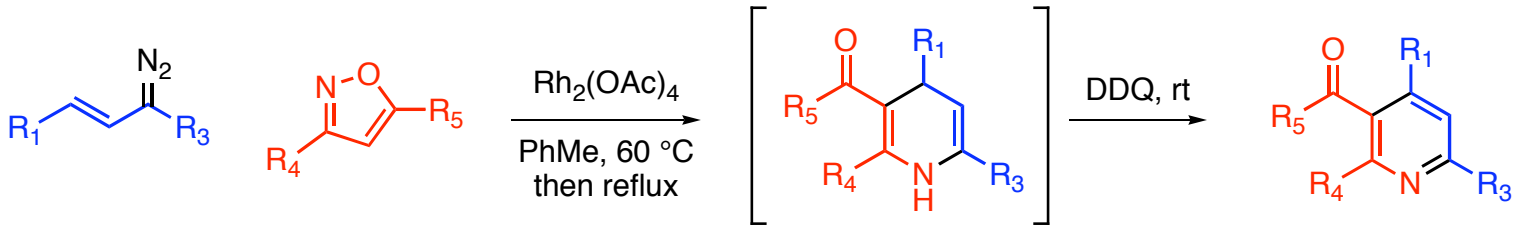
Manning, J. R.; Davies H. M. L. *Tetrahedron*. *64*. **2008**. 6901.

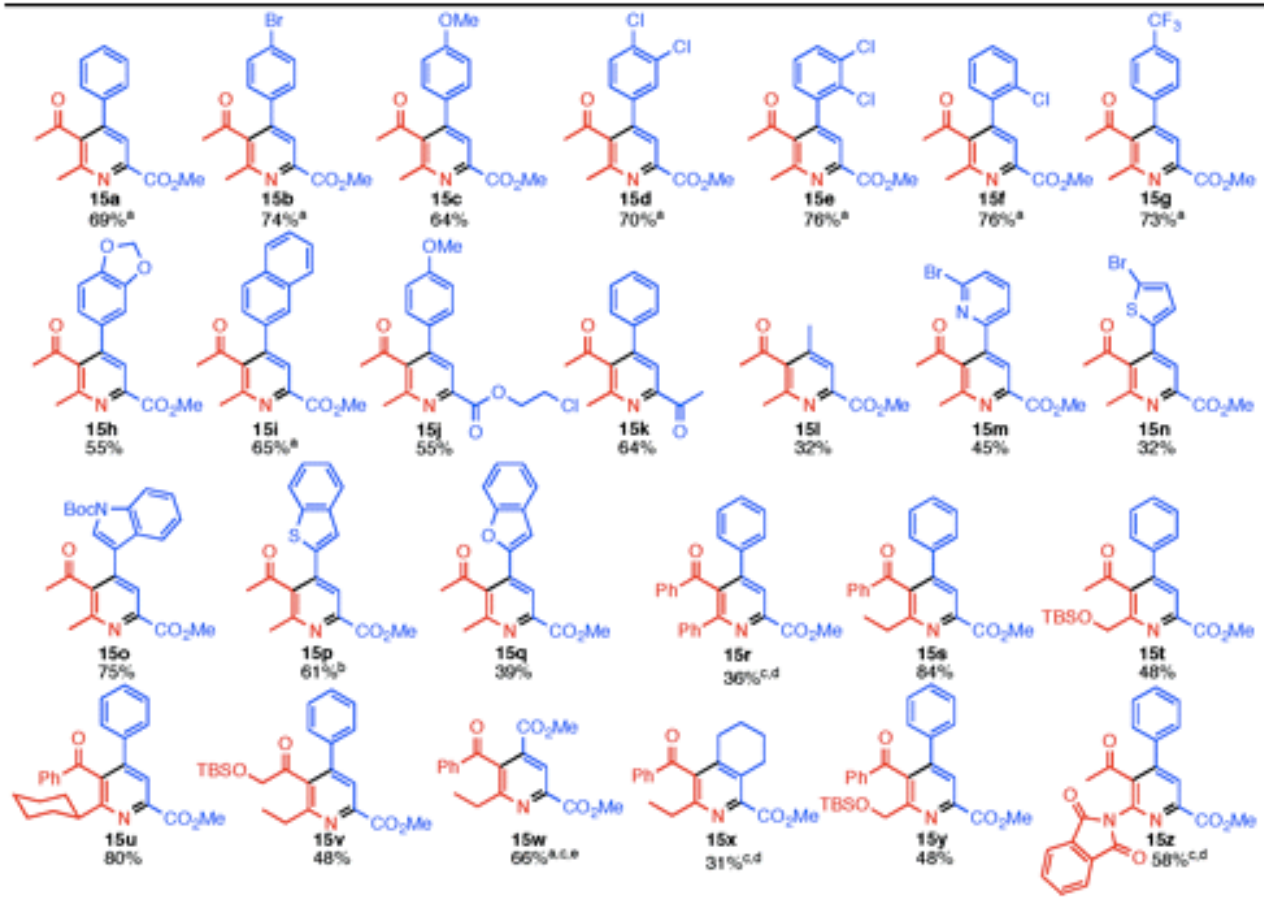
Mechanism of reaction



Manning, J. R.; Davies H. M. L. *Tetrahedron*. *64*. **2008**. 6901.
Manning, J. R.; Davies, H. M. L. *Journal of the American Chemical Society. ASAP.* **2008**. 6/13/2008

Scope of Reaction

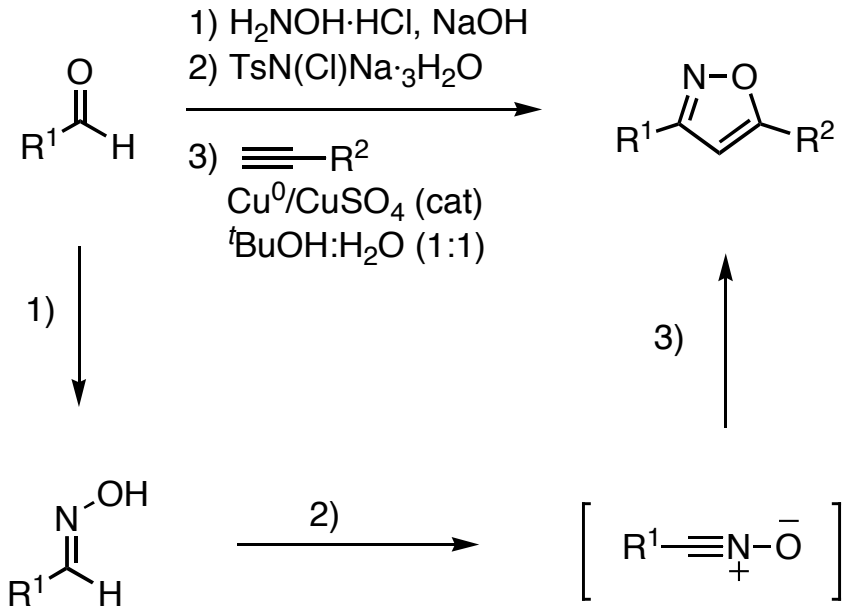




- slightly higher yields for electron-deficient aromatics
- in some cases catalyst loading could be dropped to 0.5 mol % without loss of yield
- electron rich heteroaromatics gave lower yields

Manning, J. R.; Davies, H. M. L. *Journal of the American Chemical Society. ASAP.* **2008**. 6/13/2008

Synthetic availability of isoxazoles



readily available from aldehydes and terminal alkynes in 57-74% yield

large functional group tolerance including aryl, alkyl, phenols, carboxylic acids, furans, ethers, and allylic alcohols.

Fokin, V. V. *et al. Journal of Organic Chemistry. 70.* **2005**. 7761.

Conclusion

A one-pot procedure for the synthesis of highly functionalized pyridines and 1,4-dihydropyridines was developed.

Serves as an illustration of how unexpected reactions during natural product synthesis can reveal an interesting and useful methodology

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"For each pyridine desired, the number, nature and pattern of substituents will dictate the suitability of each strategy. There are many creative and practical methods, however, every one being incompatible with certain functional groups and each synthesis must be carefully planned. To conclude, there is a continuing need to generate new and improved methods for pyridine syntheses."

Henry, G. D. *Tetrahedron*. *60*. **2004**. 6043.