Frontiers in Chemical Synthesis II
Heterocyclic Chemistry

Seminar Program
May 11-12, CH G1 495

	Speaker	**Title**
May 11, 2015		
Session I: New Synthetic Methods for Heterocycle Synthesis Chair: Paola Caramenti		
9h00-10h00	Cyril Piemontesi	*The Synthesis of Pyridine Derivatives using N-Heteroatom Pyridinium Species*
10H00-11h00	Julia Pedroni	*Gamma-Lactam Synthesis via Transition-Metal Catalyzed Carbonylation Reactions*
11h00-12h00	Daniele Perrotta	*Catalytic Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides*
Session II: Synthesis of Heterocycle-Containing Drugs and Natural Products Chair: Julia Pedroni		
13h00-14h00	Daria Grosheva	*Synthesis of Indolizidine Alkaloids*
14H00-15h00	Grigory Karateev	*Synthetic Routes to the Best Selling Drugs Containing 6-Membered Heterocycles*
15h00-16h00	Nicolas Gaeng	*Selected Syntheses of Spirocyclic Natural Products*
May 12, 2015		
Session III: Heterocycles as Catalysts and Ligands Chair: Cyril Piemontesi		
9h00-10h00	Paola Caramenti	*1,2,3 Triazoles in Catalysis*
10h00-11h00	Romain Tessier	*L-Histidine and its Derivatives as Organocatalysts*

The Synthesis of Pyridine Derivatives using *N*-Heteroatom Pyridinium Species

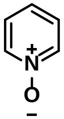
Frontier in Organic Chemistry – 11.05.2015

Cyril Piemontesi

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

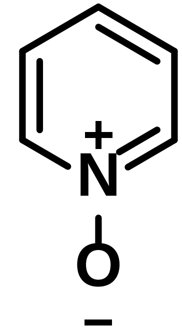
Laboratory of Synthesis and Natural Products (LSPN)

Content



Introduction to PNO

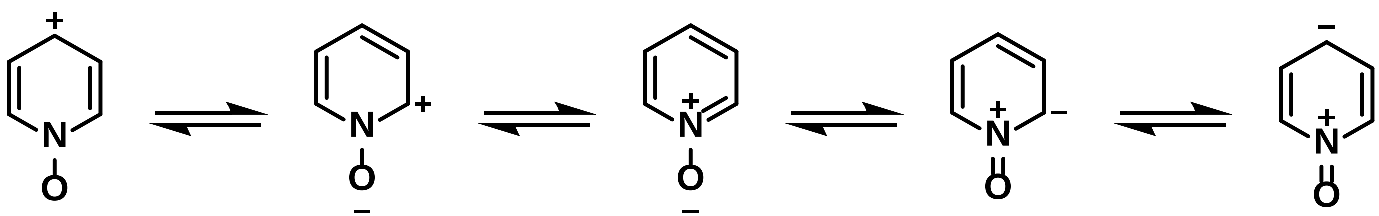
First description of PNO by Meisenheimer in 1926[1]
More than 20'000 1 step reactions of PNO (SciFinder) + patents



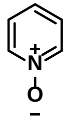
More nucleophilic than pyridine (π-back-donating character)
More electrophilic than pyridine (σ-electron-withdrawing character)

Strong dipole moment (4.37 D *vs* 2.03 D for pyridine)
Weak base (pKa = 0.79 *vs* pKa = 5.2 for pyridine)

Attack from/to positions 2, 4 and 6 and *O*

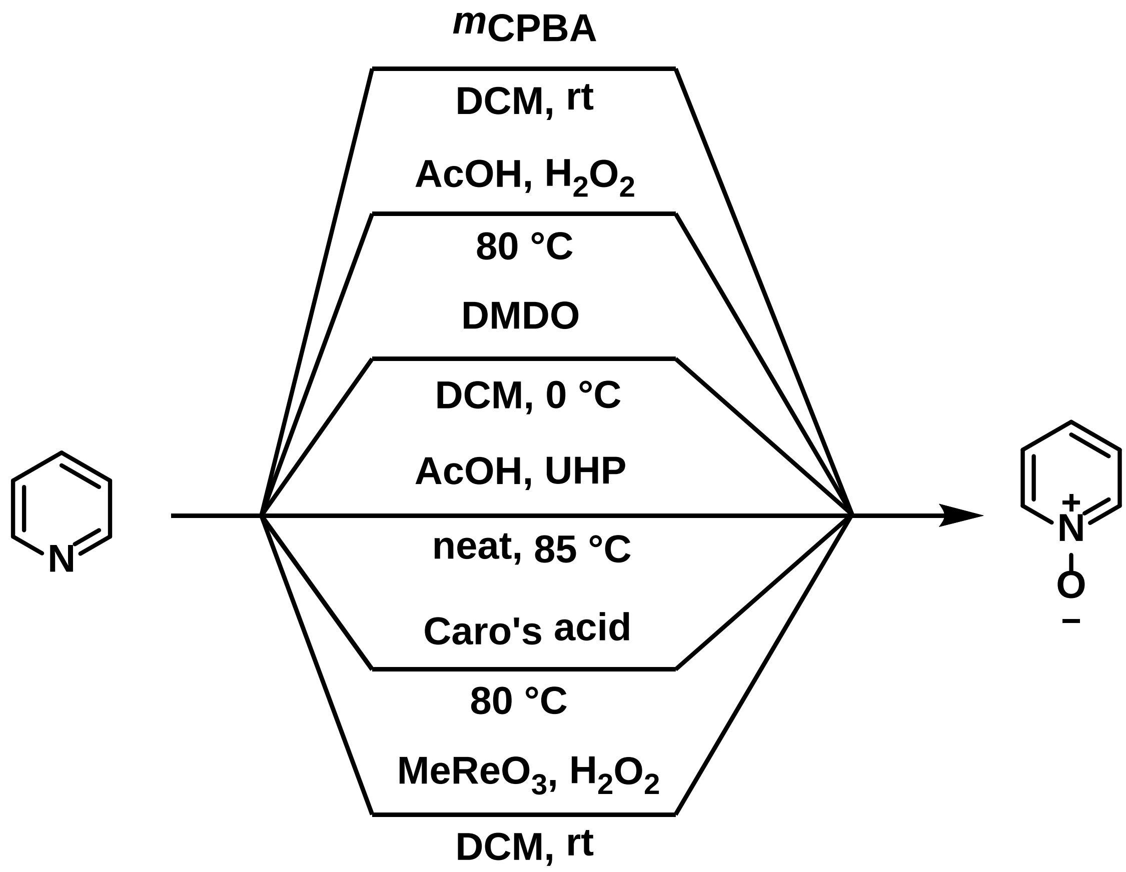


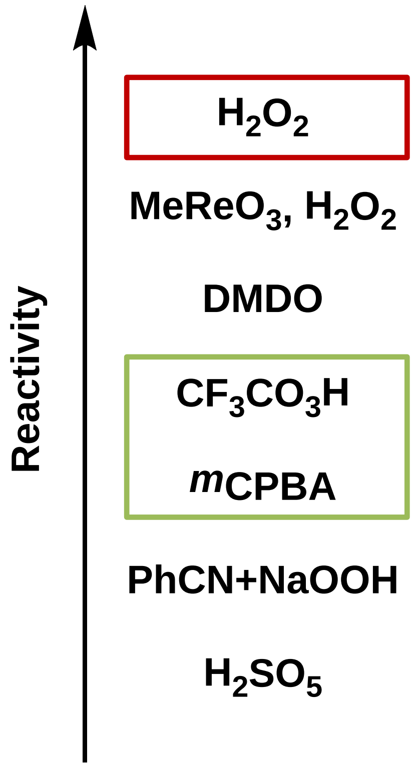
1. Meisenheimer, J. *Ber dtsch. Chem. Ges.* **1926**, *59*, 1848.
2. Review: Lam, J. N. *Heterocycles* **1992**, *33*, 1011.



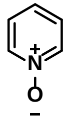
Synthesis of PNO from pyridine

Simple oxidation of pyridine to PNO



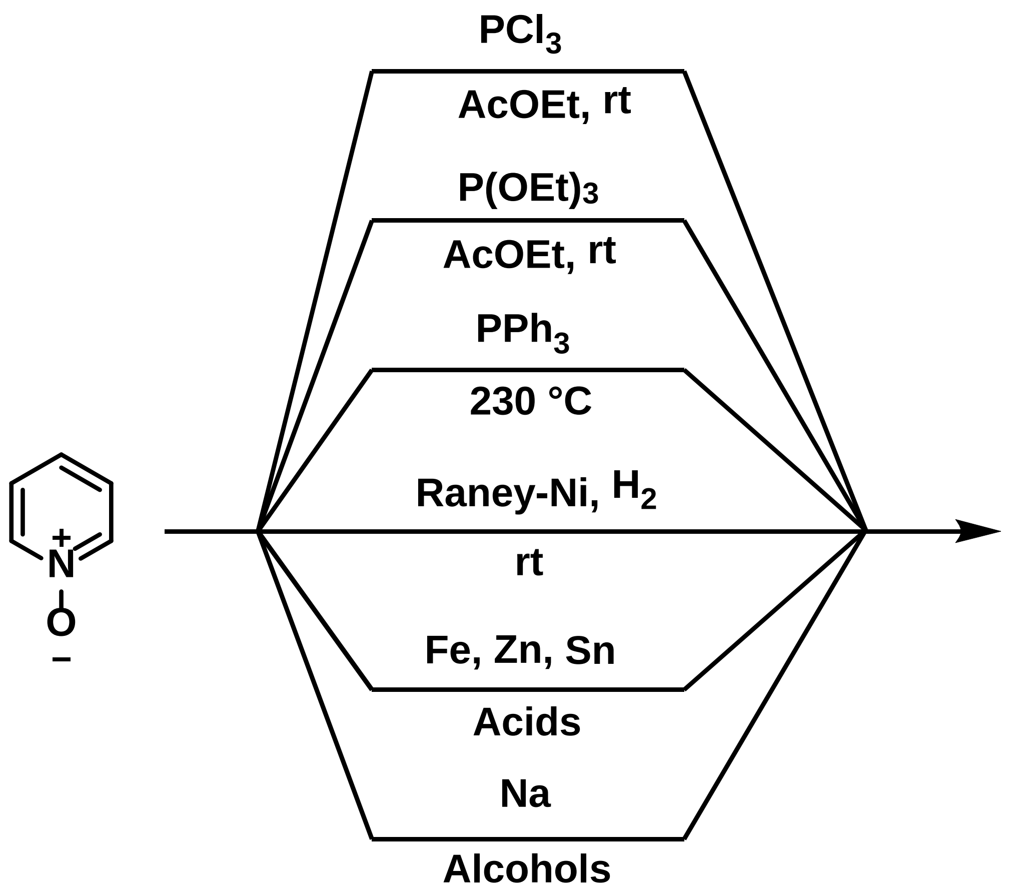


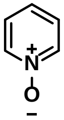
Denovo synthesis also possible (*via* condensation or rearrangement/cycloaddition)



Reduction of PNO to pyridine

Deoxygenation of PNO to pyridine

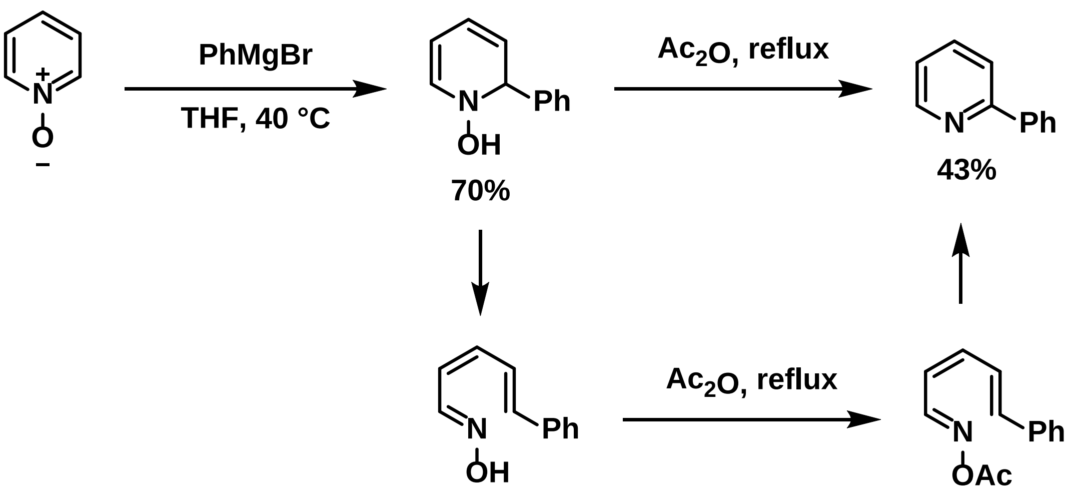




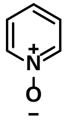
Addition of Grignard

Kato[1]: Isolation of the proposed *N*-hydroxydihydropyridine
Kellogg[2]: Revised later to be the pentadienal-oxime (standard + ^{1}H NMR *J* coupling + IR)
Ollson[3]: Practical synthesis only 40 years later!

Increased conjugation in the linear system favors its formation
Ring opening *via* disrotatory electrocyclic opening
Ac_2O promotes ring closing through Beckmann-type rearrangement



1. Kato, T. *J. Org. Chem.* **1965**, *30*, 910.
2. Kellog, R. M. *J. Org. Chem.* **1971**, *36*, 1705.
3. Ollson, R. *Org. Lett.* **2007**, *9*, 1335.

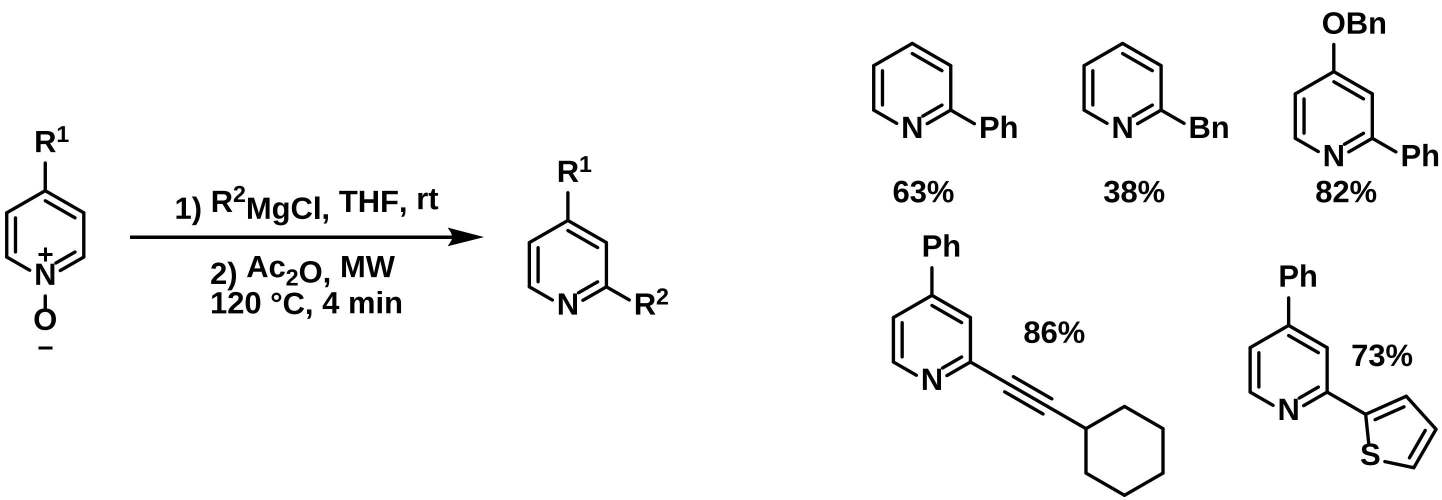


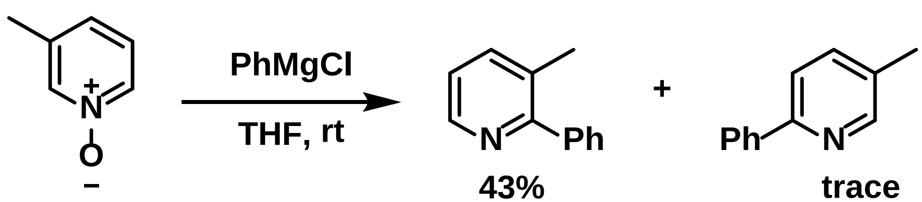
Addition of Grignard (2)

Highly selective for the 2 position *vs* the 4 one (N-O as DG)

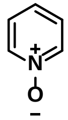
With 3-picoline: only the C-2 arylation observed + no need for the acetic anhydride

Alkyl Gringnard: only modest yield (α-metalation)





1. Ollson, R. *Org. Lett.* **2007**, *9*, 1335.

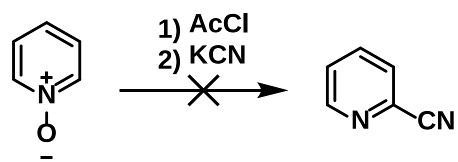


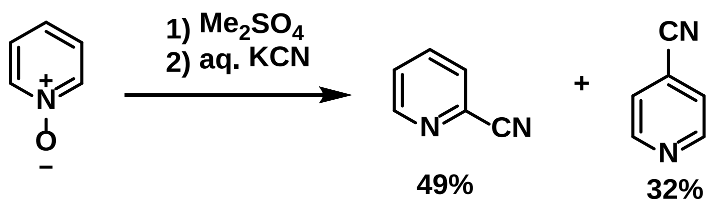
Cyanation

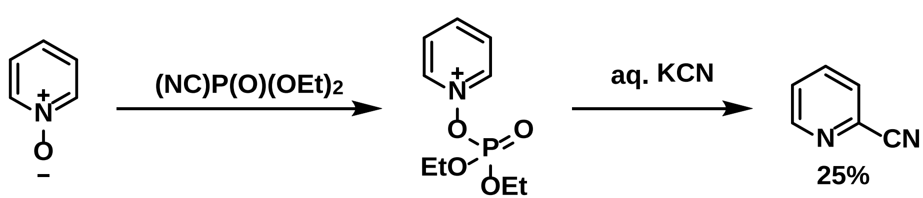
Reissert-Henze reaction not working with PNO (increased aromaticity compared to quinoline)

Feely[1]: Methylation with Me_2SO_4 (neat) then cyanation. Mixture of 2 and 4-cyanopyridine

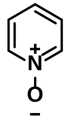
Shioiri[2]: Selectivity solution using DEPC as activating and directing reagent







1. Feely, W. E. *J. Am. Chem. Soc.* **1959**, *81*, 4004.
2. Shioiri, T. *Heterocycles* **1981**, *15*, 981.

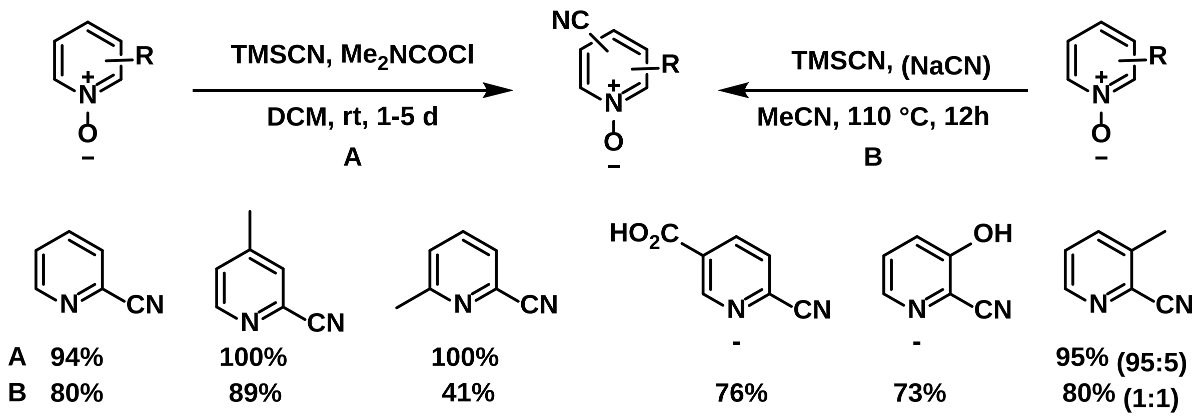


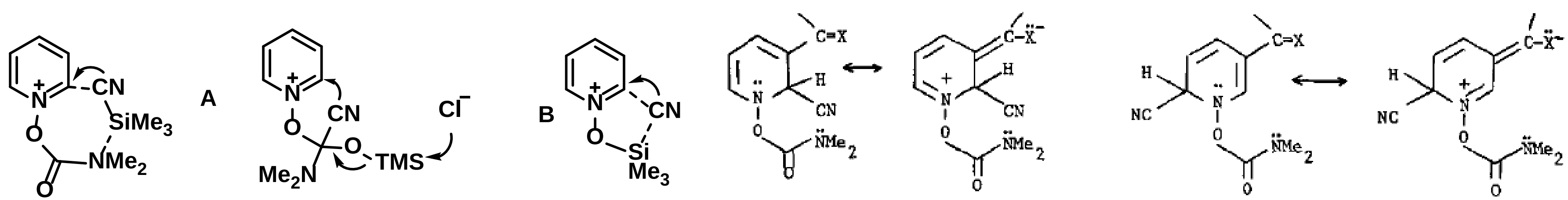
Cyanation (2)

2 practical solutions: almost simultaneously (4.10 vs 18. 10)

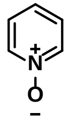
Fife[1]: Dimethylcarbamyl chloride + TMSCN (carbamyl not susceptible to CN attack)

Vorbrüggen[2]: TMSCN without further activation





1. Fife. W. K. *J. Org. Chem.* **1983**, *48*, 1375.
2. Vorbrüggen, H. *Synthesis* **1983**, 316.

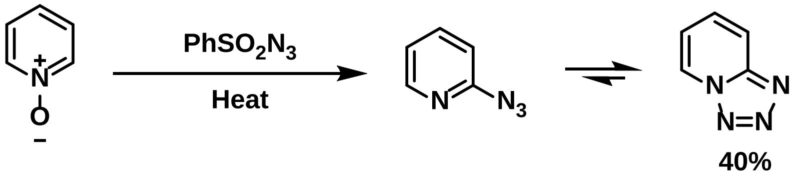


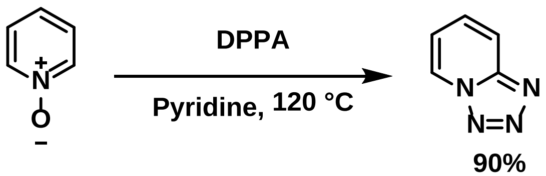
Azidation/Amination

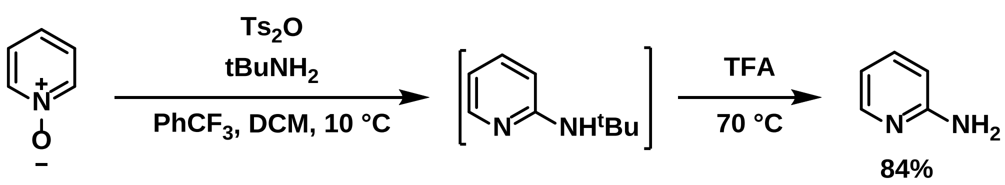
Reddy[1]: Azidation possible but unstable product

Keith[2]: Use of DPPA as activator + DG

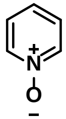
Direct amination by Merck[3]: Tosyl anhydride as activator. Perfect C-2 selectivity





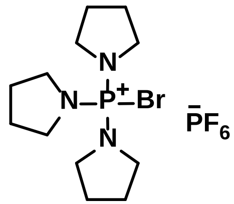


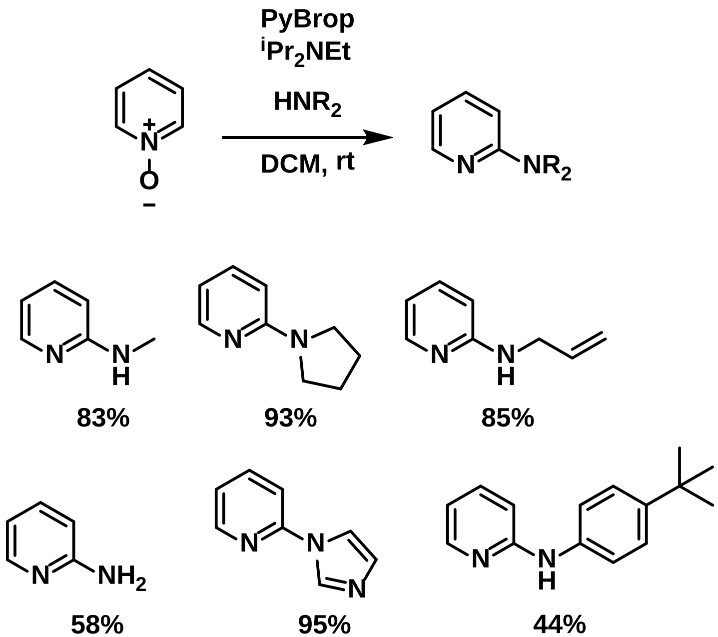
1. Reddy, K. S. *Chem. Lett.* **1983**, *12*, 1745.
2. Keith, J. M. *J. Org. Chem.* **2006**, *71*, 9540.
3. Yin. J. *J. Org. Chem.* **2007**, 72, 4554.

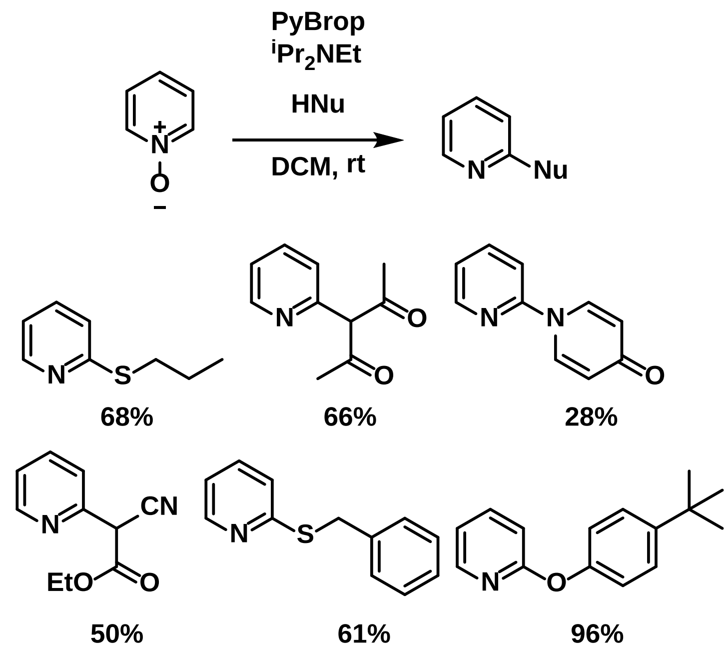


Azidation/Amination (2)

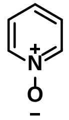
Londregan: PyBrop as activating agent for amination[1] and other nucleophiles[2]







1. Londregan. A. T. *Org. Lett.* **2010**, *12*, 5254.
2. Londregan. A. T. *Org. Lett.* **2011**, *13*, 1840.

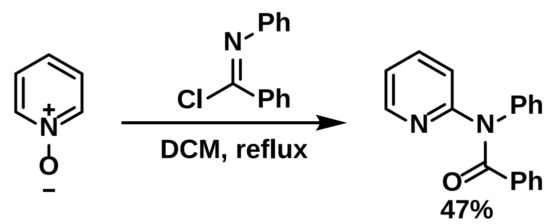


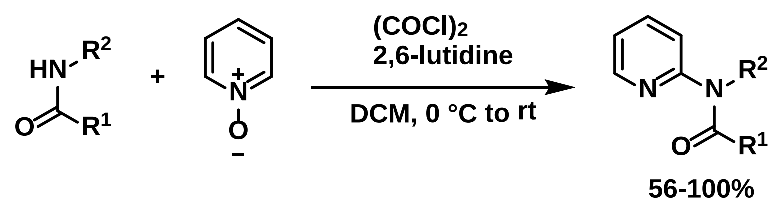
Amidation

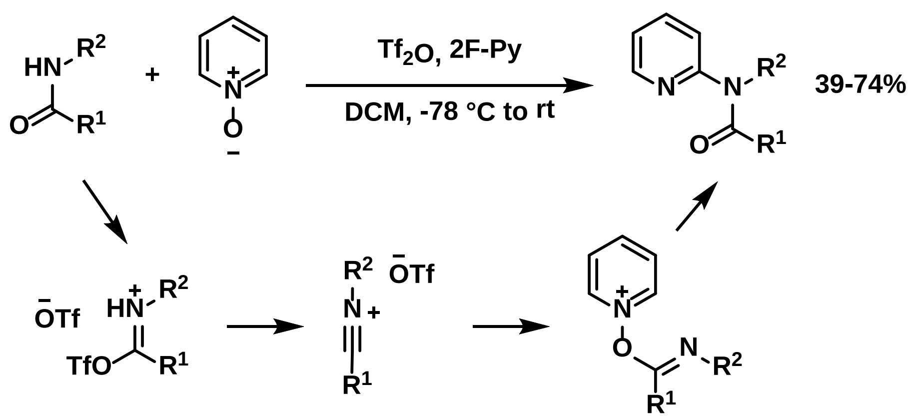
Singer[1]: Through thermal rearrangement

Bilodeau[2]: *In situ* activation of the amide with oxalyl chloride/2,6-lutidine

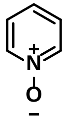
Movassaghi[3]: *In situ* activation of the amide with Tf_2O/2F-Py





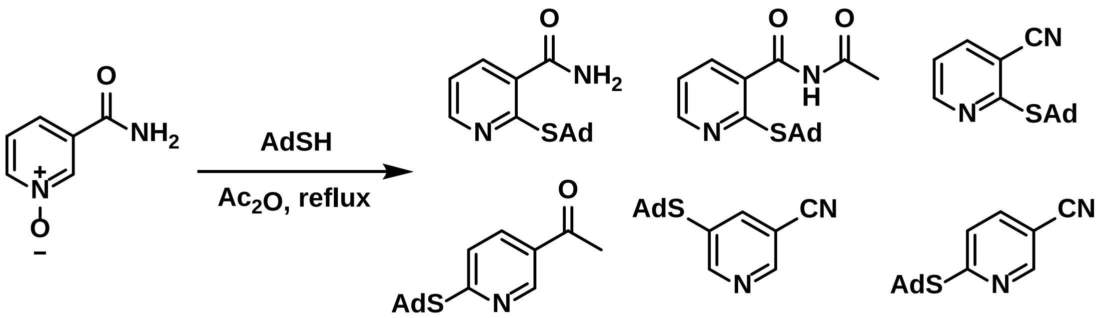


1. Singer, G. M. *J. Am. Chem. Soc.* **1969**, *91*, 5672.
2. Bilodeau. M. T. *Org. Lett.* **2002**, *4*, 3127.
3. Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 1341.



Sulfurylation

Often achieved via halogenation/substitution but regioslectivity issue + low yield
Bauer[1,2,3]: Adamantanethiol as Nu. Regioselectivity issue
Triethylamine can improve the selectivity but reduce the yield

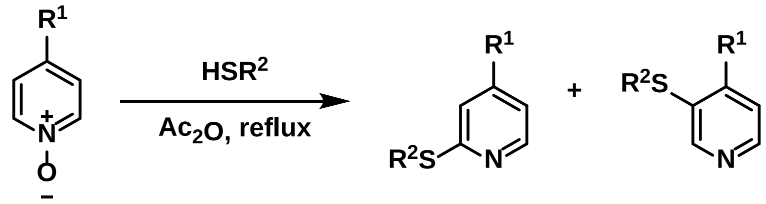


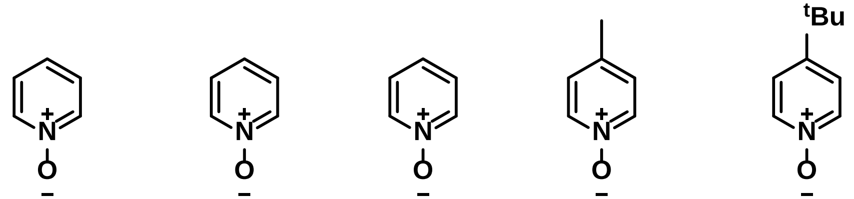
1. Bauer, L. *J. Heterocycl. Chem.* **1985**, *22*, 771.
2. Bauer, L. *Heterocycles* **1986**, *24*, 161.
3. Bauer, L. *J. Heterocycl. Chem.* **1991**, *28*, 1051.

Sulfurylation (2)

Various thiol + substitution pattern tolerated but yield + selectivity not perfect[1,2,3]

Changing the activating agent can sometimes improves the yield + selectivity



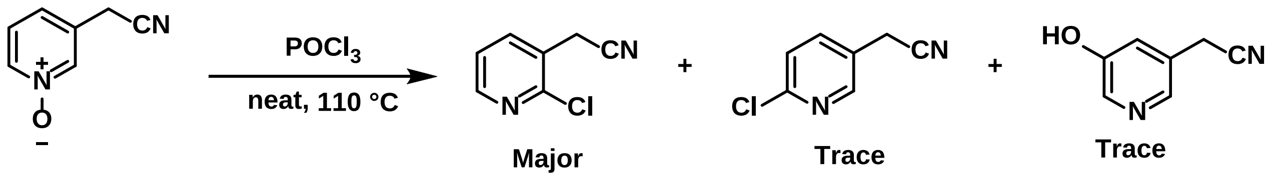


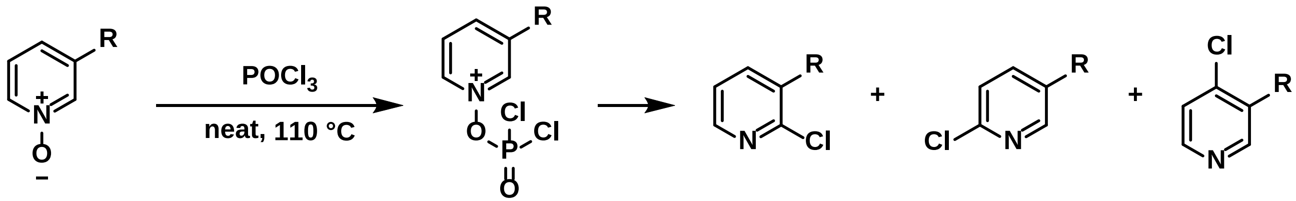
R^2 =	Me	tBu	Ad	tBu	tBu
with NEt_3	-	41% (9:1)	35% (8:2)	33% (82:12)	48% (96:4)
without NEt_3	38% (52:48)	62% (7:3)	44% (68:32)	41% (71:29)	48% (83:17)

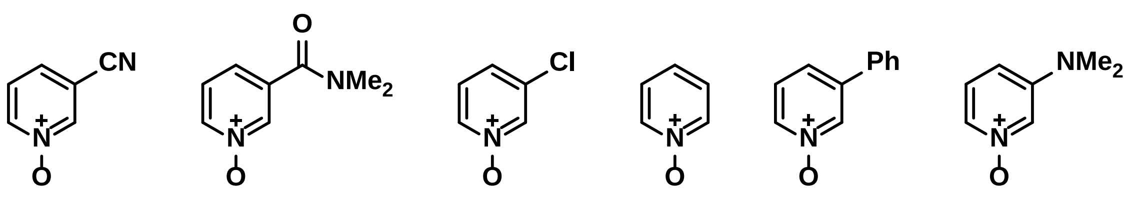
1. Bauer, L. *J. Heterocycl. Chem.* **1985**, *22*, 771.
2. Bauer, L. *Heterocycles* **1986**, *24*, 161.
3. Bauer, L. *J. Heterocycl. Chem.* **1991**, *28*, 1051.

Robison[1]: initial report

Yamanaka[2]: yield not affected by electronic/steric but the selectivity yes



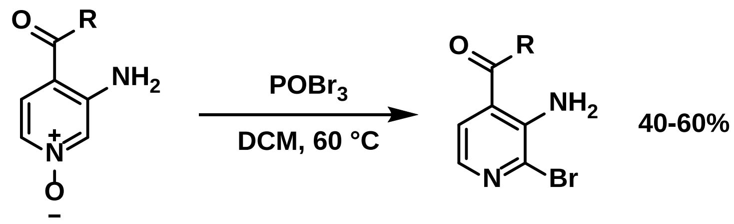


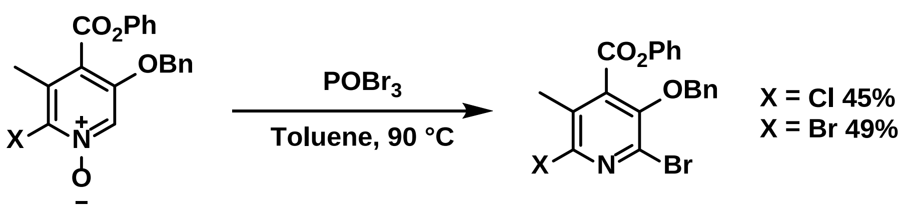


83%	93%	74%	82%	84%	80%
88:10:2	80:20:0	47:38:15	70:30	32:46:22	34:47:19

1. Robison, M. M. *J. Am. Chem. Soc.* **1959**, *81*, 740.
2. Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 2244.

Bromination with $POBr_3$ also possible[1,2]

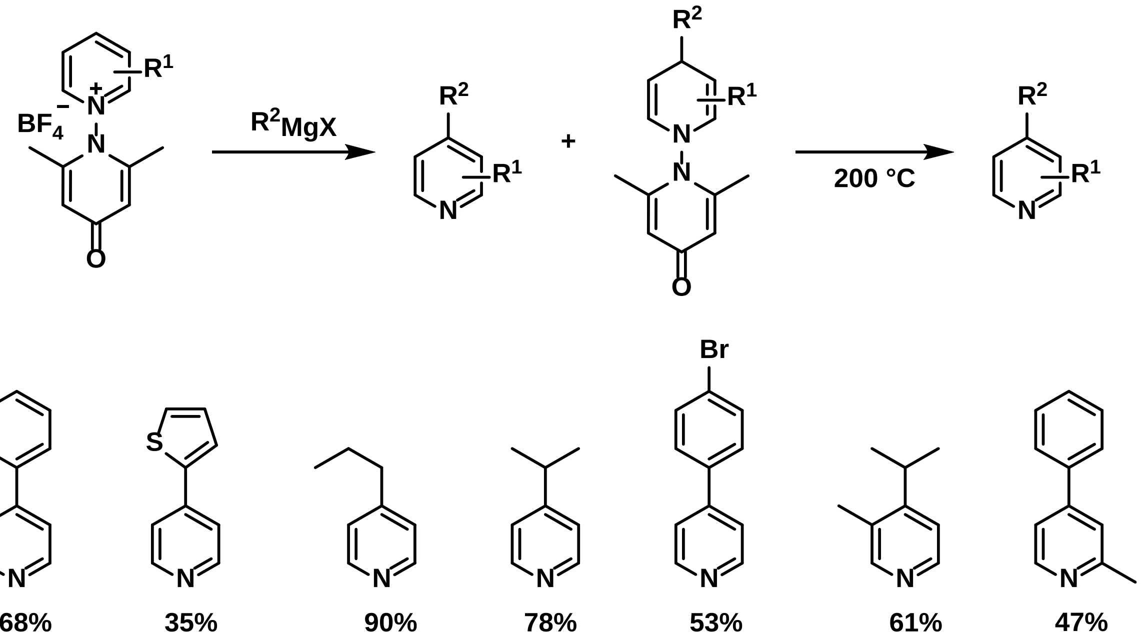




1. Clark, R. B. *J. Med. Chem.* **2011**, *54*, 1511.
2. Lumeras, W. *J. Med. Chem.* **2009**, *52*, 5531.

N-N Addition of Grignard

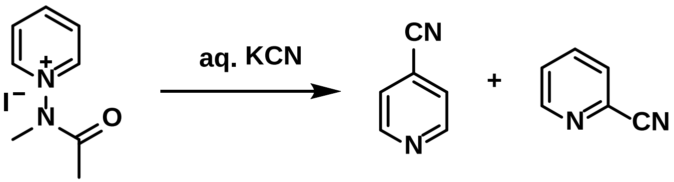
1-pyridinio-4-pyridone cation with the blocking methyl groups with Grignard[1,2,3]
No clean isolation possible of the dihydropyridine
Not working with organolithium



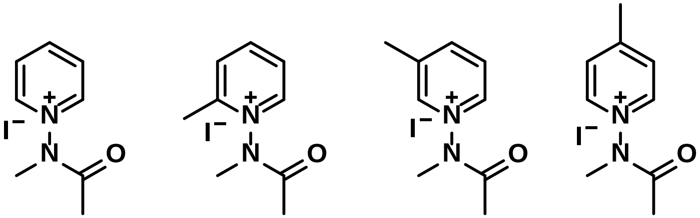
1. Katritzky, A. R. *J. Chem. Soc. Chem. Comm.* **1979**, 137.
2. Katritzky, A. R. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 792.
3. Katritzky, A. R. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2480.

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

Ohsawa[1,2]: addition of KCN to 1-(N-acylalklylamino)pyridinium
Mainly the 4-cyanopyridine but dependent of the [KCN]



6.2 M 89% of the 4-cyanopyridine
12.5 M 1.4:1 ratio 2-/4-cyanopyridine

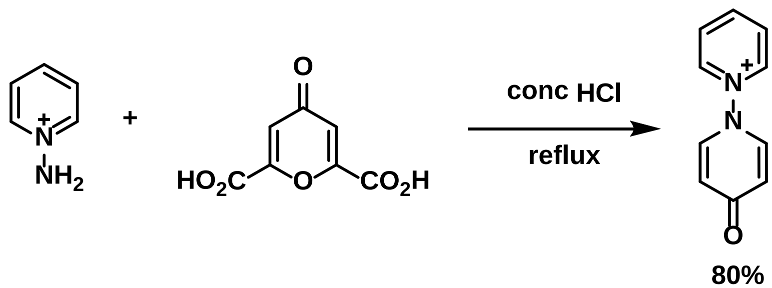


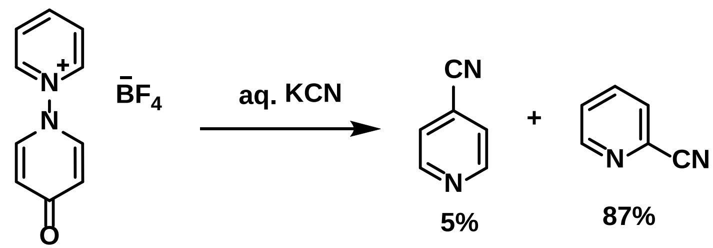
Yield for C-4/C-2	89:3	88:0	92:0	0:13

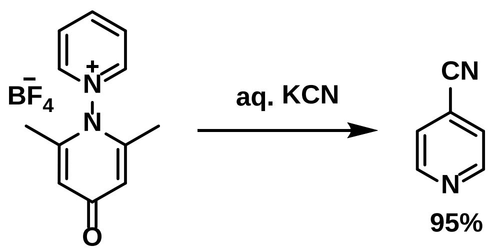
1. Ohsawa, A. *Chem. Pharm. Bull.* **1963**, *11*, 780.
2. Ohsawa, A. *Chem. Pharm. Bull.* **1966**, *14*, 518.

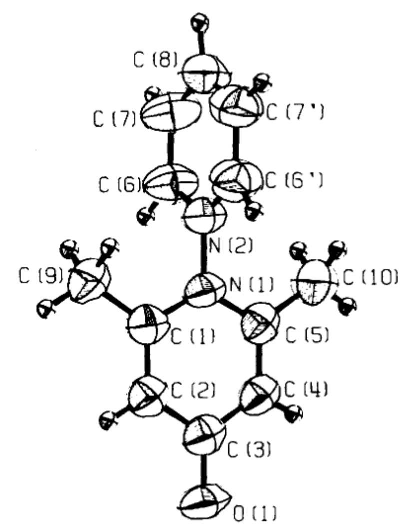
N-N Cyanation (2)

Sammes[1,2,3,4]: addition of KCN to 1-pyridinio-4-pyridone cation
Selectivity also dependent on the [KCN] (2-cyano = kinetic/4-cyano=thermo)
Use of methyl blocking group increase the selectivity
0.17 Å between the methyl hydrogen and the hydrogen at C-2/C-6



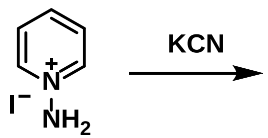


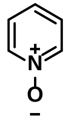




1. Sammes, M. P. *J. Chem. Soc. Chem Commun.* **1975**, 247.
2. Sammes, M. P. *J. Chem. Soc. Perkin Trans. 1* **1977**, 327.
3. Sammes, M. P. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1698.
4. Sammes, M. P. *J. Chem. Soc. Perkin Trans. 2* **1985**, 573.

N-N Cyanation (3)



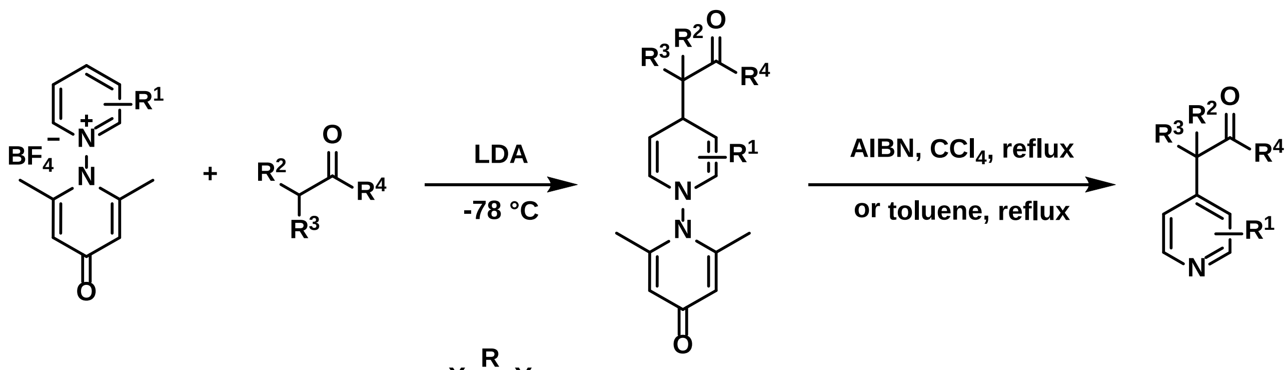


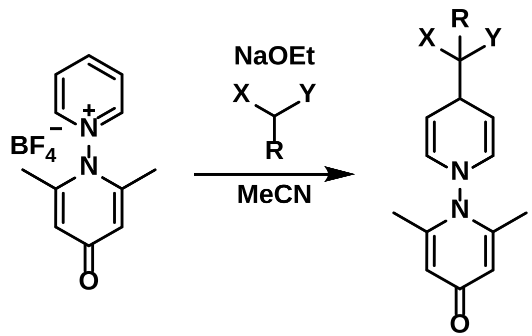
N-N Addition of Enolate

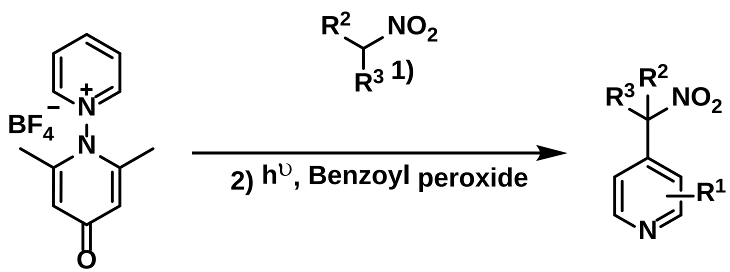
Addition of lithium enolate at the C-4 position (steric). Isolation possible of the dihydropyridine but reflux of AIBN affords the pyridine[1]

Lithium enolate of ester/nitrile gave bad yield[2]

Increase the acidity of the enolizable center: addition of malonate and cyanoacetate[3] and of nitroalkane[4]







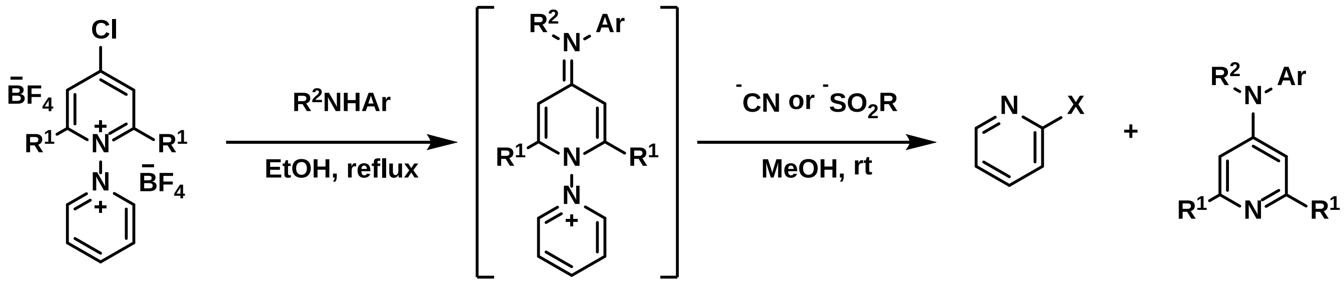
1. Katritzky, A. R. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 792.
2. Sammes, M. P. *J. Chem. Soc. Perkin Trans. 1* **1981**, 2476.
3. Sammes, M. P. *J. Chem. Soc. Perkin Trans. 1* **1981**, 2835.
4. Katritzky, A. R. *J. Chem. Soc. Perkin Trans. 1* **1981**, 588.

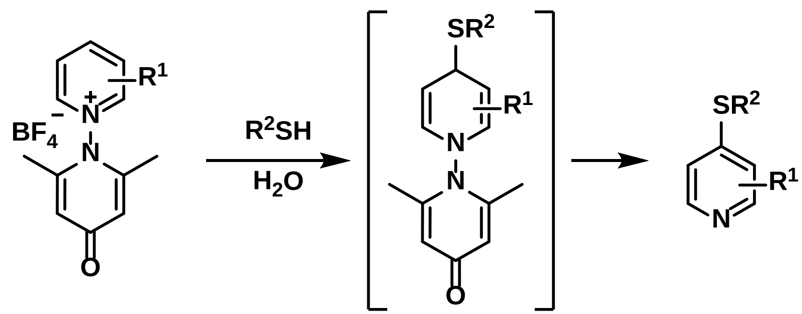
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

Addition of aniline to 4-chloro-1-pyridinopyridinium followed by cyanide or sulfinate attack[1]

1-pyridinio-4-pyridone cation with the blocking methyl groups with thiol[2,3,4]

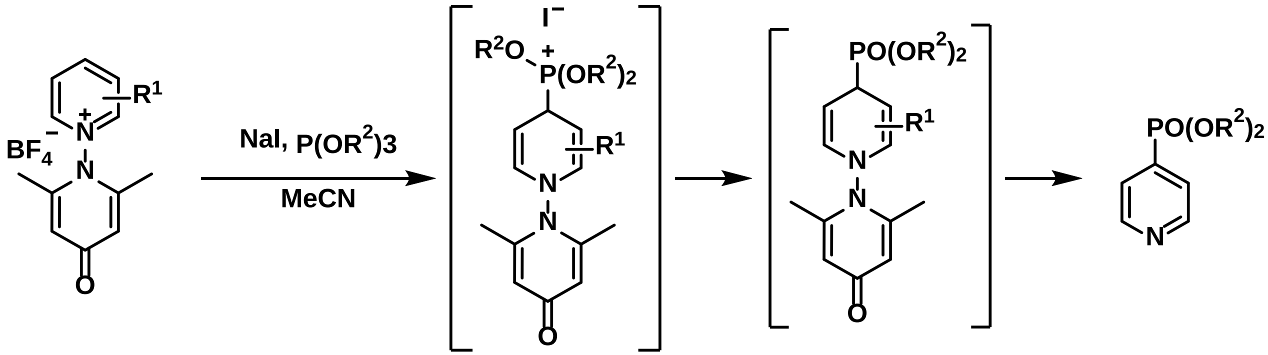
Initial addition reversible in water but driven to cleavage in MeCN (higher pK_a)





1. Katritzky, A. R. *J. Chem. Soc. Perkin Trans. 1* **1983**, 973.
2. Katritzky, A. R. *J. Chem. Soc. Chem. Comm.* **1975**, 247.
3. Sammes, M. P. *J. Chem. Soc. Perkin Trans. 1* **1977**, 327.
4. Sammes, M. P. *J. Chem. Soc. Perkin Trans. 1* **1981**, 1585.

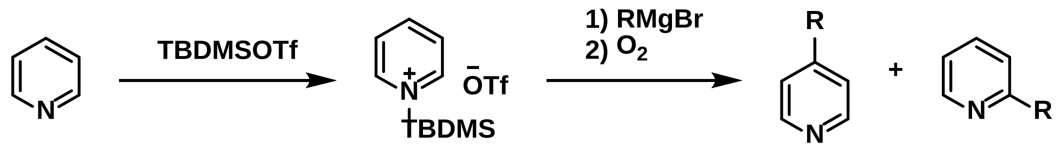
Addition of trialkylphosphite[1]

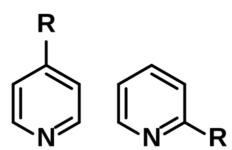


1. Katritzky, A. R. *J. Chem. Soc. Perkin Trans. 1* **1981**, 668.

N-Si Addition of Grignard

Akiba[1,2]: use of TBDMSOTf to activate pyridine
Excellent C-4 selectivity due to the steric of TBDMS
Better yield if isolation of the silylated pyridinium (10-20% more)
Facile reoxidation under air
Silyl chloride ineffective but silyl iodide as effective as OTf[3]
Organolithium = modest results / cuprate too soft / enolate attack the Si





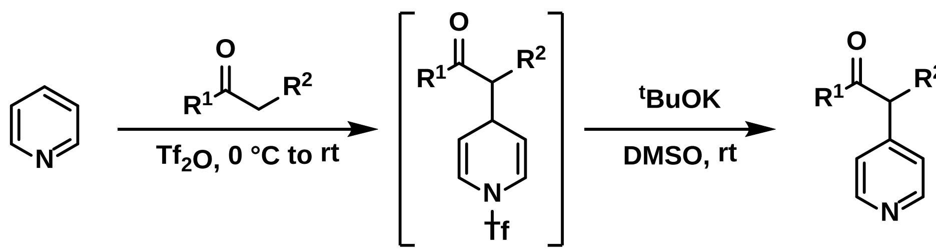
R = Ph, 73%, 99.7/0.3
R = ^{i}Pr, 79%, 99.6/0.4
R = ^{n}Hex, 72%, 99.5:0.5
R = $Ph(CH_2)_2$, 71%, 98.1/1.1

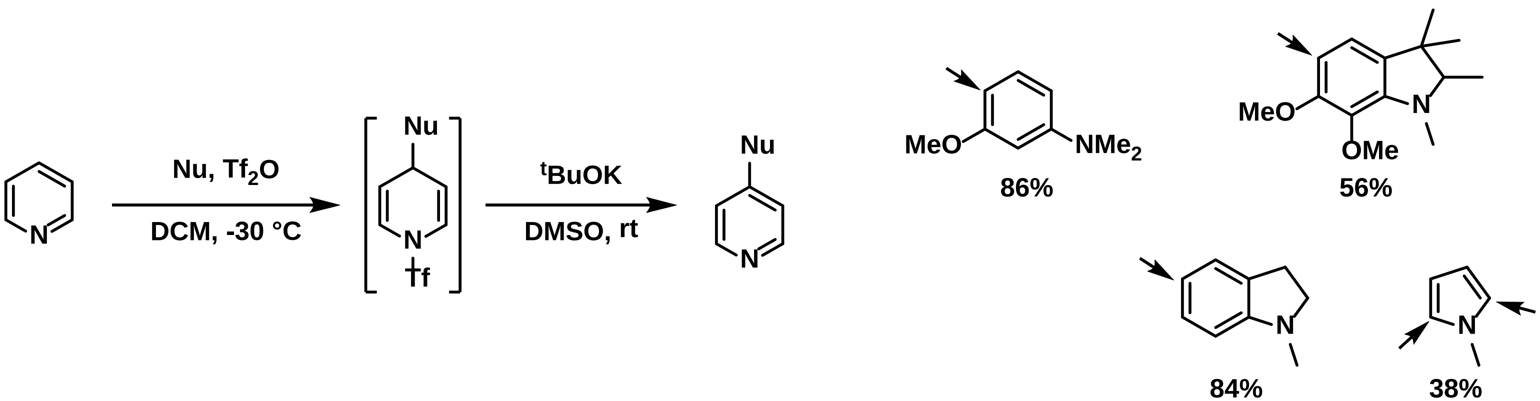
1. Akiba, K.-y. *Tetrahedron Lett.* **1982**, 23, 3935.
2. Akiba, K.-y. *Bull. Chem. Soc. Jpn.* **1984**, 57, 1994.
3. Riemer, R. *Synthesis* **1987**, 931.

Addition of enolate exclusively at the C-4 position[1]

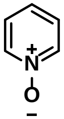
Rearomatization with KOtBu in DMSO / KOH in DMSO back to SM (reversible?)

Corey[2]: Addition of nucleophilic aromatic in high yield and selectivity





1. Katritzky, A. R. *J. Org. Lett.* **2001**, *3*, 2807.
2. Corey, E. J. *Org. Lett.* **2005**, *7*, 5535.



Metalation: PNO *vs* pyridine

C-H protons very close in acidity – regioselectivity issues

C-2 may form preferentially but destabilization with N-lone pair → isomerization to the 4-pyridine

Dimerization to the bipyridine

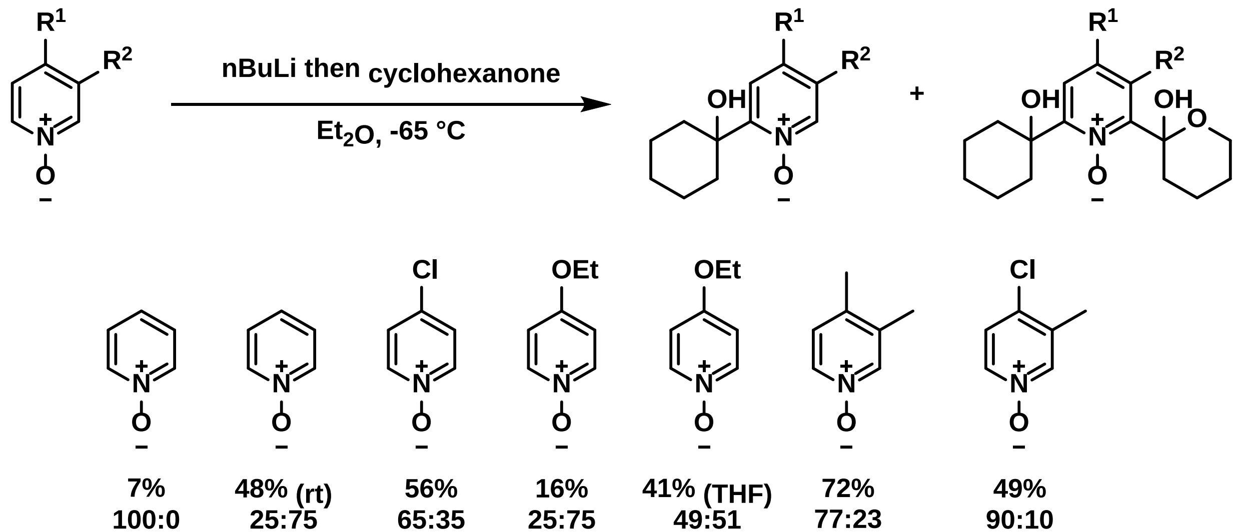
Addition of the strong base to the ring

Preferential deprotonation of the side chains

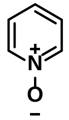
1. Schlosser, M. *Chem. Soc. Rev.* **2007**, *36*, 1161.
2. Yus, M. *ARCHIVOC* **2007**, 152.
3. Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059.
4. Kondo, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3802.

Metalation of PNO

Abramovitch[1,2,3,4]: First report of deprotonation of PNO. Disubstitution is the major side-product



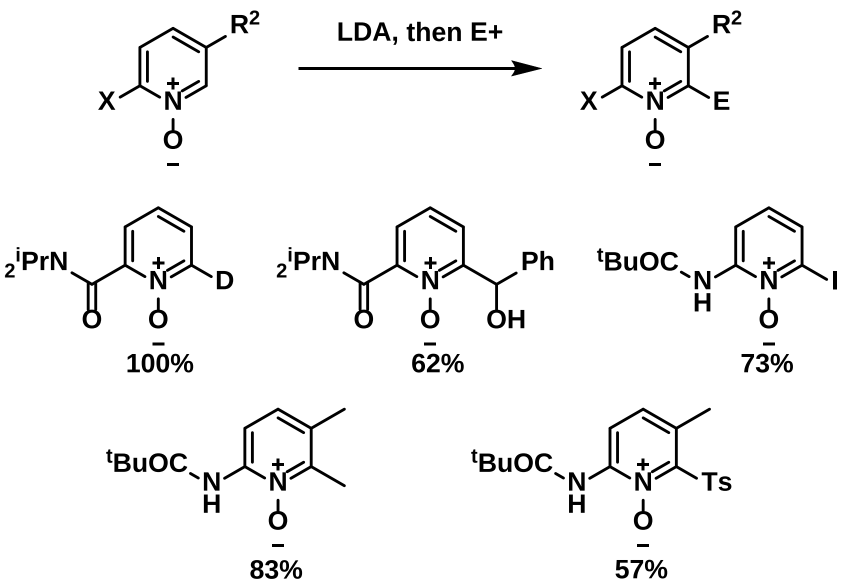
1. Abramovitch, R. A. *Chem. Commun.* **1967**, 55.
2. Abramovitch, R. A. *J. Am. Che. Soc.* **1967**, *89*, 1537.
3. Abramovitch, R. A. *J. Org. Chem.* **1972**, *37*, 1690.
4. Abramovitch, R. A. *J. Org. Chem.* **1972**, *37*, 3584.

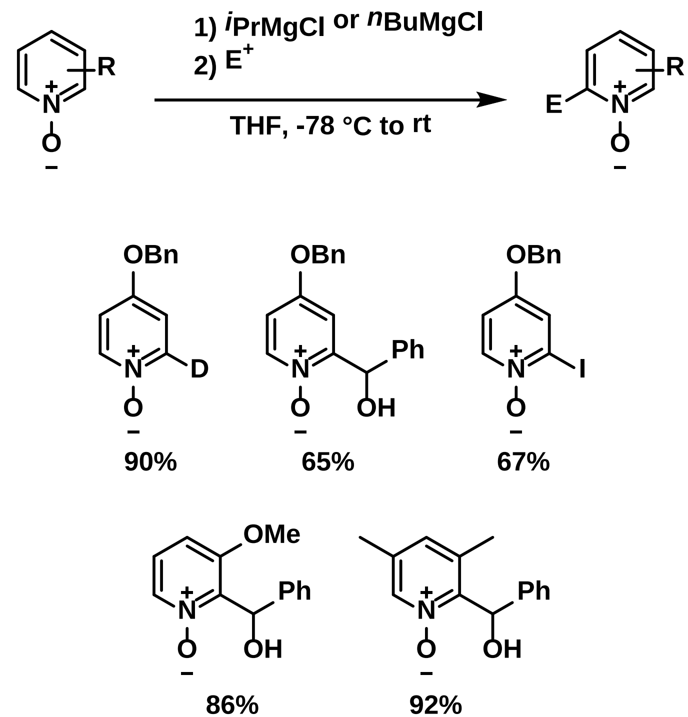


Metalation of PNO

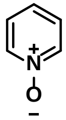
Quéguiner[1,2]: Use of bulky amine base remove the possibility for direct nucleophile addition

Almqvist[3]: deprotonation using Grignard. No disubstituted product



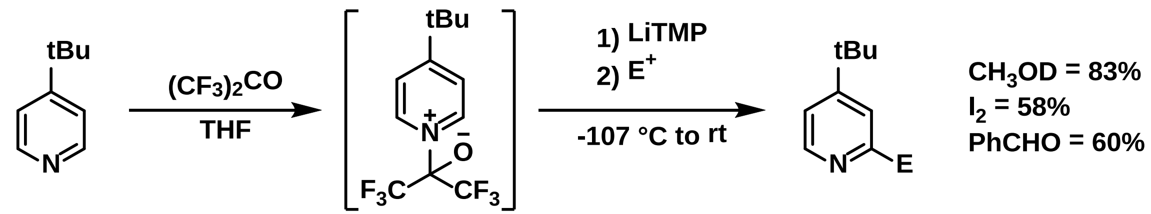


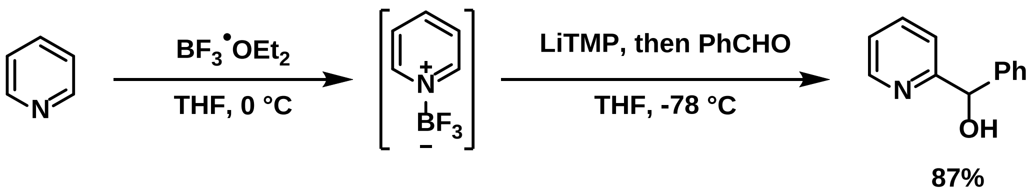
1. Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.
2. Quéguiner, G. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2503.
3. Almqvist, F. *Tetrahedron Lett.* **2008**, *49*, 6901.

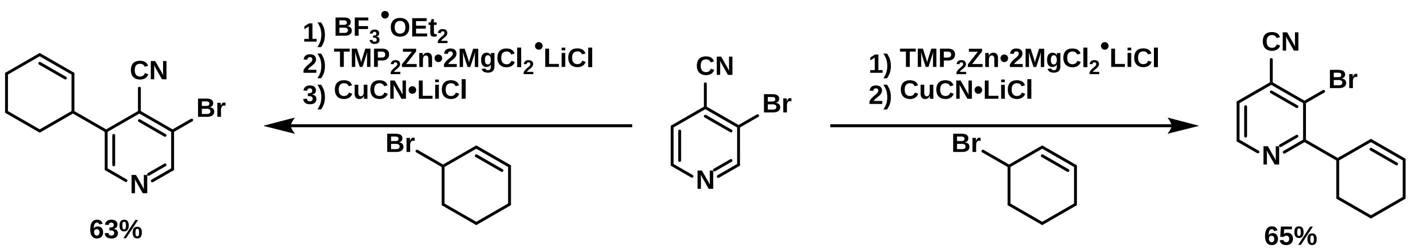


Metalation of *in situ* activated Py

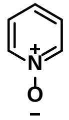
Martin[1]: Deprotonation of the adduct Py+$(F_3C)_2CO$ at low temperature
Kessar[2,3]: Activation with BF_3 then LiTMP
Knochel[4]: Cross-coupling with CuCN. Switch selectivity if BF_3





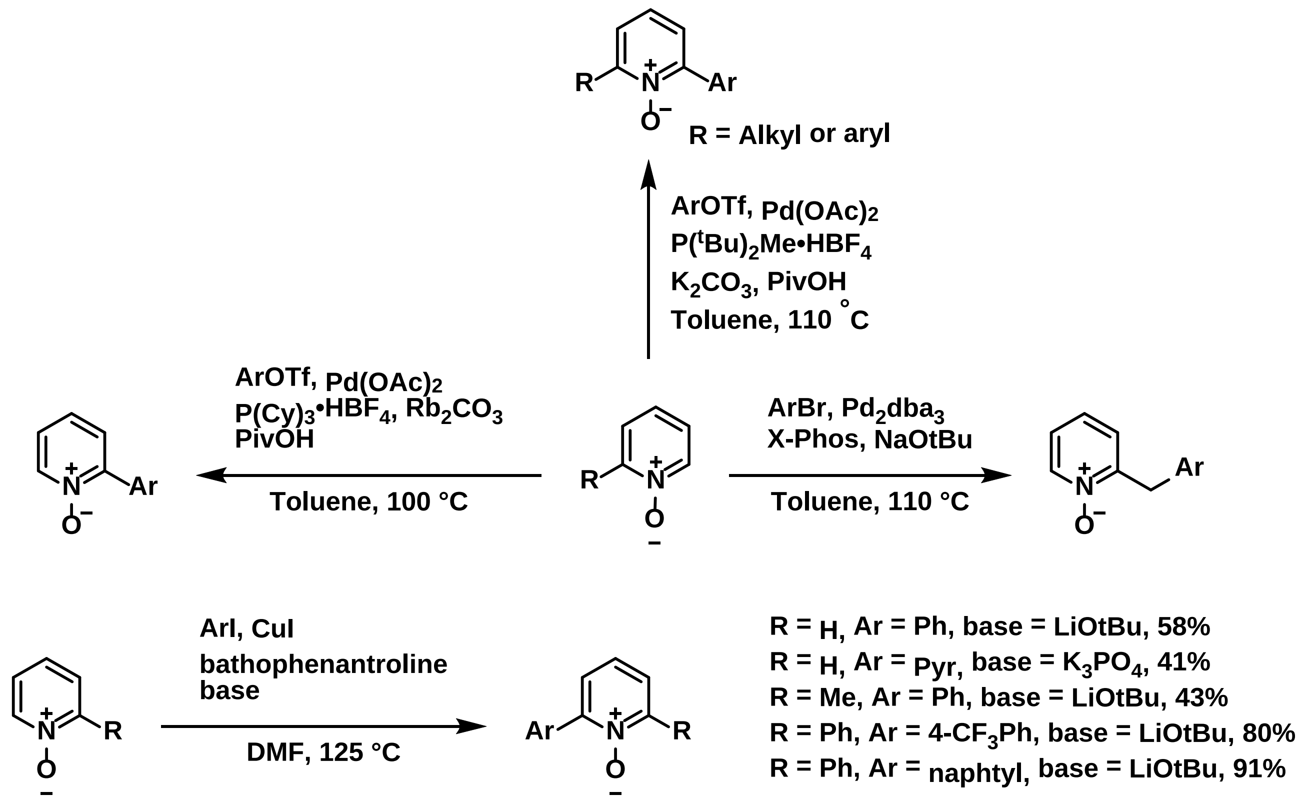


1. Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.
2. Kessar, S. V. *J. Chem. Soc. Chem. Commun.* **1991**, 570.
3. Kessar, S. V. *Chem. Rev.* **1997**, *97*, 721.
4. Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.



TM-catalyzed reaction of PNO

Pd[1,2]: by Fagnou. N-O prevent binding with N lone-pair. Increase electron density of the Py ring. Increase Brønsted acidity of the C2-H bond
Cu[3,4]: by Daugulis



1. Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266.
2. Fagnou, K. *Tetrahedron* **2009**, *65*, 4977.
3. Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404.
4. Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.

Conclusion and outlook

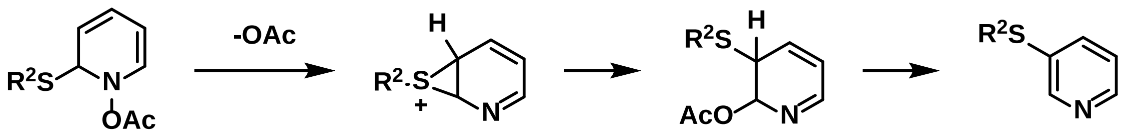
Pyridinium salts are easily accessed and versatile precursors to nitrogen containing heterocycles

Methods have been developed to achieve regioselective addition for most of the nucleophiles

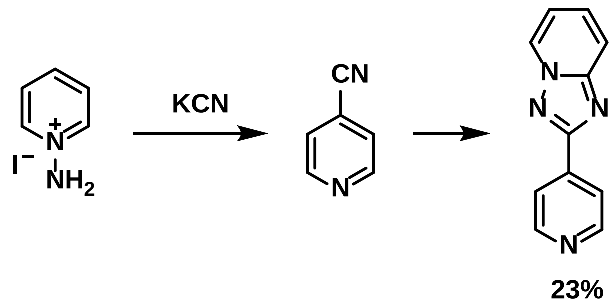
Still some work to do:

- Sulfurylation, Halogenation
- Use of *in situ* activated pyridine in order to avoid additional steps

Answers



Amino pyridinium salts undergo selective cyanation at the 4 position but direct [3+2]-cycloaddition[1,2]



1. Okamoto, T. *Chem. Pharm. Bull.* **1966**, *14*, 506.
2. Okamoto, T. *Chem. Pharm. Bull.* **1966**, *14*, 523.

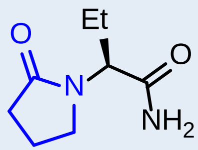
Synthesis of γ-lactams via transition metal catalysed carbonylation reactions

Frontiers in Chemical Synthesis: Heterocyclic Chemistry

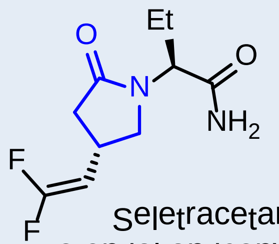
11.05.2015

Julia Pedroni

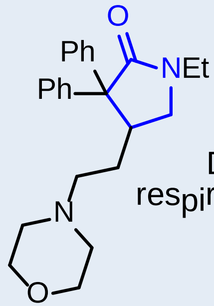
pyrrolidinones, indolinones, isoindolinones



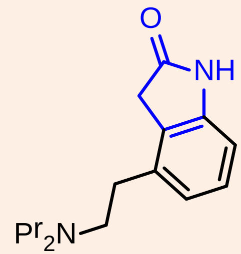
Levetiracetam
treatment of epilepsy



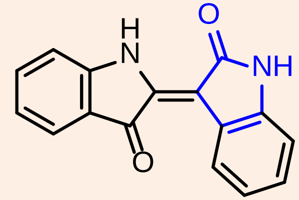
Seletracetam
potential anticonvulsant



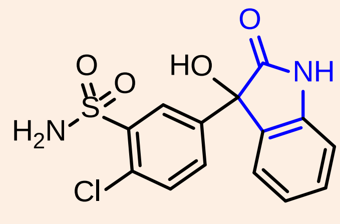
Doxapram
respiratory stimulant



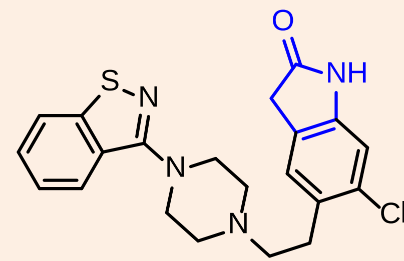
Ropinirole
treatment of Parkinson's disease



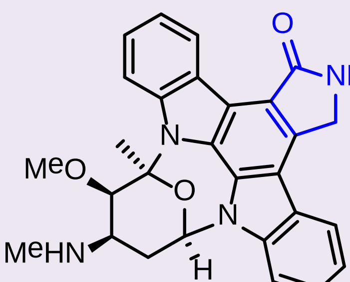
Indirubine
potential anti-tumor



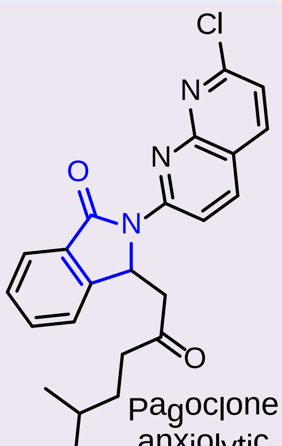
Chlortalidone
treatment of hypertension



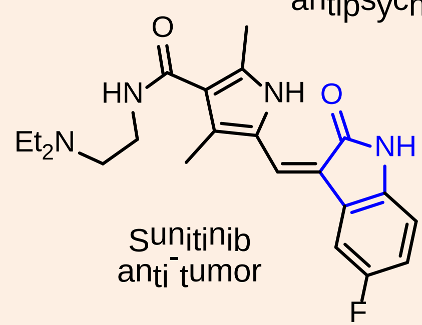
Ziprasidone
antipsychotic



Staurosporine
potential antibiotic

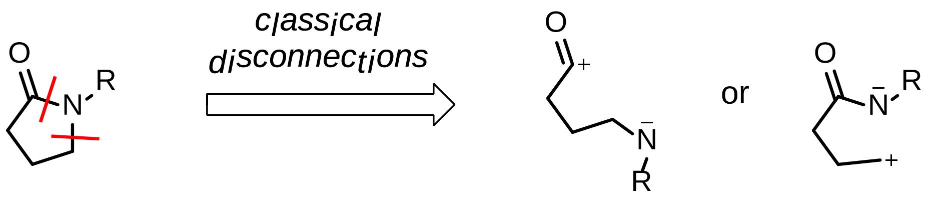


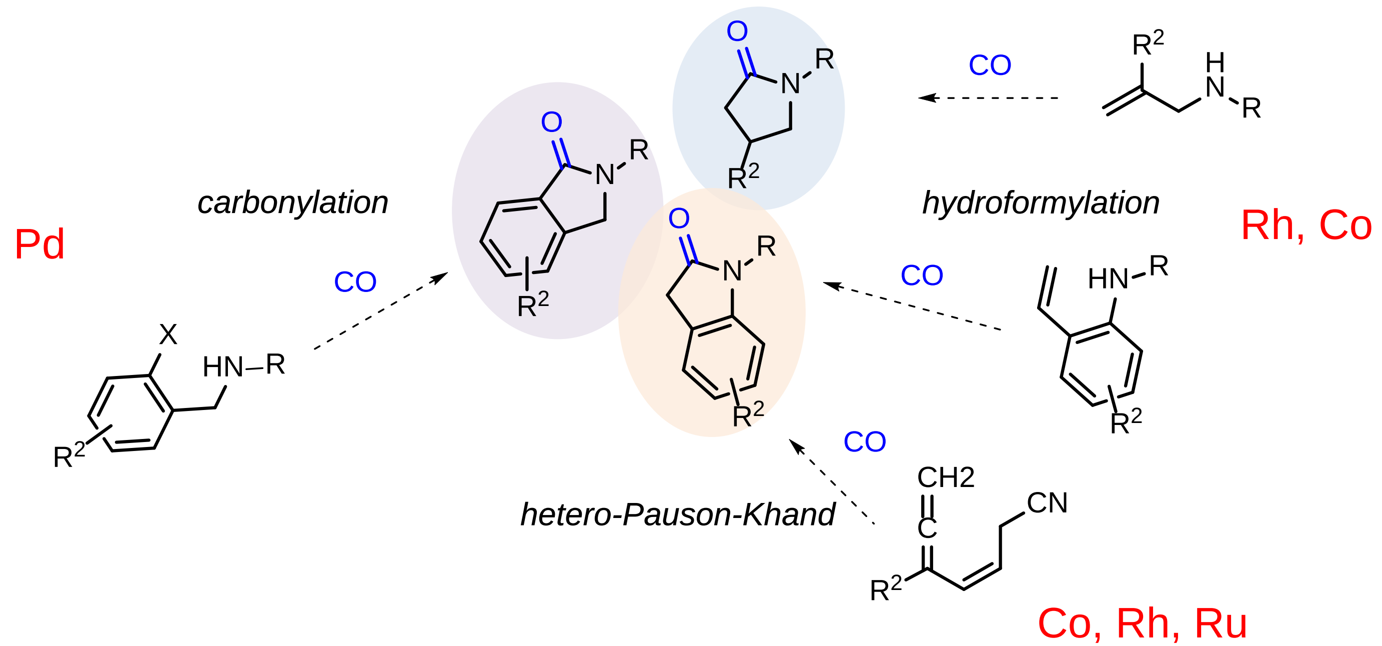
Pagoclone
anxiolytic



Sunitinib
anti-tumor

Syntheses of γ-lactams





- O. Roelen, **1938**: discovery of the OXO-process at BASF

- H. Adkins, G. Krsek, *J. Am. Chem. Soc.* **1948**, *70*, 383-386

Preparation of Aldehydes from Alkenes by the Addition of Carbon Monoxide and Hydrogen with Cobalt Carbonyls as Intermediates

By Homer Adkins and George Krsek

A U. S. patent issued to Otto Roelen[1] discloses a most interesting and rather surprising reaction, *i.e.*

$$RCH{=}CH_2 + CO + H_2 \xrightarrow[125\text{–}200\ \text{atm.}]{90\text{–}200^\circ} RCH_2CH_2CHO$$

- A. Schoenberg, R. Heck, *J. Org. Chem.* **1974**, *39*, 3327-3331

Palladium-Catalyzed Amidation of Aryl, Heterocyclic, and Vinylic Halides

A. Schoenberg and R. F. Heck*

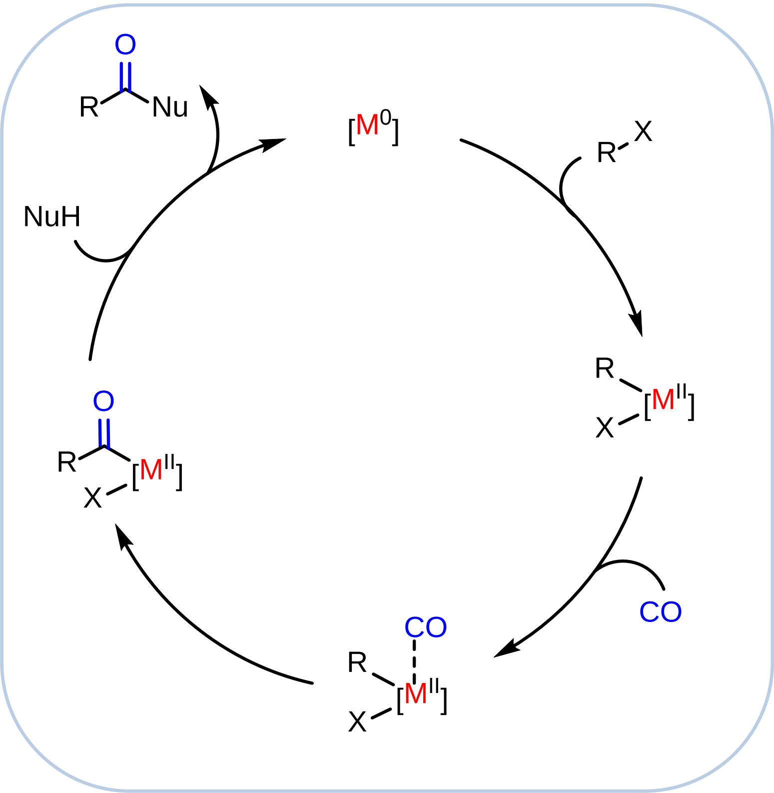
Department of Chemistry, University of Delaware, Newark, Delaware 19711

Received June 18, 1974

Aryl, heterocyclic, and vinylic halides react with CO and primary or secondary amines with a dihalobistriphenylphosphinepalladium(II) catalyst at 100° or below and 1 atm pressure to form substituted amines in good yields. If the amines are weakly basic, a strongly basic tertiary amine must also be present in stoichiometric amounts. The reaction is highly stereospecific with cis and trans vinylic halides.

Basic mechanistic pathways

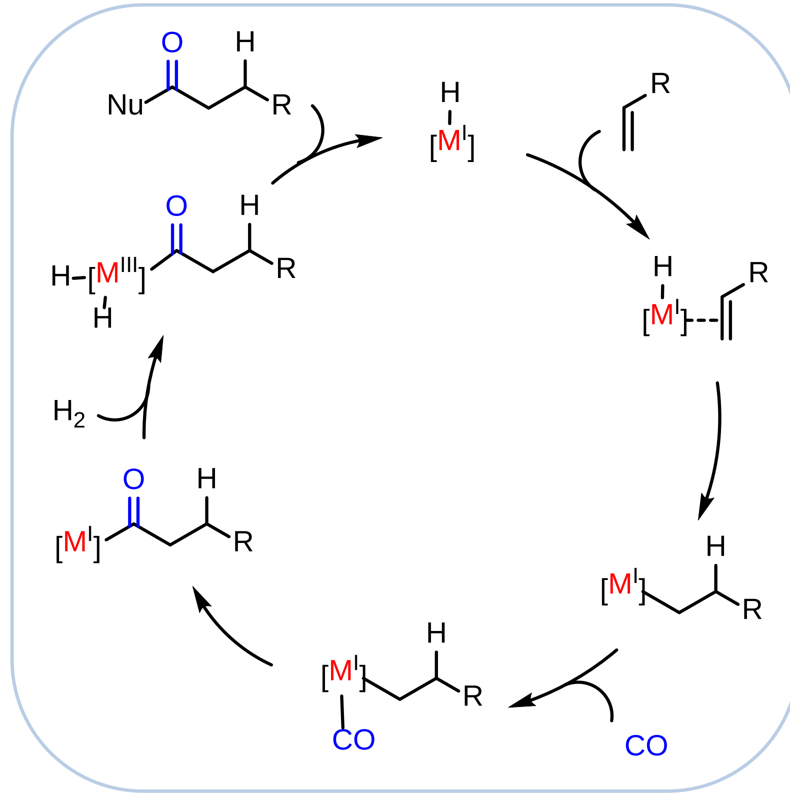
M = Pd



carbonylation type

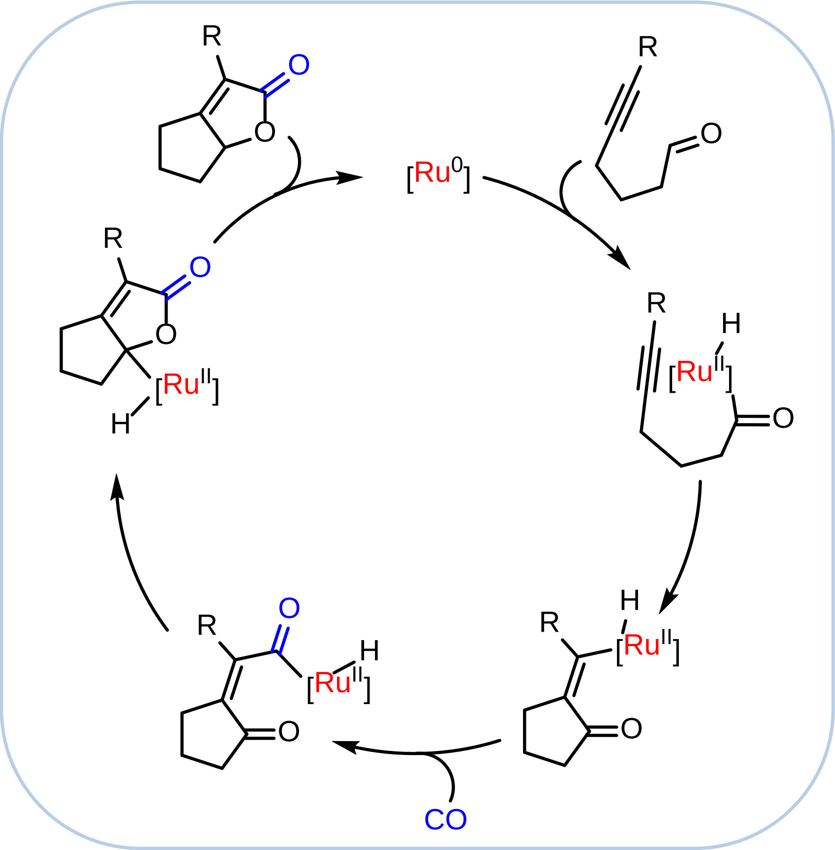
Nu = RO, RNH

M = Co, Rh



hydroformylation type

Basic mechanistic pathways

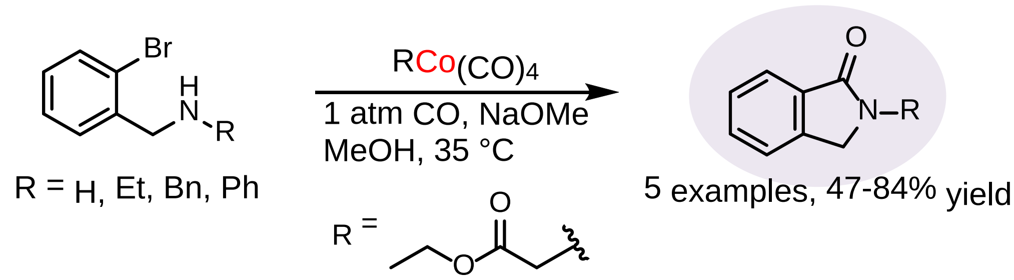


Hetero-Pauson-Khand

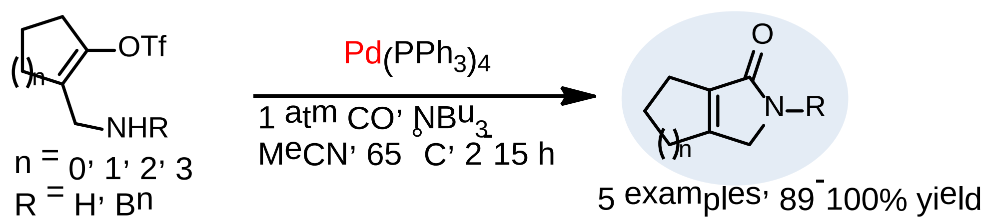
S. Murai *et al.*, *J. Am. Chem. Soc.* **1998**, *120*, 5335-5336

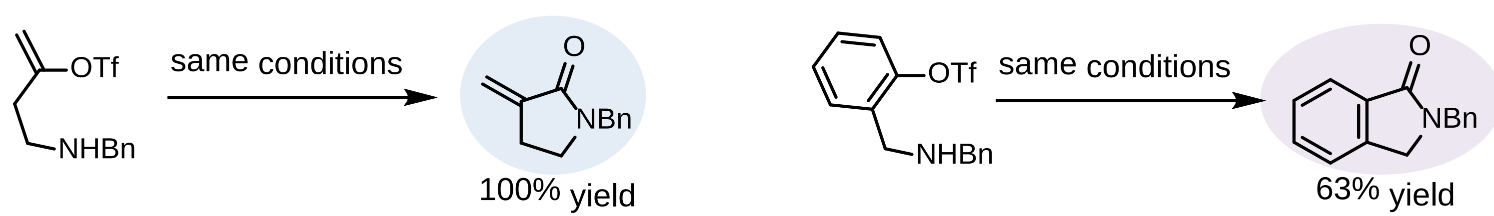
Carbonylation of amines

A. Gardano *et al.* *J. Organometal. Chem.* **1985**, *285*, 293-303



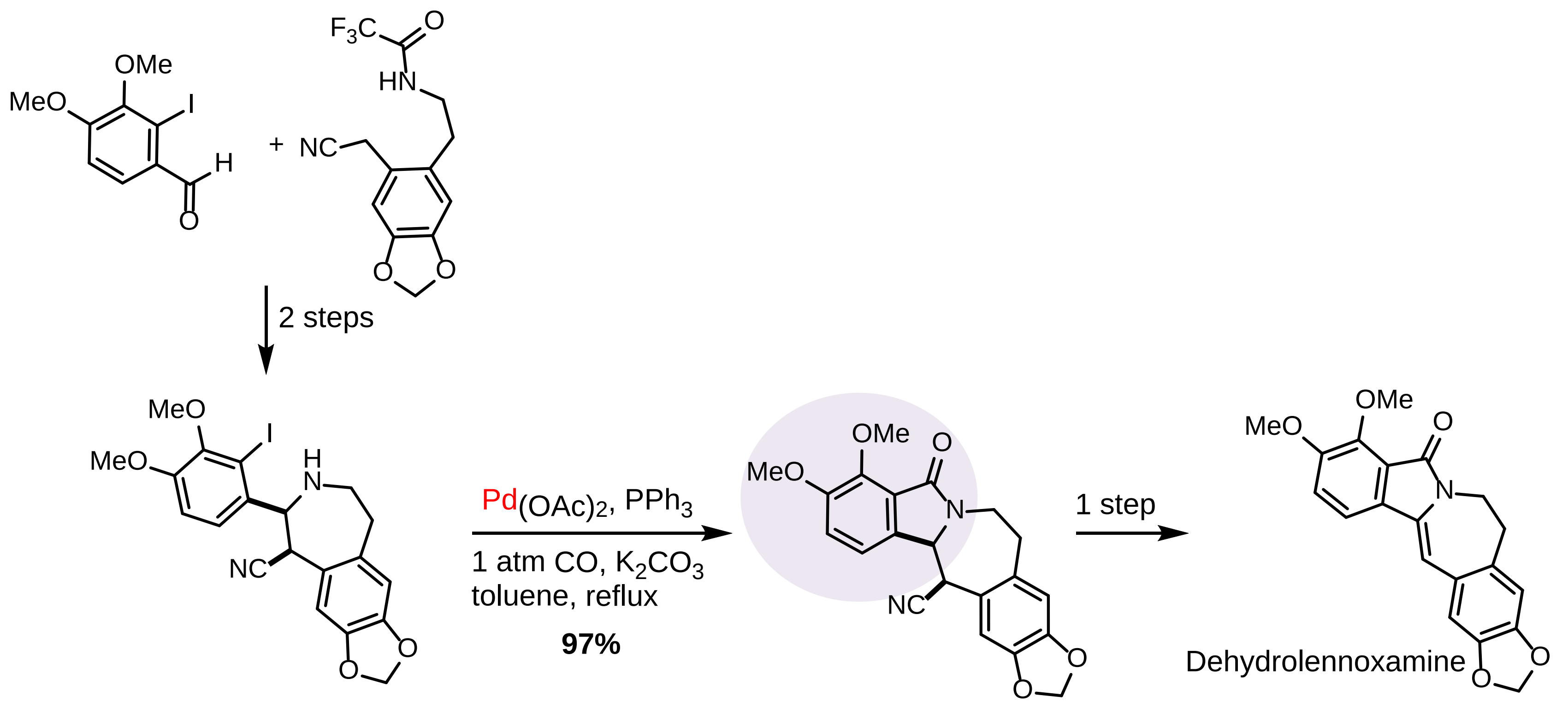
G. Crisp *et al.* *Tetrahedron* **1995**, *51*, 5585-5596





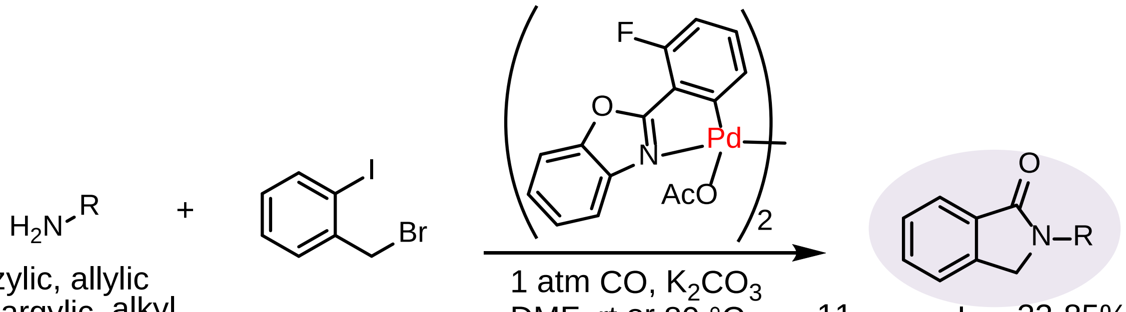
Application: synthesis of dehydrolennoxamine

K. Orito *et al*, *J. Org. Chem.* **2009**, *74*, 5486-5495



Carbonylation of amines

R. Grigg *et al*, *Tetrahedron Lett.* **2003**, *44*, 6979-6982

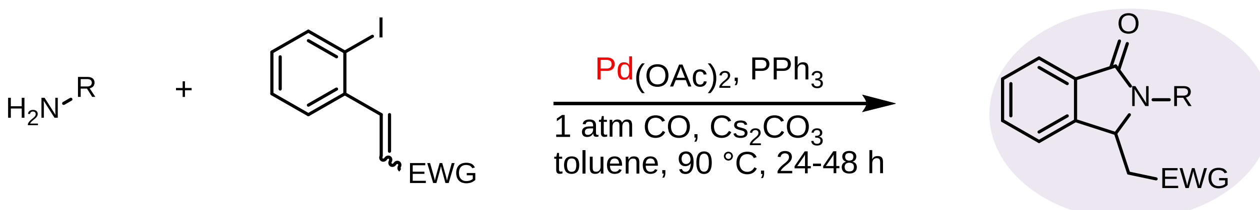


benzylic, allylic
propargylic, alkyl
amino acid ester

11 examples, 33-85% yield

benzylic amine formed in situ

R. Grigg *et al*, *Tetrahedron Lett.* **2003**, *44*, 7441-7443



R = aryl, alkyl

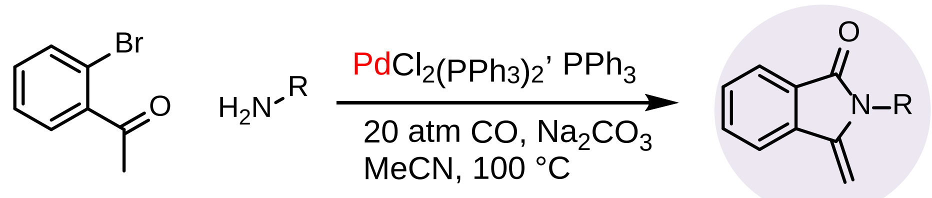
EWG = ester, amide, nitrile, ketone

20 examples, 52-95% yield

from 2-iodo-benzylbromide and RNH_2 employing $Pd(OAc)_2$ and PPh_3: L. Kollar *et al*, *Tetrahedron* **2011**, *67*, 1036-1040

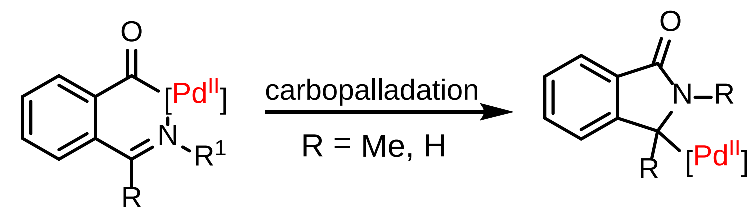
Carbonylation of imines

C. Cho *et al.* *Synth. Comm.* **2002**, *32*, 1821–1827

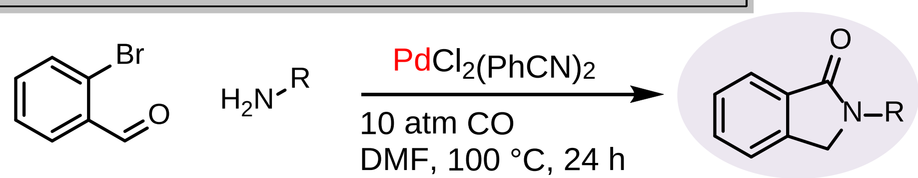


R = alkyl, benzyl, allyl

8 examples, 35-51% yield



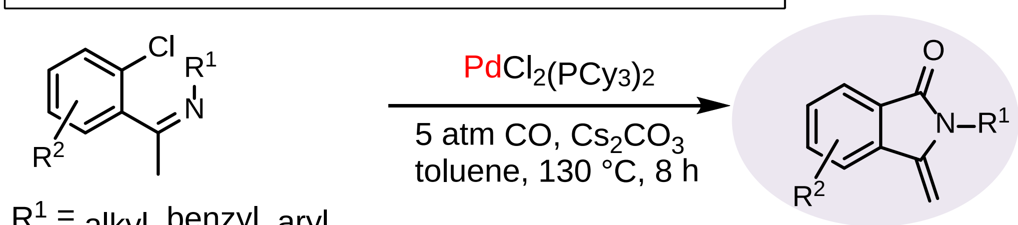
C. Cho *et al.* *Tetrahedron Lett.* **2009**, *50*, 2097–2099



R = aryl, alkyl, benzyl

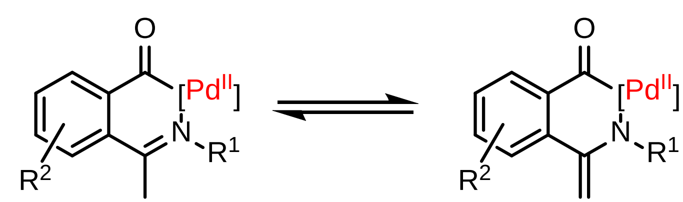
15 examples, 30-86% yield

R. Hua *et al.* *Tetrahedron Lett.* **2013**, *54*, 5159–5161



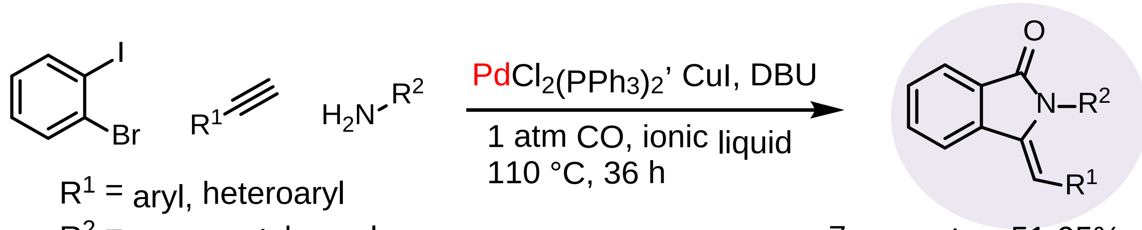
R^1 = alkyl, benzyl, aryl
R^2 = H, *m*- and *p*-Cl, *p*-F

9 examples, 31-83% yield



Sonogashira-carbonylation tandem reaction

H. Alper *et al. Org. Lett.* **2008**, *10*, 5281-5284

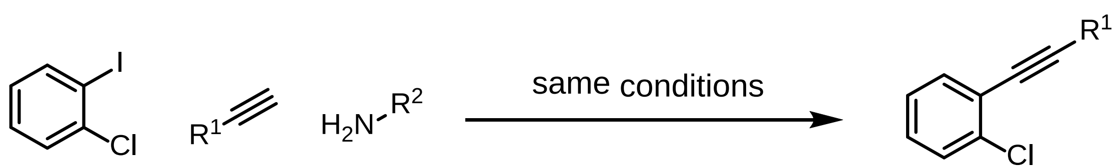


R^1 = aryl, heteroaryl
R^2 = alkyl, aryl, benzyl

7 examples, 51-95% yield

Question 1: what is the mechanism of this reaction?

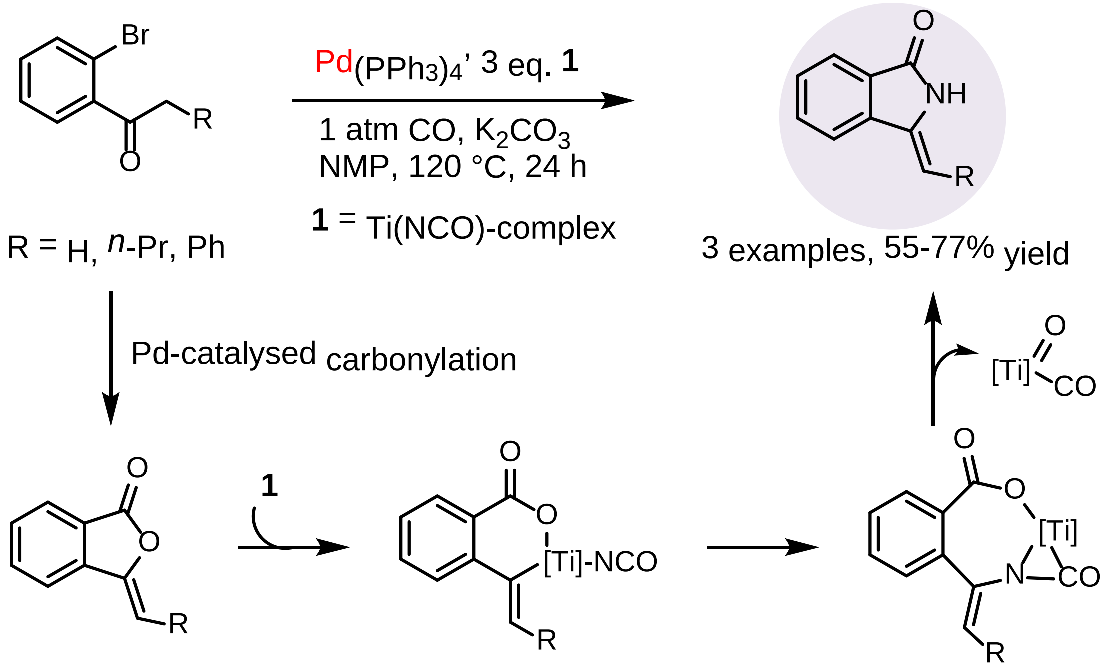
Hint:



83%

Incorporation of molecular nitrogen

M. Shibasaki *et al.*, *J. Am. Chem. Soc.* **1989**, *111*, 3725-3727

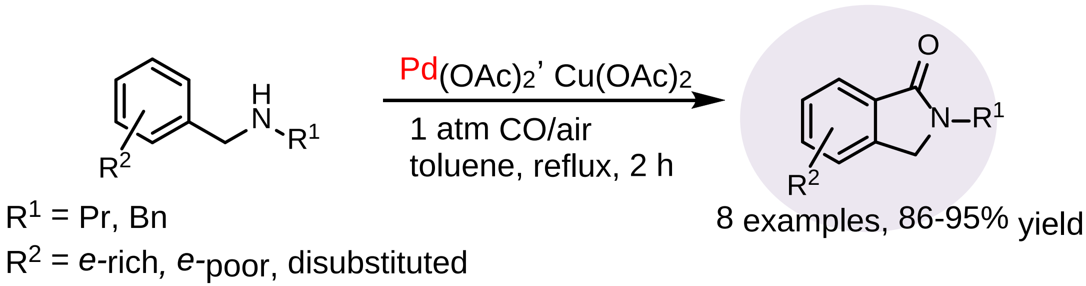


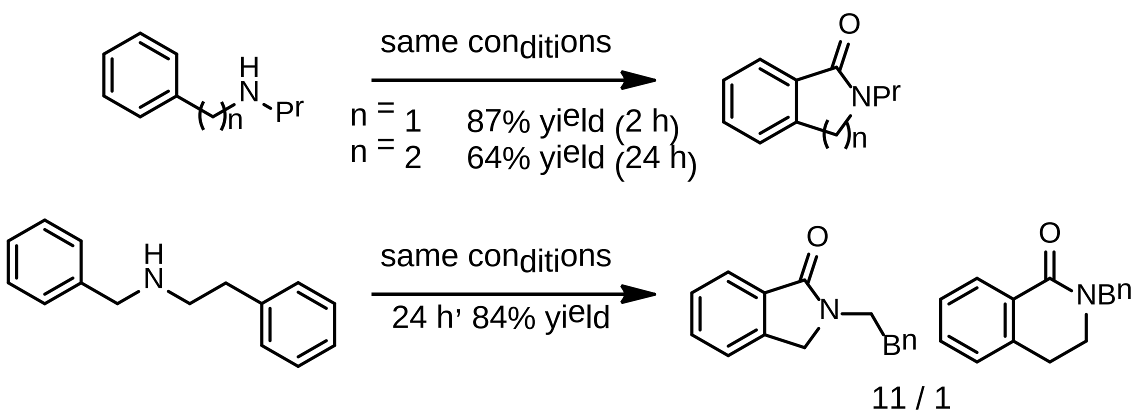
Preparation of **1**: $TiCl_4$ —(1. Mg, THF, 1 atm N_2, rt; 2. 1 atm CO_2, rt)→ [3THF·Mg_2Cl_2O·Ti(NCO)]

1

C-H activation-carbonylation tandem

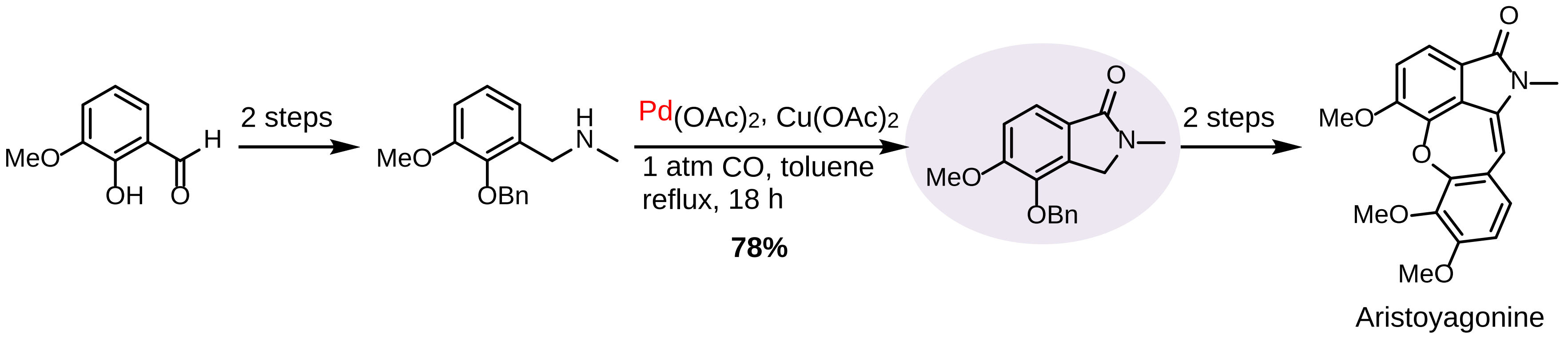
K. Orito *et al*, *J. Am. Chem. Soc.* **2004**, *126*, 14342-14343





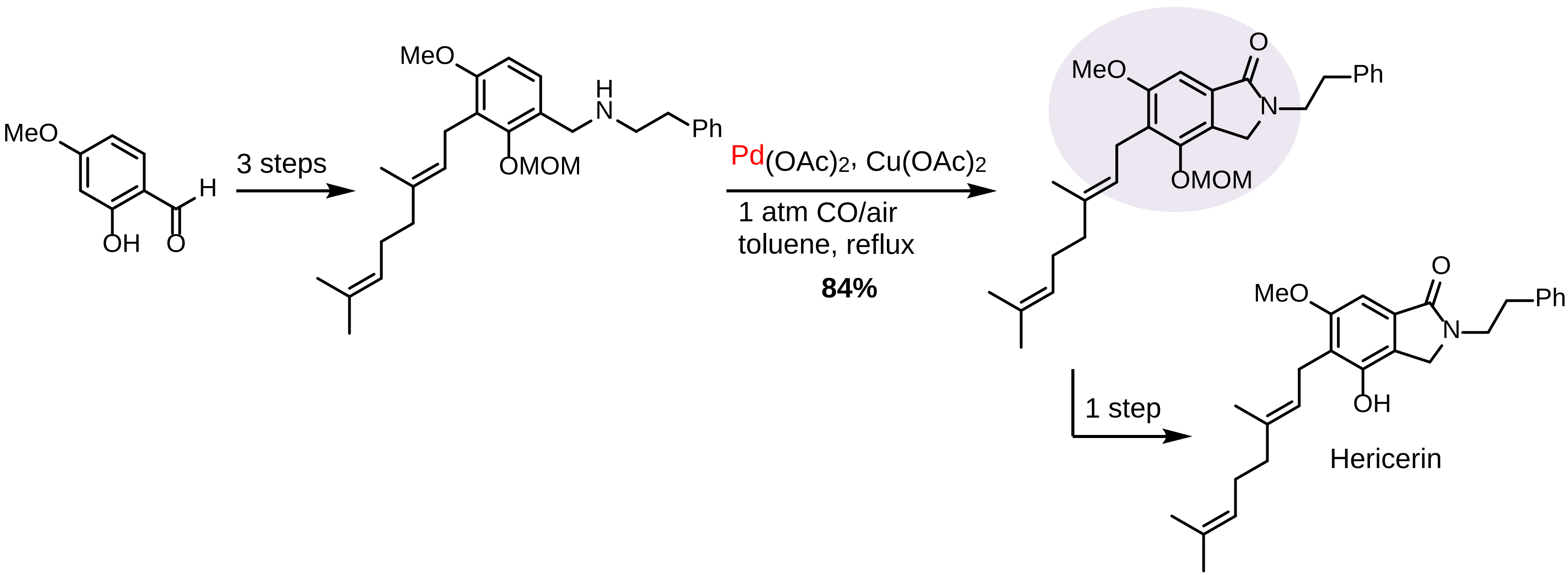
Application: synthesis of aristoyagonine

J. Heo *et al*, *Org. Lett.* **2013**, *15*, 4718-4721



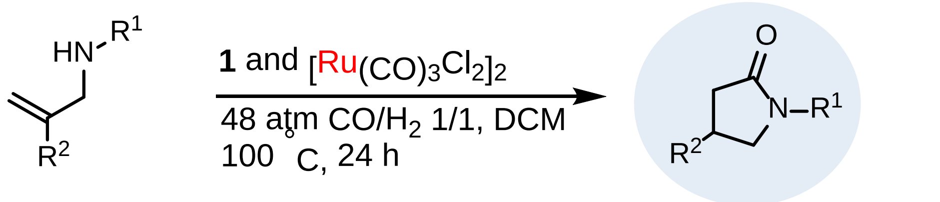
Application: synthesis of hericerin

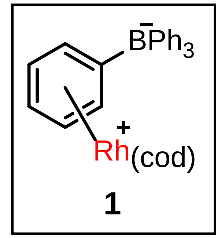
L. Miranda *et al*, *Tetrahedron Lett.* **2013**, *54*, 2131-2132



Hydroformylation of allylic amines

H. Alper *et al*, *J. Org. Chem.* **1992**, *57*, 3328-3331

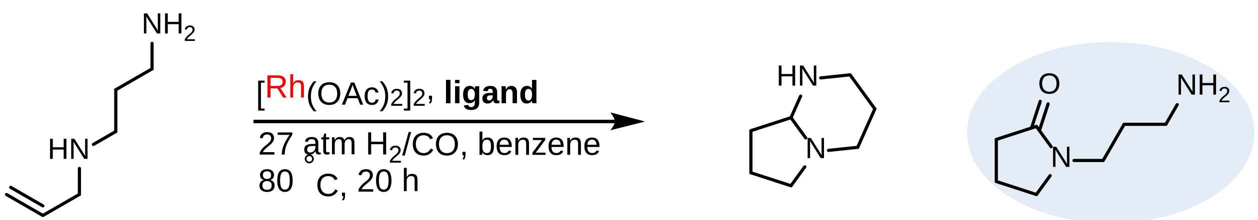




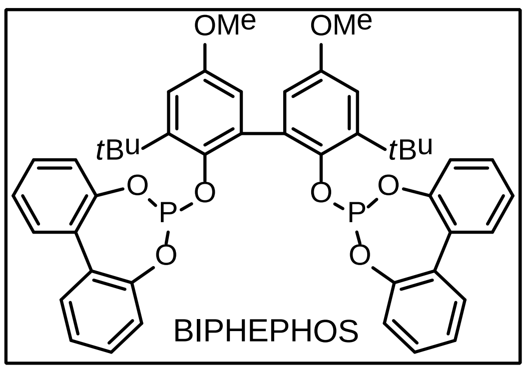
R^1 = aryl, Bn, alkyl
R^2 = H, Me

8 examples, 17-72% yield

A. Patti *et al*, *Tetrahedron Letters* **1997**, *38*, 4315-4318



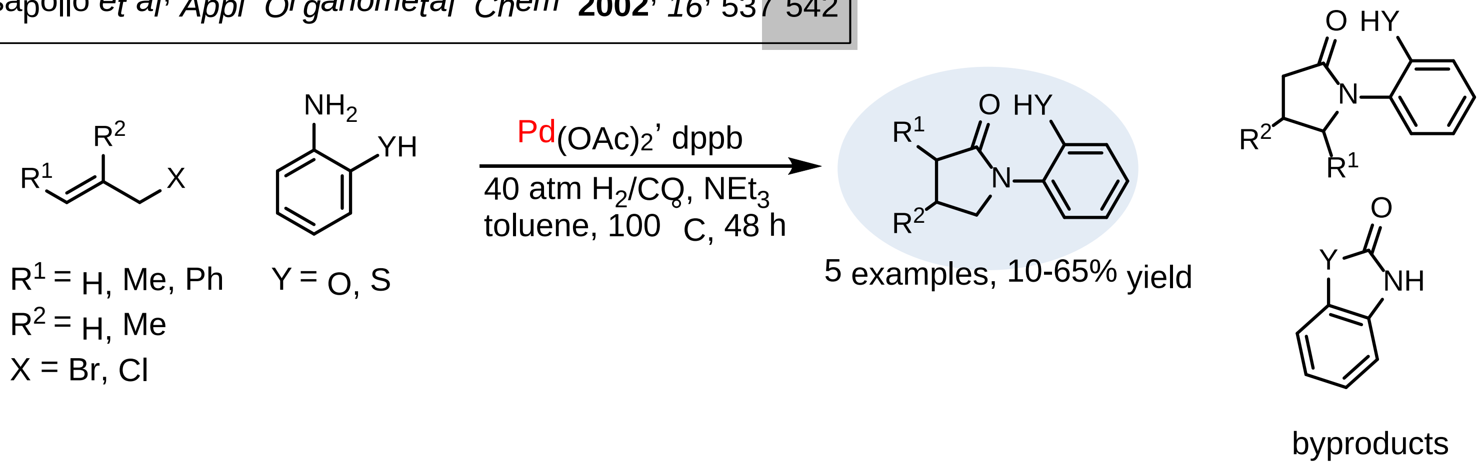
ligand	H_2/CO ratio	hydroformylation	carbonylation
PPh_3	1/1	40	60
PPh_3	9/1	95	5
PPh_3	1/9	10	90
BIPHEPHOS	1/1	100	0



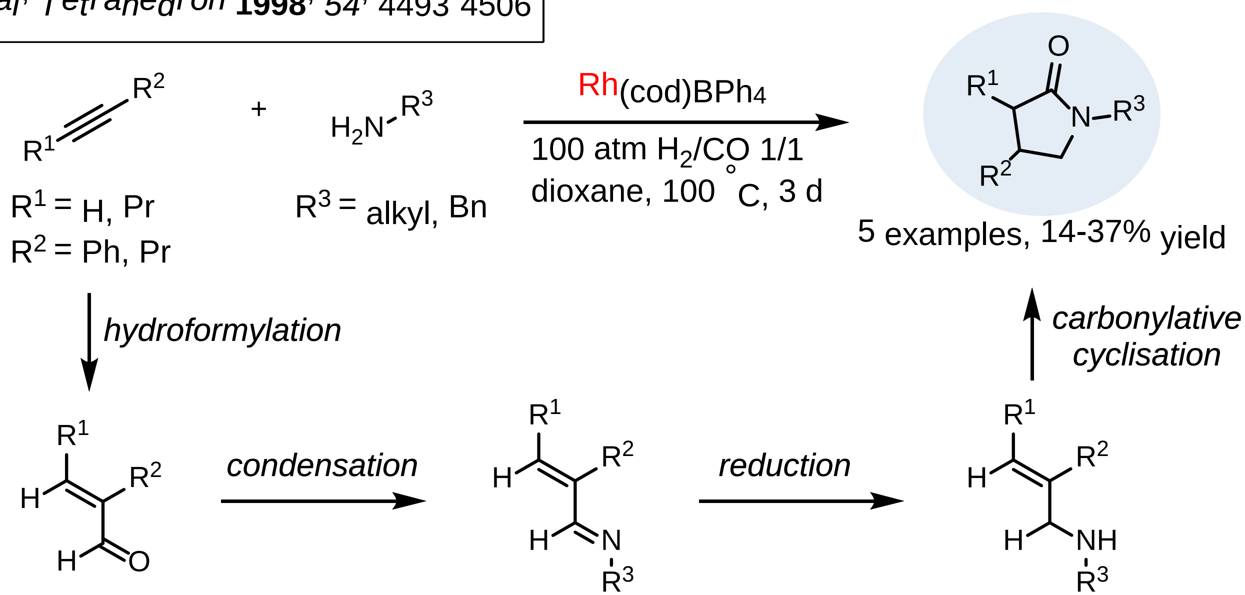
Further examples of regio- and chemoselectivity: Da Rosa *et al*, *J. Mol. Cat. A: Chemical* **2008**, *294*, 82-92.

Hydroformylation of allylic amines

G. Vasapollo *et al.*, *Appl. Organometal. Chem.* **2002**, *16*, 537-542.

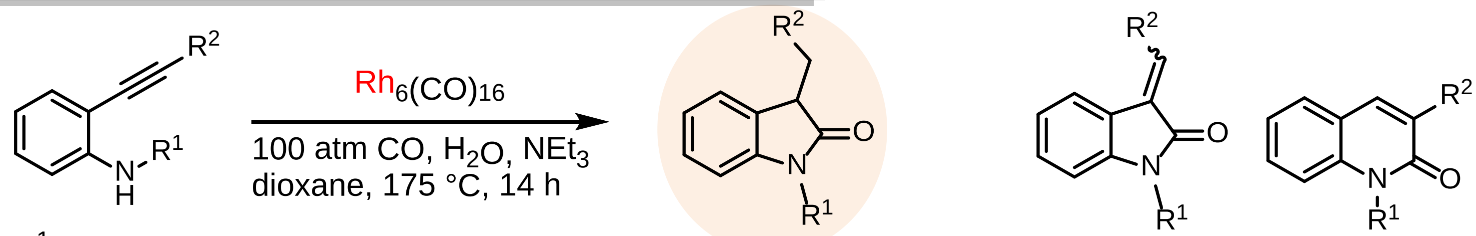


P. Eilbracht *et al.*, *Tetrahedron* **1998**, *54*, 4493-4506



Hydroformylation of 2-alkynyl anilines

S. Takahashi *et al.*, *Tetrahedron Lett.* **1995**, *36*, 6243-6246

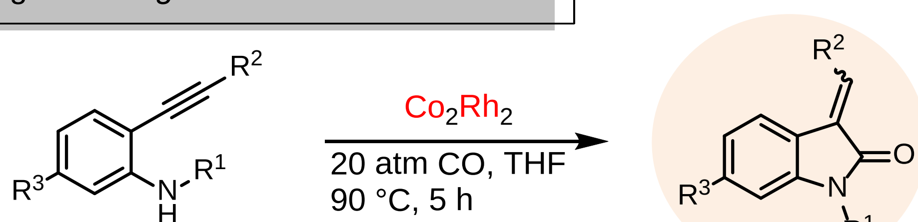


R^1 = H, Me
R^2 = aryl, alkyl

6 examples, 23-83% yield

byproducts

Y. Chung *et al.*, *Org. Lett.* **2008**, *10*, 4719-4721

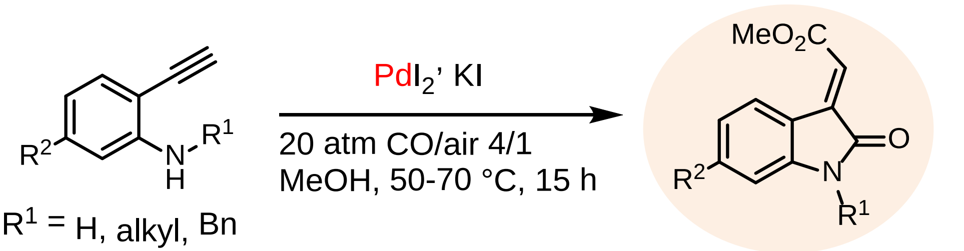


R^1 = H, alkyl, aryl, benzyl
R^2 = alkyl, vinyl, aryl
R^3 = H, Cl, *t*Bu

11 examples, 58-92% yield
E/*Z* ratio ~ 10/1

Hydroformylation of 2-alkynyl anilines

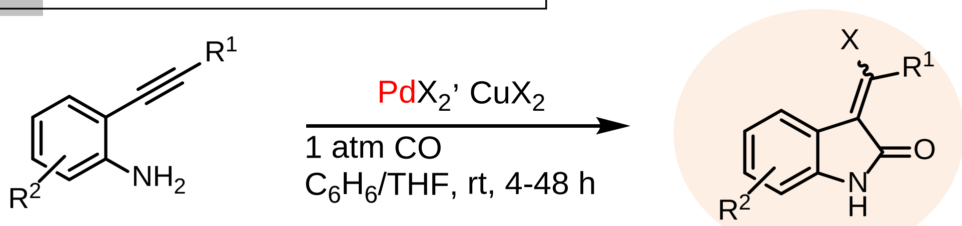
B. Gabriele *et al*, *Eur. J. Org. Chem.* **2001**, 4607-4613



R^1 = H, alkyl, Bn
R^2 = H, Me, Cl

6 examples, 48-64% yield

J. Li *et al*, *Org. Lett.* **2007**, *9*, 3413-3416



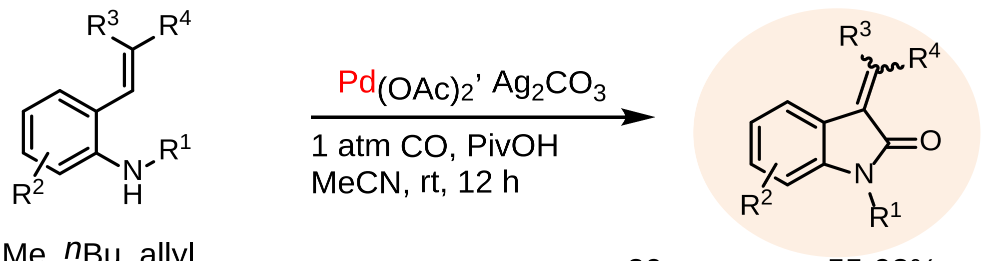
R^1 = aryl, alkyl
R^2 = H, *p*-Cl, *p*-F, *p*-NO_2

X = Br, Cl

10 examples, 31-82% yield
E/*Z* ratio 3/1 to >99/1

Carbonylation-C-H activation tandem reaction

J. Li *et al*, *Eur. J. Org. Chem.* **2014**, 616-623



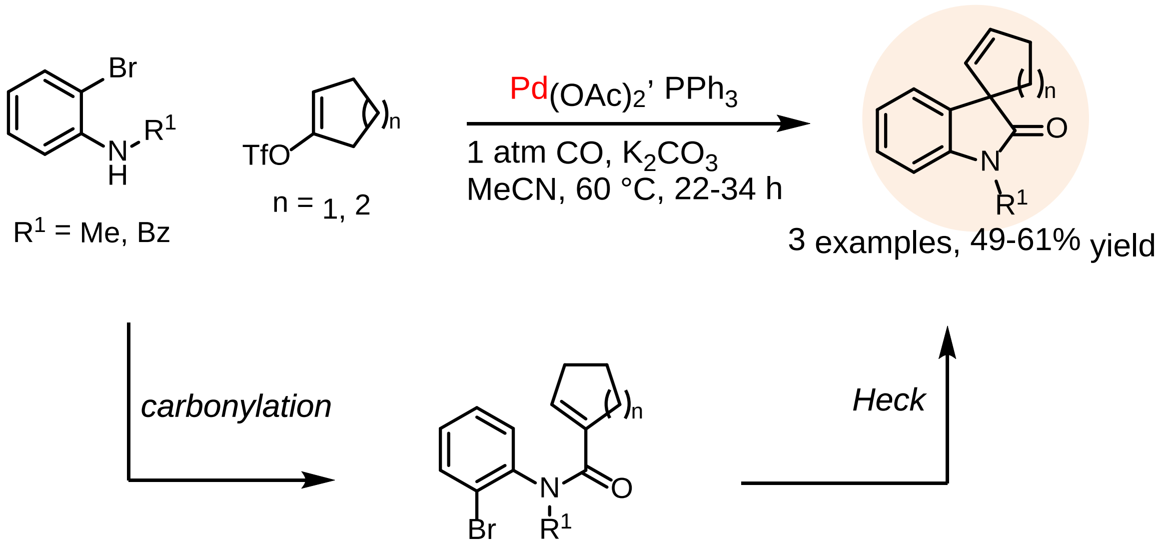
R^1 = Me, *n*Bu, allyl
R^2 = Me, Cl, ketone
R^3 = alkyl, (hetero)aryl, ester, nitrile
R^4 = H, Ph

20 examples, 55-93% yield
E/*Z* selectivity: 1/1 to 2/1

Question 2: what is the mechanism of this reaction?

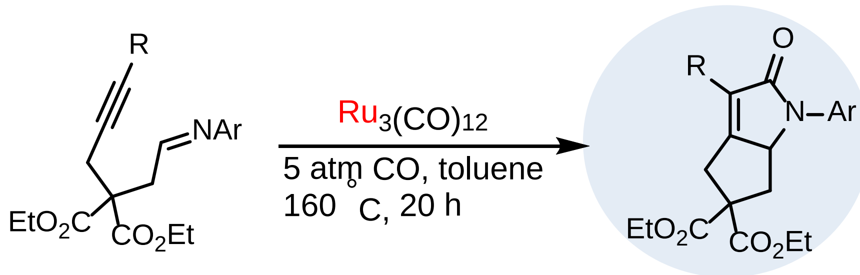
Synthesis of the indolinone core

R. Grigg *et al*, *Tetrahedron Lett.* **1996**, *37*, 695-698



Hetero-Pauson-Khand type

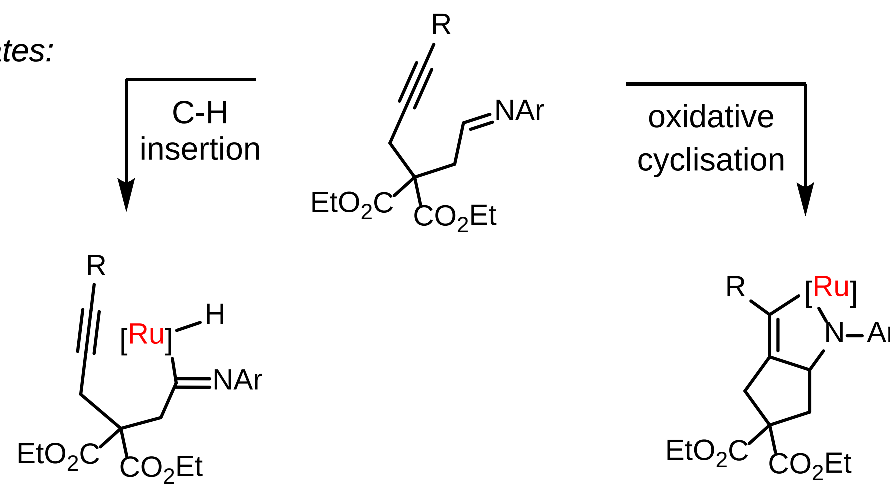
S. Murai *et al*, *J. Organomet. Chem.* **1999**, *579*, 177-181



R = TMS, Ph, alkyl
Ar = *p*-MeOC_6H_4

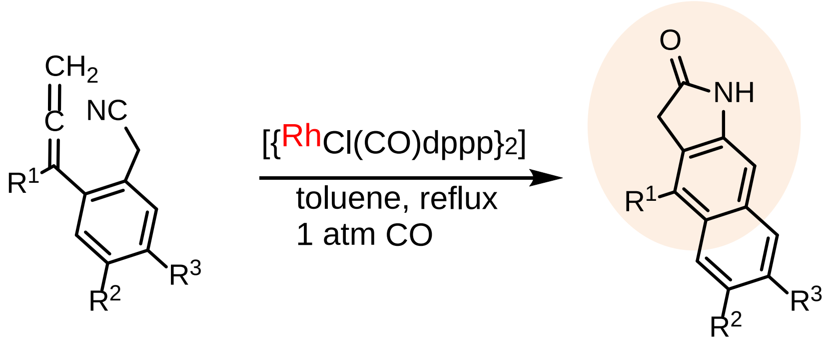
4 examples, 43-66% yield

possible intermediates:



Hetero-Pauson-Khand type

C. Mukai *et al*, *Angew. Chem. Int. Ed.* **2013**, *52*, 11138-11142

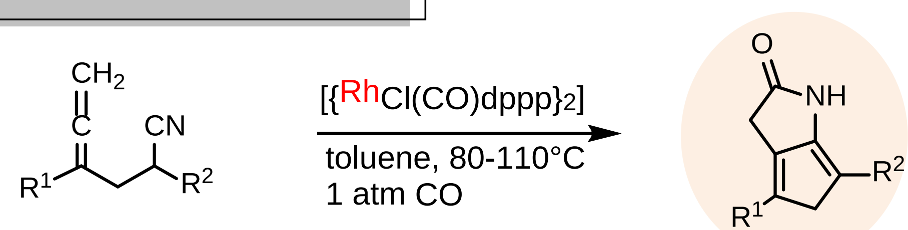


R^1 = SO_2Ph, Me, H
R^2 = H, OMe, Cl, NO_2
R^3 = H, OMe, NO_2

13 examples, 15-88% yield

Hetero-Pauson-Khand type

C. Mukai *et al*, *Angew. Chem. Int. Ed.* **2013**, *52*, 11138-11142

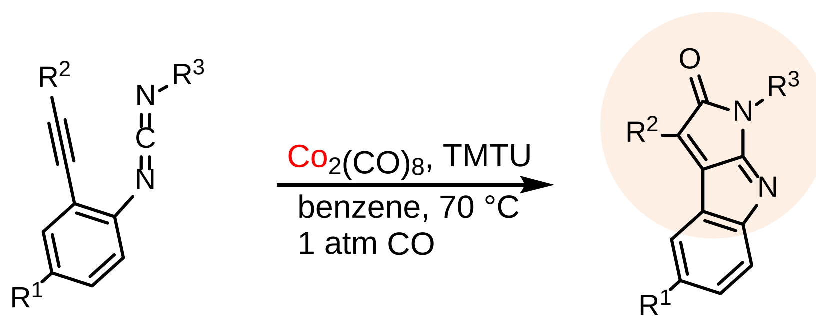


R^1 = Me, *i*Pr, *n*Bu, *t*Bu, CH_2OTBS

R^2 = CN, CO_2Et, SO_2Ph, Piv, *o*- and *p*-NO_2-C_6H_4

13 examples, 16-83% yield

C. Mukai *et al*, *Org. Lett.* **2006**, *8*, 83-86

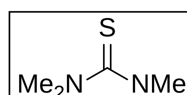


R^1 = H, Me, OMe, Cl

R^2 = TMS, alkyl, CH_2OTHP, $(CH_2)_2OTBS$

R^3 = Me, aryl

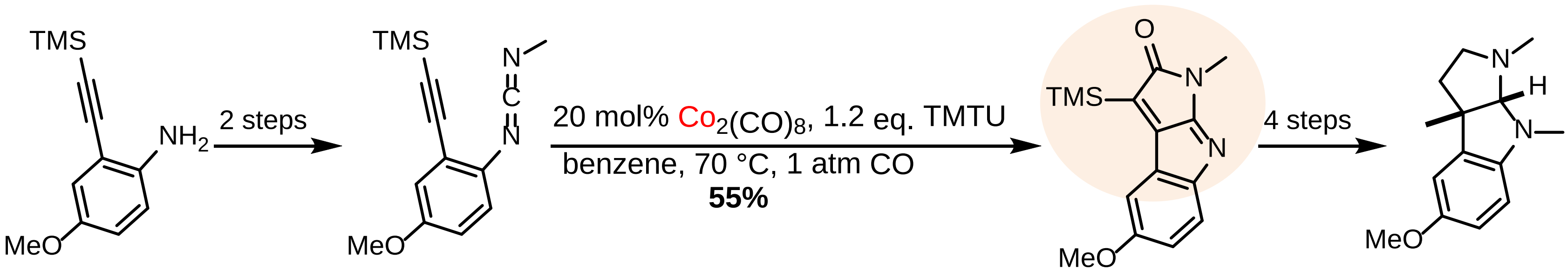
10 examples, 5-66% yield



TMTU

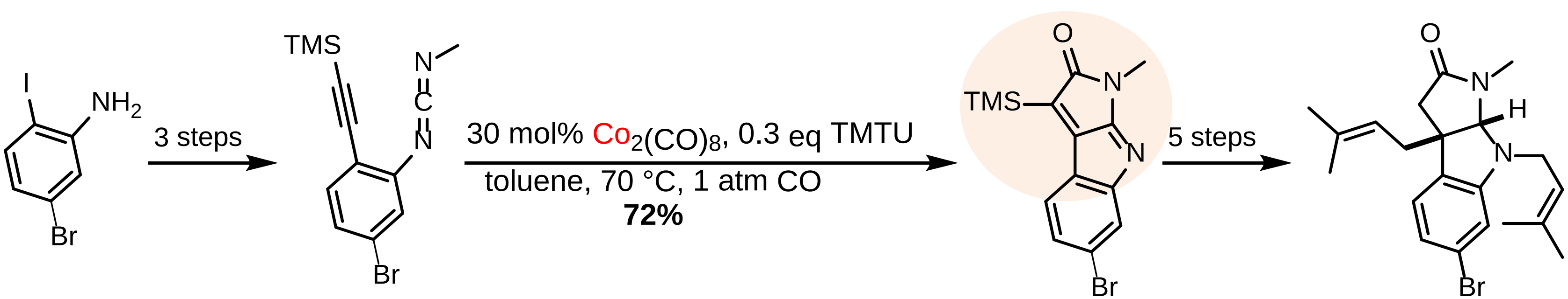
Syntheses of Esermethole and Flustramide B

C. Mukai *et al*, *Org. Lett.* **2006**, *8*, 83-86



Esermethole

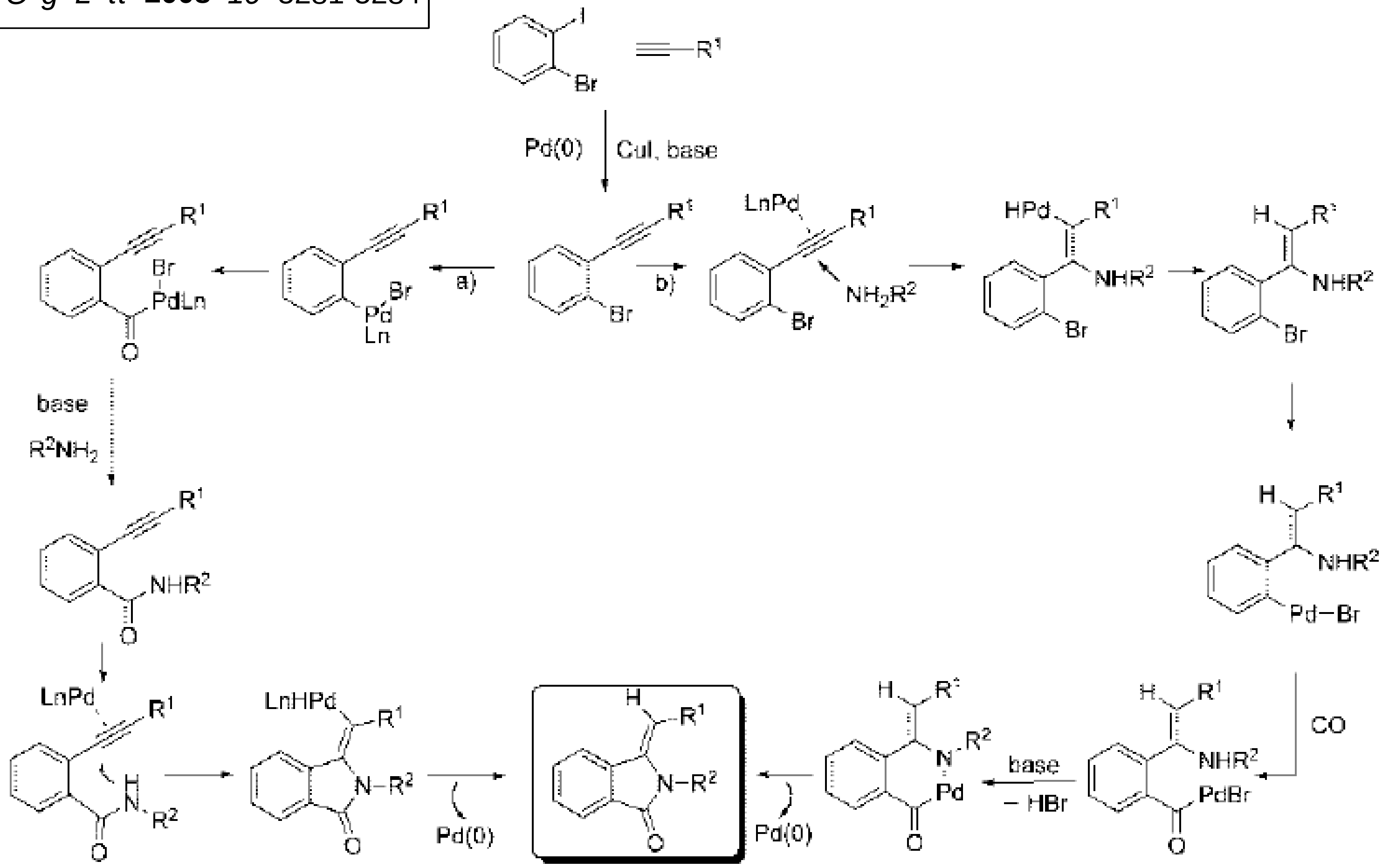
C. Mukai *et al*, *J. Org. Chem.* **2007**, *72*, 6878-6884



Flustramide B

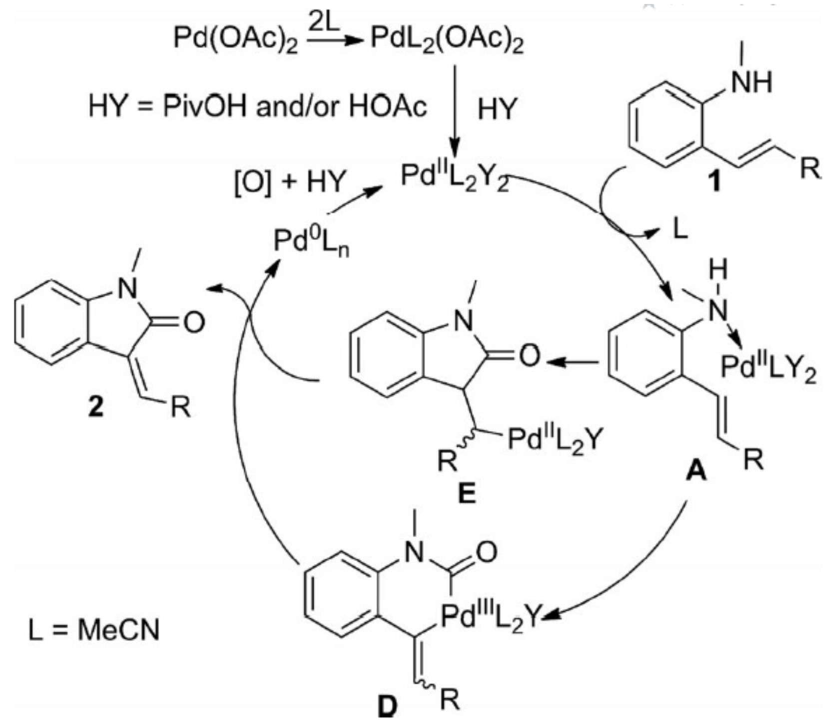
Question 1

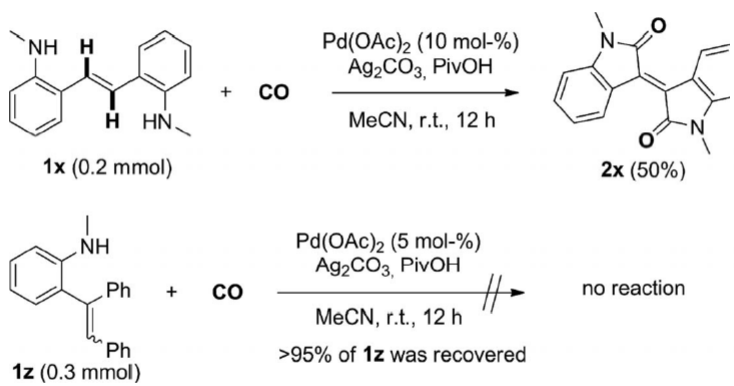
H. Alper *et al*, *Org. Lett.* **2008**, *10*, 5281-5284



Question 2

J. Li *et al*, *Eur. J. Org. Chem.* **2014**, 616-623





Catalytic enantioselective 1,3-dipolar cycloadditions of azomethine ylides

DANIELE PERROTTA
PhD under the supervision of Prof. Dr. Jérôme Waser

FRONTIERS IN CHEMICAL SYNTHESIS: HETEROCYCLIC CHEMISTRY

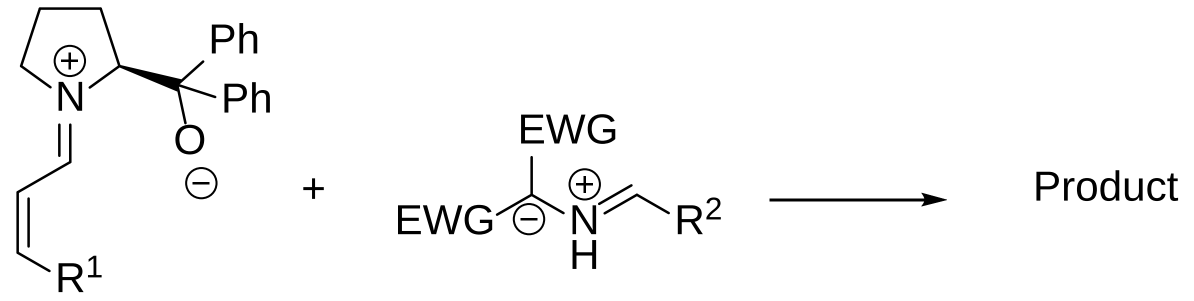
11.05.15

LCSO EPFL

Questions

1. In the work reported by Hou 'inversion of diastereoselectivity' the use of *t*BuOK as base instead of Et_3N provides higher yields. Explain.

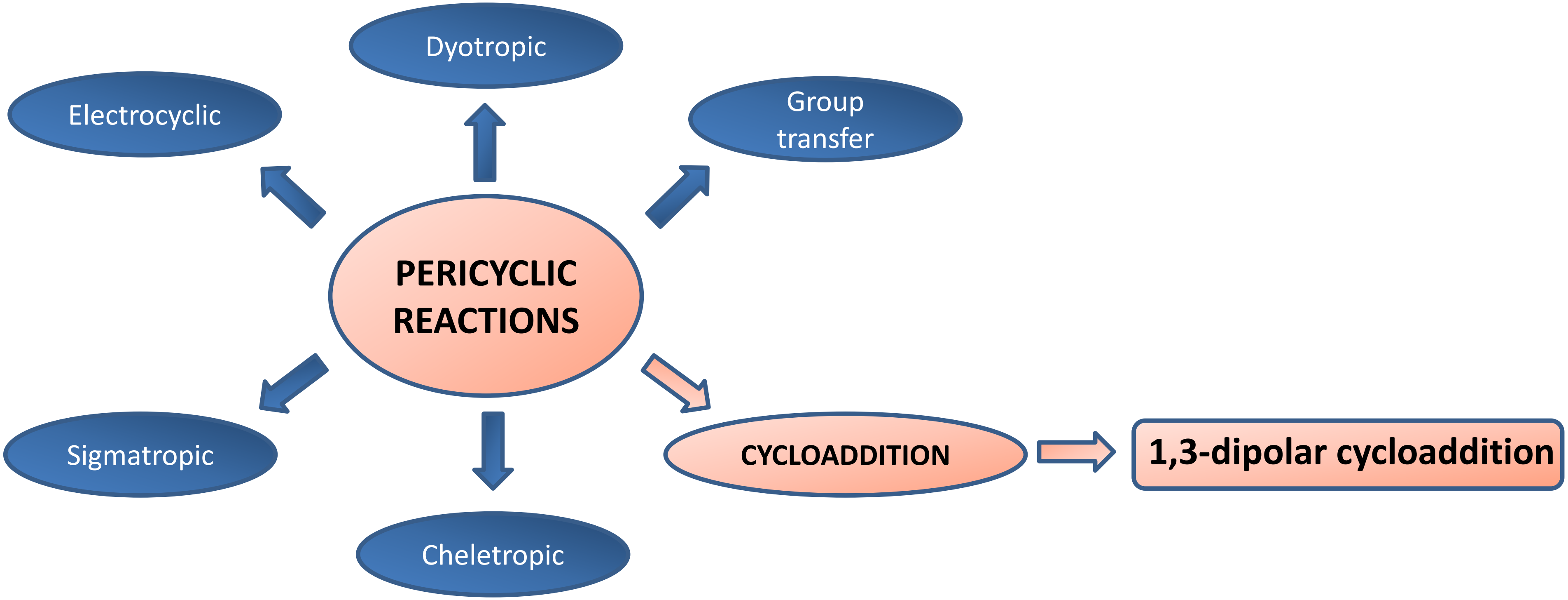
2. Draw the structure of the product (at least the correct diastereoisomer), knowing that the reaction is concerted with an *endo* transition state.



Outline of the talk

- Introduction
- Metal catalyzed 1,3-dipolar cycloadditions of azomethine ylides
- Organocatalyzed 1,3-dipolar cycloadditions of azomethine ylides
- Conclusions and outlook
- Questions

Introduction

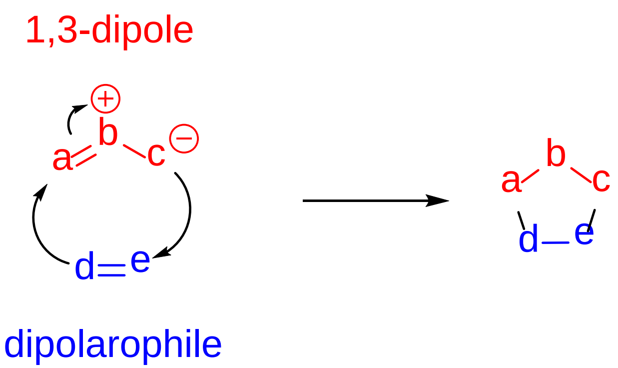


Pericyclic reaction: concerted reaction, cyclic TS.
Cycloaddition: two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity.[1]

[1] International Union of Pure and Applied Chemistry (IUPAC). "Cycloaddition".

1,3-dipolar cycloaddition (DC)

General mechanism

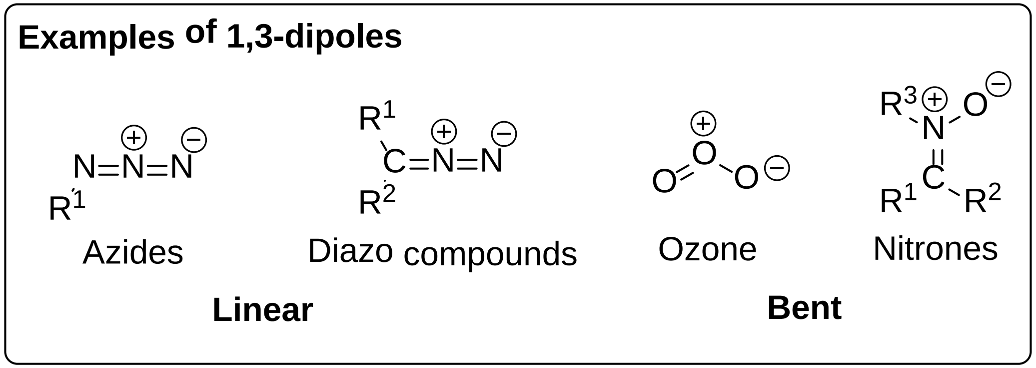


2 bonds formed

- **Atom economy**
- Rapid access to chemical complexity
- Efficient method for the synthesis of **highly functionalized heterocycles**

1,3-dipoles

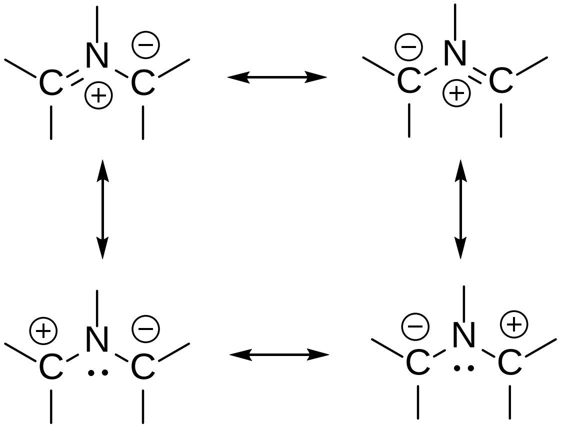
1,3-dipole: dipolar compound with delocalized electrons and a separation of charge over three atoms



Azomethine ylides:

Octet structures

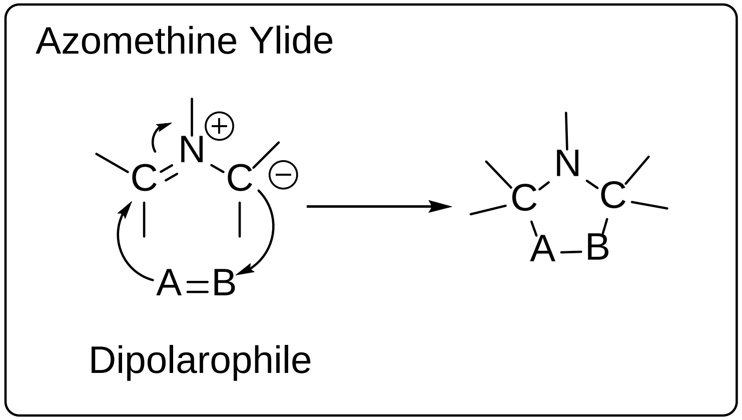
Sextet structures



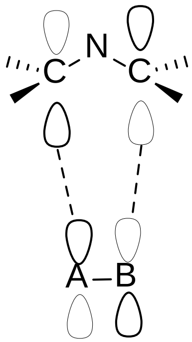
- 4 electrons in 3 parallel π orbitals
- Bent-type structure
- Enable synthesis of **nitrogen-containing heterocycles**

1,3-DC of azomethine ylides

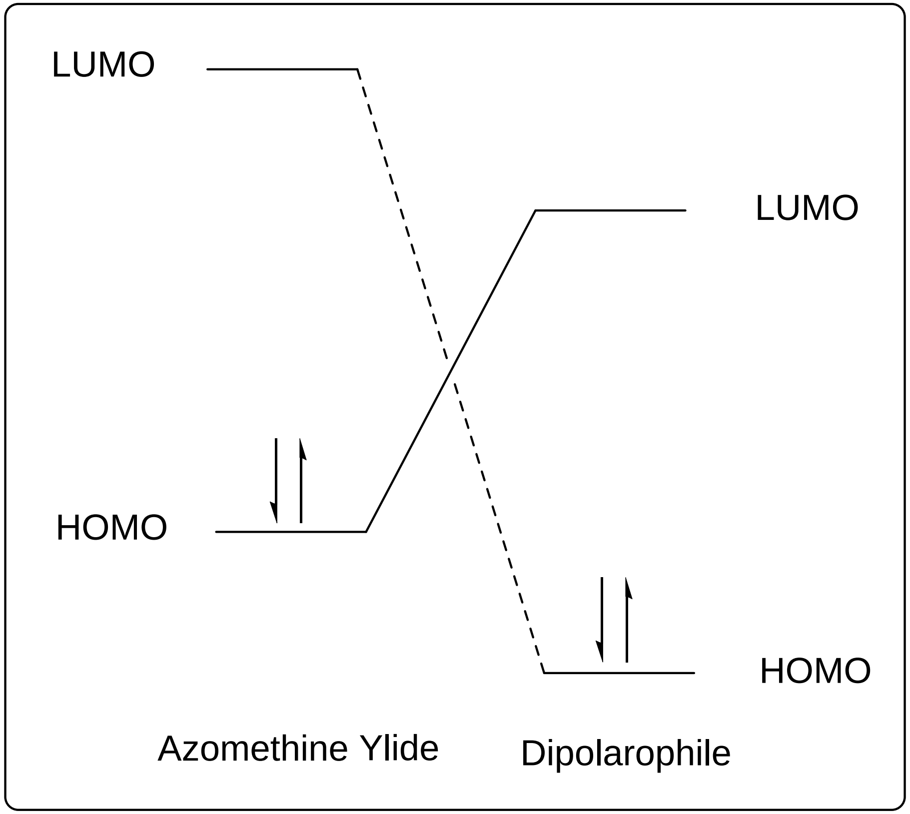
Mechanism:



Usually concerted mechanism
[π^4s + π^2s] = Suprafacial/suprafacial process thermally allowed:

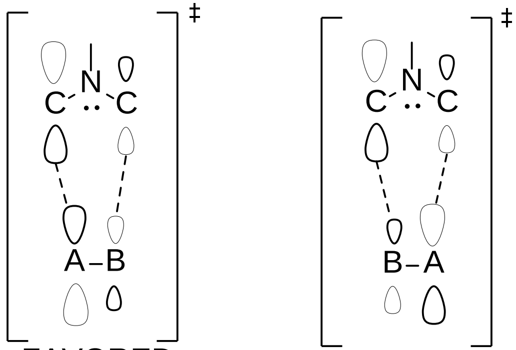


HOMO-LUMO interactions:



1,3-DC of azomethine ylides

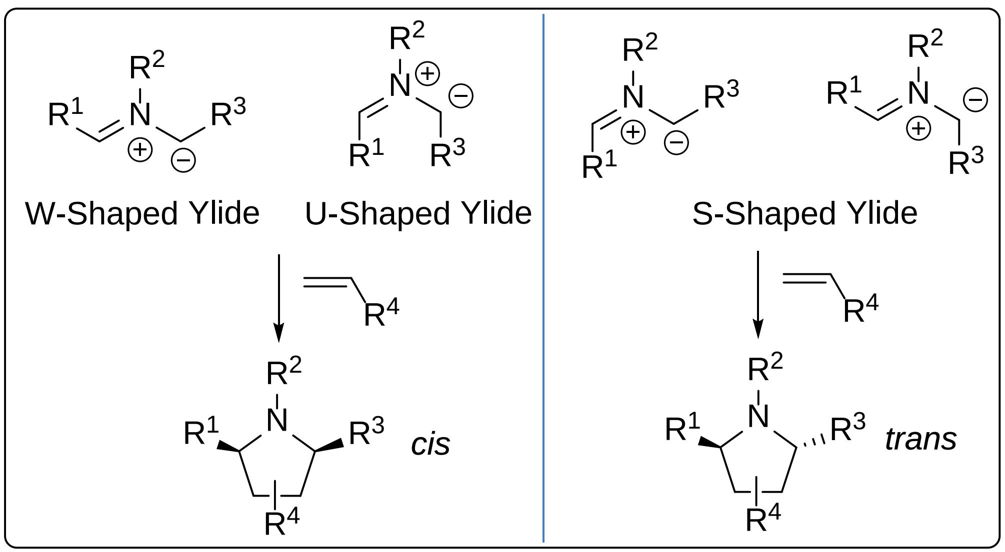
Regiochemistry:



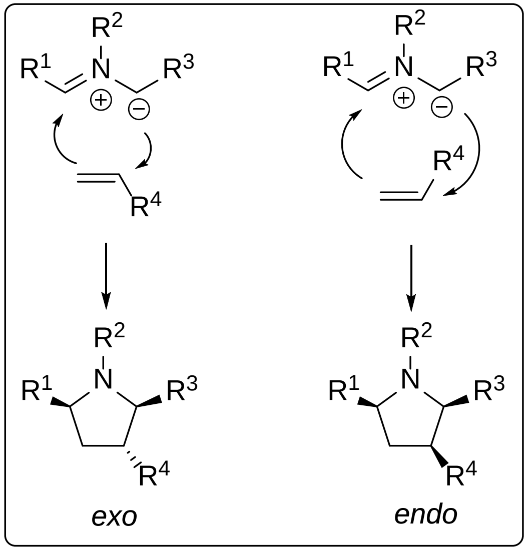
FAVORED

Stereochemistry:

1,3-dipole:

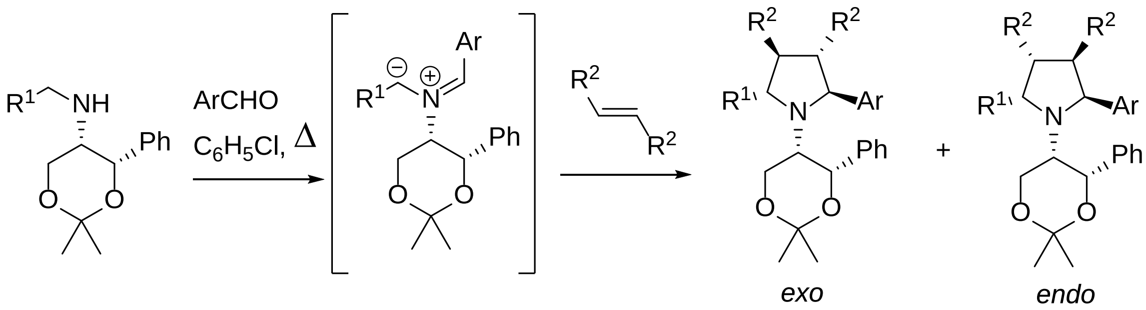


Exo/Endo TS:

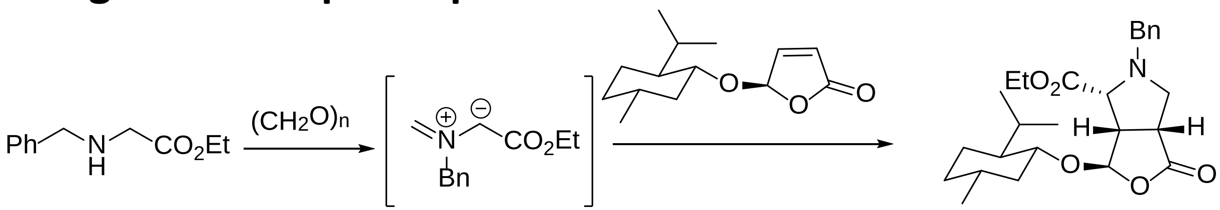


Enantioselective 1,3-DC of azomethine ylides

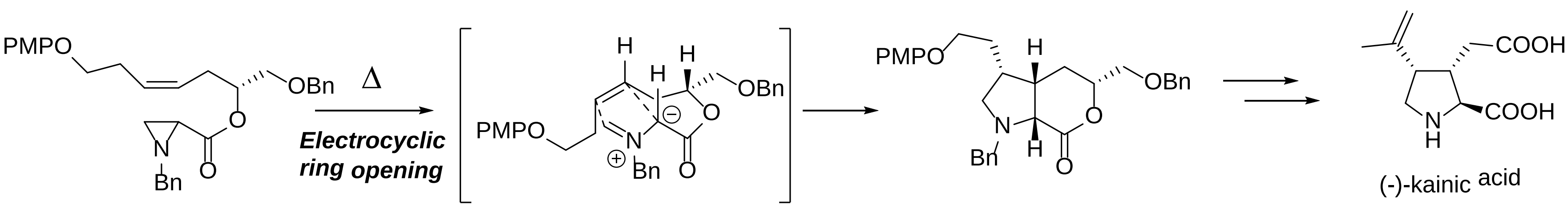
Enders: Chiral 1,3-dipole



Feringa: Chiral dipolarophile



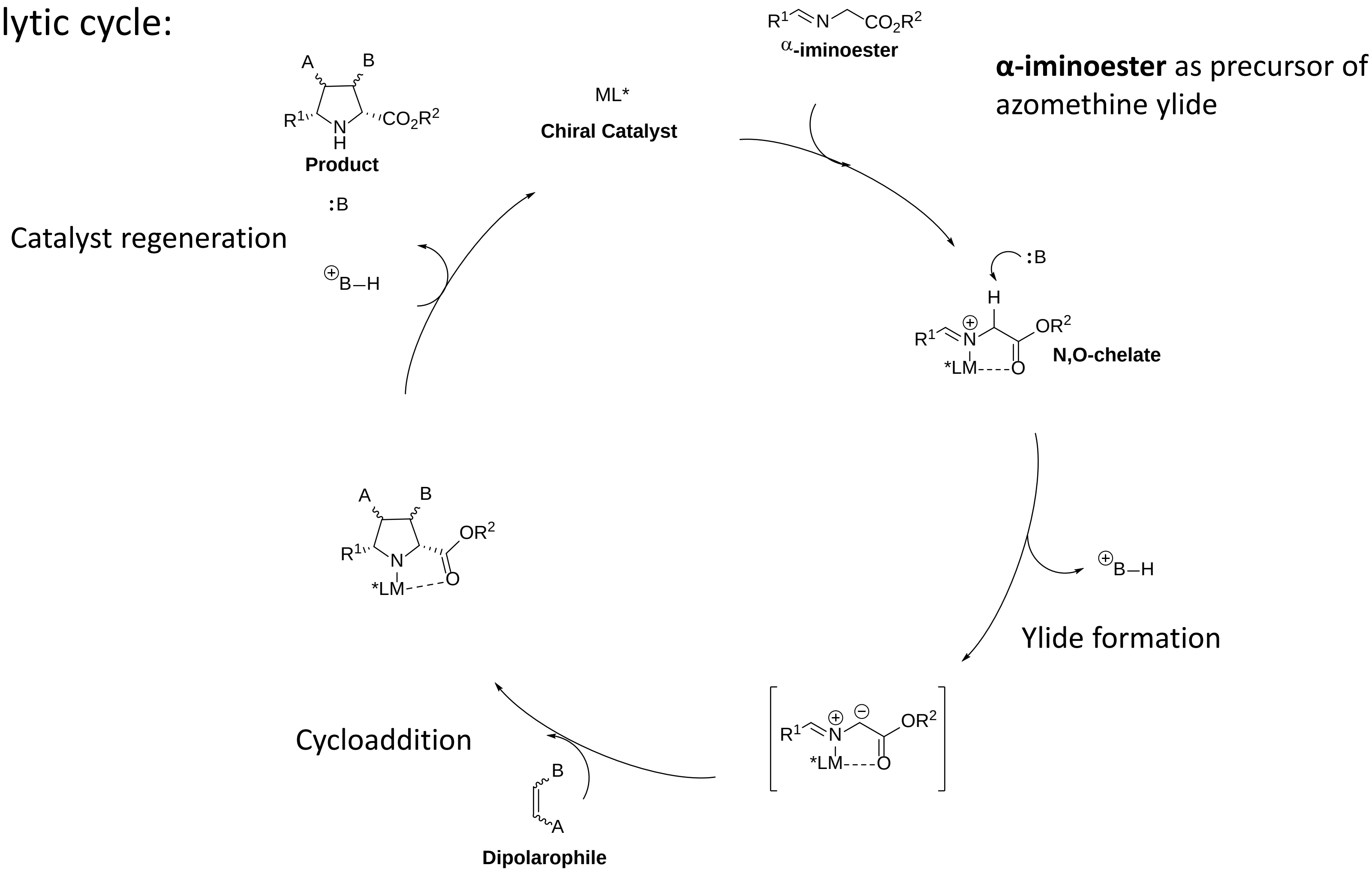
Ogasawara: Intramolecular 1,3-DC



Meyer, I.; Runsink, J.; Raabe, G.; Enders, D, *Tetrahedron* **1998**, *54*, 10733.
Rispens, M. T.; Keller, E.; de Lange, B.; Zijlstra, R. W. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 607.
Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204.

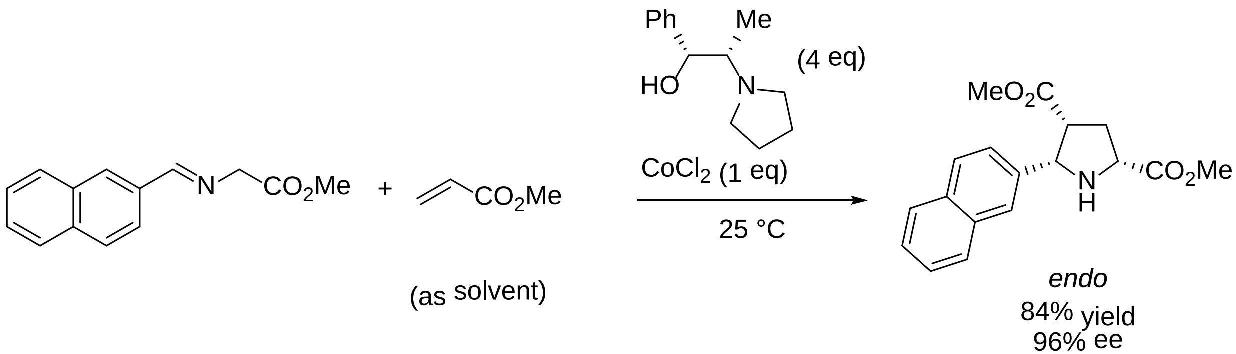
Metal catalyzed enantioselective 1,3-DC of azomethine ylides

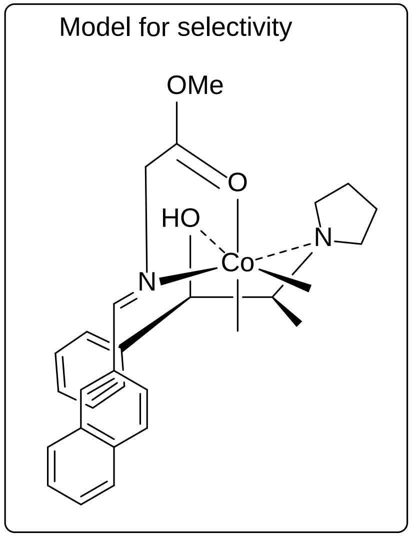
Catalytic cycle:



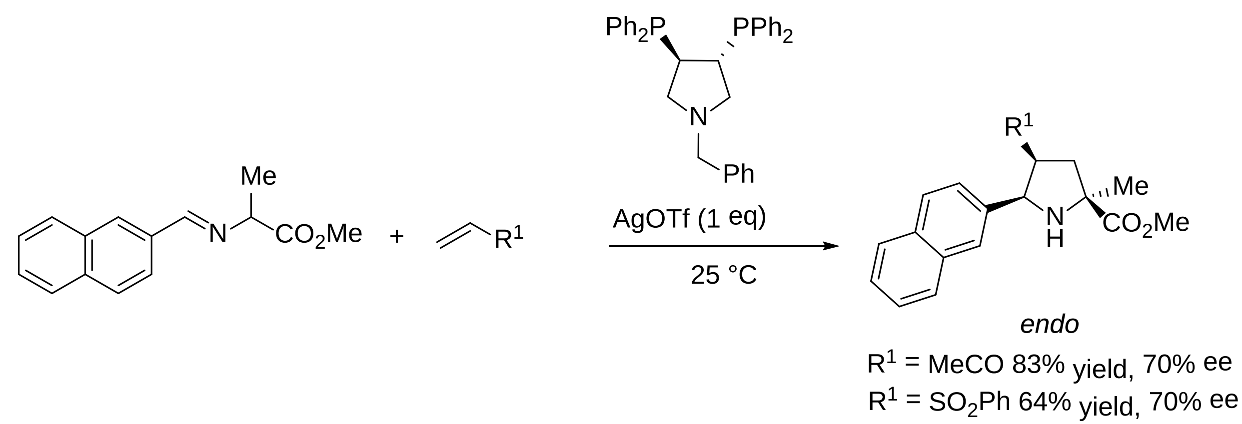
Pioneering works in catalytic enantioselective 1,3-DC

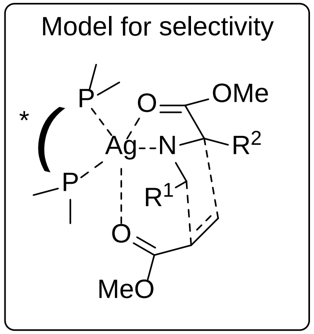
Grigg: Chiral Copper Catalyst





Grigg: Chiral Silver Catalyst

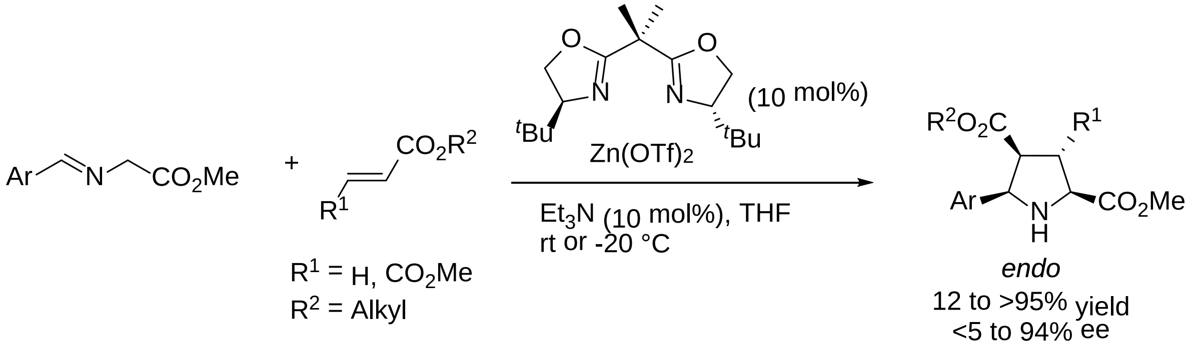




Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817.
Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475.

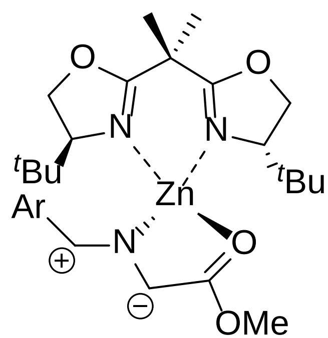
Pioneering works in catalytic enantioselective 1,3-DC

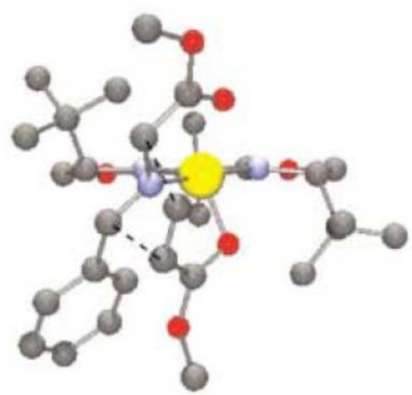
Jørgensen: Zinc catalyzed 1,3-DC



Model for selectivity:

Tetrahedral geometry:
Wrong enantiomer



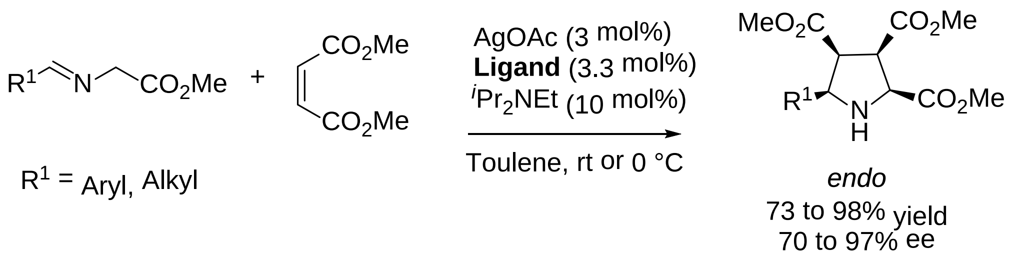


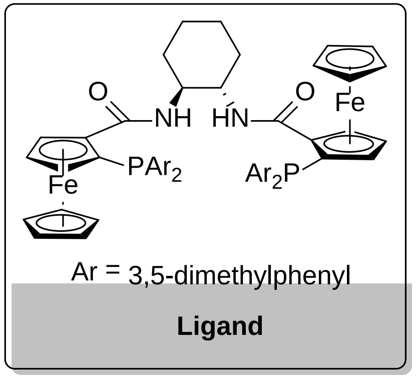
Bipyramidal geometry (dipolarophile coordinated):
Observed enantiomer

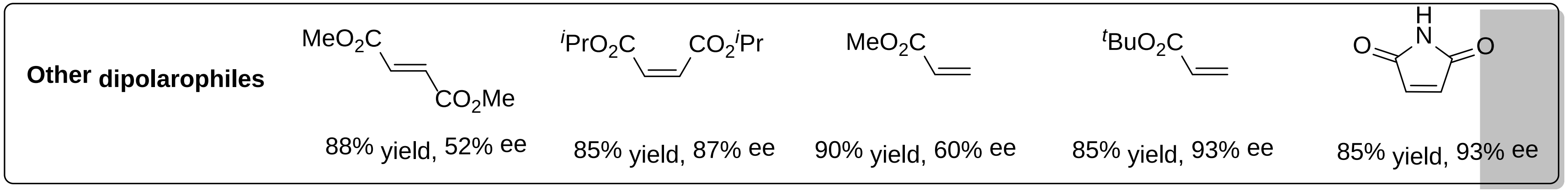
A. S. Gothelf, K. V. Gothelf, R. G. Hazell and K. A. Jørgensen, *ACIE*, **2002**, 41, 4236.

Pioneering works in catalytic enantioselective 1,3-DC

Zhang: Silver catalyzed 1,3-DC

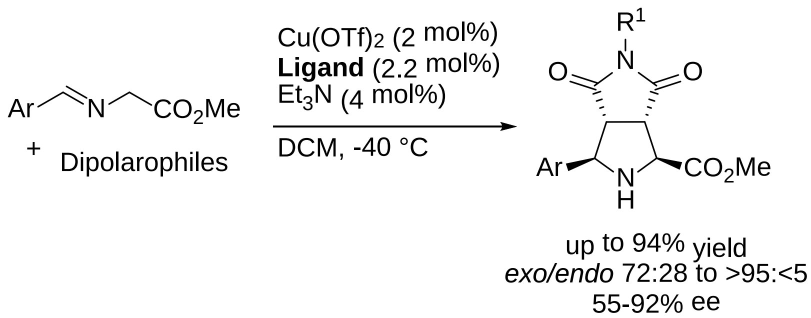


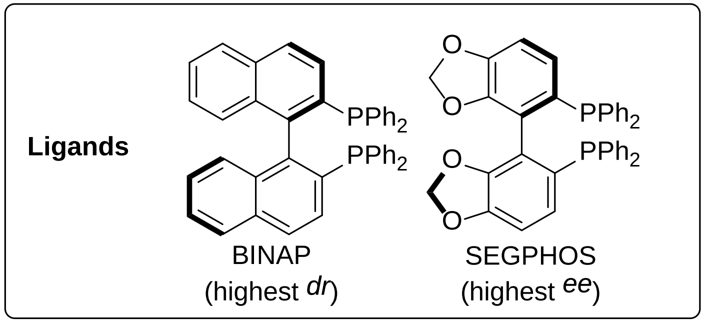


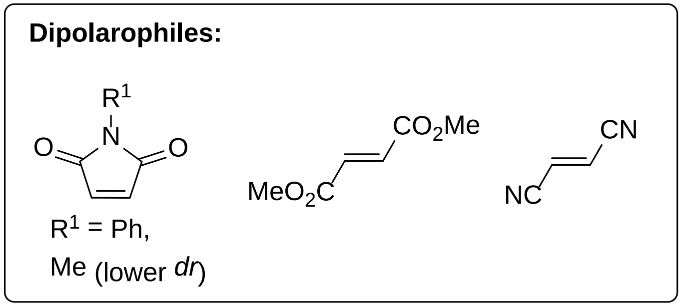


Longmire, J. M.; Wang, B.; Zhang, X. *JACS* **2002**, *124*, 13400.

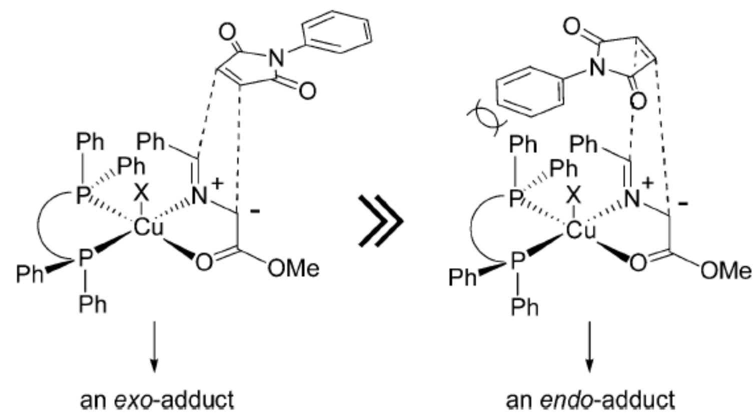
Komatsu: *exo* selective 1,3-DC





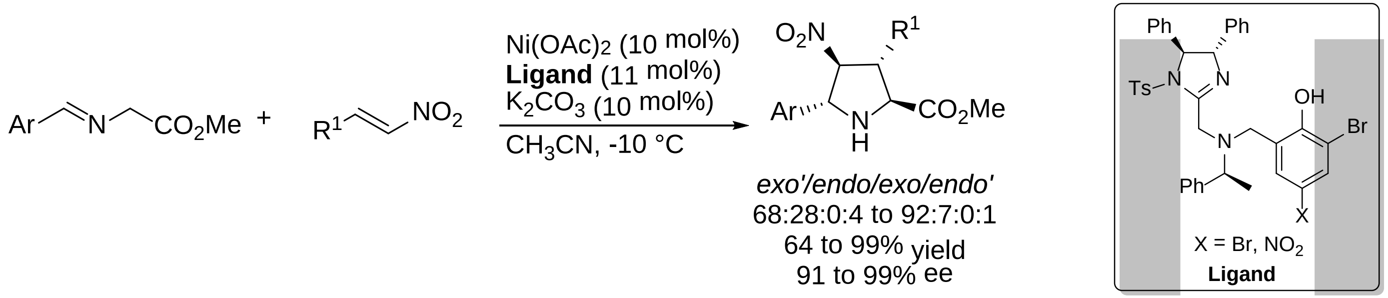


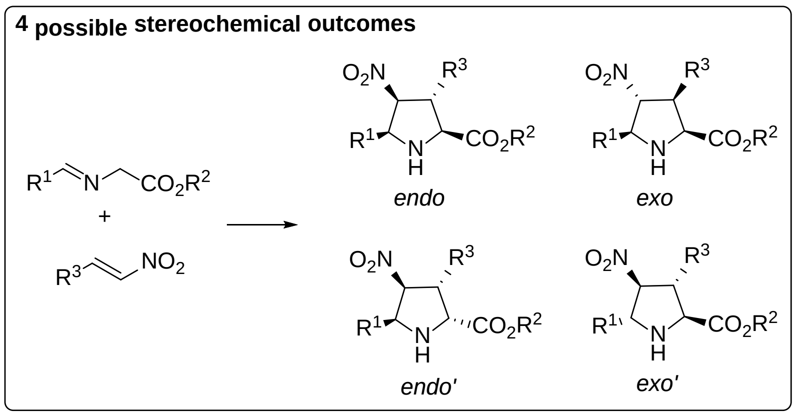
Stereochemical model



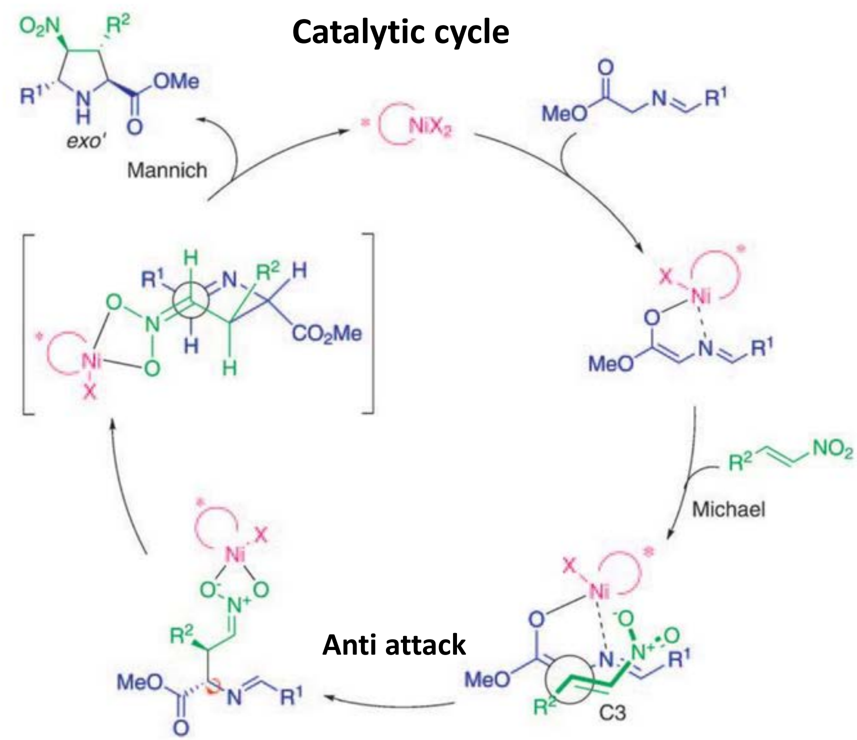
Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *OL* **2003**, *5*, 5043-5046.

Arai: *exo'* selective 1,3-DC



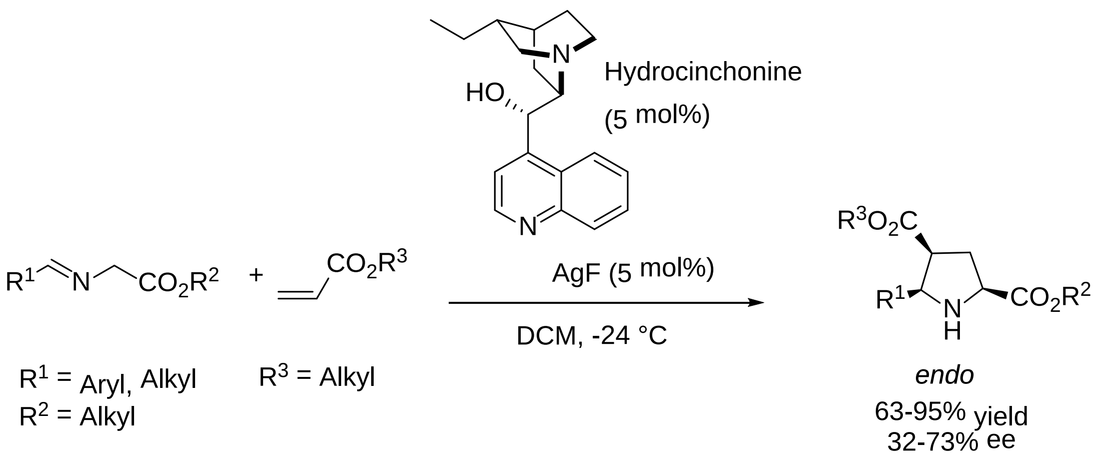


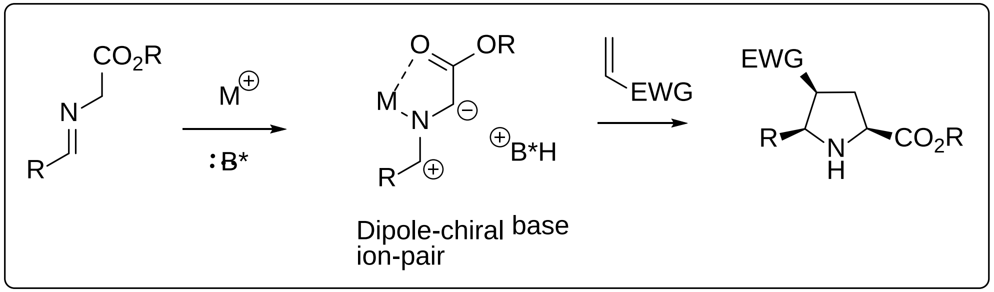
Catalytic cycle



T. Arai, N. Yokoyama, A. Mishiro and H. Sato, *ACIE* **2010**, 49, 7895.

Jørgensen: Silver/Chiral base Catalyst

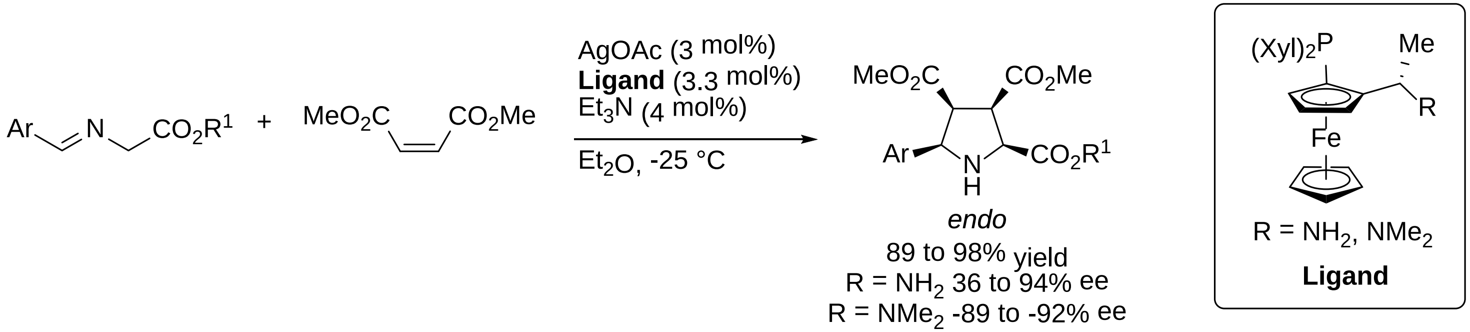




No need of dry, inert atmosphere conditions.

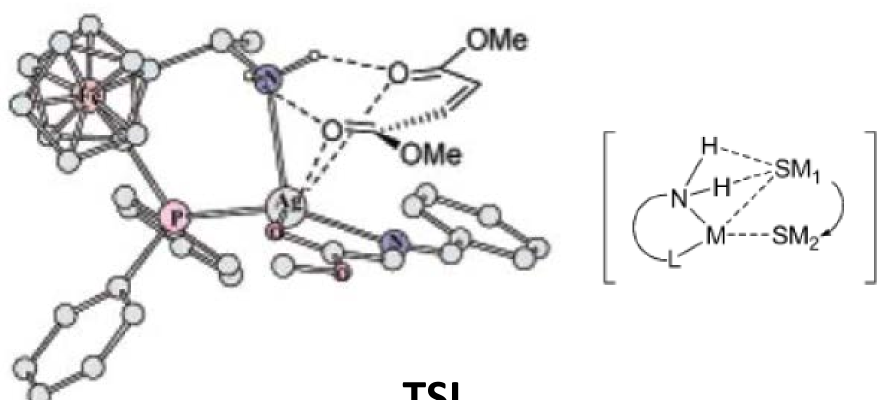
Alemparte, C.; Blay, G.; Jørgensen, K. A. *OL* **2005,** *7,* 4569-4572.

Li: H-bond mediated inversion of enantioselectivity

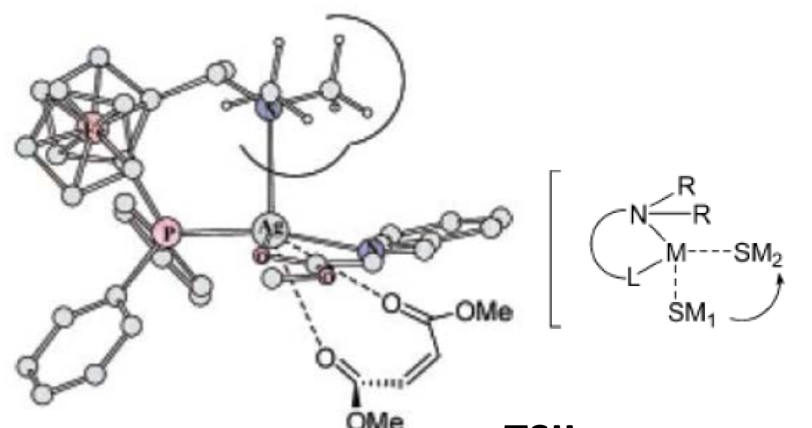


H-bonding involved: addition of *t*-amylOH and EtOH lowers *ee*

Model for selectivity:



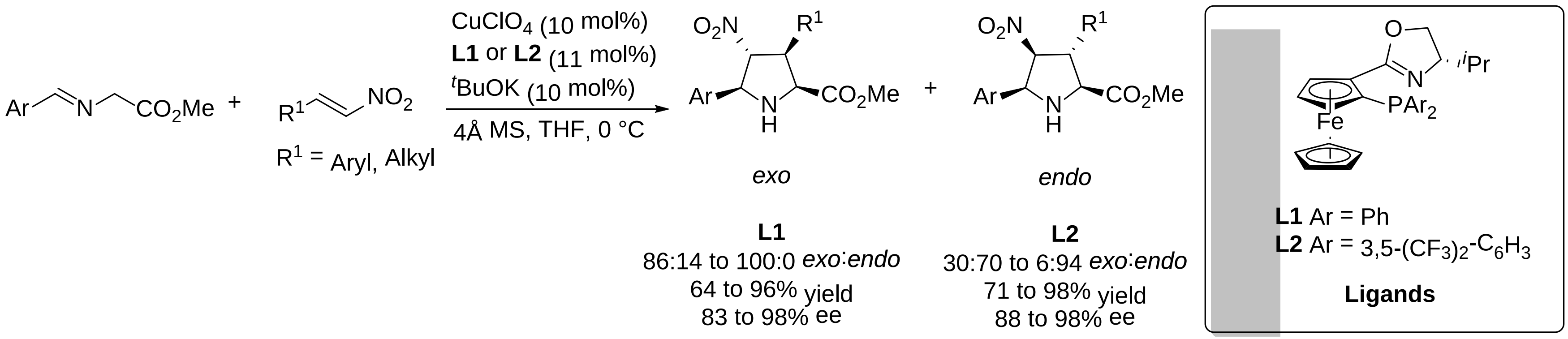
TSI



TSII

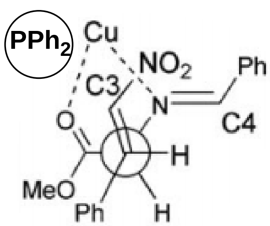
Zeng, W.; Chen, G. Y.; Zhou, Y. G.; Li, Y. X. *JACS* **2007,** *129,* 750-751.

Hou: inversion of diastereoselectivity

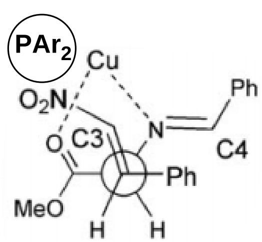


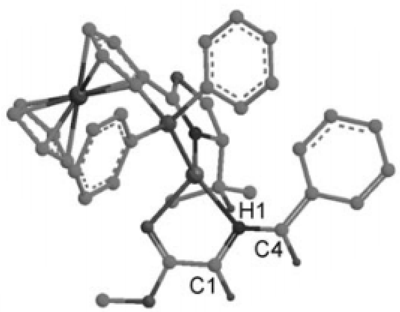
Model for selectivity:

Exo TS

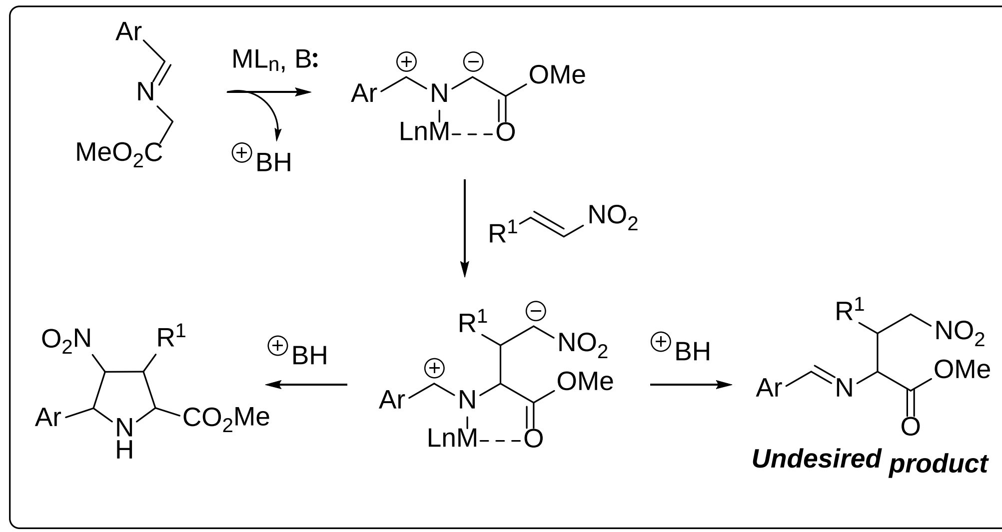


Endo TS



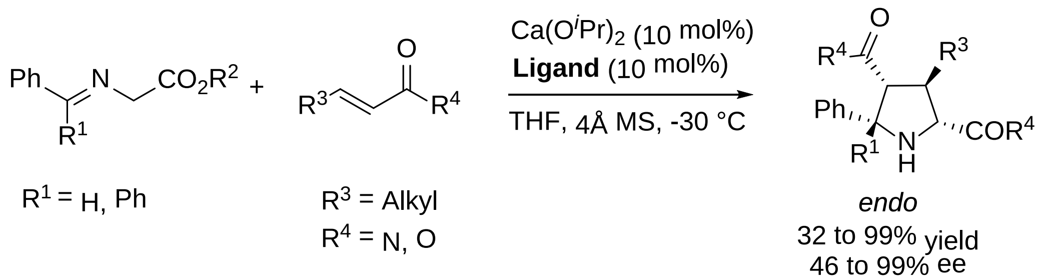


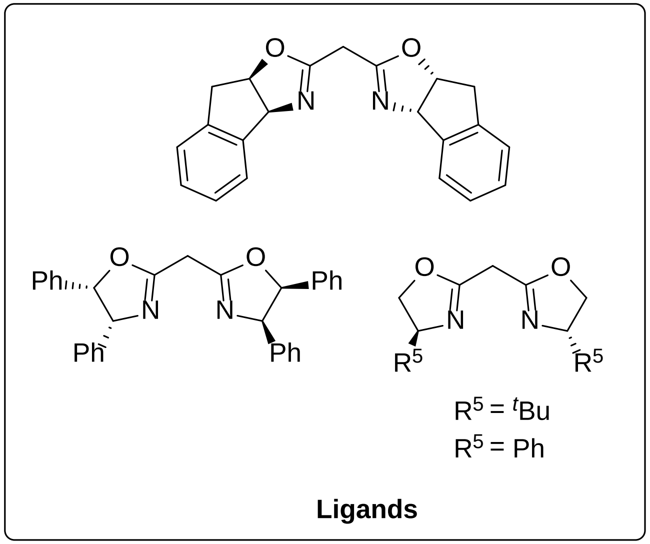
Favoured catalyst-1,3-dipole complex



Yan, X. X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X. L.; Wu, Y. D. *ACIE* **2006,** *45,* 1979-1983

Kobayashi: Calcium catalyzed 1,3-DC

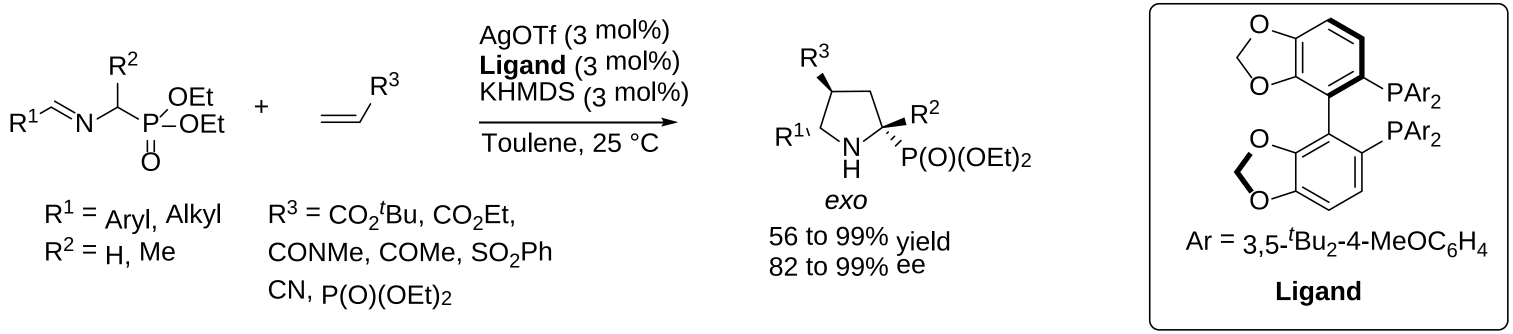




Stepwise mechanism.
Anionic ligand.

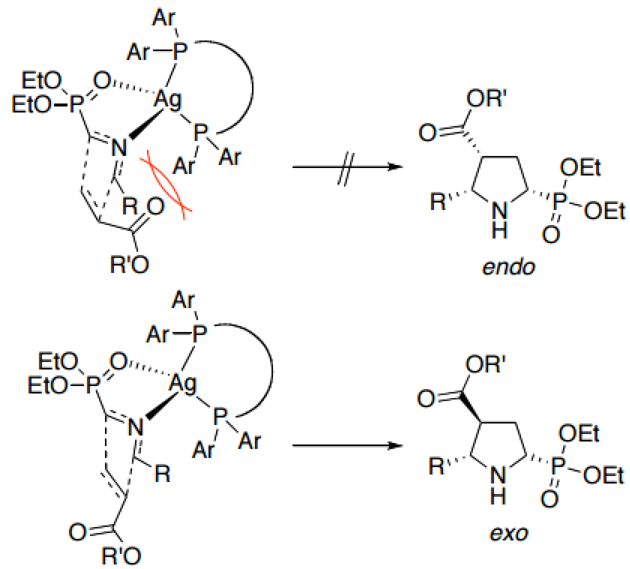
T. Tsubogo, S. Saito, K. Seki, Y. Yamashita, S. Kobayashi *JACS* **2008**, *130*, 13321–13332.

Kobayashi: α-iminophosphonates



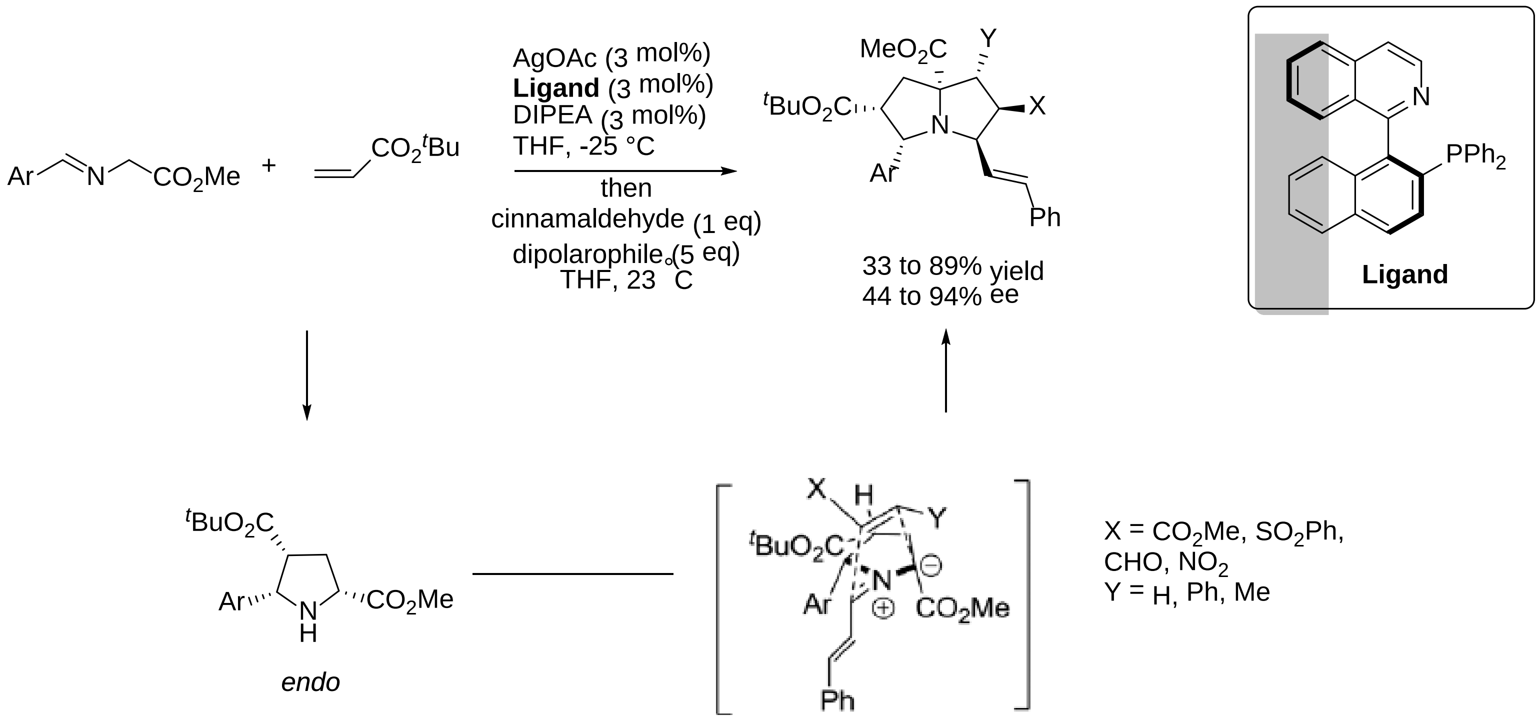
α-aminophosphonates are less acidic than α-iminoester

Model for selectivity:



Y. Yamashita, X.-X. Guo, R. Takashita and S. Kobayashi *JACS*, **2010**, 132, 3262.

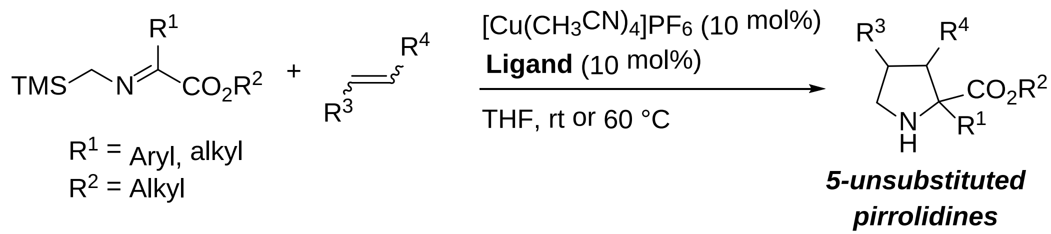
Reisman: double 1,3-DC

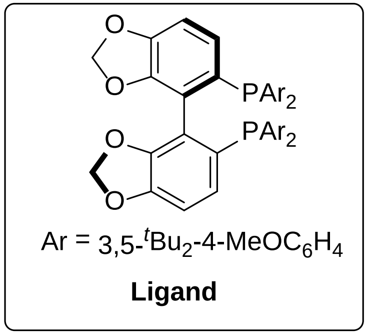


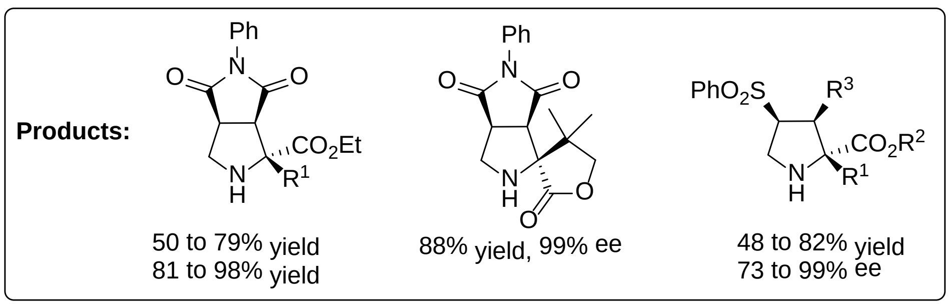
Only α,β-unsaturated aldehydes work for second 1,3-DC.

A. D. Lim, J. A. Codelli and S. E. Reisman, *Chem. Sci.*, **2013**, 4, 650

Carretero: α-silylimines



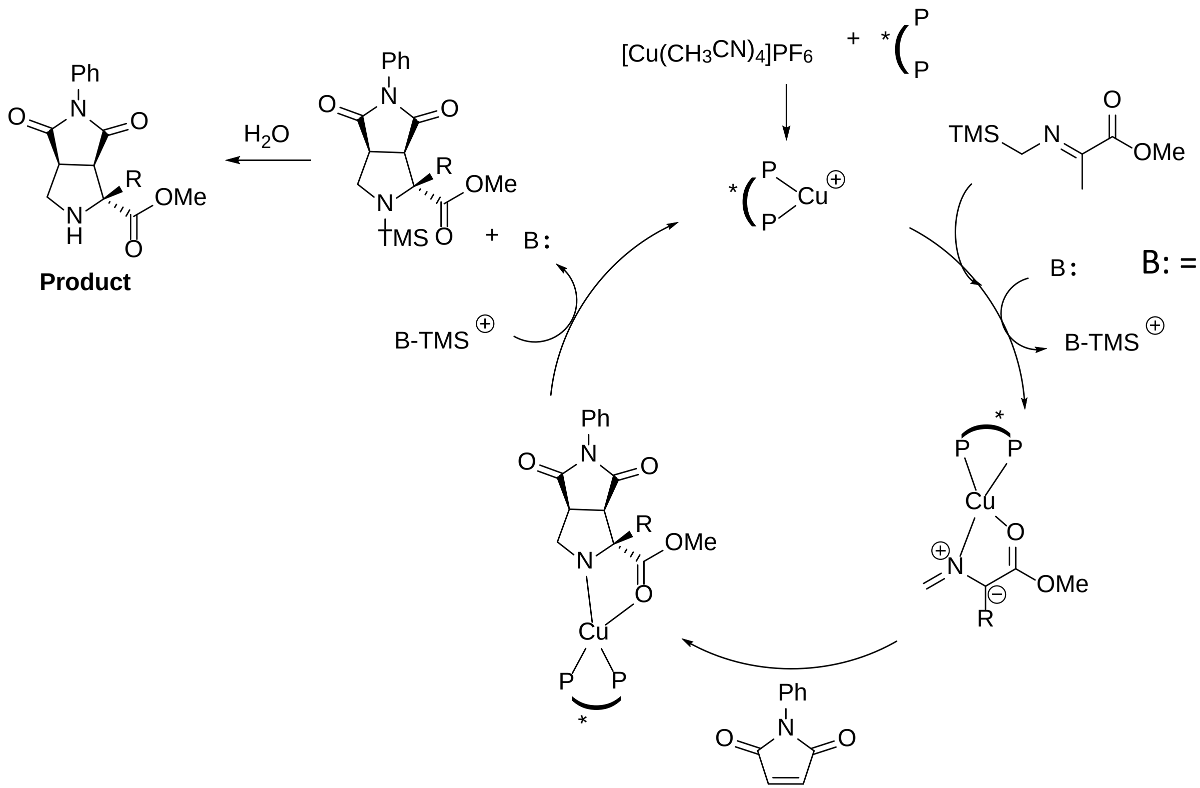




J. Hernandez-Toribio, S. Padilla, J. Adrio and J. C. Carretero, *ACIE*, **2012**, 51, 8854.

Carretero: α-silylimines

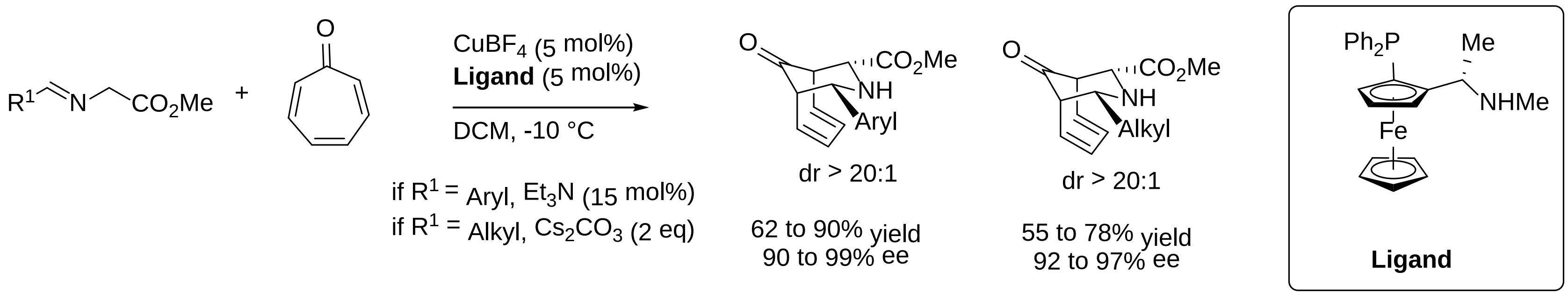
Catalytic cycle



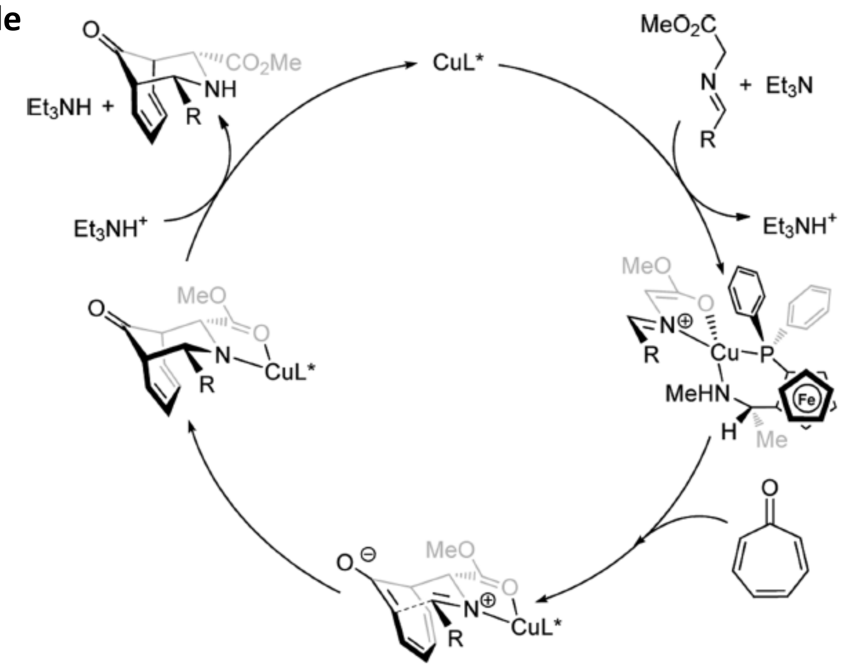
B: = imine or additive (CsF)

J. Hernandez-Toribio, S. Padilla, J. Adrio and J. C. Carretero, *ACIE*, **2012**, 51, 8854

Wang: [6+3] 1,3-DC



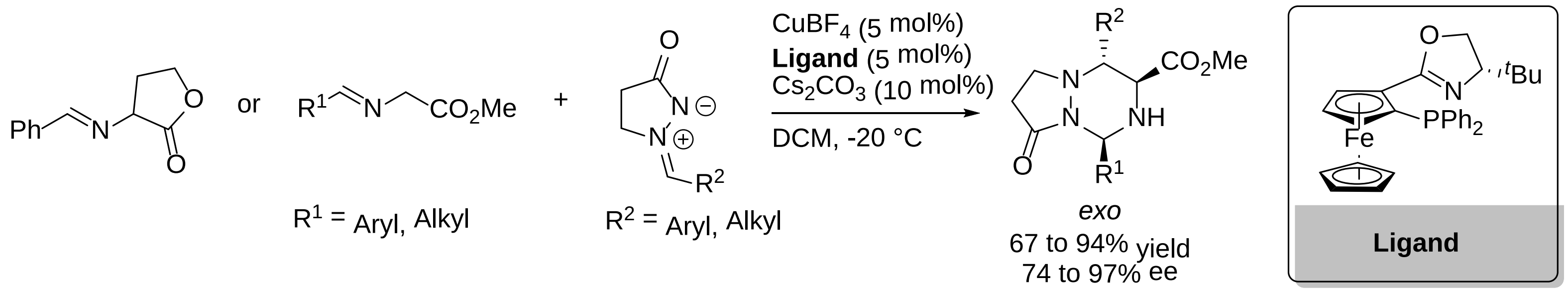
Catalytic cycle



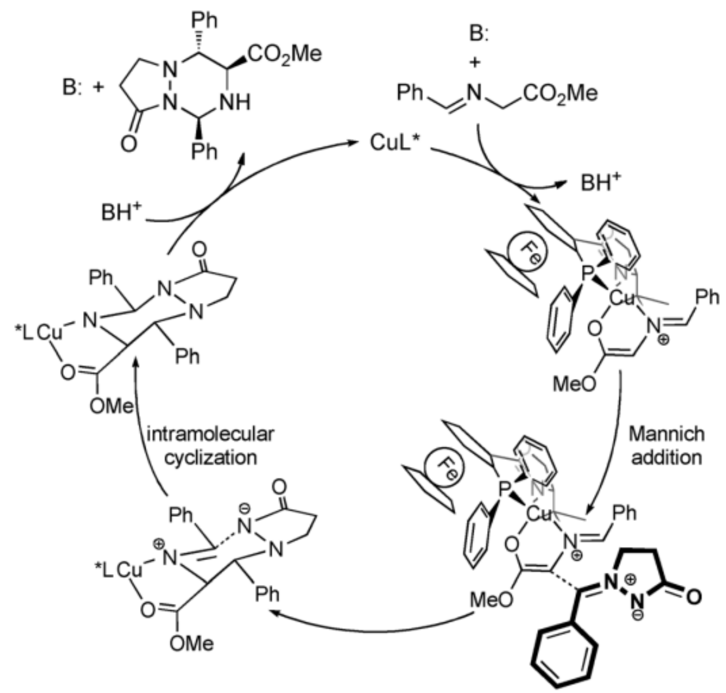
Steric bulk

H.-L. Teng, L. Yao and C.-J. Wang, *JACS*, **2014**, 136, 4075.

Wang: [3+3] 1,3-DC

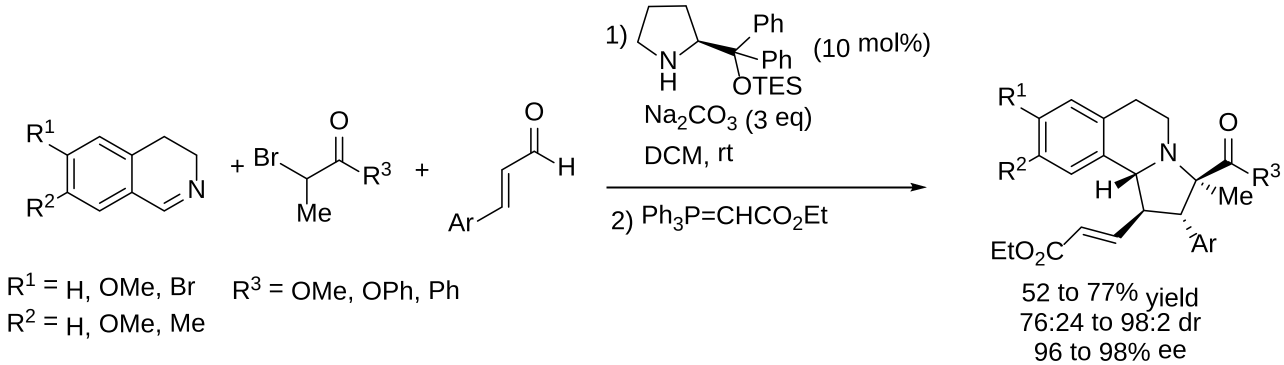


Catalytic cycle

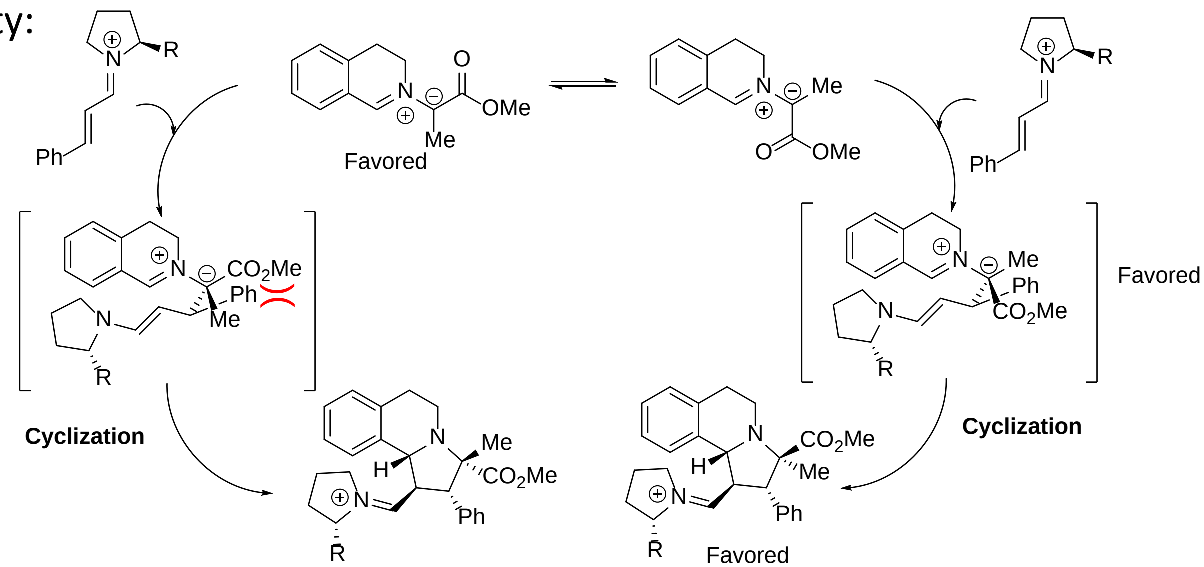


M.-C. Tong, X. Chen, H.-Y. Tao and C.-J. Wang, *ACIE*, **2013**, 52, 12377.

Jørgensen: silylated prolinol catalyst

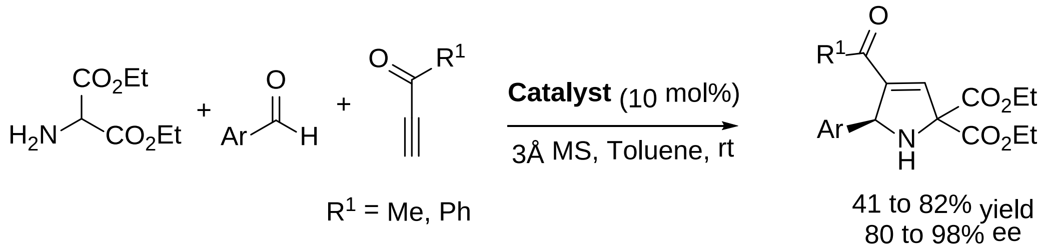


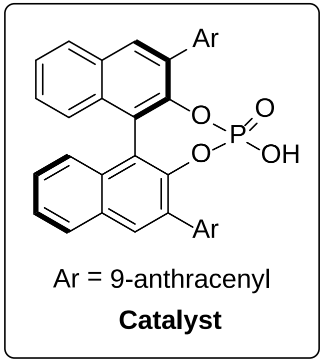
Model for selectivity:



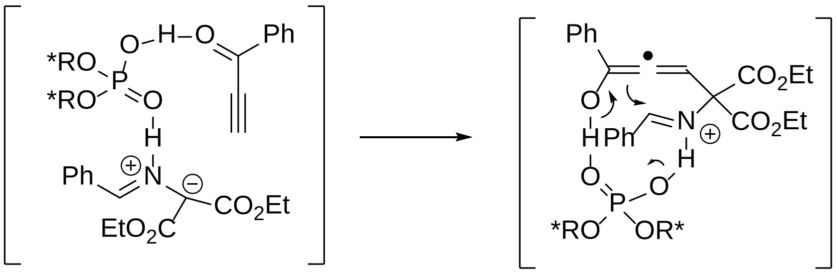
A. Fraile; D. M. S. Schietroma; A. Albrecht; R. L. Davis; K. A. Jørgensen, *Chem. Eur. J.*, **2012**, 18, 2773.

Shi: chiral Brønsted acid catalyst





Bifunctional catalyst

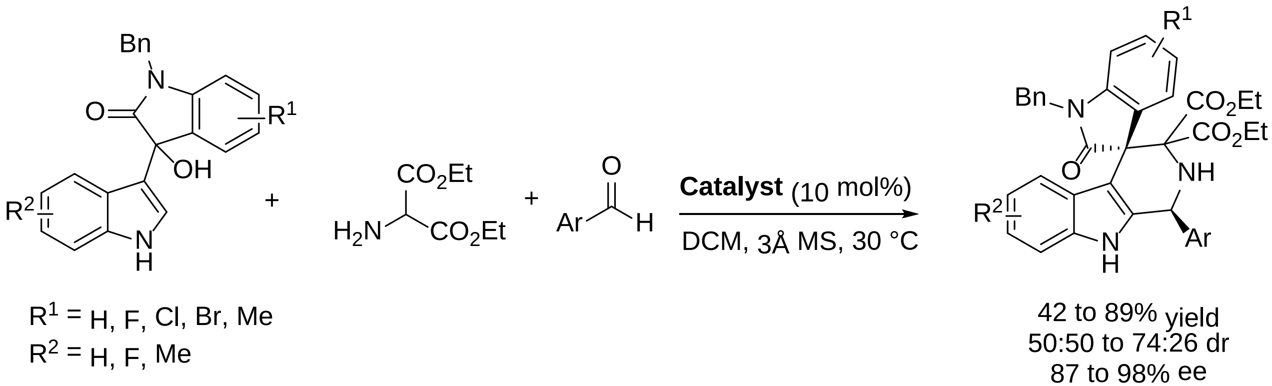


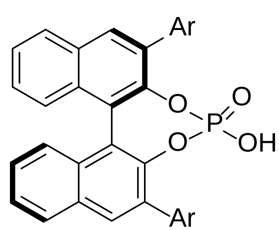
TSI TSII

Stepwise mechanism

F. Shi, S.-W. Luo, Z.-L. Tao, L. He, J. Yu, S.-J. Tu and L.-Z. Gong, *OL*, **2011**, 13, 4680.

Shi: [3+3] with 3-indolyl methanol





Ar = 9-fenanthrenyl

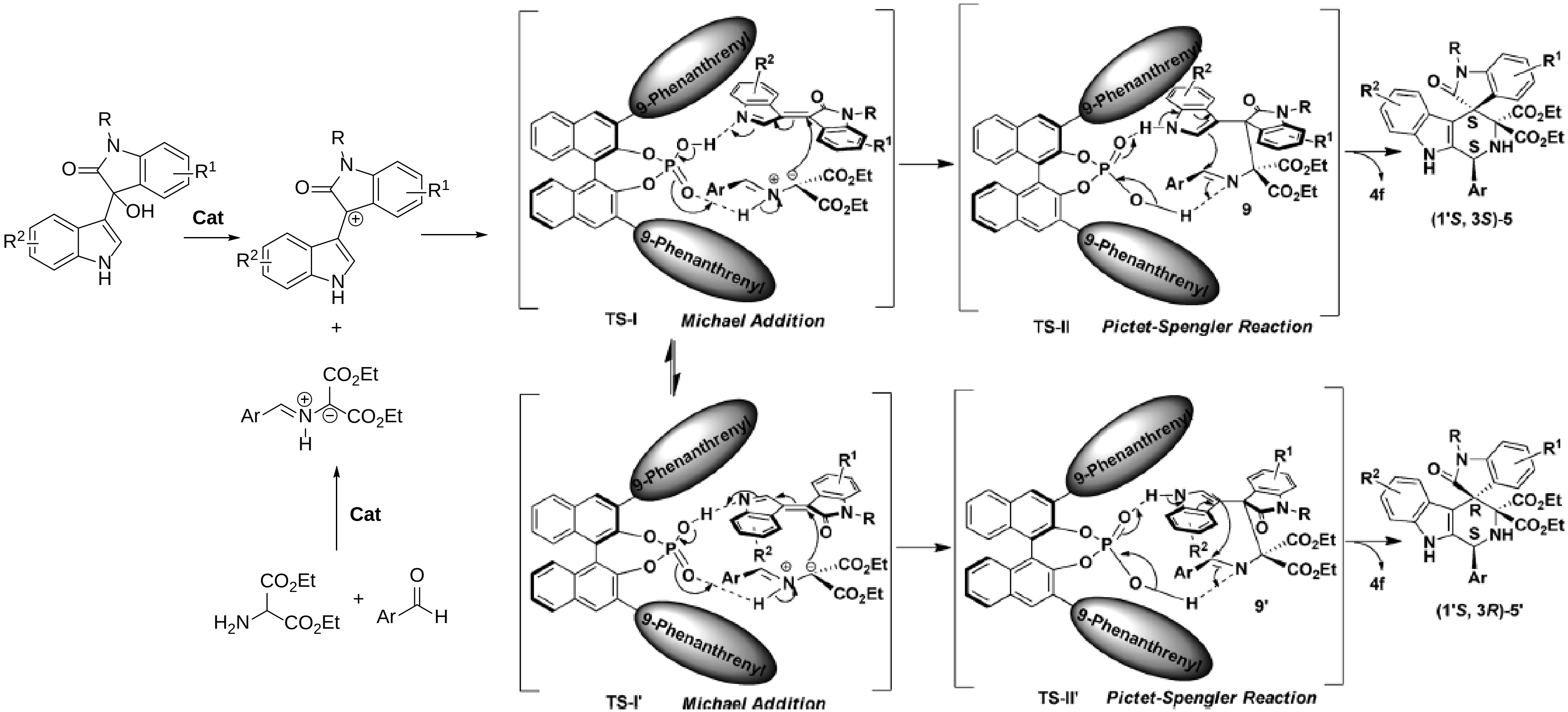
Catalyst

2 spiroquaternary stereocenters are formed.

F. Shi, R.-Y. Zhu, W. Dai, C.-S. Wang and S.-J. Tu, *Chem. Eur. J.*, **2014**, 20, 2597.

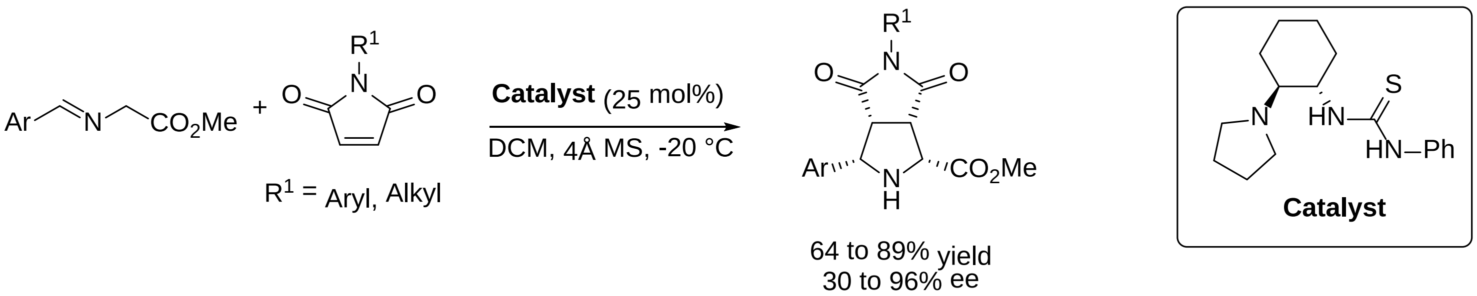
Shi: [3+3] with 3-indolyl methanol

Model for selectivity:

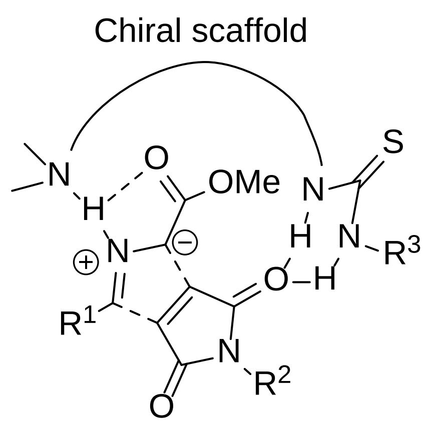


F. Shi, R.-Y. Zhu, W. Dai, C.-S. Wang and S.-J. Tu, *Chem. Eur. J.*, **2014**, 20, 2597.

Wang: chiral tertiary amine thiourea



Bifunctional catalyst



J.-F. Bai, L.-L. Wang, L. Peng, Y.-L. Guo, J.-N. Ming, F.-Y. Wang, X.-Y. Xu and L.-X. Wang, *Eur. J. Org. Chem.*, **2011**, 4472

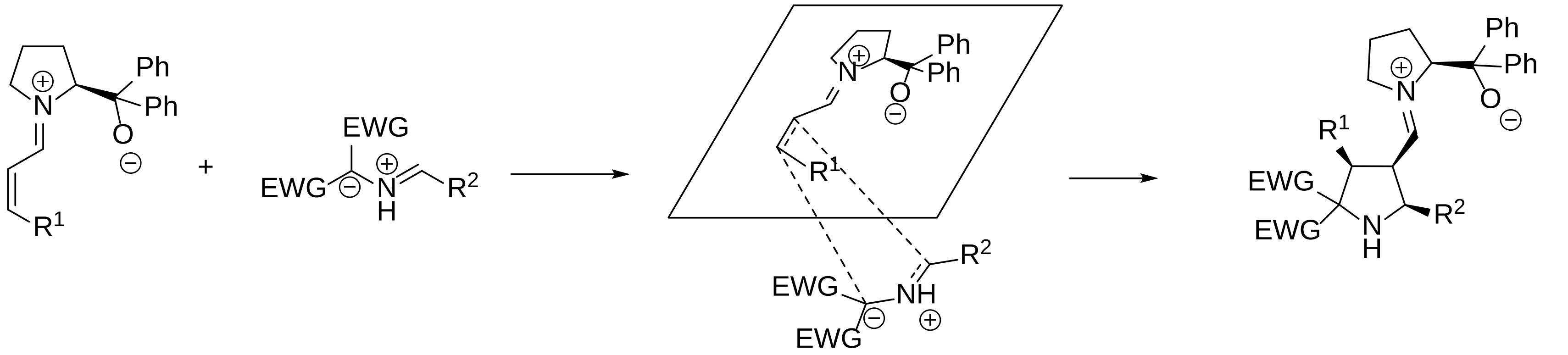
Conclusion and outlook

- Catalytic enantioselective 1,3-DC of azomethine ylides are powerful, straightforward, atom economical method to synthesize enantioenriched and highly functionalized nitrogen containing heterocycles
- More work on high order cycloadditions (new dipolarophiles, synthesis of 6-membered rings)
- More work on organocatalytic procedures
- More environmentally friendly methodologies

THANK YOU FOR YOUR ATTENTION!

Answers

2.



Ph
Ph
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O
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+
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EWG
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R2
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Ph
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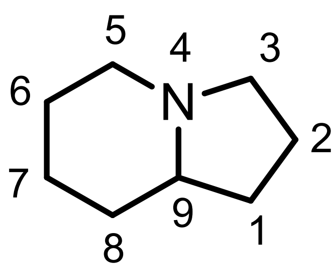
O
R1
R2
EWG
NH
EWG
Ph
Ph
N
O
R1
EWG
EWG
N
H
R2

Daria Grosheva

Synthesis of Indolizidine Alkaloids: Selected Examples



Frontiers in Chemical Synthesis I: *Heterocyclic Chemistry*

(Prof. Jérôme Waser, Prof. Xile Hu)

Lausanne, May 11, 2015

Questions

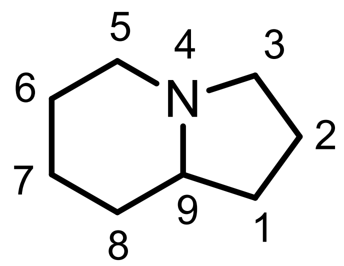
1. What is the key step of Baskaran’s synthesis of Indolizidines 167B and 209D?

2. Could you identify the mechanism underlying Denmark’s Castanospermine synthesis?

- Introduction
- Selected Examples of Indolizidine Synthesis
  - Gephyrotoxin
  - Indolizidines 167B and 209D
  - Castanospermine
  - Lepadiformine
  - Allopumiliotoxins 339A and 267A
  - Rhazinilam
- Summary
- Questions

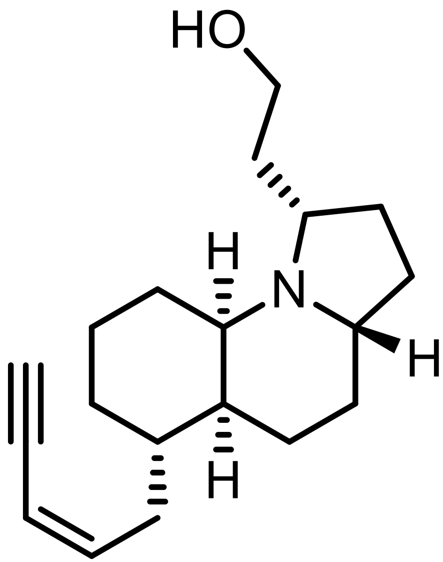
INDOLIZIDINE ALKALOIDS

- **sources**: ants, frogs, trees, legumes
- **activities**: phytotoxic, insecticidal, antibacterial, antiviral, etc.
- some representatives could be extremely toxic
- the **core** limiting the family:



- challenging structures, many synthetic approaches were developed
- **main players**: Kibayashi, Overman, Denmark

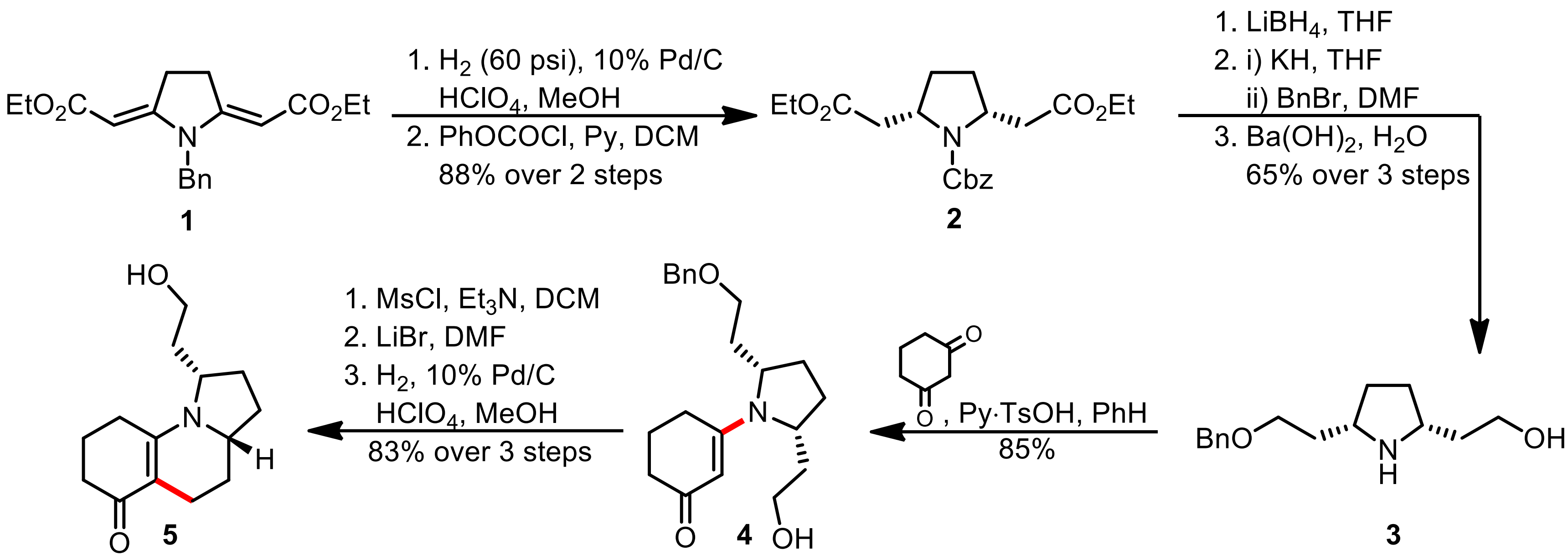
Gephyrotoxin: General Features

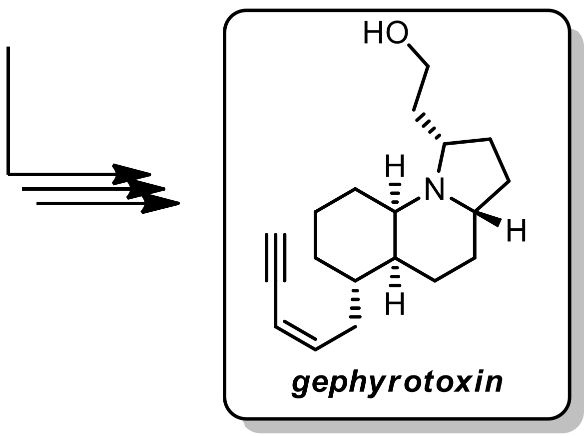


- isolated from the skin extracts of the *Dendrobates histrionicus*

- neurological activities
- contains 5 asymmetric centers
- extremely scarce

Gephyrotoxin: Kishi's Approach

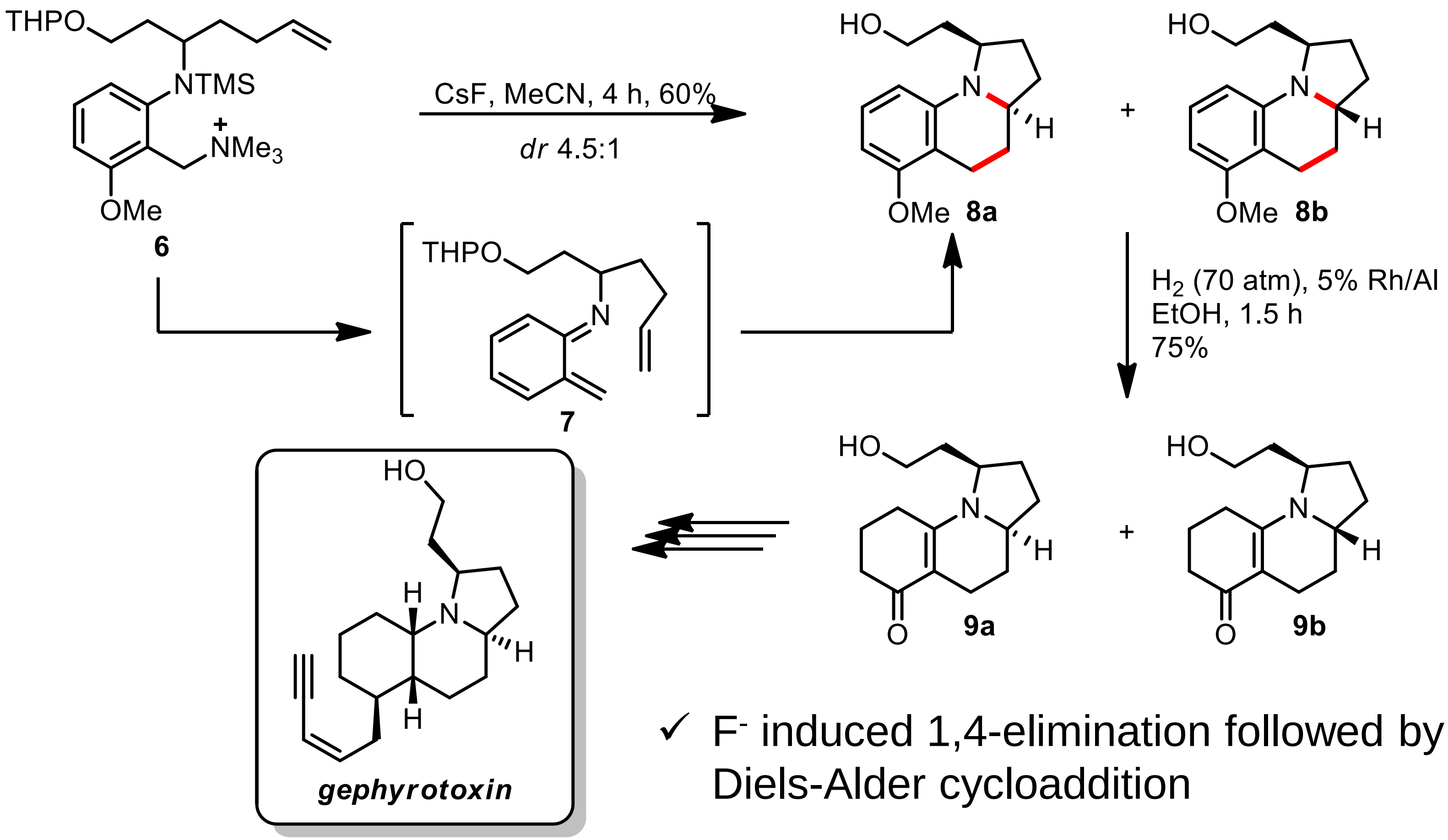




- ✓ the 1st total synthesis of gephyrotoxin
- ✓ introduction of stereocenters through hydrogenation reactions

Kishi, *J. Am. Chem. Soc.* **1980**, *102*, 7154-7156

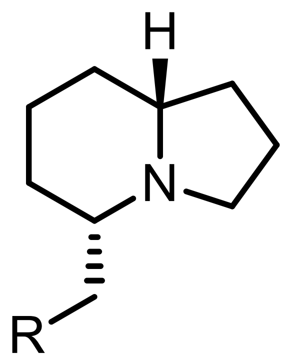
Gephyrotoxin: Saegusa's Approach



✓ F^- induced 1,4-elimination followed by Diels-Alder cycloaddition

Saegusa, *Tetrahedron Lett.* **1983**, *24*, 2881-2884

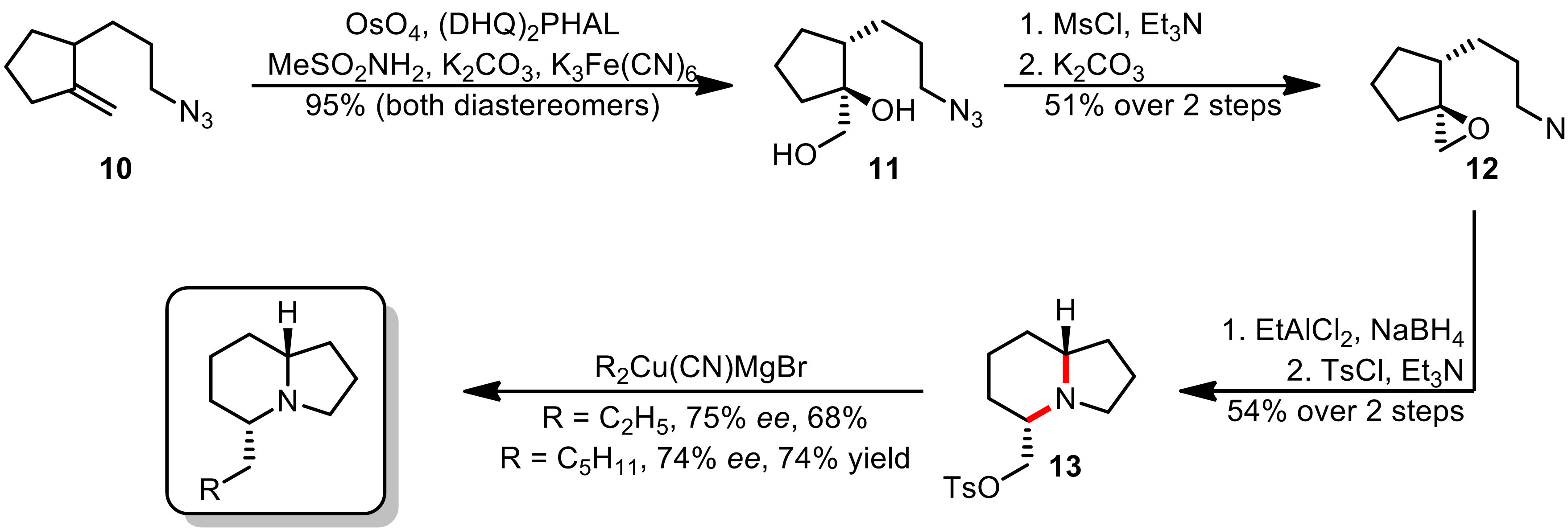
Indolizidines 167B and 209D: General Features



Alkylindolizidine alkaloids:

- noncompetitive blockers of neuromuscular transmission
- interaction with the ganglionic nicotinic acetylcholine receptor-ion channels
- stepwise annulations and consecutive amination reactions are the most commonly used strategies

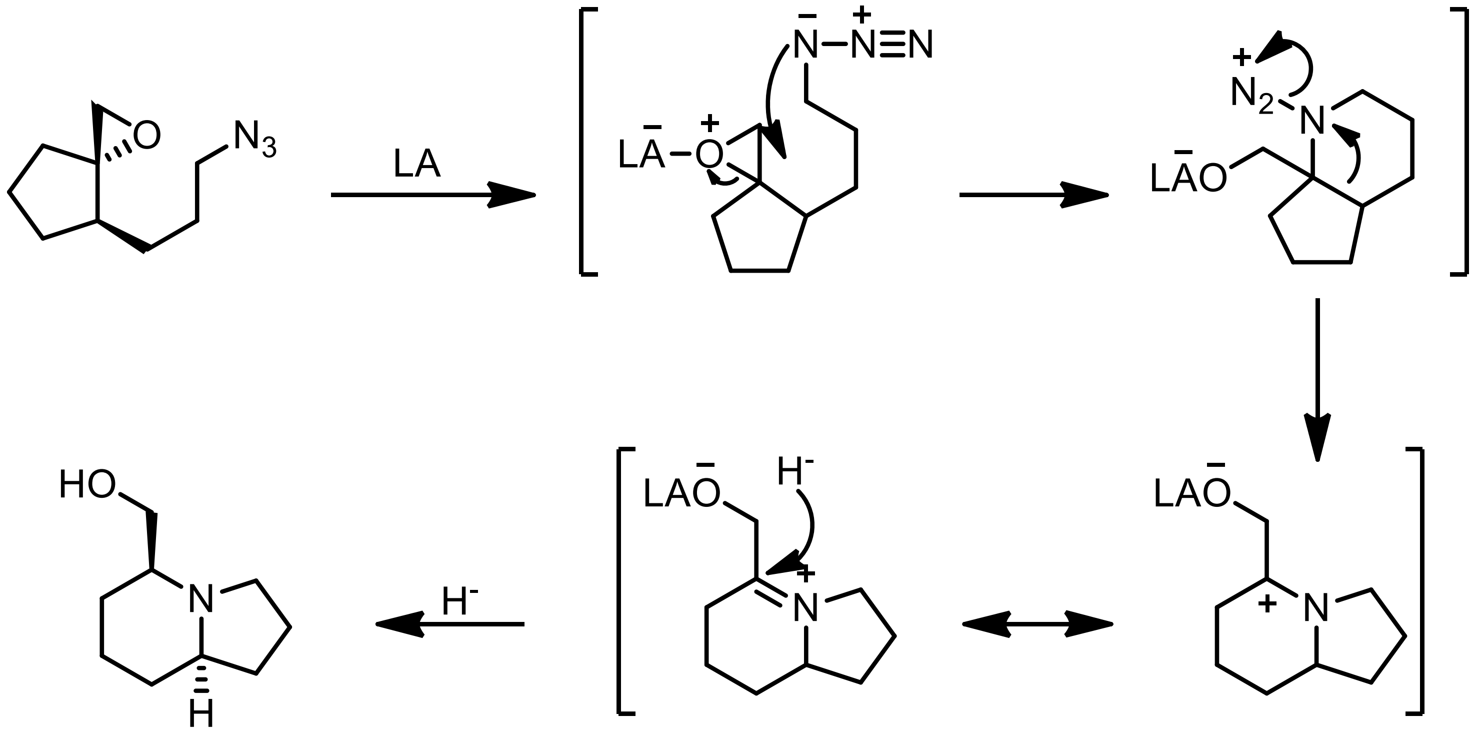
Indolizidines 167B and 209D: Synthesis

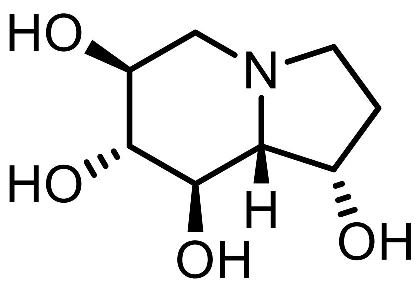


R = C_2H_5 → ***indolizidine 167B***
R = C_5H_{11} → ***indolizidine 209D***

✓ epoxide-initiated cationic cyclization of azides

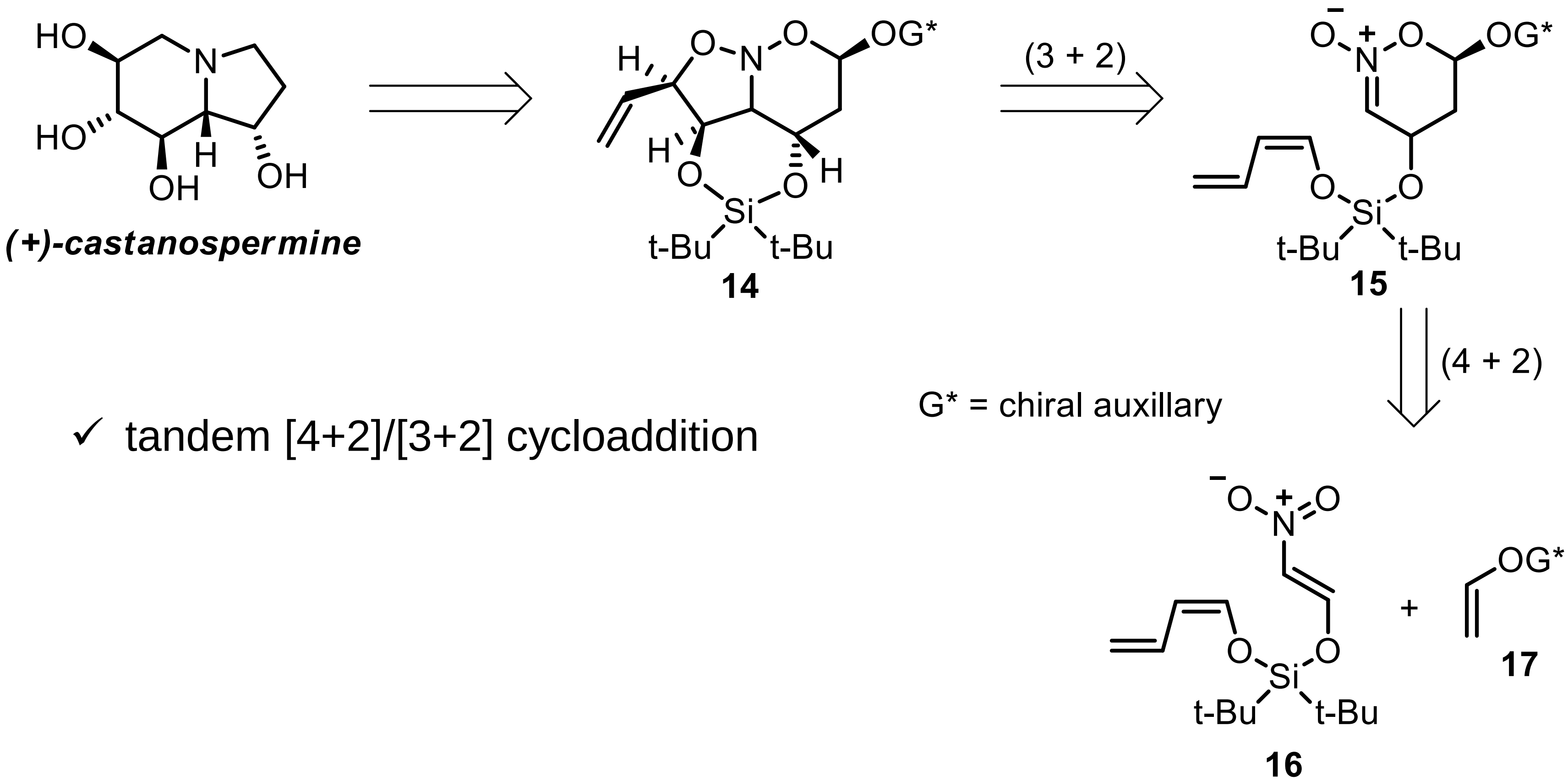
Indolizidines 167B and 209D: The Key Step





- the dominant alkaloidal component of the Australian legume *Castanospermum australe*
- potent inhibitor of a variety of glycosidases
- has shown antiviral activity
- most of the reported syntheses use the intrinsic chirality of carbohydrate precursors

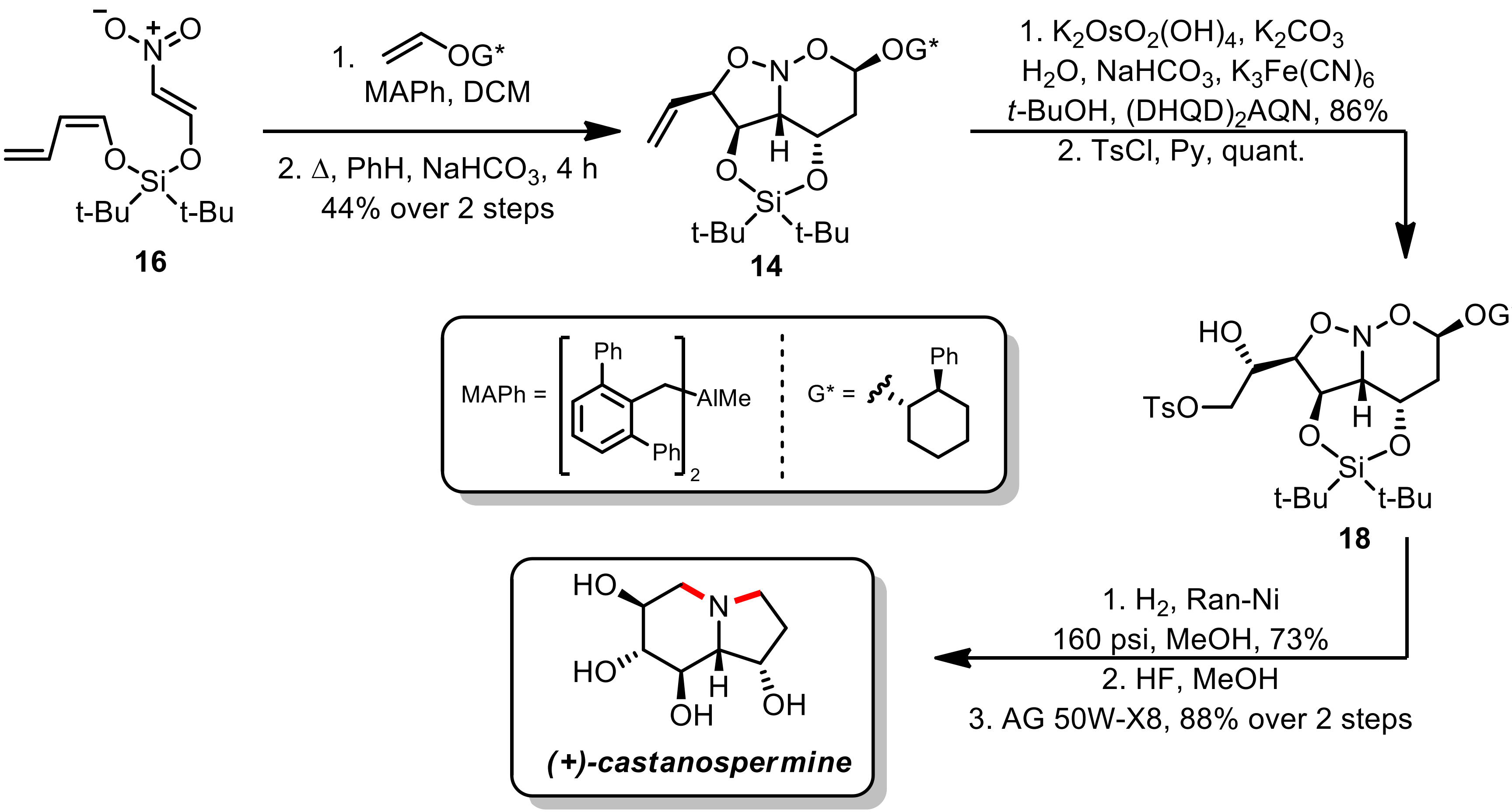
(+)-Castanospermine: Retrosynthetic Analysis



✓ tandem [4+2]/[3+2] cycloaddition

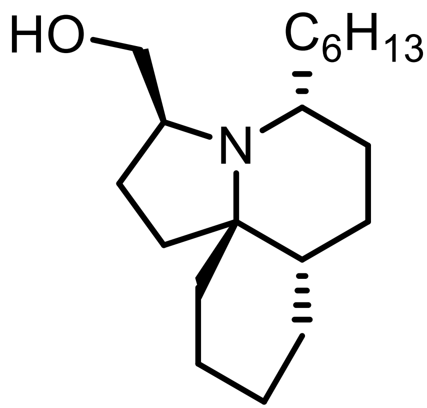
Denmark, *J. Am. Chem. Soc.* **1999**, *121*, 3046-3056

(+)-Castanospermine: Synthesis



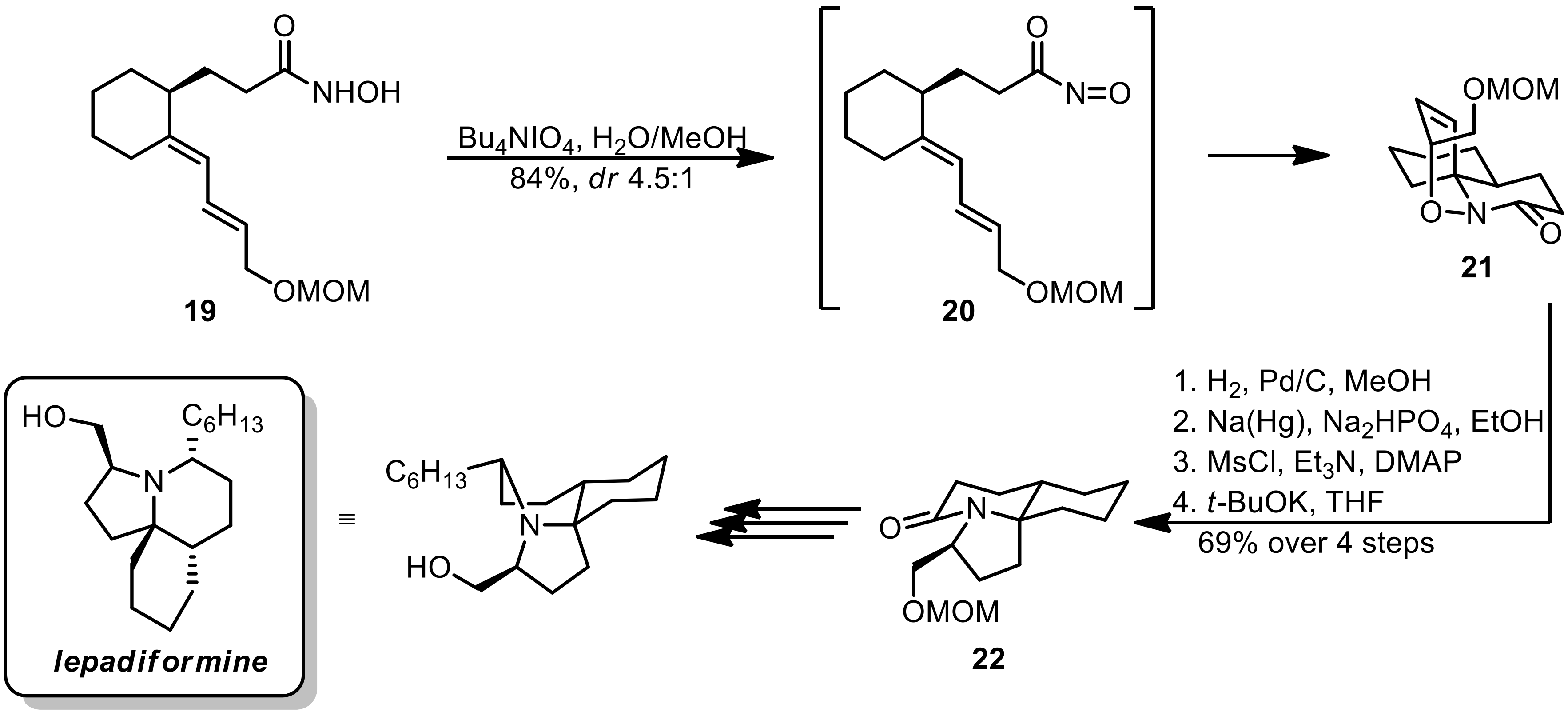
Denmark, *J. Am. Chem. Soc.* **1999**, *121*, 3046-3056

Lepadiformine: General Features



- isolated from Tasmanian ascidians
- bears a tricyclic ring system
- moderately cytotoxic toward various tumor cell lines
- very active in the cardiovascular system; has antiarrhythmic properties

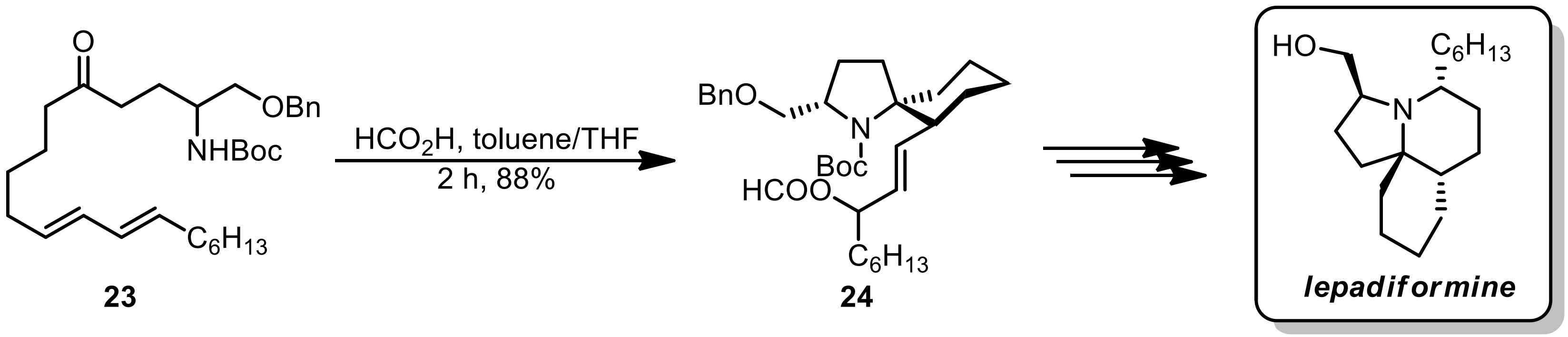
Lepadiformine: Kibayashi's Approach, 2000



✓ hetero-Diels-Alder reaction of *N*-acylnitroso compounds

Kibayashi, *J. Am. Chem. Soc.* **2000**, *122*, 4583-4592

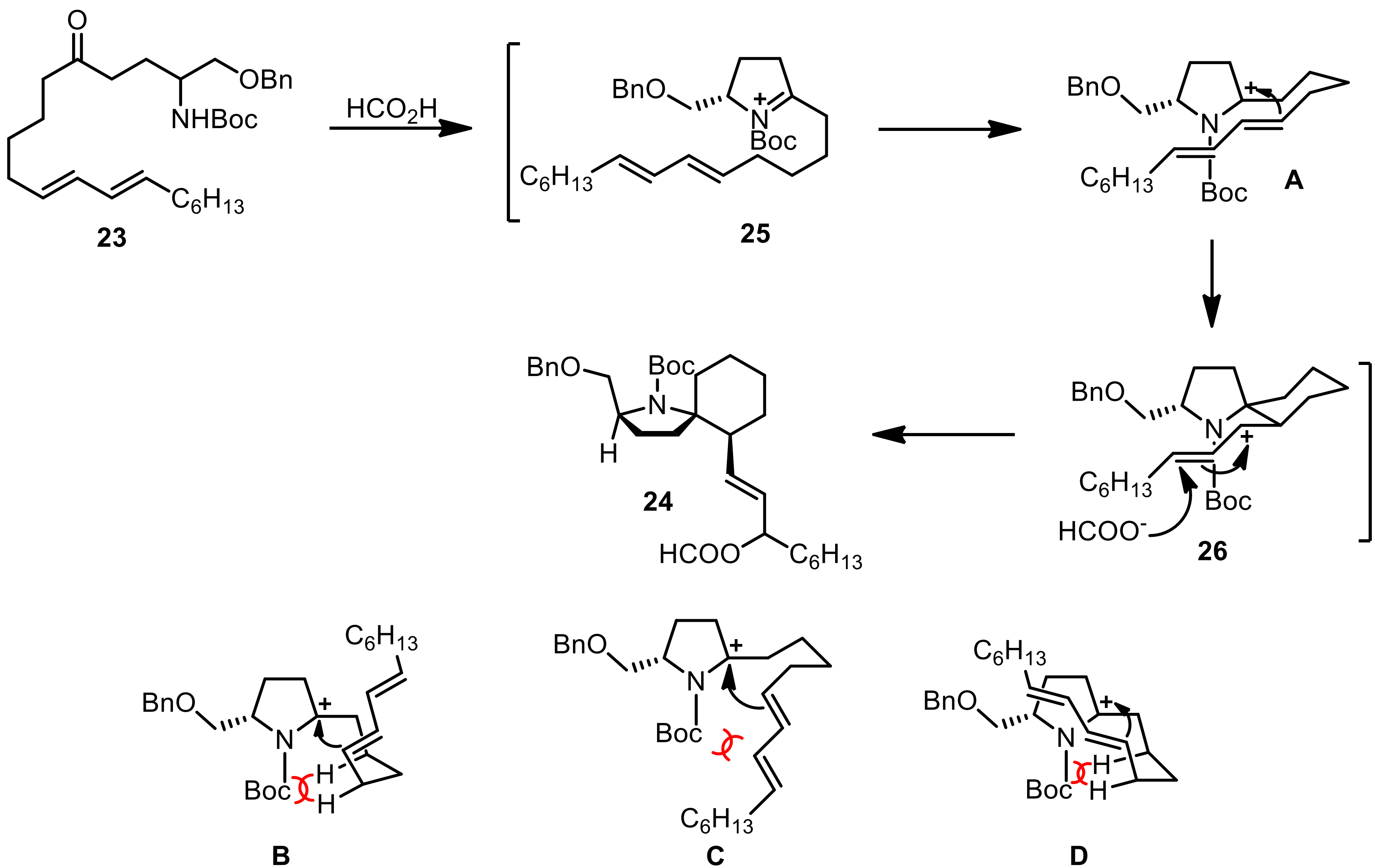
Lepadiformine: Kibayashi's Approach, 2002



✓ *N*-acylaminium-ion-initiated olefin azacyclization

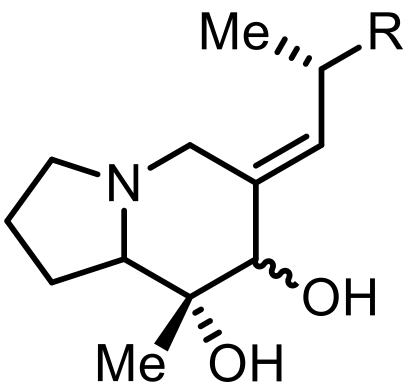
Kibayashi, *Angew. Chem. Int. Ed.* **2002**, *41*, 3017-3020

Lepadiformine: Kibayashi's Approach, 2002

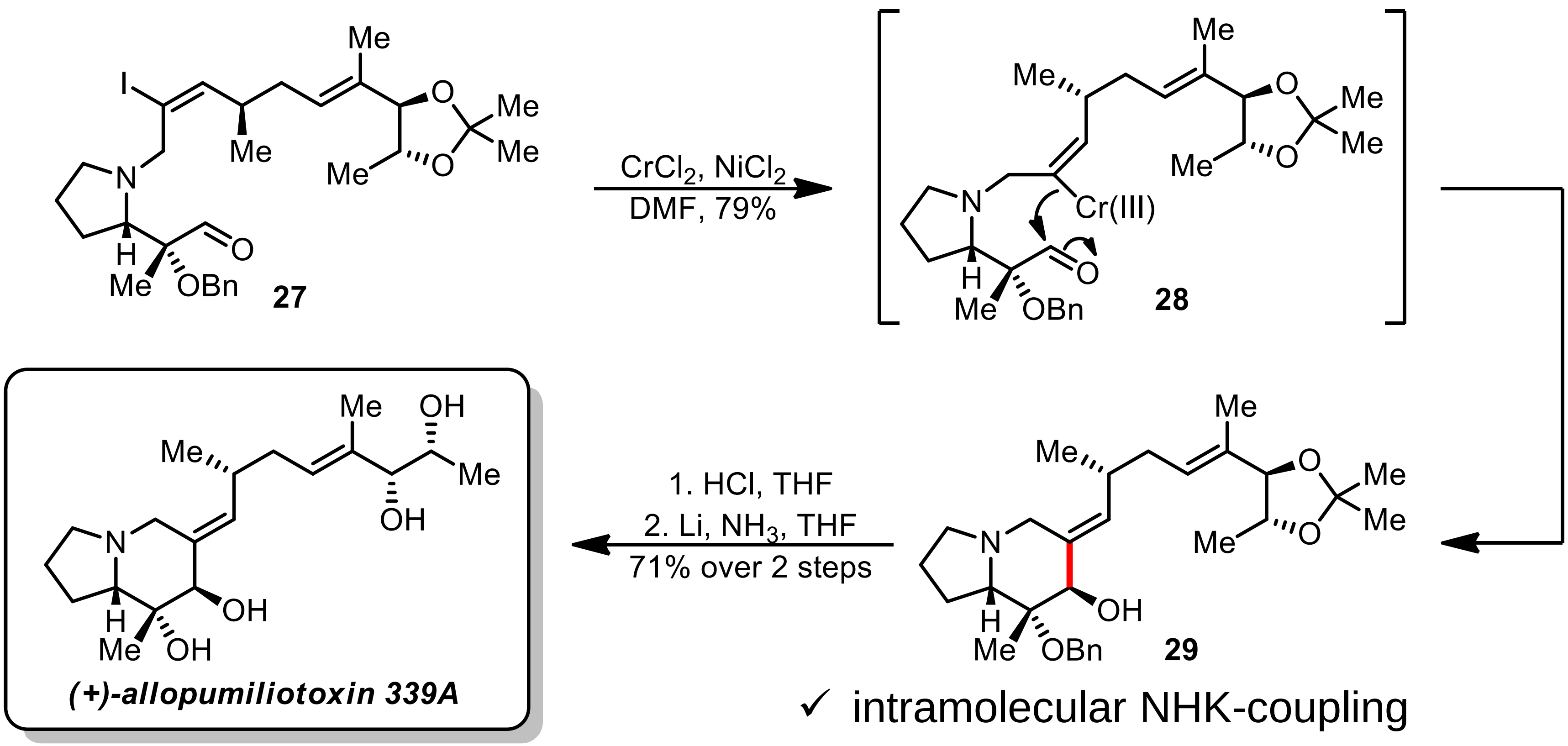


Kibayashi, *Angew. Chem. Int. Ed.* **2002**, *41*, 3017-3020

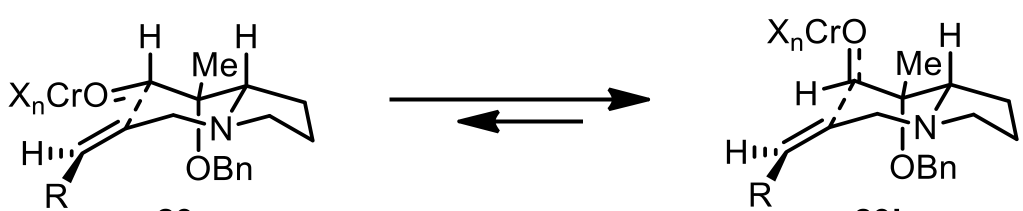
Allopumiliotoxins A: General Features



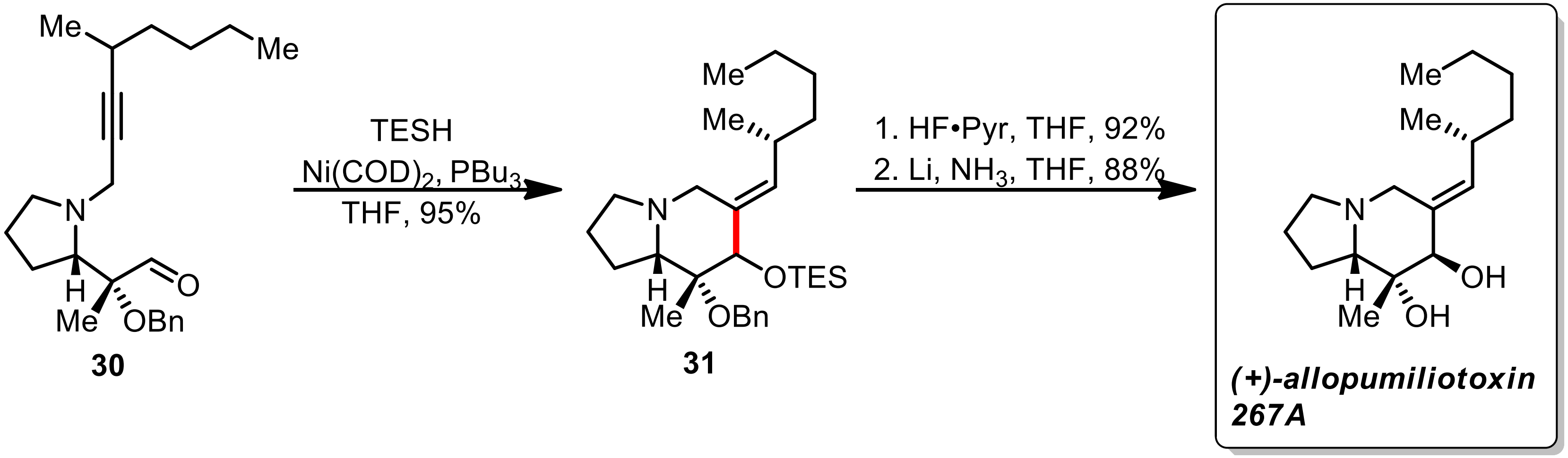
- one of the most structurally complex indolizidines produced in nature
- stimulate sodium influx
- cause muscle rigidity
- very toxic



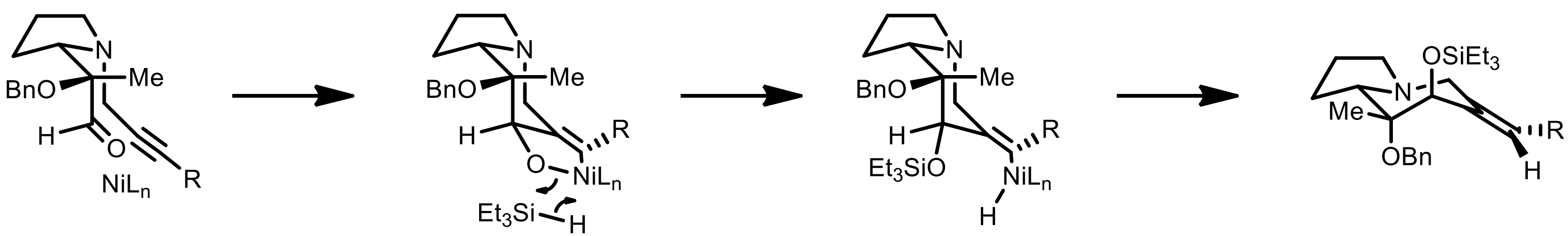
✓ intramolecular NHK-coupling



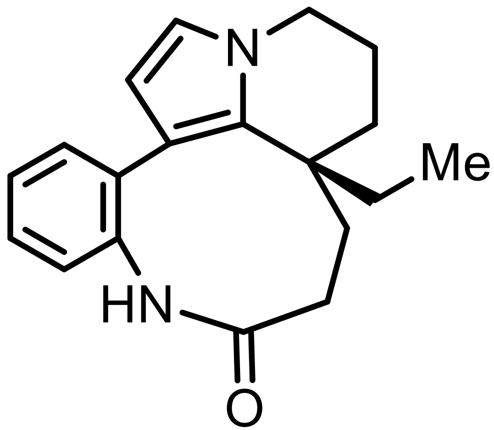
Kibayashi, *J. Am. Chem. Soc.* **1992**, *114*, 10654-10656



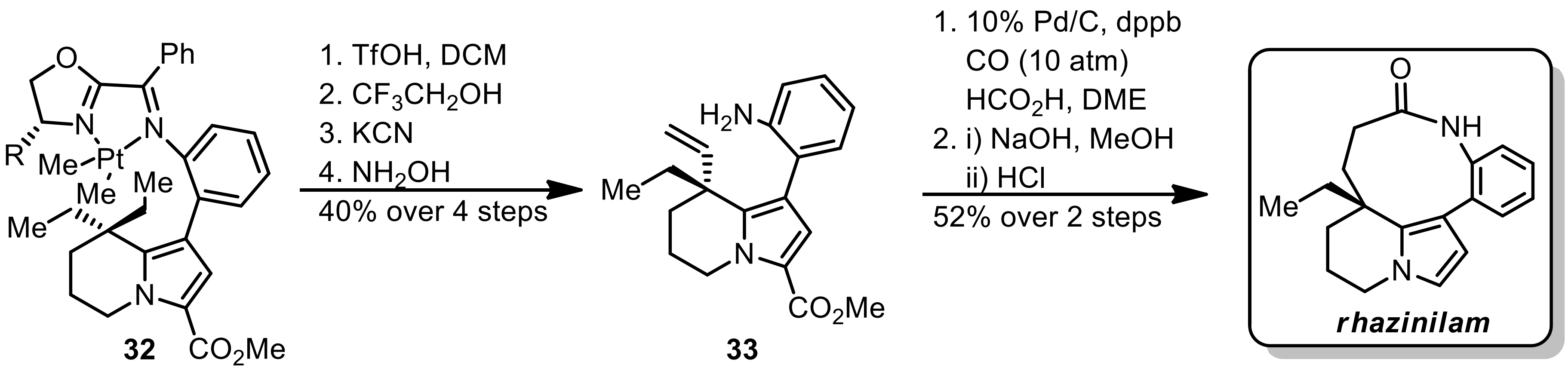
✓ Ni-catalyzed ynal reductive cyclization



Rhazinilam: General Features

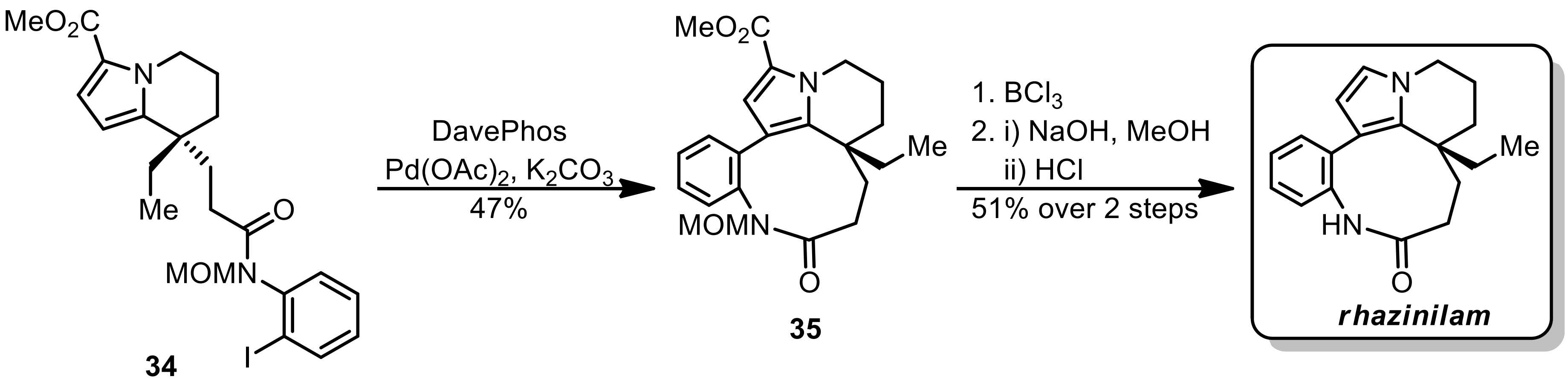


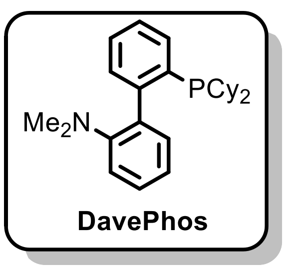
- interferes with tubulin polymerization dynamics
- potential anticancer agent
- possesses a strained nine-membered lactam ring, a biaryl moiety and a quaternary stereocenter



- ✓ Pt-mediated C-H bond functionalization
- ✓ macrolactam formation via direct carbonylation

Rhazinilam: Trauner's Approach

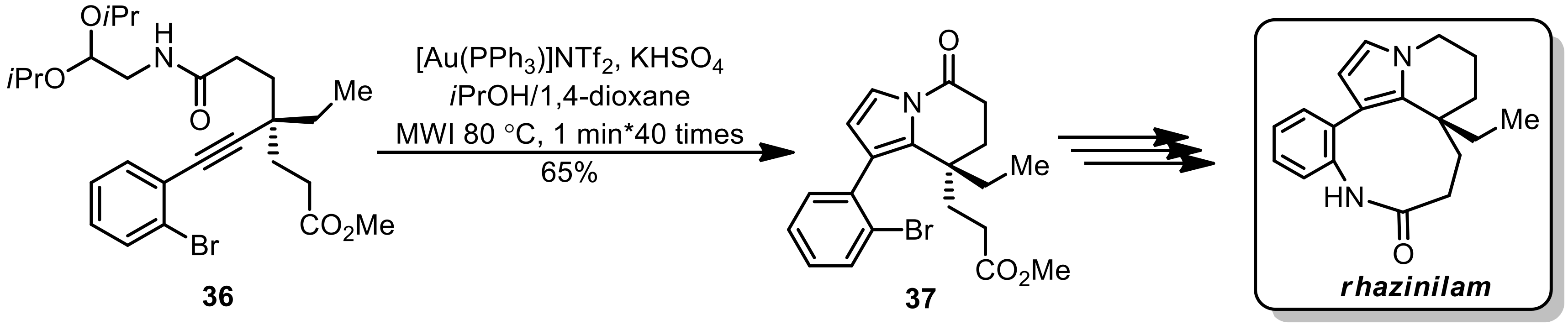




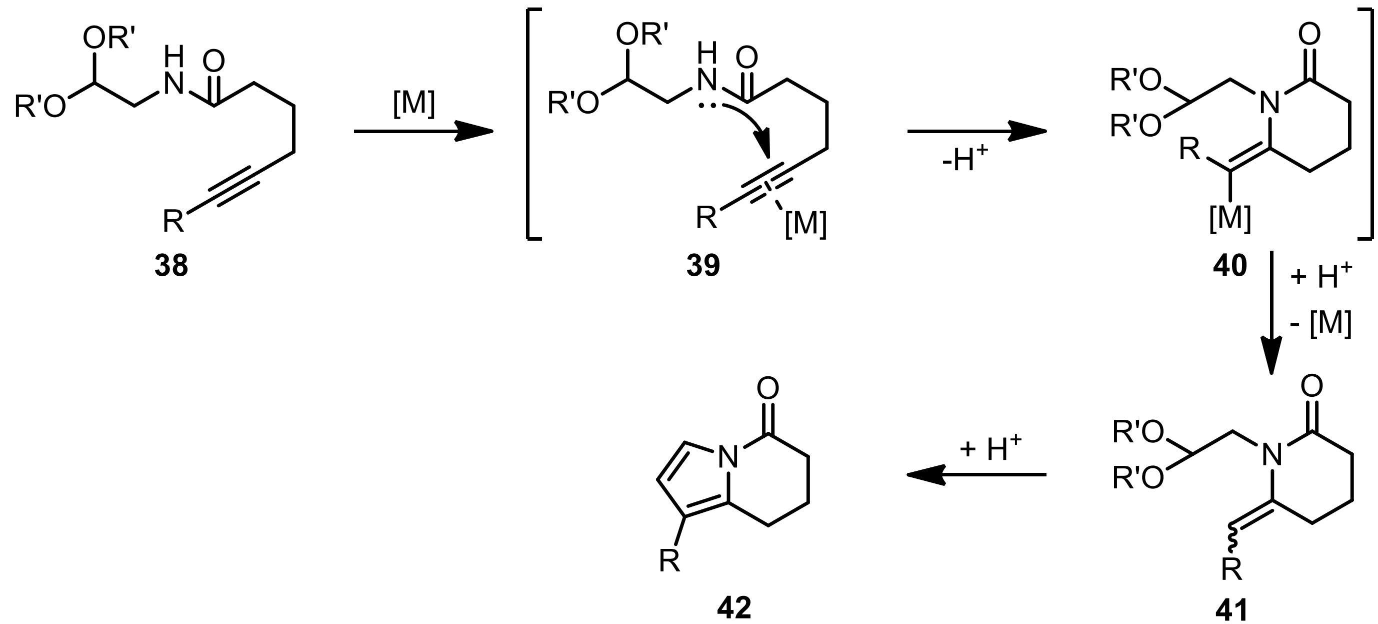
- ✓ Pd-catalyzed biaryl coupling
- ✓ exceptionally concise synthesis

Trauner, *Org. Lett.* **2005**, *7*, 5207-5209

Rhazinilam: Tokuyama's Approach



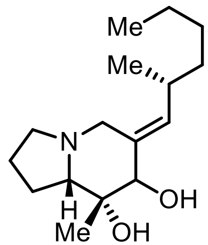
- ✓ Au-catalyzed cascade cyclization
- ✓ protecting-group-free total synthesis



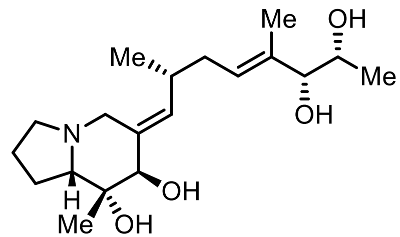
Tokuyama, *Angew. Chem. Int. Ed.* **2013**, *52*, 7168-7171

Summary

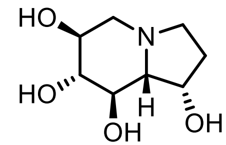
INDOLIZIDINE ALKALOIDS



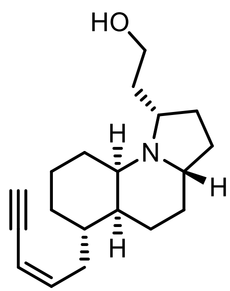
(+)-allopumiliotoxin 267A



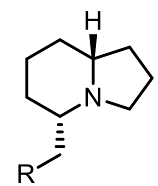
(+)-allopumiliotoxin 339A



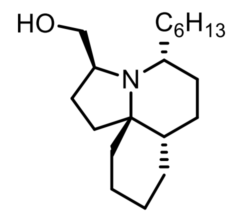
(+)-castanospermine



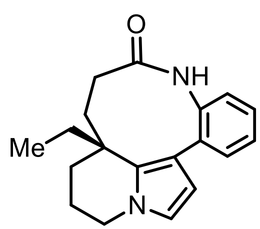
gephyrotoxin



R = C_2H_5 → ***indolizidine 167B***
R = C_5H_{11} → ***indolizidine 209D***



lepadiformine



rhazinilam

FURTHER READING:

J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139-165

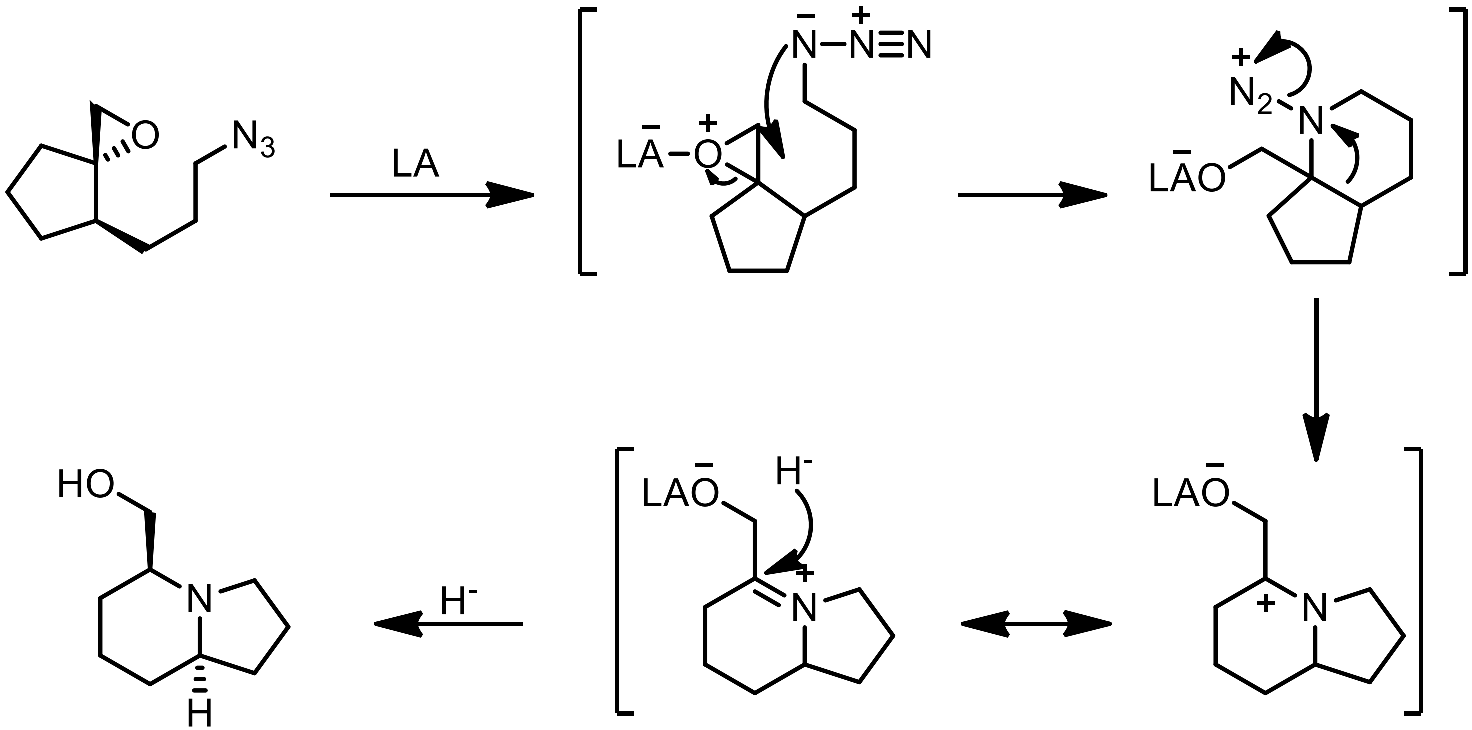
Questions

1. What is the the key step of Baskaran's synthesis of Indolizidines 167B and 209D?

2. Could you identify the mechanism underlying Denmark's Castanospermine synthesis?

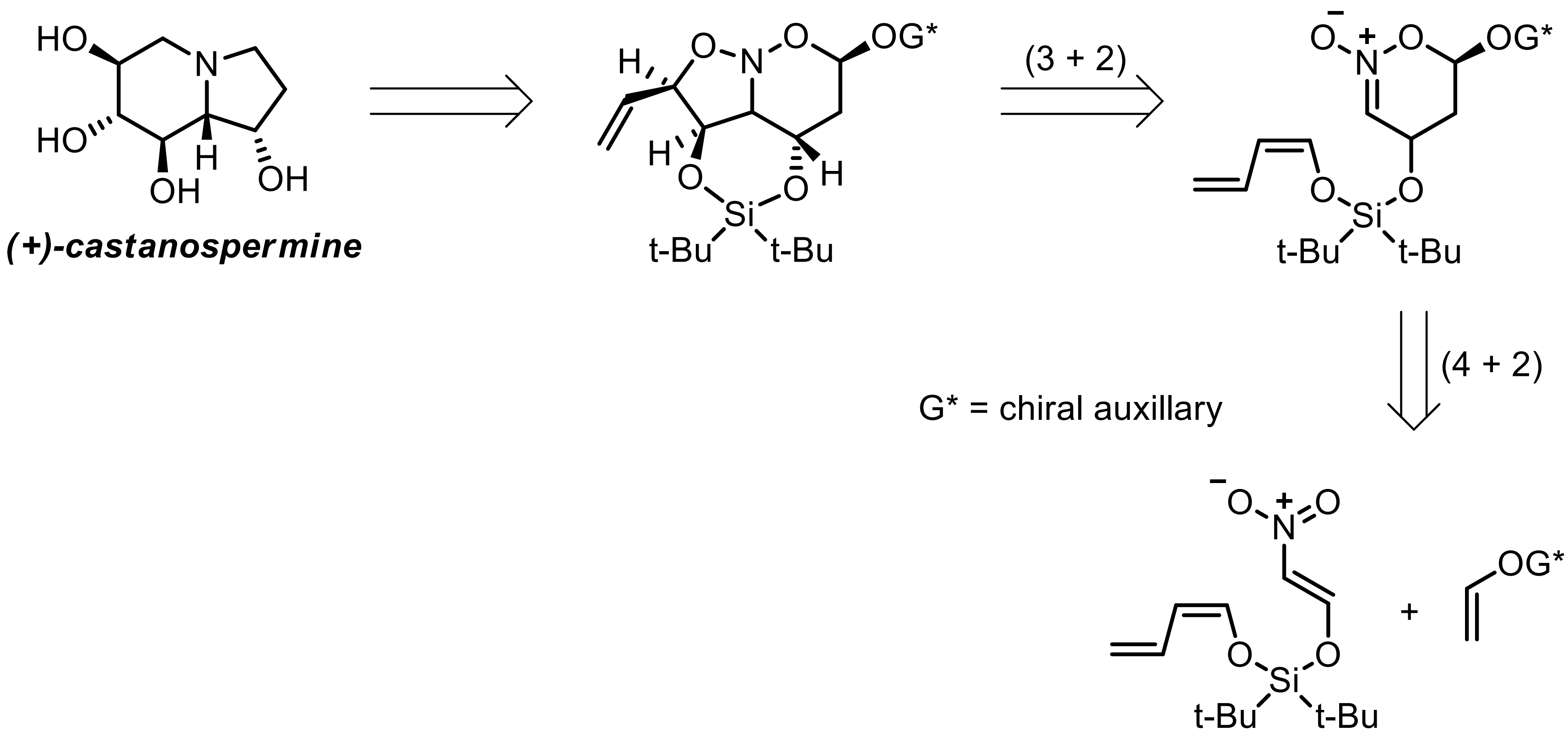
1. What is the the key step of Baskaran's synthesis of Indolizidines 167B and 209D?

✓ epoxide-initiated cationic cyclization of azides

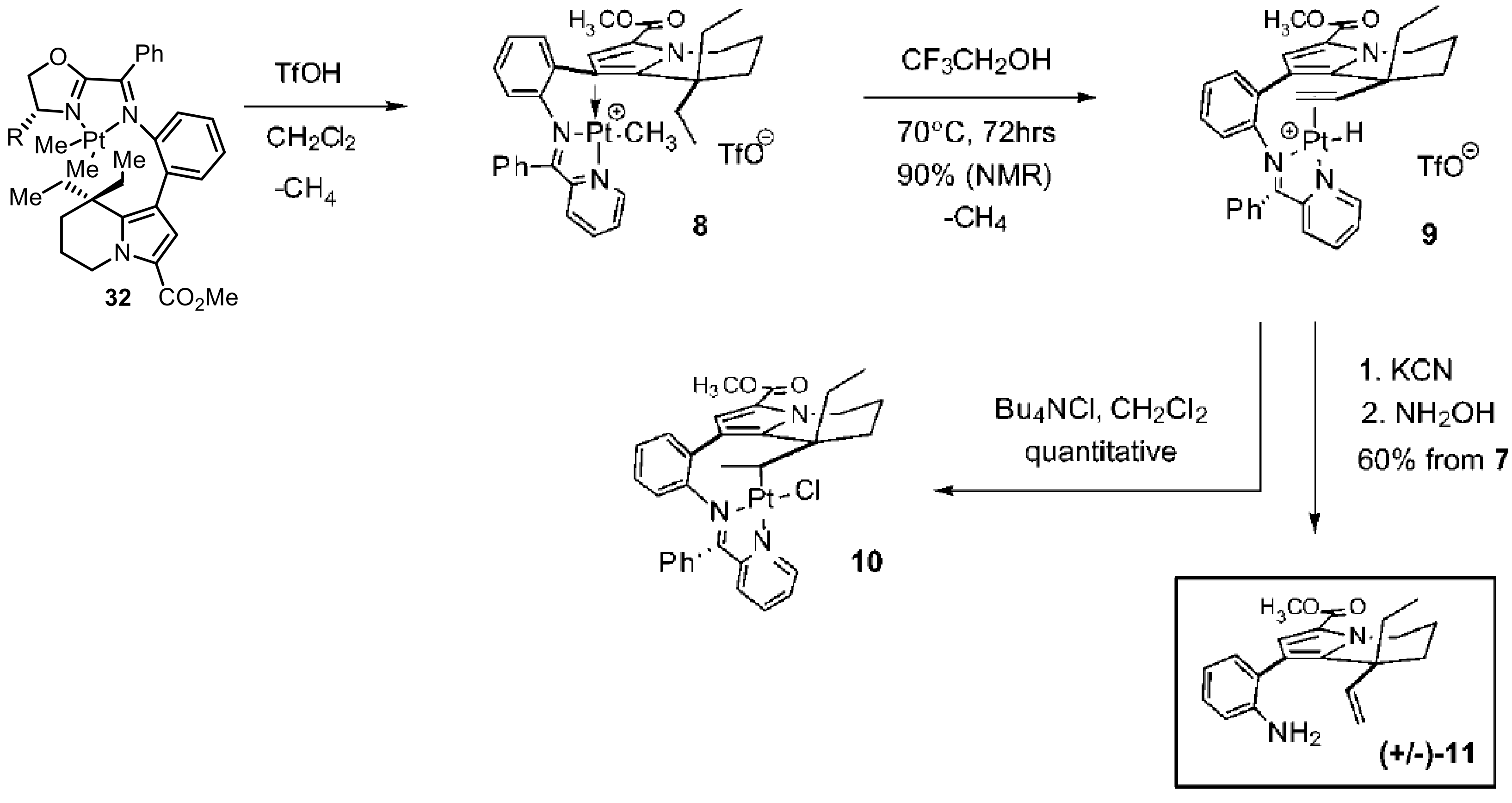


2. Could you identify the mechanism underlying Denmark's synthesis of Castanospermine?

✓ tandem [4+2]/[3+2] cycloaddition



A/


Ph
O
N
N
R
Me
Pt
Me
Me
Me
N
32
CO2Me
TfOH
CH2Cl2
-CH4
H3CO
O
N
N
Pt
CH3
Ph
N
TfO
8
CF3CH2OH
70°C, 72hrs
90% (NMR)
-CH4
H3CO
O
N
Pt
H
N
N
Ph
TfO
9
Bu4NCl, CH2Cl2
quantitative
1. KCN
2. NH2OH
60% from 7
H3CO
O
N
N
Pt
Cl
N
Ph
10
H3CO
O
N
NH2
(+/-)-11

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Synthetic Routes to the Best Selling Drugs Containing 6-Membered Heterocycles

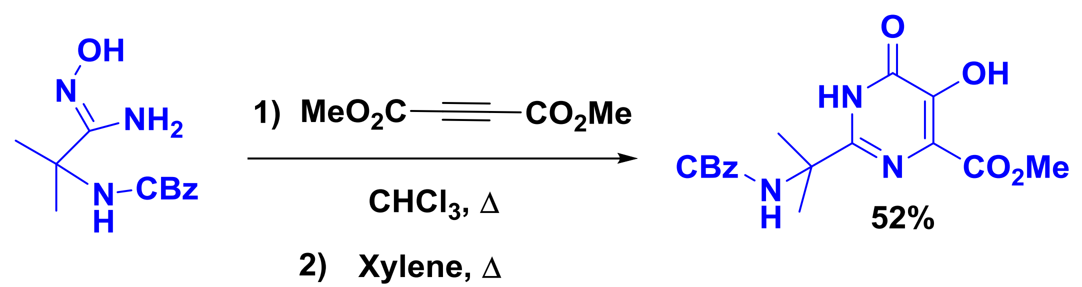
Literature Talk

Grigory Karateev

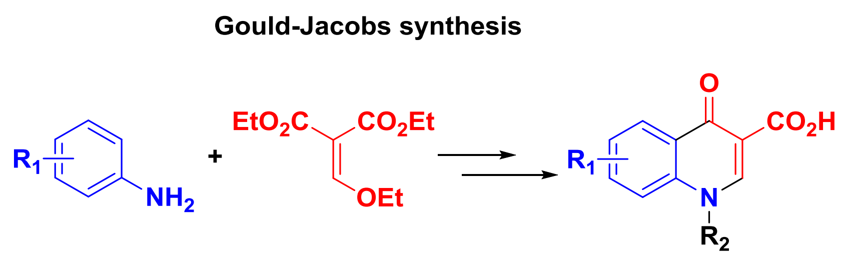
May 2015

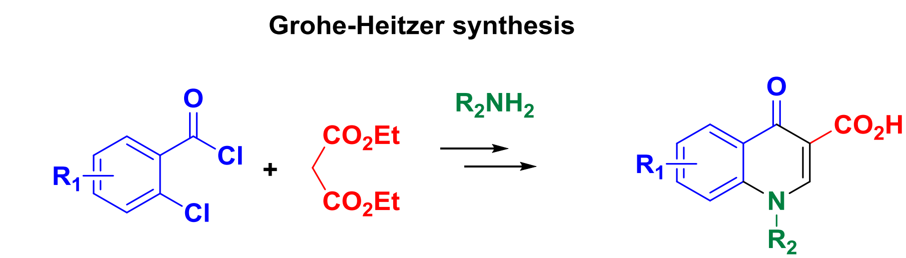
Questions.

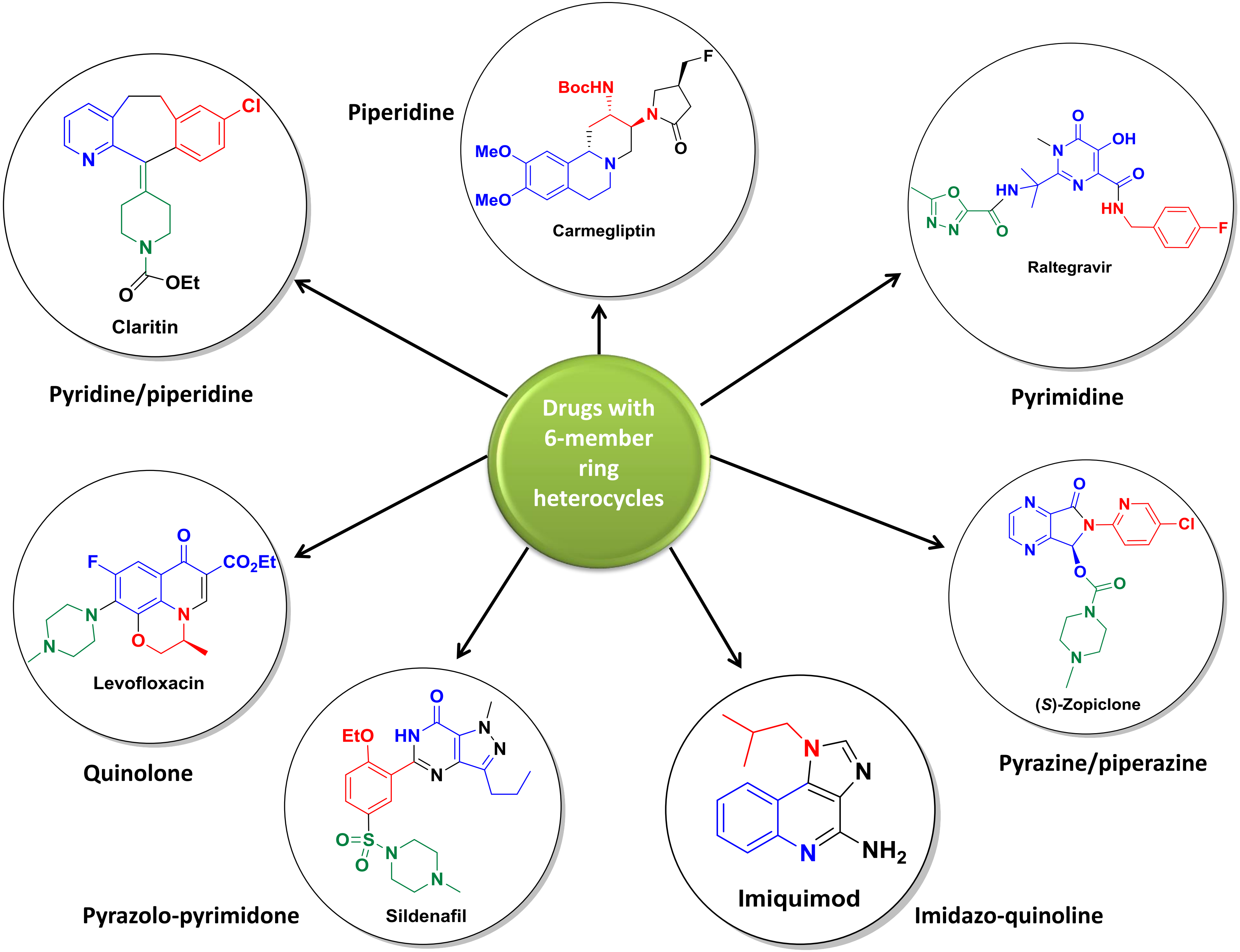
1. Propose the mechanism for the following reaction (a key step in the synthesis of raltegravir):



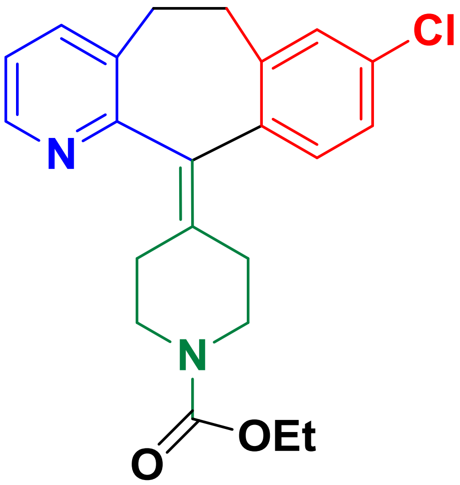
2. Which of the methods depicted below is more powerful and why?






Drugs with 6-member ring heterocycles
Piperidine
Carmegliptin
Pyridine/piperidine
Claritin
Pyrimidine
Raltegravir
Quinolone
Levofloxacin
Pyrazolo-pyrimidone
Sildenafil
Imiquimod
Imidazo-quinoline
Pyrazine/piperazine
(S)-Zopiclone

Pyridine and piperidine containing drugs.
Claritin.

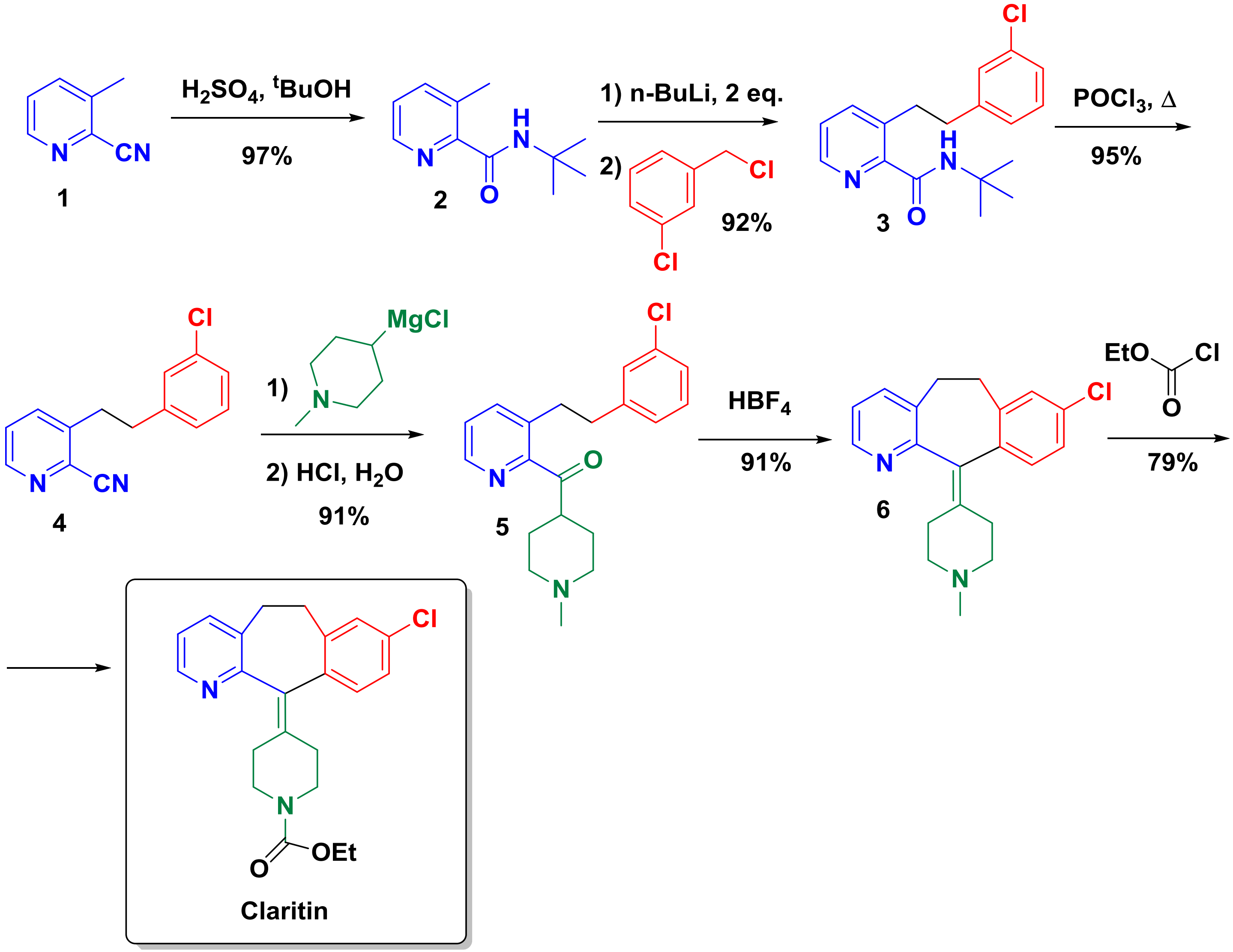


Claritin

- An antiallergic drug
- A second generation inhibitor of H1-histamine receptors
- Developed by Schering-Plough (now part of Merck & Co)
- FDA approved in 1993

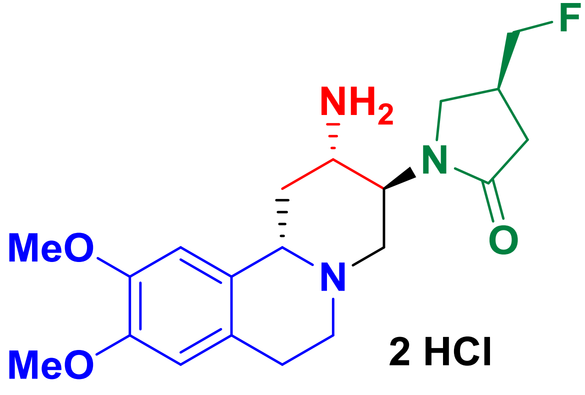
Worldwide sales $ 250.000.000 (2013)

Pyridine and piperidine containing drugs.
Claritin.



D. P. Schumacher, B. L. Murphy, J. E. Clark, P. Tahbaz, T. A. Mann, *The Journal of Organic Chemistry* **1989**, *54*, 2242-2244.
http://www.evaluategroup.com/View/13982--1002-modData/product/claritin

Piperidine containing drugs. Carmegliptin.

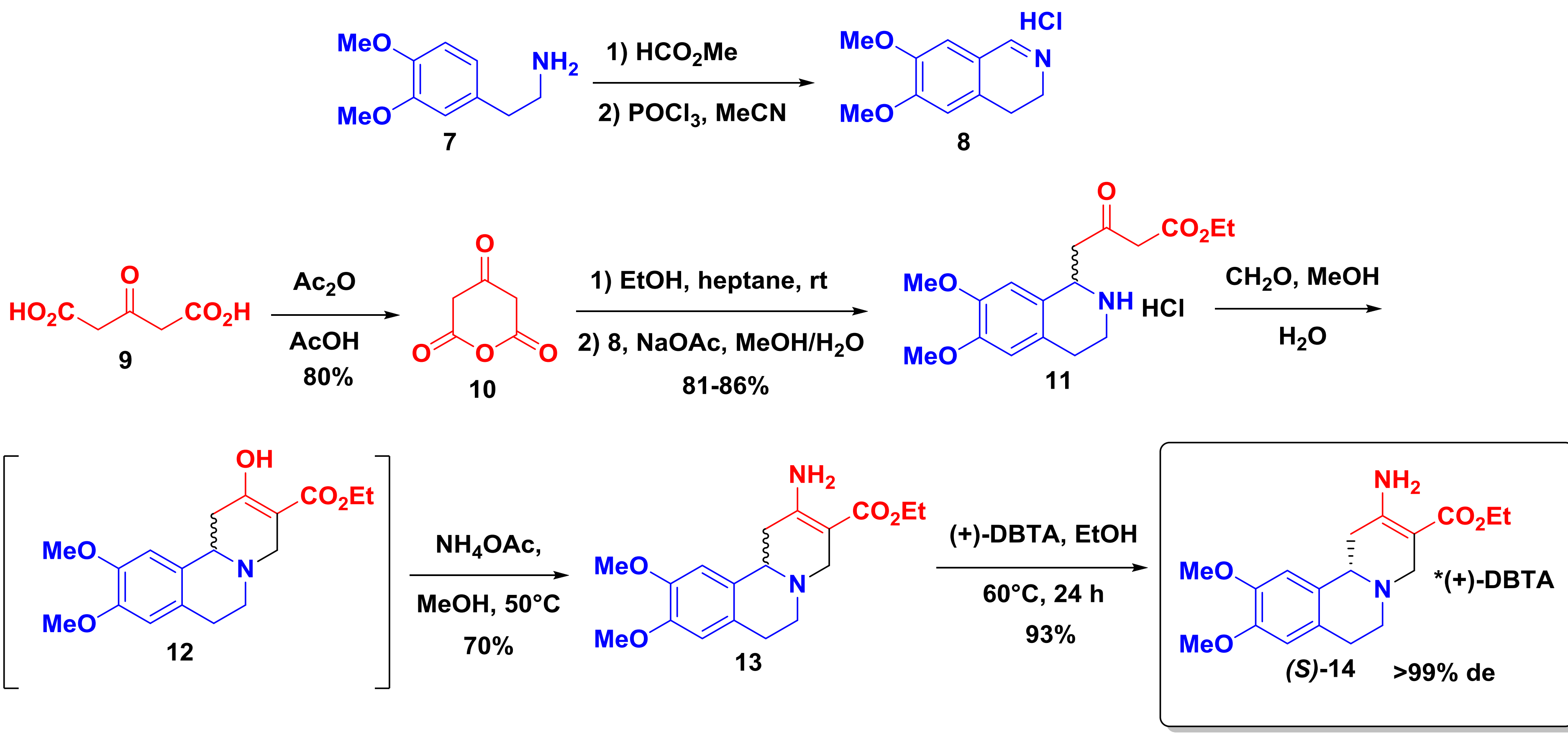


Carmegliptin

- An antidiabetic drug (for type II diabetes)
- A new generation of DPP-IV inhibitors
- Prevents deactivation of GLP1 (glucagon-like peptide) and normalizes insulin secretion
- In the late stage of clinical trials

P. Mattei, M. Boehringer, P. Di Giorgio, H. Fischer, M. Hennig, J. Huwyler, B. Koçer, B. Kuhn, B. M. Loeffler, A. MacDonald, R. Narquizian, E. Rauber, E. Sebokova, U. Sprecher, *Bioorganic & medicinal chemistry letters* **2010**, *20*, 1109-1113.

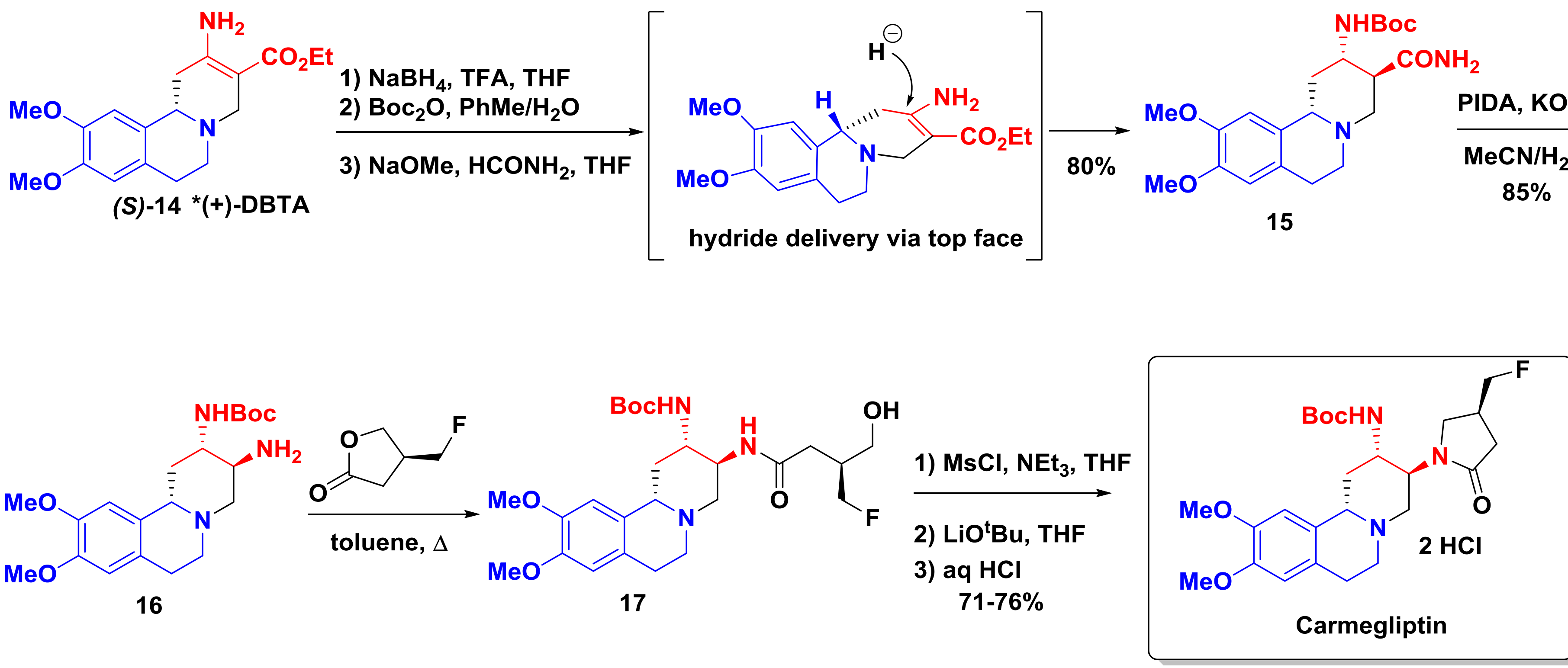
Piperidine containing drugs.
Carmegliptin.



Intermediate

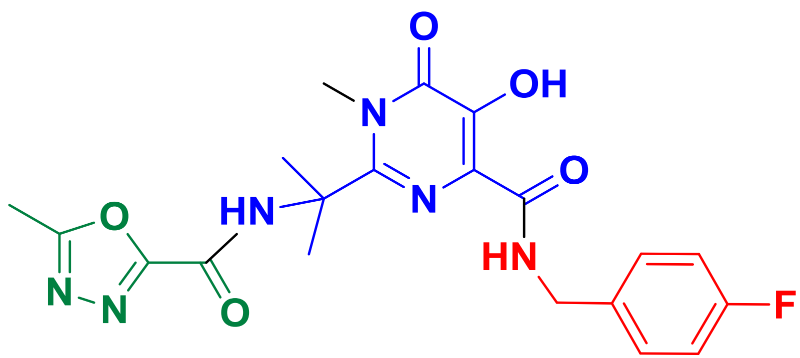
S. Abrecht, J.-M. Adam, U. Bromberger, R. Diodone, A. Fettes, R. Fischer, V. Goeckel, S. Hildbrand, G. Moine, M. Weber, *Organic Process Research & Development* **2011**, *15*, 503-514.

Piperidine containing drugs.
Carmegliptin.



S. Abrecht, J.-M. Adam, U. Bromberger, R. Diodone, A. Fettes, R. Fischer, V. Goeckel, S. Hildbrand, G. Moine, M. Weber, *Organic Process Research & Development* **2011**, *15*, 503-514.

Pyrimidine containing drugs.
Raltegravir.

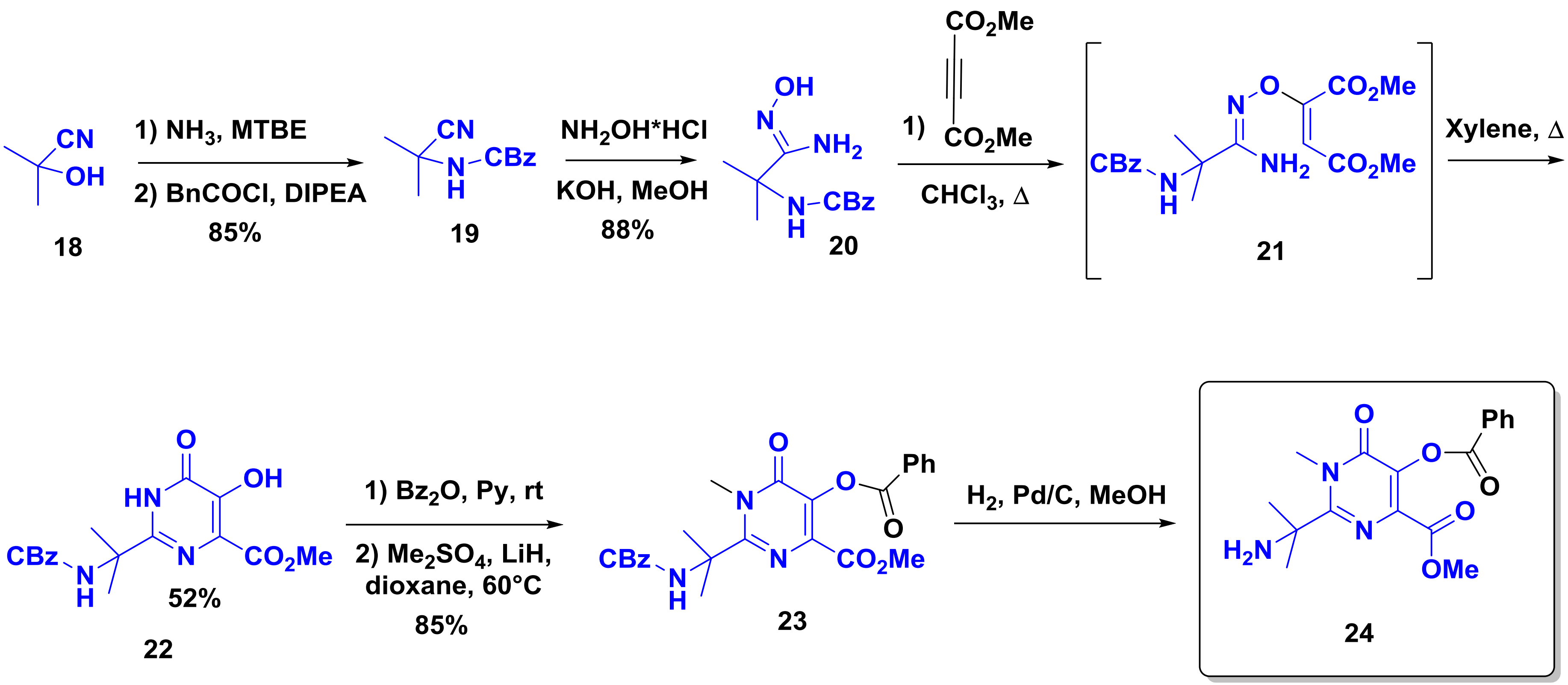


Raltegravir

- Antiretroviral drug to treat HIV infection
- Targets enzyme **Integrase** and prevents integration of viral RNA into chromosomes
- FDA approved in 2007
- Produced by Merck & Co

Worldwide sales: $ 1.6 billion (2013)

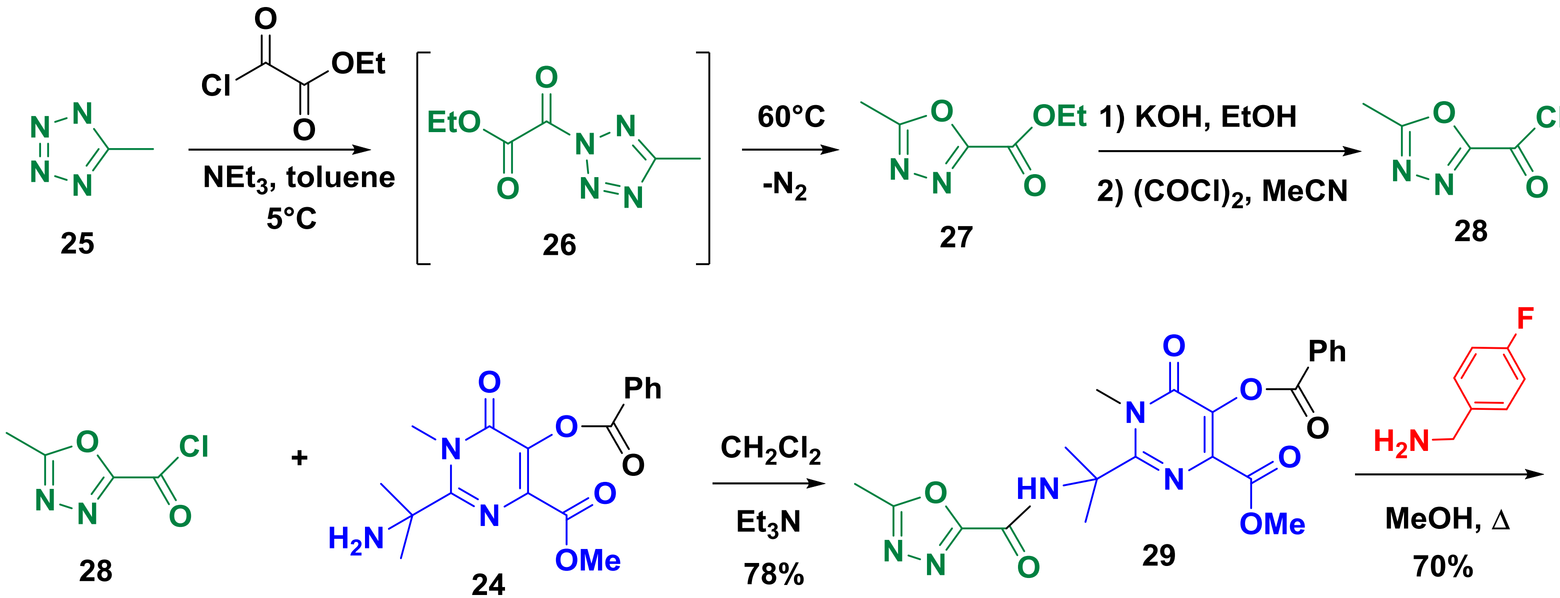
Pyrimidine containing drugs.
Raltegravir.

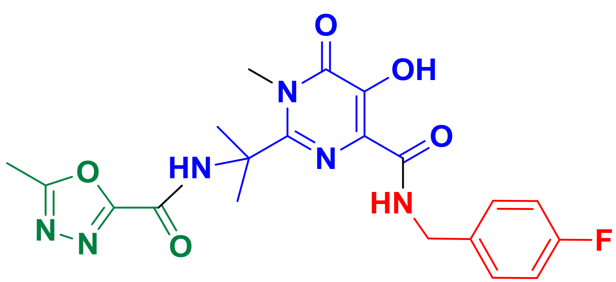


Key intermediate

V. Summa, A. Petrocchi, F. Bonelli et al., *Journal of medicinal chemistry* **2008**, *51*, 5843-5855.

Pyrimidine containing drugs.
Raltegravir.

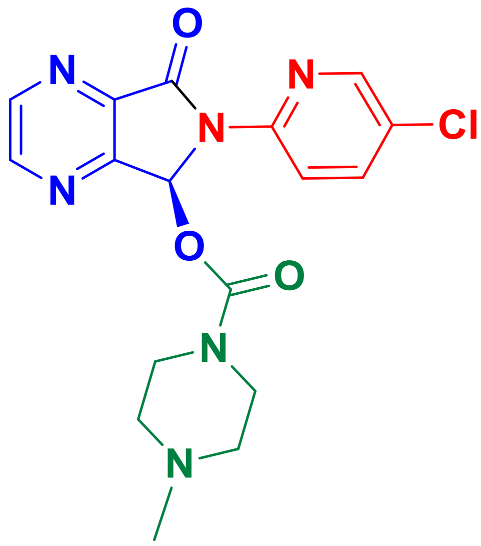




Raltegravir

V. Summa et al., *Journal of medicinal chemistry* **2008**, *51*, 5843-5855.

Pyrazine-piperazine containing drugs.
Eszopiclone.

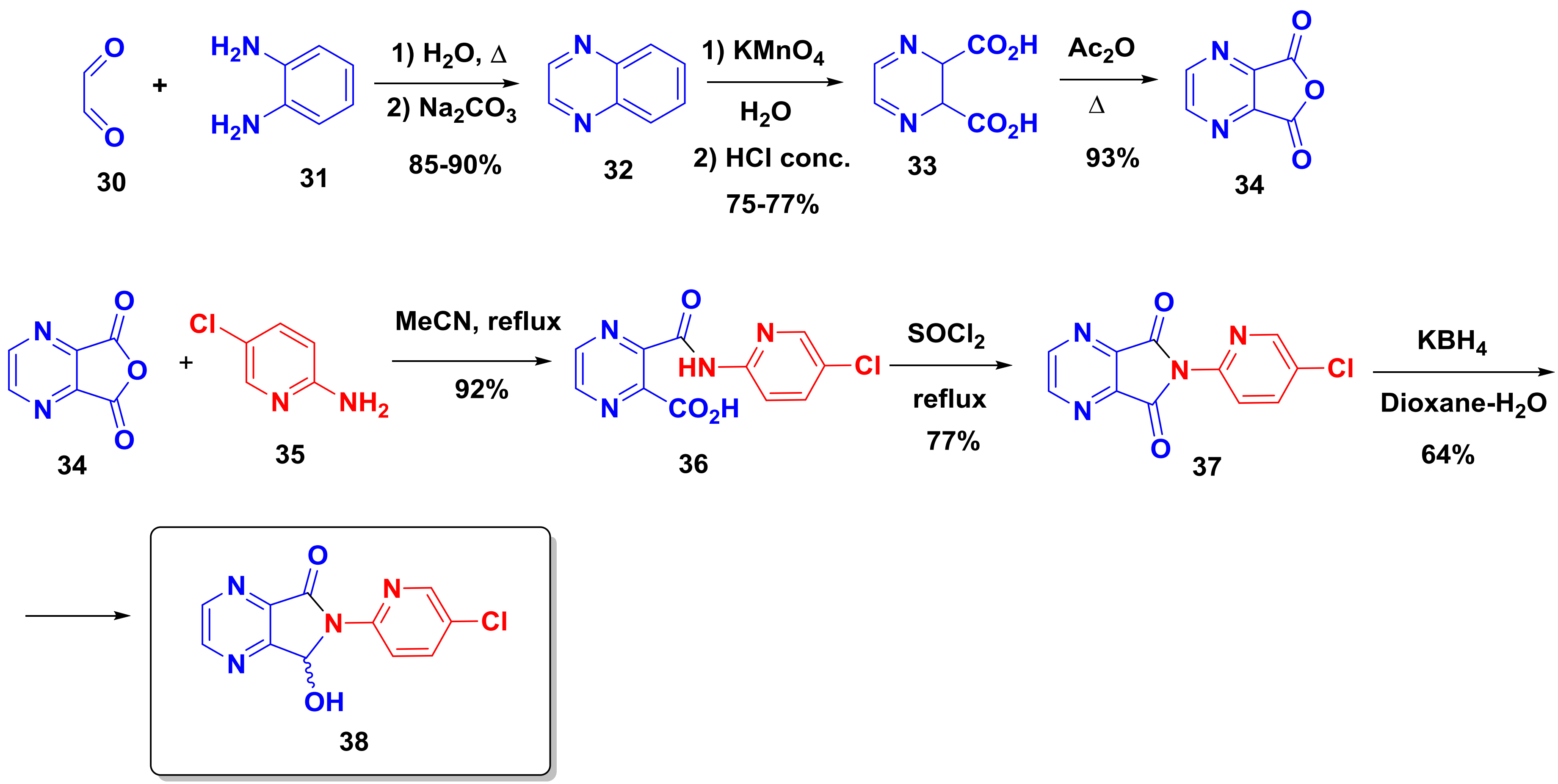


(*S*)-Zopiclone

- A drug for treatment insomnia
- Binds to $GABA_A$ receptors
- (*S*)-enantiomer has 50-fold higher binding affinity than (*R*)-enantiomer and therefore is more active
- Discovered and marketed by Rhone-Poulenc Rorer (now part of Sanofi-Aventis)

Worldwide sales: $ 630 million (2013)

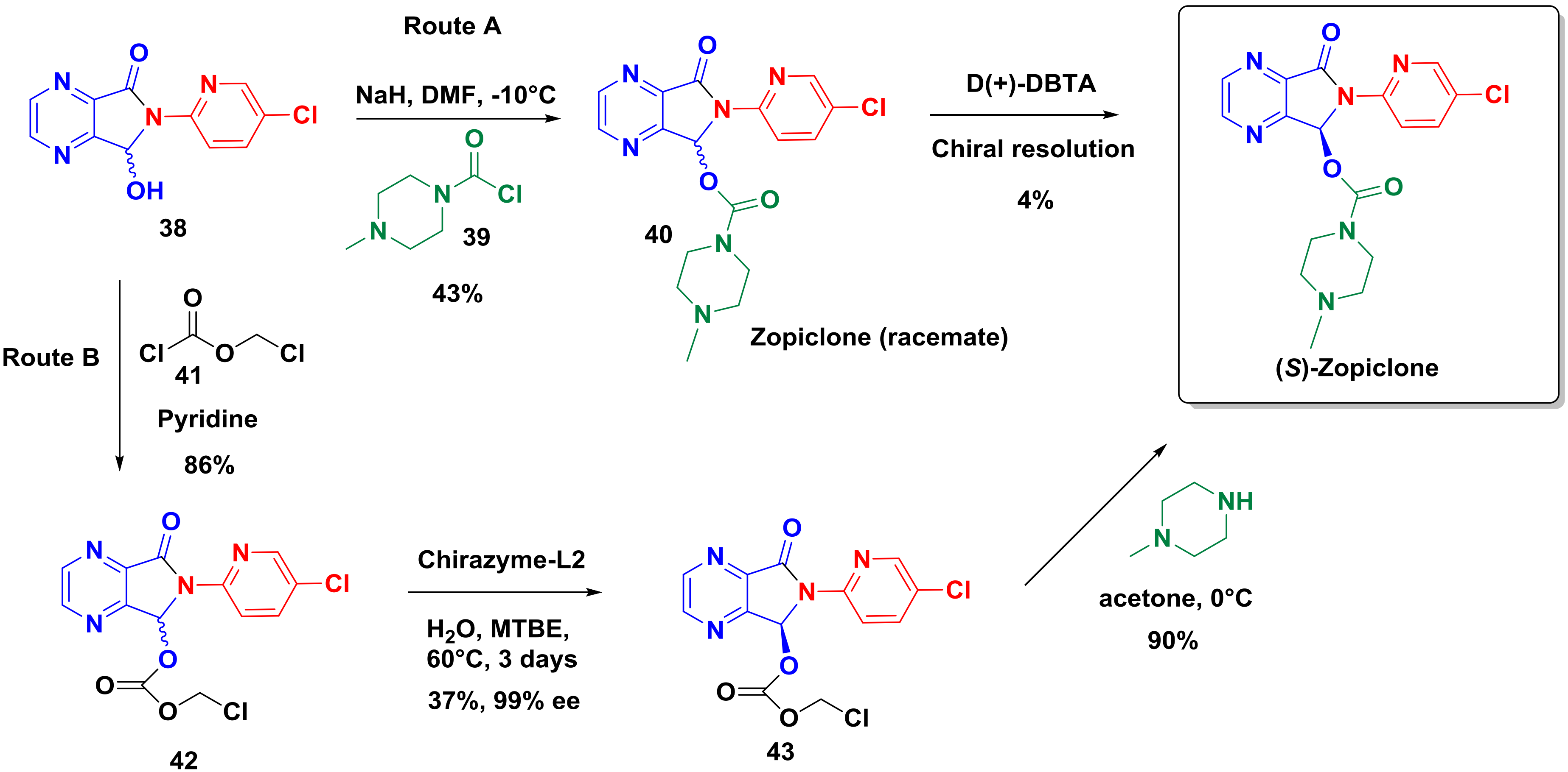
Pyrazine-piperazine containing drugs.
Eszopiclone.



Key intermediate

Cotrel, C., Jeanmart, C., and Messer, M. N. (1975). US 3,862,149. (to Rhone-Poulenc S.A.).
Jeanmart, C., Cotrel, C., and Janot, M. M.-M. (1978). Chimie Organique, 377–378.

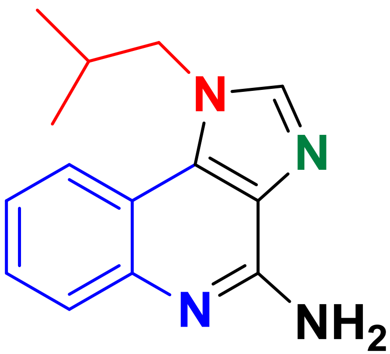
Pyrazine-piperazine containing drugs.
Eszopiclone.



Chirazyme - immobilized form of lipase B from *Candida ataractica*

Cotrel, C. and Roussel, G. (1992). EP 0495717.
Palomo, J. M. et al. (2003). Tetrahedron: Asymmetry, 14: 429–438.

Imidazo-quinoline containing drugs.
Imiquimod.

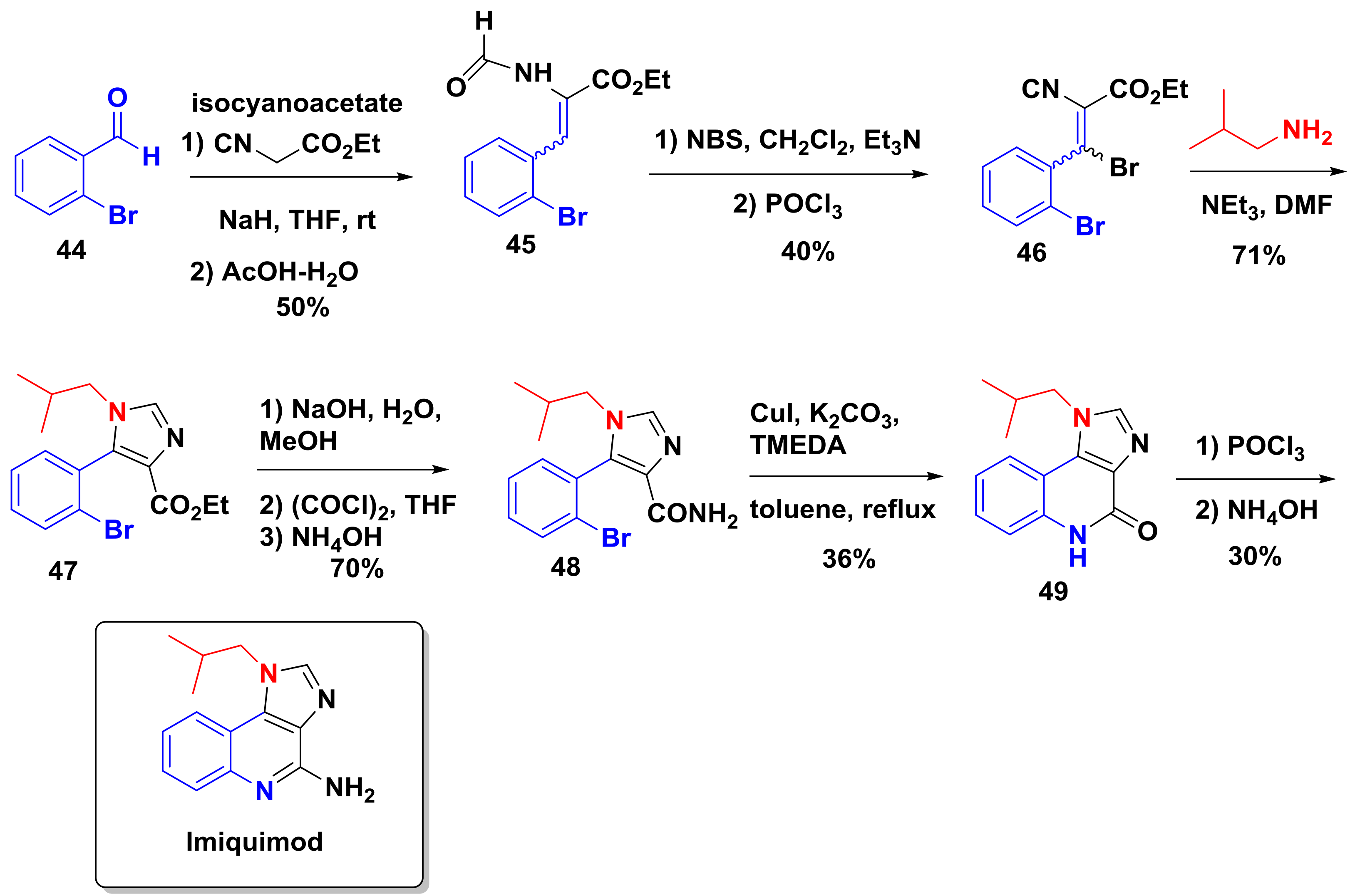


Imiquimod

- An immune response modifier
- Used to treat skin diseases including skin cancer
- Used as a cream for topical administration
- FDA approved in 1997
- Marketed by Graceway Pharmaceuticals

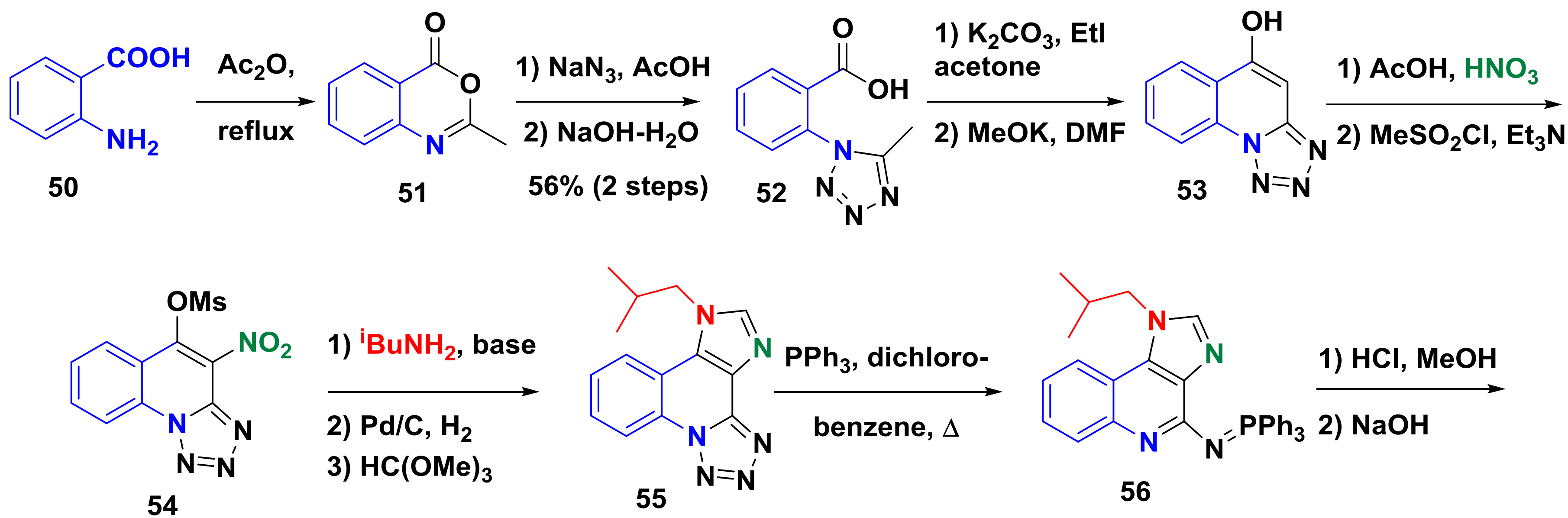
Worldwide sales: $ 146 million (2013)

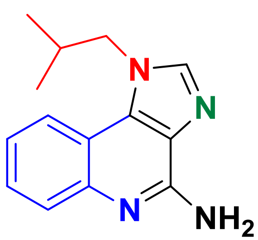
Imidazo-quinoline containing drugs.
Imiquimod. Route 1.



P. Allegrini, G. Castaldi, L. Colombo, E. Mariotti, **EP 1529781 A1**, **2005**.

Imidazo-quinoline containing drugs.
Imiquimod. Route 2.

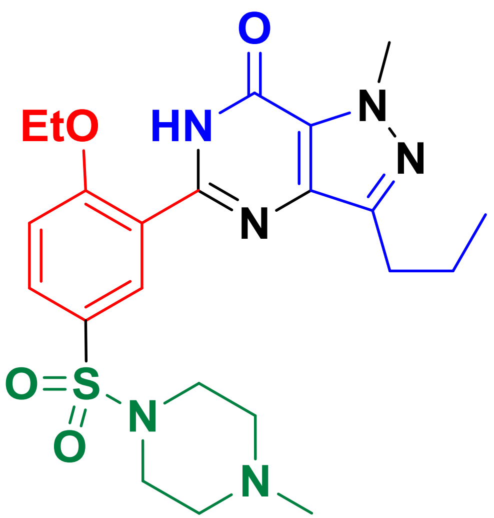




Imiquimod

Gerster, J. F.; Lindstrom, K. J. Process for Preparing Imidazoquinolinamines. WO Patent 97 48704, 1997.

Pyrazolo-pyrimidone containing drugs.
Sildenafil.



Sildenafil

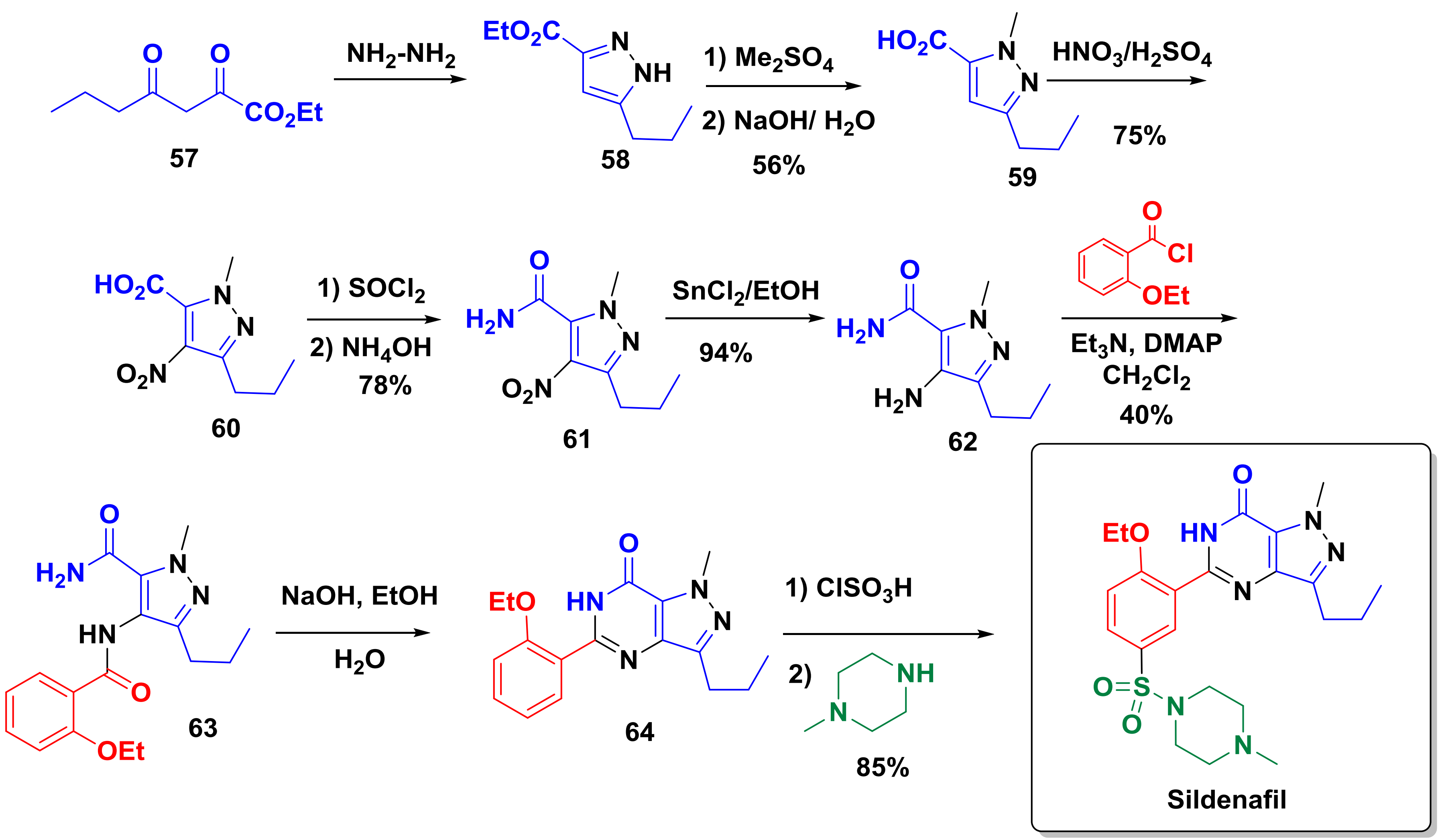
- A drug for treatment of erectile dysfunction and pulmonary arterial hypertension

Sold under commercial name **Viagra**

- Developed and manufactured by Pfizer
- FDA approved in 1998

Worldwide sales: $ 2.2 billion (2013)

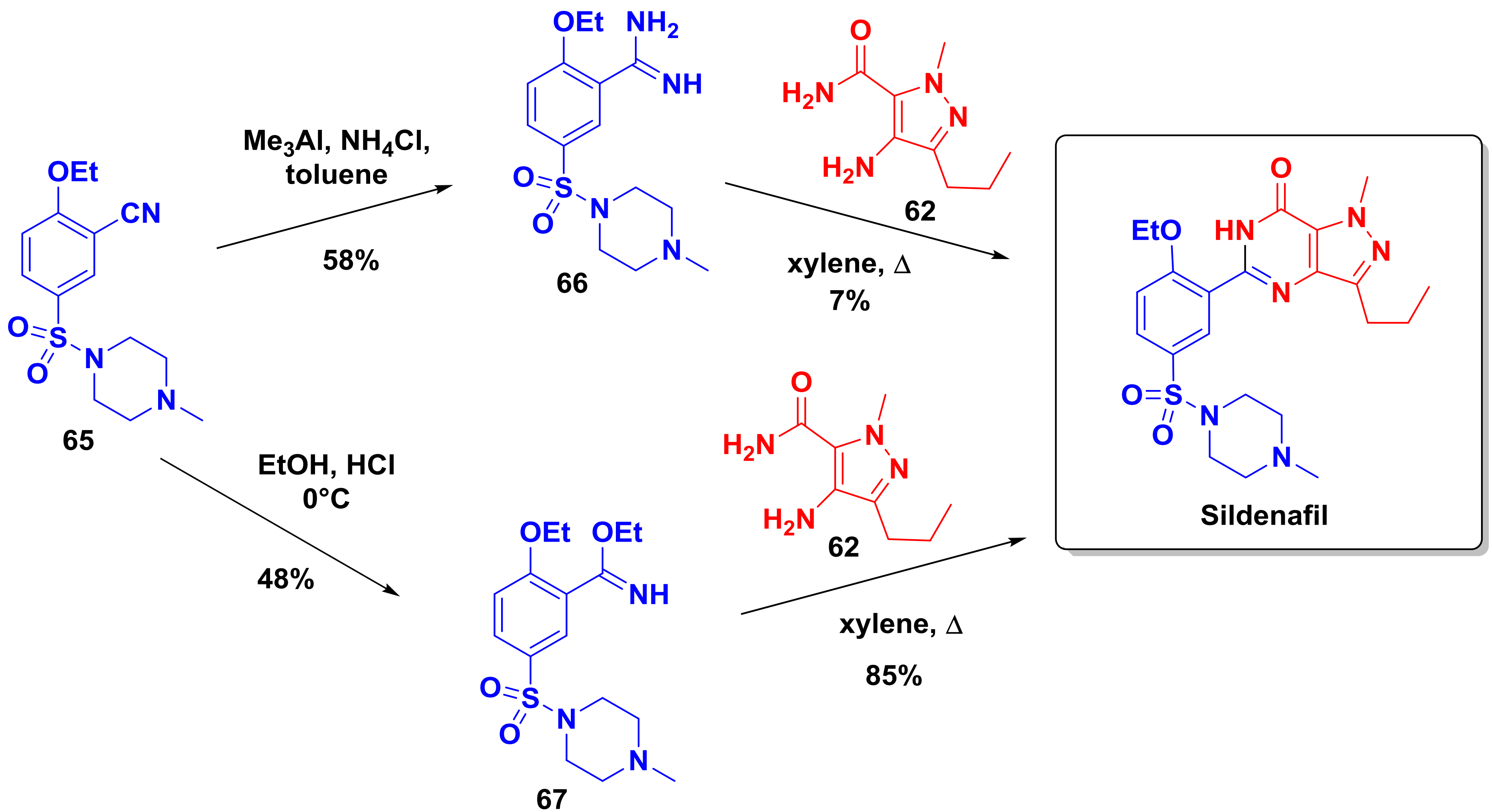
Pyrazolo-pyrimidone containing drugs.
Sildenafil. Linear route.



Bell, A. S.; Brown, D. EP 0463756 A1, **1992**.

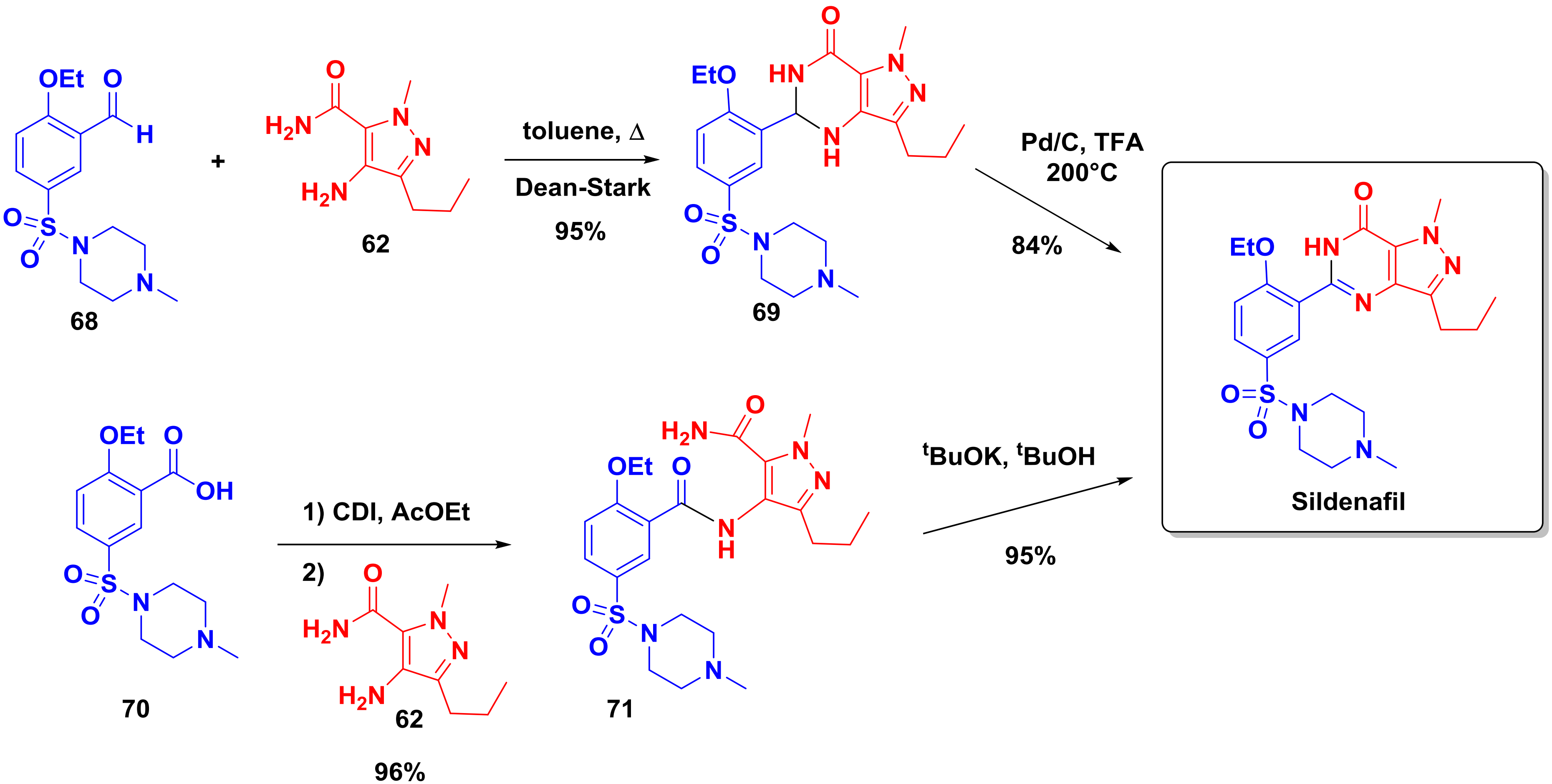
N. K. Terrett, A. S. Bell, D. Brown, P. Ellis, *Bioorganic & medicinal chemistry letters* **1996**, *6*, 1819-1824.

Pyrazolo-pyrimidone containing drugs.
Sildenafil. Convergent route 1.



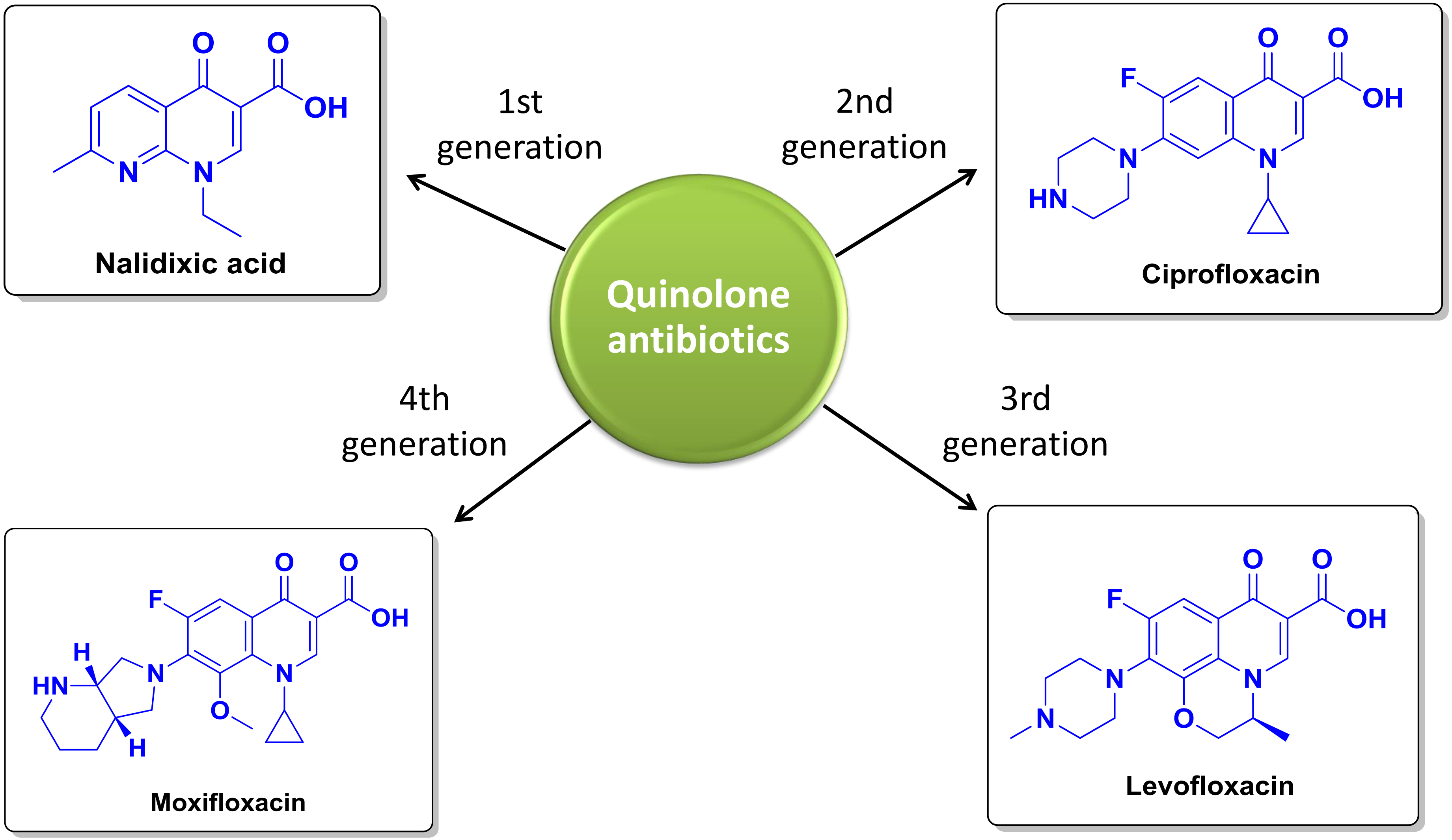
Dunn, P. J.; Dunne, C. World Patent, WO 01/98284.

Pyrazolo-pyrimidone containing drugs.
Sildenafil. Convergent route 2.



Bunnage, M. E.; Levett, P. C.; Thomson, N. M. World Patent, WO 01/ 98303.
Achmatowicz, O. et al., World Patent, WO 01/22918.
Boolell, M. et al. *Int. J. Impot. Res.* **1996**, 8, 47-52.

Quinolone Antibiotics.

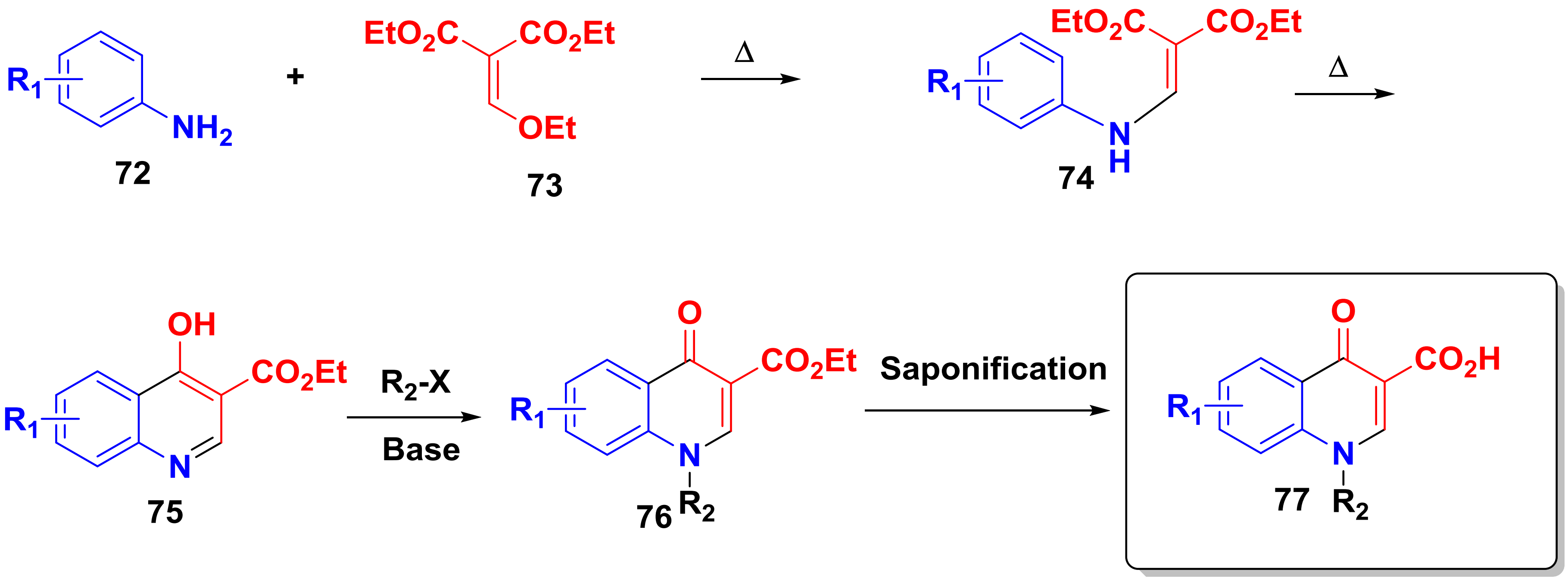


Avelox® US sales $ 195.000.000 (2013)

Levaquin® US sales $ 1.5 billion (2011)

Quinolone Antibiotics.

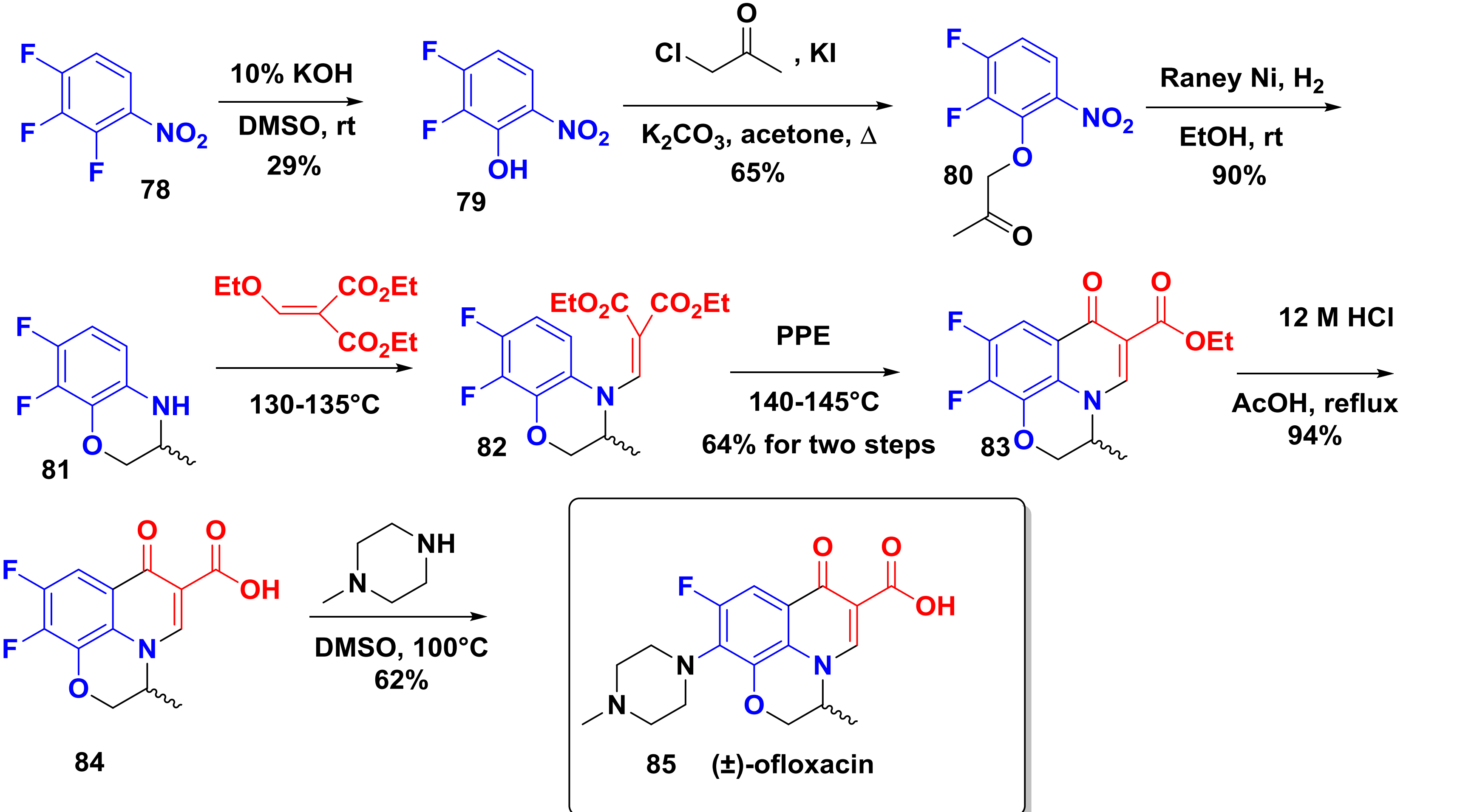
The Gould-Jacobs sequence (1939)[1]



[1]R. G. Gould, W. A. Jacobs, *Journal of the American Chemical Society* **1939**, *61*, 2890-2895.

Quinolone Antibiotics.
Ofloxacin.

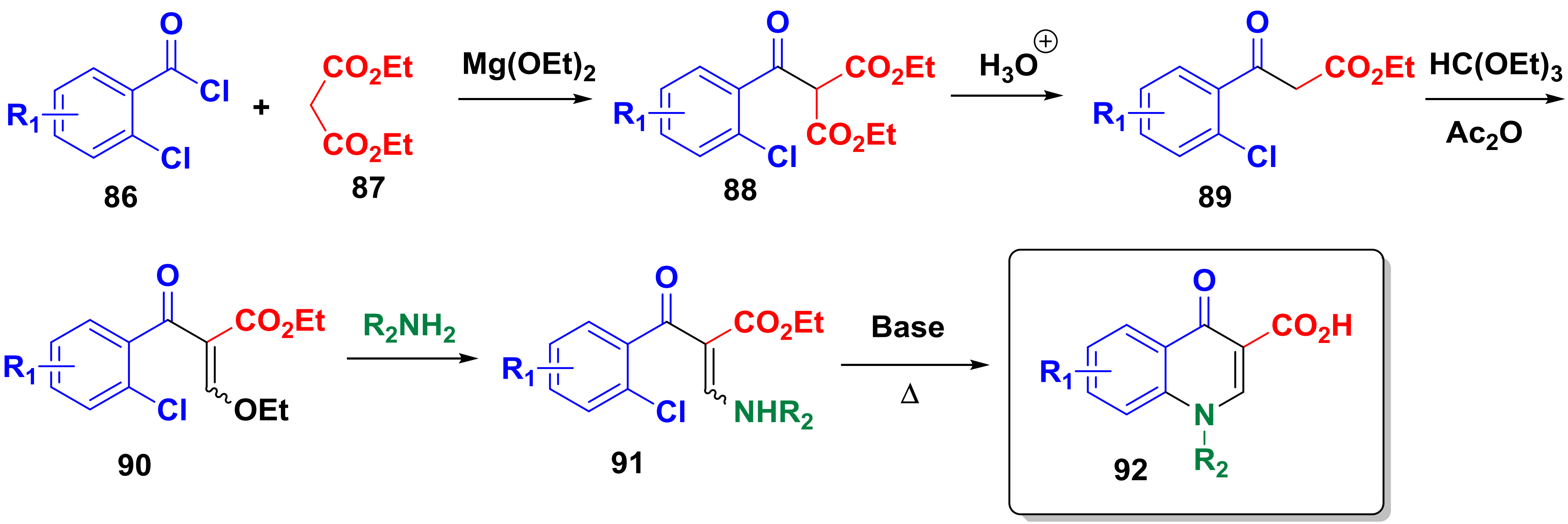
I. Gould-Jacobs sequence -> Hayakawa synthesis (1984)



I. Hayakawa, T. Hiramitsu, Y. Tanaka, *CHEMICAL & PHARMACEUTICAL BULLETIN* **1984**, *32*, 4907-4913.

Quinolone Antibiotics

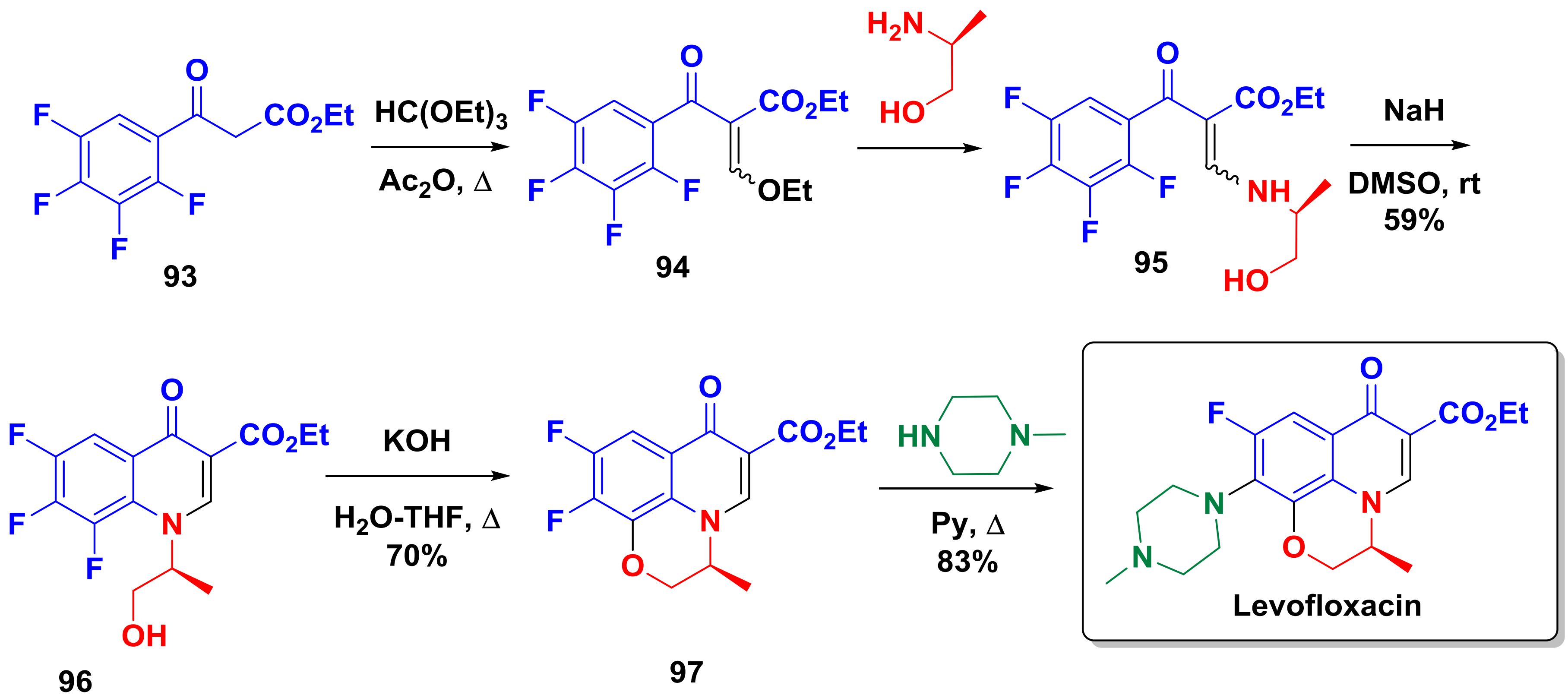
Grohe-Heitzer sequence



K. Grohe, H. Heitzer, *Liebigs Annalen der Chemie* **1987**, *1987*, 871-879.

Quinolone Antibiotics.
Levofloxacin.

Grohe-Heitzer sequence -> Chu−Mitscher Synthesis (1987)



L. A. Mitscher, P. N. Sharma, D. T. W. Chu, L. L. Shen, A. G. Pernet, *Journal of medicinal chemistry* **1987**, *30*, 2283-2286.

Conclusions and perspectives

- Six member heterocycles are very abundant among important top selling drugs

- Reduced forms of parent heterocycles (piperidines, piperazines…) are also common structural elements of drugs due to their beneficial features (hydrophilicity, H-bonding, role as a pharmacophore…)

- Further advances in synthetic methods are extremely important for pharmaceutical industry

Thank you for your attention

Selected examples of spirocyclic natural product synthesis

Nicolas Gaeng

Frontiers in Chemical Synthesis – Heterocyclic Chemistry – May 11th 2015

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Table of contents

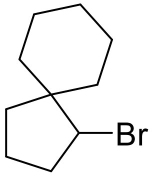
- Introduction

Baeyer, A. *Berichte der deutschen chemischen Gesellschaft* **1900**, *33*, 3771.

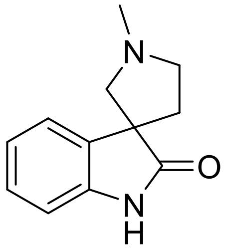
Introduction – spirocyclic compounds

- Structures with multiple rings connected through one atom

- Nomenclature proposed by Adolf Baeyer in 1900



1-bromospiro[4.5]decane



1'-methylspiro[indoline-3,3'-pyrrolidin]-2-one

Horsfiline

- Challenging quaternary carbon center

Baeyer, A. *Berichte der deutschen chemischen Gesellschaft* **1900**, *33*, 3771.

Introduction – spirocyclic compounds

- Variety of different spirocyclic

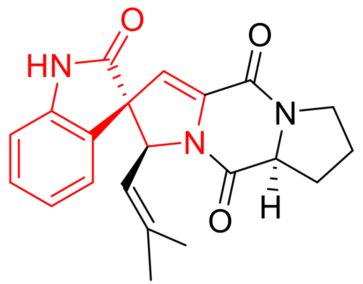
Baeyer, A. *Berichte der deutschen chemischen Gesellschaft* **1900**, *33*, 3771.

Main families

- Spirooxindole:

  Isolated from *Apocynaceae* and *Rubiacae*

  → Biological activites

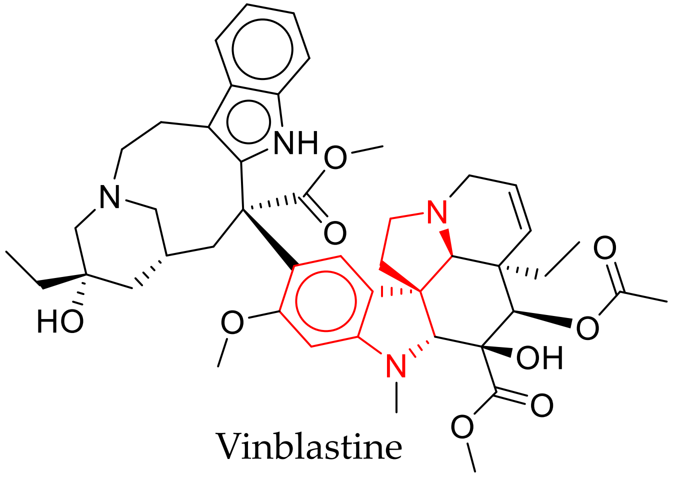


(-)-spirotryprostatin B

- Spiroindoline:

  Isolated from *Strychnos*

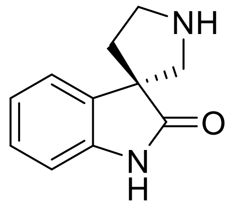
  → Antitumor activities



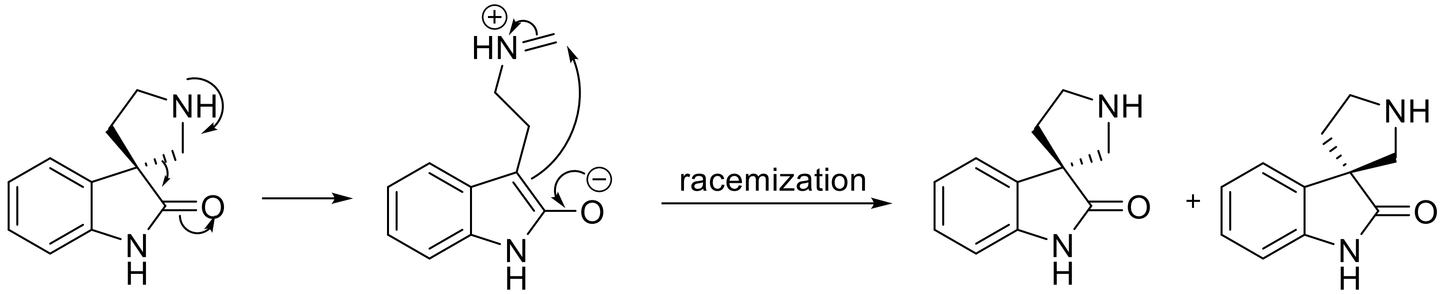
Vinblastine

Bindra, J. S. *In The Alkaloids* **1973**, *14*, 84.

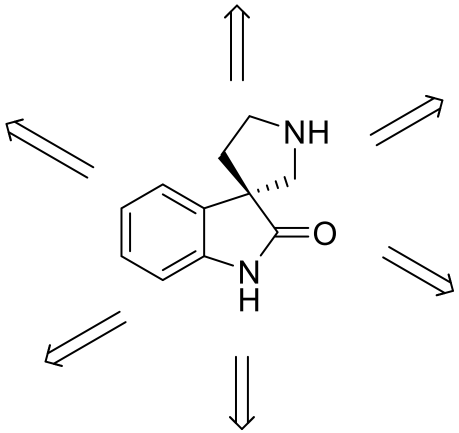
General consideration



Racemization through a retro-Mannich reaction

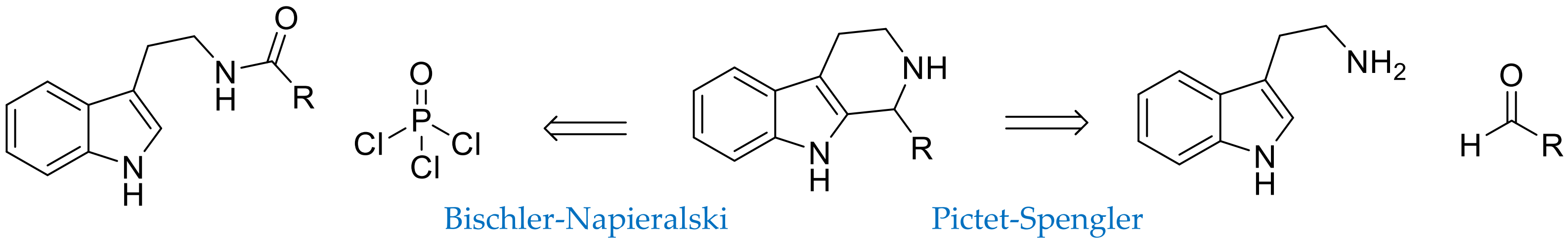


Retrosynthesis analysis



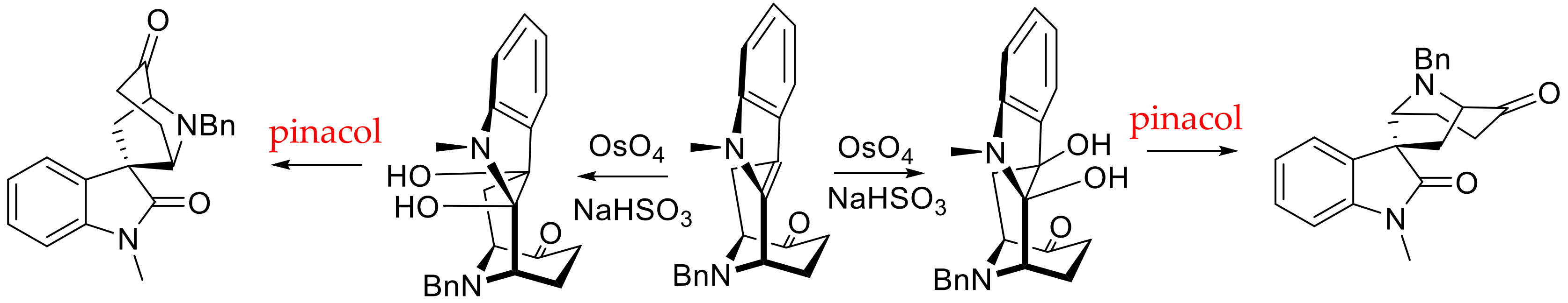
Oxidative Rearrangements

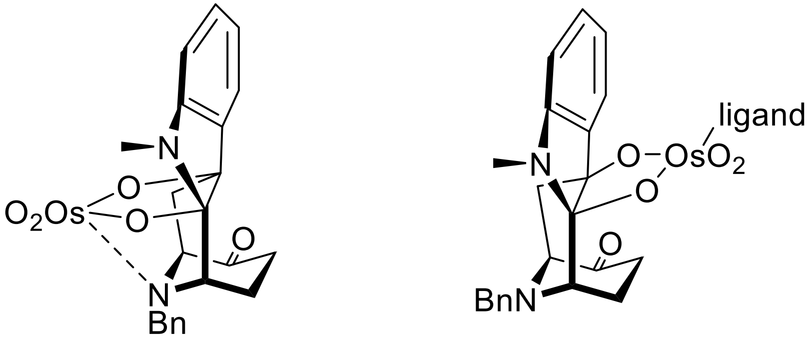
- One of the most common methods
- Usual reagents: OsO_4, $Pb(OAc)_4$, $^{t}BuOCl$, NBS, Na_2WO_4
- From tetrahydro-β-carbolines (tryptoline)



Oxidative Rearrangements

Cook's studies on alstonisine





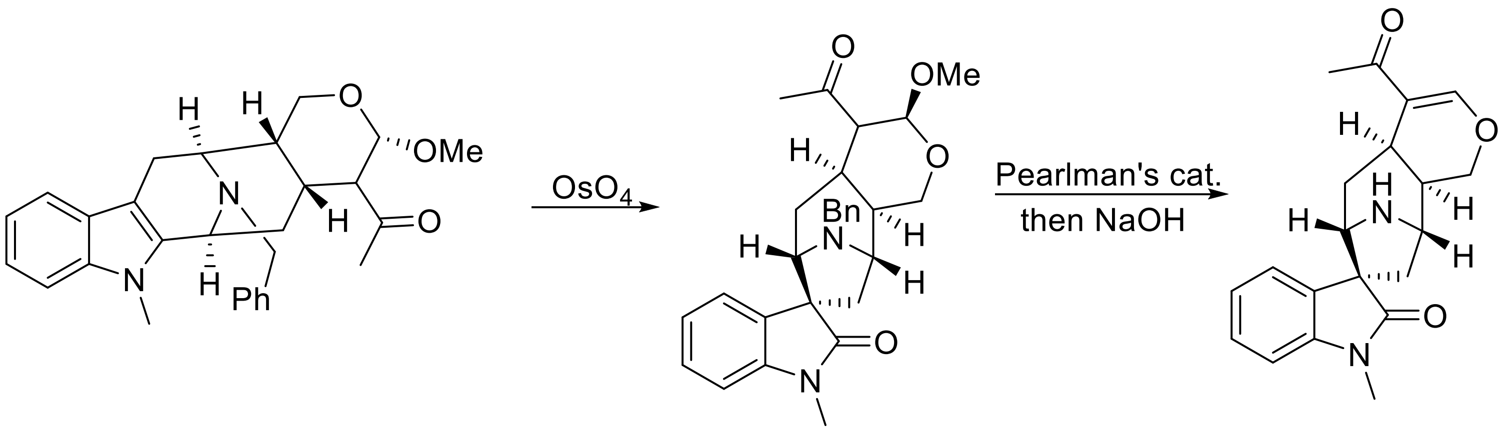
convex vs concave

Cinchona type ligand

Cook, J. M. et al. *J. Org. Chem.* **1995**, *60*, 120.
Cook, J. M. et al. *Org. Lett.* **2002**, *4*, 4237.

Oxidative Rearrangements

Cook's synthesis of alstonisine

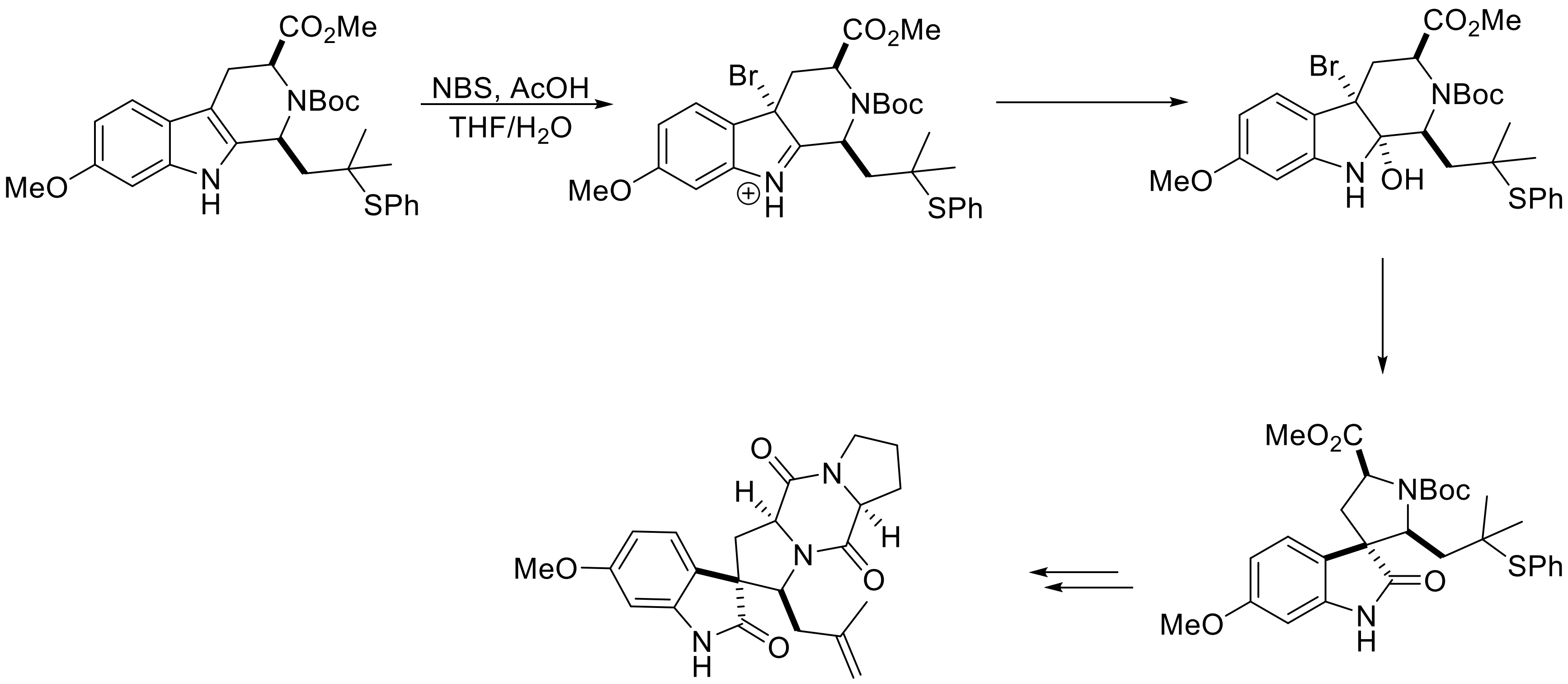


Pearlman's cat.: $Pd(OH)_2/C, H_2$

Cook, J. M. et al. *J. Org. Chem.* **1995**, *60*, 120.
Cook, J. M. et al. *Org. Lett.* **2002**, *4*, 4237.

Oxidative Rearrangements

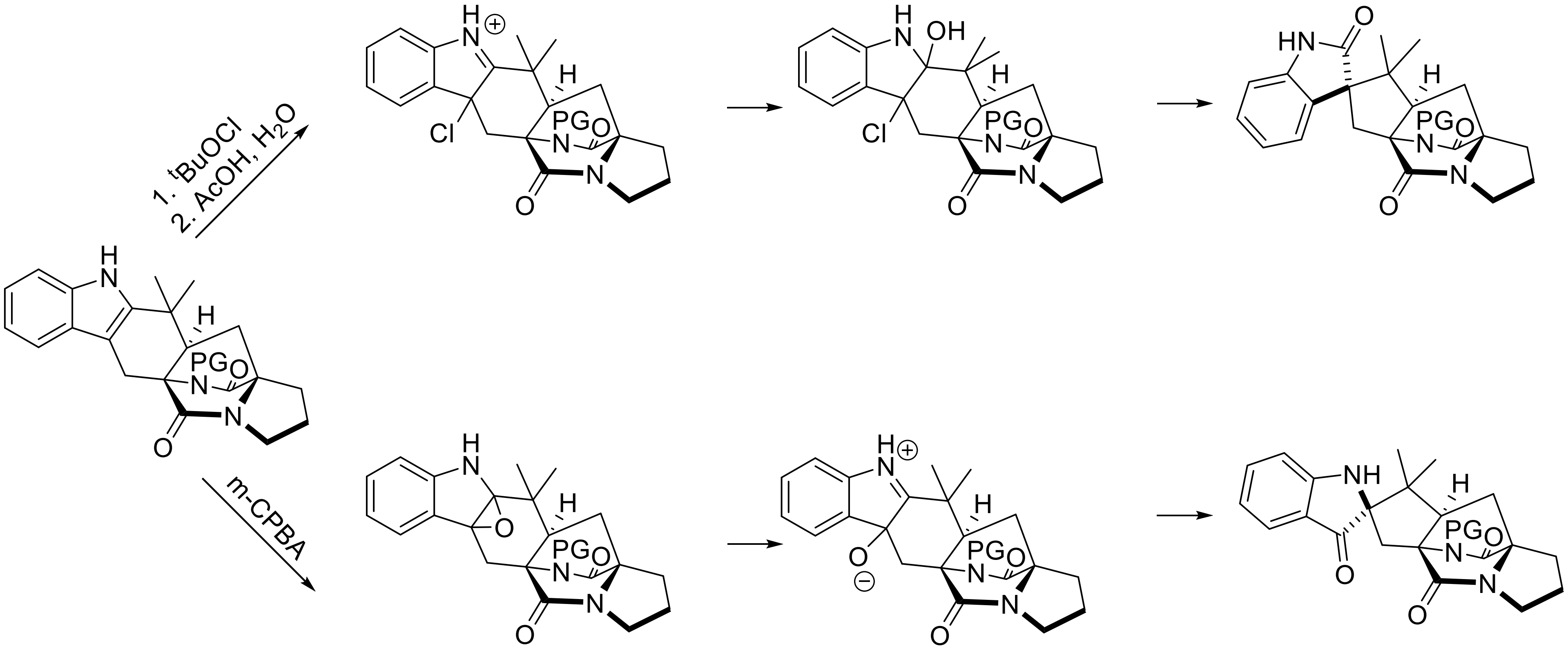
Danishefsky's synthesis of spirotryprostatin A



Danishefsky, S. J. et al. *J. Am. Chem. Soc.* **1999**, *121*, 2147.

Oxidative Rearrangements

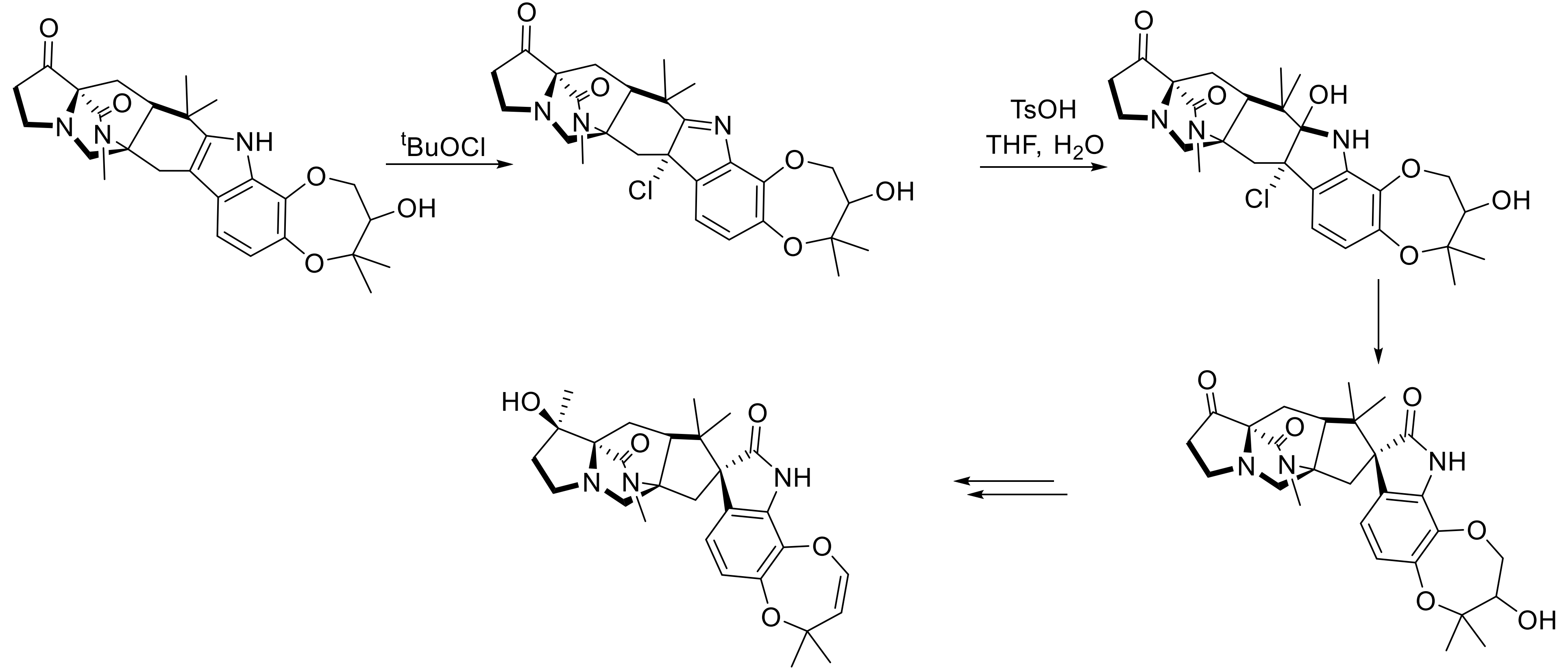
Williams' studies on paraherquamide



Williams, R. M. et al. *Tetrahedron Lett.* **1989**, *30*, 5575.

Oxidative Rearrangements

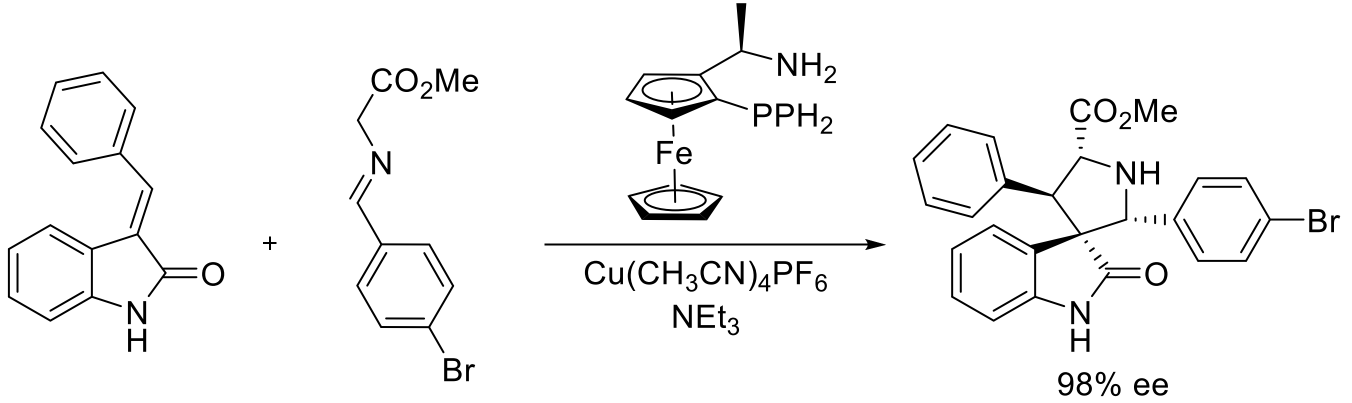
Williams' synthesis of paraherquamide A

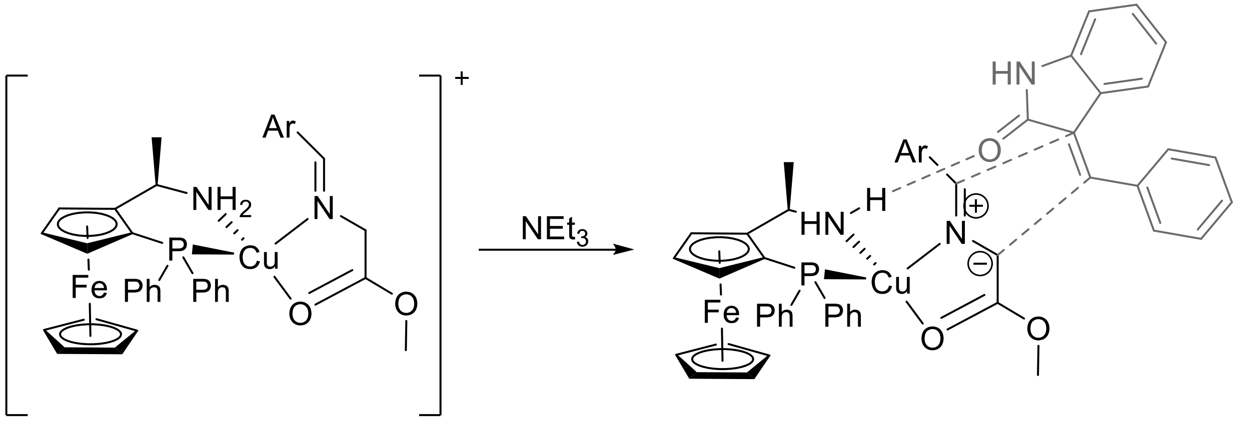


Williams, R. M. et al. *J. Am. Chem. Soc.* **2003**, *125*, 12172.

1,3-dipolar cycloaddition

Waldmann's studies based on spirotryprostatin

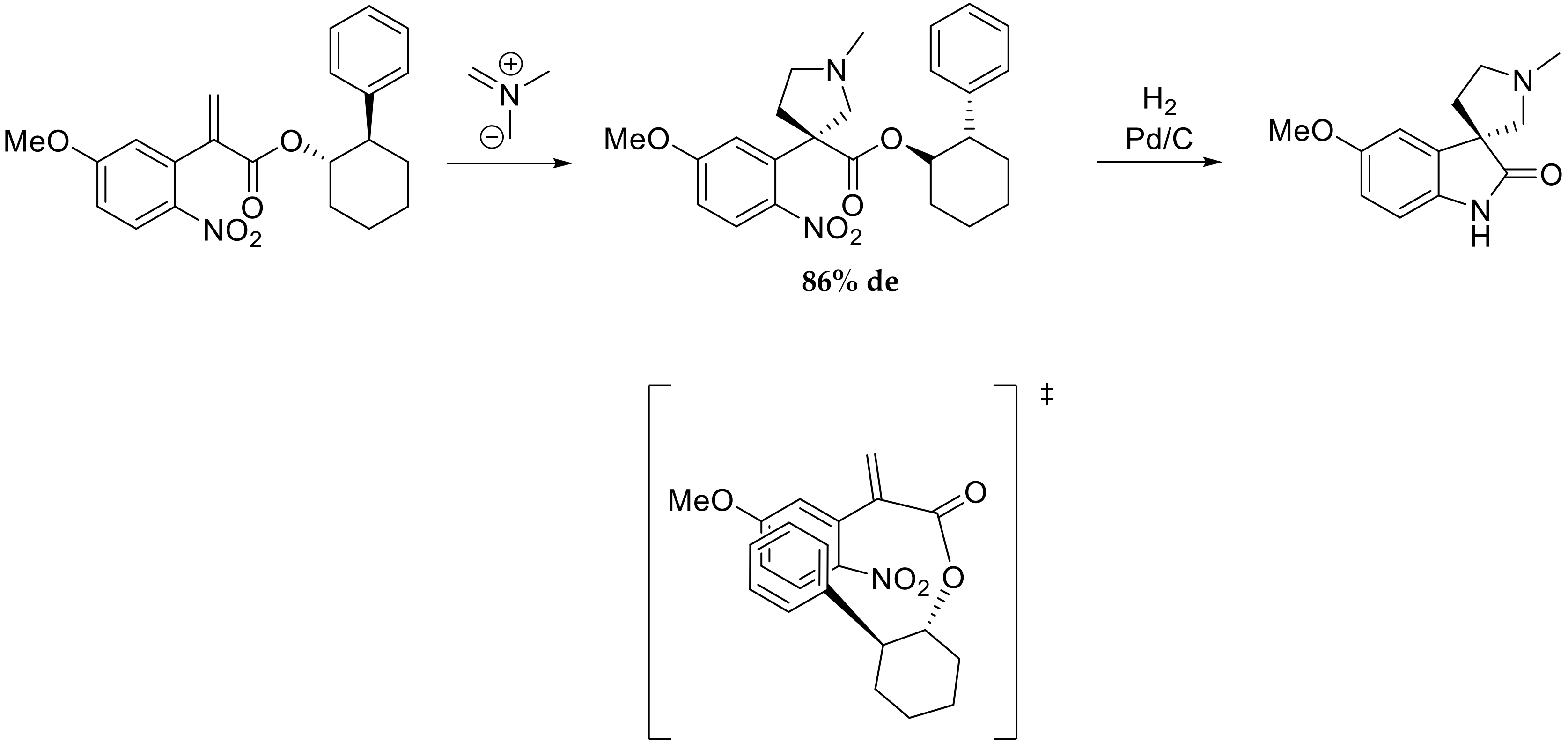




Waldmann, H. et al. *Nat. Chem.* **2010**, *2*, 735.

Azomethine Ylide Cycloaddition

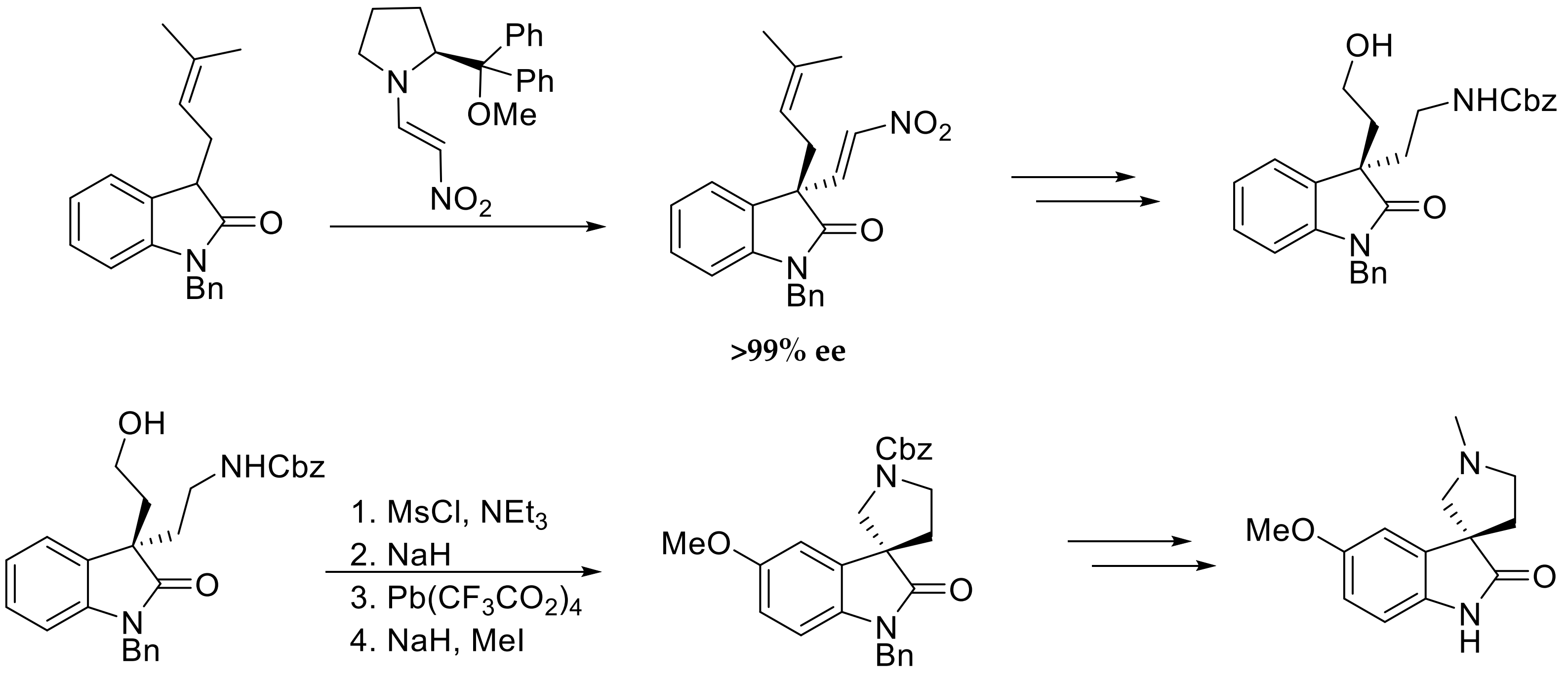
Palmisano's synthesis of (-)-horsfiline



Palmisano, G. J. et al. *J. Org. Chem.* **2001**, *66*, 8447.

Asymmetric Addition-Elimination

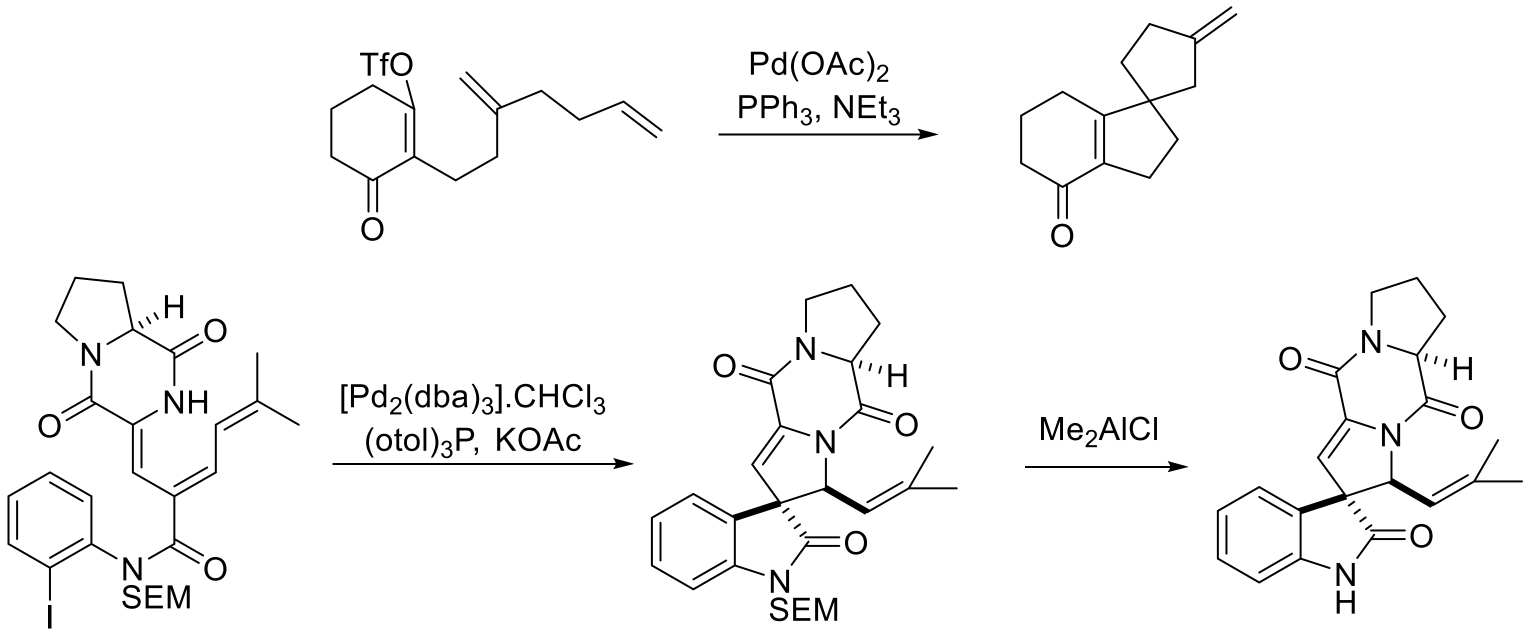
Fuji's synthesis of (-)-horsfiline



Fuji, K. L. et al. *J. Am. Chem. Soc.* **1989**, *111*, 7921.
Fuji, K. L. et al. *J. Org. Chem.* **1999**, *64*, 1699.

Pd-Catalyzed Heck Reactions

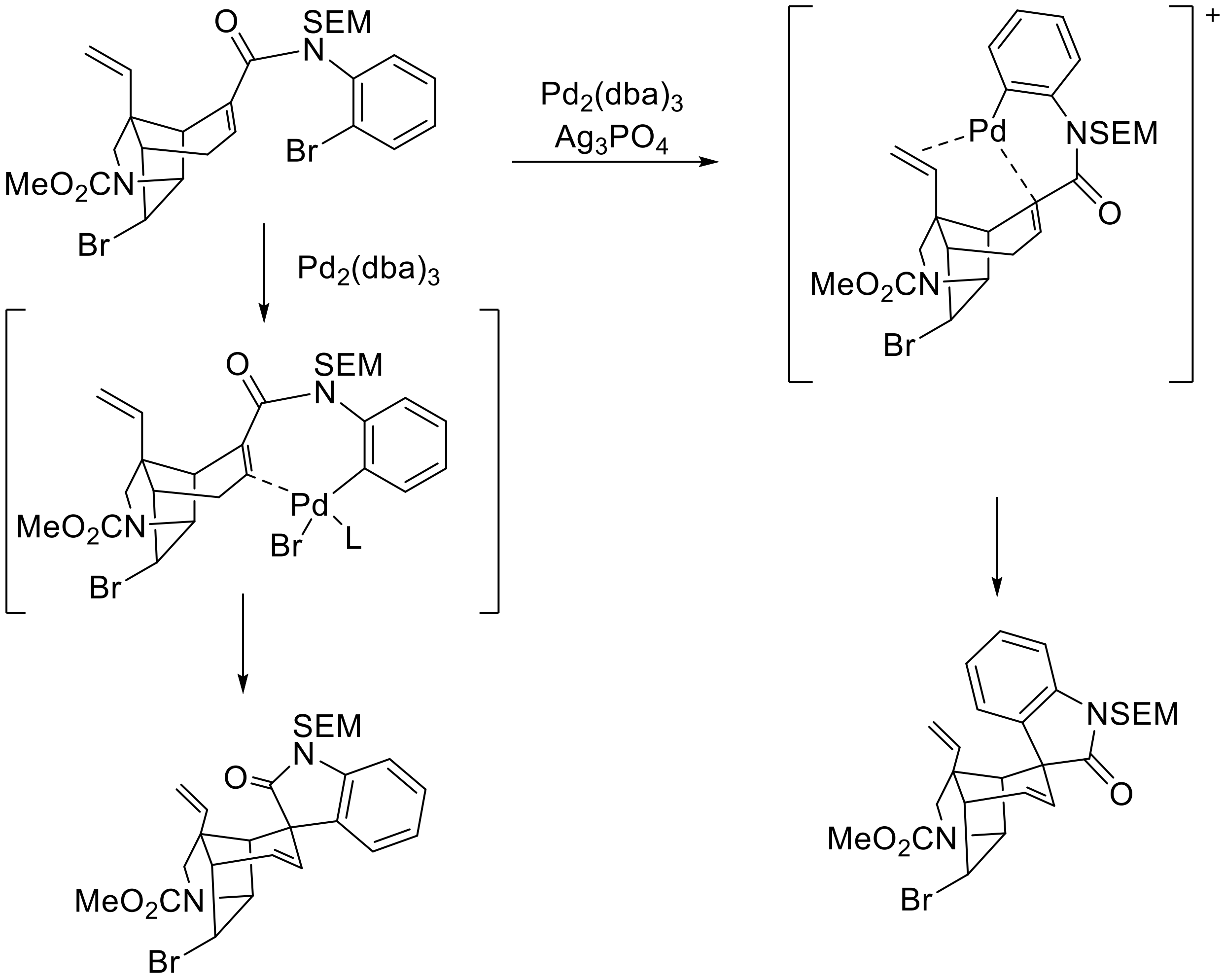
Overman's synthesis of (-)-spirotryprostatin B



Overman, L. E. et al. *J. Org. Chem.* **1989**, *54*, 5846.
Overman, L. E. et al. *Angew. Chem. Int. Ed.* **2000**, *39*, 4596.

Pd-Catalyzed Heck Reactions

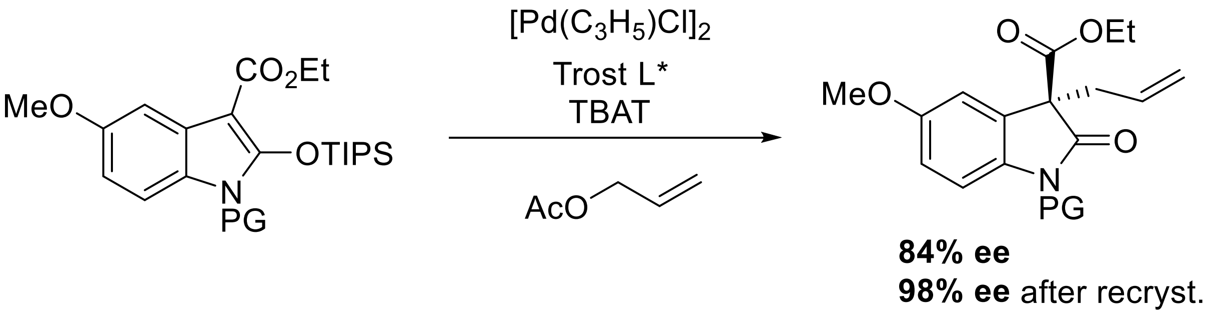
Overman's synthesis of gelsemine

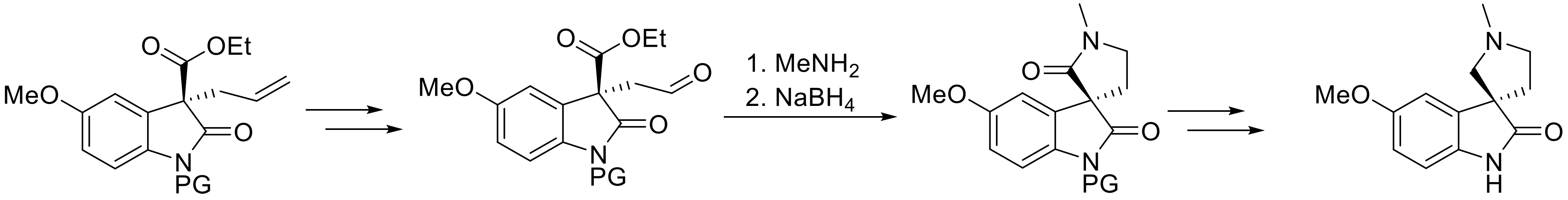


Overman, L. E. et al. *J. Am. Chem. Soc.* **2005**, *127*, 18054.

Pd-Catalyzed Allylic Alkylation

Trost's synthesis of (+)-horsfiline

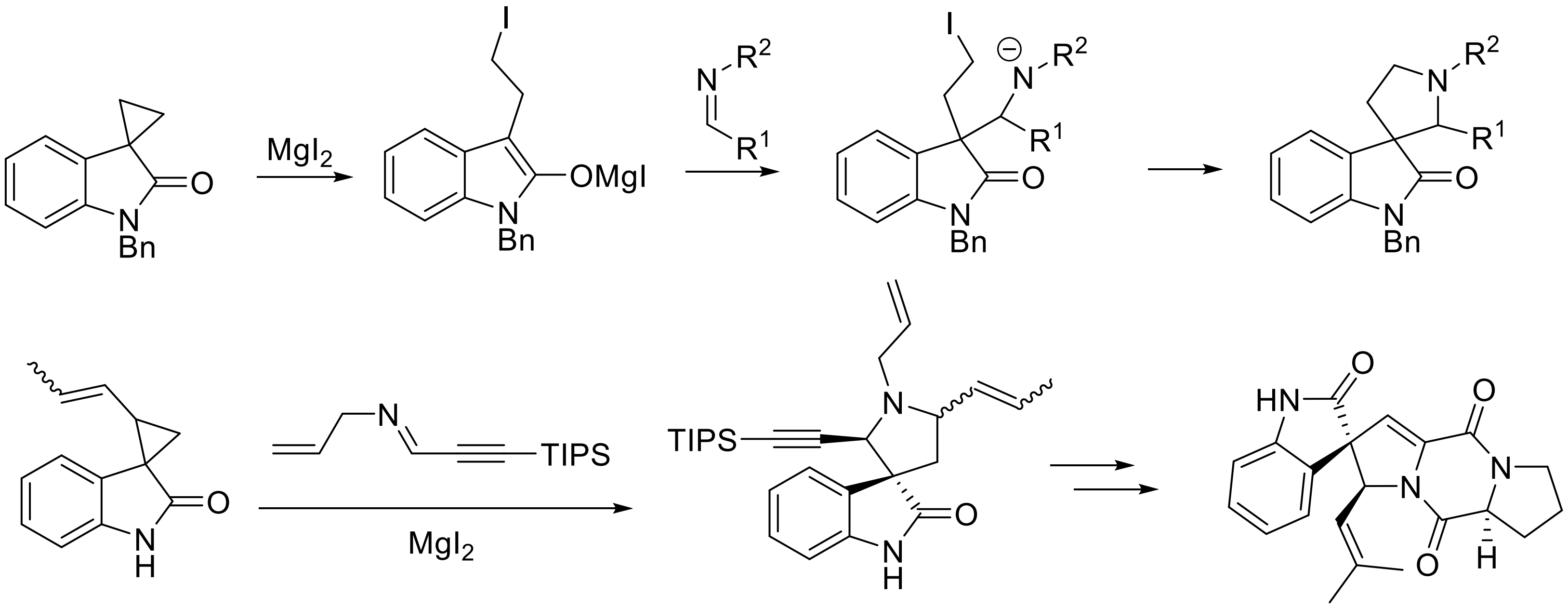




Trost, B. M. et al. *Org. Lett.* **2006**, *8*, 2027.

Ring Expansion

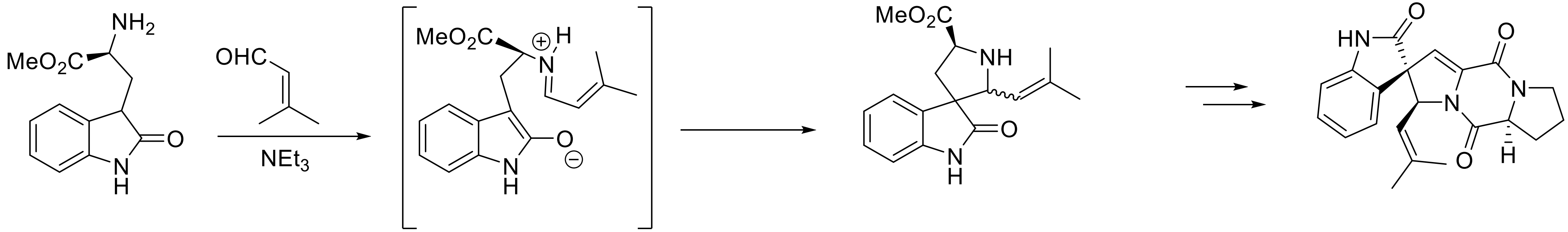
Carreira's synthesis of (-)-spirotryprostatin B



Carreira, E. M. et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 694.

Mannich Reaction

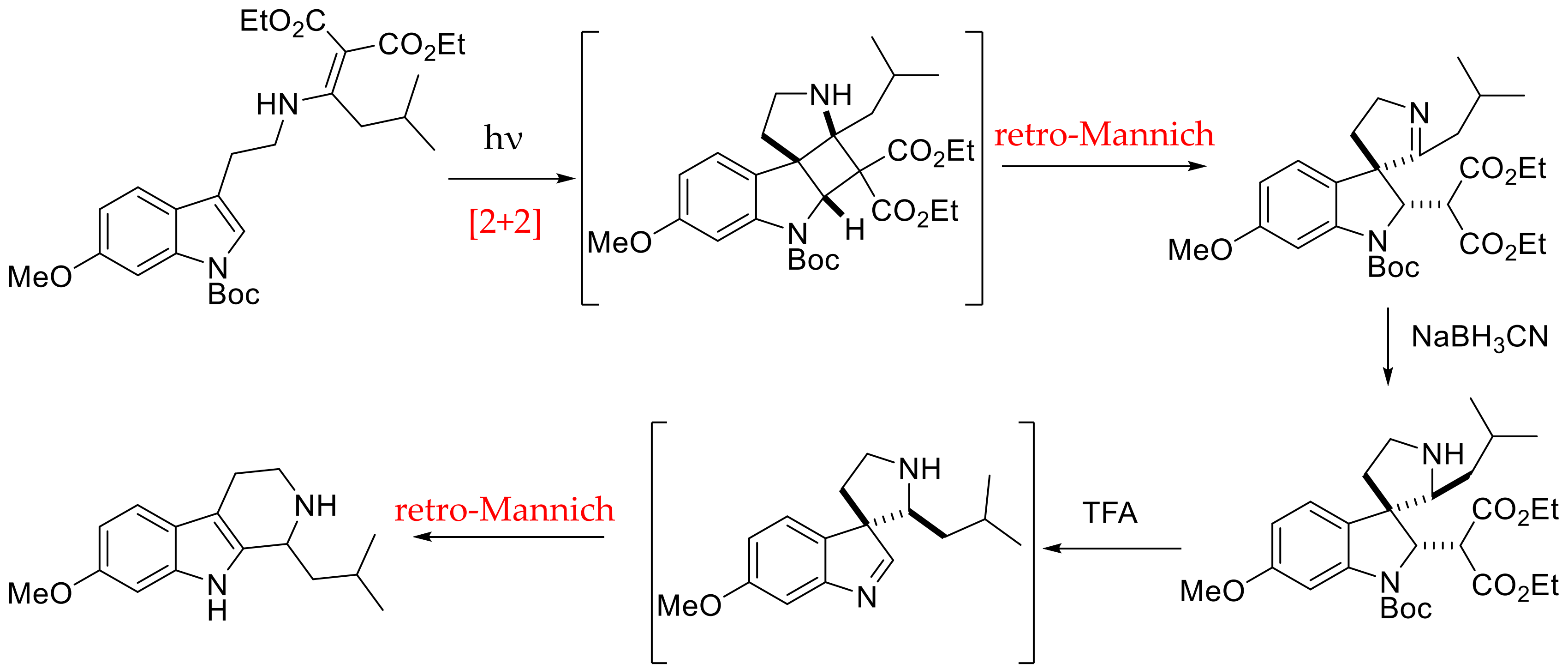
Danishefsky's synthesis of (-)-spirotryprostatin B



Danishefsky, S. J. et al. *Angew. Chem. Int. Ed.* **2000**, *39*, 2175.

Retro-Mannich Reaction

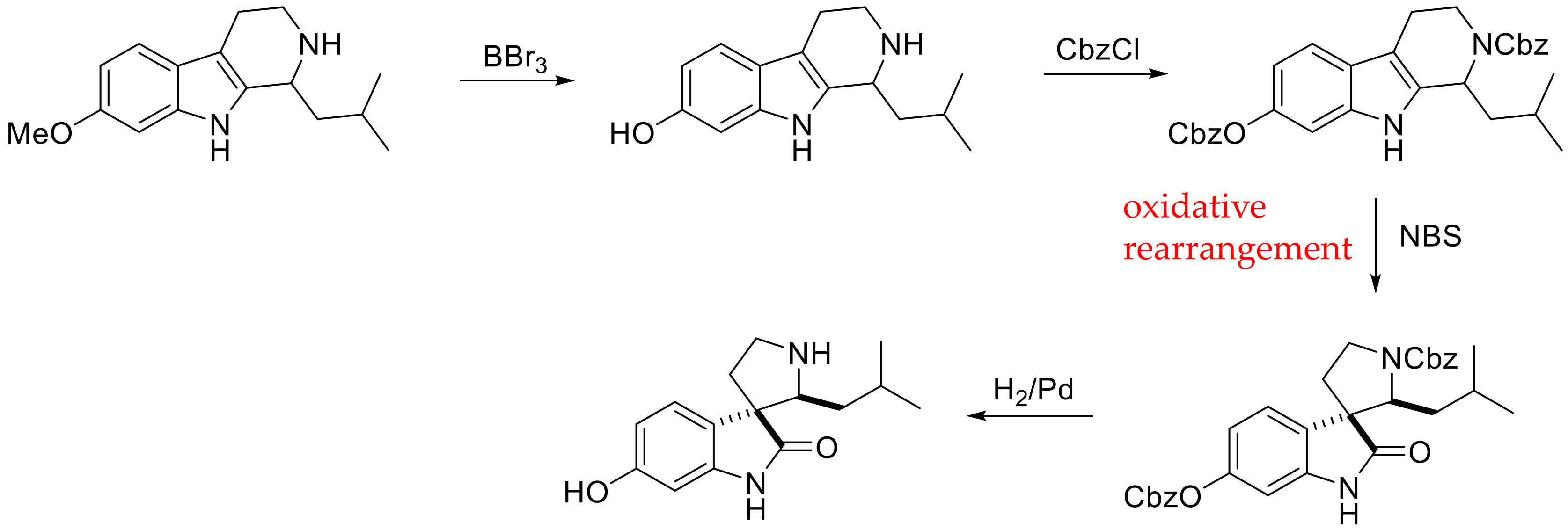
White's synthesis of elacomine



White, J. D. et al. *J. Org. Chem.* **2010**, *75*, 3569.

Retro-Mannich Reaction

White’s synthesis of elacomine



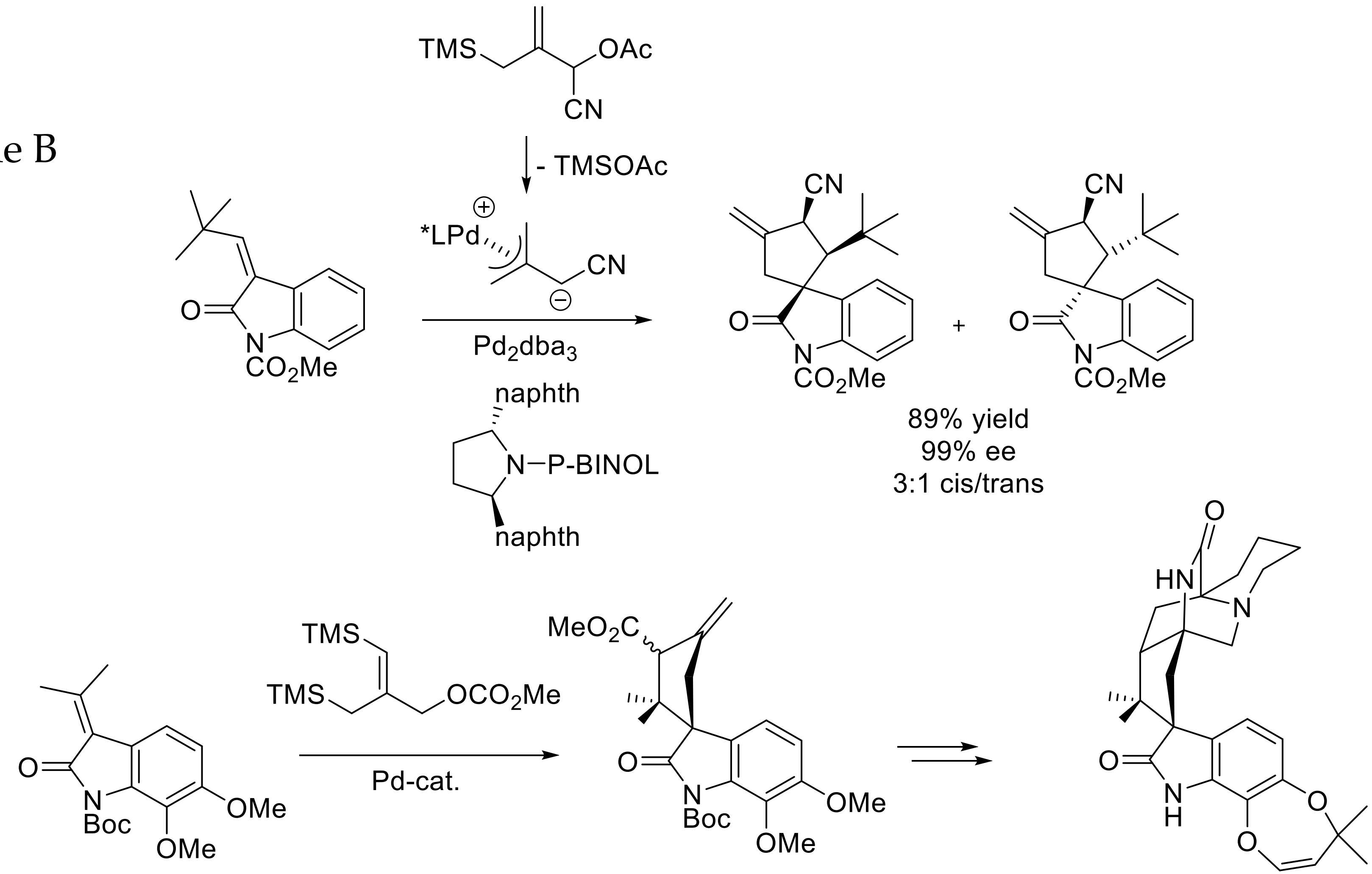
White, J. D. et al. *J. Org. Chem.* **2010**, *75*, 3569.

Conclusion

- Pros
  - Variety of methods
  - Metal-catalyzed processes promising
  - Many more to come…
- Cons
  - Selectivity issue
  - Auxiliary – not atom economic

Outlook

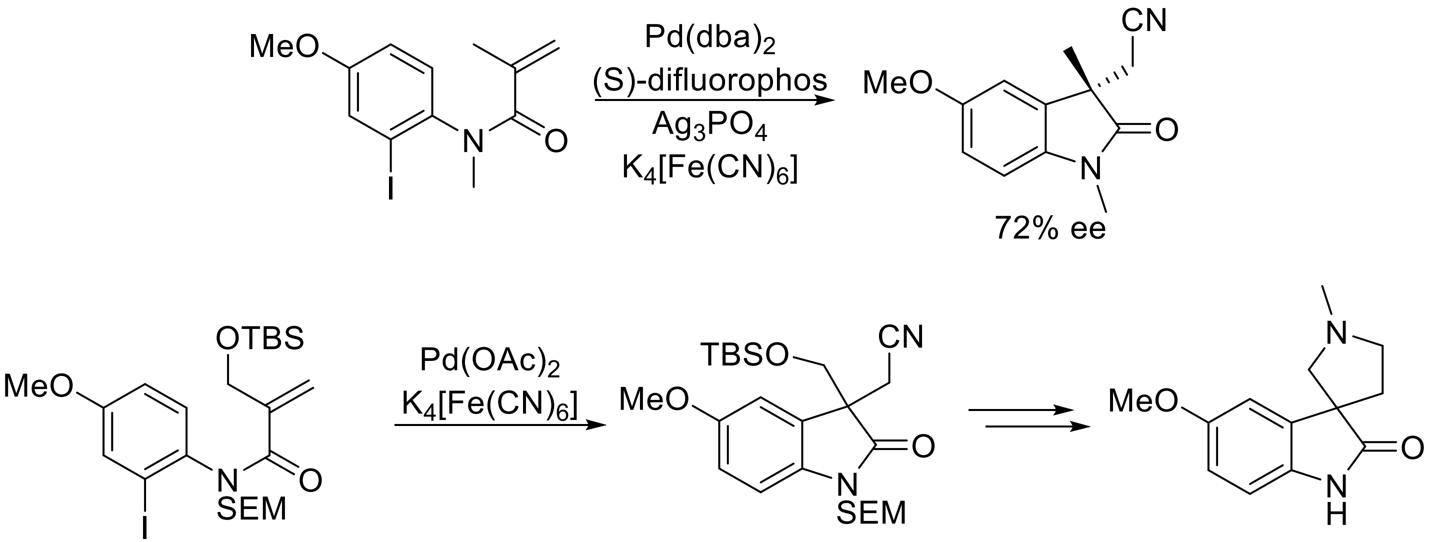
Trost's synthesis of marcfortine B



Trost, B. M. et al. *J. Am. Chem. Soc.* **2007**, *129*, 3086.
Trost, B. M. et al. *J. Am. Chem. Soc.* **2007**, *129*, 12396.

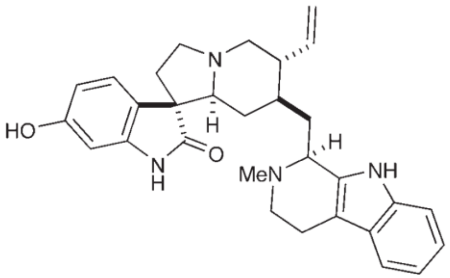
Outlook

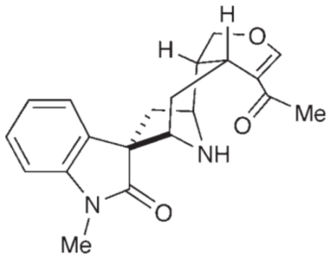
Zhu's synthesis of horsfiline

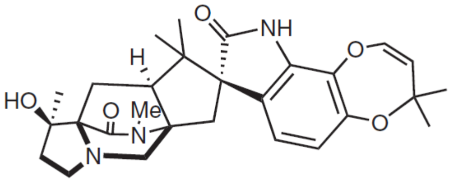


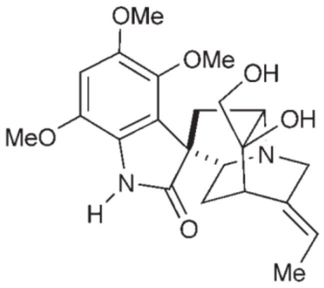
Zhu, J. et al. *Chem. Eur. J.* **2007**, *13*, 961.
Zhu, J. et al. *Synlett* **2009**, *18*, 2997.

Thank you for your attention









ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

1,2,3 triazoles in catalysis

Frontier in Chemical Synthesis II: Heterocycle Chemistry

12 May 2015

Paola Caramenti - LCSO

Table of content

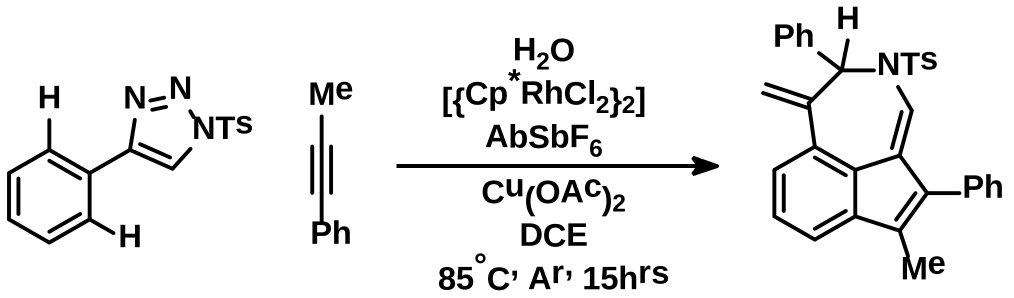
1. General introduction on the 1,2,3 triazole moiety
2. Synthesis
3. 1,2,3-triazoles as ligands
   - Cu(I) stabilizing agents
   - TA-Au(I) and Pyr-TA complexes for hydroamination
   - P-N ligands
   - Chiral enzyme inspired PAs
   - MICs
4. 1,2,3-triazoles as directing groups
   - TA/Ta-Py-Pd complexes in C-H activation
5. 1,2,3-triazoles as heterocycles precursors
   - Transannulation RhII azavinyl carbenes

Questions:

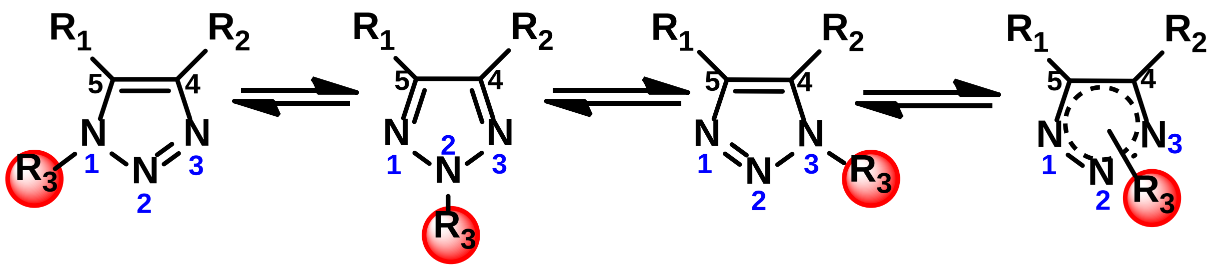
- ***Question 1***

Are 1,2,3-triazoles useful for other than biofunctionalities, bioactivity and/or late stage functionalization?

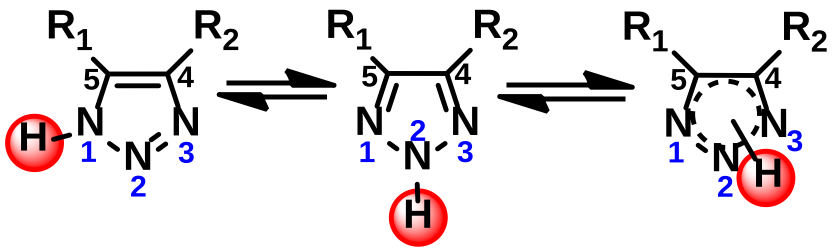
- ***Question 2: can you provide a mechanism for this reaction?***



1,2,3 Triazoles - a general introduction

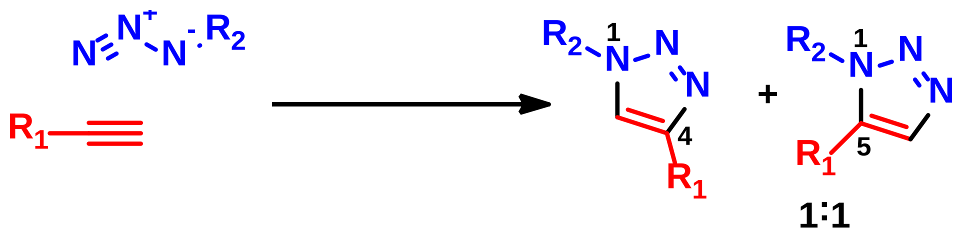


- General formula: $C_2H_3N_3$
- Termodinamically tautomers
- Strongly resistant to thermal, oxidative, reductive and hydrolitic conditions
- 6e-heterocycles with aromatic character



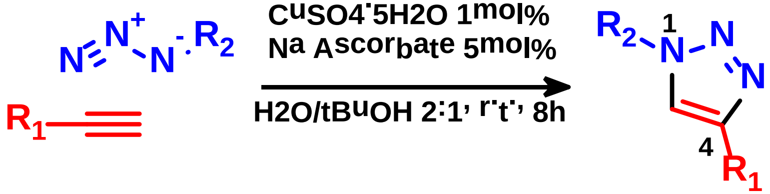
- Spectroscopic ^{14}N and ^{15}N NMR data reveal that unsymmetrical 1,2,3- triazoles 4–5 exist in the 2H-tautomer form (70–100%).
- ^{1}H, ^{13}C, ^{15}N and ^{14}N NMR shifts are identical for the hydrogen and carbon atoms in positions 4 and 5 and nitrogen atoms at positions 1, 2 and 3 of 1,2,3-triazoles for both tautomers
- N-Substituted isomers of 1H and 2H-1,2,3-triazoles can be differentiated based on their polarity.
- the dipole moment of the 1H-isomer is substantially higher than for 2H isomer
- 1,2,3-Triazoles demonstrate amphoteric properties and can behave as a weak base or a weak acid.

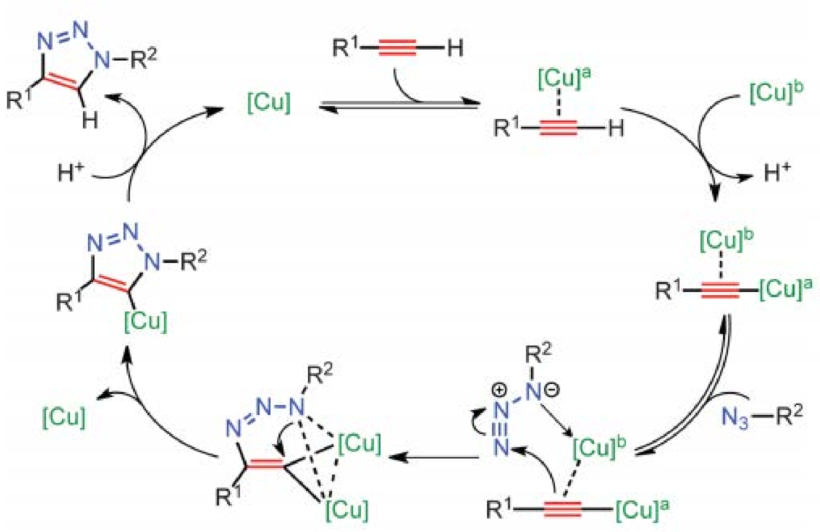
Synthesis of 1,4 disubstituted triazoles



- High activation barrier (24-26Kcal/mol)
- 1:1 mixture of the two regioisomers

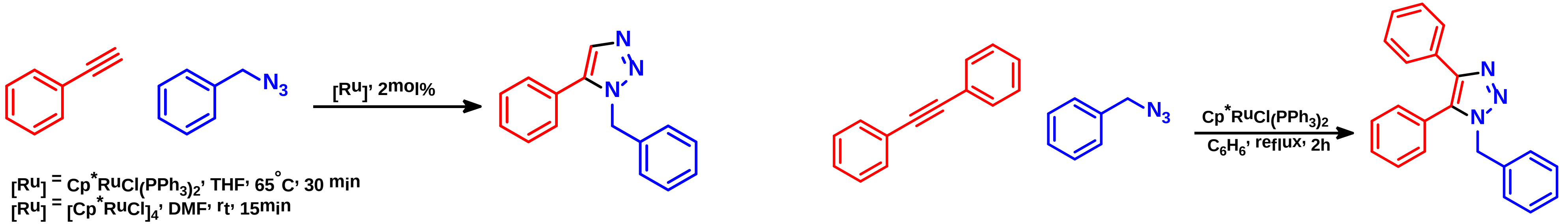
- Broad scope: all groups on alkyne widely tolerated
- Primary, secondar, tertiary and aromatic azides partecipated in the reaction
- **1,4 regioselective**

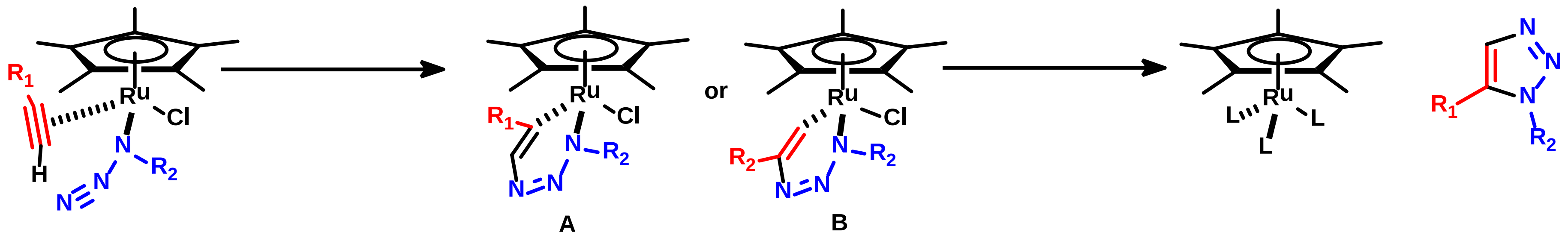


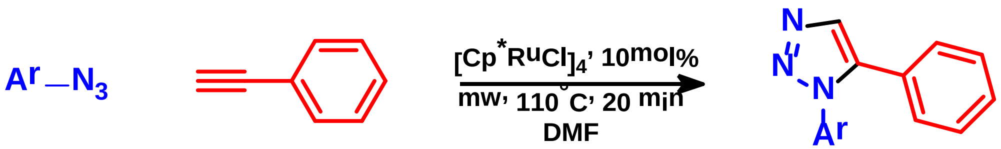


Angew. Chem. Int. Ed., **2002**, *41*, No 14, Science Vol. 340 no. 6131 pp. 457-460

Synthesis of 1,5 disubstituted triazoles

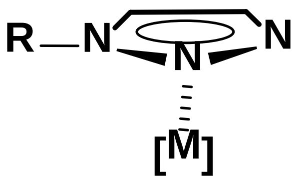




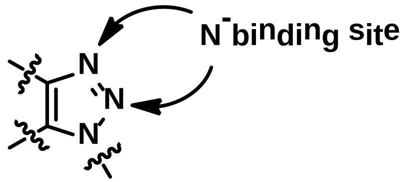


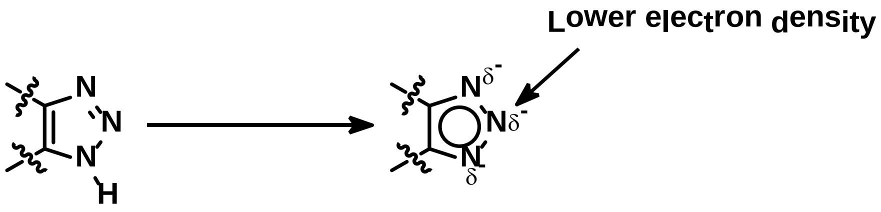
J. Am. Chem. Soc., **2005**, *127*, 15998-15999, *Org. Lett.*, **2007**, *Vol 9*(26), 5337-5339

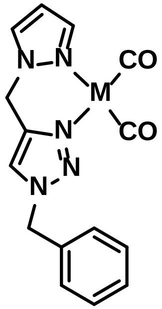
1,2,3 triazoles as ligands in catalysis

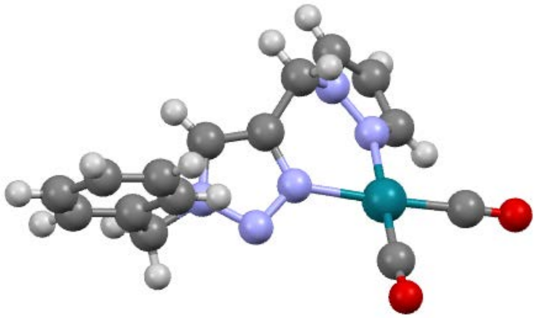


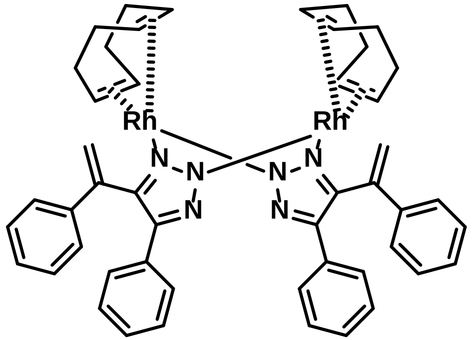
- The strenght of metal-N bond (sp^2 -hybridized nitrogen) depend from the degree of σ-covalency and π-back bonding effect
- Established coordinative properties
- Strong dipole moment

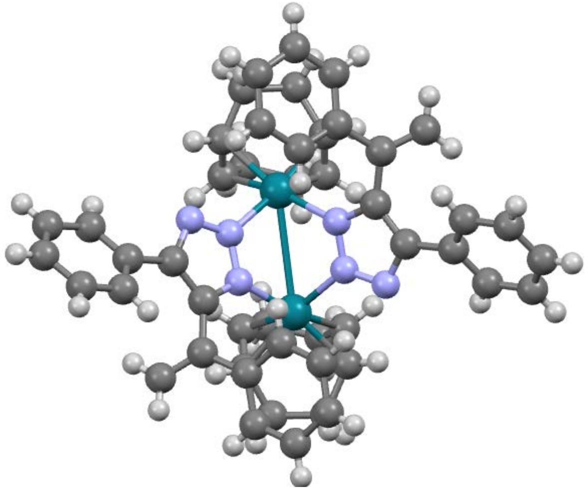






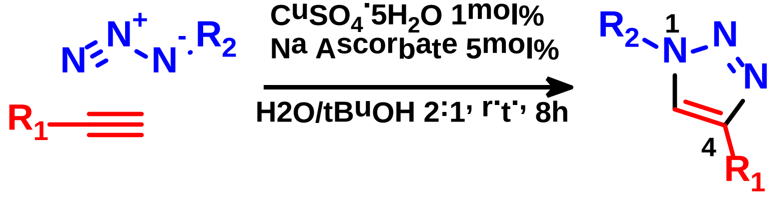




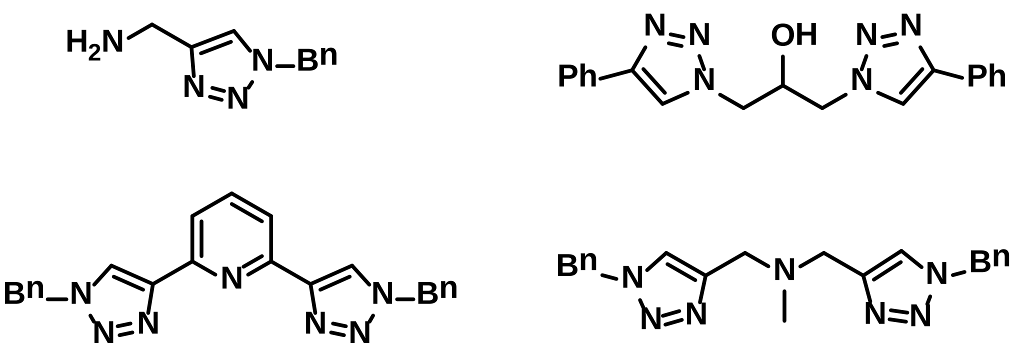


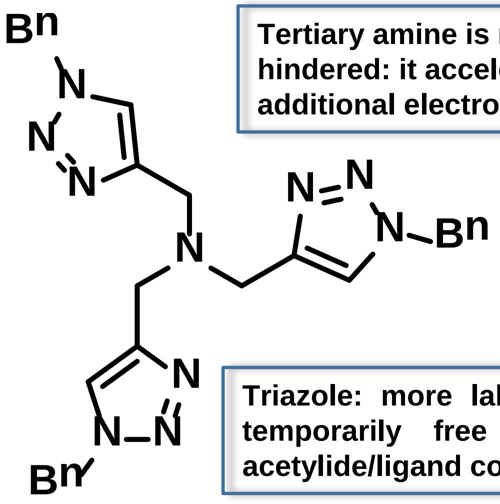
Organometallics **2012** *31* 1790-1800, *Organometallics* **2009** *28* 2352; *Dalton. Trans*., **2010**, *39*, 675;

Polytriazoles as Cu(I)-stabilizing Ligands



- soft ligands such as guanidines, imines, thiols, nitriles… are too labile (compromise the redox stability of the metal center) or too strong (copper catalytic activity is completely suppressed)



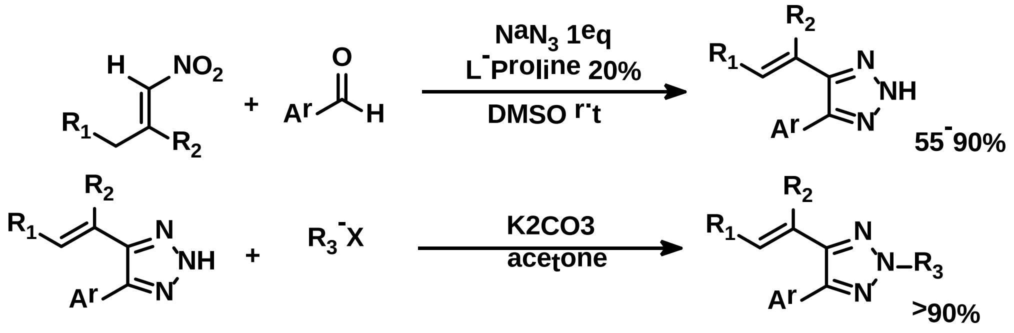


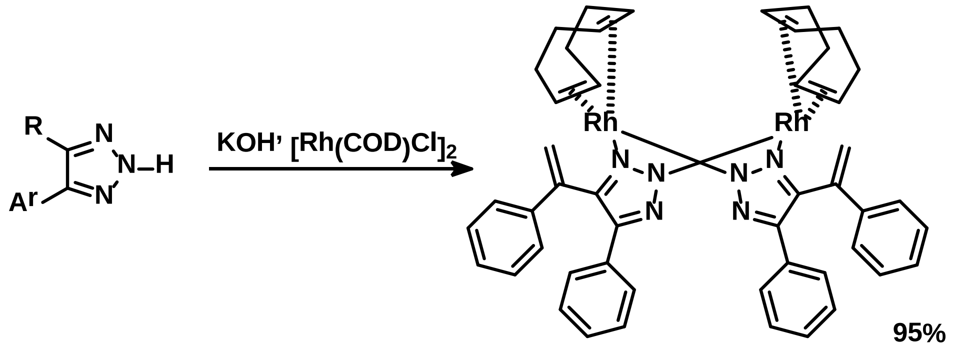
Tertiary amine is more basic and sterically hindered: it accelerates the catalysis providing additional electron density

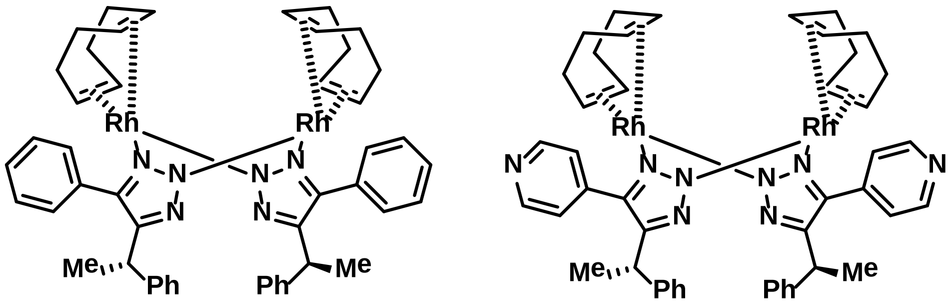
Triazole: more labile, the metal center is temporarily free to form the copper-acetylide/ligand complex

Org. Lett. **2004** *6* 2853, *J. Am. Chem. Soc* **2007** *129* 12705;

NH-Triazole Rh complex

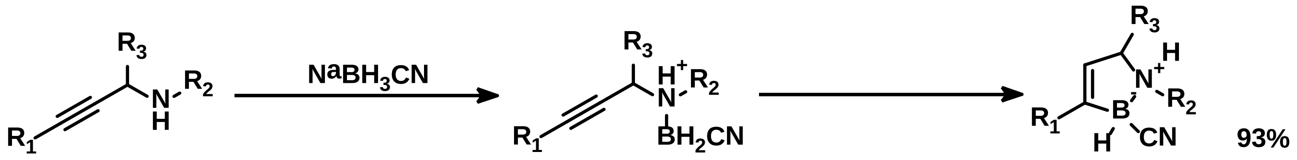


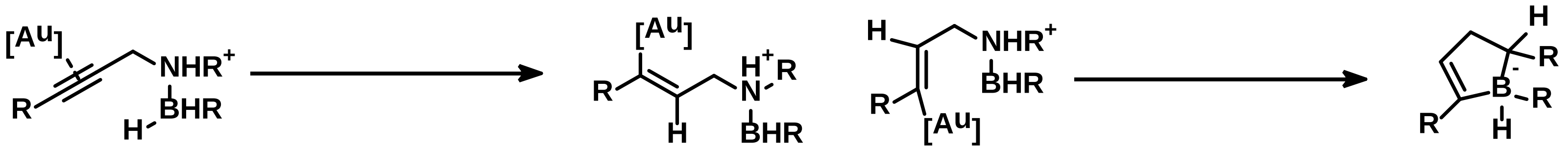




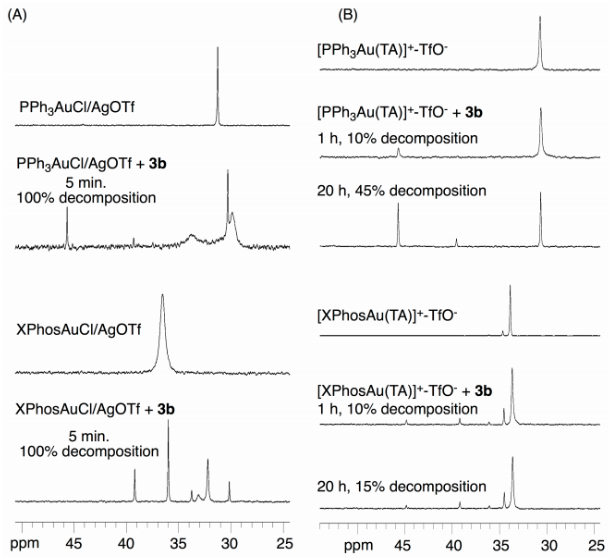
Organometallics, **2009**, *28*, 2352 - 2355

1,2,3 triazoles as ligands in catalysis



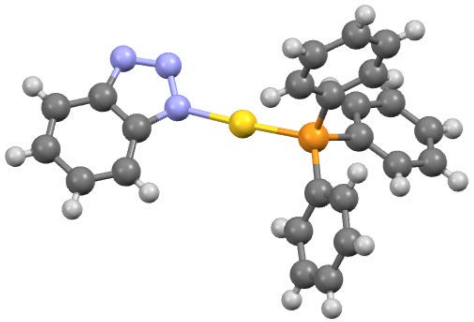


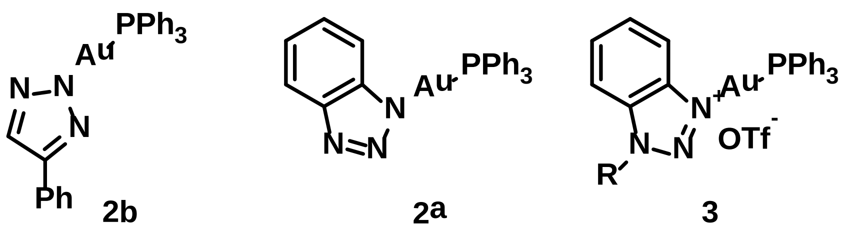
Entry	Catalyst	Solvent	*t* [h]	*T* [°C]	Conv. [%]	Yield [%]
1	PPh_3AuCl	CH_2Cl_2	72	RT	< 5	n.d.
2	$PPh_3AuCl/AgOTf$	CH_2Cl_2	0.5	RT	19	17
3	IPrAuCl/AgOTf	CH_2Cl_2	0.5	RT	15	11
4	XPhosAuCl/AgOTf	CH_2Cl_2	24	RT	< 5	n.d.
5	$[PPh_3Au\text{-}TA]^+TfO^-$	CH_2Cl_2	72	RT	< 5	n.d.
6	$[XPhosAu\text{-}TA]^+TfO^-$	CH_2Cl_2	72	RT	< 5	n.d.
7	PPh_3AuCl	DCE	72	80	< 5	n.d.
8	$[PPh_3Au\text{-}TA]^+TfO^-$	DCE	24	80	35	24
9	$[XPhosAu\text{-}TA]^+TfO^-$	DCE	72	80	> 99	93
10	$[XPhosAu\text{-}TA]^+TfO^-$	THF	72	65	85	73
11	$[XPhosAu\text{-}TA]^+TfO^-$	DMF	72	80	84	63
12	$[XPhosAu\text{-}TA]^+TfO^-$	toluene	72	90	39	36
13	$[XPhosAu\text{-}TA]^+TfO^-$	MeCN	72	80	88	65

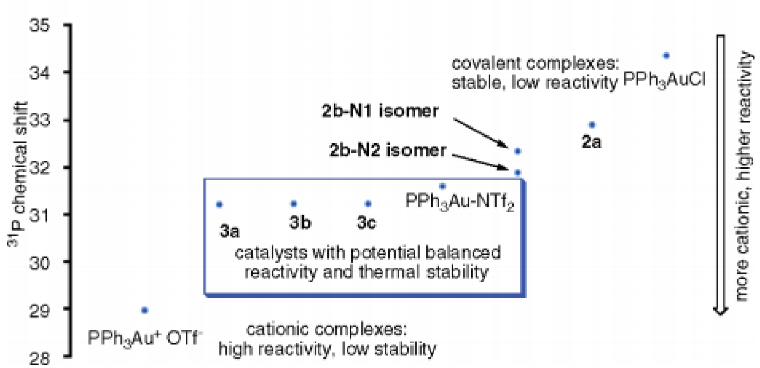


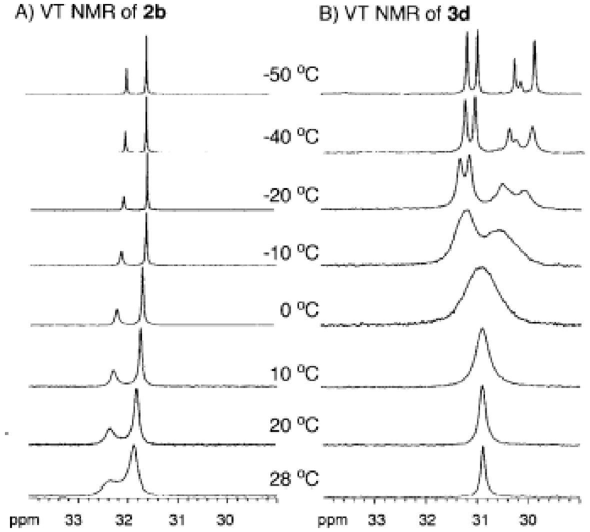
Angew Chem. Int. Ed. **2014** *53*, 5418-5422

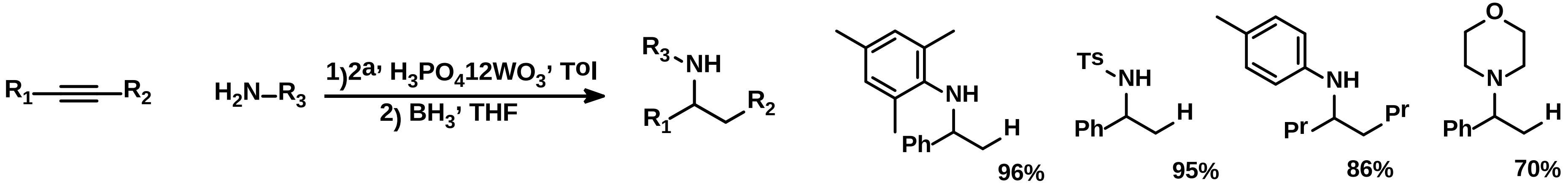
TA-Au(I) complexes for intermolecular alkyne hydroamination





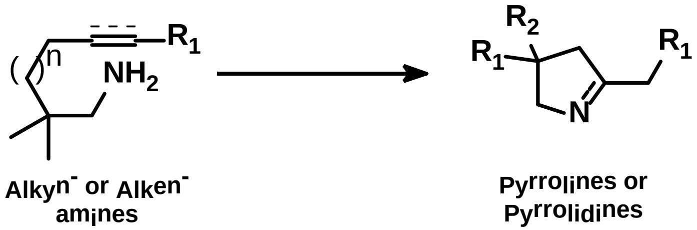


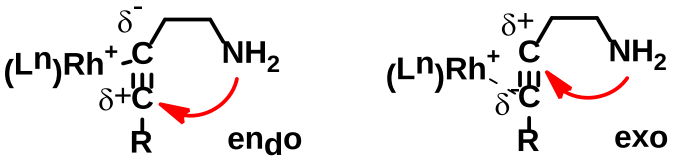


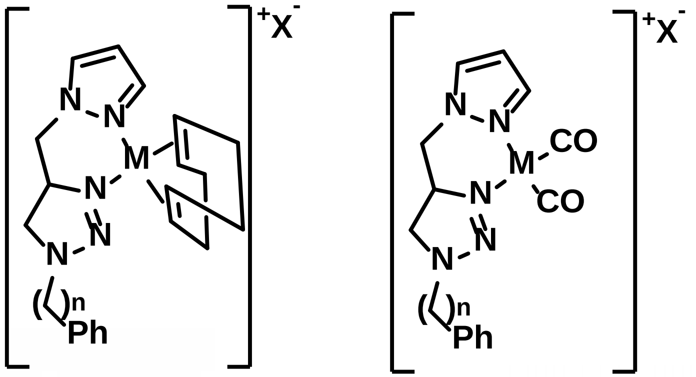


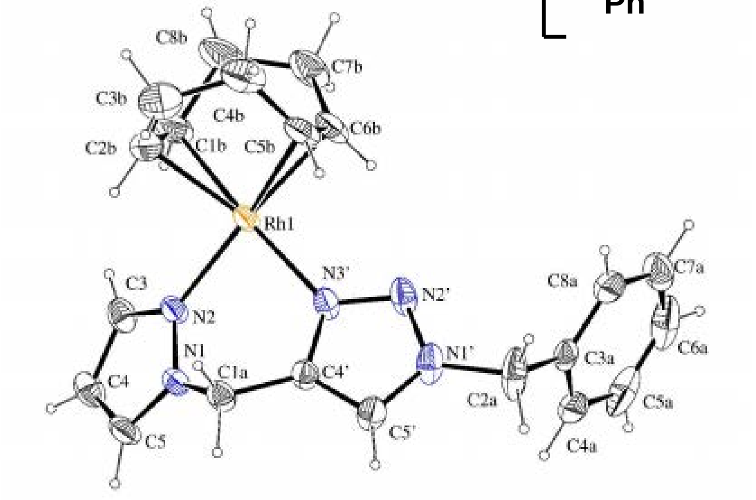
J. Am Chem. Soc., **2009**, *131*, 12100;

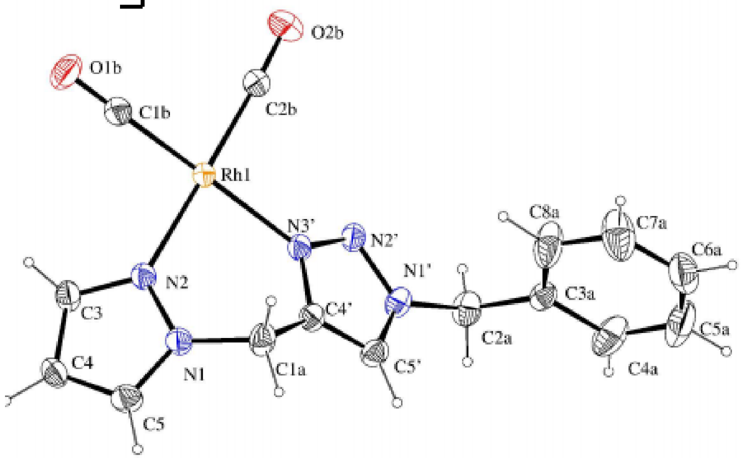
Pyrazolil-TA mixed ligands for intramolecular alkyne hydroamination





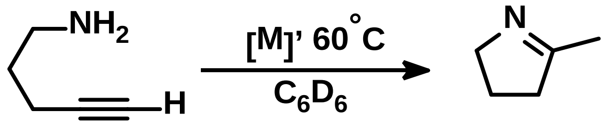


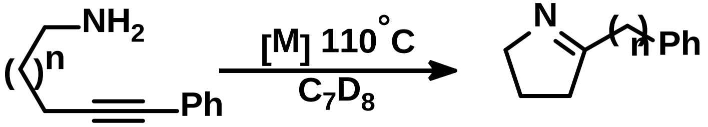


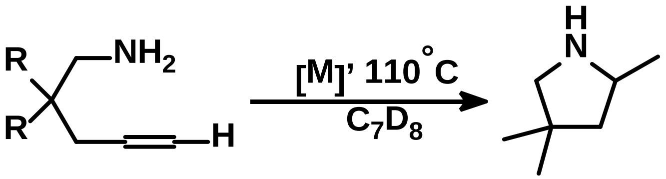


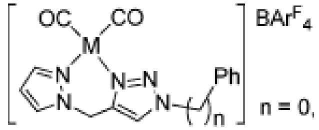
Organometallics, **2007**, *26*, 4335-4343 , Organometallics **2012,** *31*, 1790

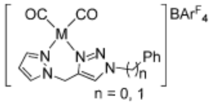
Pyrazolil-TA mixed ligands for intramolecular alkyne hydroamination







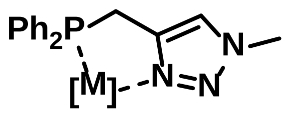
		n = 1, PyT (1a)	
		TOF[b] (h^{-1})	Time (h) at >98% Conv.
Rh	Ph–≡–NH_2 **8a**	>172[c]	0.5
	Ph–≡–NH_2 **8b**	144	2.4
Ir	Ph–≡–NH_2 **8a**	>186[c]	0.5
	Ph–≡–NH_2 **8b**	202	2.4

		n = 1, PyT (1a)		
		TOF[e] (h^{-1})	% Conv. at 5 h	% Conv. at 40 h
Rh	NH_2 **10a**	1.6[b]	40	74
	NH_2 **10b**	4.6[b]	72	93 (22 h)
	Ph Ph NH_2 **10c**	9.5[c]	75	>98 (22 h)
Ir	NH_2 **10a**	6.3	69	96
	NH_2 **10b**	16	71	92
	Ph Ph NH_2 **10c**	7.5	75	98

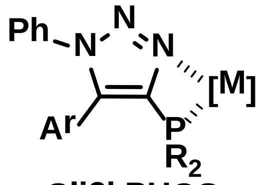
- The efficiency varied significantly even with subtle changes to the ligand donor set
- Formation of side product is largely reduced to a minimum
- New Py-TA ligands exhibit better reactivity than NHCs, Pyrazolil-Imidazole and Phos ligands already in use.

Organometallics, **2012**, *31*, 1790- 1800; *J. Am. Chem. Soc*., **2008**, *130*, 1570-1571

Clickphine and ClickPhos: a new P,N ligand class

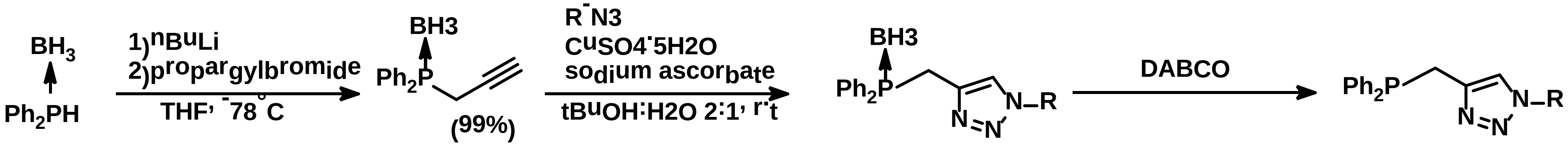


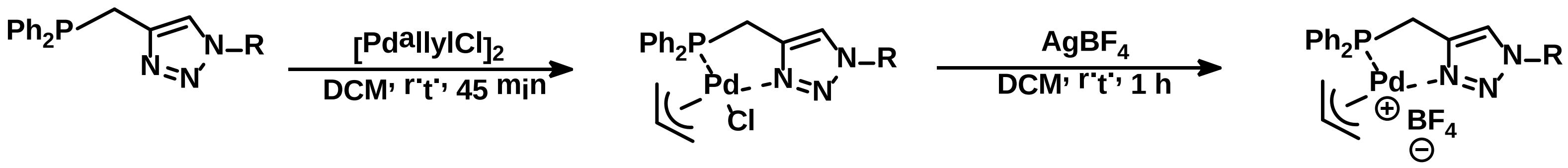
Clickphine

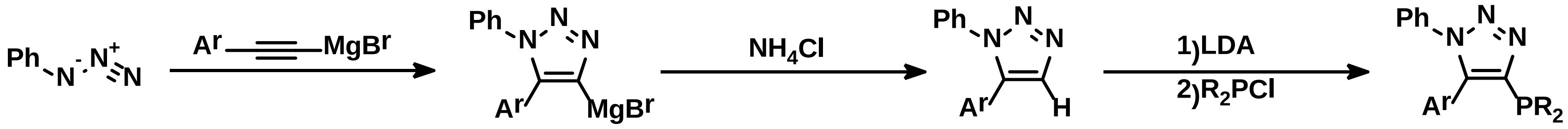


ClickPHOS

- Bidentate P,N-type ligands are well known and applied in chemistry
- Possibility of individual tuning of the substituent
- Easiness of preparation



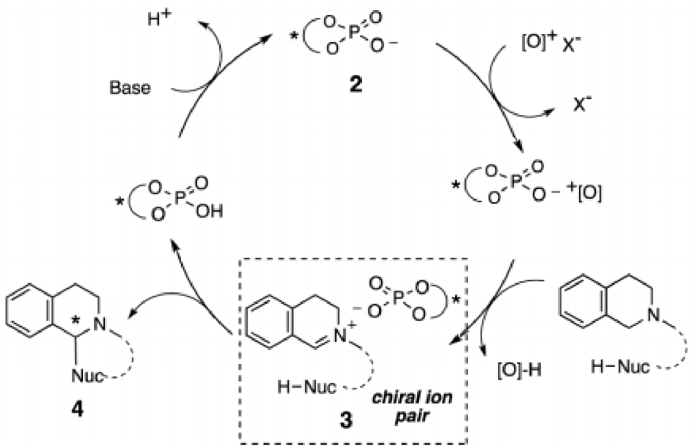


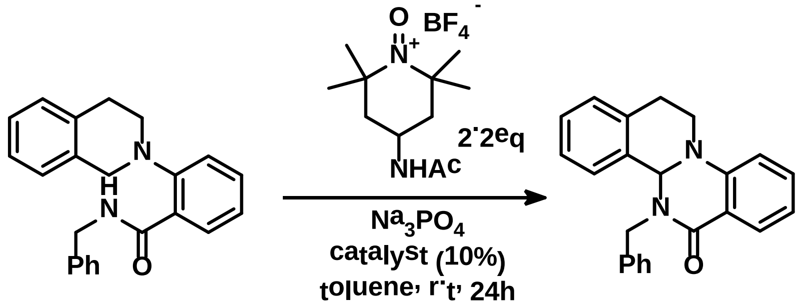


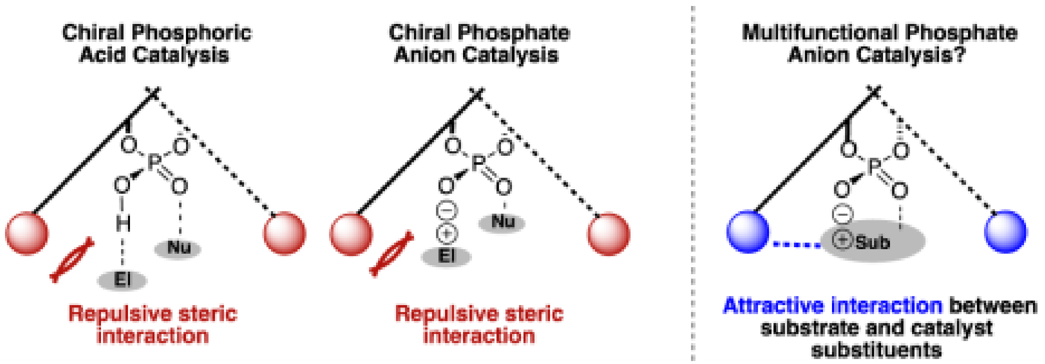
Org. Lett., **2006**, *8*(15) 3227.3230; *Org. Lett.*, **2005**, *7* (22), 4907–4910

Chiral TA-Phosphoric acids for CDC

- Chiral phosphate could undergo anion exchange with a cationic oxidant ensuring that the phosphate would be in close proximity to form a tight ion-pair
- Preferential attack on one of the prochiral faces would provide an enantioenriched product
- amine-tethered tetrahydroisoquinoline, oxoammonium salt and various conventionally axially chiral PAs gave no results

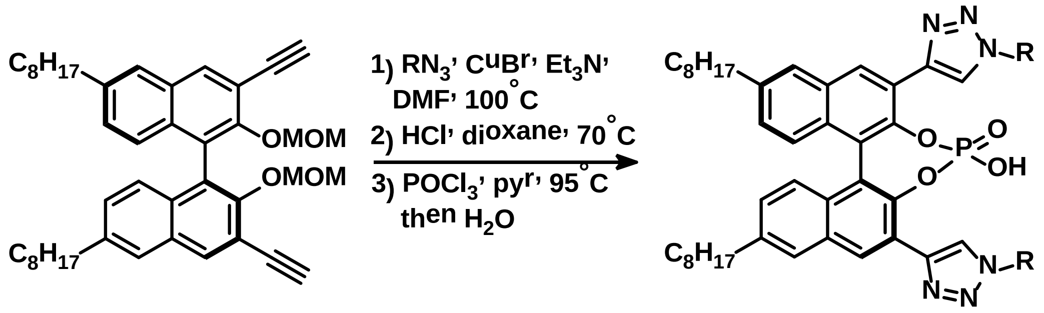


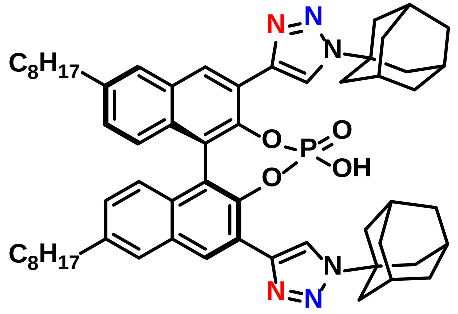




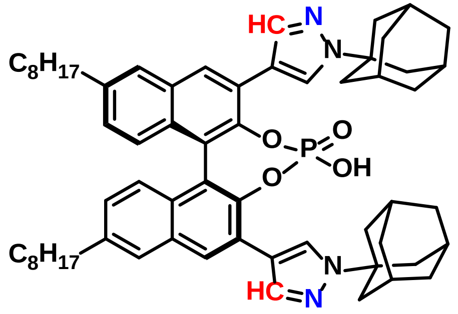
jacs 2013 135 140044

Chiral TA-Phosphoric acids

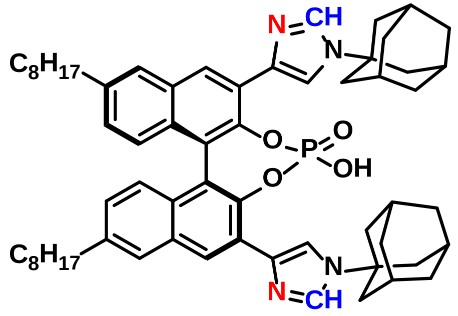




97% yield
83% ee

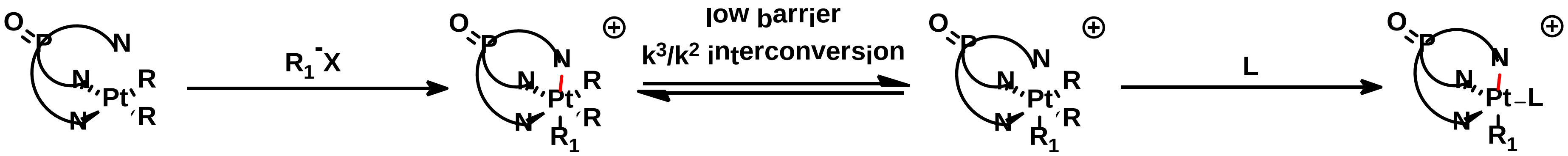


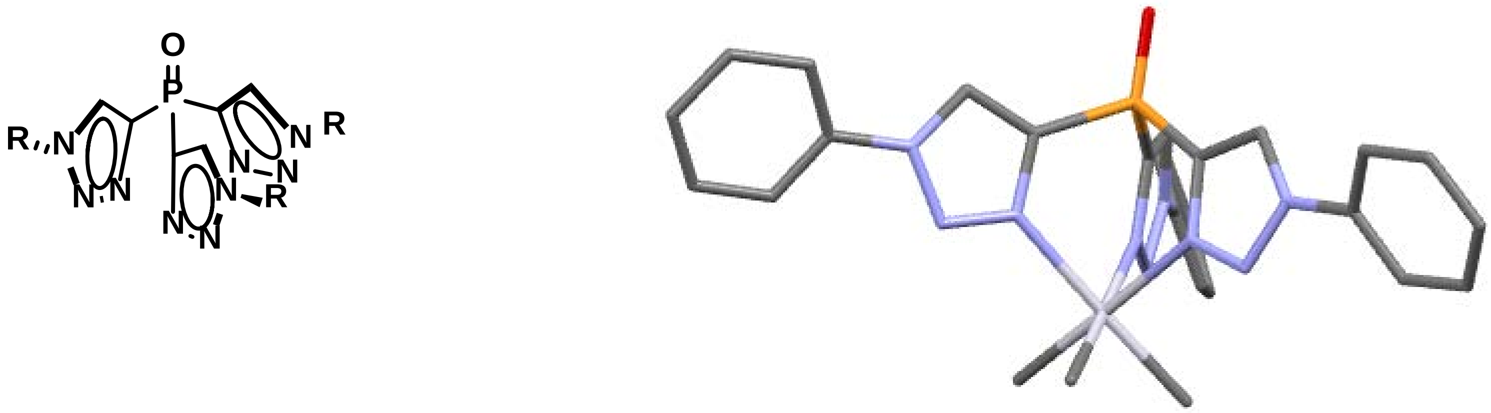
88% yield
41% ee

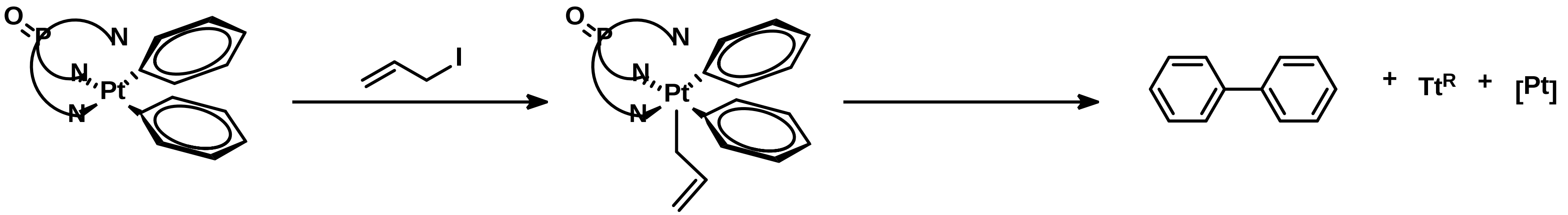


93% yield
45% ee

Hemilabile Click-TA Scorpionates

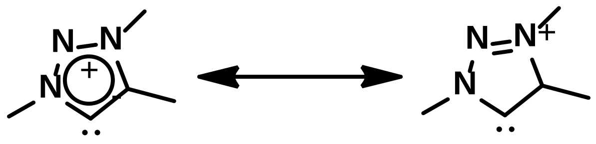


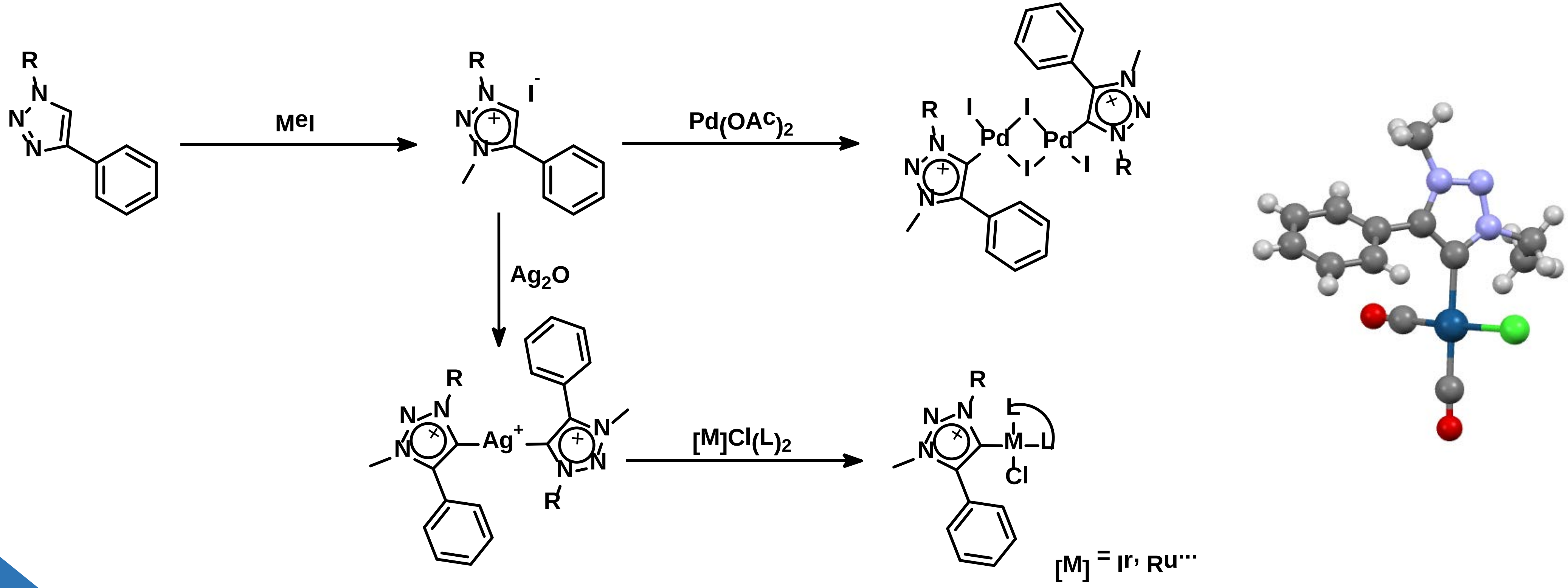




Organometallics **2012**, *31*, 225-237

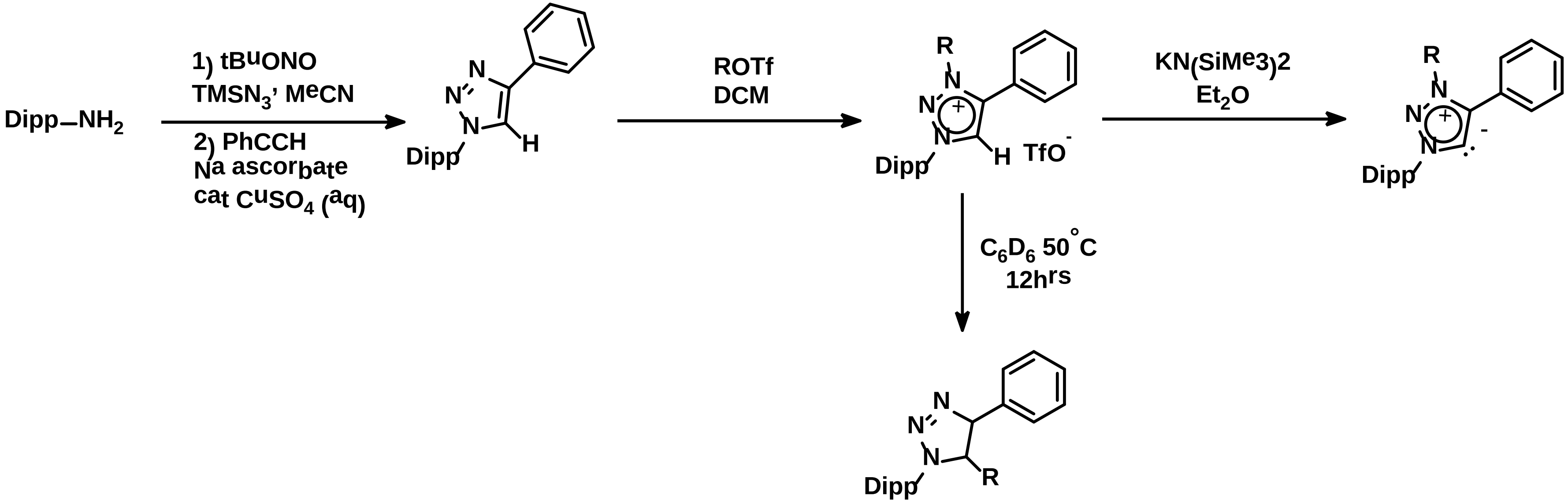
1,2,3 triazoles as MICs in catalysis

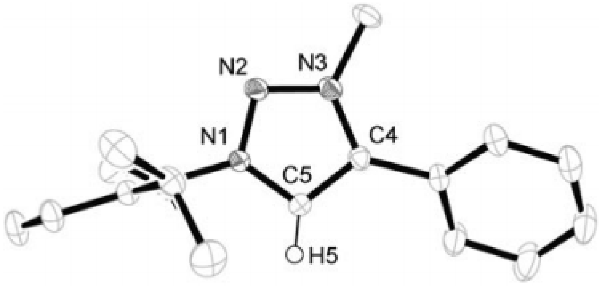


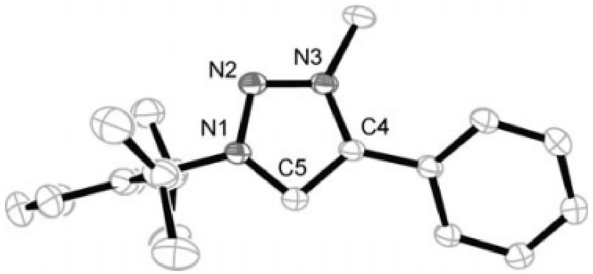


J. Am Chem. Soc.,**2008**, *130*, 13534-13535

1,2,3 triazoles as MICs in catalysis

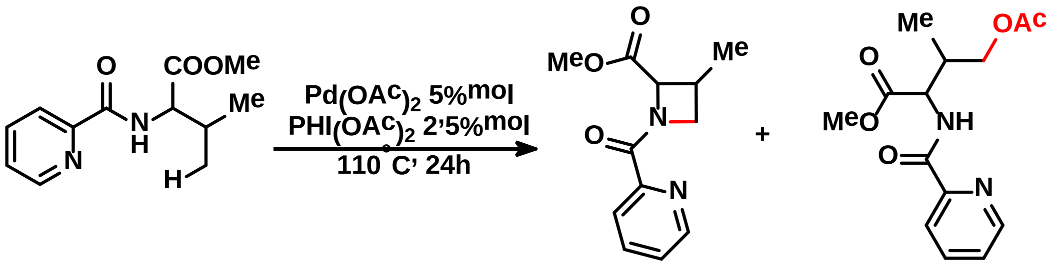




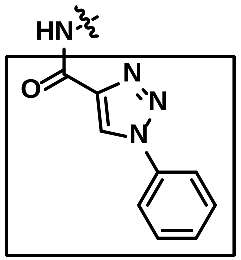


Angew. Chem. Int. Ed., **2010**, *49*, 4759-4762

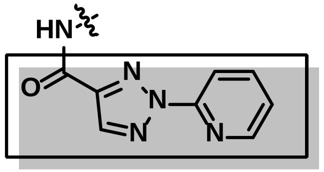
1,2,3 triazoles for C-H activation



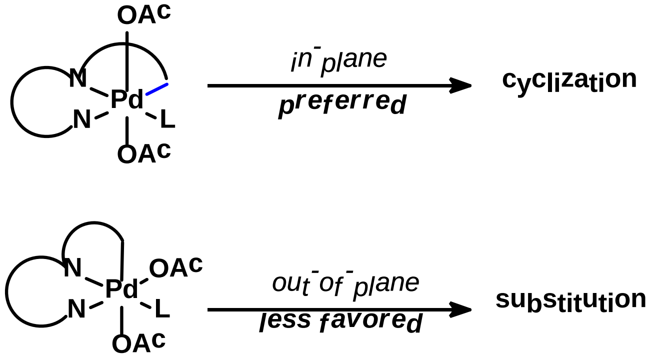
in Toluene	78%	7%
in AcOH	20%	27%



TAA: N1-aryl-1,2,3-triazole-4-carboxylic acid

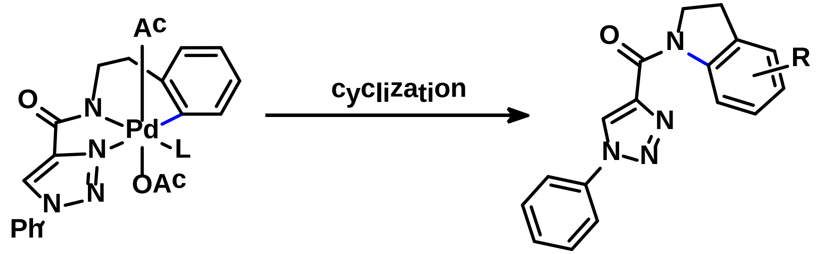


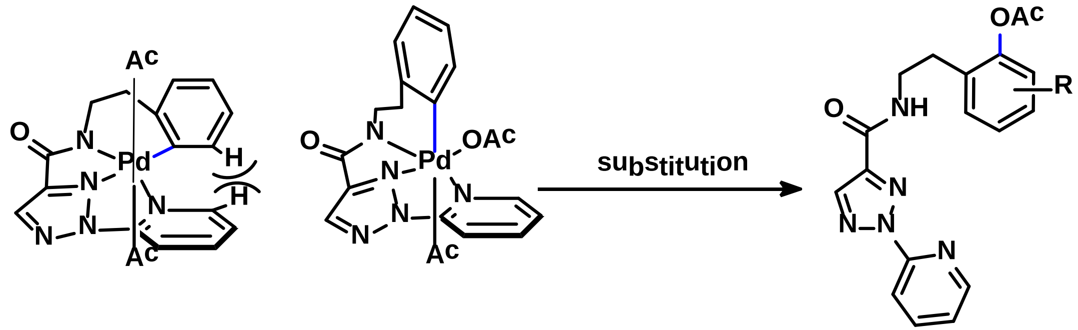
TA-Py:N2-pyridine-1,2,3-triazole-4carboxylic acid

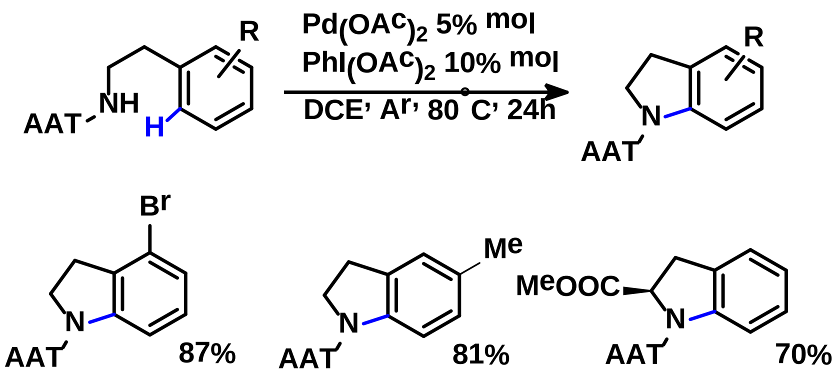


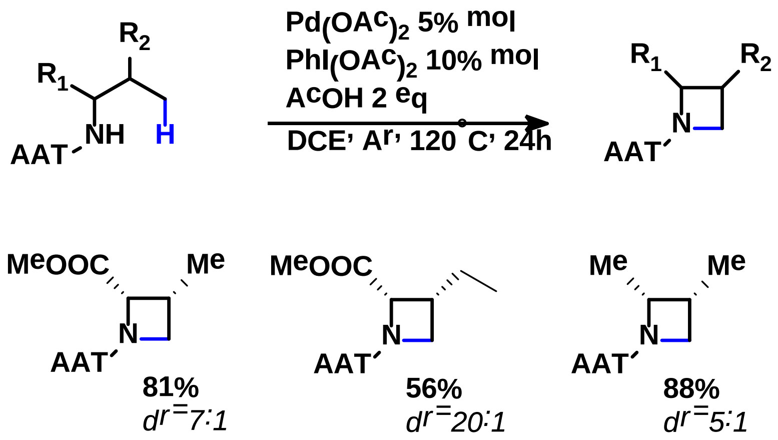
J. Am, Chem. Soc., **2013**, *135*, 2124-2127 *Chemical science*, **2013**, *4*, 3712-3716

1,2,3 triazoles for CH-activation



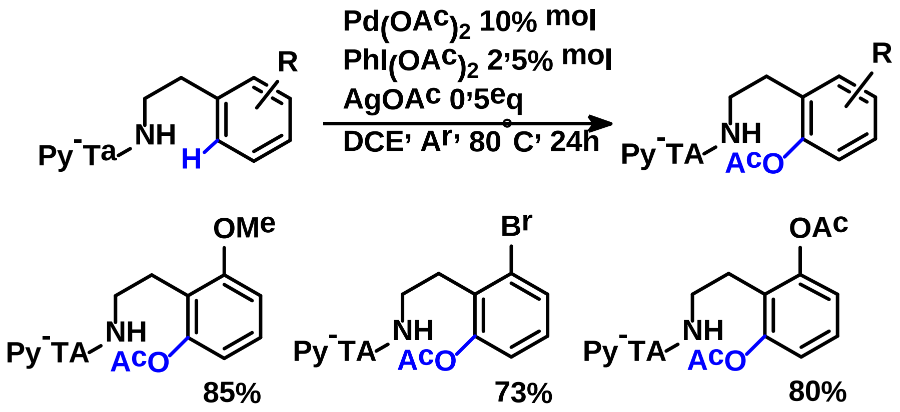


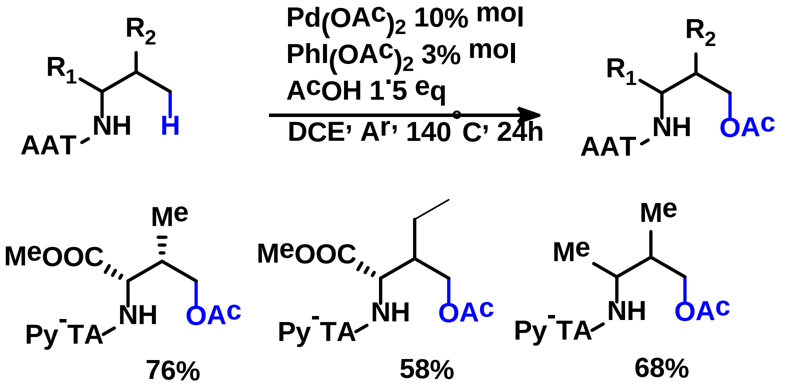


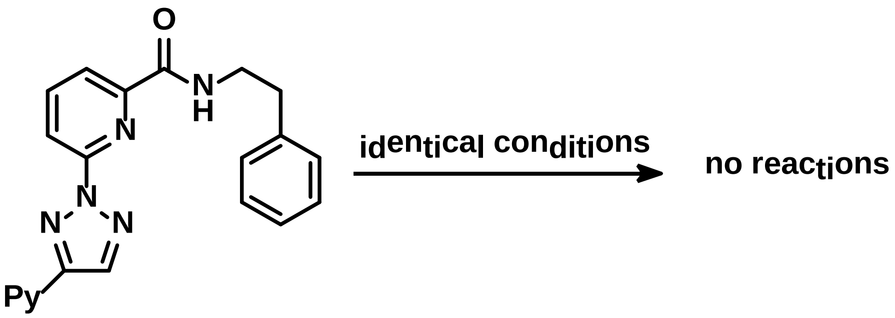


Chemical science, **2013**, *4*, 3712-3716

1,2,3 triazoles for C-H activation

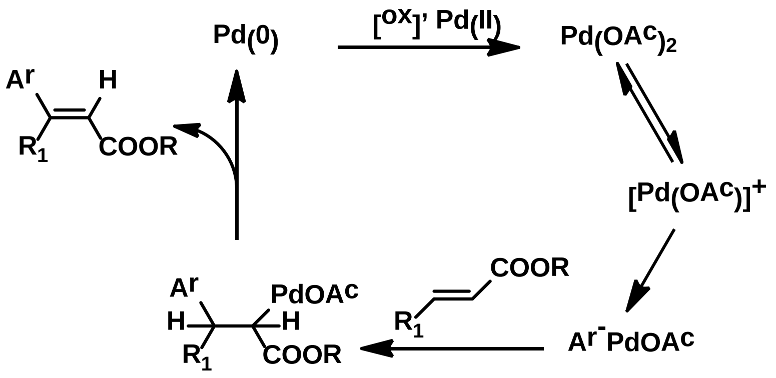


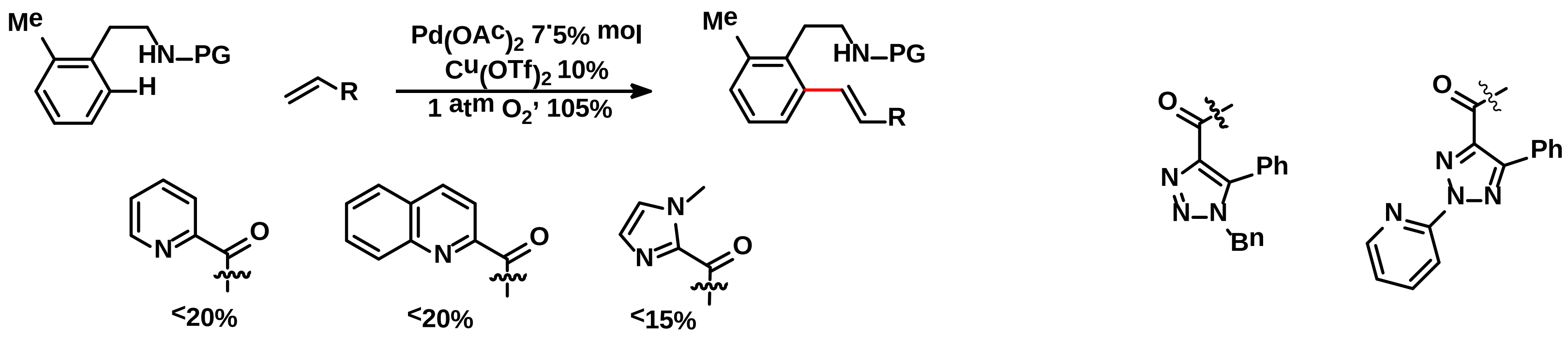


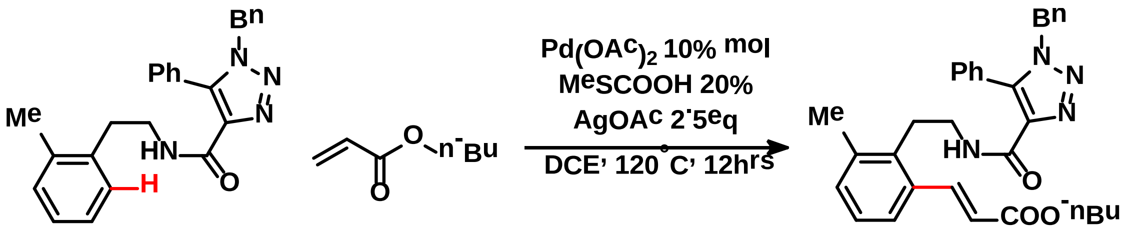


Chemical science, **2013**, *4*, 3712-3716

1,2,3 triazoles for C-H olefination

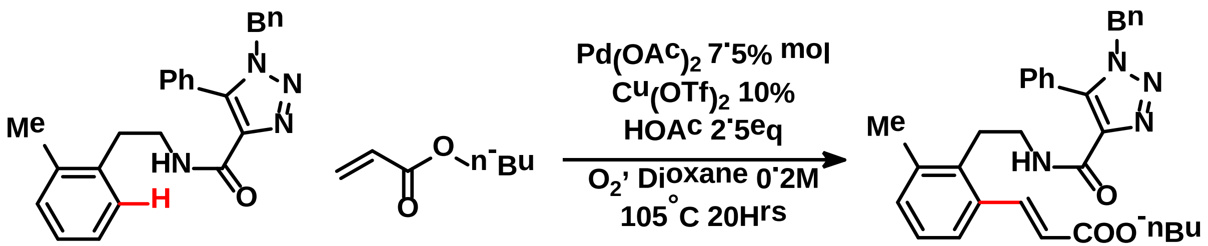


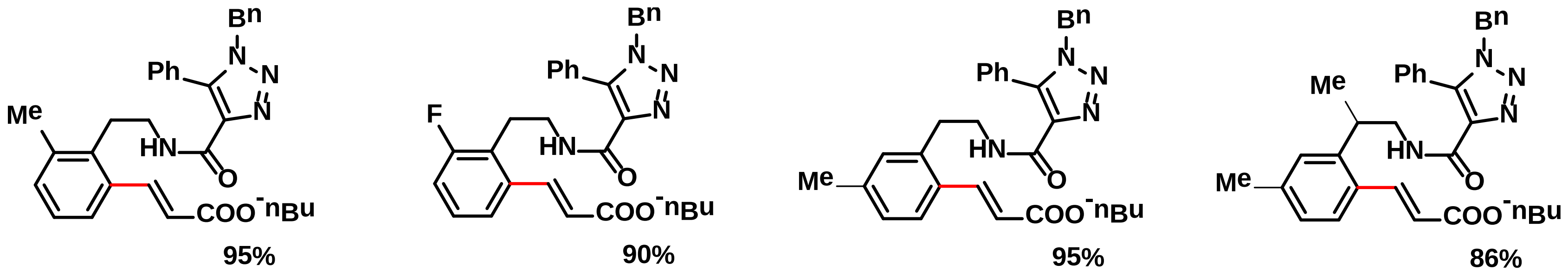


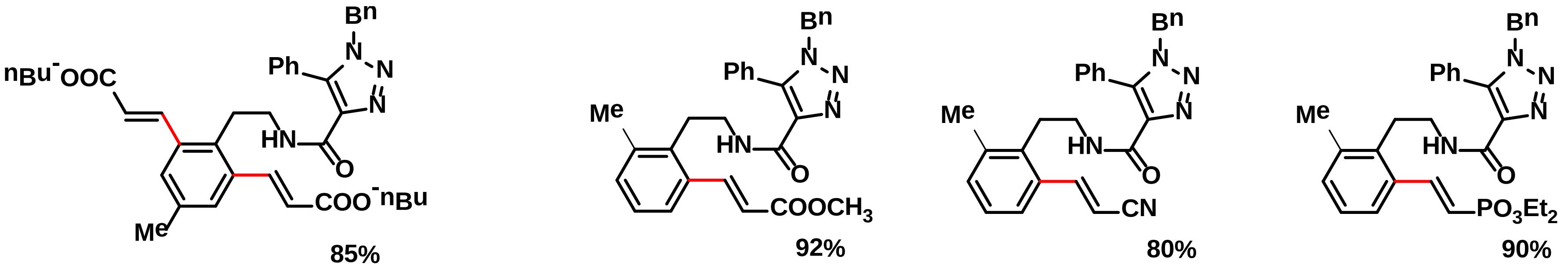


Org. Lett., **2014**, *16*, 4448-4451

1,2,3 triazoles for C-H olefination



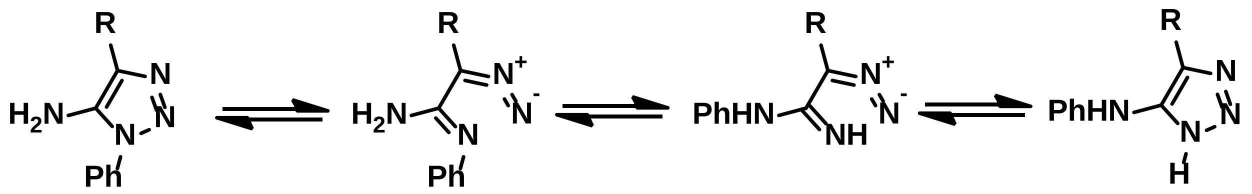


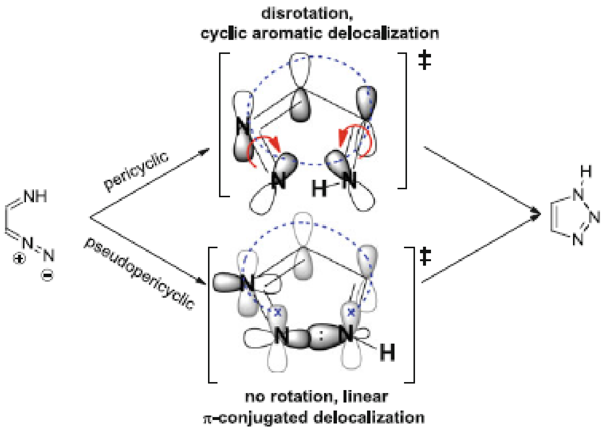


Org. Lett., **2014**, *16*, 4448-4451

1,2,3 triazoles as heterocycles precursors

- Broad spectrum of biological activities
- Triazole core should be an extremely robust heterocyclic unit, thus most of the relative chemistry revolves around its functionalizazion

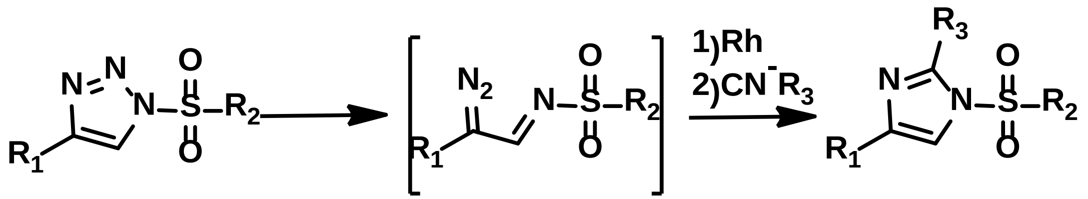


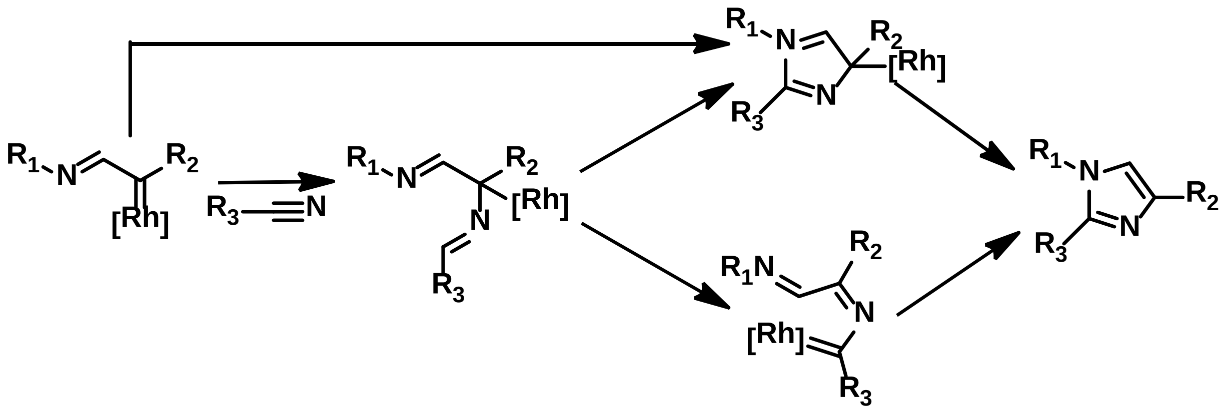


- 1,2,3 triazoles (in solution) exist in a closed/opened form equilibrium with their diazocompounds
- This equilibrium is depending from solvent, temperature and nature of the substituents: halogen or EWG on 4 and 5 position push the equilibrium toward the diazoform, which could be explained in terms of non bonding repulsion between the lone pair of electron on the the halogen and nitrogen atom in the periposition
- weak N1–N2 weak bond

‘’Chemistry of 1,2,3-triazoles’’ (Springer ed), *Angew. Chem. Int.Ed.*, **2012**, *51,* 862

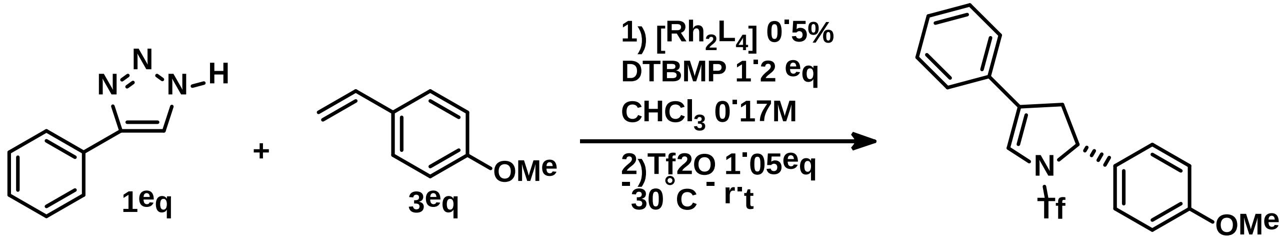
1,2,3 triazoles as heterocycles precursors



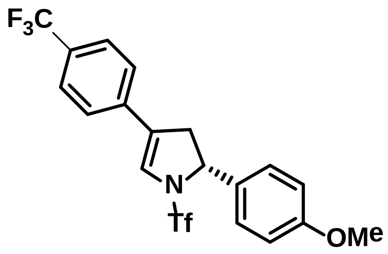


J. Am. Chem. Soc., **2008**, *130*, 14972

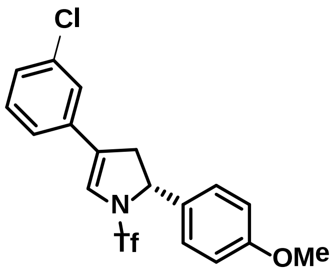
1,2,3 triazoles as heterocycles precursors



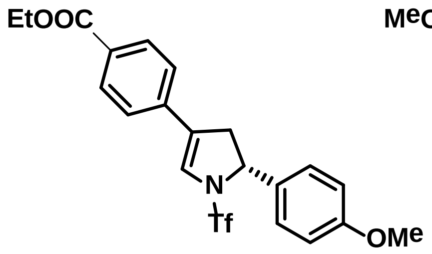
Entry	Chiral catalyst	Yield [%][b]	*ee* [%]
1	$[Rh_2(S\text{-NTA})_4]$	68	23
2	$[Rh_2(S\text{-NTL})_4]$	74	20
3	$[Rh_2(S\text{-NTPA})_4]$	67	44
4	$[Rh_2(S\text{-NTV})_4]$	61	55
5	$[Rh_2(S\text{-NTTL})_4]$	92	72
6	$[Rh_2(S\text{-4-Br-NTTL})_4]$	40	70
7	$[Rh_2(S\text{-PTTL})_4]$	15	46
8	$[Rh_2(S\text{-TFPTTL})_4]$	56	70
9	$[Rh_2(S\text{-4-Me-PTTL})_4]$	34	66
10	$[Rh_2(S\text{-BPTTL})_4]$	33	64



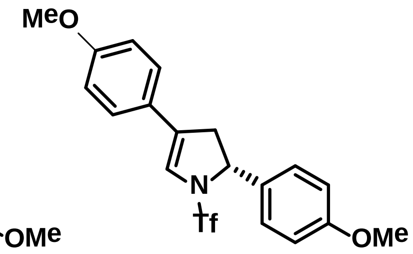
84% yield
63% ee



80% yield
74% ee



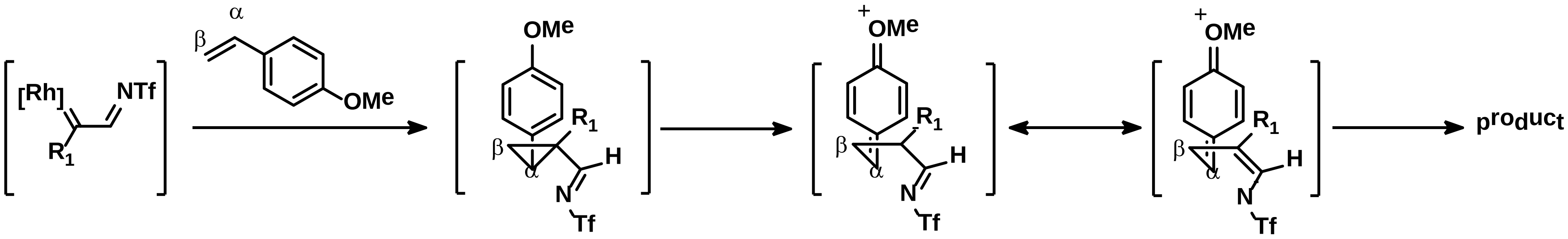
38% yield
0% ee

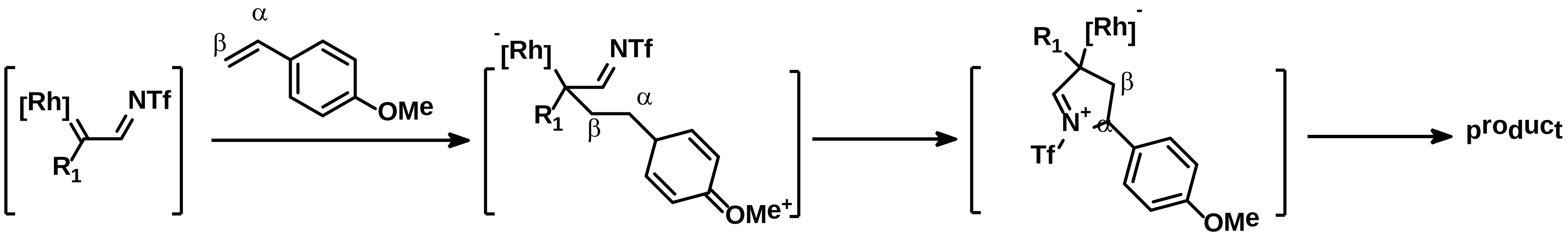


34% yield
15% ee

Angew. Chem. Int. Ed., 2**014**, *53*, 3452

1,2,3 triazoles as heterocycles precursors

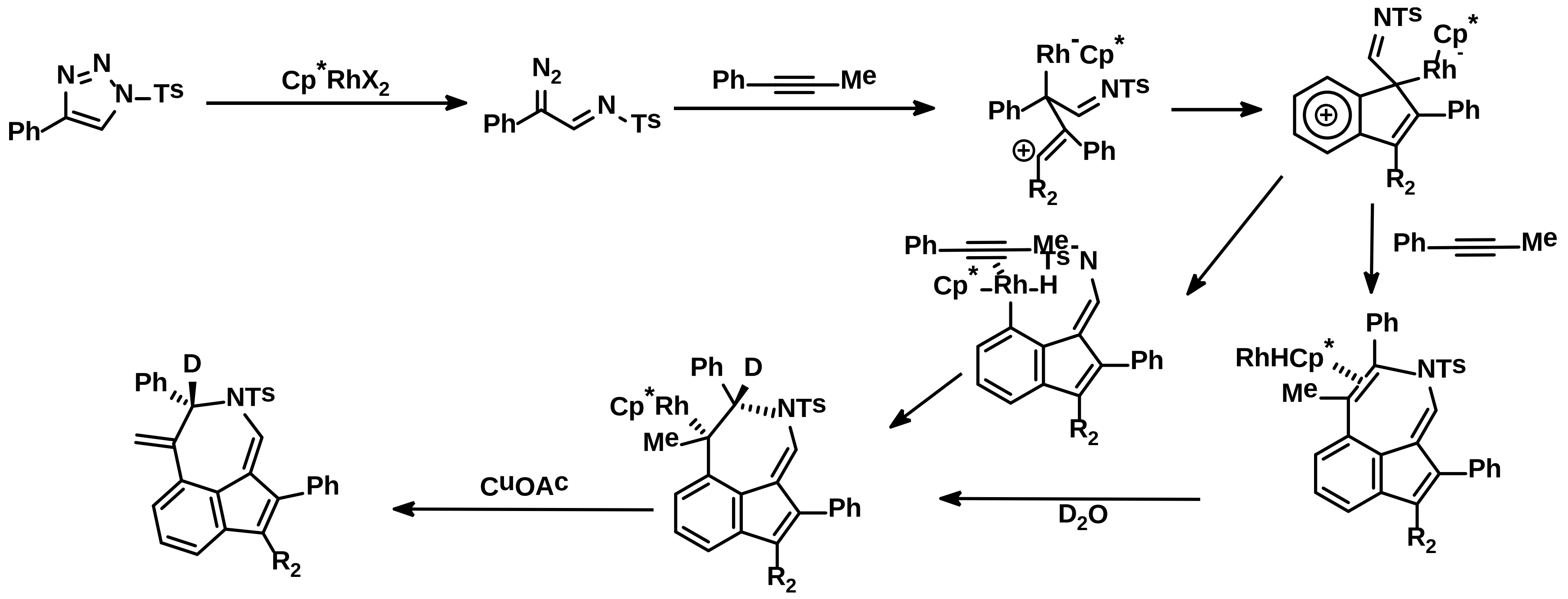




Angew. Chem. Int. Ed., 2**014**, *53*, 3452

Thanks for your attention!

Answer:



Cp*RhX2
Ph
N
N
N
Ts
N2
Ph
Me
Rh⁻Cp*
NTs
R2
Cp*
Rh
Cp*–Rh–H
D2O
CuOAc
RhHCp*
D

L-Histidine, a «passe-partout» organocatalyst

May 12, 2015

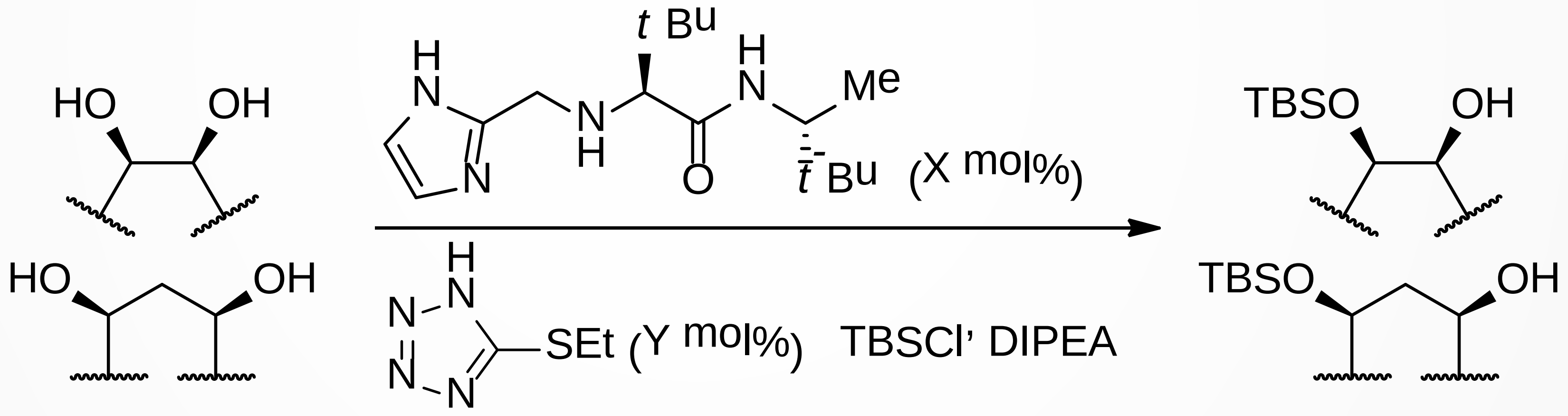
Ecole Polytechnique Fédérale de Lausanne

Romain Tessier

Questions

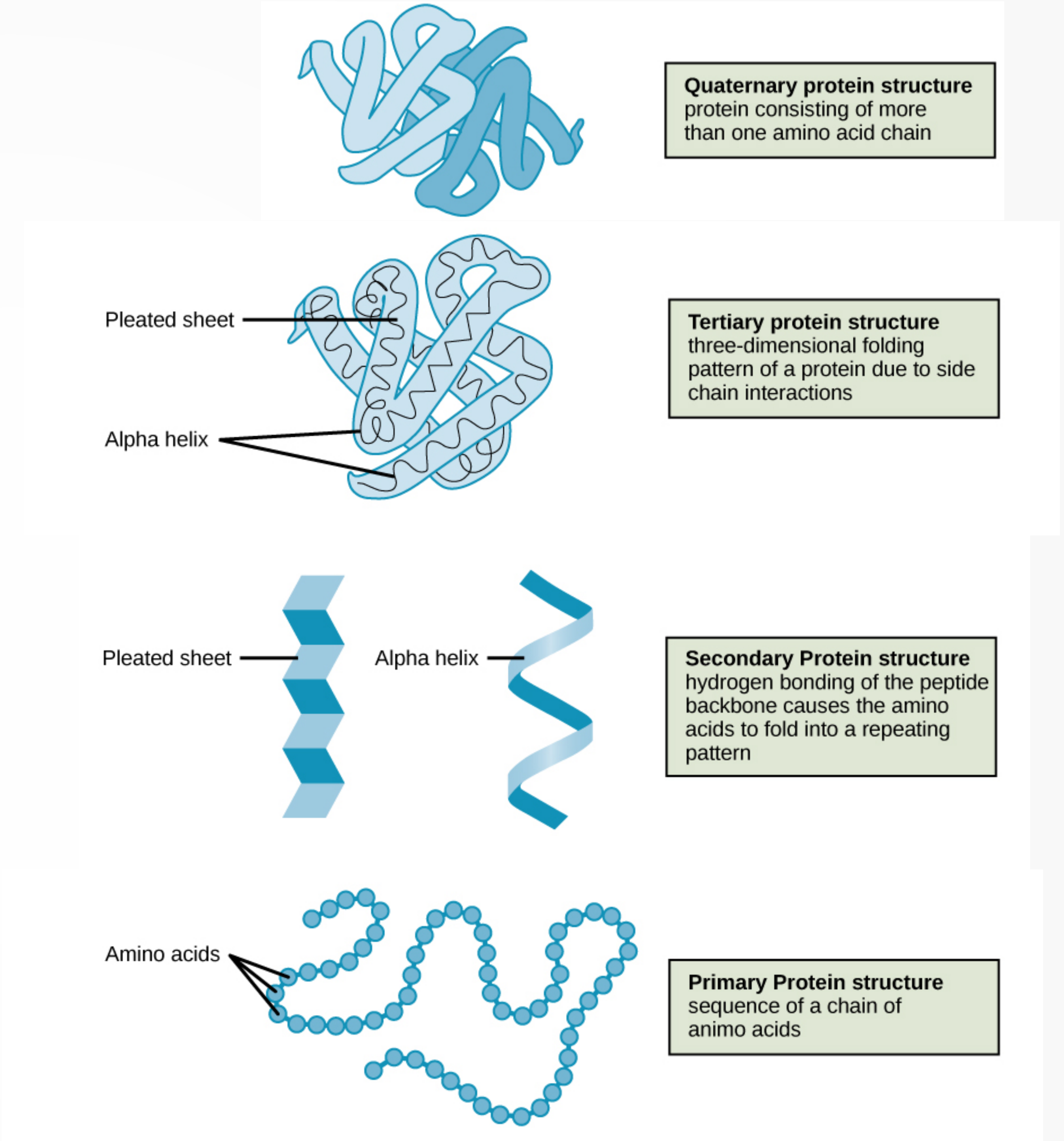
What are advantages of small peptide catalysts over enzymes ?

Can you explain the role of the co-catalyst in this reaction ?



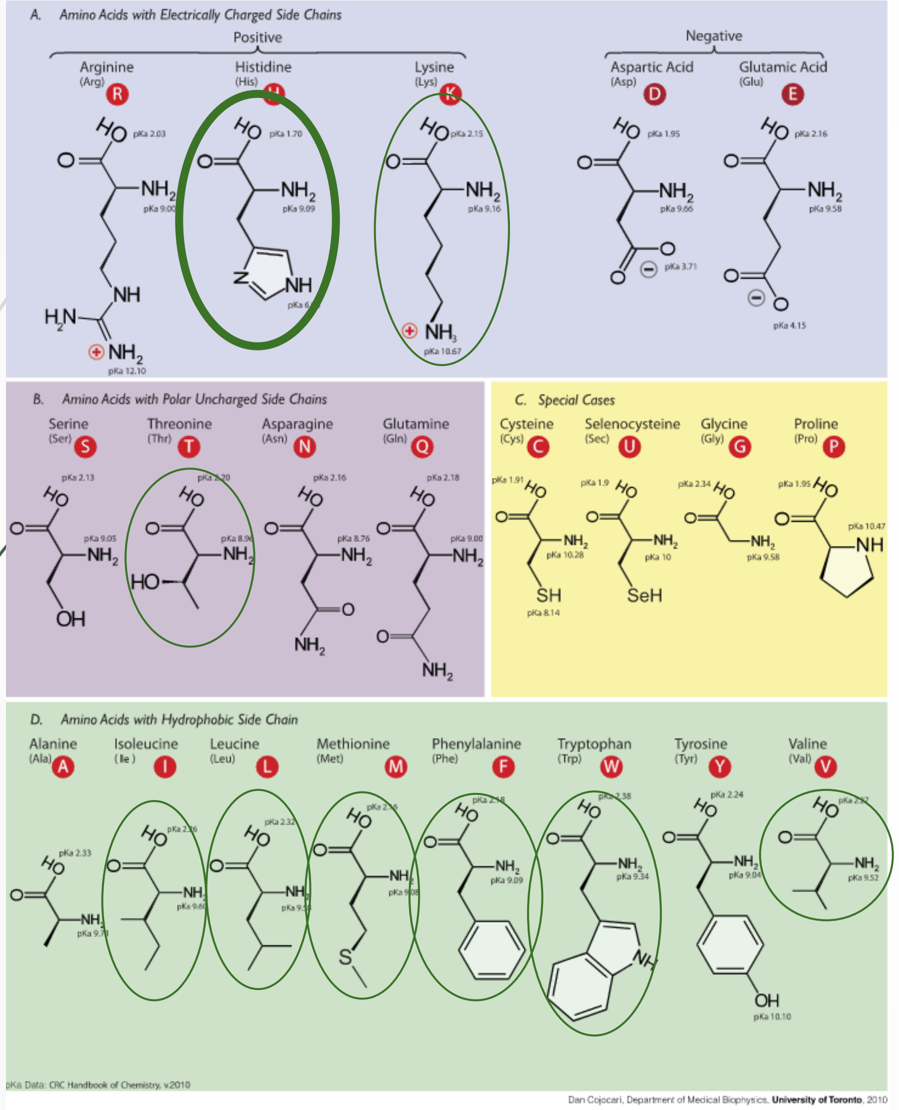
Once upon a time…

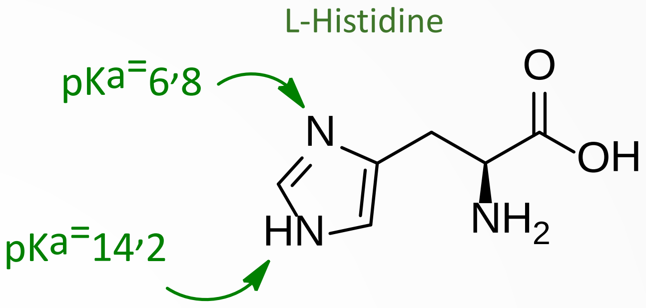
Angiotensin-converting enzyme 2



Keidar, S.; Kaplan, M.; Gamliel-Lazarovich, A. *Cardiovasc Res.* **2007**, *73*, 463. Schomburg, I.; Chang, A.; Placzek, S.; Söhngen, C.; Rother, M.; Lang, M.; Munaretto, C.; Ulas, S.; Stelzer, M.; Grote, A.; Scheer, M. Schomburg, D. *Nucleic Acids Research* **2013**, *41*, 764.

…L-Histidine





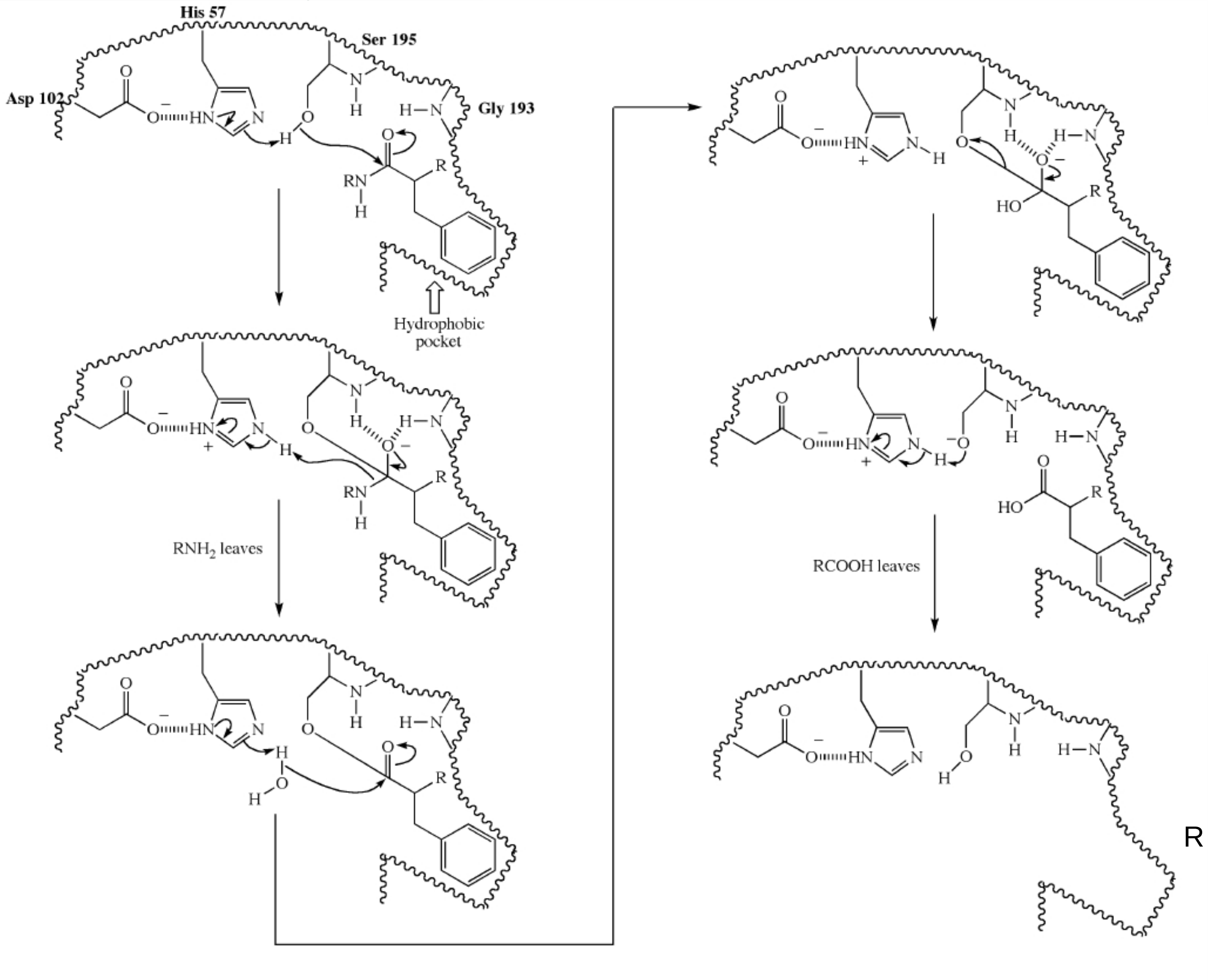
Implied in:

- TEV proteases
- Cytomegalovirus proteases
- Chymotrypsin
- Histidine kinases

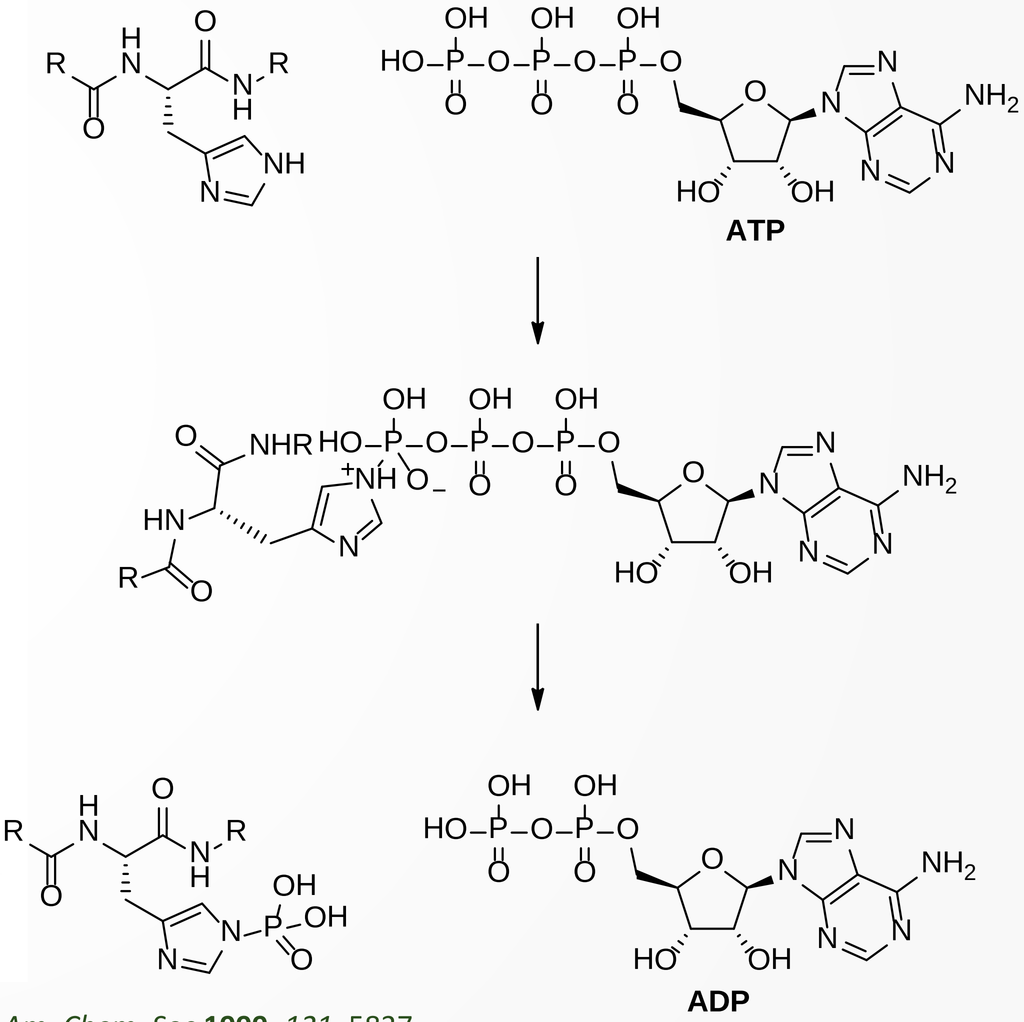
Kossel, A. *Z. Physiol. Chem.* **1896**, *xxii*, 176. Hedin, S. G. *Z. physiol. Chem.* **1896**, *xxii*, 191. Brenner, C.; Bieganowski, P.; Pace, H. C.; Huebner, K. J. Cell. Physiol. **1999**, *181*, 179. Stifel, F. B.; Herman, R. H. *Am. J. Clin. Nutr.* **1972**, *25*, 182.

L-Histidine impact in catalytic triads

Chymotrypsin



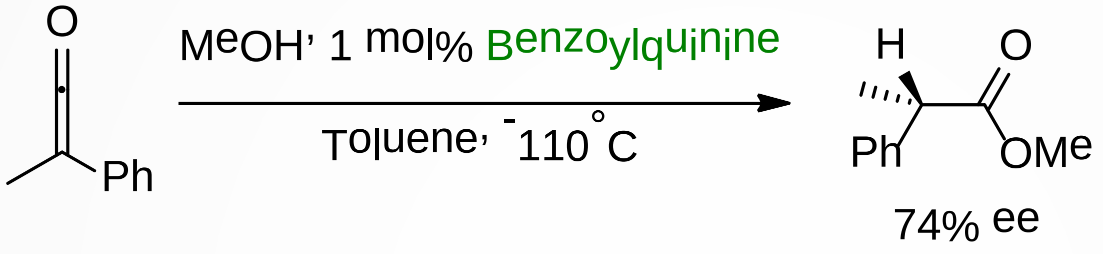
Histidine kinases

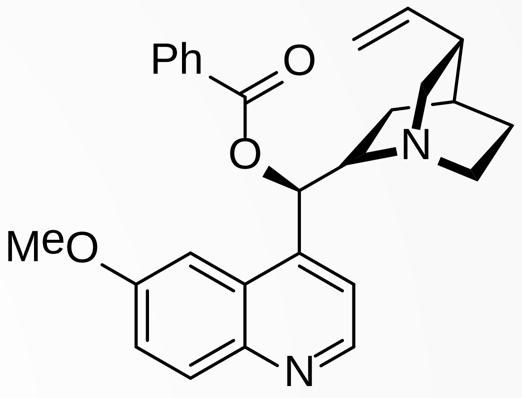


UCLA Illustrated Glossary of Organic Chemistry. Admiraal, S. J.; Herschlag, D. *J. Am. Chem. Soc.* **1999**, *121*, 5837.

Organocatalysis & chiral amines : an old romance

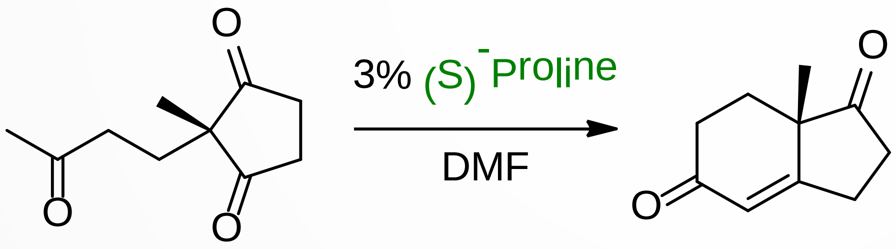
1960: Pracejus

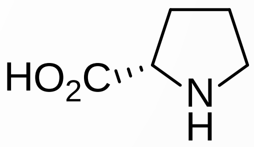




Benzoylquinine

1971: Hajos-Parrish-Eder-Sauer-Wiechert



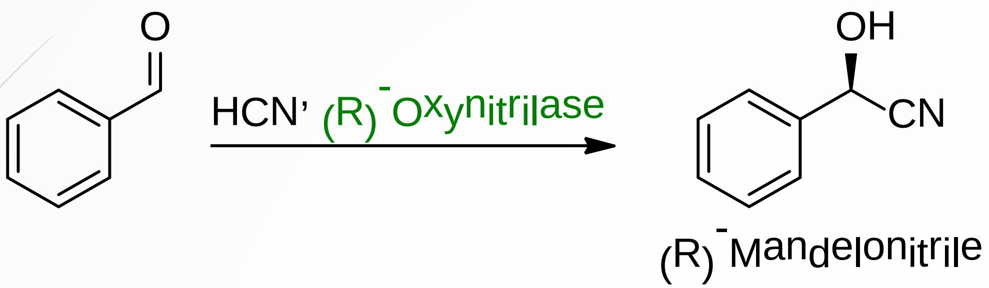


(S)-Proline

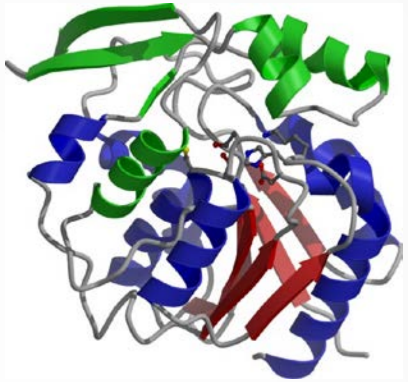
"As yet there has been no compelling evidence that small polypeptides can approach the larger naturally occurring proteolytic enzymes in terms of activity and specificity." Matthews, B. W.; Craik, C. S.; Neurath, H. *Proc. Nad. Acad. Sci. USA* **1994**, *91*, 4103,

Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9. Hajos, Z. G.; Parrish, D. R. *Ger. Pat.* **1971**, *DE 2102623*. Eder, U.; Sauer, G.; Wiechert, R. *Ger. Pat.* **1971**, *DE 2014757*. Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496.

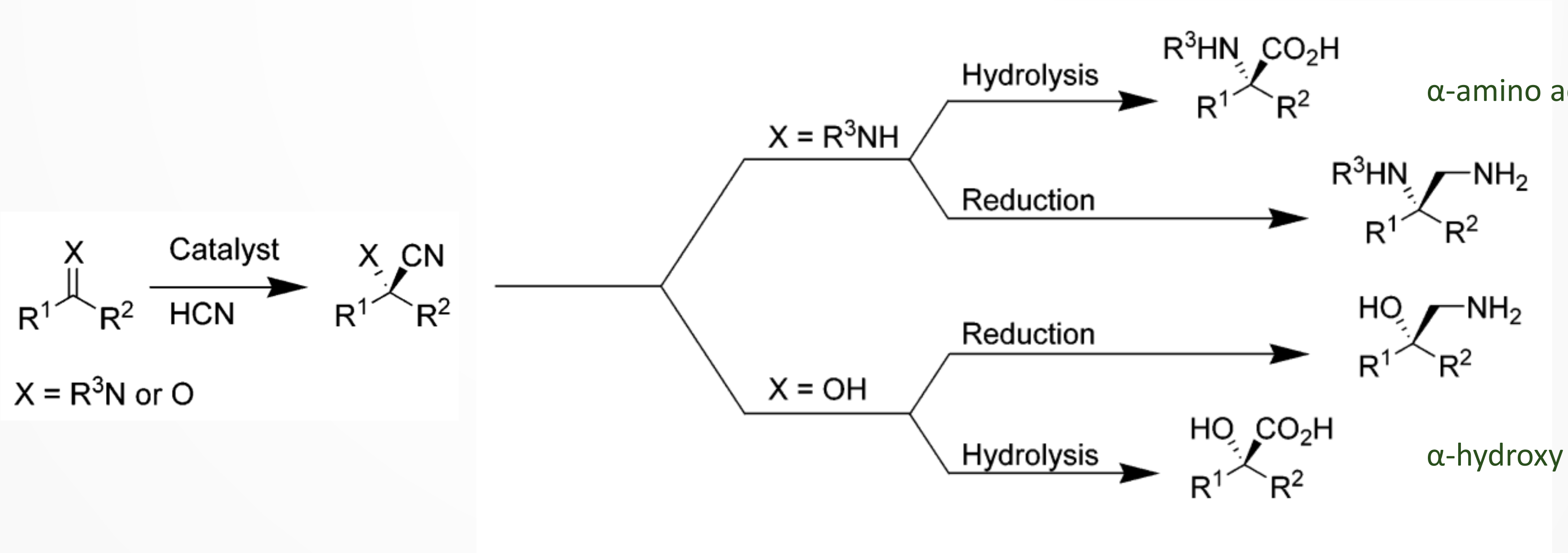
A pioneering work



Oxynitrilase



Isolated in 1908



α-amino acids

1,2-diamines

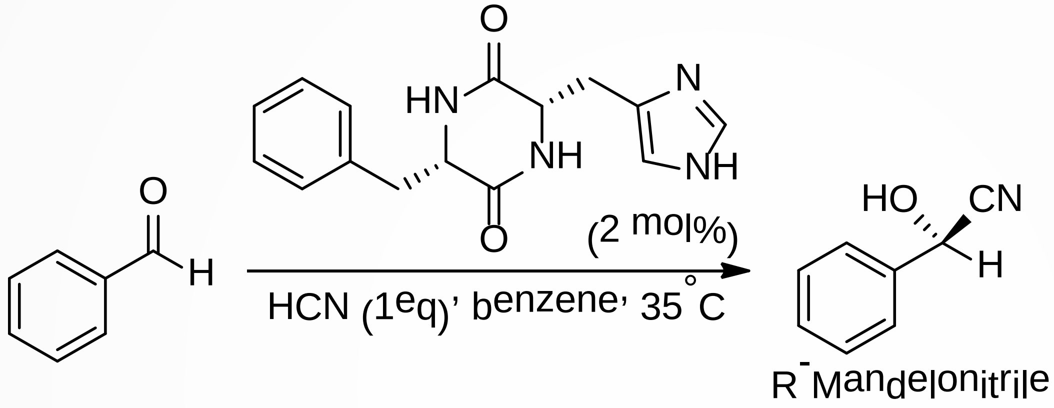
1,2-diamino alcohols

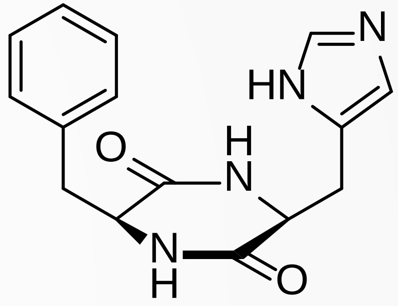
α-hydroxy acids

Rosenthaler, L. *Biochem. Z.* **1908**, *14*, 238. Becker, W.; Freund, H.; Pfeil, E. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1079.
Zuegg, J.; Gruber, K.; Gugganig, M.; Wagner, U. G.; Kratky, C. *Protein Science* **1999**, *8*, 1990. Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649.

Diketopiperazine: an effective dipeptide catalyst

1979: Inoue and Oku

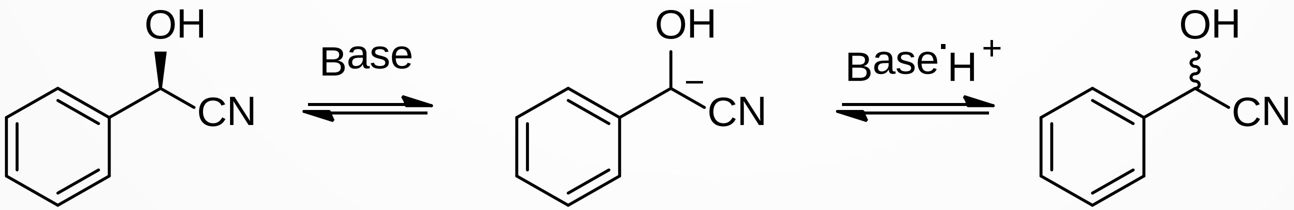




Diketopiperazine

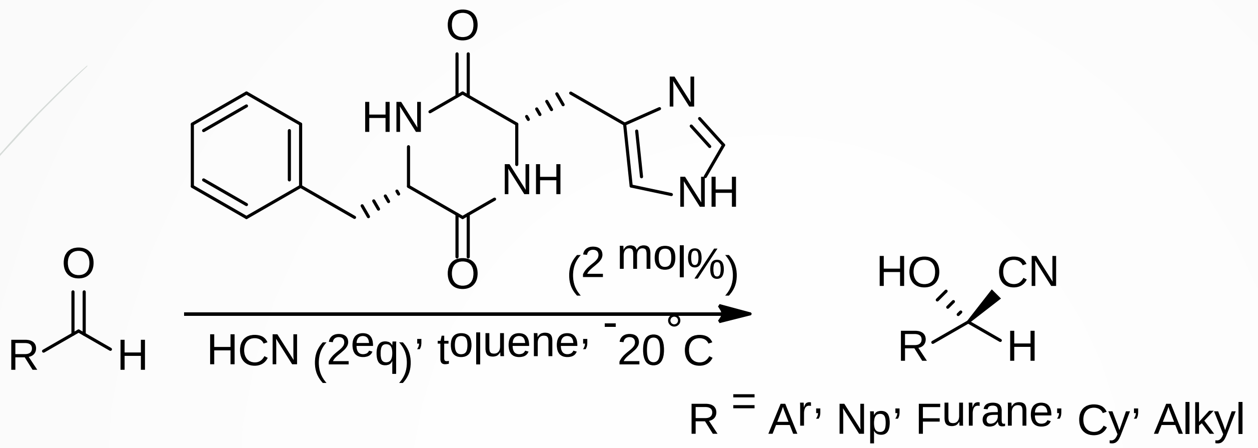
Time reaction: 30 minutes = 40% conversion + 90% ee
960 minutes = 90% conversion + 21% ee

Racemization pathway

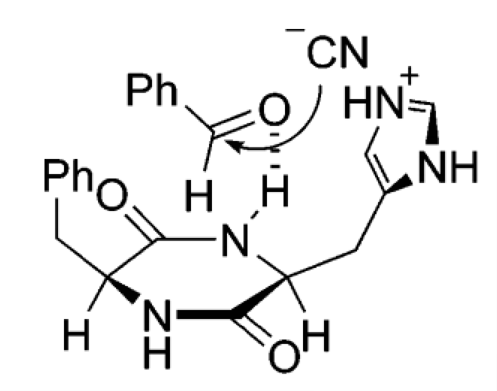


Oku, J.; Inoue, S. *Makromol. Chem.* **1979**, *180*, 1089. Oku, J.; Inoue, S. *J. Chem. Soc. Chem. Commun.* **1981**, 229.
Oku, J.; Ito, N.; Inoue, S. *Makromol. Chem.* **1982**, *183*, 579. Asada, S.; Kobayashi, Y.; Inoue, S. *Makromol. Chem.* **1985**, *186*, 1755.

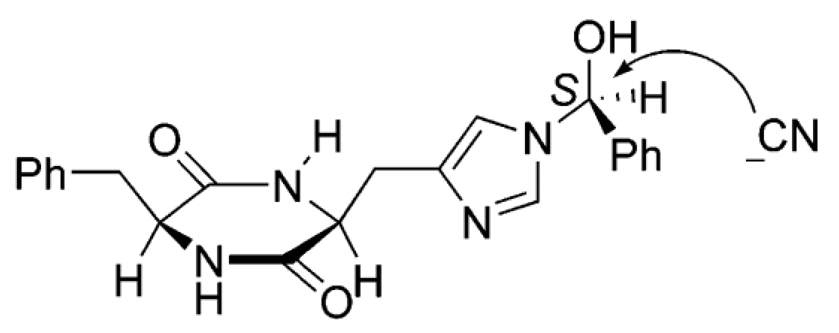
Reaction scope and mechanism propositions



Time reaction = 0.5-10h
Yield = 44-100%
Enantiomeric excess = 4-97%



Inoue proposition

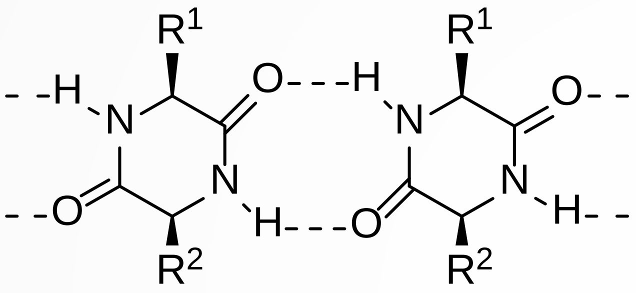


North proposition

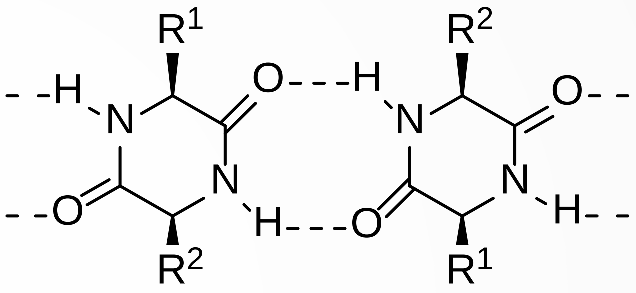
Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. Apperley, D.; North, M; Stokoe, R. B. *Tetrahedron: Asymmetry* **1995**, *6*, 1869.
Hogg, D. J. P.; North, M.; Stokoe, R. B.; Teasdale, W. G. *Tetrahedron: Asymmetry* **1993**, *4*, 1553.

A reaction of interest

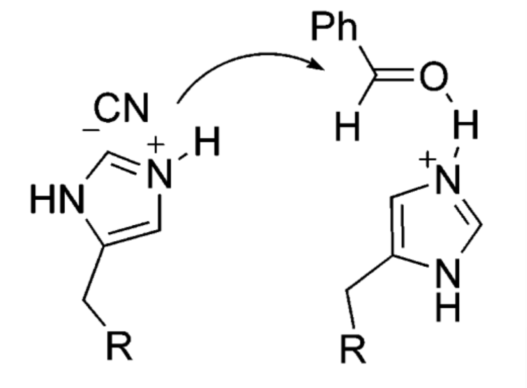
Catalyst is like a polymer but active under dimeric or oligomeric form



Head-to-Head



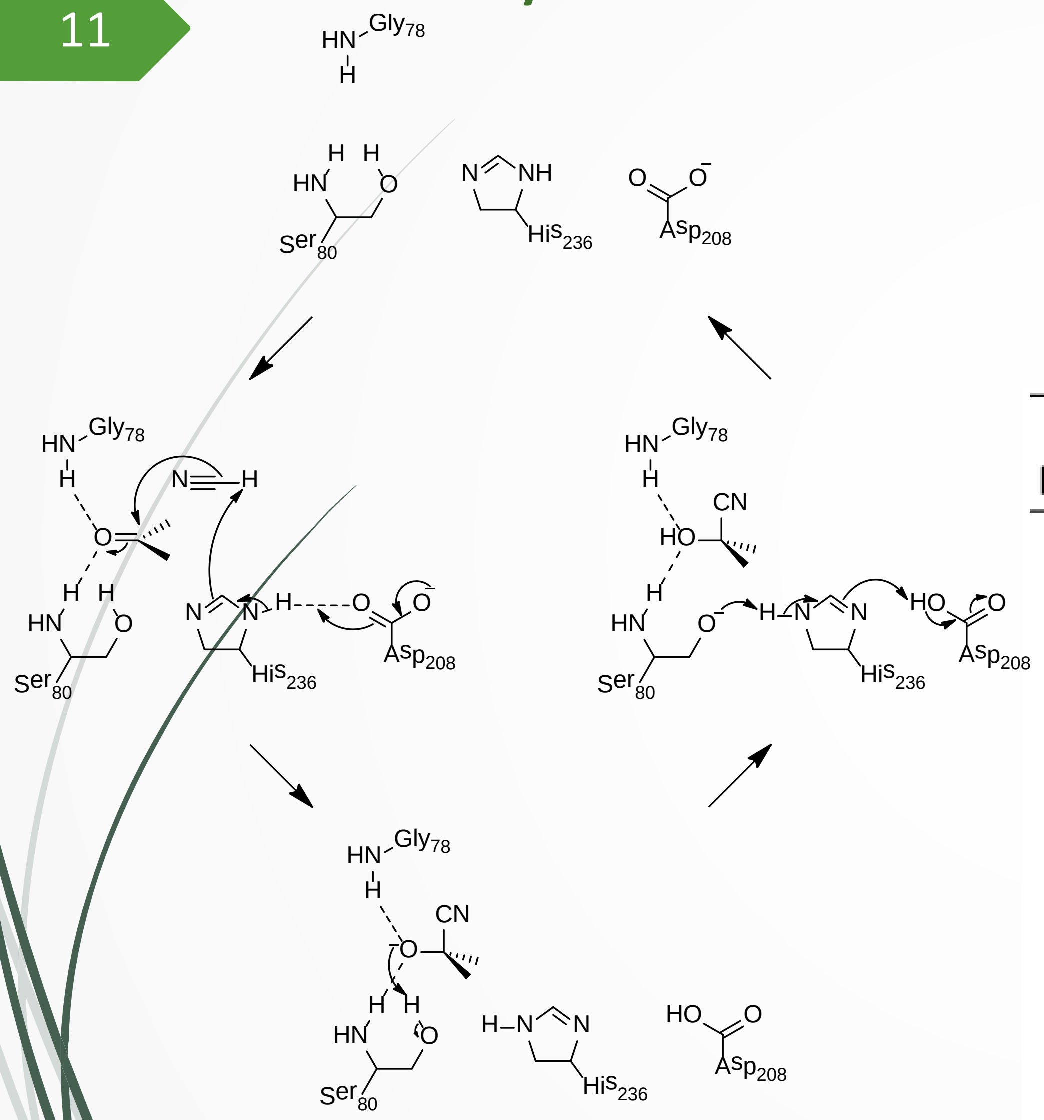
Head-to-Tail

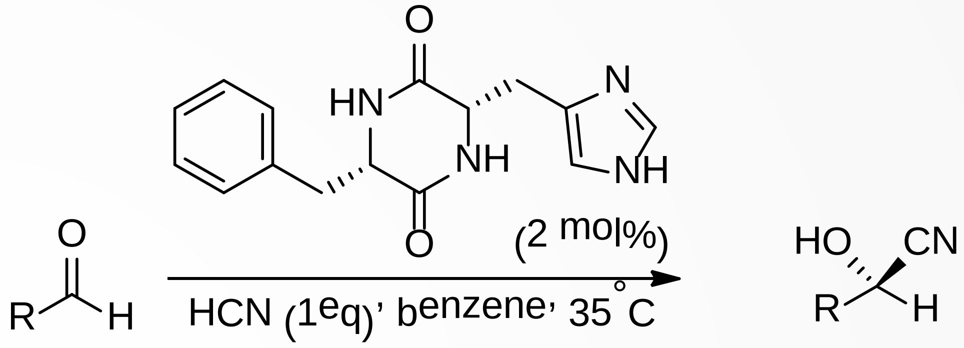


Shvo proposition

Shvo, Y.; Gal, M.; Becker, Y.; Elgavi, A. *Tetrahedron: Asymmetry* **1996**, *7*, 911. Schoenebeck, F.; Houk, K. N. *J. Org. Chem.* **2009**, *74*, 1464.

Oxynitrilase vs Diketopiperazine: who's the best ?

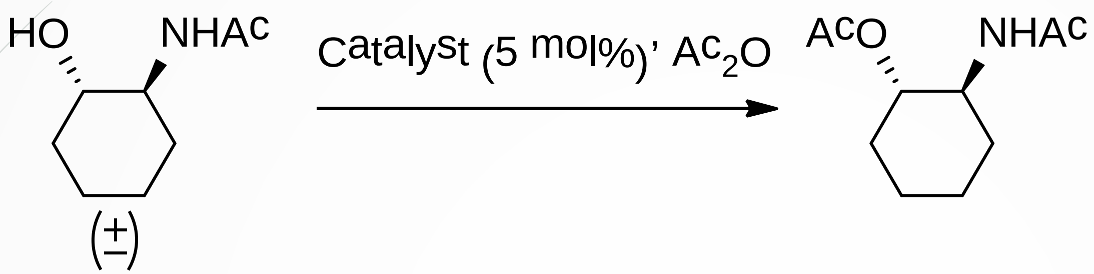




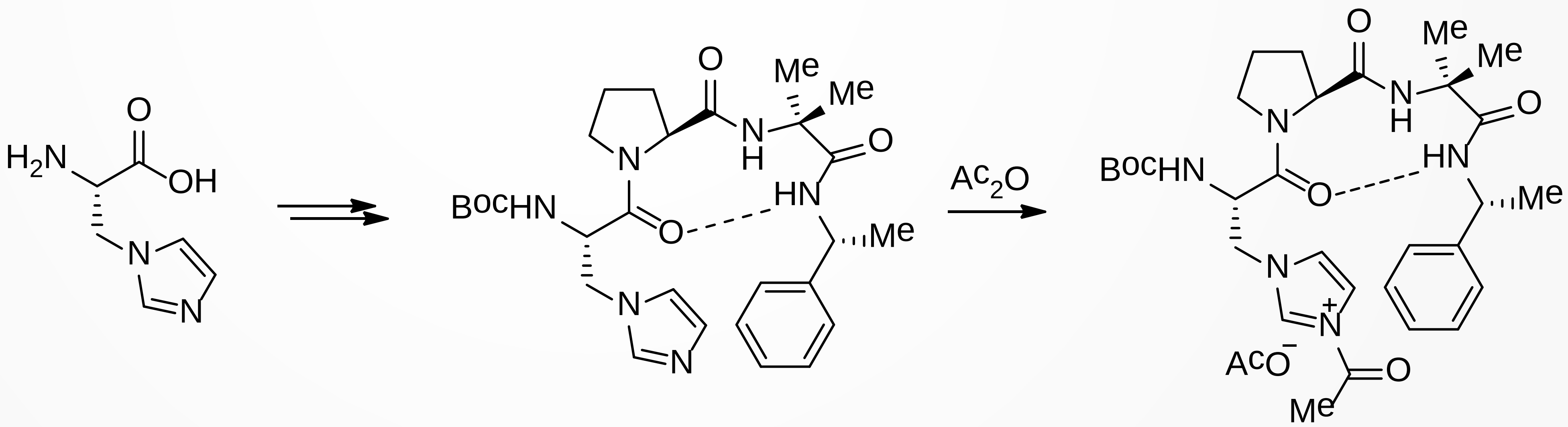
Entry	Aldehyde	Time (min.)	Conv. (%)	ee (%) by 1	ee (%) by D-oxynitrilase
1	benzaldehyde	30	40	90	100
2	benzaldehyde	240	80	69	100
3	benzaldehyde (*p*-Me)	30	80	33	28
4	benzaldehyde (*m*-Me)	30	83	82	60
5	benzaldehyde (*o*-Me)	30	67	70	not reported
6	benzaldehyde (*m*-MeO)	30	71	54	51
7	benzaldehyde (*m*-PhO)	30	70	61	not reported
8	butyraldehyde	35	100	28	20
9	pentanal	40	100	43	31
10	*iso*-butyraldehyde	35	100	35	25
11	cyclohexane carboxyaldehyde	15	100	25	not reported

Davie, E. A. C.; Mennen, S.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759. Asada, S.; Kobayashi, Y.; Inoue, S. *Makromol. Chem.* **1985**, *186*, 1755. Kobayashi, Y.; Asada, S.; Watanabe, I.; Hayashi, H.; Motoo, Y.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 893. Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649.

Kinetic resolution of alcohols: dawn of a catalyst

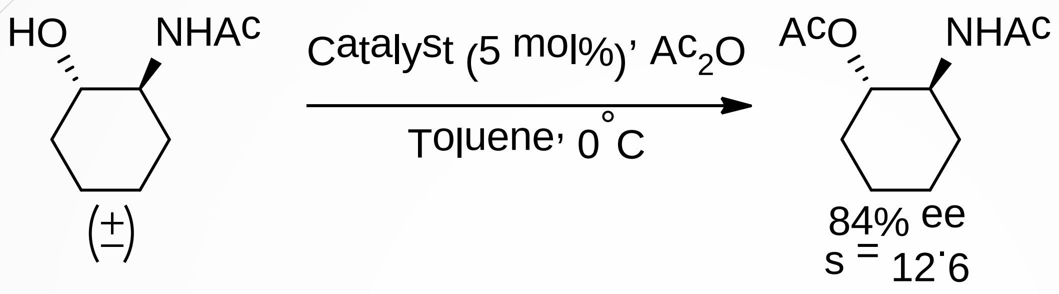


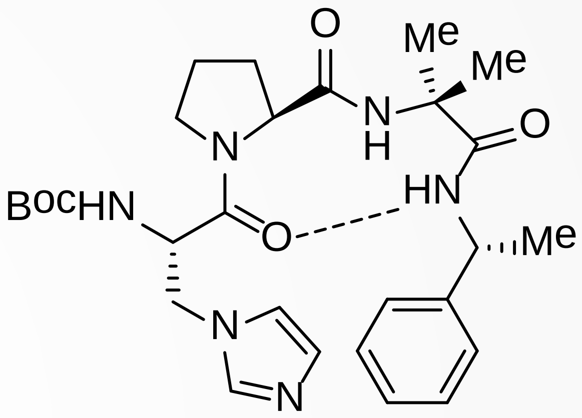
- Metal-free, mild conditions (no rigorous exclusion of moisture or oxygen), good substrate tolerance.
- Need conformational rigidity.
- Need to contain a functional group carrying catalysis.

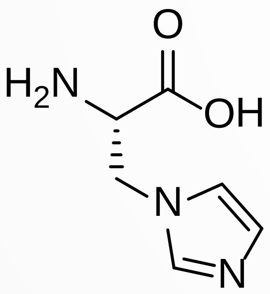


Davie, E. A. C.; Mennen, S.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759.

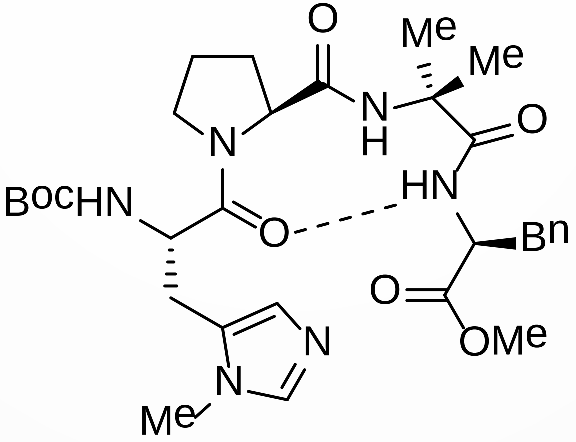
Catalyst structure and its repercussions



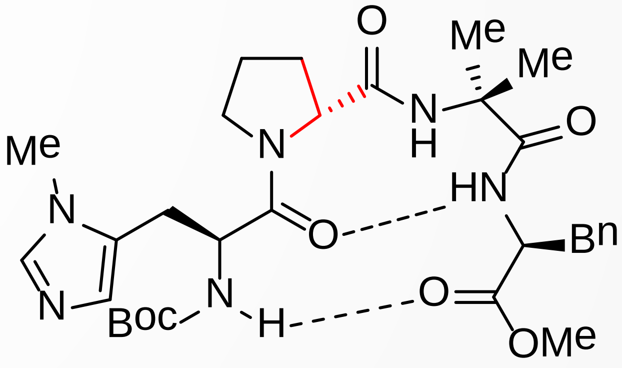




$k_{(S,S)}/k_{(R,R)} = 1$



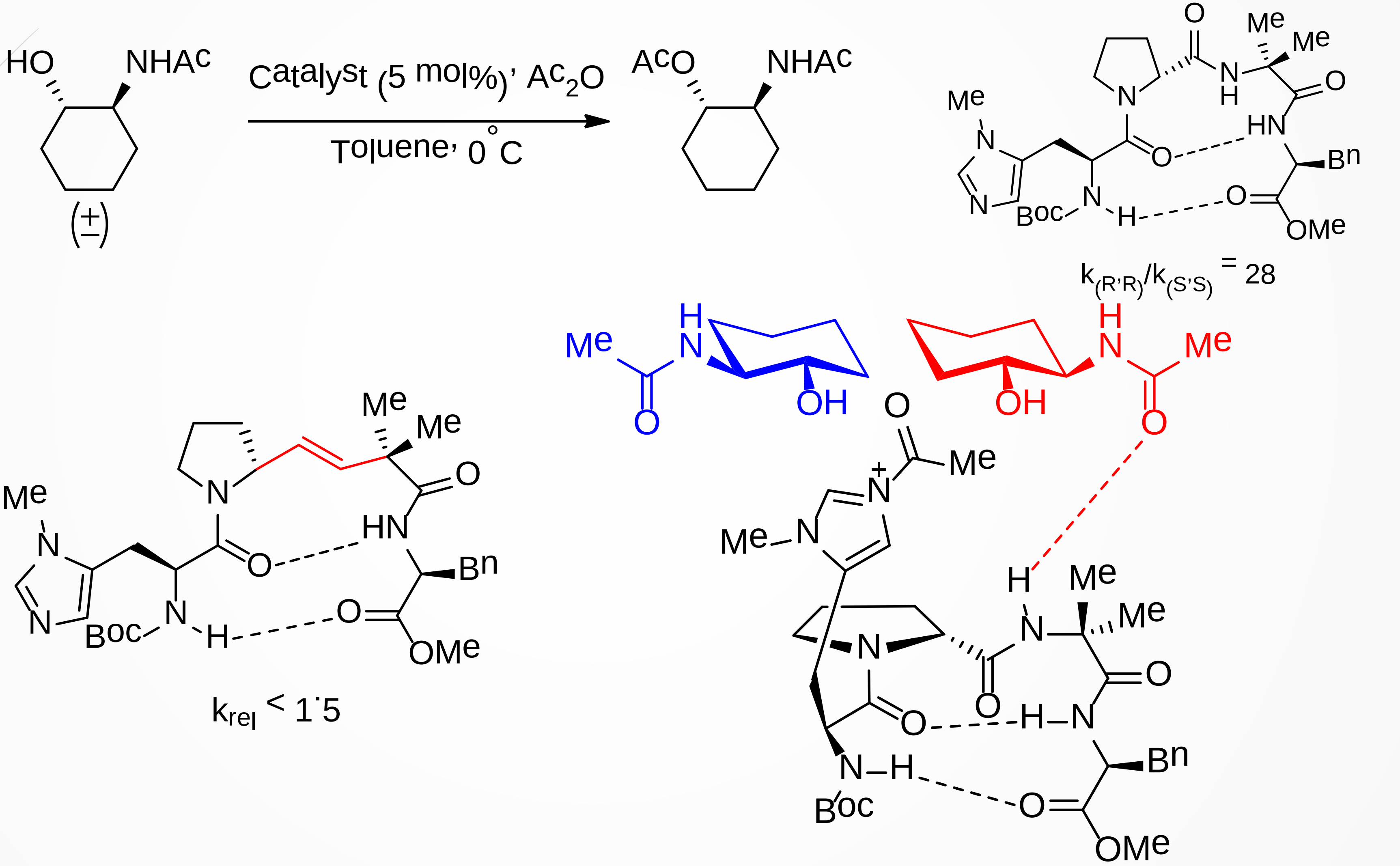
$k_{(S,S)}/k_{(R,R)} = 3.1$



$k_{(R,R)}/k_{(S,S)} = 28$

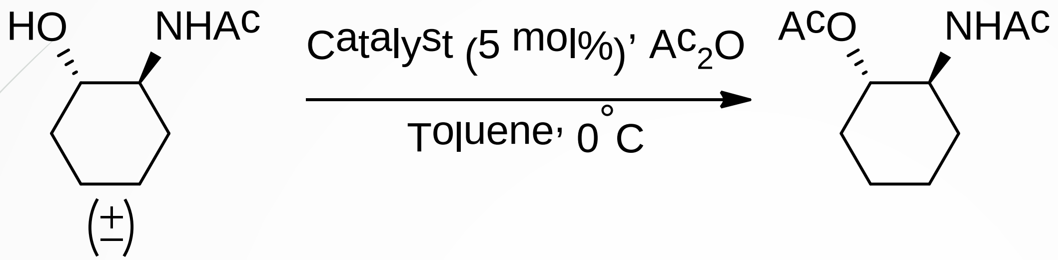
Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629.
Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306. Copeland, G. T.; Jarvo, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784

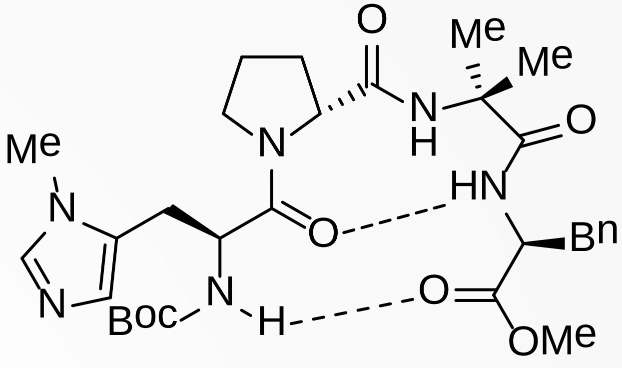
A peptidic bond in a small peptide: essential ?



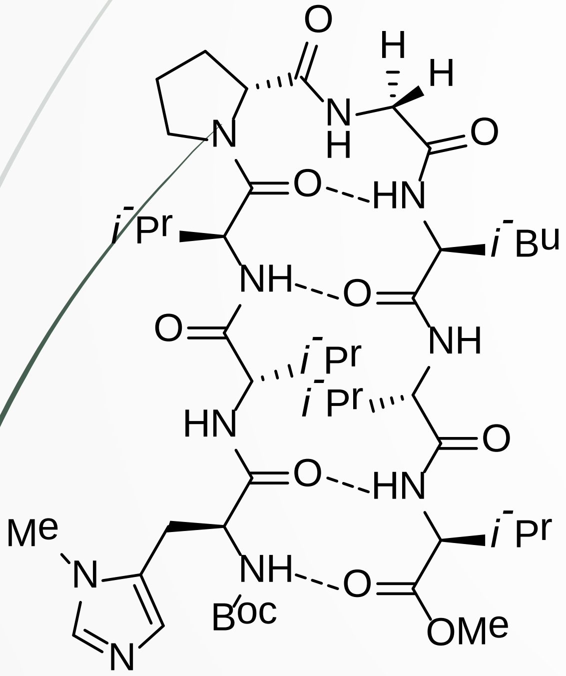
Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629.
Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306. Copeland, G. T.; Jarvo, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784.
Vasbinder, M. M.; Jarvo, E. J.; Miller, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 2824.

An inflexible catalyst ?

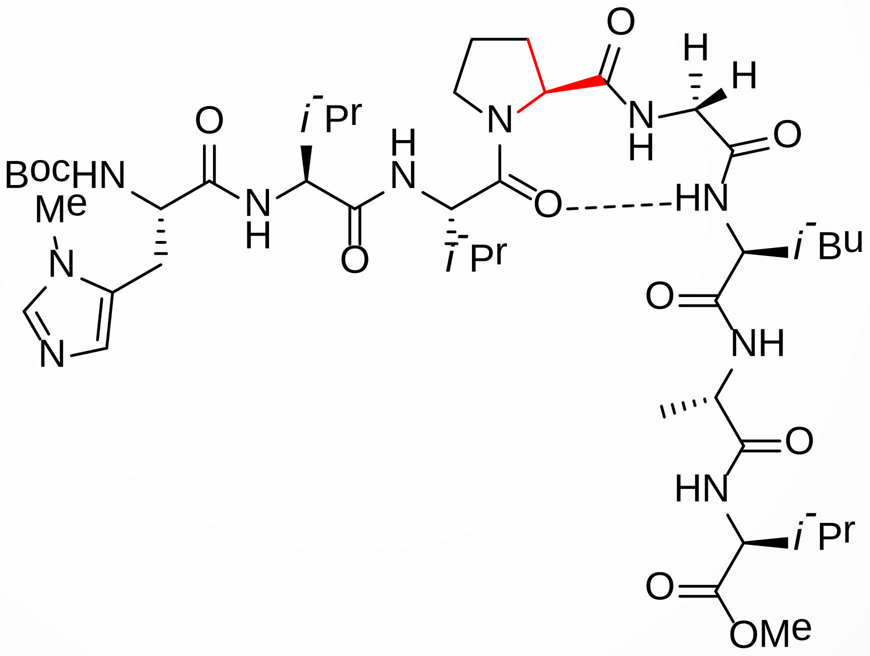




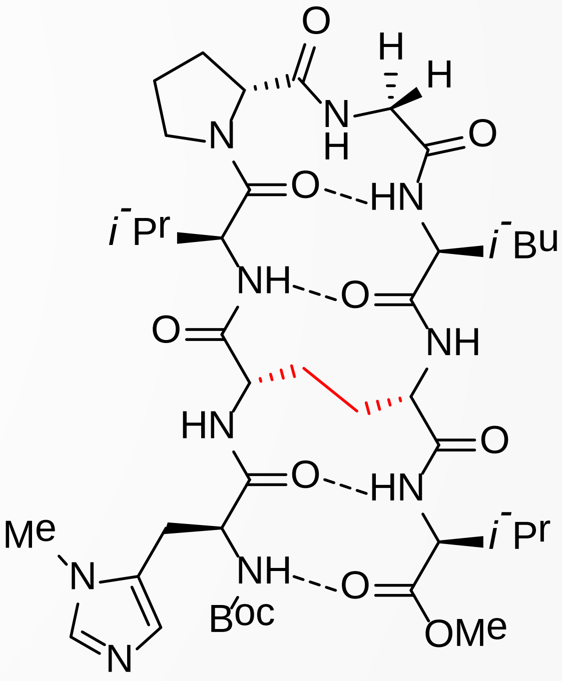
$k_{(R,R)}/k_{(S,S)} = 28$



$k_{rel} = 51$



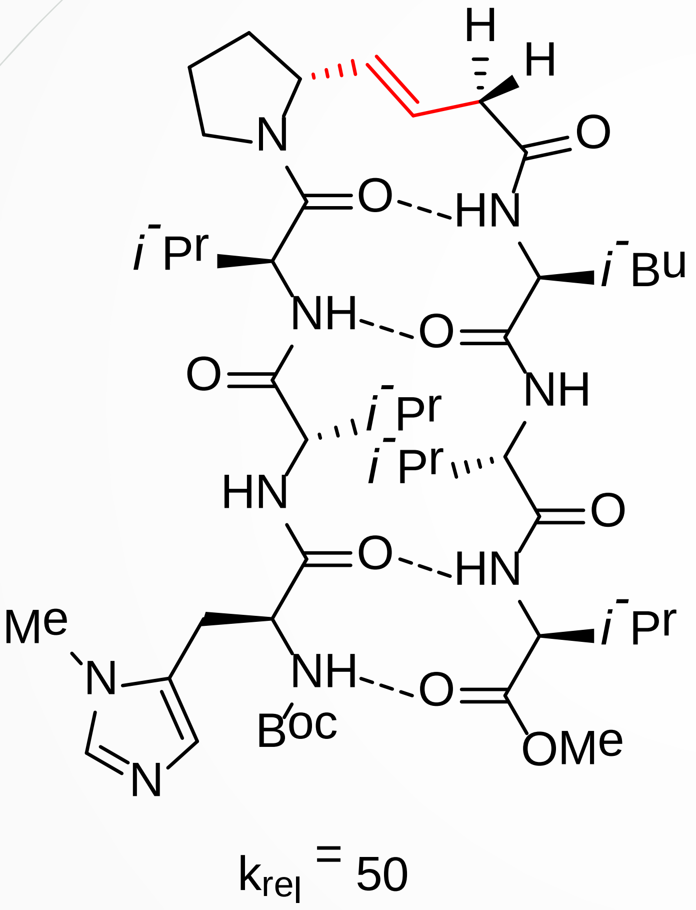
$k_{rel} = 7$

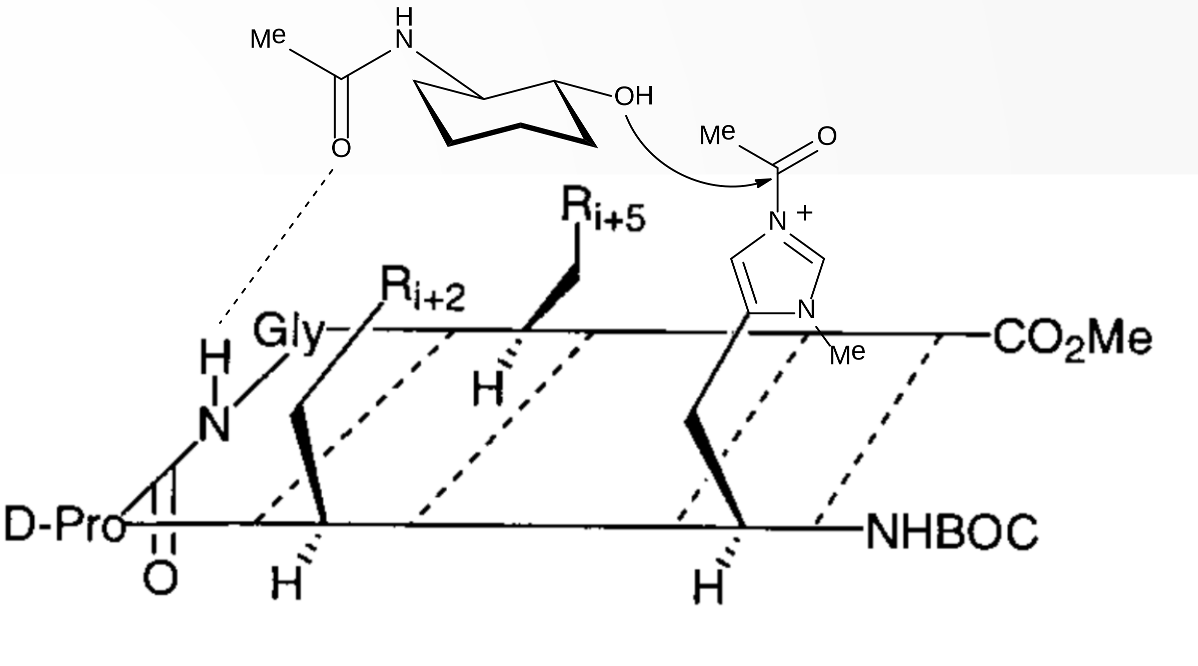


$k_{rel} = 12$

Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629.
Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306.

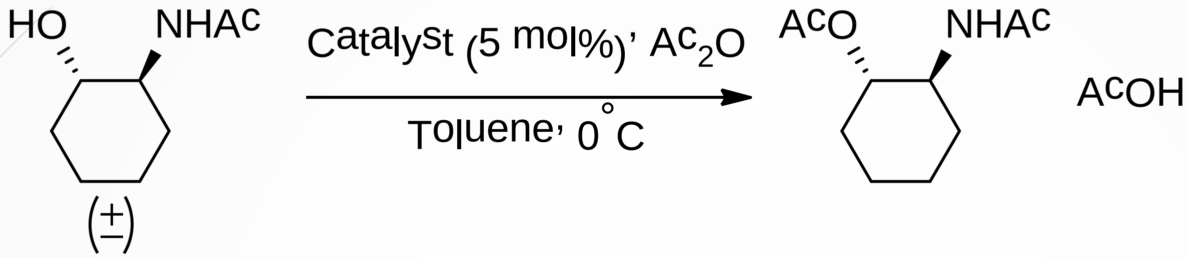
A peptidic bond in a bigger peptide: still essential ?

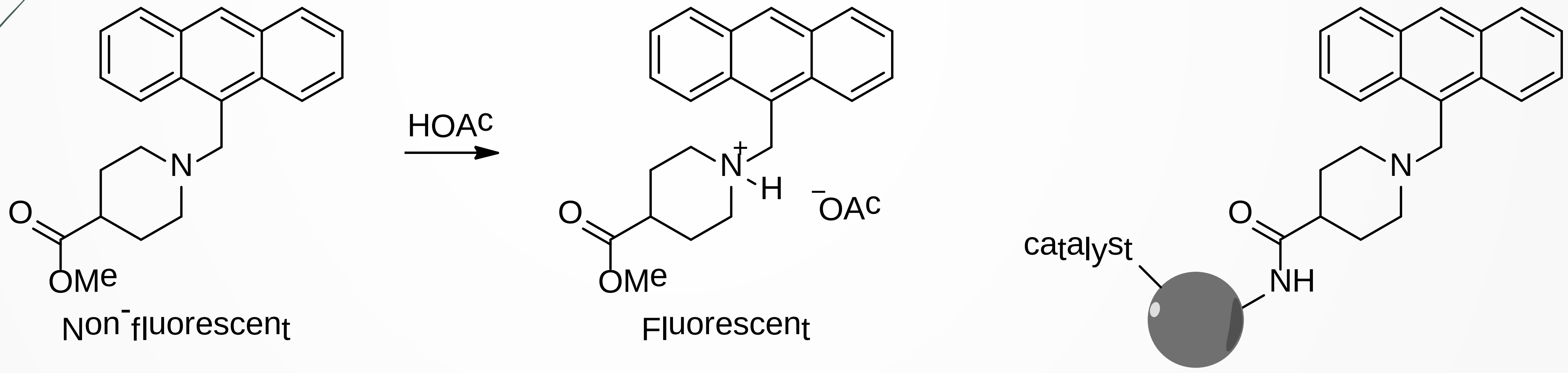




Blank, J. T.; Miller, S. J. *Biopolymers (Pept. Sci.)* **2006**, *84*, 38. Vasbinder, M. M.; Jarvo, E. J.; Miller, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 2824.

A boring screen ? Find a shortcut

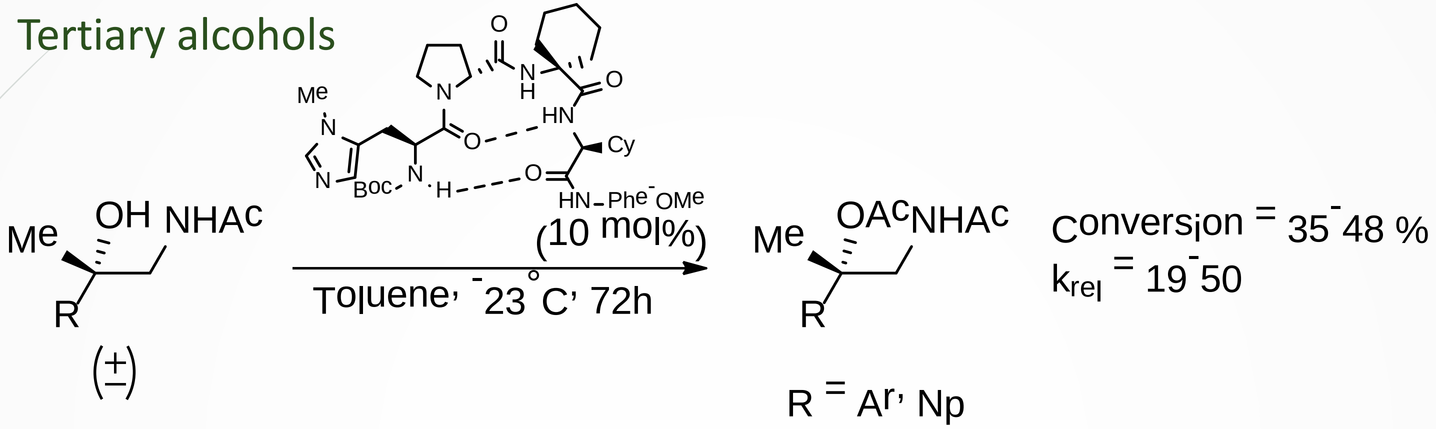




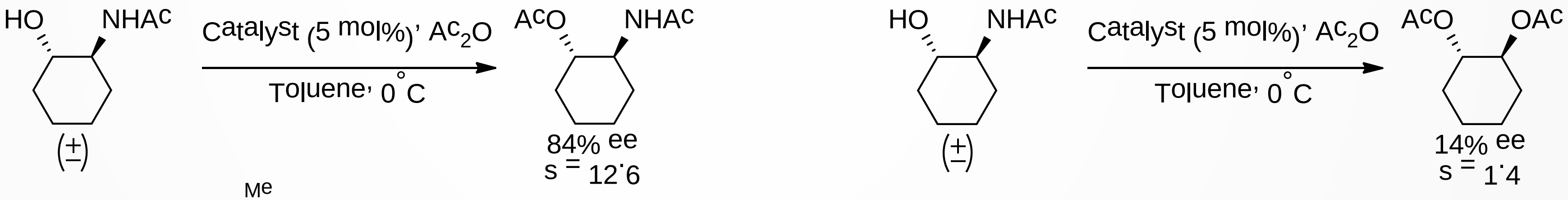
Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306. Harris, R. F.; Nation, A. J.; Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 11270. Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496. Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522.

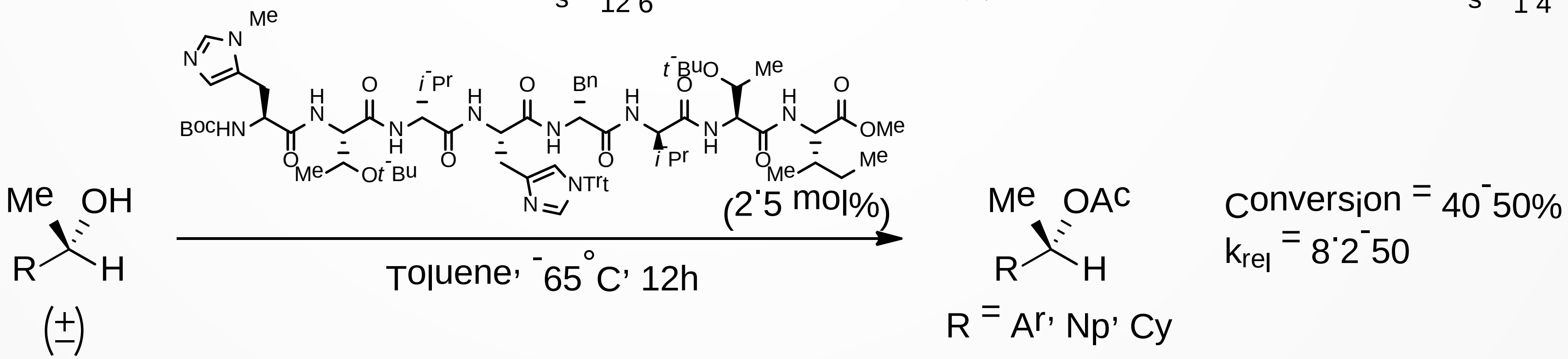
New purposes

Tertiary alcohols



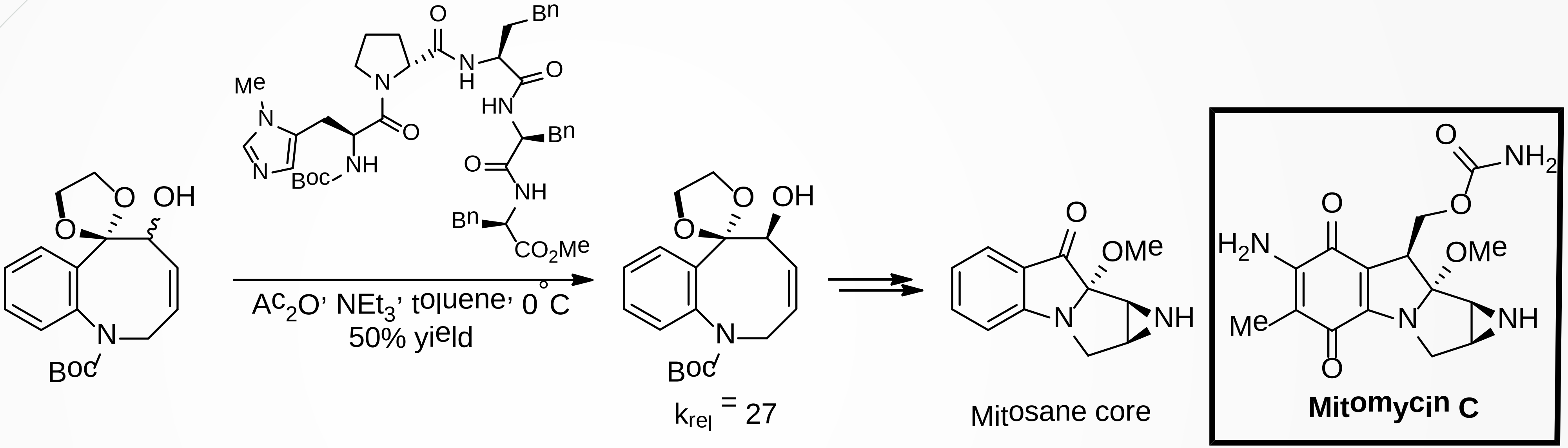
Absence of amide function





Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496. Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522. Fierman, M. B.; O'Leary, D. J.; Steinmetz, W. E.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6967.

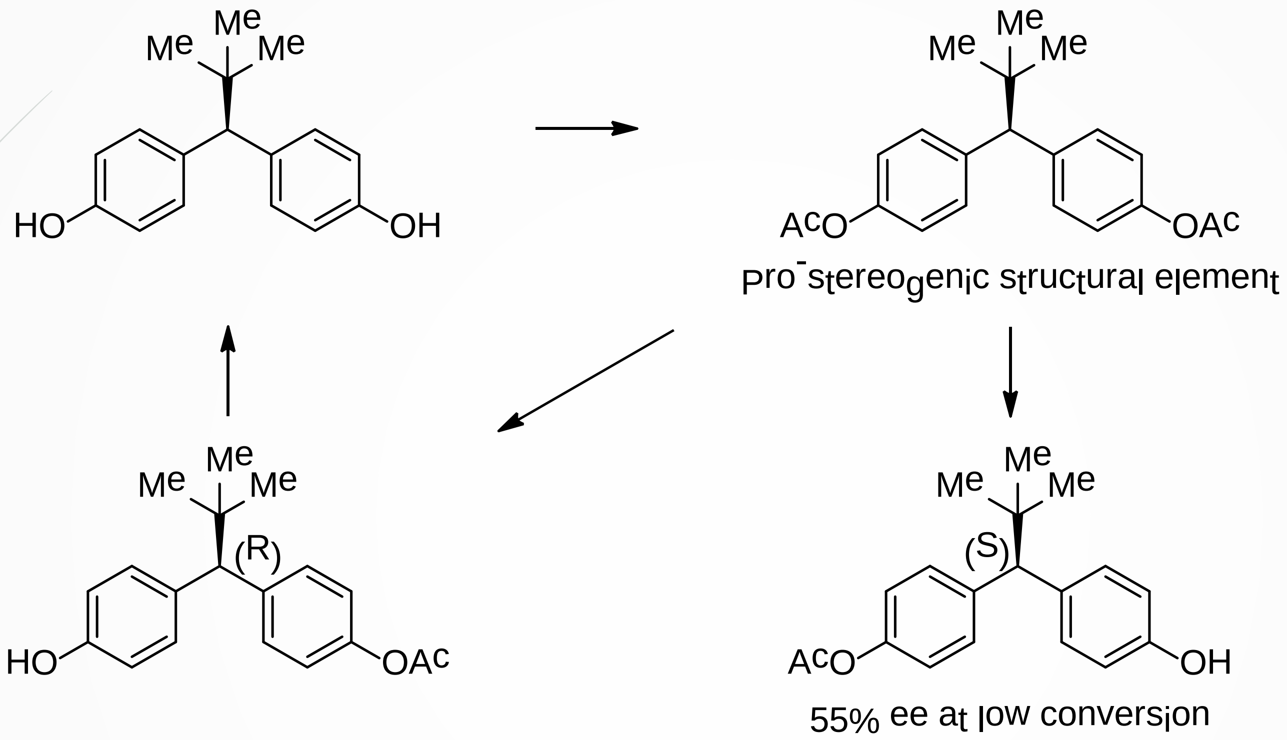
Total synthesis application



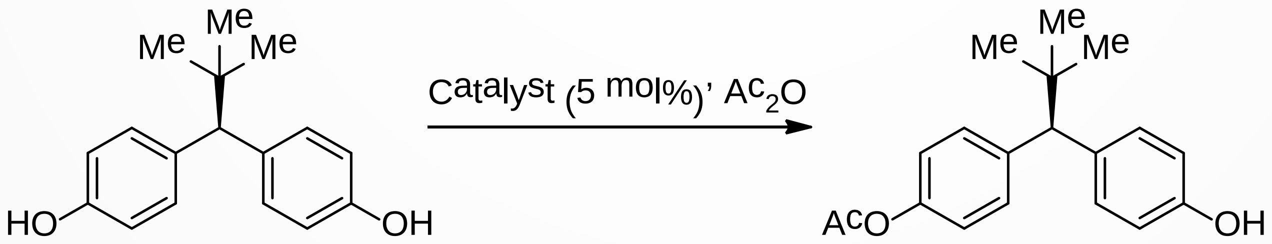
Antitumor agent

Papaioannou, N.; Evans, C. A.; Blank, J. T.; Miller, S. J. *Org. Lett.* **2001**, *3*, 2879. Papaioannou, N.; Blank, J. T.; Miller, S. J. *J. Org. Chem.* **2003**, *68*, 2728.

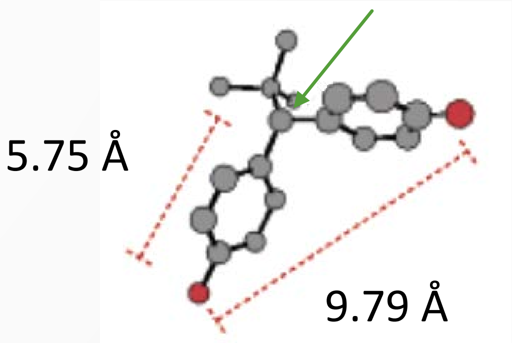
Remote desymmetrization at near-nanometer



Unsactifactory results

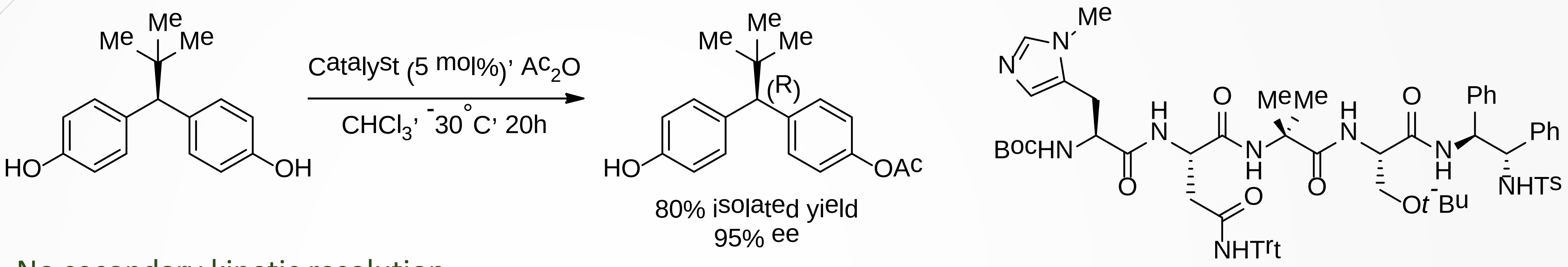


Prochiral stereogenic center

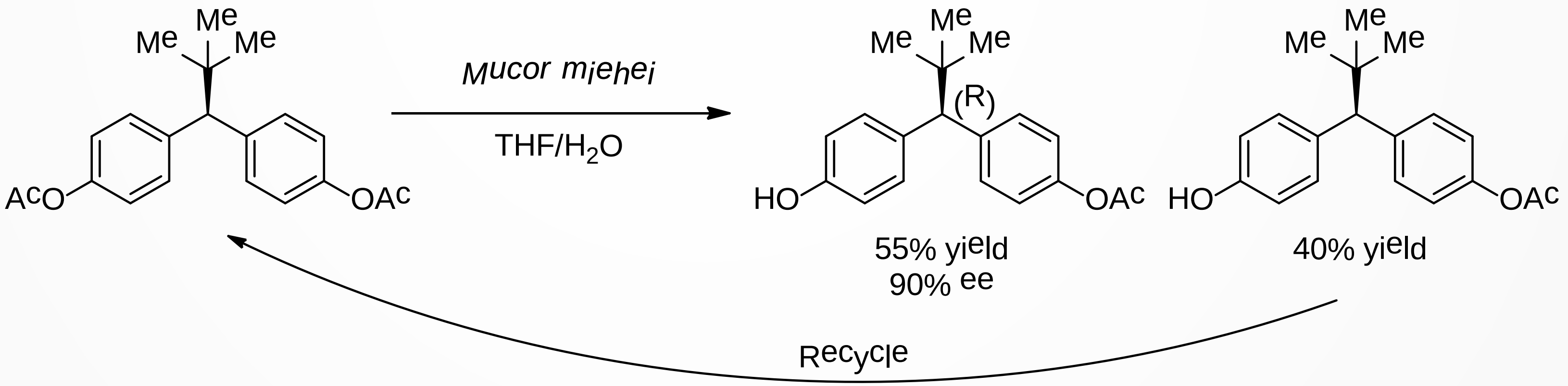


Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16454.
Lewis, C. A.; Gustafson, J. L.; Chiu, A.; Balsells, J.; Pollard, D.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 16358-16365.

The catalyst, better than the enzyme ?



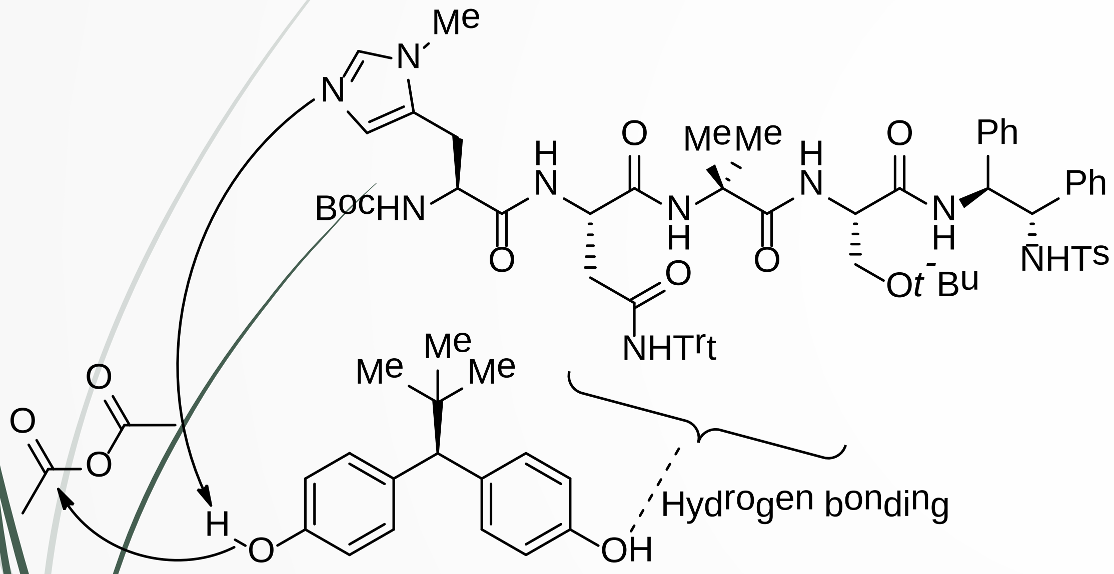
No secondary kinetic resolution



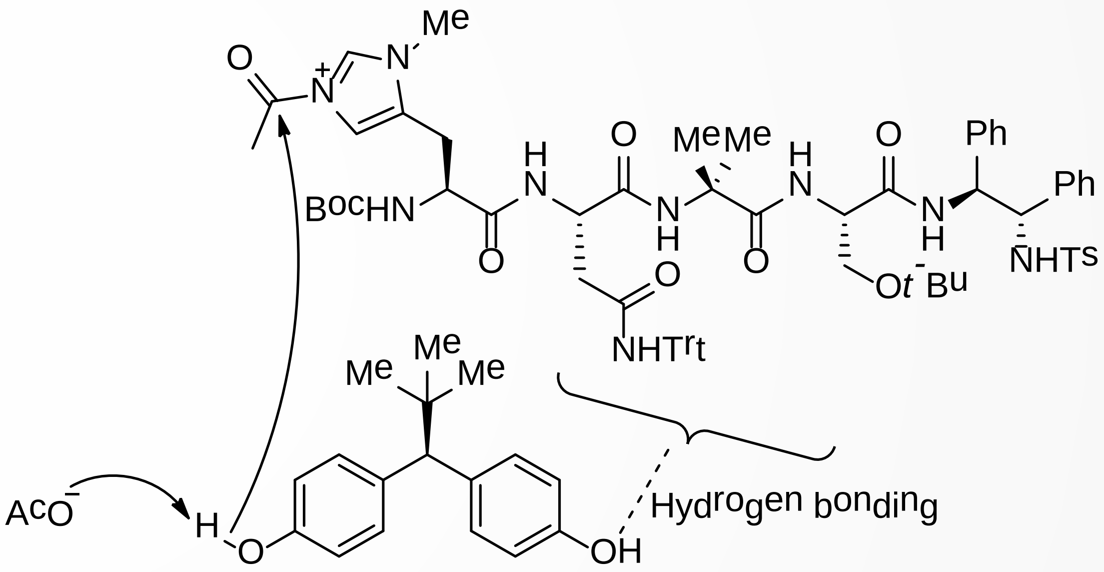
Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16454.
Lewis, C. A.; Gustafson, J. L.; Chiu, A.; Balsells, J.; Pollard, D.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 16358-16365.

Two plausible pathways

General base catalysis

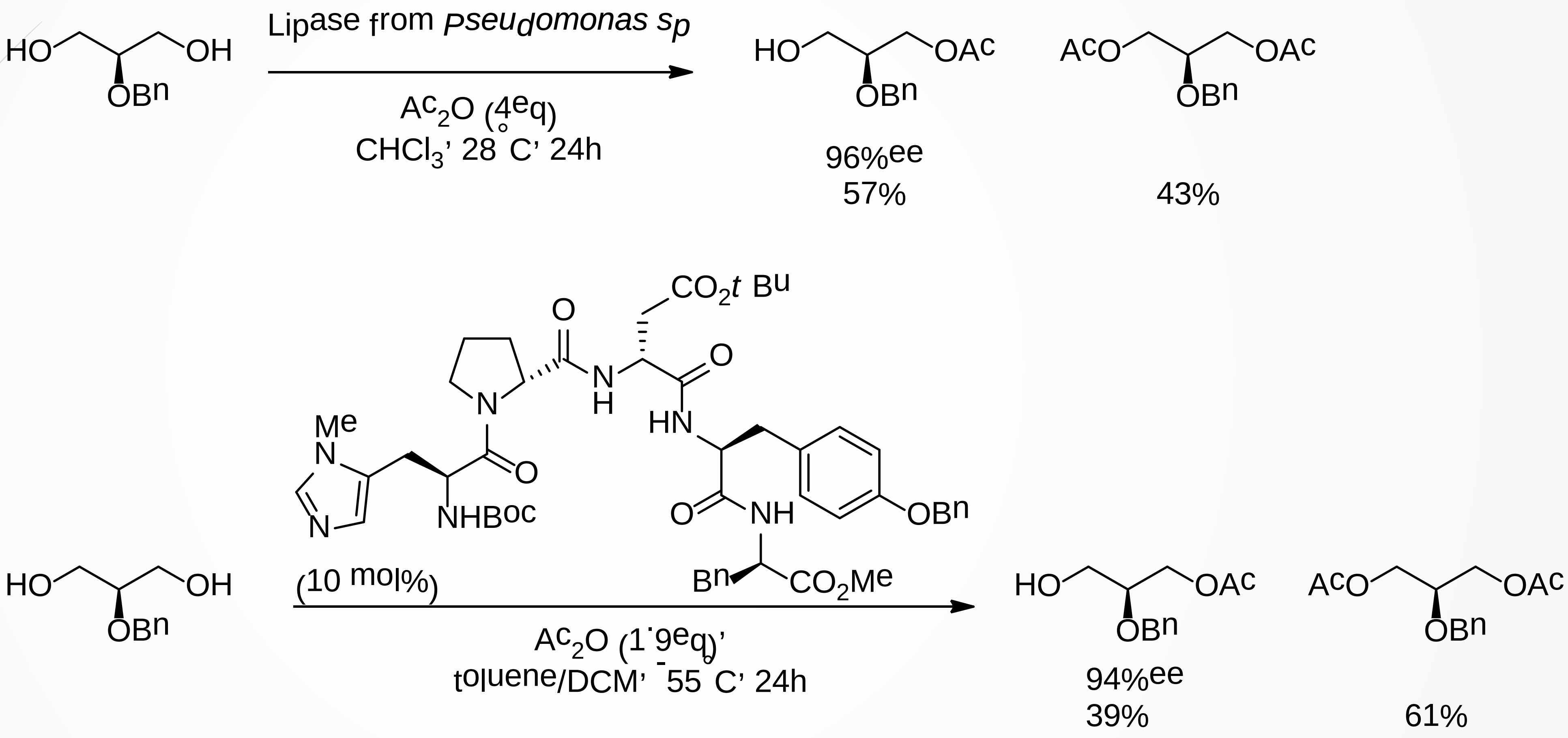


Nucleophilic catalysis



Lewis, C. A.; Gustafson, J. L.; Chiu, A.; Balsells, J.; Pollard, D.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 16358-16365.

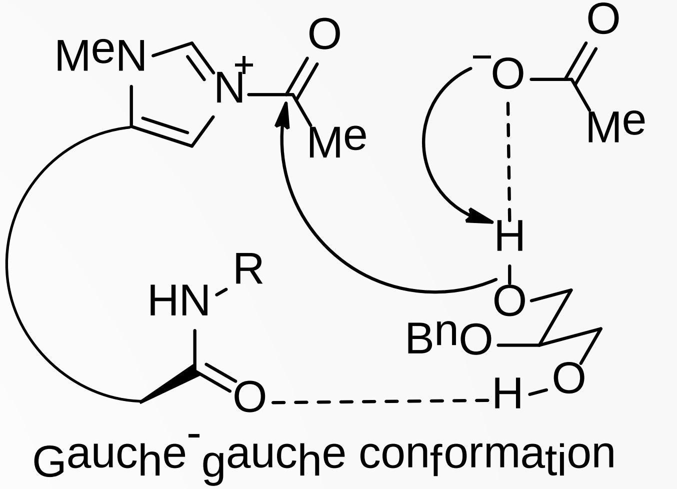
A competitive catalyst

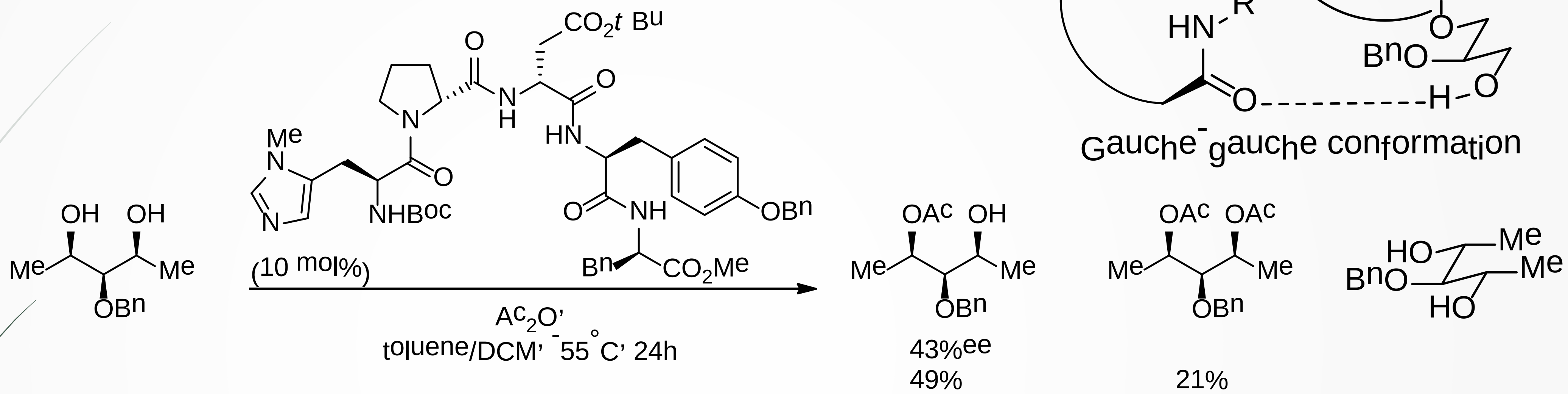


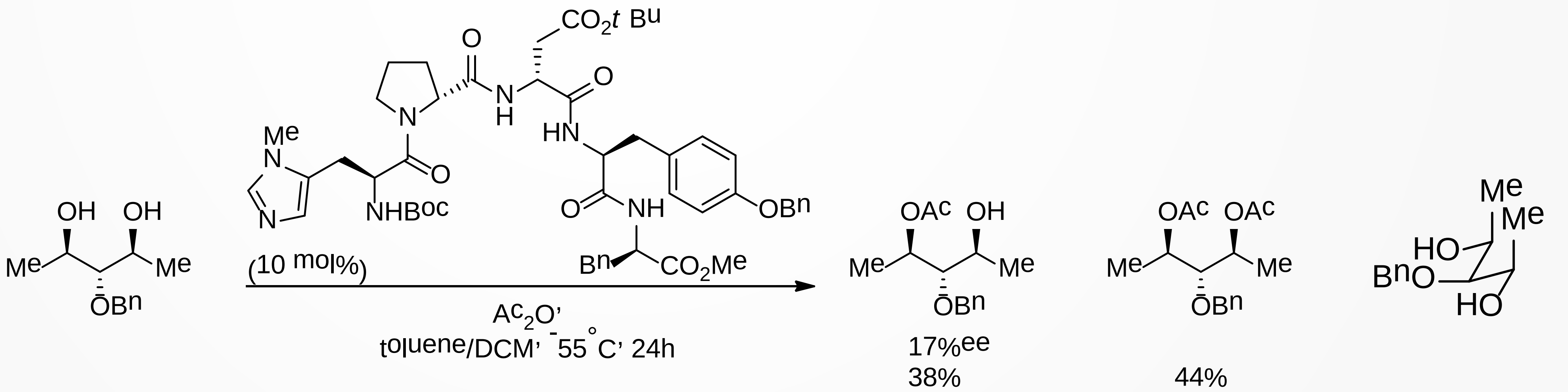
Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3021.

Reaction limitations

Secondary alcohols less reactive

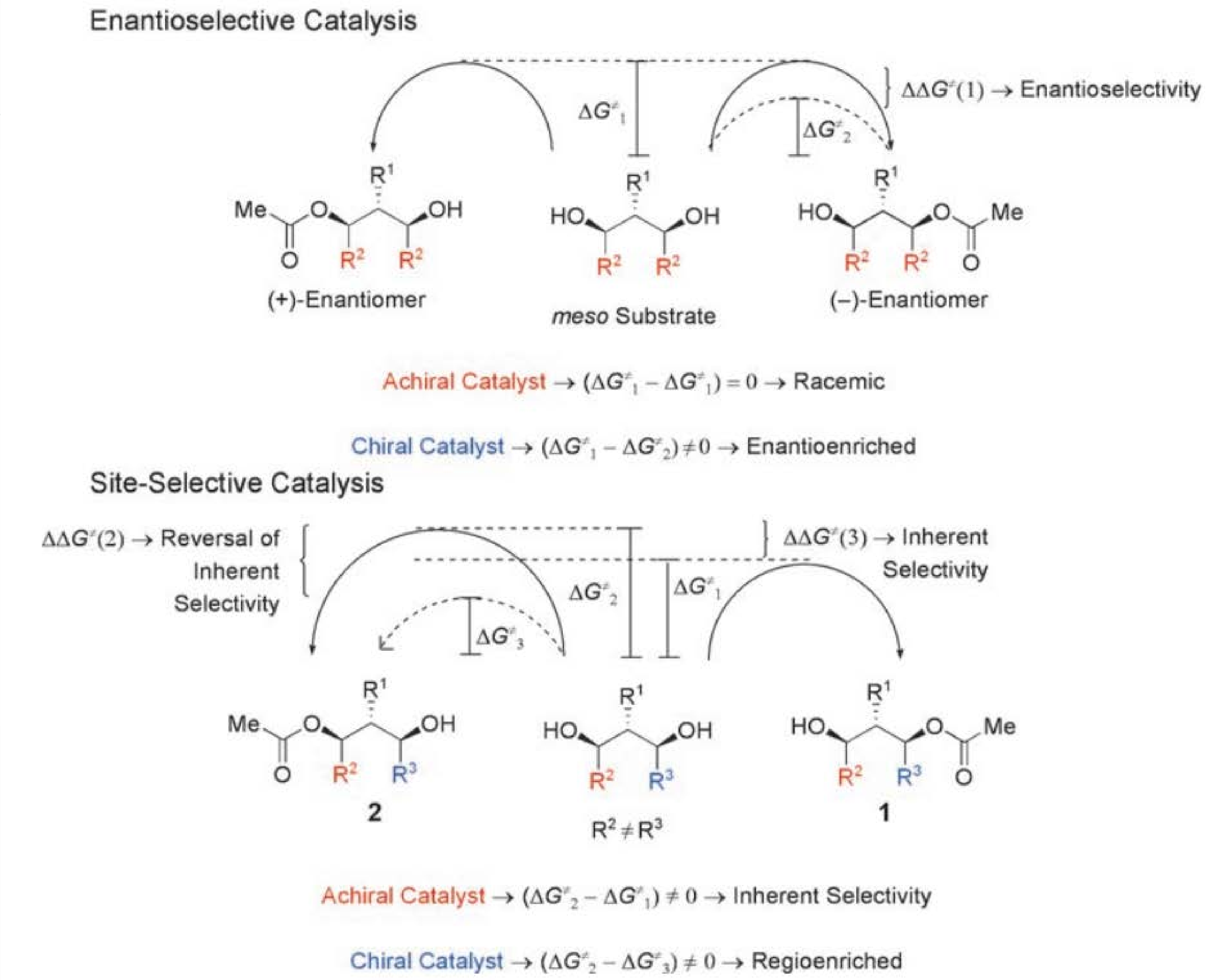






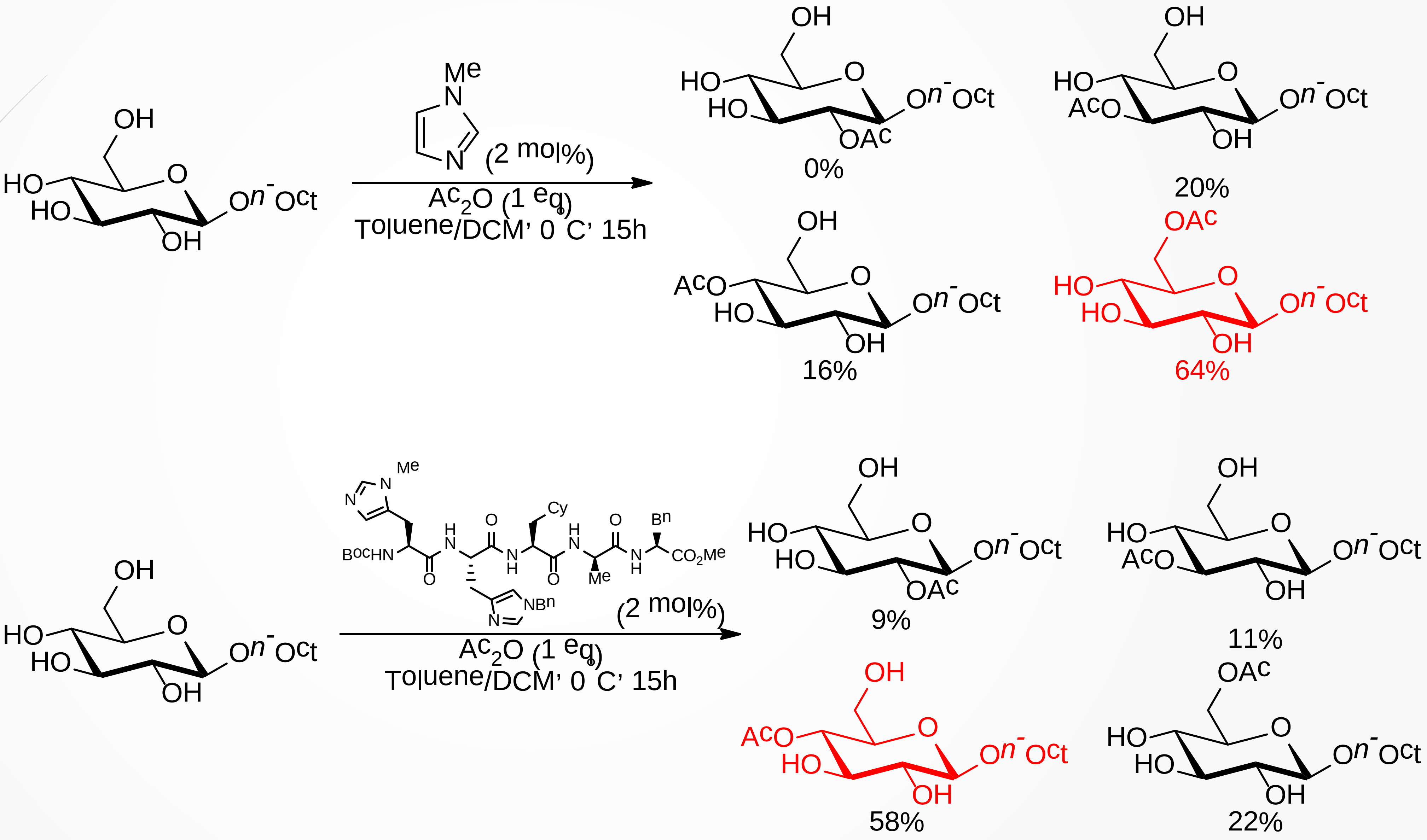
Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3021.

How to be site-selective ?



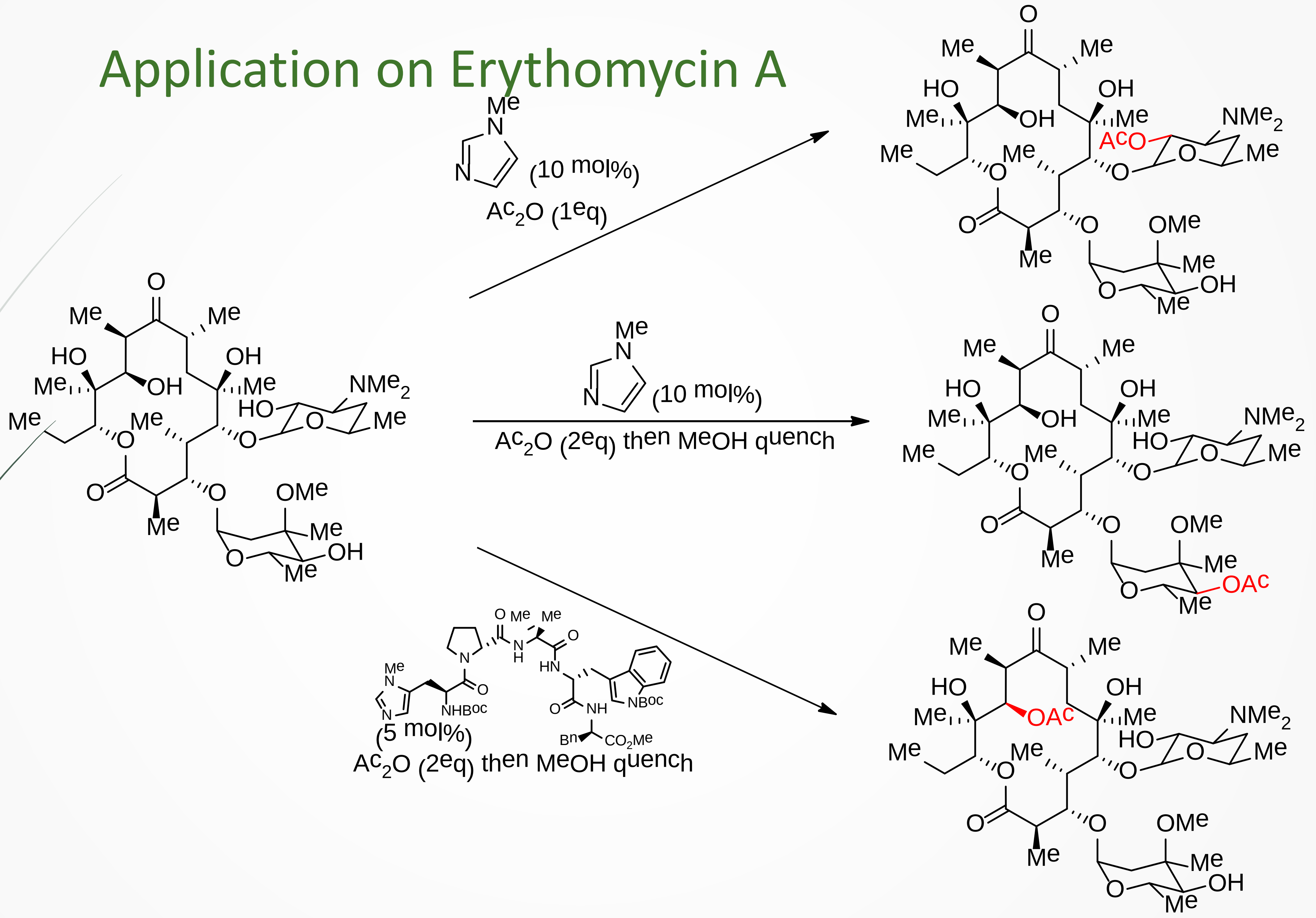
Lewis, C. A.; Miller, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 5616.

Regio-selective functionalization of carbohydrates



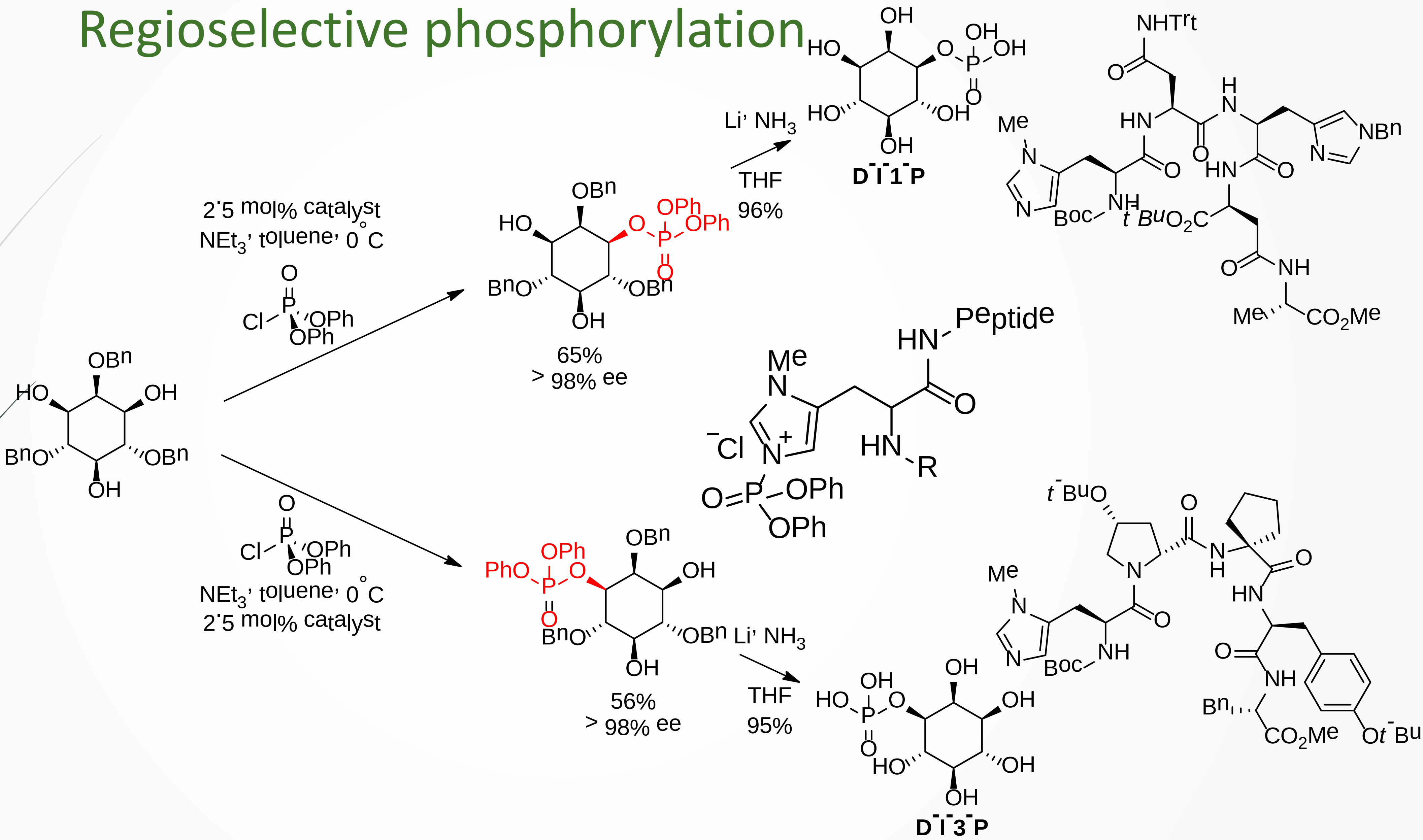
Griswold, K. S.; Miller, S. J. *Tetrahedron* **2003**, *59*, 8869.

Application on Erythomycin A



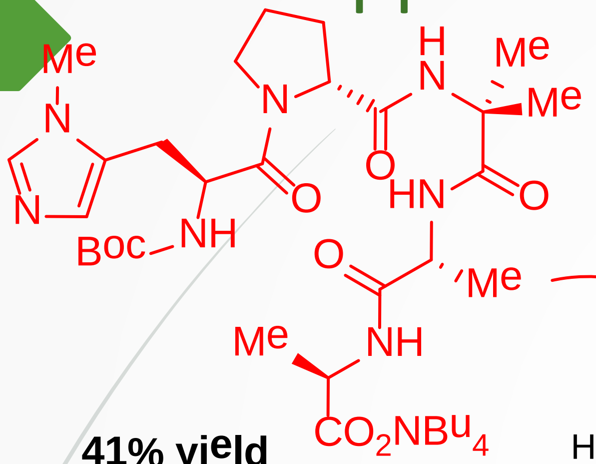
Lewis, C. A.; Miller, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 5616.

Regioselective phosphorylation

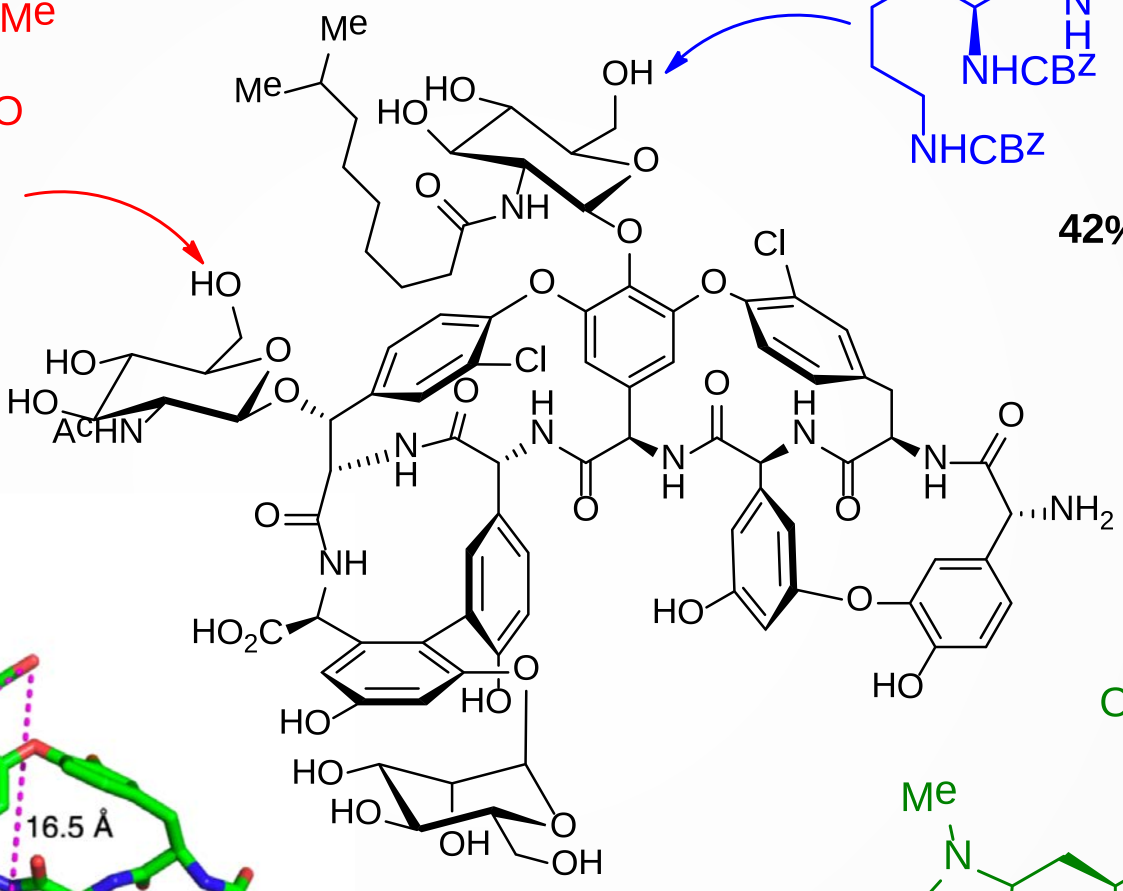


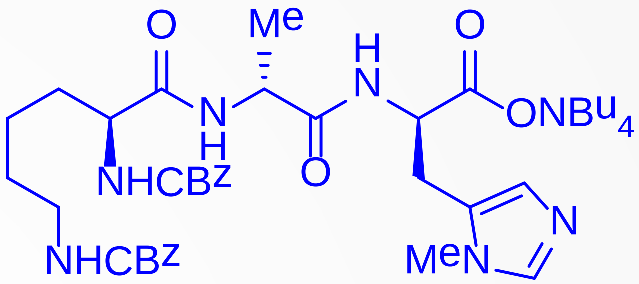
Sculimbrene, B. R.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10125. Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 11653. Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 13182.

Application on Teicoplanin A_2-2

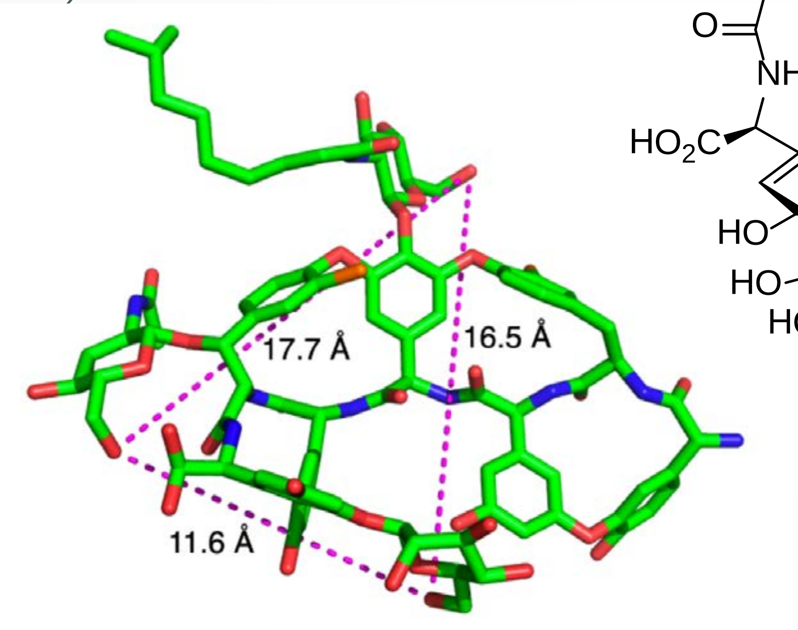


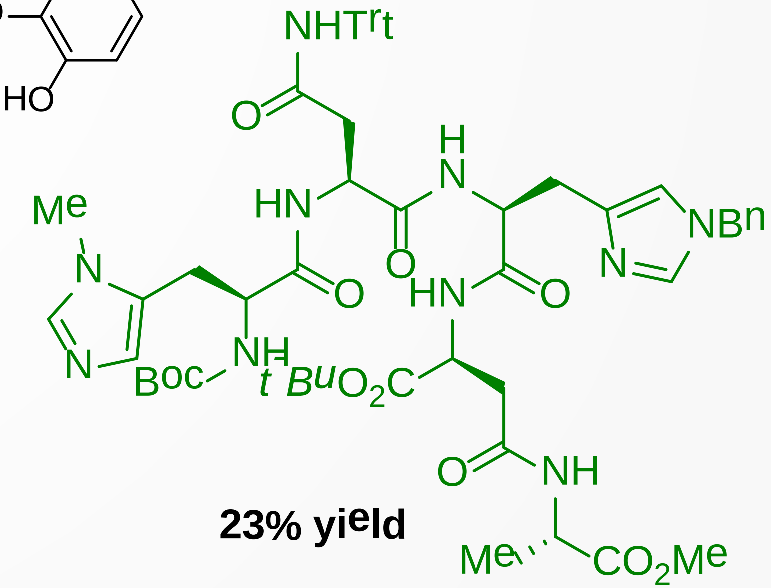
41% yield





42% yield

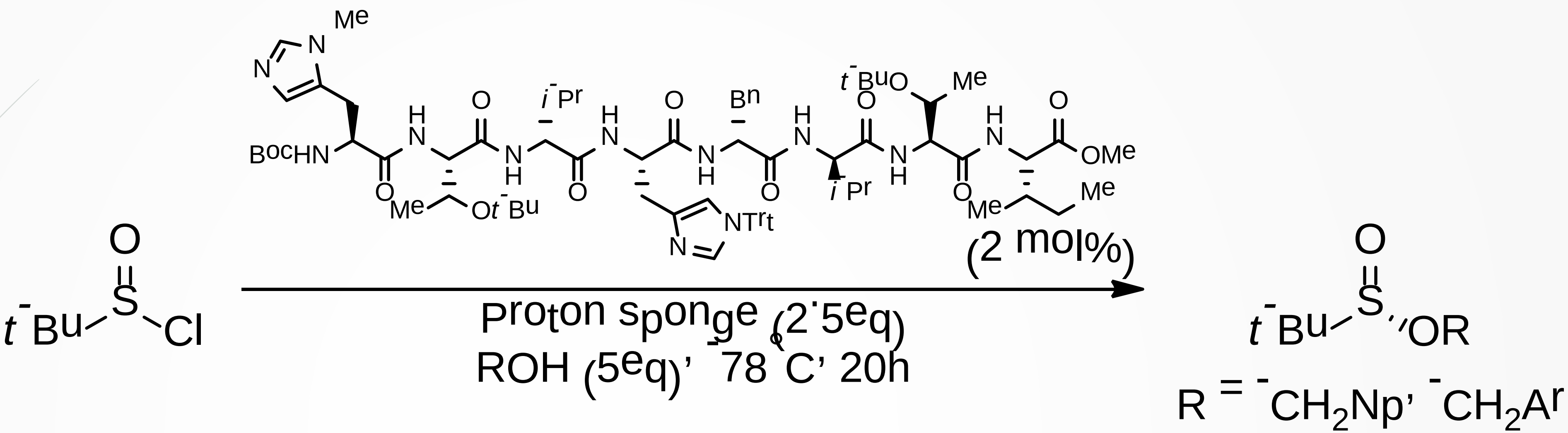




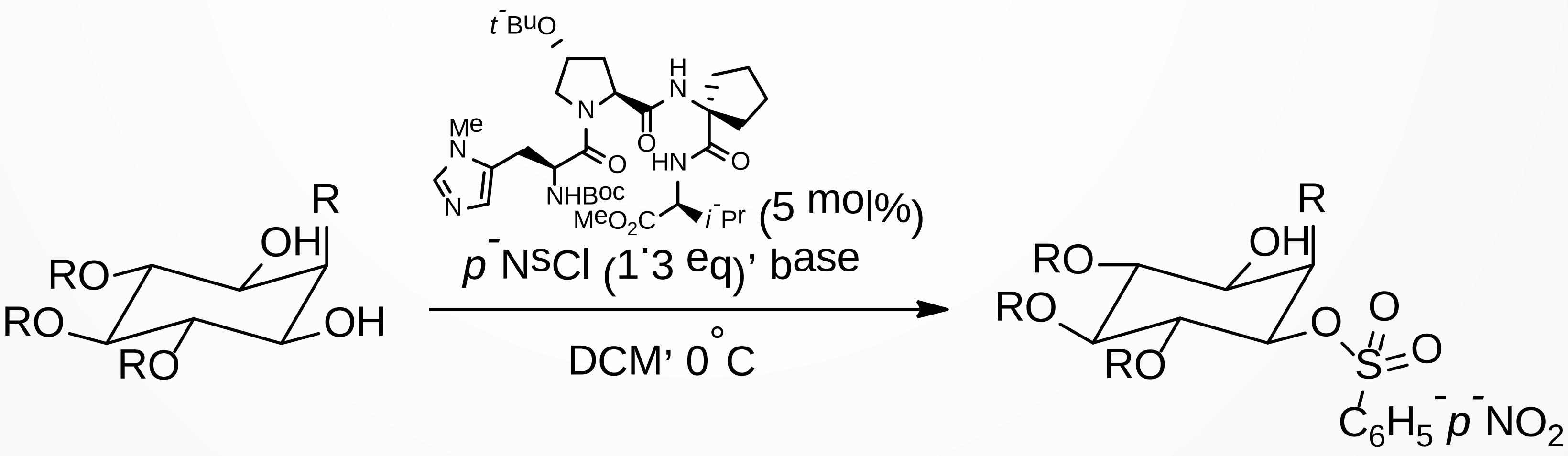
23% yield

Pathak, T. P.; Miller, S. J. *J. Am. Chem. Soc.* **2013**, *135*, 8415.

When a concept works…



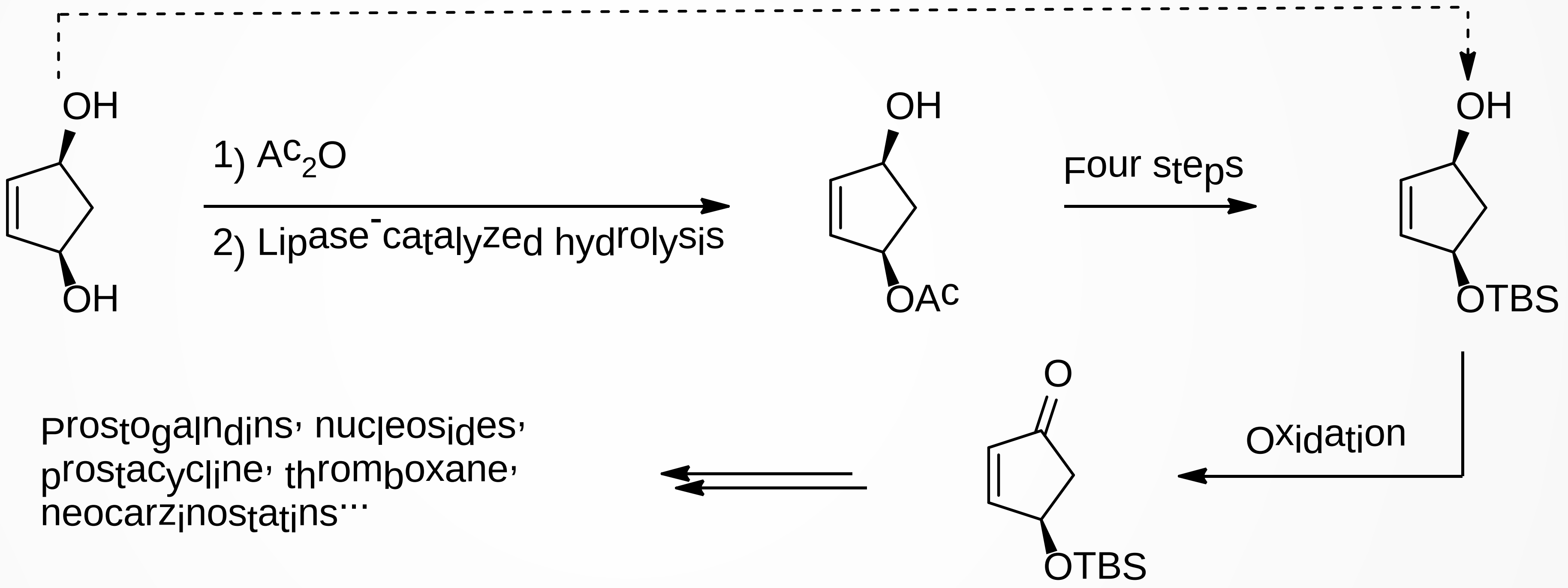
Dynamic Kinetic Resolution via epimerization



Yield = 57-76%
ee = 65-94%

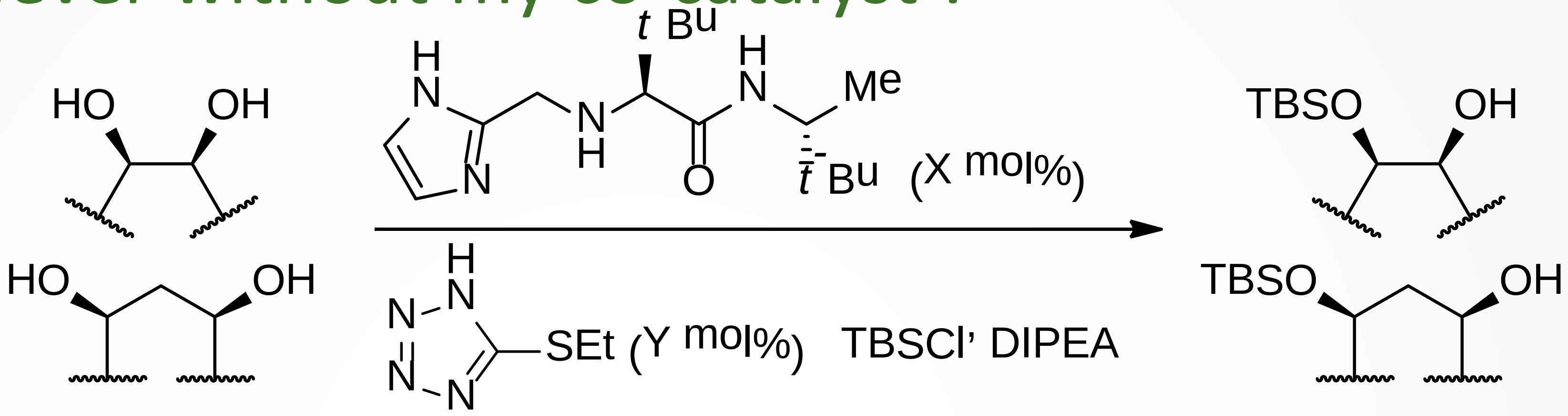
Evans, J. W.; Fierman, M. B.; Miller, S. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134.
Fiori, K. W.; Puchlopek, A. L. A.; Miller, S. J. *Nature Chem.* **2009**, *1*, 630.

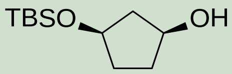
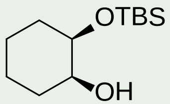
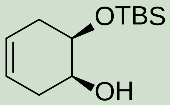
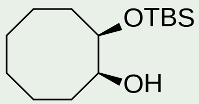
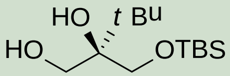
The three musketeers : C, P, S and… Si



Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nat. Lett.* **2006**, *7*, 443.

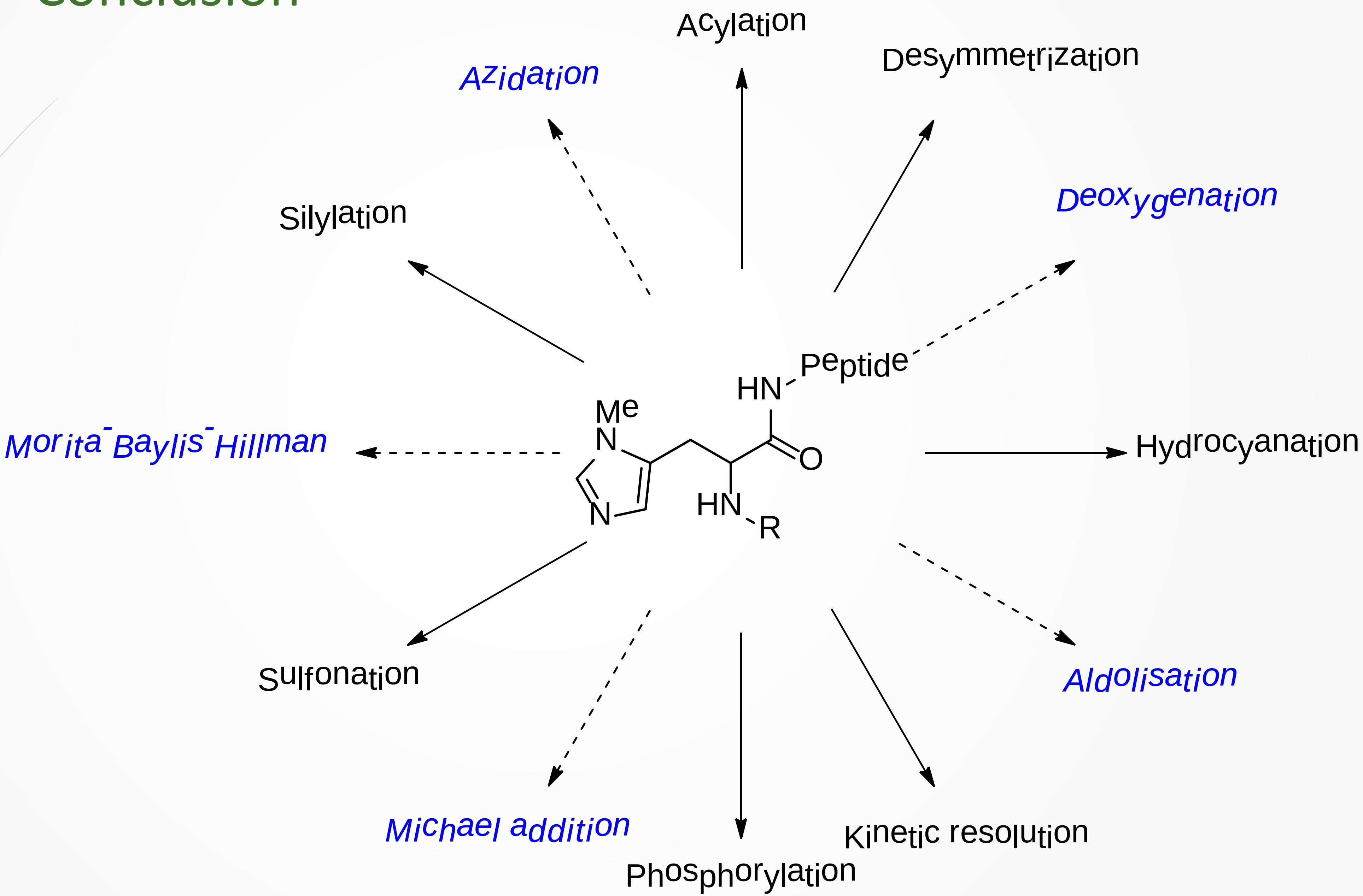
Never without my co-catalyst !



Product	X mol%	Y mol%	Time (h)	Temp. (°C)	Yield (%)	ee (%)
	30 20	None 7.5	48 1	-78 -78	82 78	96 88
	30 20	None 7.5	120 1	-40 -40	82 93	92 94
	30 20	None 7.5	72 1	-40 -40	75 82	94 95
	30 20	None 7.5	120 1	-40 -40	96 96	95 95
	30 20	None 7.5	24 12	-30 -40	<10 93	N.D. 90

Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nat. Lett.* **2006**, *7*, 443.
Mannville, N.; Alite, H.; Haeffner, F.; Hoveyda, A. H.; Snapper, M. L. *Nature Chem.* **2013**, *5*, 768.

Conclusion


Acylation
Azidation
Desymmetrization
Silylation
Deoxygenation
Peptide
HN
Me
N
O
N
HN
R
Morita-Baylis-Hillman
Hydrocyanation
Sulfonation
Aldolisation
Michael addition
Kinetic resolution
Phosphorylation

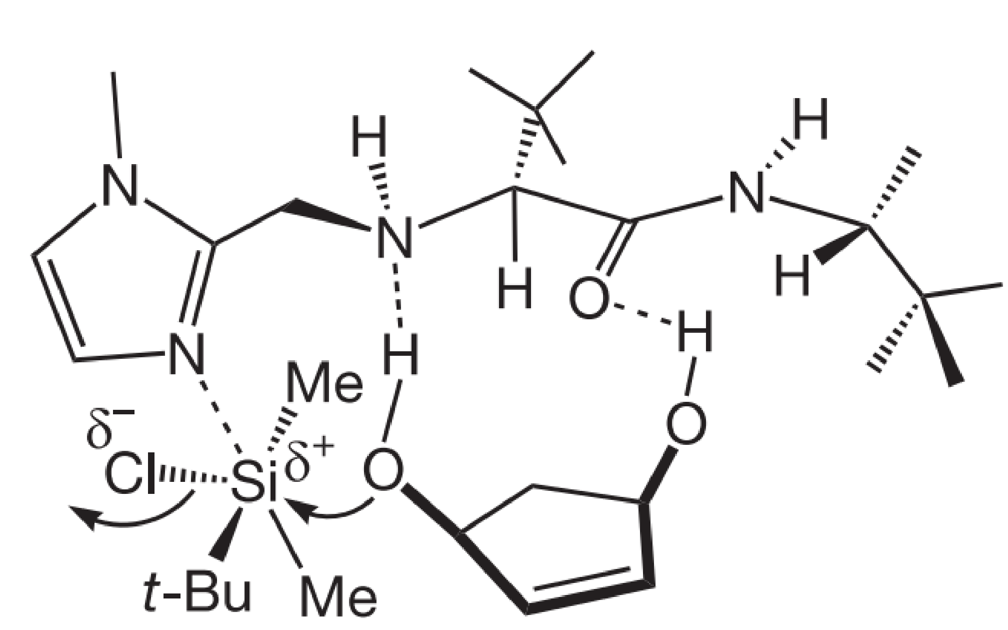
Question time

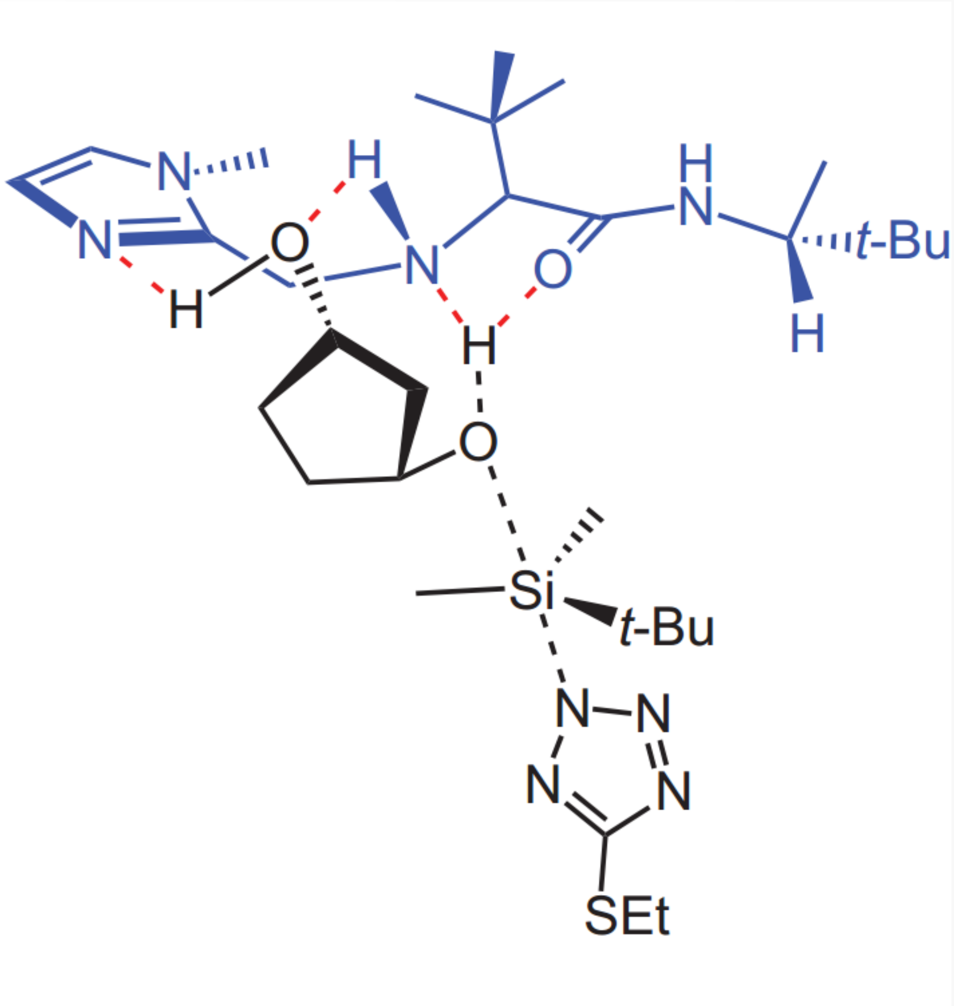
What are advantages of small peptide catalysts over enzymes ?

- Easier diversification (bigger libraries)
- Less substrate selective
- Allow straightforward strategy
- Faster reactions
- Can work better
- Better tolerance to organic solvent
- Histidine can play more than only basic role

Can you explain the role of the co-catalyst in silylation work ?

Rationalization of co-catalyst role





Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nat. Lett.* **2006**, *7*, 443.
Mannville, N.; Alite, H.; Haeffner, F.; Hoveyda, A. H.; Snapper, M. L. *Nature Chem.* **2013**, *5*, 768.