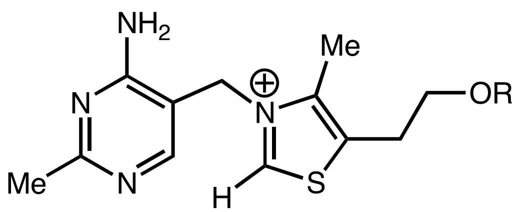
Organocatalysis with N-Heterocyclic Carbenes

Frontiers of Chemistry

Robert B. Lettan II
March 28th, 2009

Key References: Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606-5655.
Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988-3000.
Johnson, J. S. *Curr. Opinion Drug. Discov. Develop.* **2007**, *10*, 691-703.

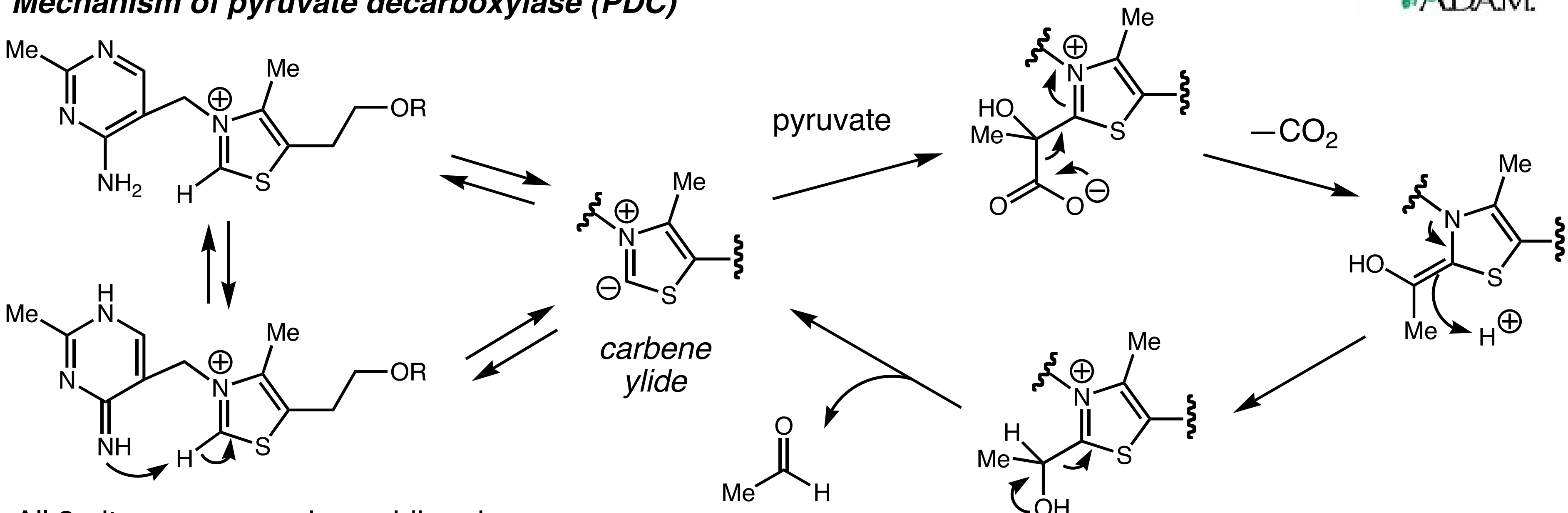
Thiamine-Dependent Enzymes



Thiamine: R = H
TPP: R = $P_2O_6^{3-}$

Thiamine diphosphate (TPP) is required by a number of enzymes that catalyze the cleavage and formation of bonds to the carbon atom of a carbonyl group.

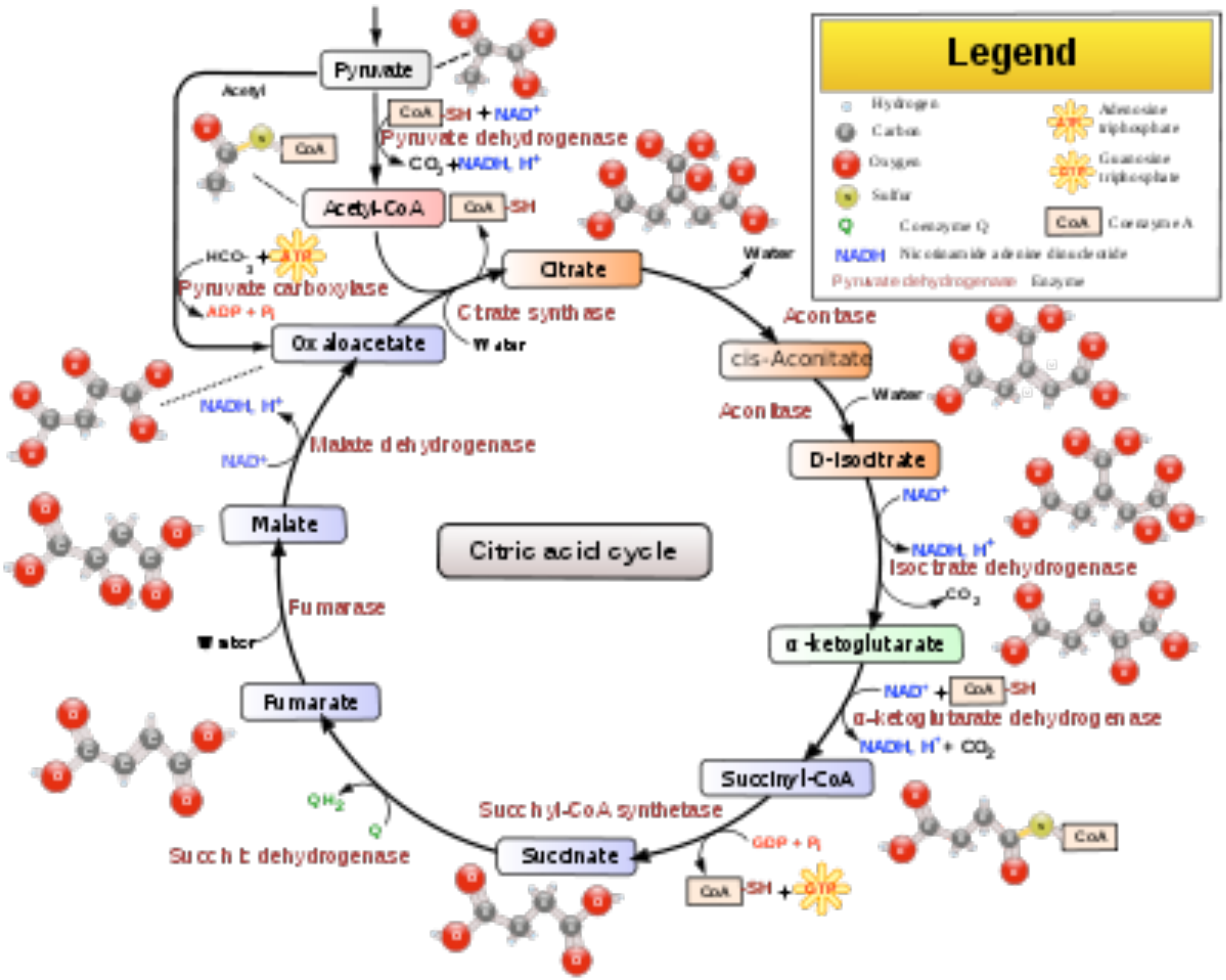
Mechanism of pyruvate decarboxylase (PDC)



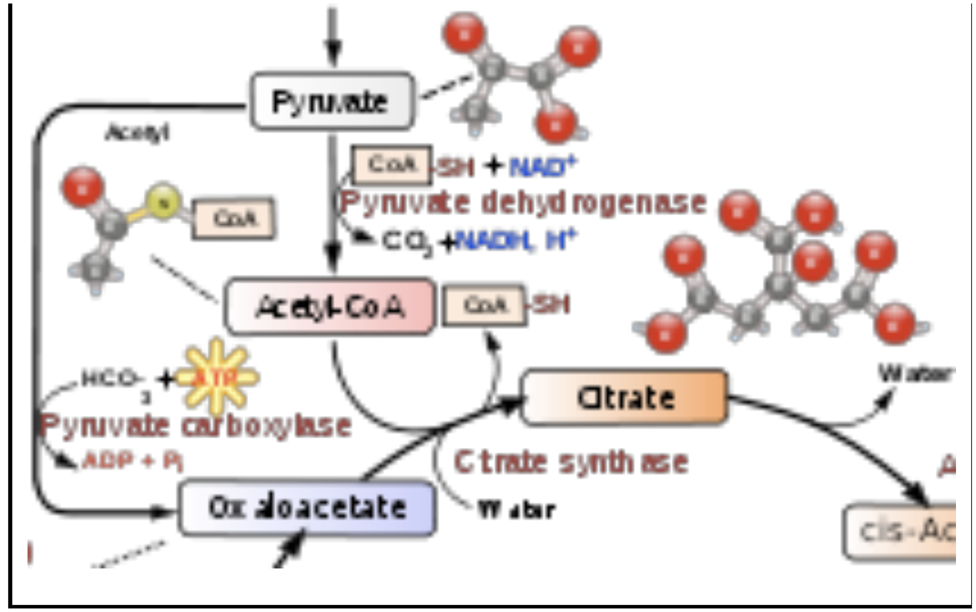
All 3 nitrogens on aminopyridine ring involved in hydrogen binding to enzyme.

Jordan, F. *Nat. Prod. Rep.* **2003**, *20*, 184-201.

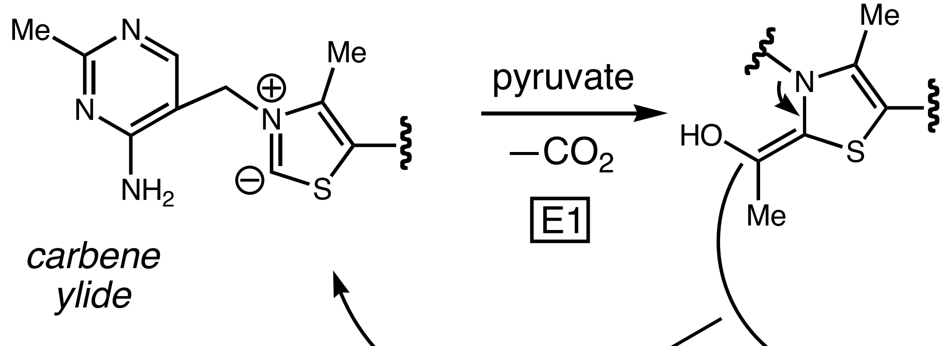
Thiamine-Dependent Enzymes

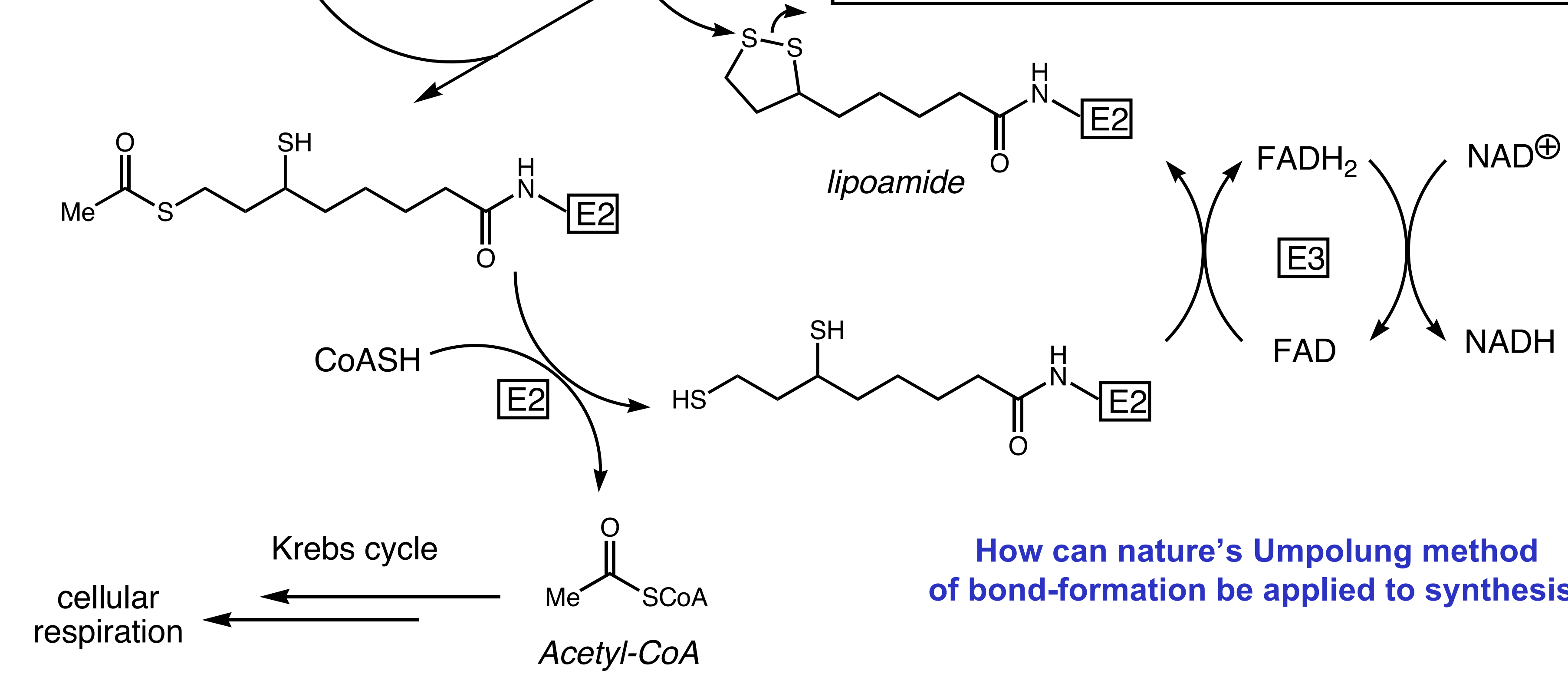


Thiamine-Dependent Enzymes



Mechanism of pyruvate dehydrogenase (E1)





How can nature's Umpolung method of bond-formation be applied to synthesis?

Leeper, F. J. et al. *Biochem. Soc. Trans.* **2005**, *33*, 772.

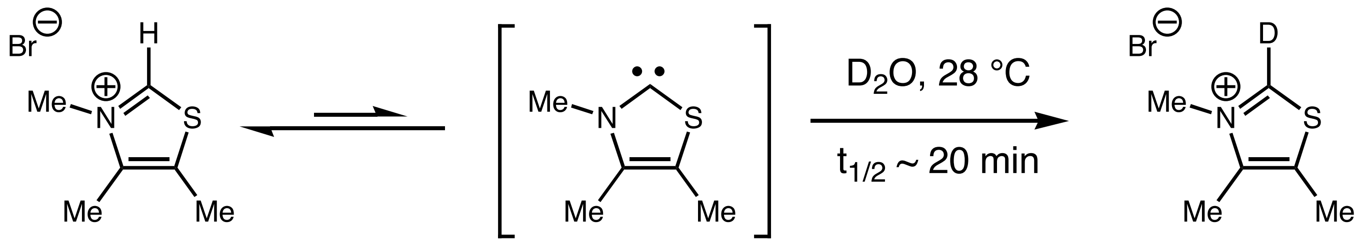
Persistent Carbene

A "stable" carbene that is a reactive intermediate.

***1943**: Ugai*

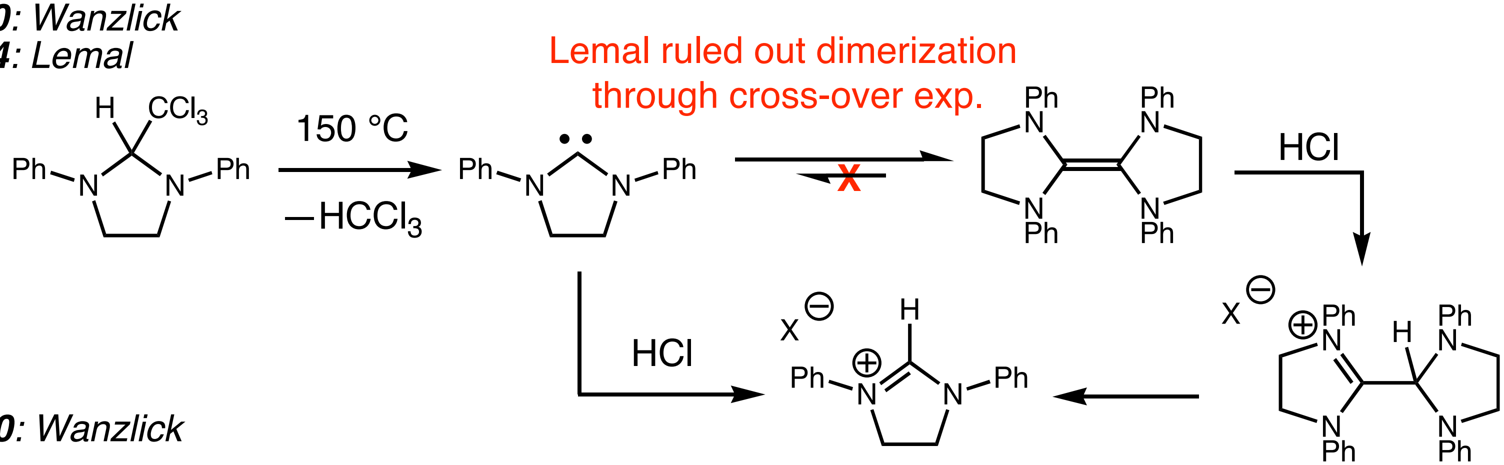
Recognized that thiamine can be used as a catalyst for the benzoin condensation.

***1957**: Breslow*

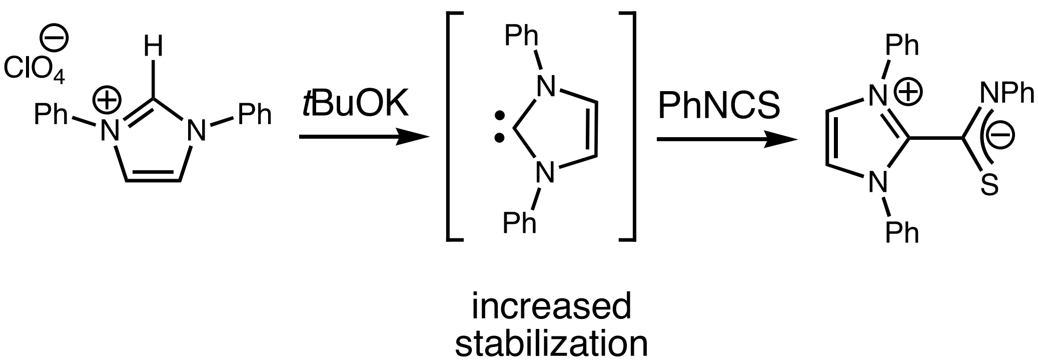


***1960**: Wanzlick*

***1964**: Lemal*



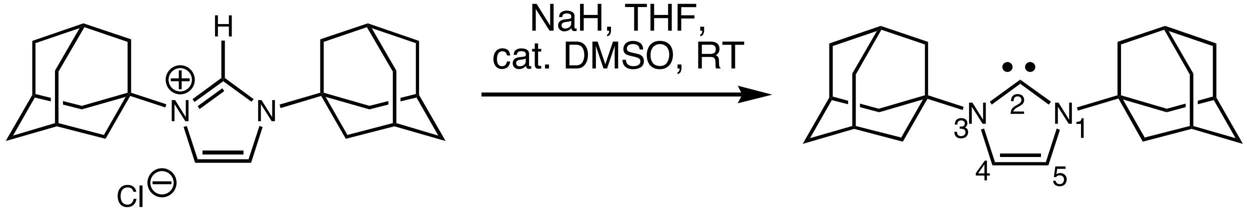
***1970**: Wanzlick*



Ugai, T. et al. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296.
Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 1762.
Wanzlick, H. W. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 75.
Lemal, D. M. et al. *J. Am. Chem. Soc.* **1964**, *86*, 2518.
Wanzlick, H. W. et al. *Liebigs Ann. Chem.* **1970**, *731*, 176.

Isolated Carbenes

***1991**: Arduengo*



isolated crystal structure

Bond angles: N_1-C_2-N_3 = 102.2 ° (imid = 109 °).

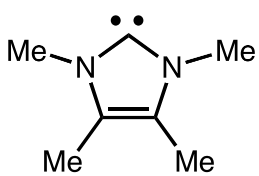
In agreement with theoretical studies on singlet (^{1}A') carbenes bearing π–donor substituents.

Change in π-delocalization supported by upfield shift of imidazole ring protons (7.92 → 6.91).

^{13}C NMR of C_2: δ = 211 ppm

No dimerization.

Some other isolated *N*-heterocyclic carbenes by Arduengo



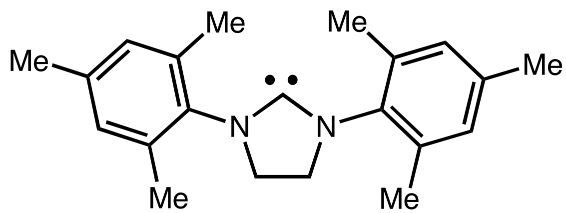
1992

δ_C = 214 ppm

N-C-N angle = 102 °

Less hindered tetramethyl-imidazol-2-ylidene

No dimerization suggests this is due to electronic stabilization.

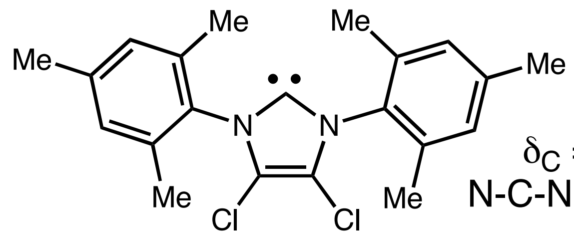


1995

δ_C = 245 ppm

N-C-N angle = 105 °

cyclic diamino carbene dimesityl

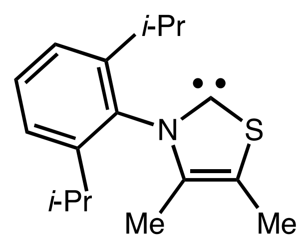


1997

δ_C = 220 ppm

N-C-N angle = 102 °

Air Stable



1997

δ_C = 254 ppm

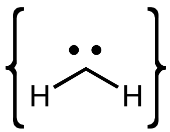
N-C-N angle = 104 °

thiazolium carbene also stable

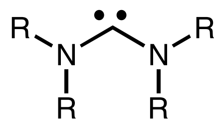
Arduengo, A. J., et al. *J. Am. Chem. Soc.* **1991**, *113*, 361.

Carbene Stability

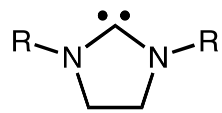
Carbene Stability ≈ Singlet Character ≈ Electron Donation into Vacant p-Orbital of Carbene



ca. –87 kcal/mol

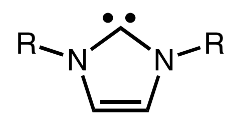


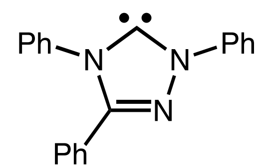
ca. –6 kcal/mol



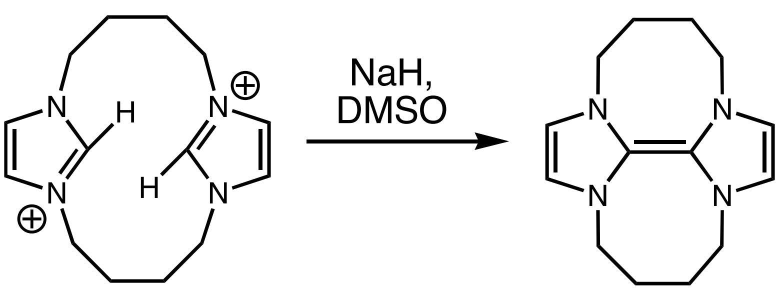
ca. –20 kcal/mol

Electron donating groups promote more stable singlet carbene





Further stabilized by aromatization. Does not dimerize.

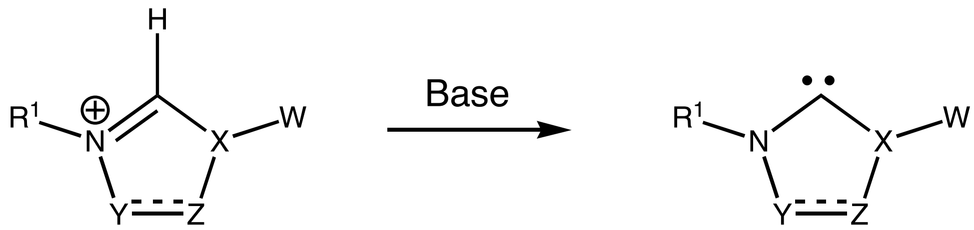


Electron lone pairs in close proximity. Repulsive electrostatic interactions would have a significant destabilzing effect.

Herrmann, W. A.; Kocher, C. *Angew. Chem. Ind. Ed., Engl.* **1997**, *36*, 2162.

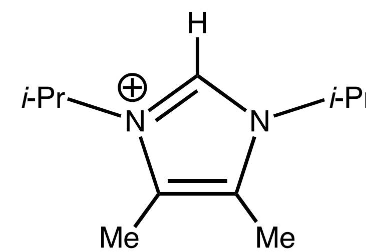
Preparation of Stable Carbenes

Deprotonation



	W	X	Y	Z
a	R^2	N	CR^3	CR^4
b	—	S	CR^2	CR^4
c	R^2	N	N	CR^3
d	R^2	N	CH_2	CH_2
e	R^2	N	CH_2	C_2H_4

pKa = 24 (DMSO)



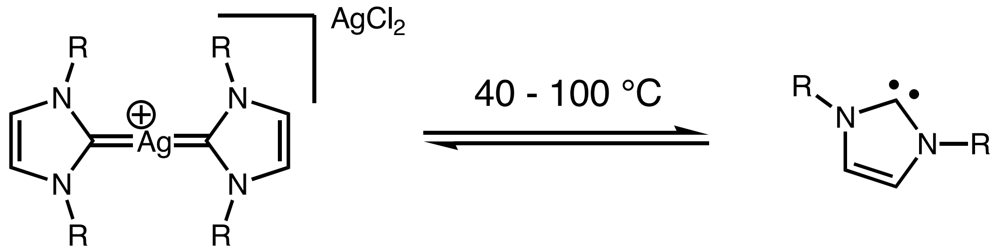
NHC formation caveats:
— strongly basic
— react with oxygen
— their imidazole precursor's are susceptible to nucleophilic attack
— sometimes difficult to isolate free carbene from metal ions used to prepare

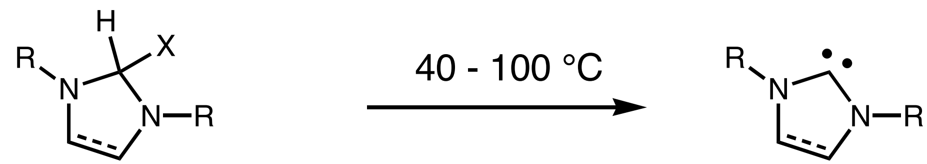
Bases:
Metal hydrides: Work, but often sluggish due to relative insolubilitiy in suitable solvents (THF)
Catalysts (DMSO, *t*-BuOH) improve solubility and reactivity, but ineffective for non-imidazolium adducts due to nucleophilicity.
Must avoid hydroxide, especially with non-aromatic salts.
KO*t*-Bu: Has been shown to be effective.
Alkyllithiums: Unreliable. *n*-BuLi and PhLi can act as nucelophiles, *t*-BuLi can act as a hydride donor.
Lithium Amides: LDA and LiTMP work well, if not too much LiOH in *n*-BuLi during preparation.
Metal hexamethyldisilazides: Works very well for the most part.

Alder, R. W., et al. *J. Chem. Soc., Chem. Commun.*, **1995**, 1267.

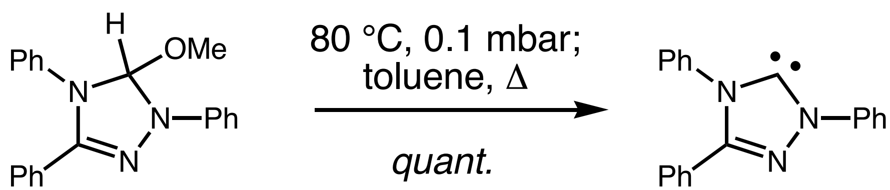
Preparation of Stable Carbenes

Some Other Methods

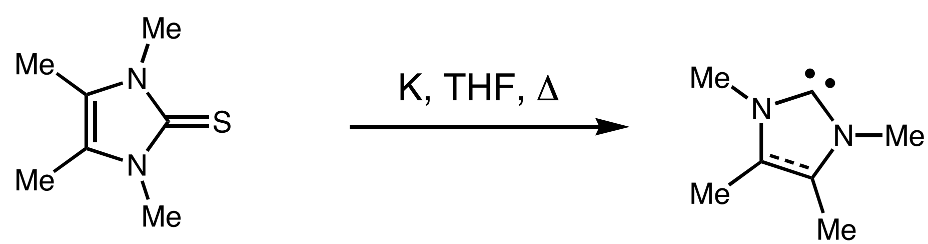




X = C_6F_5, CF_3, CCl_3

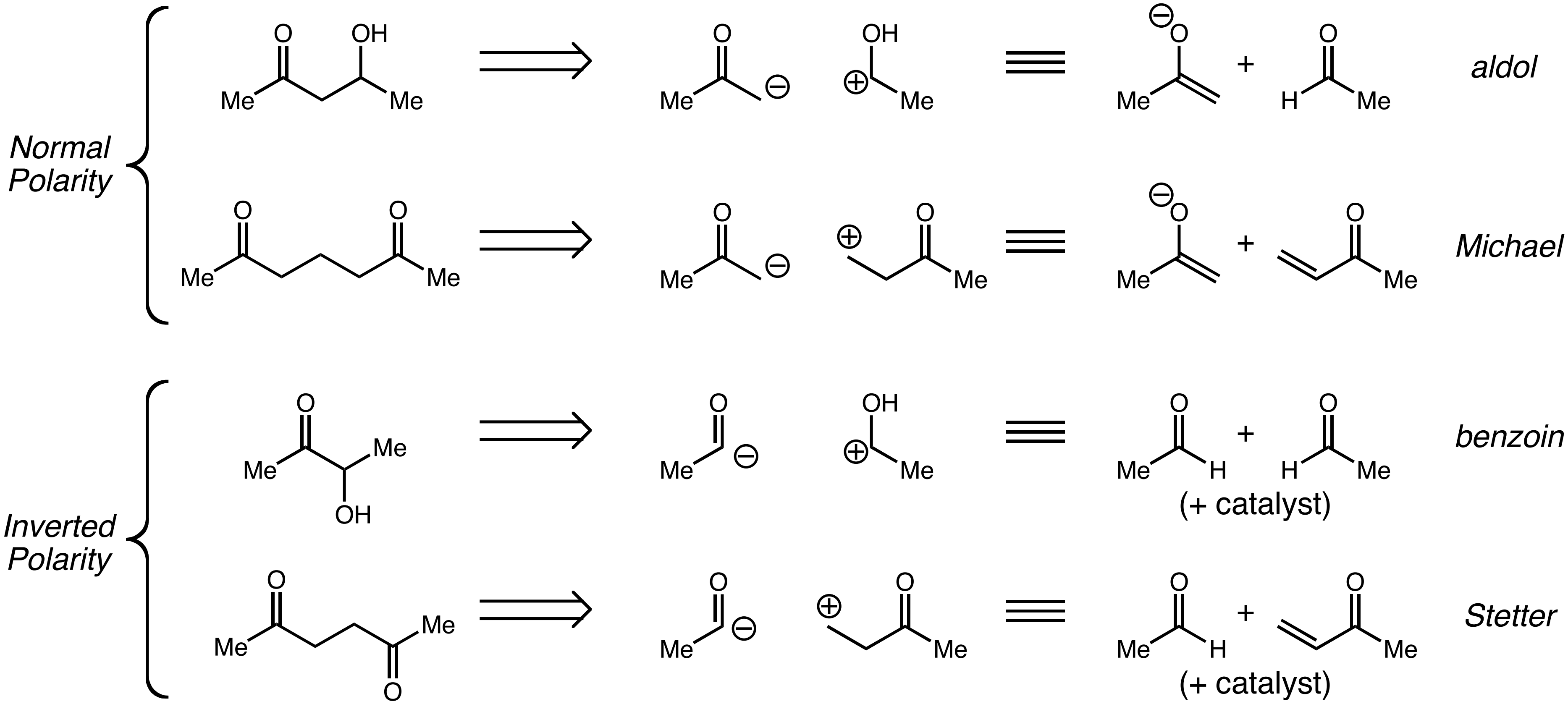


X = N, CH_2; R' = alkyl



Nolan, S. P. *N-Heterocyclic Carbenes in Synthesis*, Wiley -VCH & Co., **2006**.

NHC/Umpolung Reactivity



NHC Catalyzed Umpolung Reactions

benzoin condensation
Stetter reaction
hydroacylations
acylation of aryl flourides
nucleophilic substitution
homoenolate reactivity
 - cross condensations
 - Diels-Alder reaction
 - Heck-type cyclizations

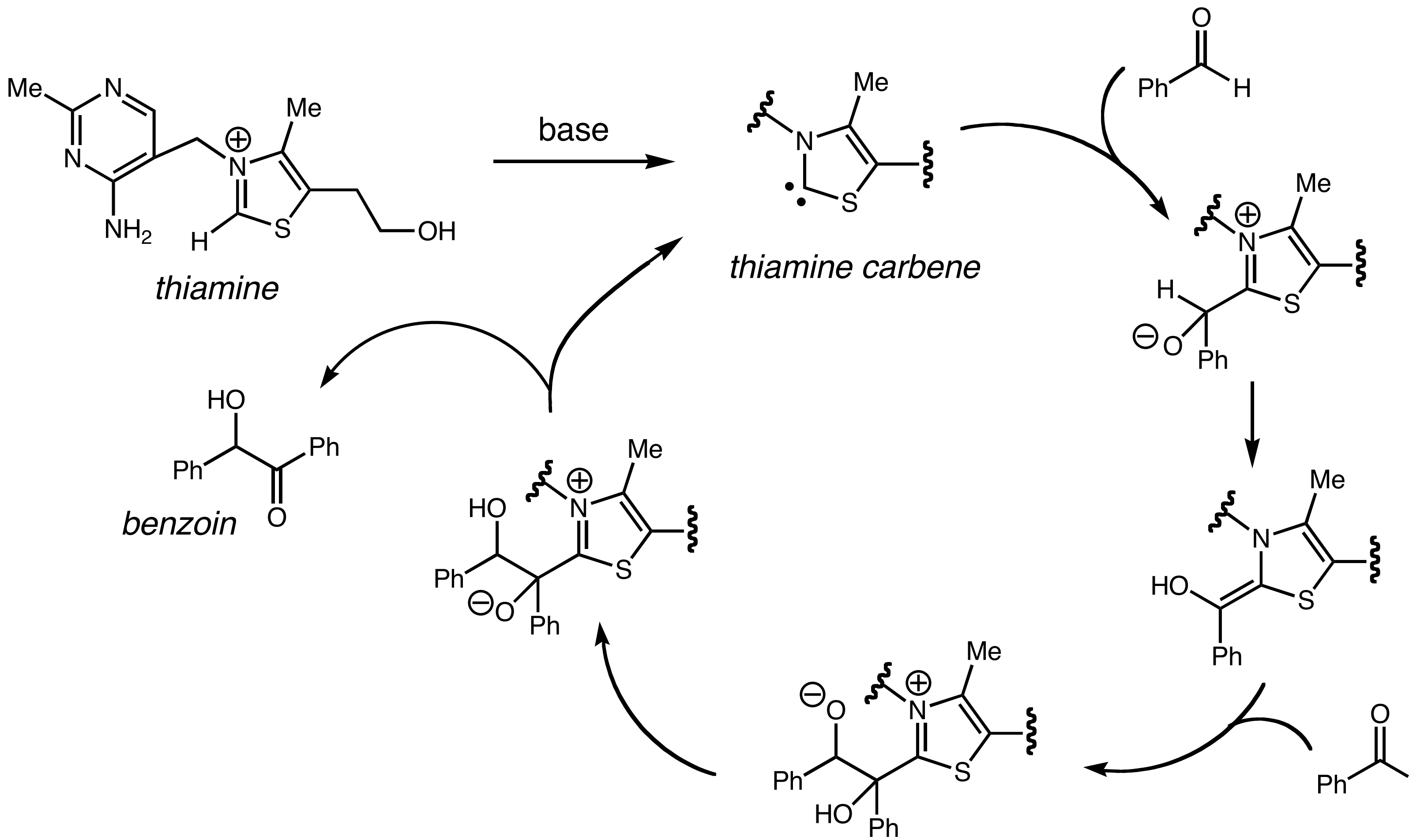
Additional NHC Catalyzed Reactions

transesterification
 - oxidation
 - polymerization
ring-opening reactions
1,2-additions

Seebach, D. *Angew. Chem. Int. Ed., Engl.* **1979**, *18*, 239.
Johnson, J. S. *Curr. Opin. Drug Disc. Dev.* **2007**, *10*, 691.

Benzoin Condensation

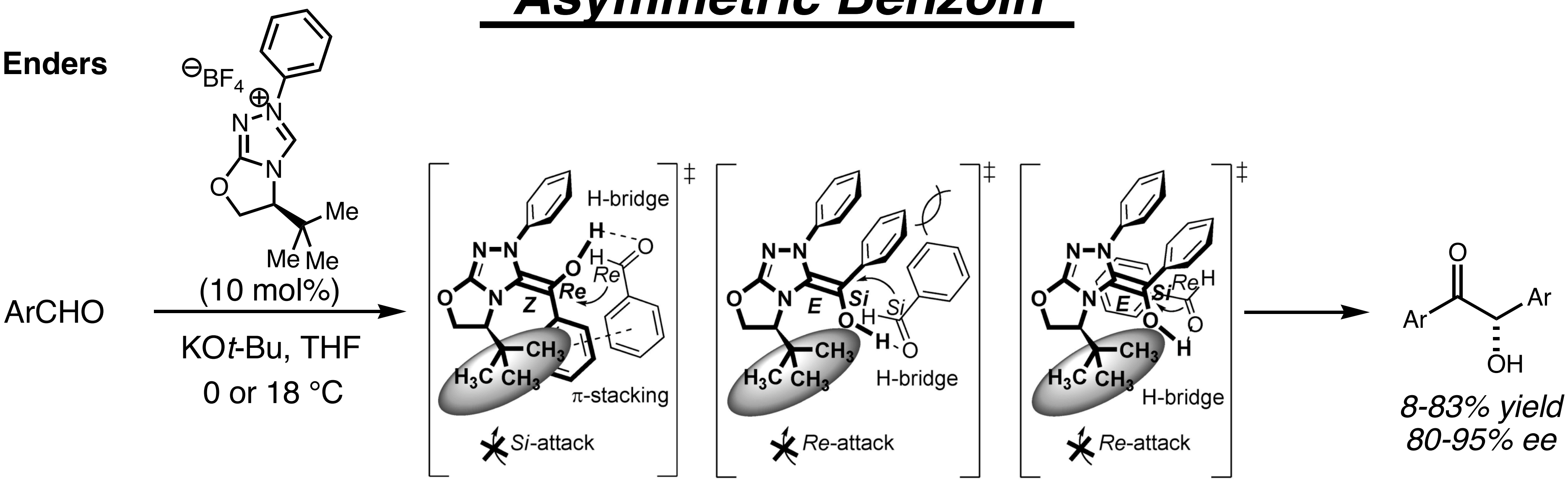
Breslow Mechanism



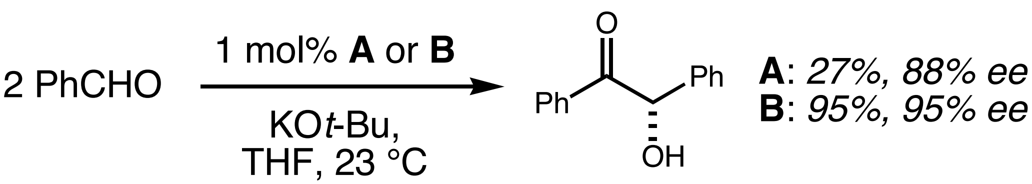
Ugai, T. et al. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296.
Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 1762.

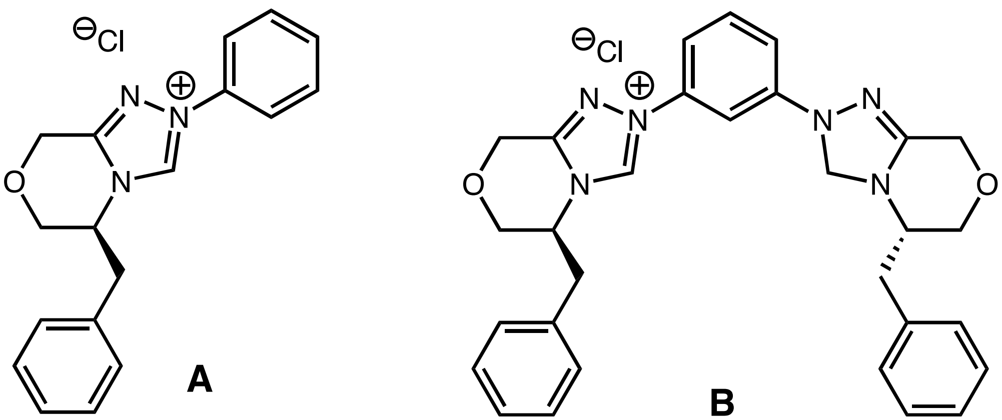
Asymmetric Benzoin

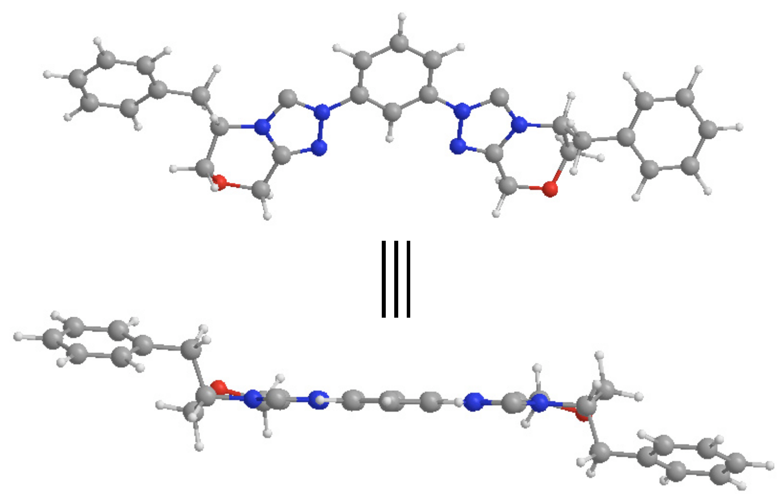
Enders



J. You





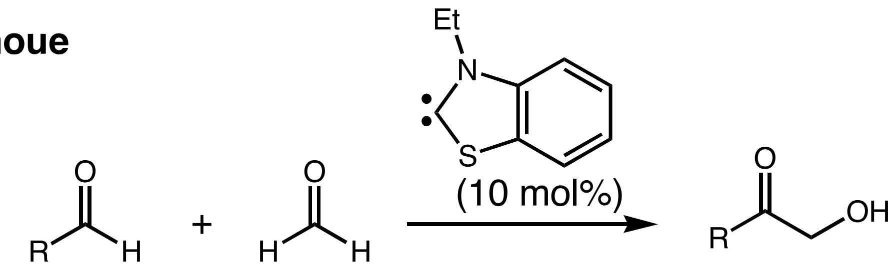


DFT calculations show **B** has a larger conjugation interaction over mono-triazolyldine **A**.

Enders, D.; Kallfass, U. *Ang. Chem. Int. Ed.* **2002**, *41*, 1743.
You, J. et al. *Adv. Synth. Catal.* **2008**, *350*, 2645.

Crossed Benzoin

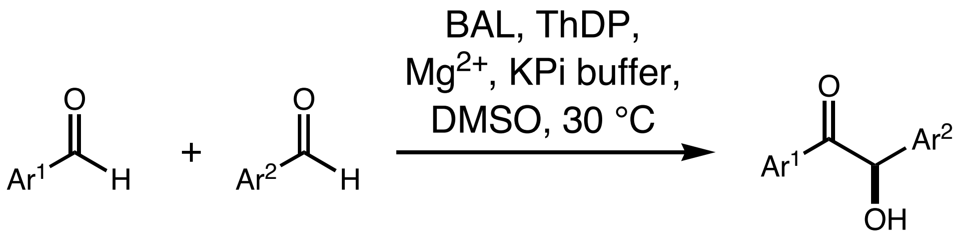
Inoue



64-100% selectivity

R = Me, Et, *n*-Pr, *i*-Pr, Cy, Ph, 2-furyl

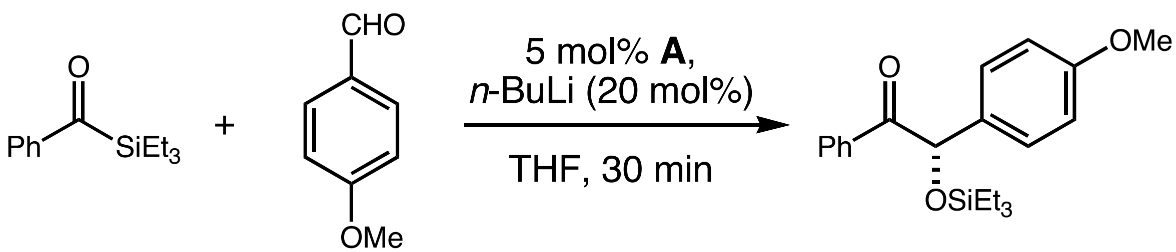
Müller: enzymatic



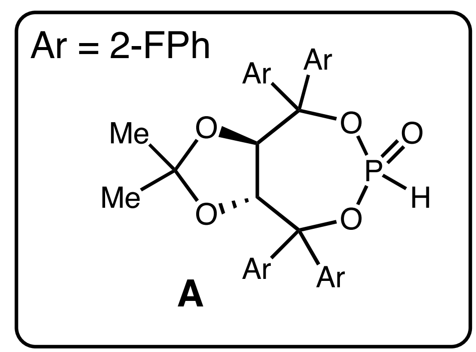
BAL = benzaldehyde lyase
ThDP = thiamine diphosphate

Ar^2 must be a better electron acceptor that Ar^1.
conversion, selectivity, *ee* up to > 99%

Johnson: metallophosphite catalyzed



87% yield
91% ee

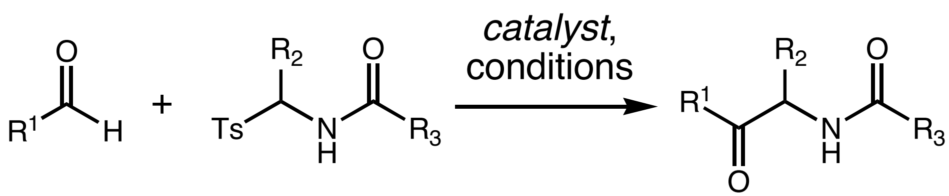


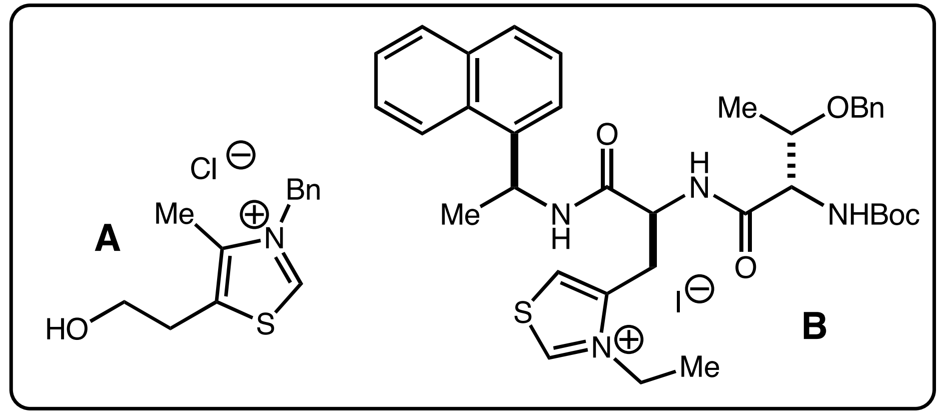
via a Brook rearrangement pathway

Inoue, S. et al. *J. Org. Chem.* **1985**, *50*, 603.
Müller, M. et al. *J. Am. Chem. Soc.* **2002**, *124*, 12084.
Johnson, J.S. et al. *J. Am. Chem. Soc.* **2004**, *126*, 3070.

Azabenzoin

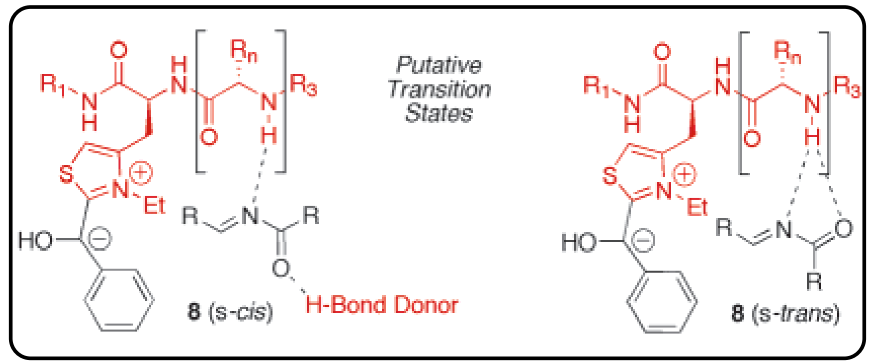
Murray/Frantz & Miller



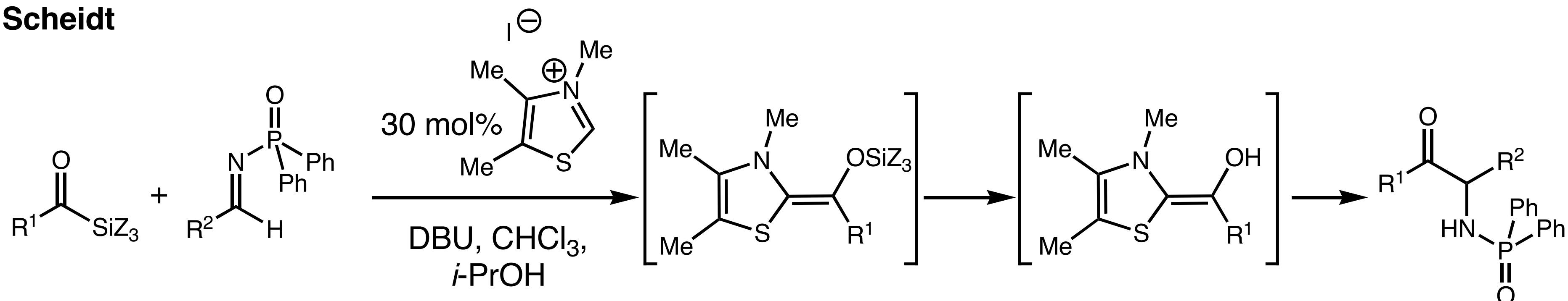


Murray/Frantz:
10 mol% **A**, NEt_3, DCM, 35-60 °C, 0.5-24 h — *58-98% yield*

Miller:
15 mol% **B**, PEMP, DCM, 23 °C, 2 h — *57-100% yield*
75-87% ee



Scheidt



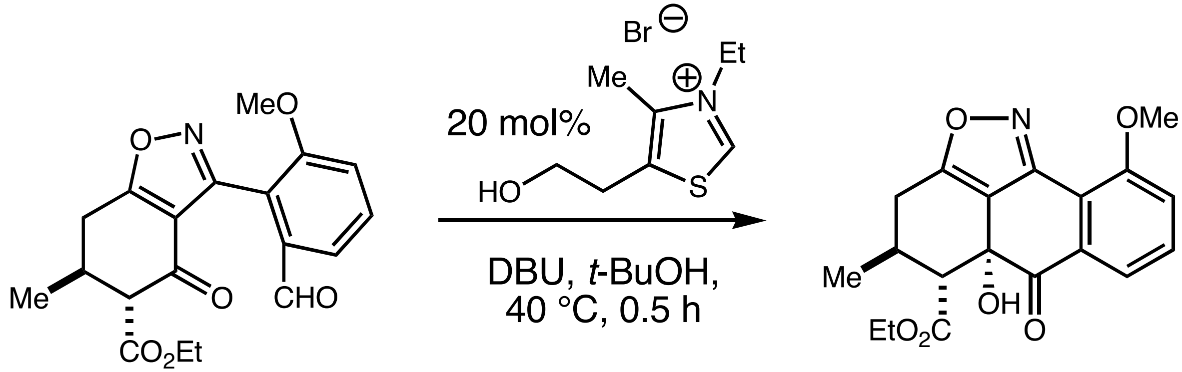
Breslow Intermediate

51-94% yield

Murray, J. A.; Frantz, D. E. et al. *J. Am. Chem. Soc.* **2001**, *123*, 9696.
Miller, S. J. et al. *J. Am. Chem. Soc.* **2005**, *127*, 1654.
Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 4363.

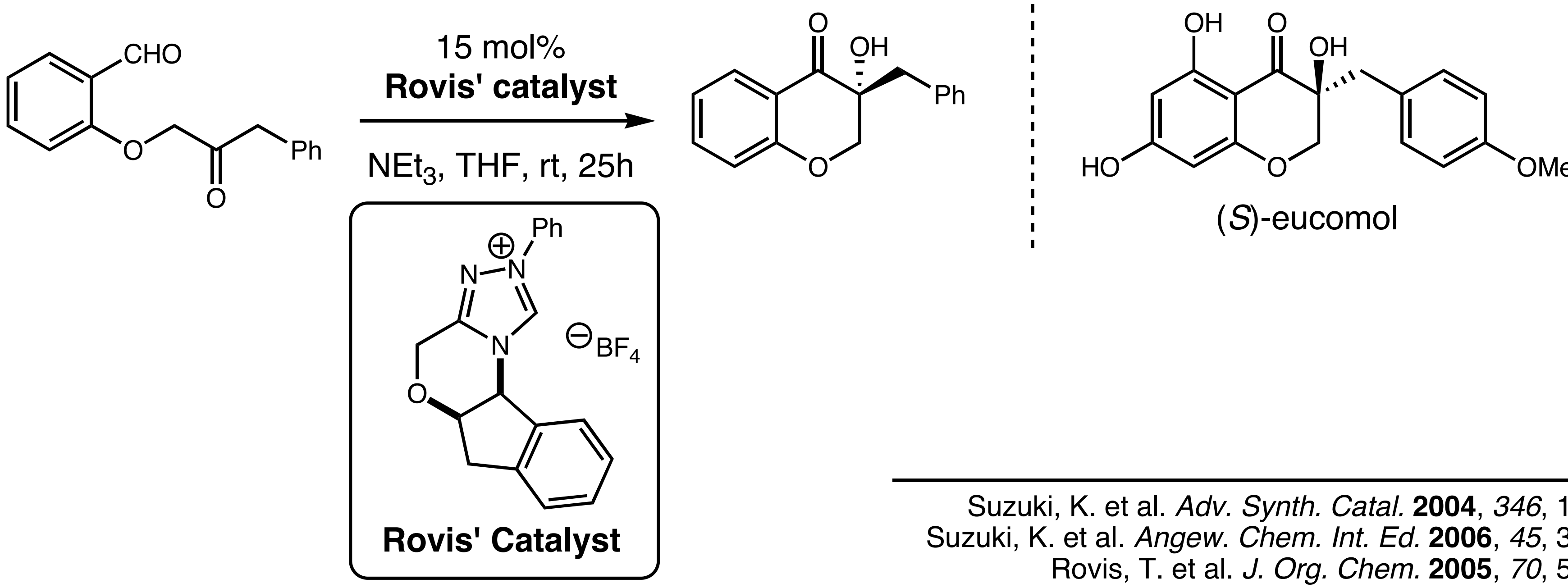
Intramolecular Crossed Benzoin

Complex Anthraquinone Precursors



79% yield
dr = 20:1

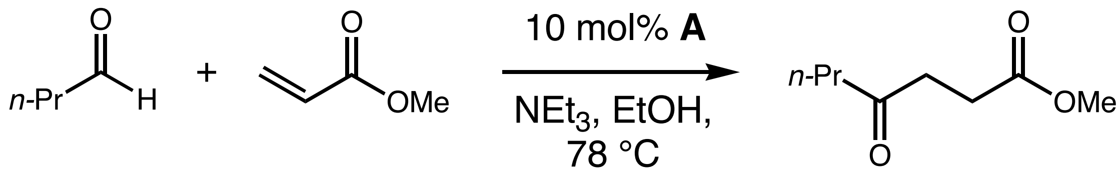
Enantioselective Synthesis of the Eucomol Core



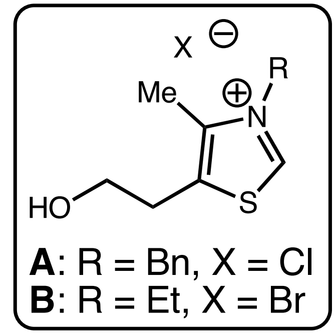
Suzuki, K. et al. *Adv. Synth. Catal.* **2004**, *346*, 1097.
Suzuki, K. et al. *Angew. Chem. Int. Ed.* **2006**, *45*, 3492.
Rovis, T. et al. *J. Org. Chem.* **2005**, *70*, 5725.

Stetter Reaction

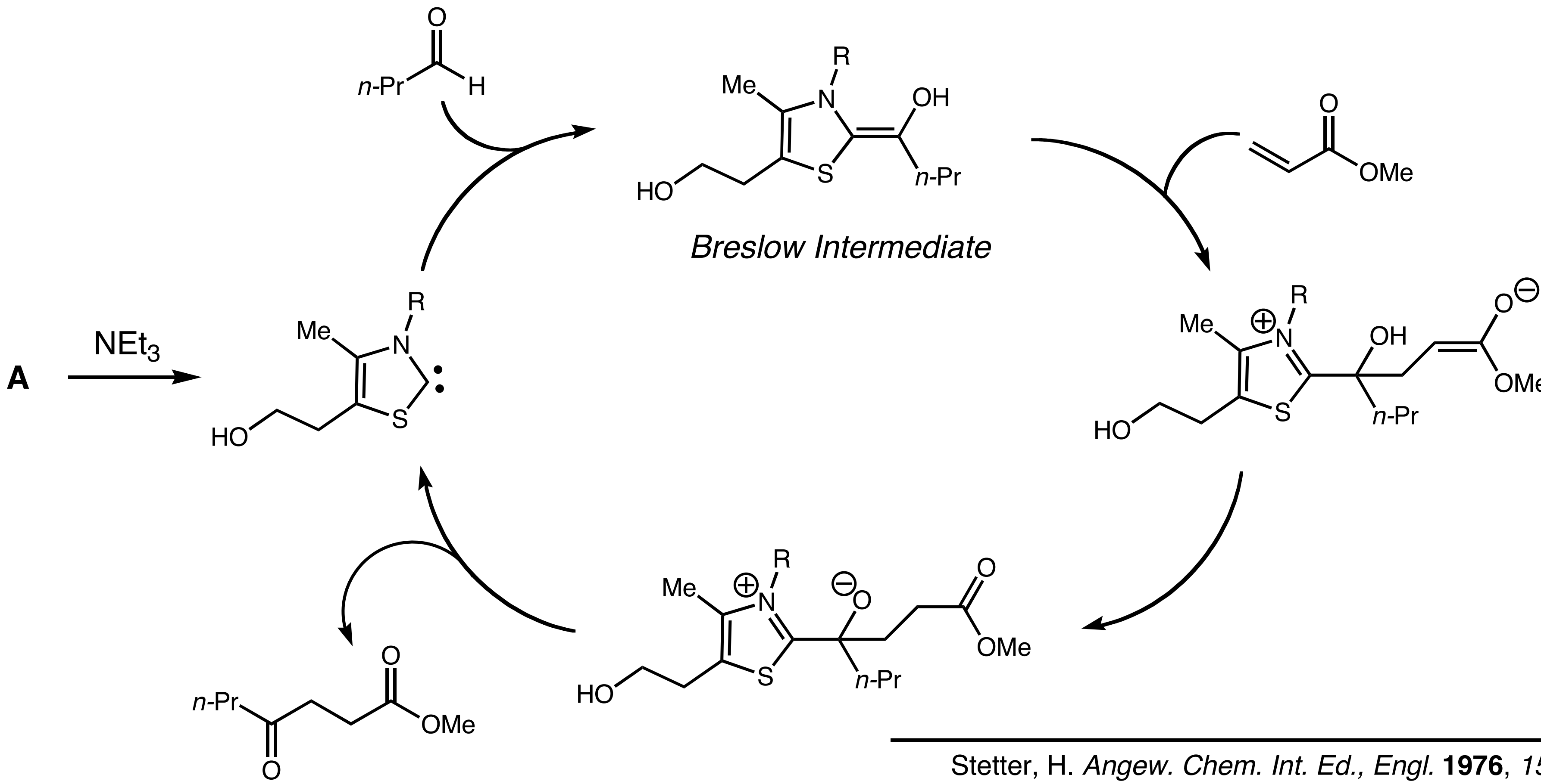
Stetter, 1976



95% yield



A for aliphatic
B for aromatic

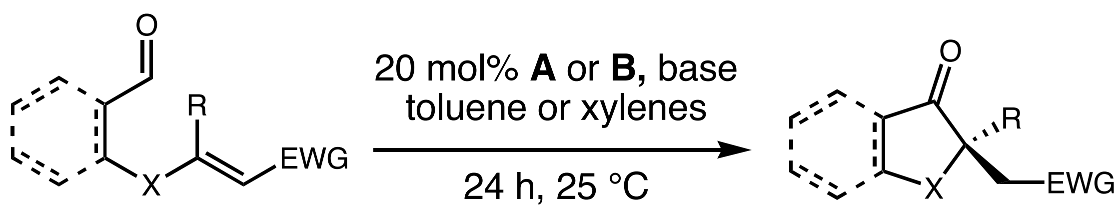


Stetter, H. *Angew. Chem. Int. Ed., Engl.* **1976**, *15*, 639.
Yates, B. F.; Hawkes, K. J. *Eur. J. Org. Chem.* **2008**, 5563.

Asymmetric Intramolecular Stetter Reaction

— Ciganek was the first to report and intramolecular Stetter reaction (1995).
— Enders was the first to report an asymmetric intramolecular Stetter reaction (1996, 41-74% ee).
— Significant progress has been more recently acheived by Rovis (2004-present).

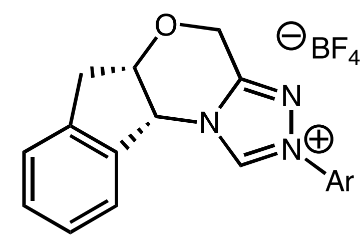
Rovis



X = O, S, NR, CH_2
R = H, alkyl, aryl

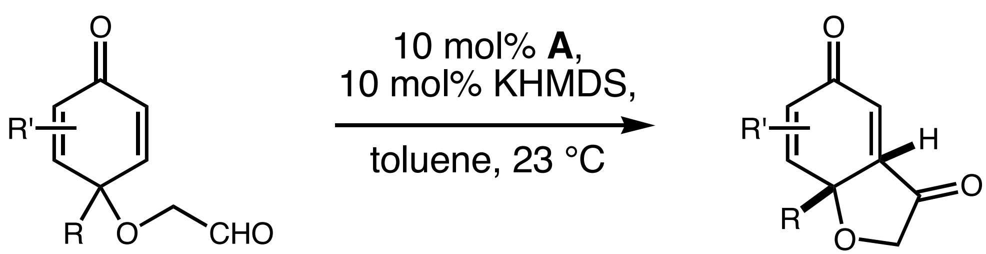
82-99% ee

air and water stable, crystalline solid



if R = H: catalyst **A**, Ar = 4-OMePh
base = 20 mol% KHMDS
if R = alkyl/aryl: catalyst **B**, Ar = C_6F_5
base = 2 equiv. NEt_3

Desymmetrization

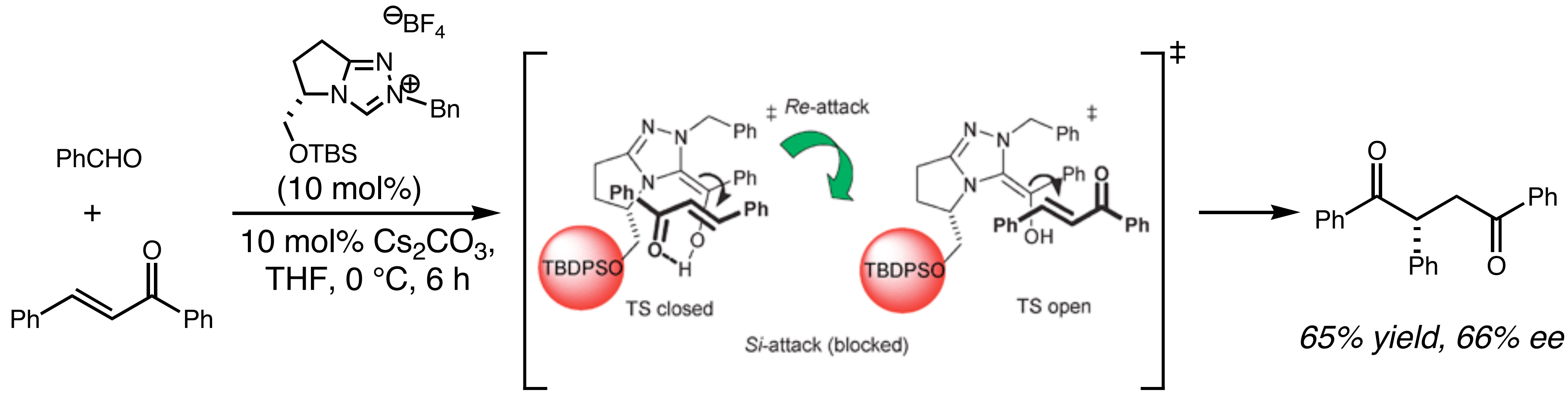


60-94% yield
82-99% ee
>95:5 dr

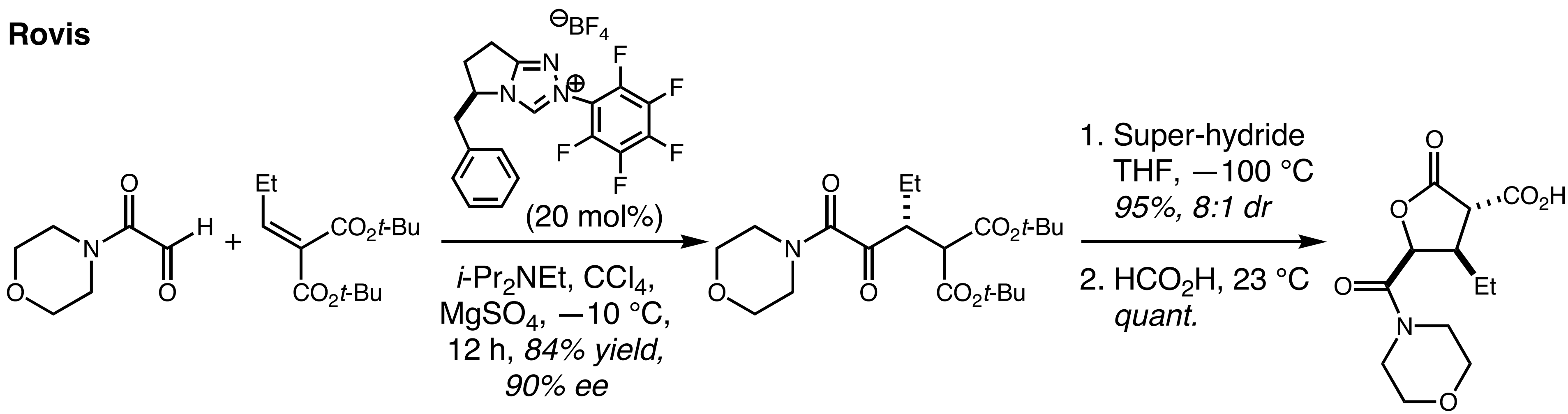
Ciganek, E. *Synthesis* **1995**, 1311.
Ender, D. et al. *Helv. Chim. Acta.* **1996**, *79*, 1899.
Rovis, T. et al. *J. Am. Chem. Soc.* **2004**, *126*, 8876.
Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552.

Asymmetric Intermolecular Stetter Reaction

Enders

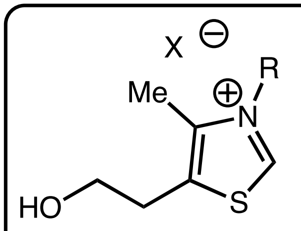


Rovis



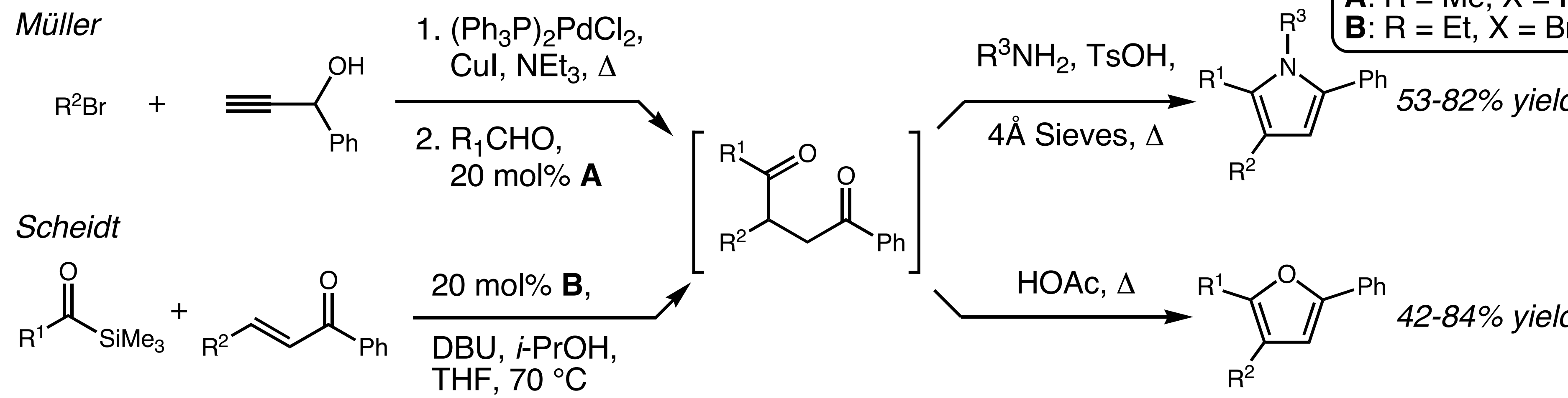
Enders, D.; Han, J. *Synthesis* **2008**, *3864.*
Rovis T. et al. *J. Am. Chem. Soc.* **2008**, *130*, 14066.

Special Intermolecular Stetter Reactions

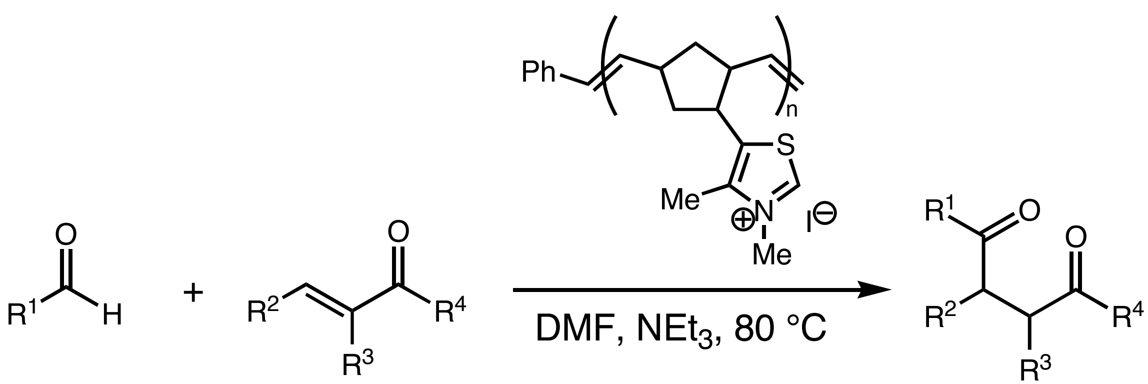


A: R = Me, X = I
B: R = Et, X = Br

One-Pot Synthesis of Pyrrols and Furans (Stetter-Paal-Knorr)



Polymer-Supported Stetter Reactions



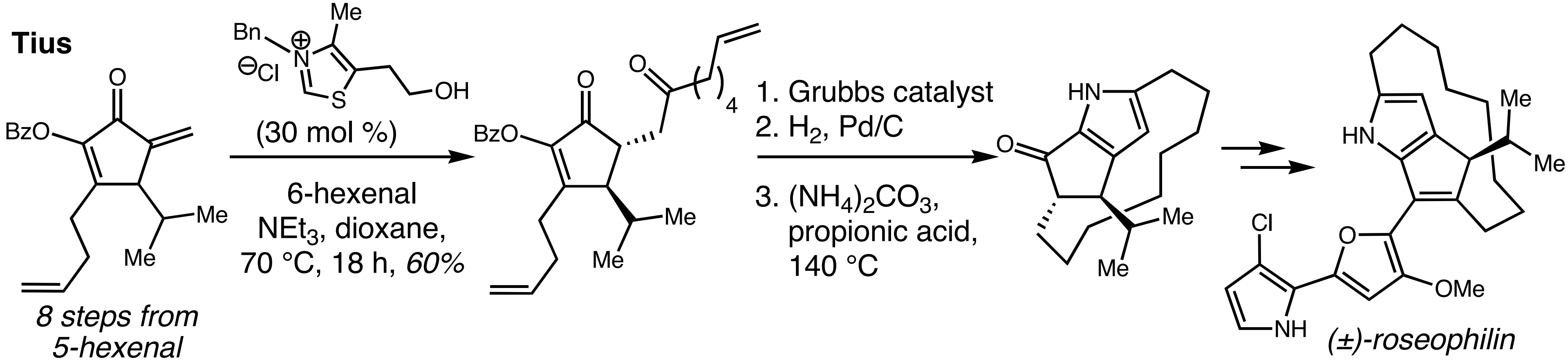
Can easily recover polymer and use up to 4 times without loss of reactivity.

68-99% yield
66->95% purity

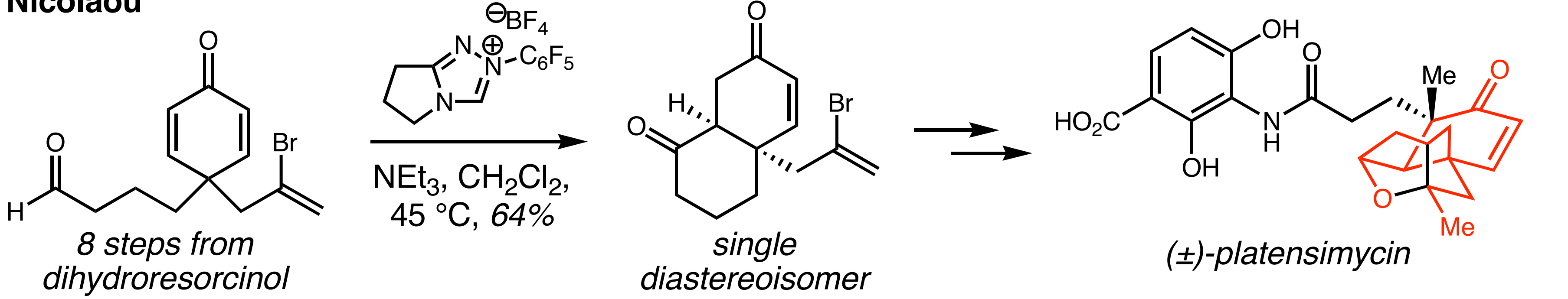
Müller, T. J. J. et al. *Org. Lett.* **2001**, *3*, 3297.
Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465.
Barrett, A. G. M. et al. *Org. Lett.* **2004**, *6*, 3377.

Natural Product Synthesis using the Stetter Reaction

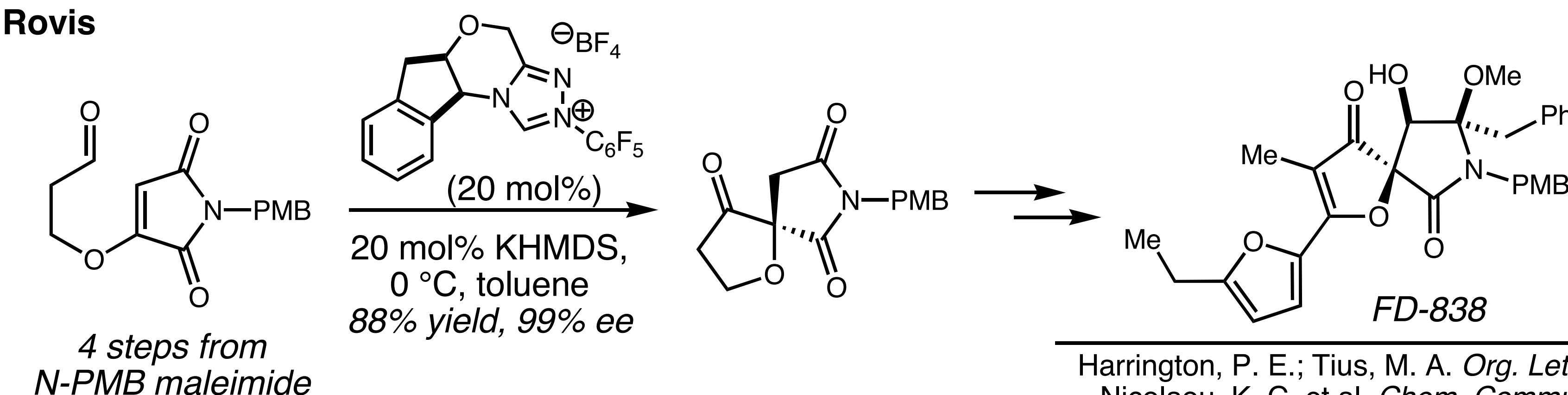
Tius



Nicolaou



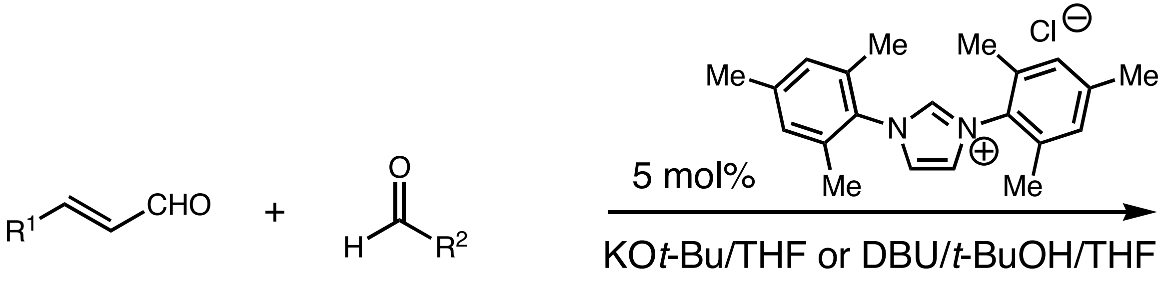
Rovis

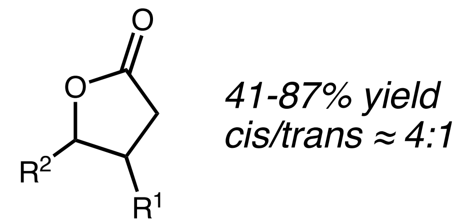


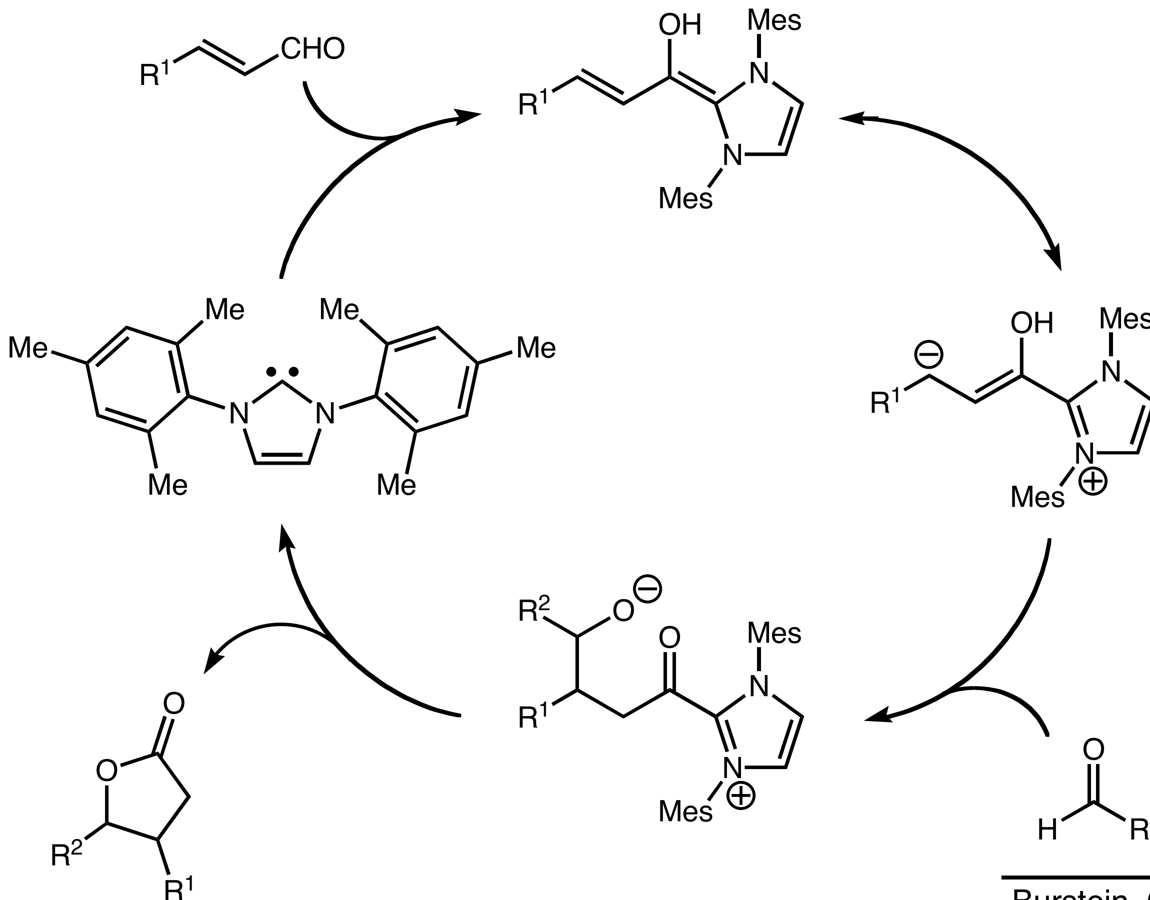
Harrington, P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649.
Nicolaou, K. C. et al. *Chem. Commun.* **2007**, 1922.
Orellana, A., Rovis, T. *Chem. Commun.* **2008**, 730.

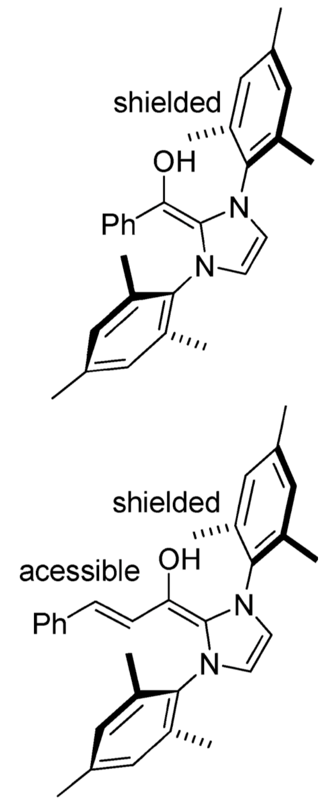
Homoenolates

Can also access γ-lactams if imines are used as the electrophile.



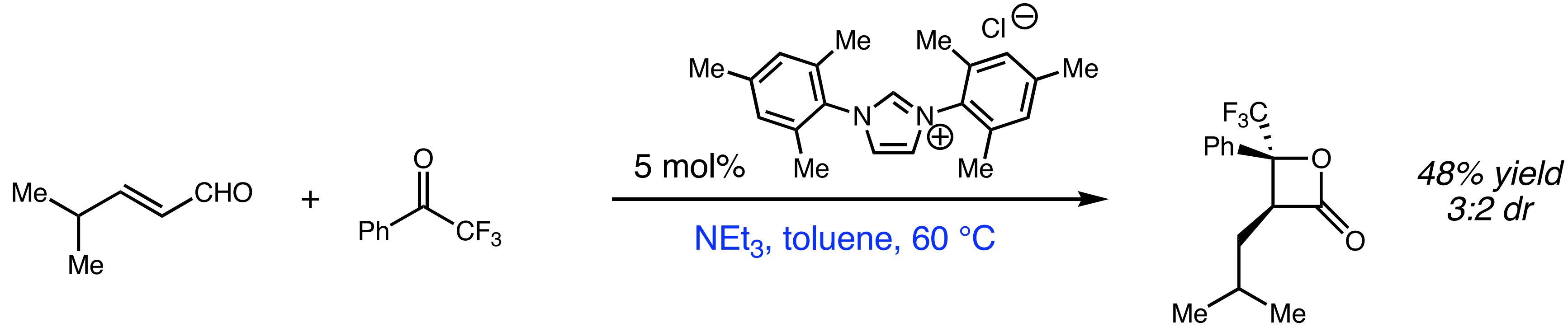


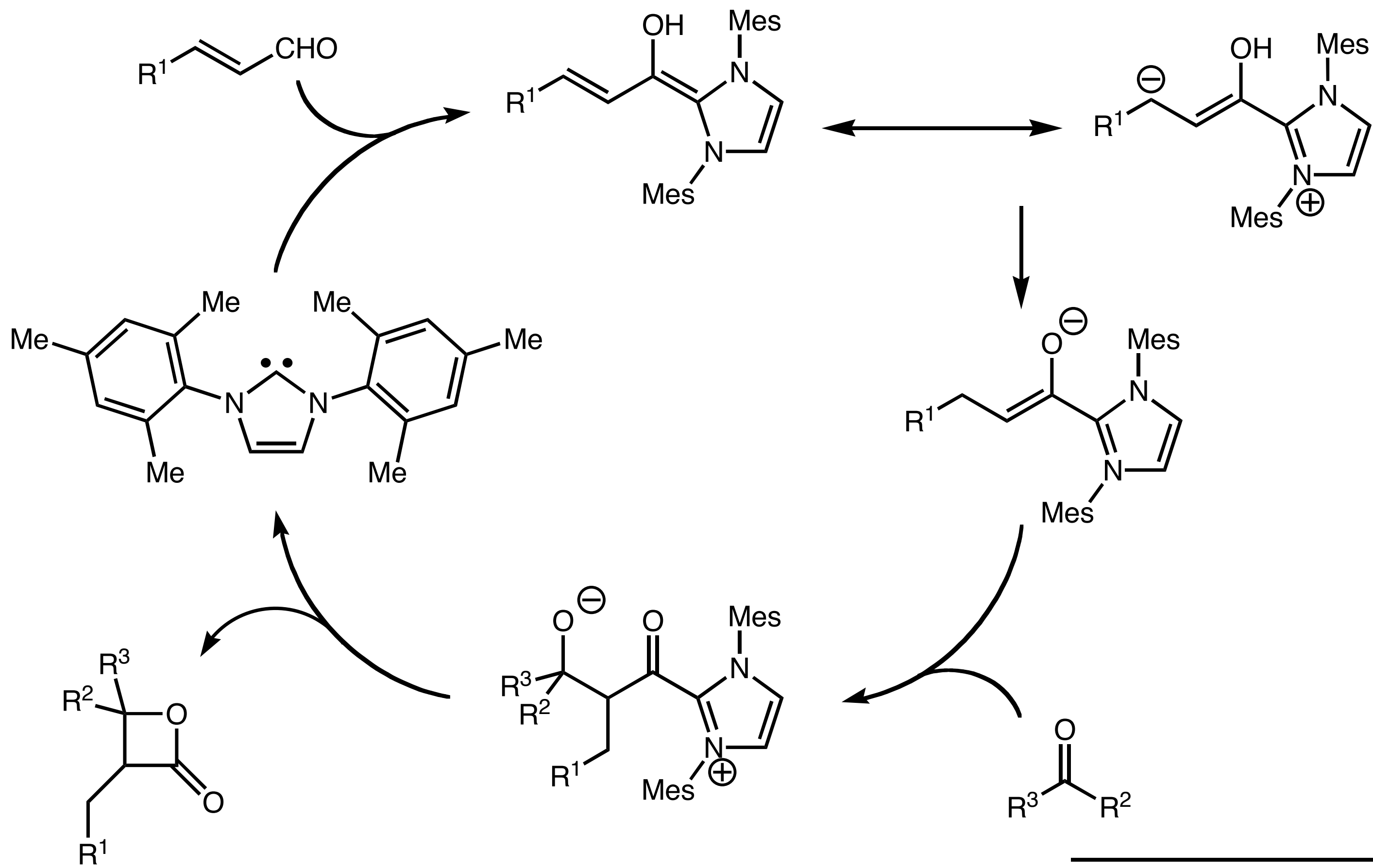




Burstein, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 6205.
Bode, J. W. et al. *J. Am. Chem. Soc.* **2004**, *126*, 14370.
Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873.

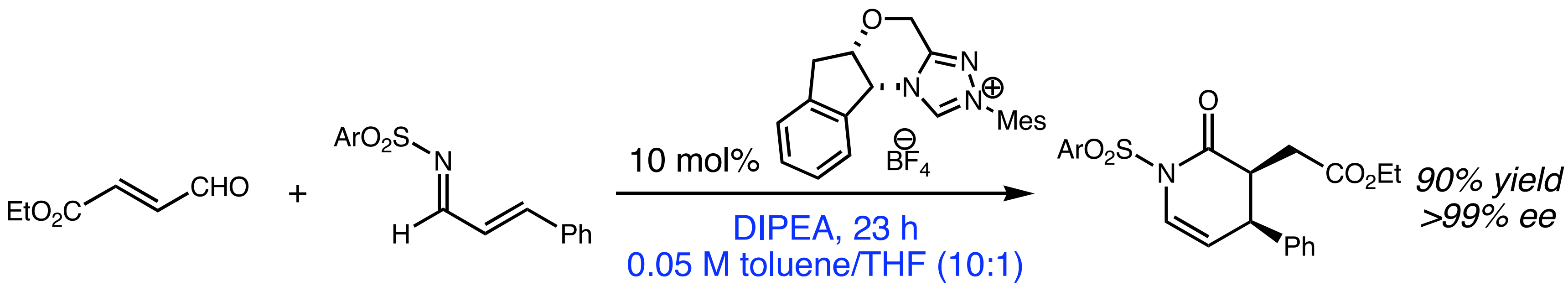
β-Lactones

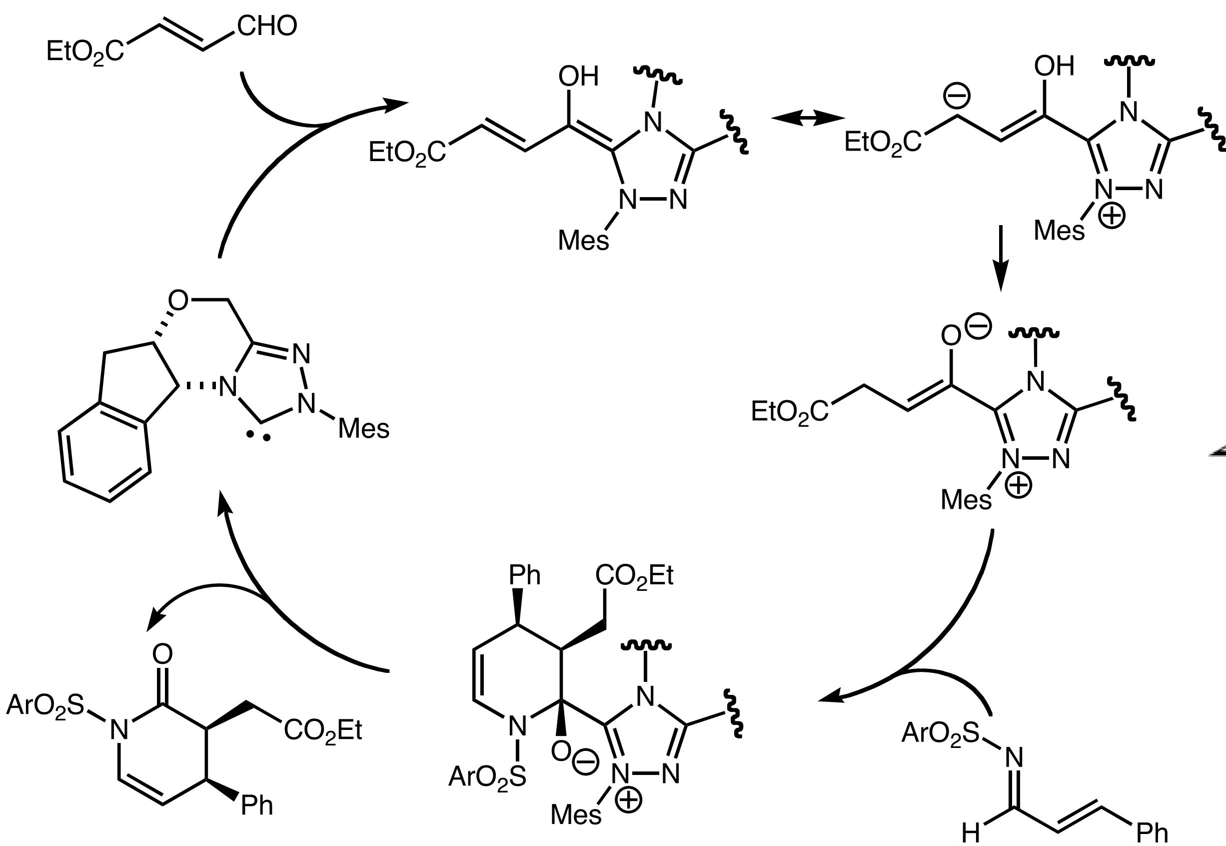


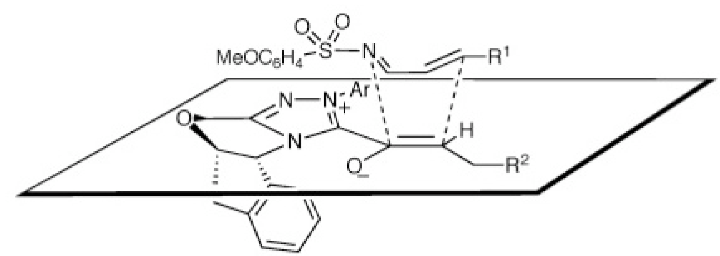


Glorius, F. et al. *Synthesis* **2006**, *2418.*

Azadiene Diels-Alder Reaction

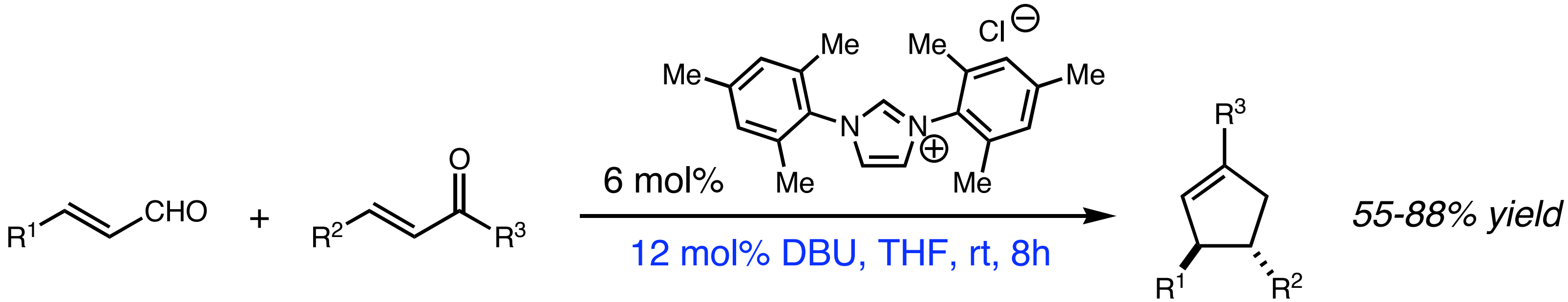


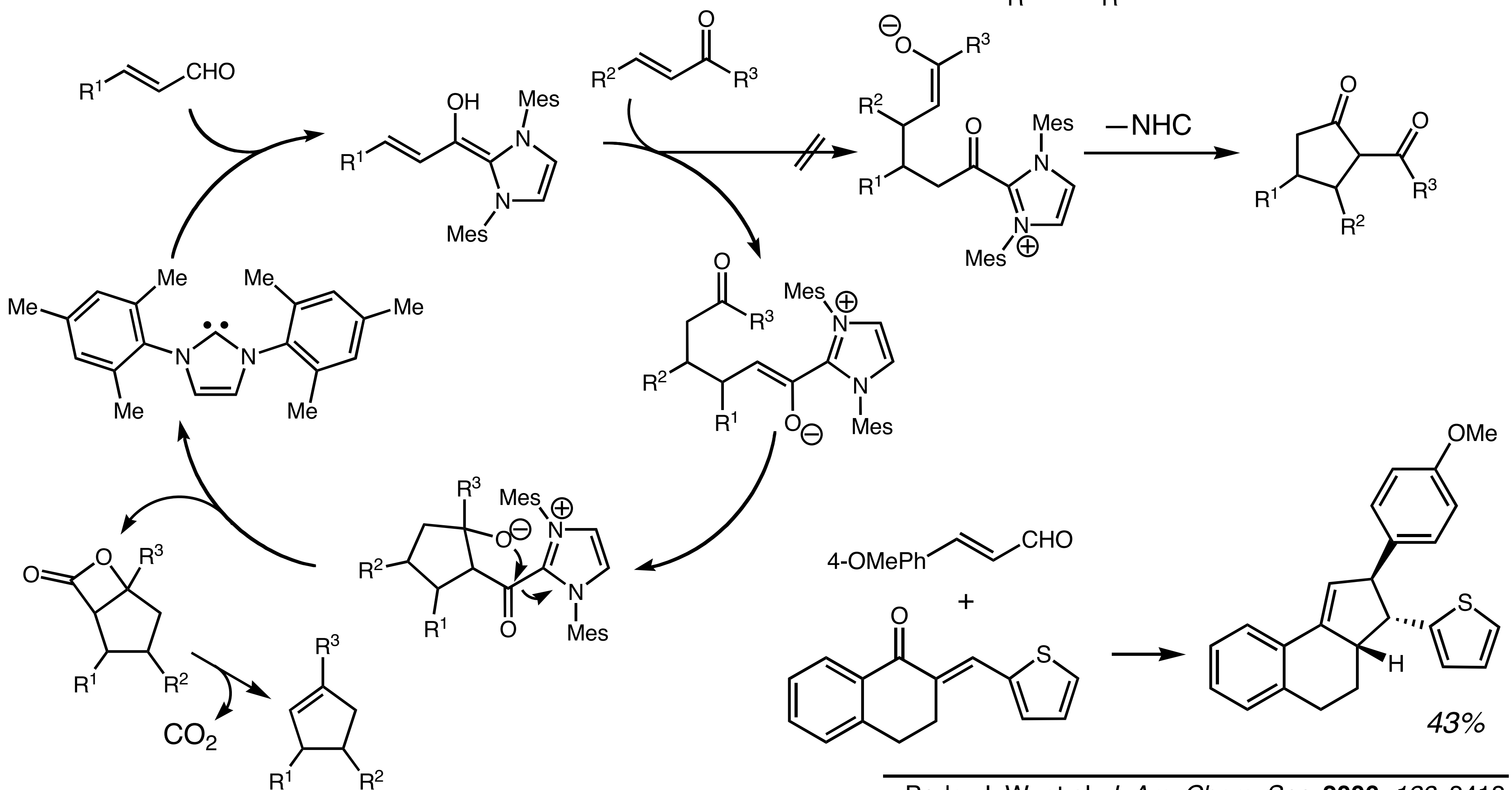




Bode, J. W. et al. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

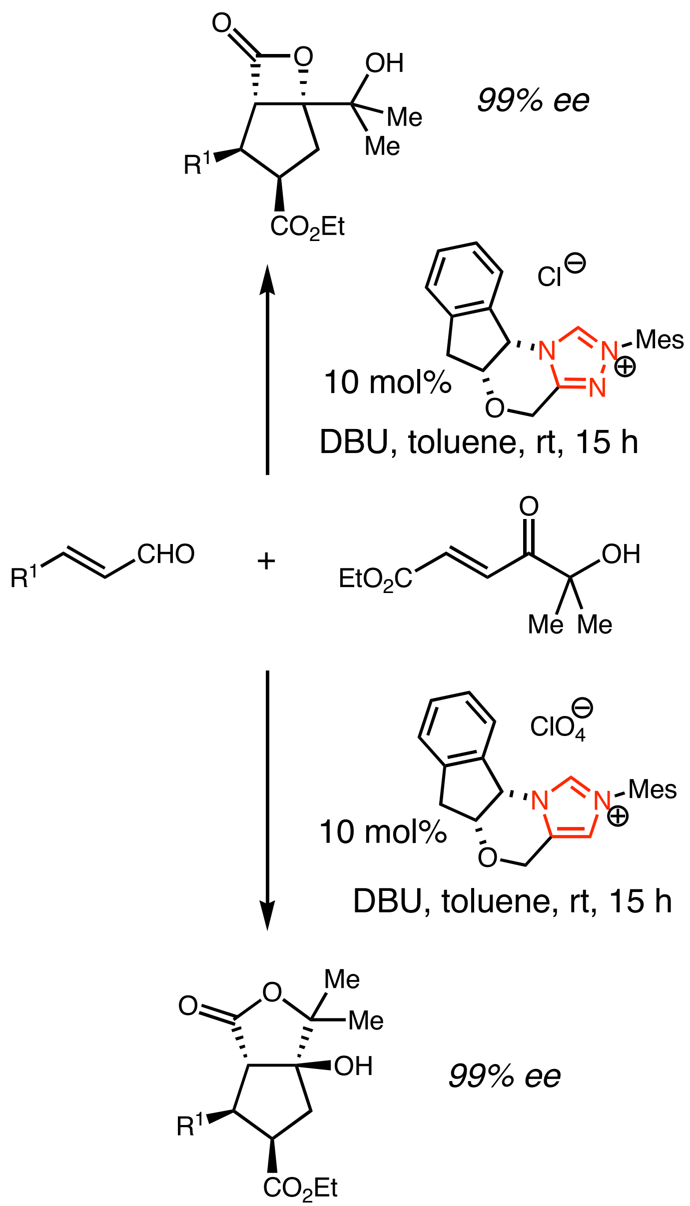
1,3,4-Trisubstituted Cyclopentenes

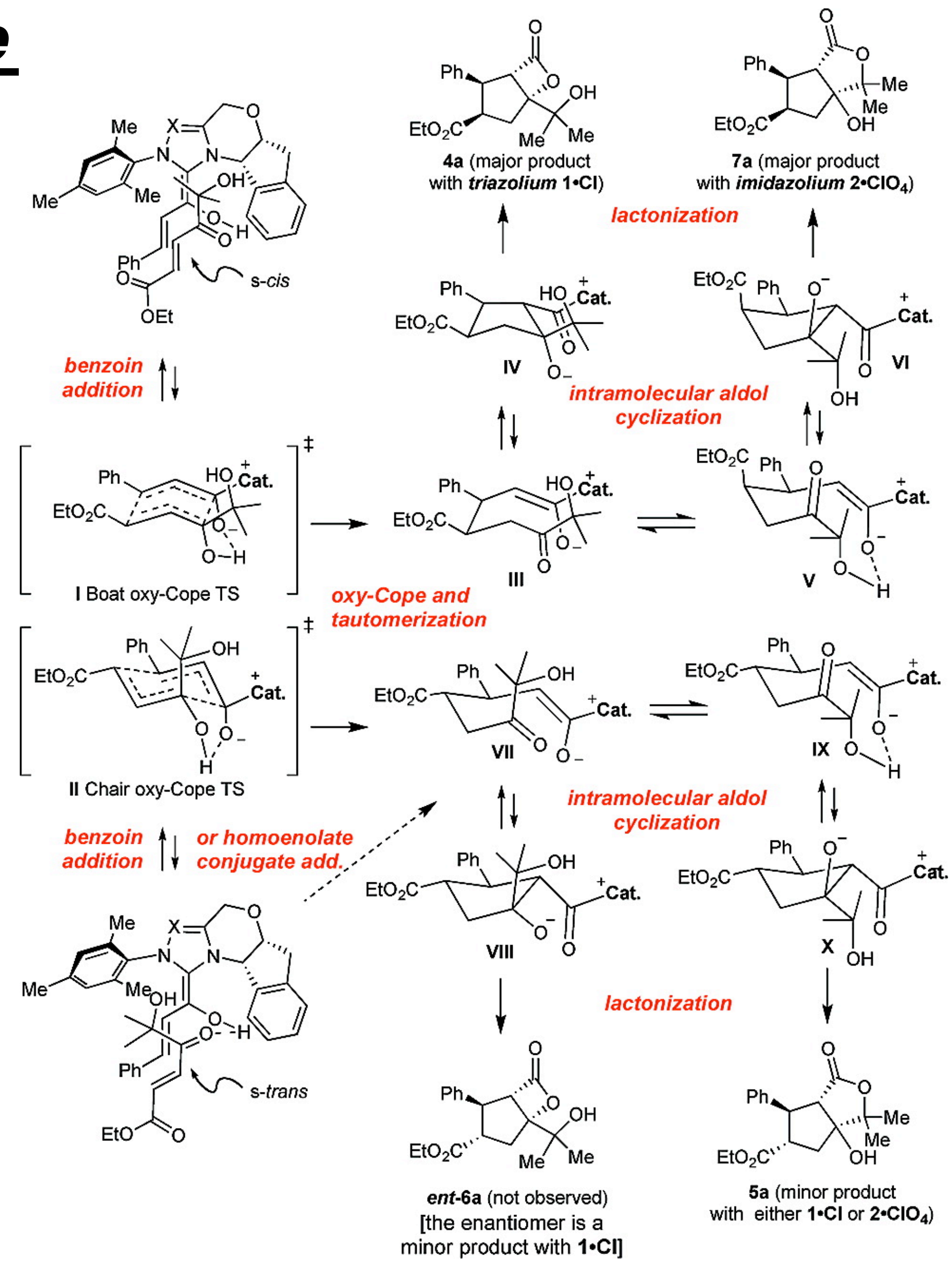




Bode, J. W. et al. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

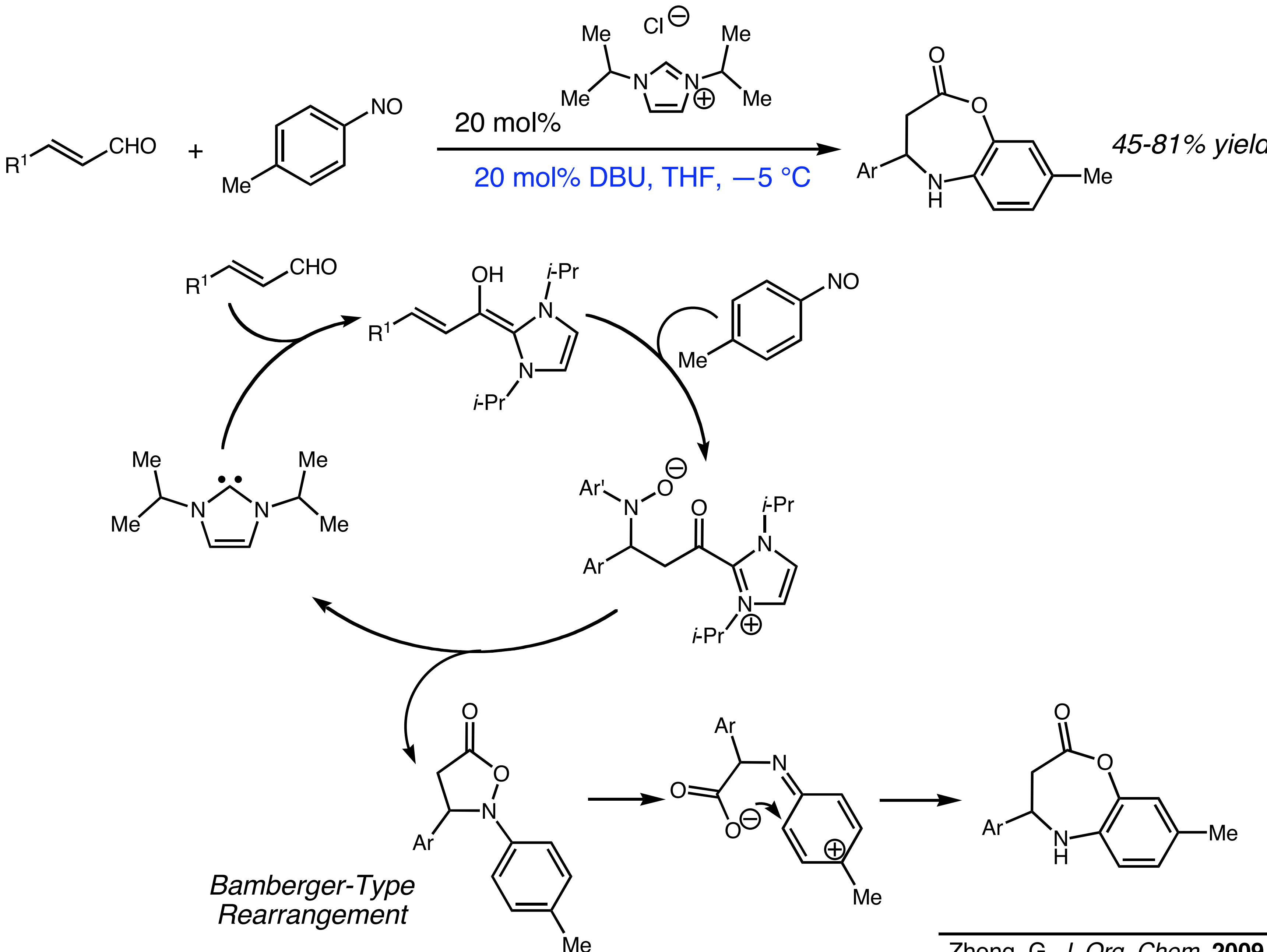
Enantioselective Cyclopentane Synthesis





Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2009**, *11*, 677.

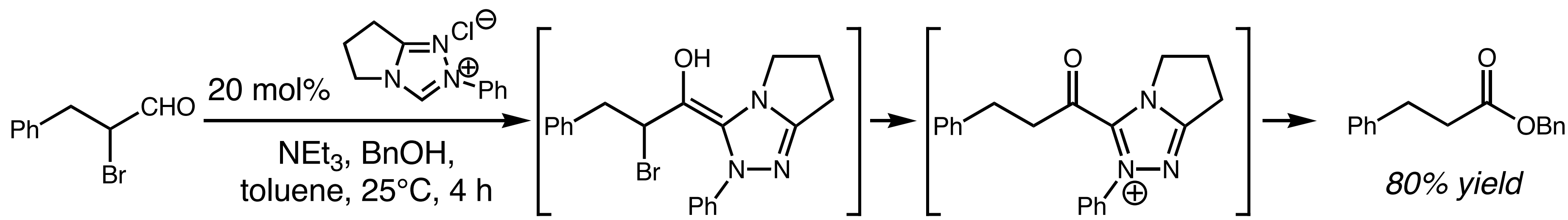
Annulation with Aryl Nitroso Compounds



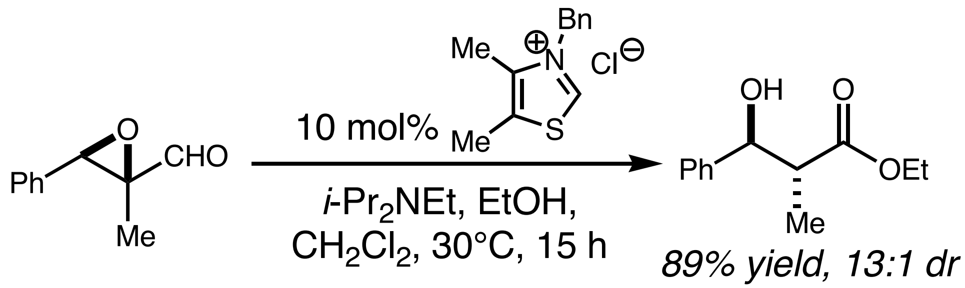
Zhong, G. *J. Org. Chem.* **2009**, *74*, 1744.

NHC-Catalyzed Redox Processes

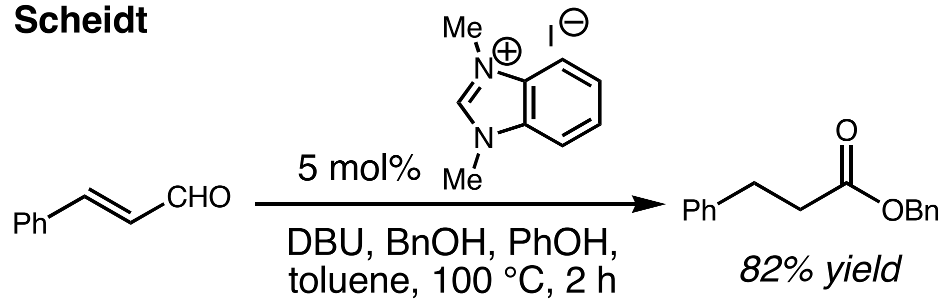
Rovis



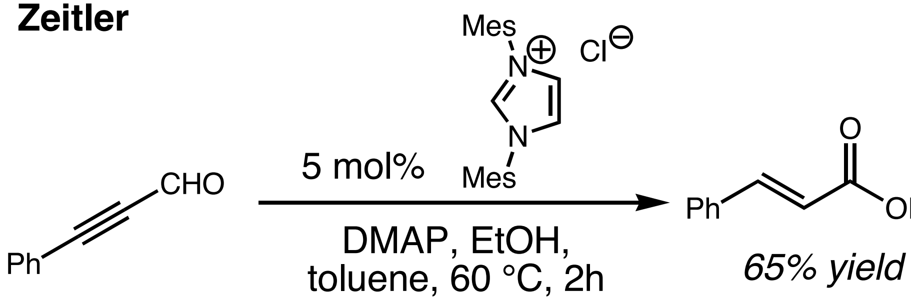
Bode



Scheidt

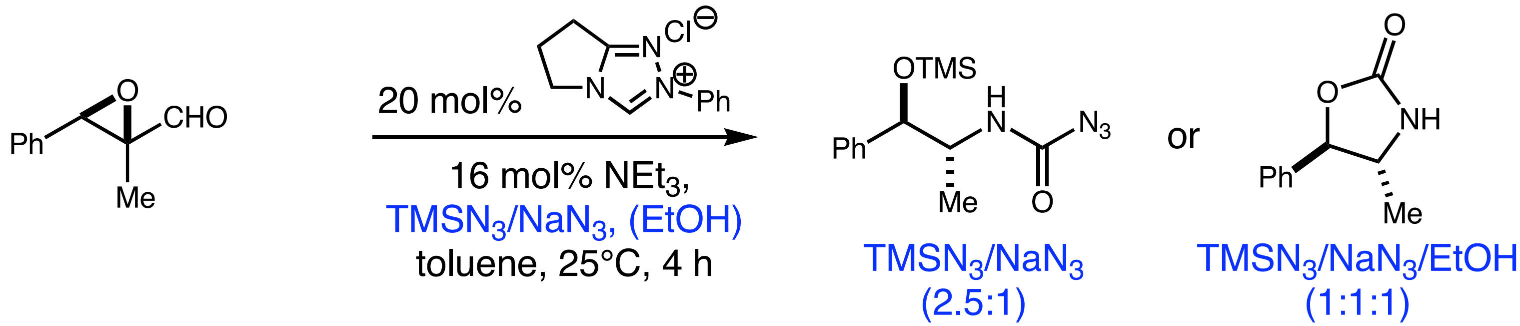


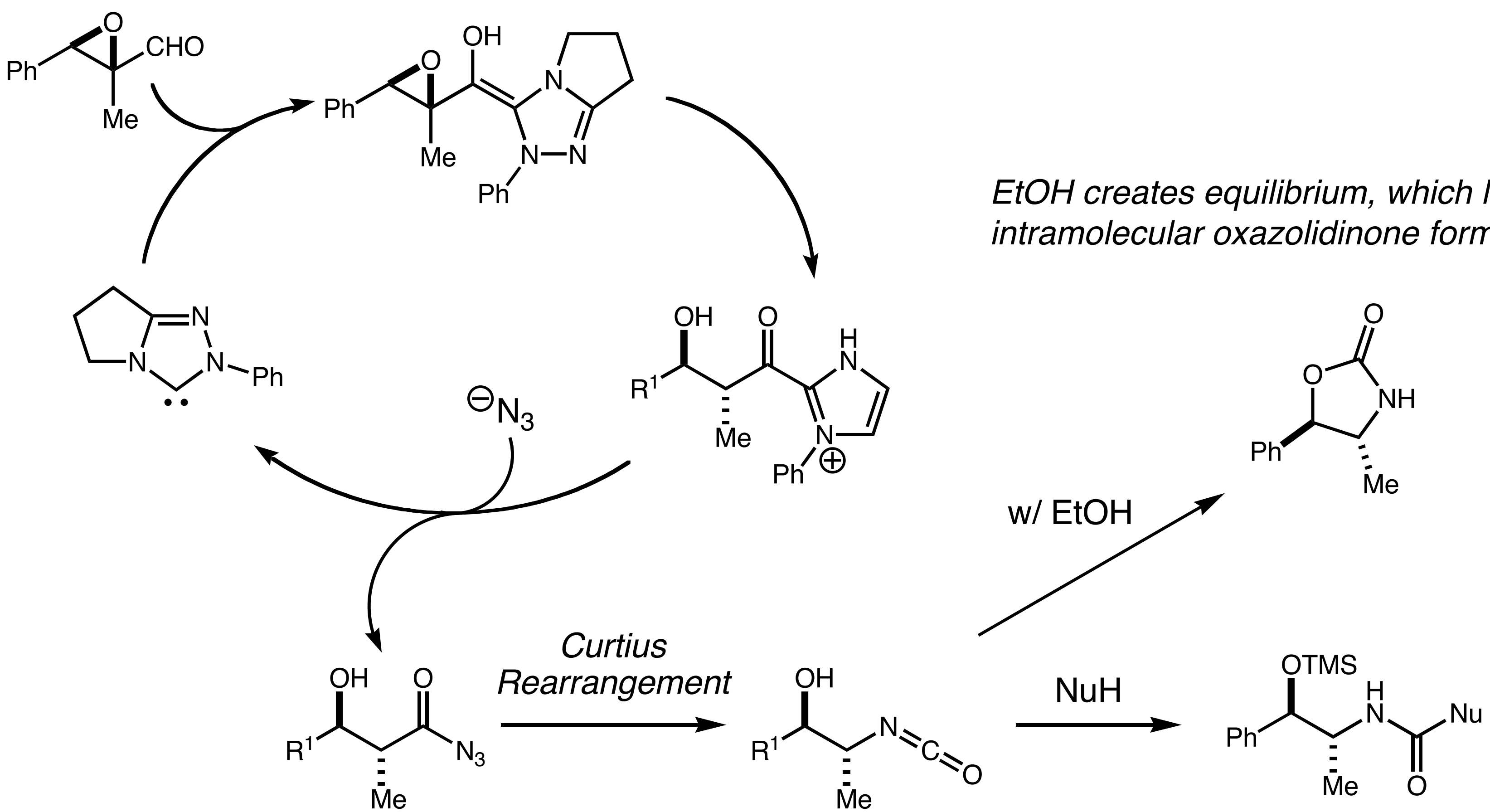
Zeitler



Rovis, T. et al. *J. Am. Chem. Soc.* **2004**, *126*, 9518.
Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126.
Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 3873.
Zeitler, K. *Org. Lett.*, **2006**, *8*, 637.

NHC-Catalyzed Azidation of Epoxy-Aldehydes

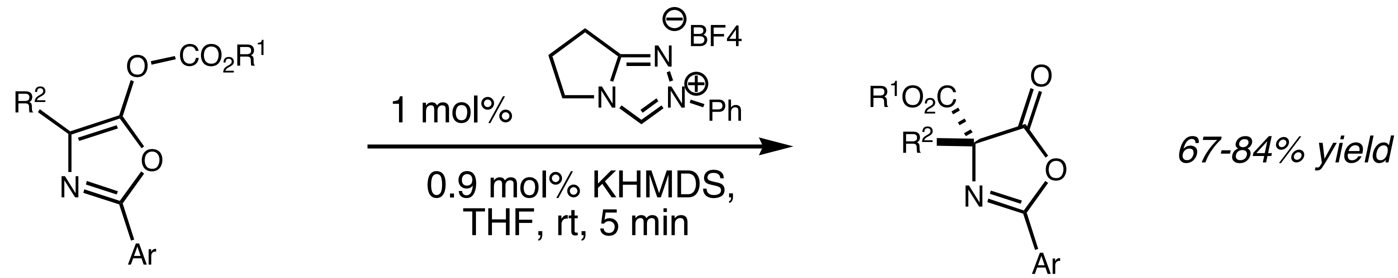


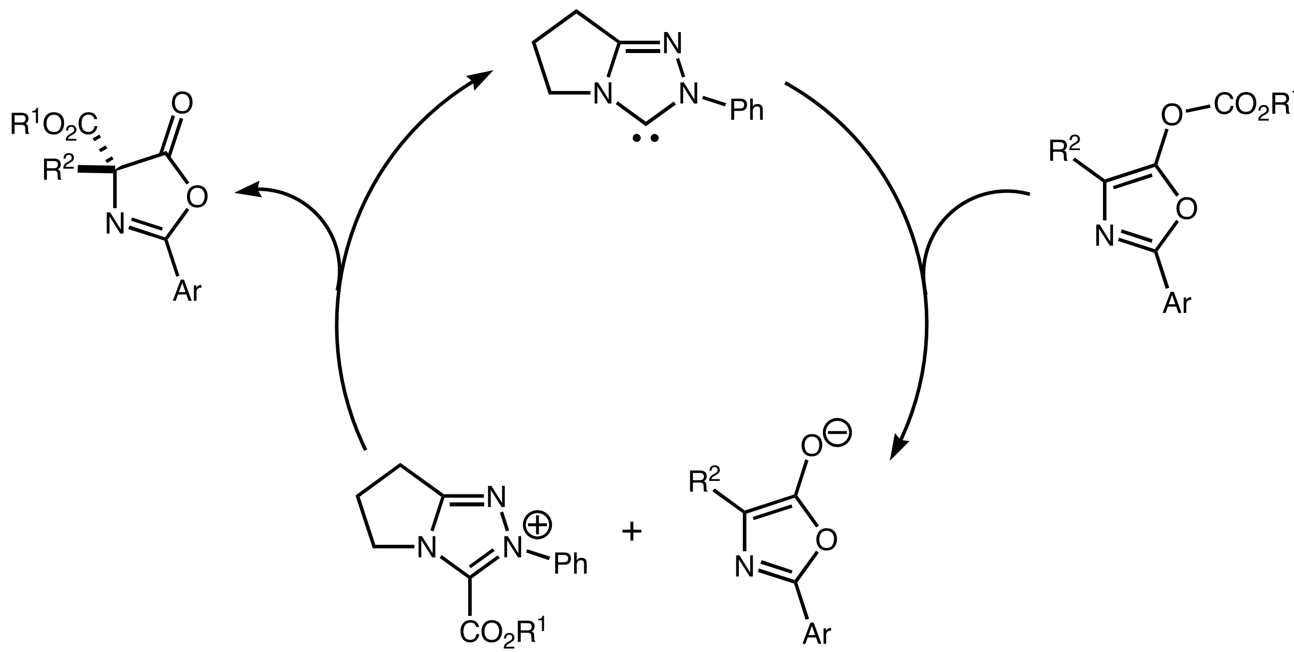


EtOH creates equilibrium, which leads to intramolecular oxazolidinone formation.

Rovis, T. et al. *J. Org. Chem.* **2008**, *73*, 9727.

O- to C-Acyl Transfer





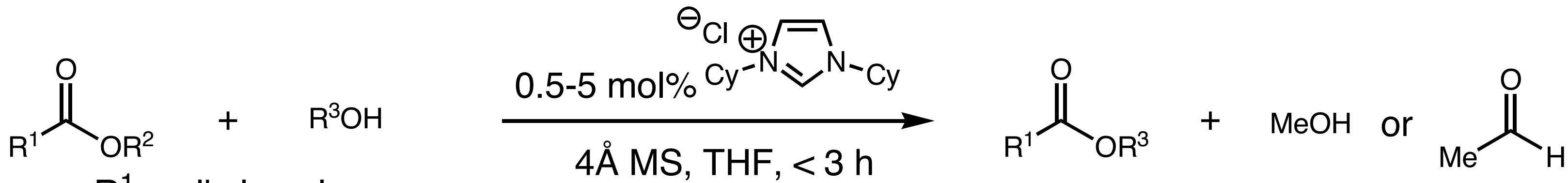
Crossover experiment supports mechanism:

2 different starting materials (R1/R2 and R1'/R2') give 4 different products.

Rovis, T. et al. *J. Org. Chem.* **2008**, *73*, 9727.

Trans-Esterification

Nolan

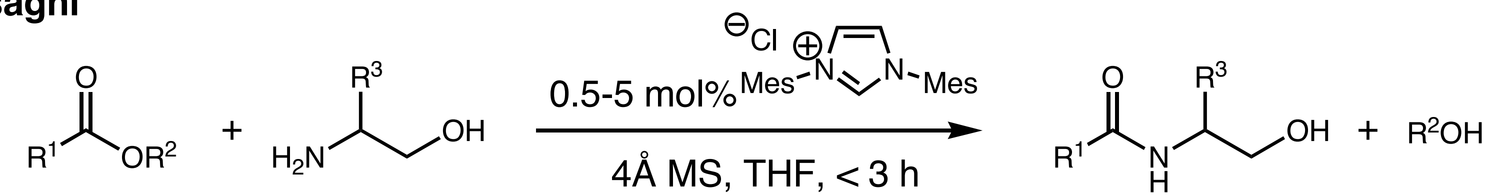


R^1 = alkyl, aryl
R^2 = Me, vinyl
R^3 = 1° and 2° alkyl

90-99% yield

Equilibrium process that favors product under reaction conditions.

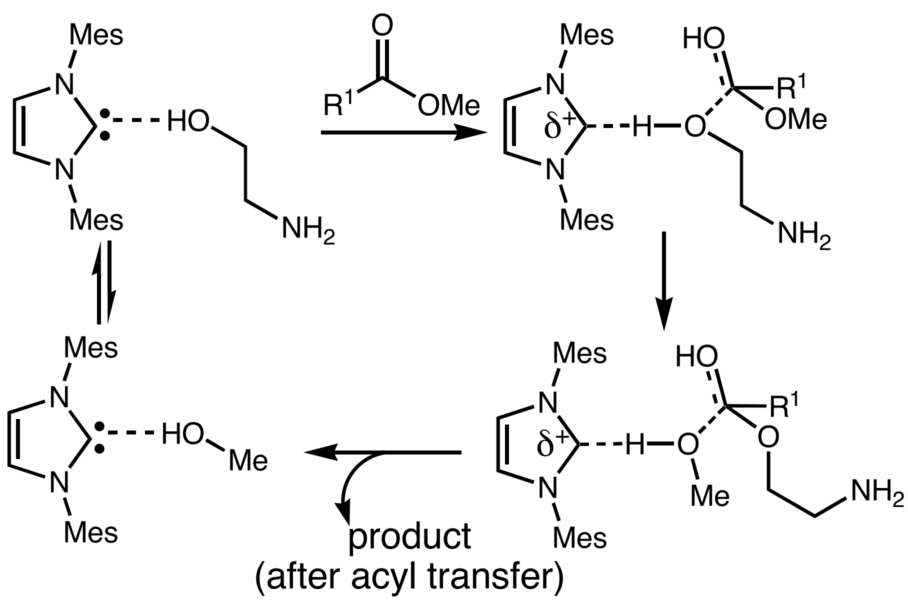
Movassaghi

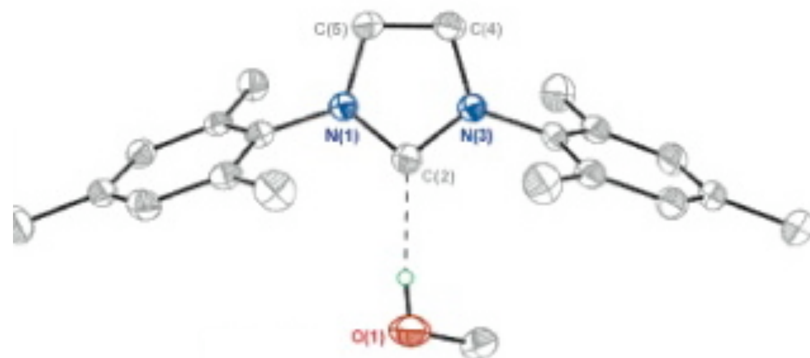


R^1 = alkyl, aryl
R^2 = 1° alkyl

66-99% yield

Competitive experiment with H_2NBn gives only the desired product. ⟶ *Alcohol is necessary.*

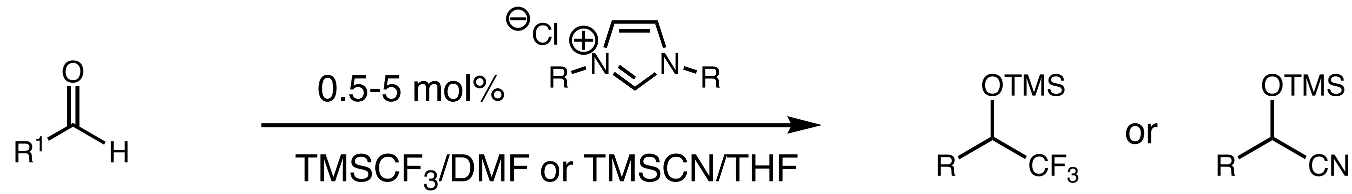




Theoretical studies by Hu support this mechanism.

Nolan, S. P. et al. *Org. Lett.* **2002**, *4*, 3583.
Hedrick, J. L. et al. *Org. Lett.* **2002**, *4*, 3587.
Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453.
Hu, C.-H. *Tetrahedron Lett.* **2005**, *46*, 6265.

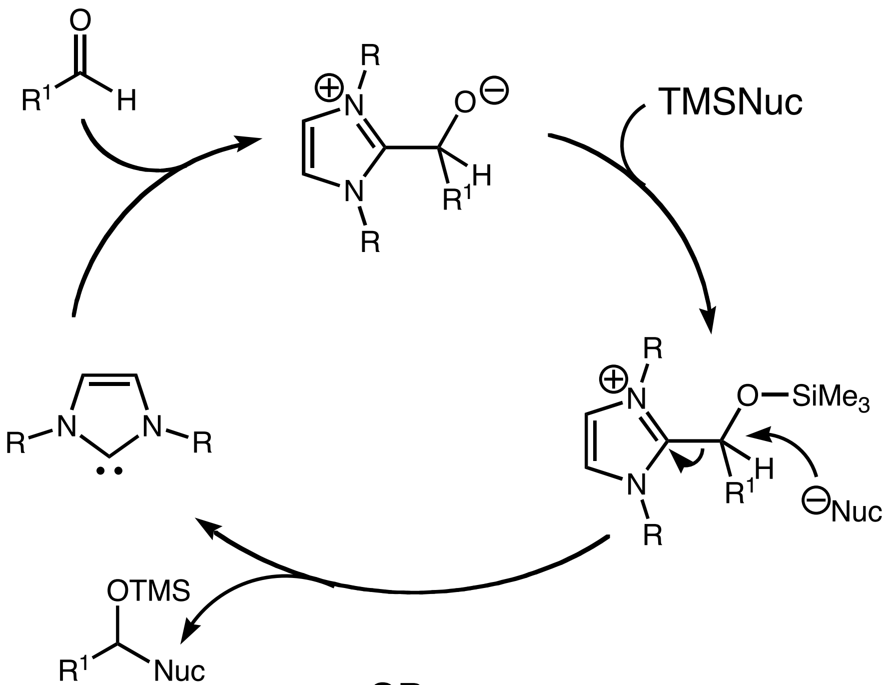
NHC-Catalyzed 1,2-Additions



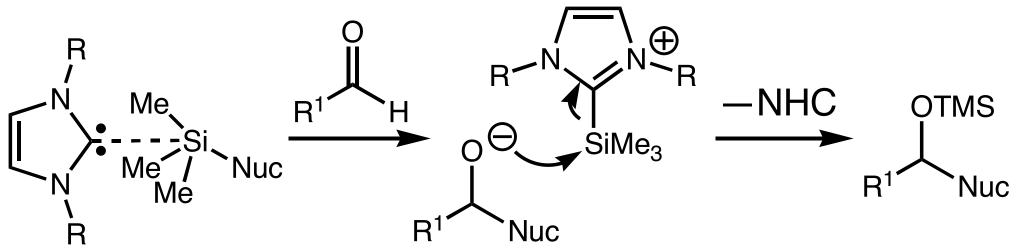
R^1 = aromatic, aliphatic, branched aliphatic

R = adamantyl, Mes

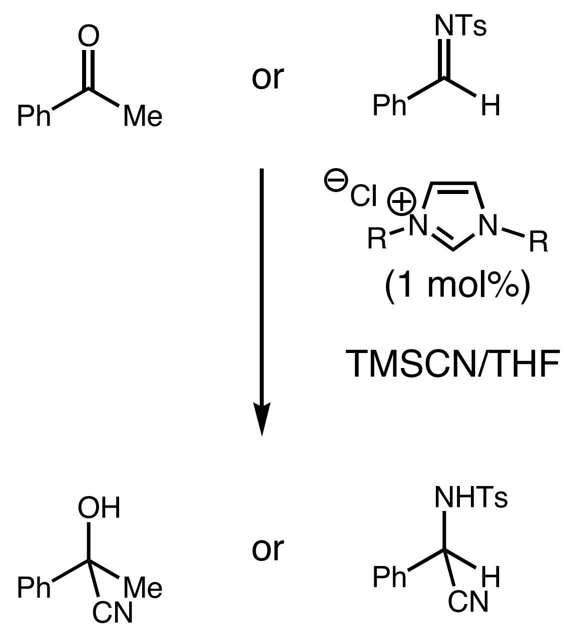
79-99% yield



OR



Maruoka



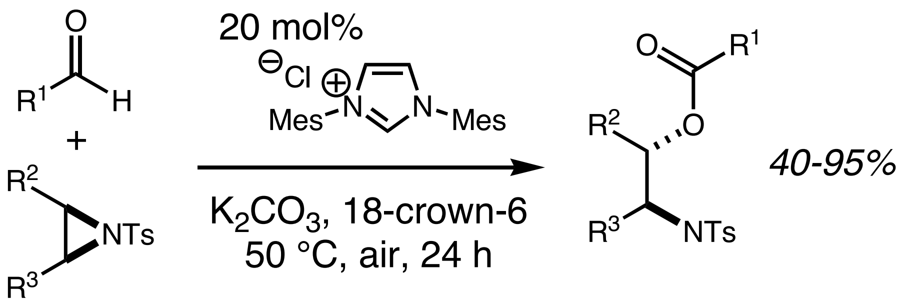
99% *92%*

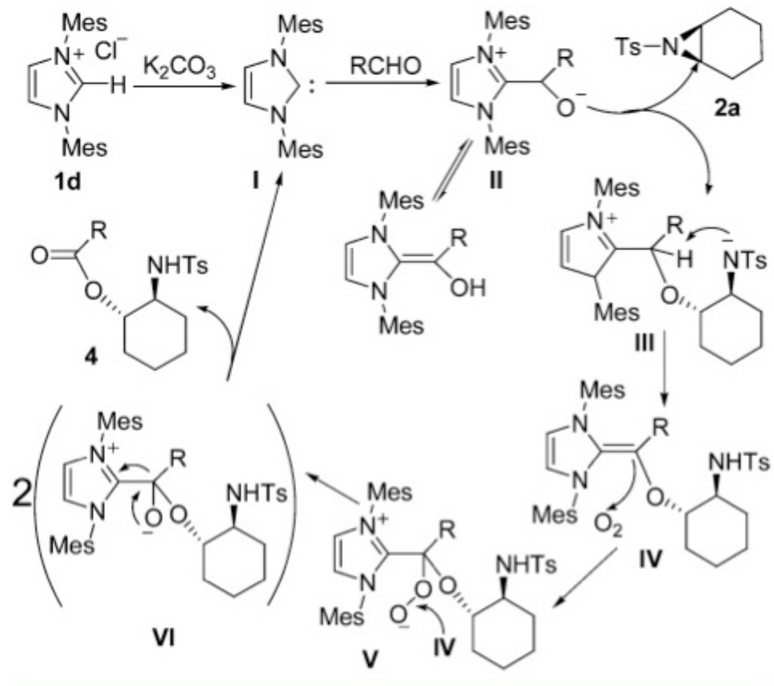
Lewis-base mechanism more plausible.

Song, J. J. et al. *Org. Lett.* **2005**, *7*, 2193.
Suzuki, Y.; Sato, M. et al. *Tetrahedron*, **2006**, *62*, 4227.
Maruoka, K. et al. *Tetrahedron Lett.* **2006**, *47*, 4615.

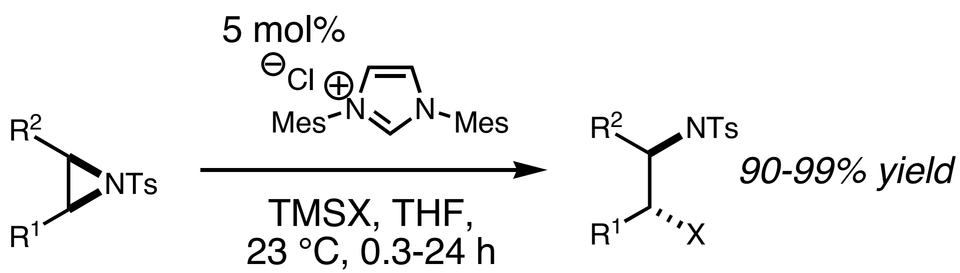
Aziridine Ring-opening

Chen





Wu

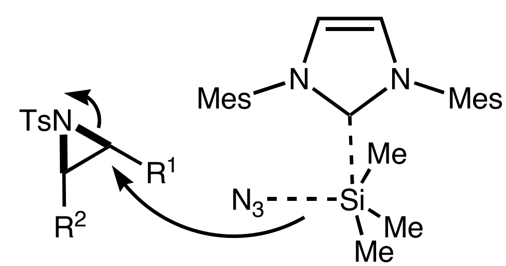


X = N_3, Cl, I

Rate: I > Cl >> N_3

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

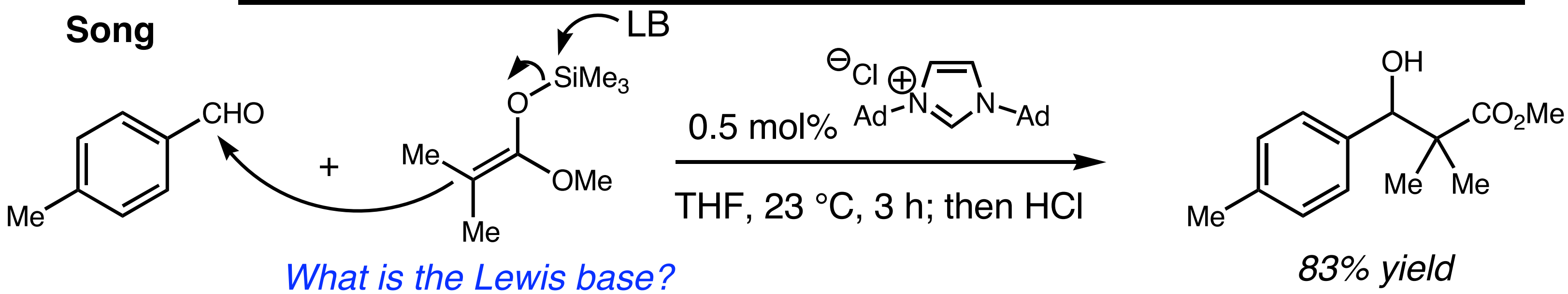
Lewis base-catalyzed pathway proposed.



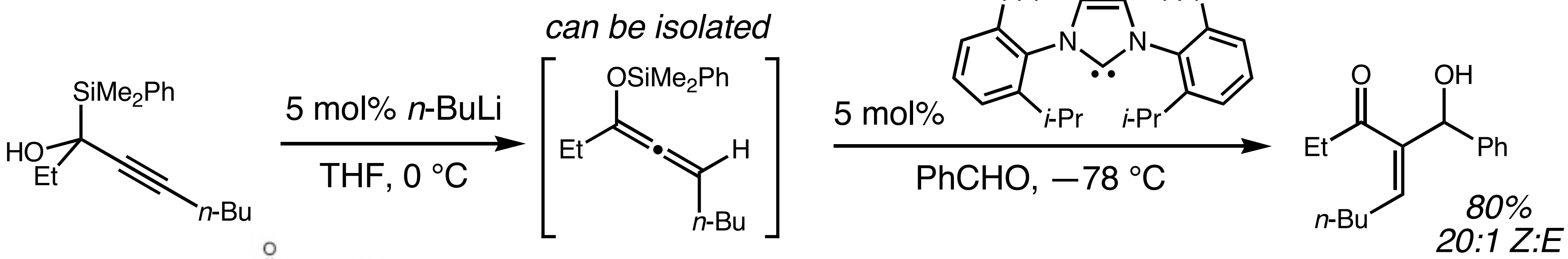
Chen, Y.-C. et al. *Org. Lett.* **2006**, *8*, 1521.
Wu, J. et al. *Tetrahedron Lett.* **2006**, *47*, 4813.

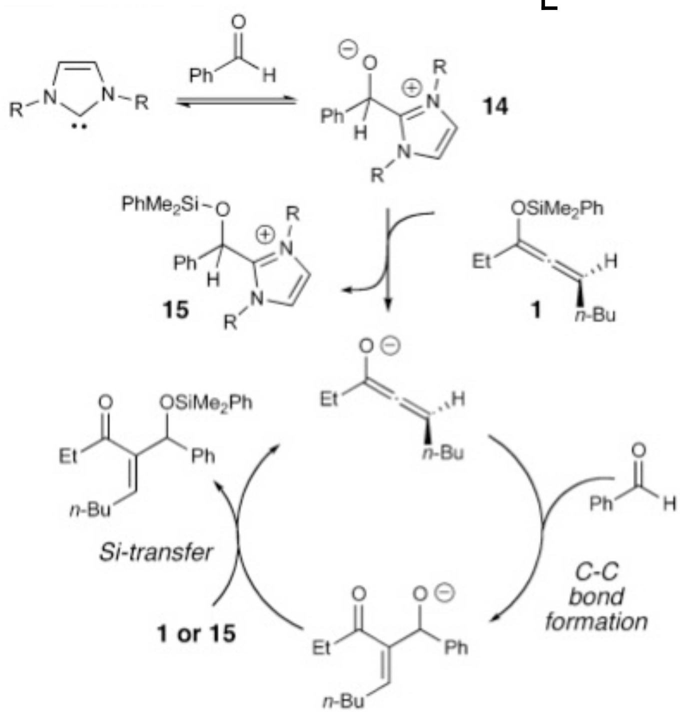
NHC-Catalysis/Initiation of Silyl Enol Ethers

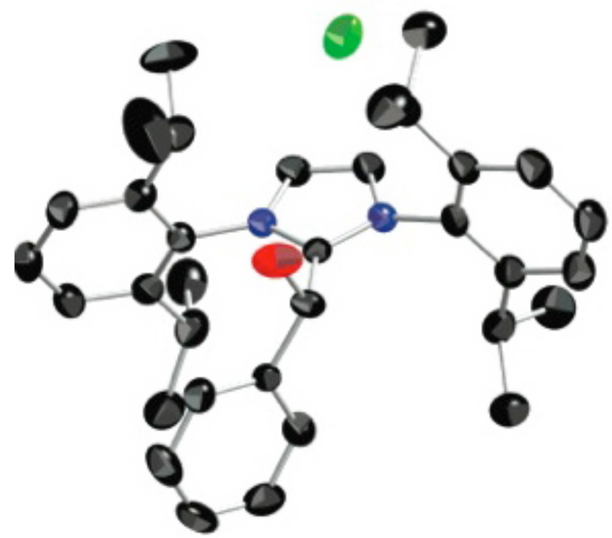
Song



Scheidt







Song, J. J. et al. *Org. Lett.* **2007**, *9*, 1013.
Scheidt, K. A. et al. *Org. Lett.* **2007**, *9*, 2581.

In Conclusion

— N-Heterocyclic carbenes are powerful reagents for the synthesis that have seen a remarkable growth in application over recent years.
— NHC organocatalysis has given chemists the ability to access unusual reactivity patterns (Umpolung) along with other reactions (1,2-additions, redox, opening of small rings).
— New synthetic opportunities are just beginning to be explored, along with improvements in enantioselective NHC catalysis.
— Although not covered in this discussion, it is worth mentioning that NHC's have also proven as valuable compounds for ring-opening polymerizations and have been utilized effectively as ligands in metal catalysis.