

An Introduction to N-heterocyclic Carbenes:

Prior to 1960, a school of thought that carbenes were too reactive to be isolated thwarted widespread efforts to investigate carbene chemistry.

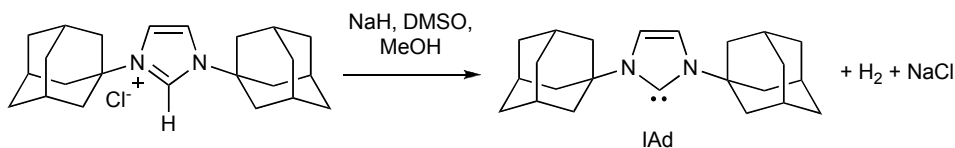
Perhaps true for the majority of carbenes, this proved to be an inaccurate assessment of the N-heterocyclic carbenes.

In the early 1960's Wanzlick (*Angew. Chem. Int. Ed.* **1962**, 1, 75-80) first investigated the reactivity and stability of N-heterocyclic carbenes.

Shortly thereafter, Wanzlick (*Angew. Chem. Int. Ed.* **1968**, 7, 141-142) reported the first application of NHCs as ligands for metal complexes.

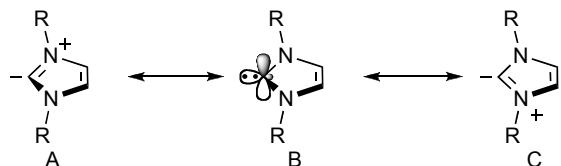
Surprisingly, the field of NHCs as ligands in transition metal chemistry remained dormant for 23 years.

In 1991, a report by Arduengo and co-workers (*J. Am. Chem. Soc.* **1991**, 113, 361-363) on the extraordinary stability, isolation and storability of crystalline NHC IAd.

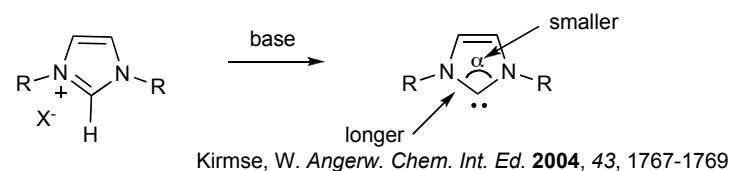


N-heterocyclic carbenes are electronically (orbital overlap) and sterically (Me vs. Ad) stabilized.

Different from traditional carbenes, NHCs are electron rich: (resonance)



How viable is resonance contributor B?

**Attractive Features of NHCs as Ligands for transition metal catalysts:**

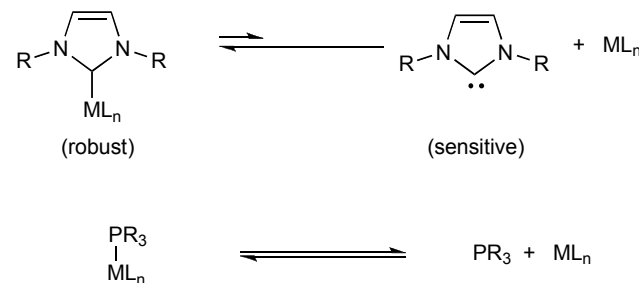
NHCs are electron-rich, neutral σ -donor ligands (evidenced by IR frequency of CO/metal/NHC complexes).

Electron donating ability of NHCs span a very narrow range when compared to phosphine ligands

Electronics can be altered by changing the nature of the azole ring: benzimidazole < imidazole < imidazoline (order of electron donating power).

NHC-metal complex stability:

NHCs form very strong bonds with the majority of metals (stronger than phosphines!)

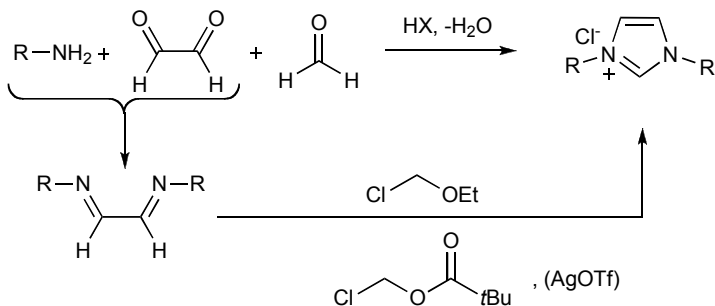


NHCs are most frequently prepared via deprotonation of the corresponding azolium salts (**imidazolium**, triazolium, tetrazolium, pyrazolium, benzimidazolium, oxazolium, thiazolium salts - pK_a - 21-24).

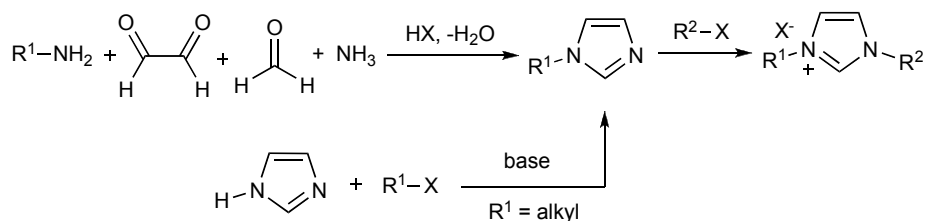
Imidazolium synthesis:

- Existing imidazoles can be alkylated with appropriate electrophiles.
- The imidazolium ring can be built:

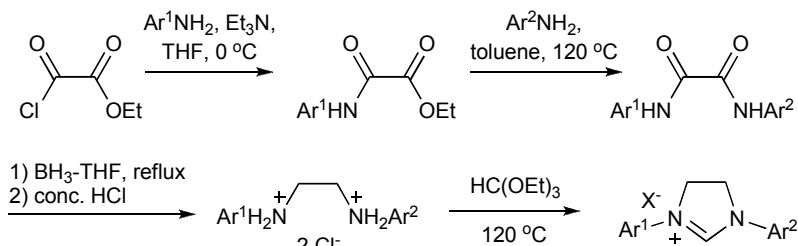
a) symmetric synthesis:



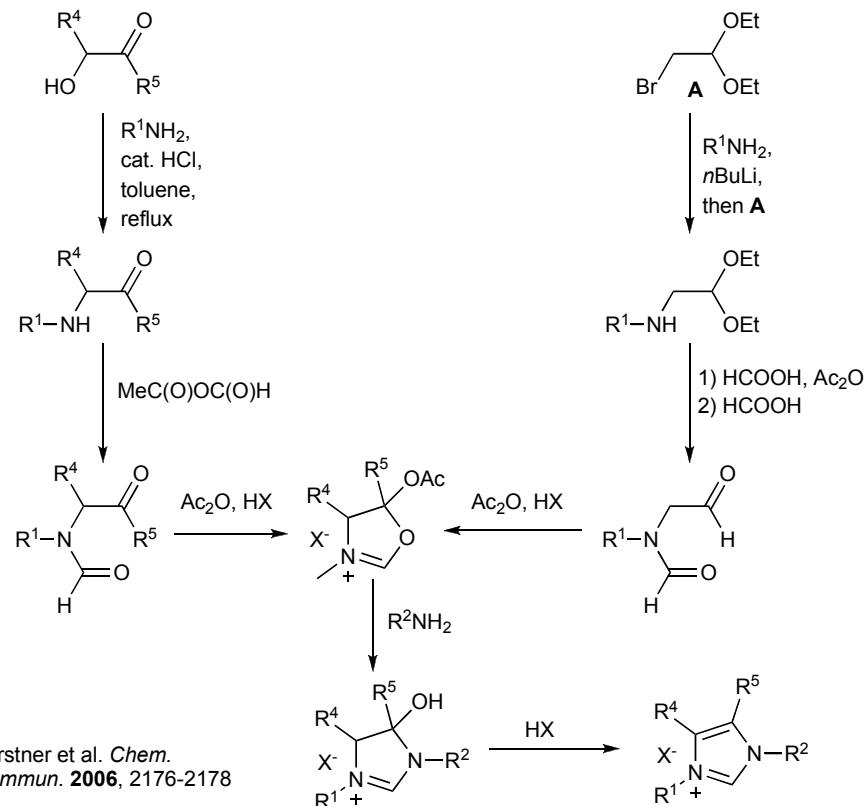
b) unsymmetrical synthesis:



c) unsymmetrical synthesis of imidazolium salts:



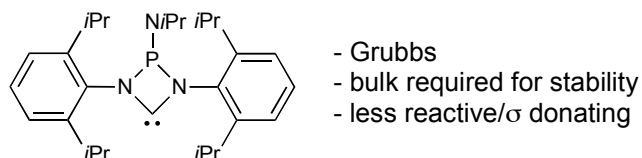
d) unsymmetrical synthesis of imidazolium salts:



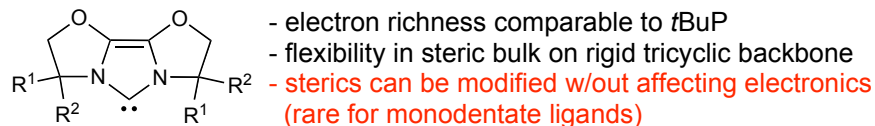
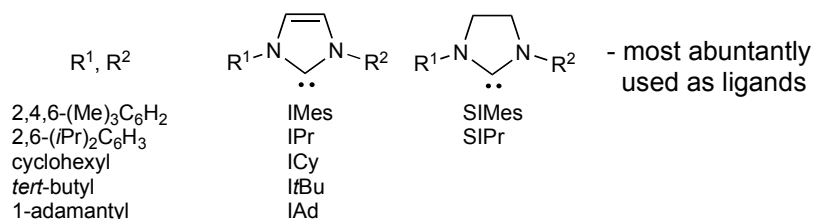
Furstner et al. *Chem. Commun.* **2006**, 2176-2178

Different Monodentate NHC Ligand Classes:

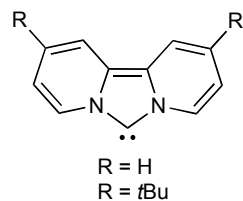
4-membered NHC



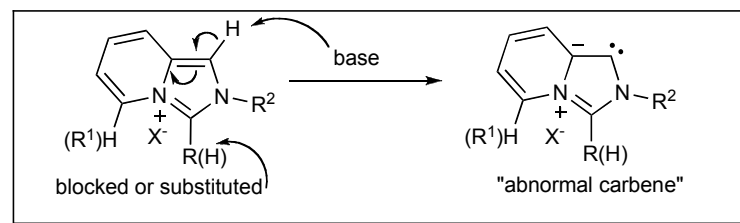
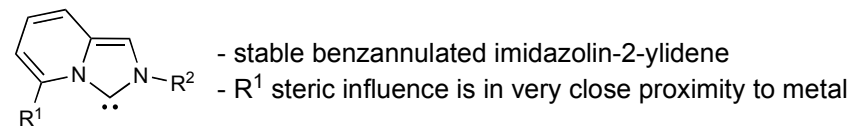
5-membered NHC



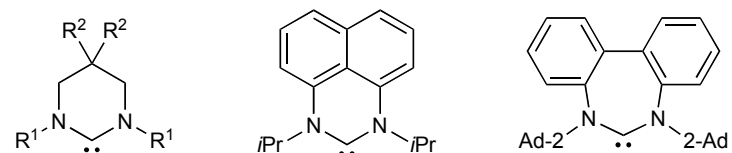
$R^1, R^2 = (CH_2)_4$: IBiox 5
 $R^1, R^2 = (CH_2)_5$: IBiox 6
 $R^1, R^2 = (CH_2)_6$: IBiox 7
 $R^1, R^2 = (CH_2)_7$: IBiox 8
 $R^1, R^2 = (CH_2)_{11}$: IBiox 12



- R = H - very electron rich, but also unstable
- R = *t*Bu - very electron rich and stable



6 and 7-membered NHC



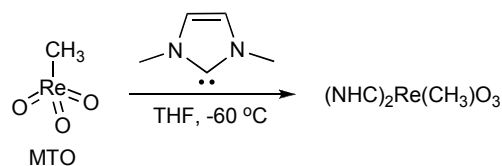
- rarely seen outside of initial preparation and testing
- only complexes of 7-member ring carbene isolable

NHC as ligands for high-oxidation-state metal complexes and oxidation catalysts:

Points to consider:

- 1) Phosphines are not used as ancillary ligands in oxidation chemistry. Why?
- 2) Are free NHC subject to the same fate as free phosphines?
- 3) Promise held by NHC for oxidation chemistry.

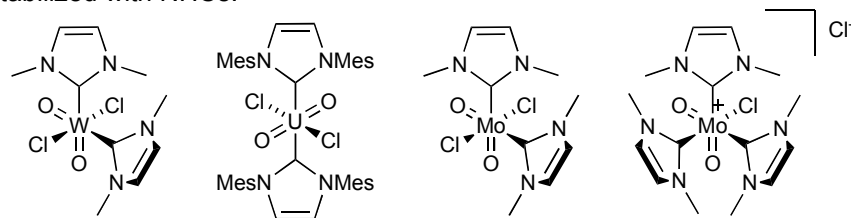
NHC as a ligand for the stabilization of high-oxidation-state metals:



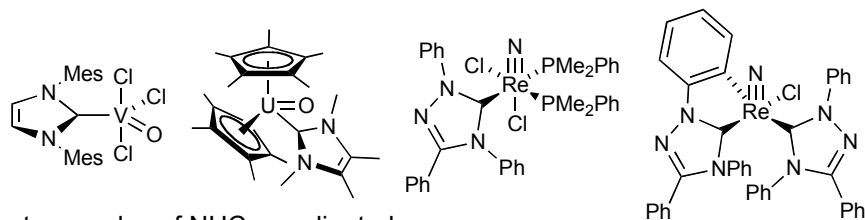
Herrmann et al. *J. Organomet. Chem.* **1994**, 480:C7

- stable complex below -20°C
- NHC **NOT** oxidized at -60°C
- phosphines are rapidly oxidized with MTO

A number of additional high-valent metal complexes have been stabilized with NHCs:

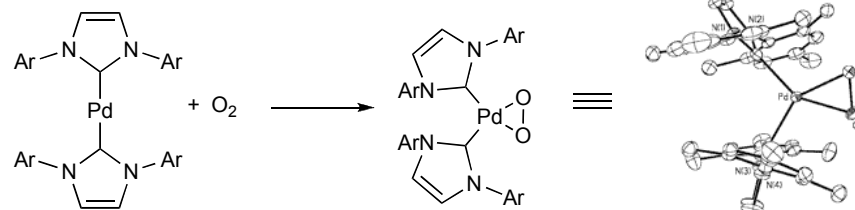
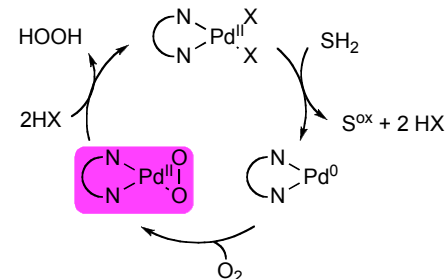


- first cationic Mo(VI) complex



- first examples of NHC-coordinated metal-oxo complexes characterized by X-ray crystallography

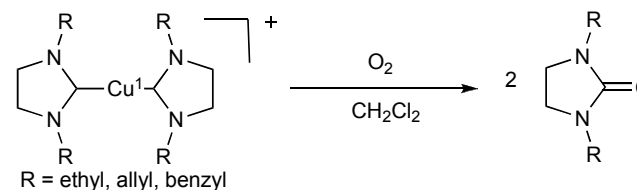
Recent independent studies by Stahl and Kawashima show NHCs playing a role as stabilizing ligands in palladium oxidation reactions (*J. Am. Chem. Soc.* **2001**, 123, 7188-7189, *J. Am. Chem. Soc.* **2004**, 126, 10212-10213 and *J. Am. Chem. Soc.* **2005**, 127, 7294-7295.)



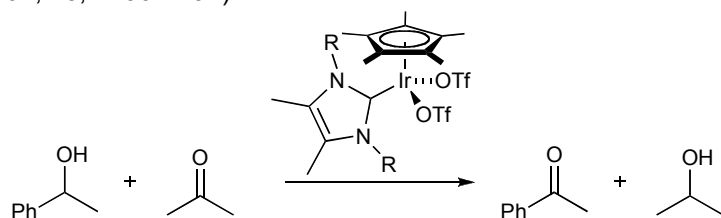
- stability of these metal-complexed NHCs relative to phosphines will permit further analysis of these fundamental reactions

NHCs have been found to be useful with cobalt and nickel as stabilizing ligands for oxidation (allylic oxidations).

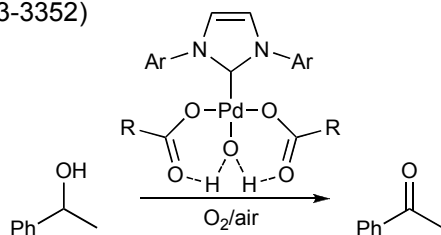
However, sterically hindered bis-carbene complexes of Cu(I) undergo rapid oxidation:



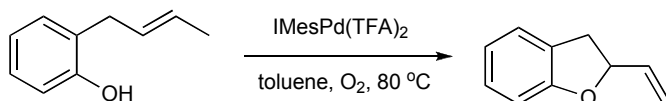
NHCs are not yet universally applicable to metal-mediated oxidation

Oxidation Reactions Catalyzed by NHC-Coordinated Metal ComplexesOppenauer-Type Alcohol Oxidation: (Yamaguchi *et al. Organometallics* **2004**, *23*, 1490-1492)

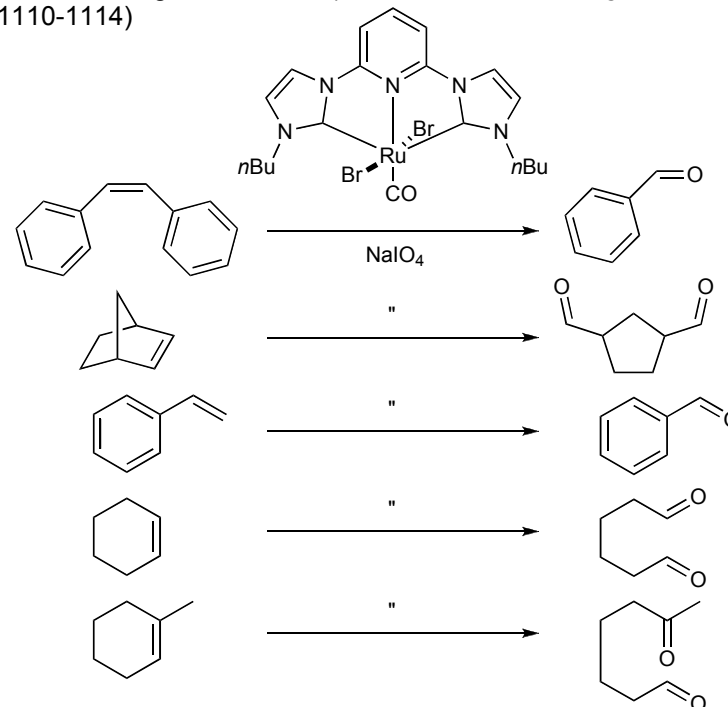
- smaller R-substituents promoted catalytic activity
- R = Me - cat. loading = 0.025 mol % w/ 3200 turnovers
- Analogs with PPh₃ or P*n*Bu₃ ligands were not active

Palladium-Catalyzed Aerobic Alcohol Oxidation: (Sigman *et al. J. Org. Chem.* **2005**, *70*, 3343-3352)

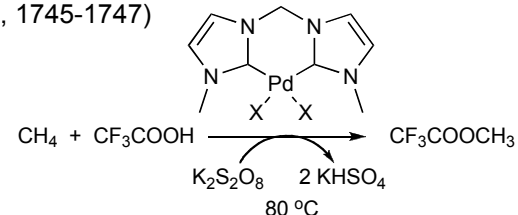
- A single NHC ligand can withstand the aerobic oxidation conditions
- Suggesting, despite numerous cycling between Pd^{II} and Pd⁰, the ligand does not dissociate from the palladium center

Wacker-Type Oxidation: (Muniz, K. *Adv. Synth. Catal.* **2004**, *346*, 1425-1428)

- Nitrogen-containing heterocycles have been prepared similarly
- seven membered NHC ligands have been successfully employed

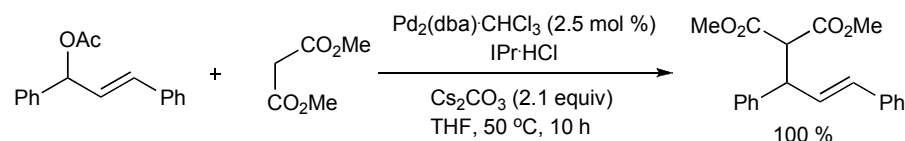
Oxidative Cleavage of Alkenes: (Crabtree and Persis *Organometallics* **2003**, *22*, 1110-1114)

- small reaction scope - electron-deficient alkenes appear to react slower than electron-rich alkenes
- evidence supports the NHC-Ru complex remaining in tact during the reaction

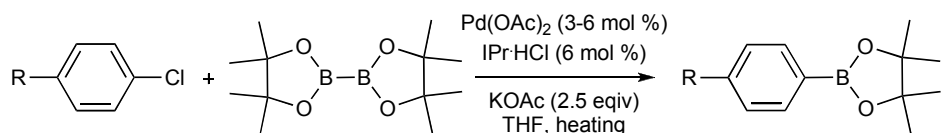
Oxidation of Methane: (Herrmann and Strassner *Angew. Chem. Int. Ed.* **2002**, *41*, 1745-1747)

- Chelating nitrogen ligands did not work under comparable conditions
- Yield is only 2-3 times higher than with Pd(OAc)₂ without ligands

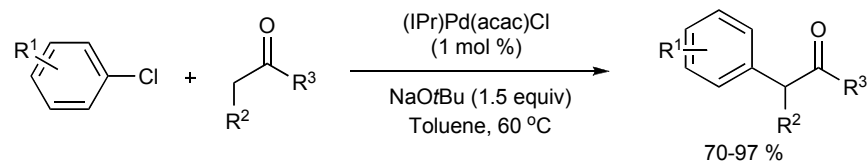
Palladium Catalyzed Reactions (Other than Oxidations) Using NHCs

Allylic Alkylation: (Mori et al. *Org. Lett.* **2003**, 5, 31-33)

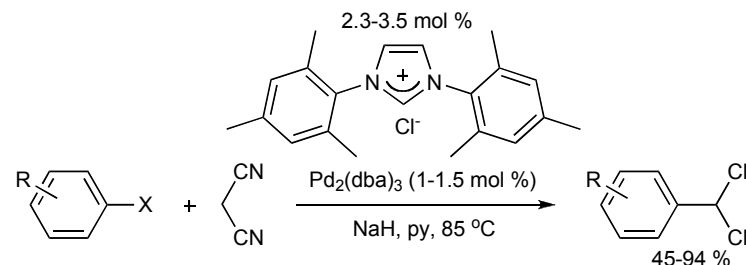
- no conversion in the absence of the NHC ligand
- asymmetric version has been reported (*Organometallics* **2003**, 22, 4187-4189)

Borylation of Aryl Chlorides: (Furstner et al. *Org. Lett.* **2002**, 4, 541-543)

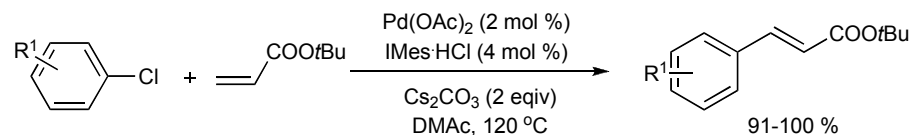
- first general NHC/palladium cat. coupling of ArX with pinacolborane
- more mild conditions can be used with aryl-diazonium salts (r.t./no base)

 α -Arylation of Carbonyl Compounds: (Nolan et al. *Tetrahedron* **2005**, 61, 9716-9722)

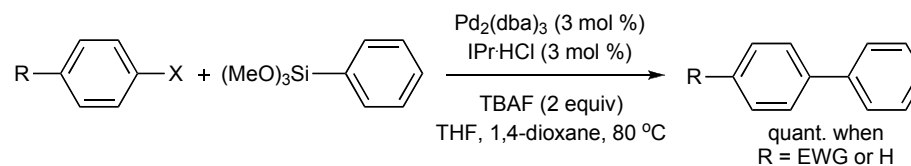
- short reaction times of 1-3 h with one exception (10 h)
- moderate temperature
- has been extended to esters (*J. Am. Chem. Soc.* **2001**, 123, 8410-8411) and amides (*J. Org. Chem.* **2001**, 66, 3402-3415) by Hartwig

 α -Arylation of Malonitrile: (Huang et al. *Chem. Commun.* **2003**, 1444-1445)

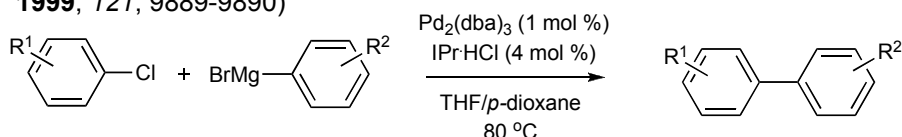
- aryl chlorides were low yielding
- rxn can be run in THF when using aryl iodides

Heck reaction: (Herrmann et al. *Angw. Chem. Int. Ed.* **1995**, 34, 2371-2374)

- 1st catalytic application of Pd-NHC complexes
- considered a standard for new palladium systems (for reactivity and stability - long rxn times/harsh conditions)
- mixed-carbene phosphine ligands have been developed
- r.t. and short reaction times with diazonium salts

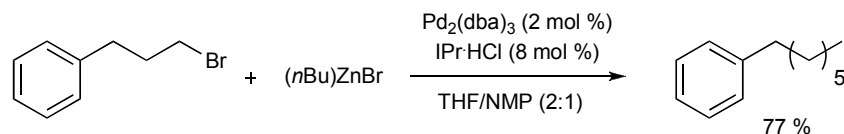
Hiyama Reaction: (Nolan et al. *Organic Letters* **2000**, 2, 2053-2055)

Kumada-Tamao-Corriu Reaction: (Nolan et al. *J. Am. Chem. Soc.* **1999**, 121, 9889-9890)



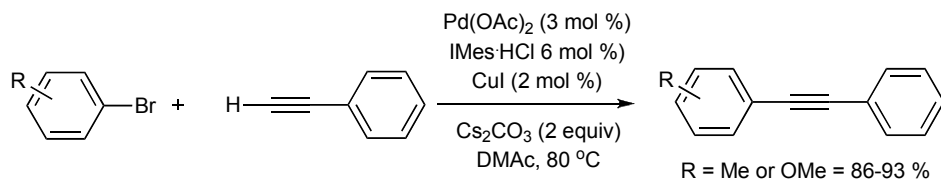
- first successful coupling between unactivated aryl chloride with ArMgBr
- NHCs are also efficient ligands for the palladium-catalyzed coupling of primary alkyl halides with ArMgBr (*J. Organomet. Chem.* **2003**, 687, 403-9)

Negishi Reaction: (Organ et al. *Org. Lett.* **2005**, 7, 3805-3807)



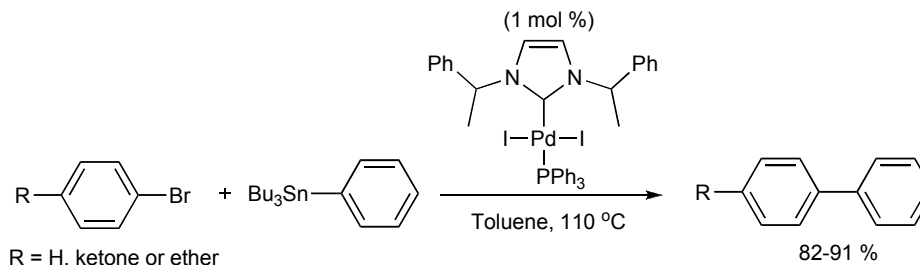
- one noteworthy point is the good functional group tolerance: esters, nitriles, amides, alkynes, and acetals!

Sonogashira Reaction: (Batey et al. *Org. Lett.* **2002**, 4, 1411-1414)



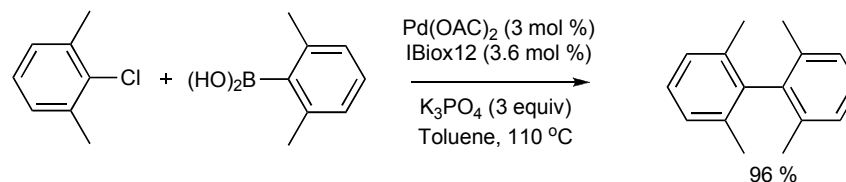
- there is currently no efficient application of carbene ligands to the coupling of aryl chlorides!
- a method for cross-coupling of unactivated, β-hydrogen containing alkyl electrophiles using NHCs has been described (*J. Am. Chem. Soc.* **2003**, 125, 13642-13643)
- bulky ligands work best, phosphine ligands don't work!

Stilli Reaction: (Herrmann et al. *J. Organomet. Chem.* **1999**, 585, 348-352)



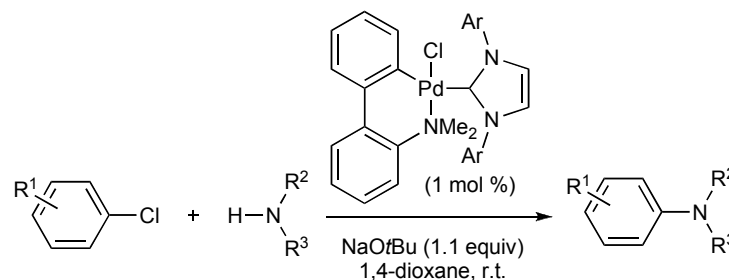
- this transformation remains largely unexplored with NHC ligands

Suzuki-Miyaura Reaction: (Buchwald et al. *Angew. Chem. Int. Ed.* **2004**, 43, 1871-1876)



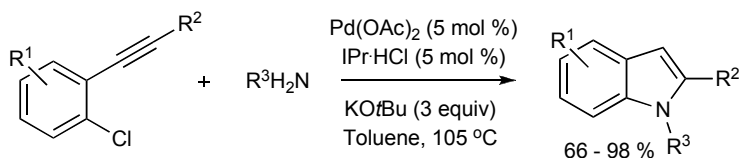
- greater than 15 papers on this transformation with NHCs
- first report of tetra-ortho-substituted biaryl coupling from aryl chlorides

Buchwald-Hartwig Reaction: (Nolan et al. *Org. Lett.* **2003**, 5, 1479-1482)



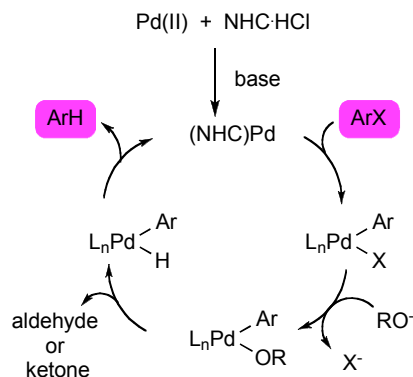
- reaction can be carried out in 2 h at room temperature with ArCl

Tandem Coupling Reaction: (Ackermann, L. *Org. Lett.* **2005**, 7, 439-442)



- reaction proceeds via amination with short reaction times - 2 h

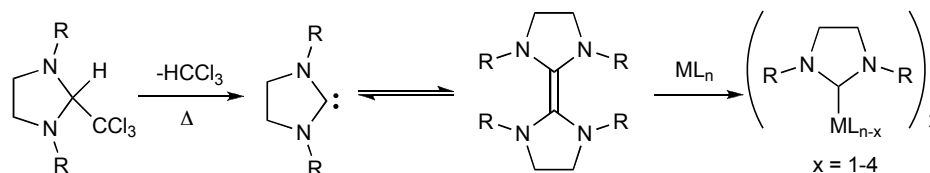
Dehalogenation Reactions: (Nolan et al. *Organometallics* **2001**, 20, 3607-3612)



- SIMes·HCl works well for bromides and chlorides at high temperature
- the use of a base containing a β -hydrogen is essential
- aryl chlorides have been removed with (IPr)Pd(allyl)Cl at low catalyst loading (0.5-0.025 mol %) and moderate temperature (60 °C) (*J. Org. Chem.* **2004**, 69, 3173-3180)

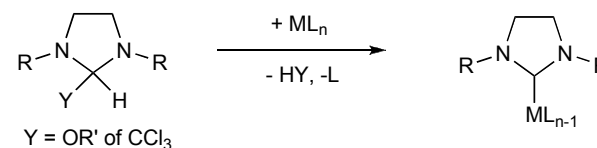
Routes to NHC Complexes

Insertion of a Metal into the C=C Bond of Bis(imidazolidin-2-ylidene) Olefins

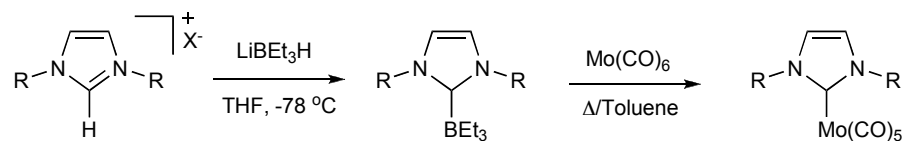


- Wanzlick's attempt at obtaining NHC - postulated equilibrium
- basis for preparation of NHC complexes from electron rich alkenes
- all NHC obtained this way are saturated

Use of Carbene Adducts or "Protected" Forms of Free NHCs



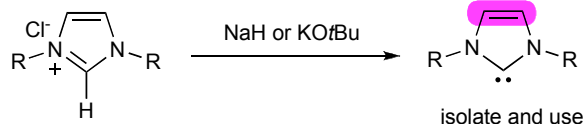
- readily eliminate alcohol or chloroform to give carbene
- it is not clear whether the so formed NHC reacts with the metal or if the adduct first dimerizes and subsequently complexes with the metal.



Yamaguchi et al. *Chem. Commun* **2004**, 2160-2161

- the NHC-borane adduct can be used as a versatile stable synthon for the preparation of NHC complexes.

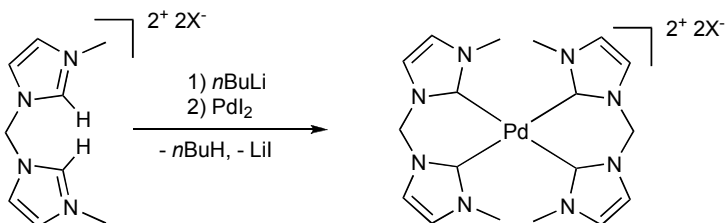
Preformed, Isolated Free Carbene:



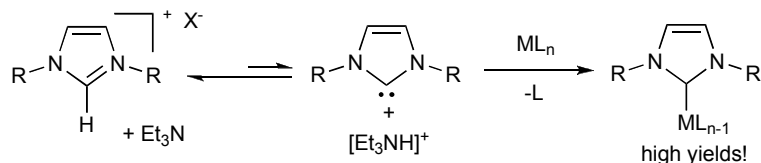
- Arduengo's work shattered the idea that NHC were too unstable
- Initially thought to be stable due to STERICs, but now it is assumed ELECTRONICS play a more important role (unsaturated more stable)
- Advantage - can be used directly to replace labile ligands

In Situ Deprotonation of Azolium Salt with a Base

Deprotonation with an External Base: (Fehlhammer et al. *J. Organomet. Chem.* **1995**, 490, 149-153)

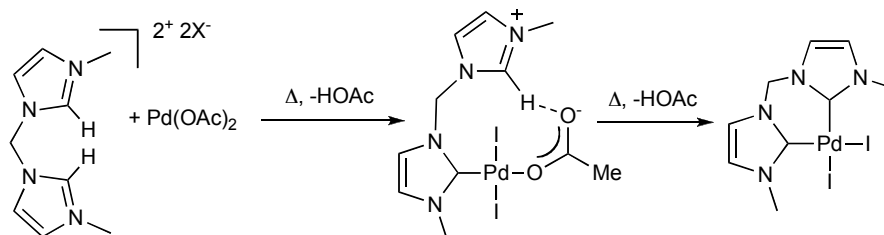


- mono, bi and tridentate NHC ligands have been prepared this way
- use of strong base is convenient BUT can't use in presence of other (than C-2) acidic or electrophilic center



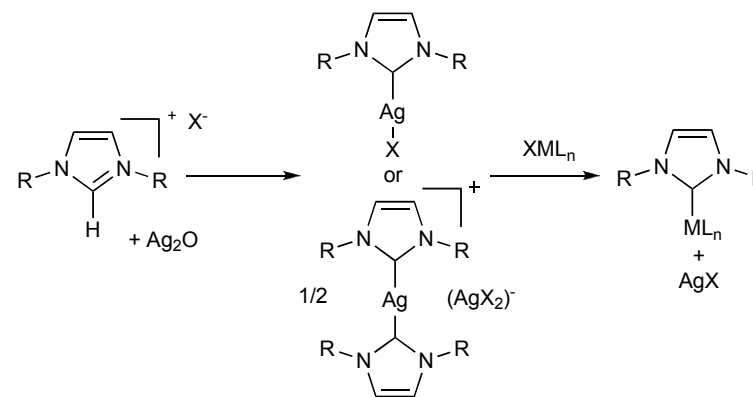
- pK_a values 25.6 - 39.1 (most basic phosphine $pK_a = 10$)
- thermodynamics ??? this equilibrium needs to be studied

Deprotonation with Metal Complex Containing Basic Ligand:



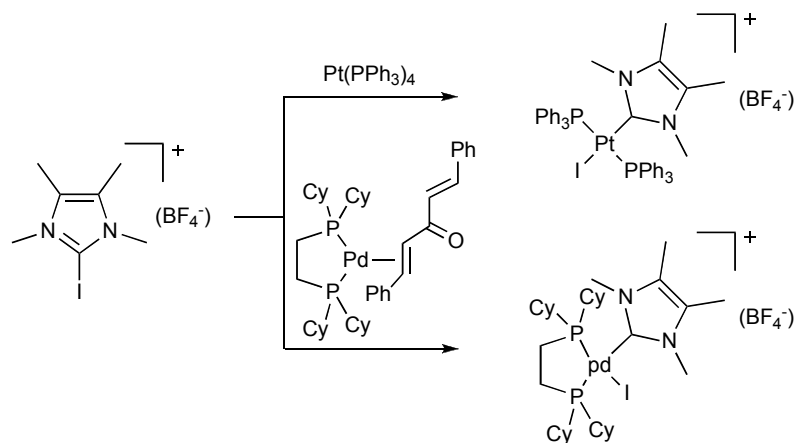
- convenient method - many metal complexes with acetate, hydride, or acetylacetonate ligands are \$ or easy to make

Transmetalation from a Silver-NHC Complex:



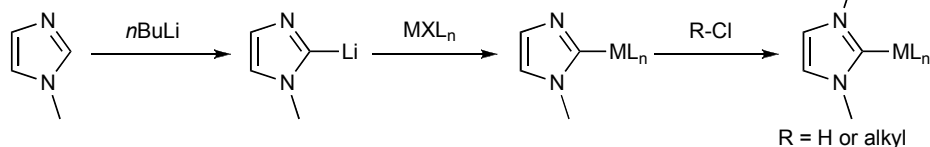
- weak NHC-Ag bond makes this reagent a good transfer reagent
- overcomes the difficulty associated with strong bases, inert atmosphere and complicated workups
- complexes with Au, Cu, Ni, Pd, Pt, Rh, Ir or Ru - lability of NHC-Ag bond and insolubility of the silver halide are driving forces for reaction
- saturated NHCs are relatively inactive in this process

Oxidative Addition Via Activation of the C2-X Bond (X = Me, Halogen or H):
(Yates et al. *J. Am. Chem. Soc.* **2001**, 123, 8317-8328)

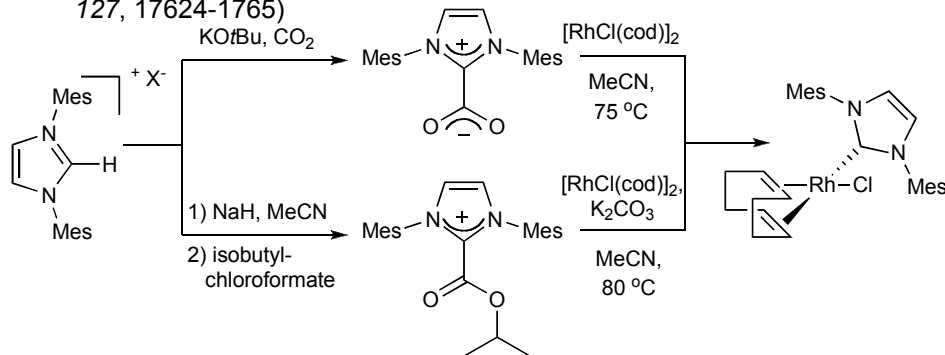


Less Utilized Methods of Complex Formation:

Transmetalation of Lithiated Heterocycles:



Via the C2 Carboxylate or Ester: (Crabtree et al. *J. Am. Chem. Soc.* **2005**, 127, 17624-1765)

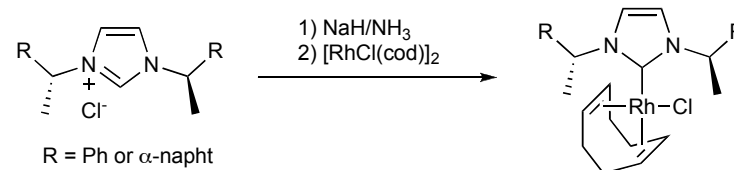


Chiral NHCs as Stereodirecting Ligands in Asymmetric Catalysis:

Five Major Families of Chiral NHC Ligands:

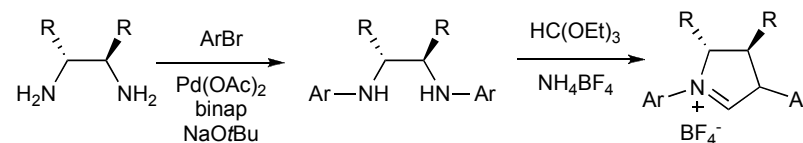
- 1) NHC ligands with N-substituents containing centers of chirality
- 2) NHC ligands containing chiral elements within the N-heterocycle
- 3) NHC ligands containing an element of axial chirality
- 4) NHC ligands containing an element of planar chirality
- 5) NHC ligands incorporating oxazoline units

1) NHC Ligands with N-Substituents Containing Centers of Chirality:
(Herrmann et al. *Angew. Chem. Int. Ed.* **1996**, 35, 2805-2807)



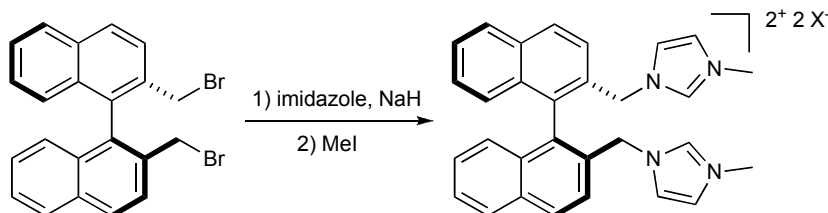
- initially these types of ligands showed good activity but poor stereoselectivity - free rotation about C-N axis?
- newer catalysts work very well for Michael additions (>90 % ee)
- bidentate ligands improve enantioselectivity
- some derived from amino acids

2) NHC Ligands Containing Chiral Elements Within the N-Heterocycle:
(Grubbs et al. *Org. Lett.* **2001**, 3, 3225-3228)



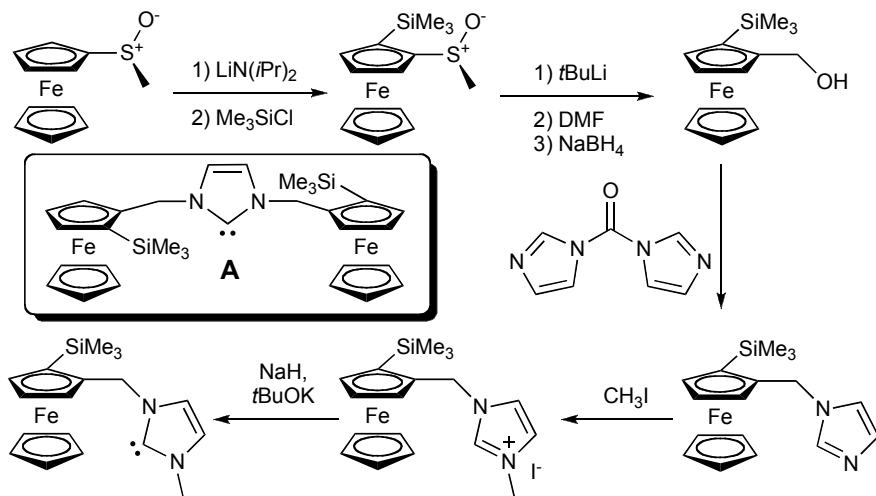
- more bulk at R(s) forces Ar onto reactive center for better ee's
- *ortho*-monosubstituted N-aryl substituents in the carbene ligands lead to greater selectivity than more symmetrically substituted derivatives
- ee's are very good overall

3) NHC Ligands Containing an Element of Axial Chirality: (RajanBabu et al. *Org. Lett.* **2000**, 2, 1125-1128)



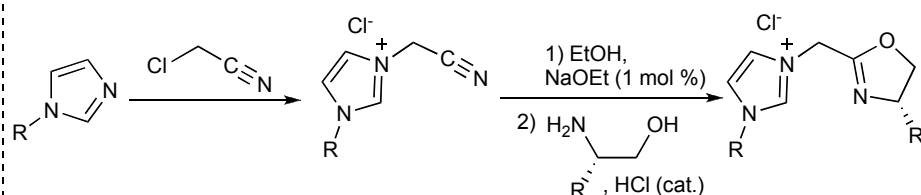
- first example of an axially chiral NHC complex
- can be complexed with Pd by refluxing in DMSO
- good illustration, but no activity - too much flexibility in 11-mem. ring
- direct functionalization on BINAP gives better results (bidentate)

4) NHC Ligands Containing an Element of Planar Chirality: (Bolm et al. *Organometallics* **2002**, 21, 707-710) (A: Togni et al. *Helv. Chim. Acta.* **2002**, 85, 2518-2522)

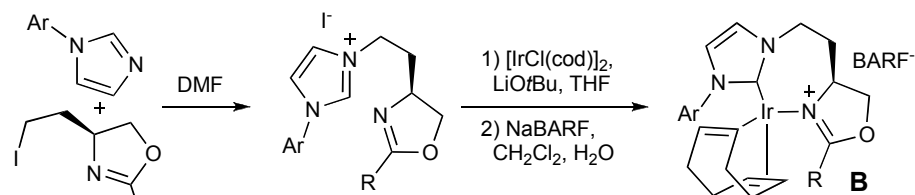


- first example of an NHC complex containing planar chirality
- again, good illustrations, but no reported activity yet
- directly linked ferrocene derivatives work well
- paracyclophanes show promising results

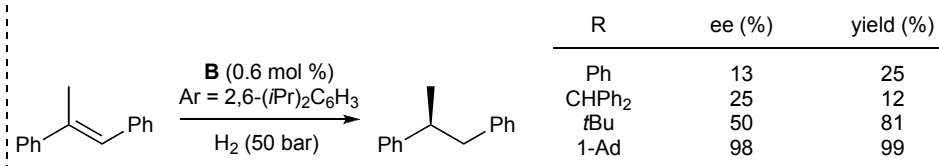
5) NHC Ligands Incorporating Oxazoline Units: (Herrmann et al. *Organometallics* **1998**, 17, 2162-8)



- this ligand has been coordinated to rhodium (I) and palladium (II)

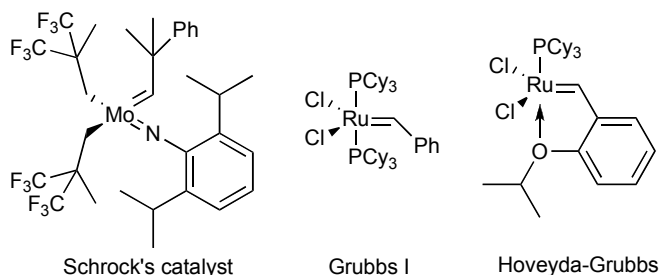


Burgess et al. *J. Am. Chem. Soc.* **2001**, 123, 8878-8879



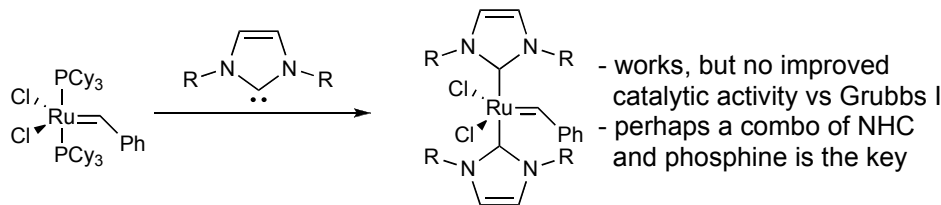
- inspired by the chiral bidentate phosphine-oxazoline ligands (*Phox*)
- this design allows for facile and rapid access to a large library of ligands through variation at C-2 (oxazoline) and N-atom of NHC
- this ligand has been successfully employed in the cat. hydrogenation of dienes (Burgess et al. *Chem. Commun.* **2005**, 672-674)

NHC-Ruthenium Complexes in Olefin Metathesis:

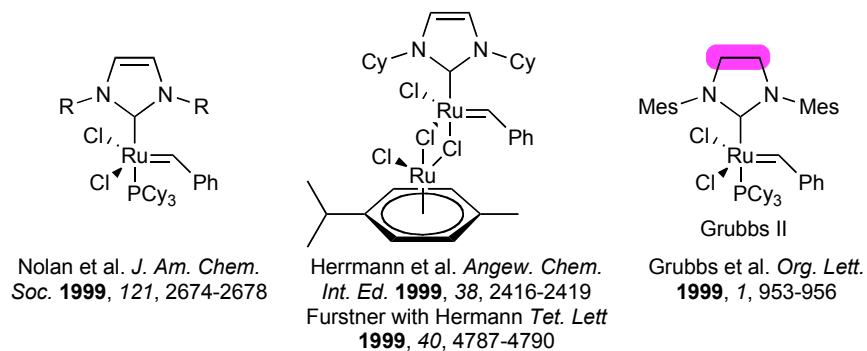


- Grubbs I is less active than Schrock's catalyst
- Grubbs I has greater functional group tolerance
- Grubbs I has relatively low thermal stability
- How to make it better??? - mechanism?

First attempt at NHC ligated cat. for RCM: (Herrmann et al. *Angew. Chem. Int. Ed.* **1998**, 37, 2490-2494)

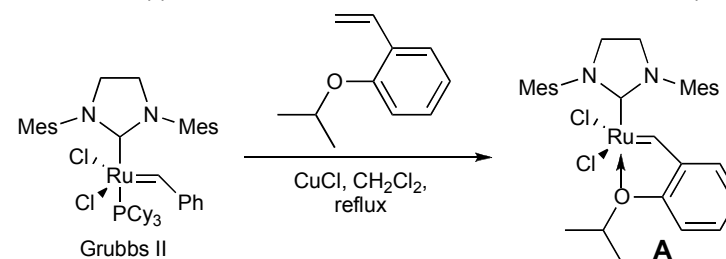


Combination catalysts for RCM:

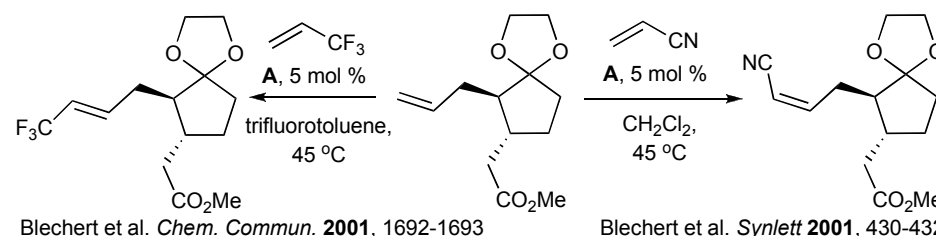


- greater stability (to air) better activity than Grubbs I
- reactivity in some cases surpasses Schrock's catalyst
- useful for tri- and tetrasubstituted olefins
- good E/Z selectivity depending on catalyst (E or Z)
- Grubbs II most active - saturated = more basic = more reactive

Viable phosphine-free catalysts: (Hoveyda et al. *J. Am. Chem. Soc.* **2000**, 122, 8168-8179)(Blechert et al. *Tet. Lett.* **2000**, 41, 9973-9976)



- now one of the most widely used catalysts for metathesis
- works in CM for electron-deficient olefins (high yield, selectivity)



Additional Variations:

- Chiral Grubbs II
- Chiral phosphine free Grubbs II
- Solid supported NHC-Ru complexes
 - Immobilization via the NHC Ligand
 - Attachment through the anionic ligand
- Homogenous catalysts
- Ionic liquids

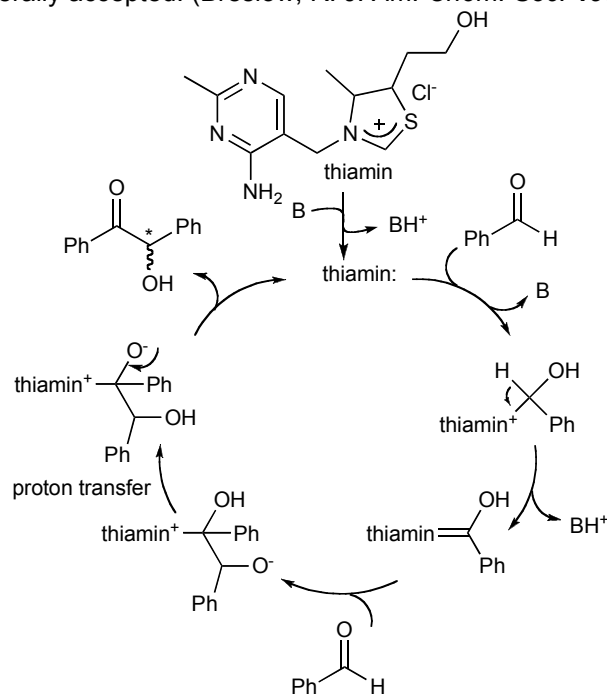
N-Heterocyclic Carbenes as Organocatalysts:**Benzoin Condensation:**

It's been known that cyanide anions catalyze the benzoin condensation since 1832: (Wohler, F. *Liebig. J. Ann. Pharm.* **1832**, 3, 249-282)

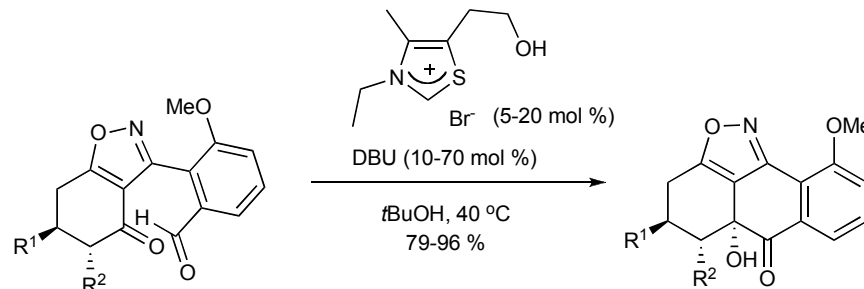
The mechanism was elucidated in 1903: (Lapworth, A. J. *J. Chem. Soc.* **1903**, 83, 995-1005)

The first report on carbene organocatalysis appeared in 1943: (van den Berg, H. J. *J. Mol. Cat.* **1943**, 51, 1-12)

Despite a good deal of debate, Breslow's 1958 description of the mechanism is still generally accepted: (Breslow, R. *J. Am. Chem. Soc.* **1958**, 80, 3719-26)



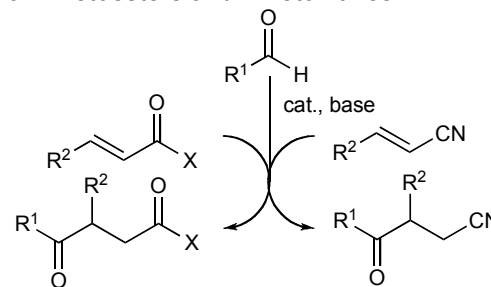
- a great deal of effort has gone into preparing asymmetric versions of the thiazolium salts with marked success in inducing chirality: (Sheehan et al. *J. Am. Chem. Soc.* **1966**, 88, 3666-3667; Sheehan et al. *J. Org. Chem. Soc.* **1966**, 39, 1196-1199; Takagi et al. *Bull. Chem. Soc. Jpn.* **1980**, 478-480; Marti et al. *Tet. Lett.* **199**, 521-524; Leeper et al. *Tet. Lett.* **1997**, 3611-3614; Leeper et al. *Tet. Lett.* **1997**, 3615-3618; Rawal et al. **1998**, 2925-2928; Leeper et al. *J. Chem. Soc. Perkin Trans. I*, **1998**, 1891-1893)
- surprisingly it was only recently (2003) that an intramolecular version of the NHC catalyzed acyloin condensation appeared: (Suzuki et al. *J. Am. Chem. Soc.* **2003**, 125, 8432-8433)

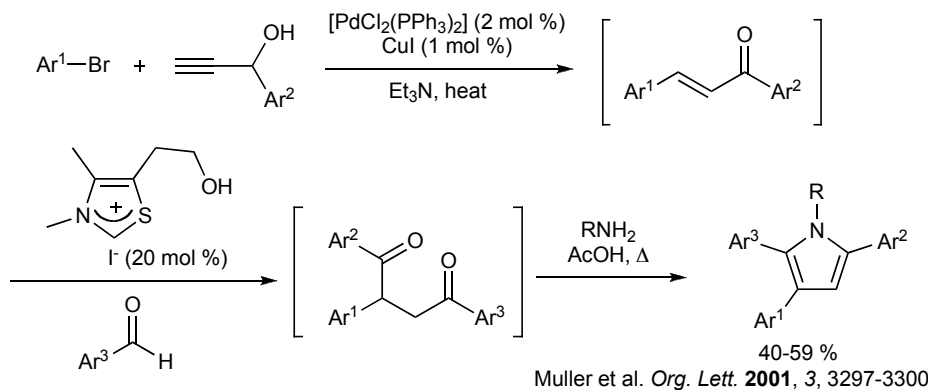


- the benzoin condensation can be catalyzed by a large number of NHCs ranging from chiral complexes to simple ionic liquids

Stetter Reaction:

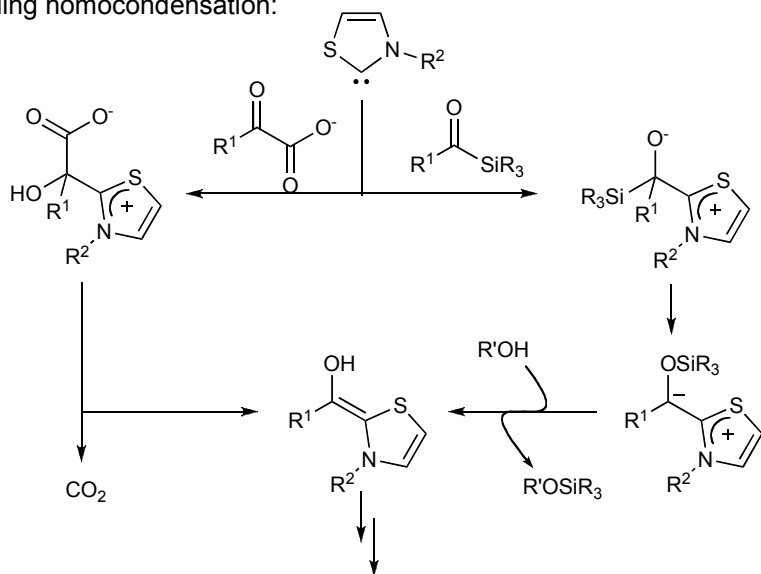
- simply extending the benzoin condensation to Michael acceptors
- well known for the formation of 1,4-diketones, but also works for the preparation of 4-ketoesters and 4-ketonitriles





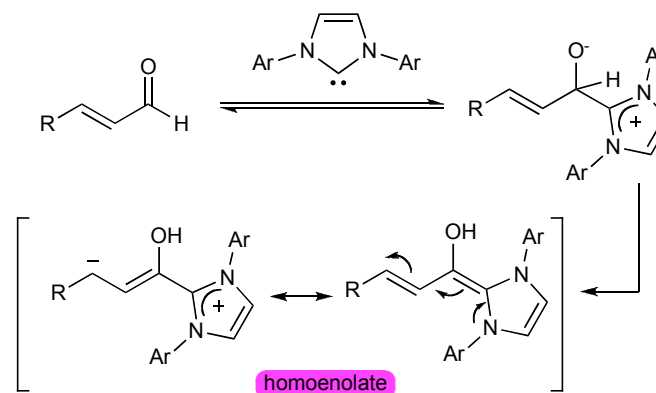
- the Stetter reaction is commonly employed in the synthesis of cyclopentanone derivatives and heterocycles
- above is an example of a one-pot four-step procedure to a pyrrole derivative

Avoiding homocondensation:

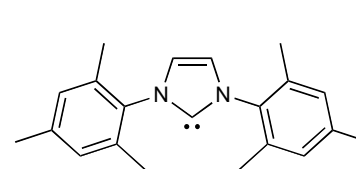


- employ carbonyl anion precursors such as α -keto carboxylates or acylsilanes

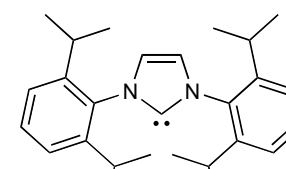
Generation of Homoenolates:



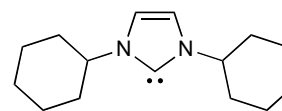
- Glorius (*Angew. Chem. Int. Ed.* **2004**, 43, 6205–6208) and Bode (*J. Am. Chem. Soc.* **2004**, 126, 14370-14371) have both shown that it is necessary to carefully adjust the steric bulk of the NHC



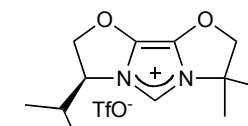
IMes - works well



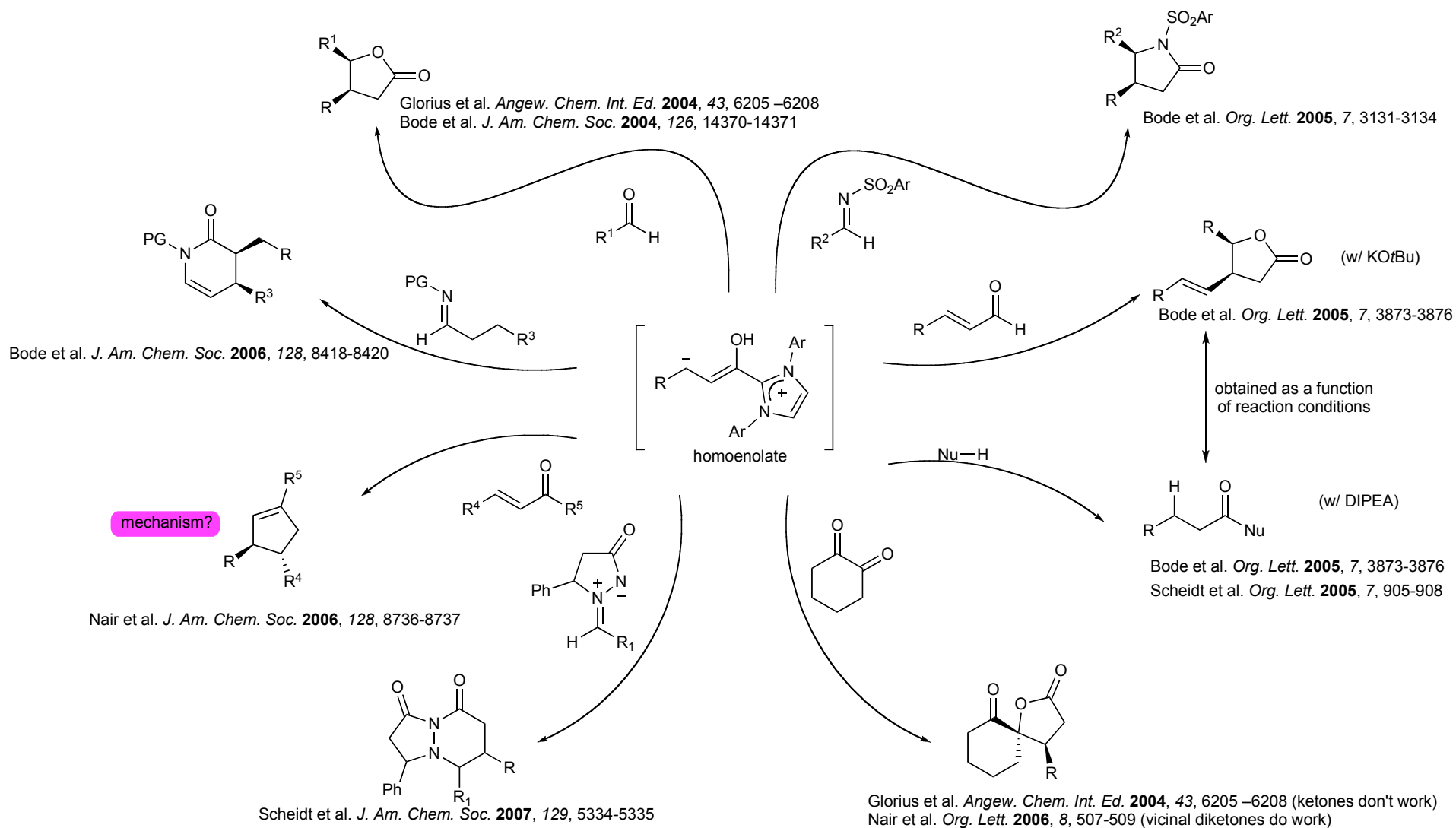
IPr = unselective



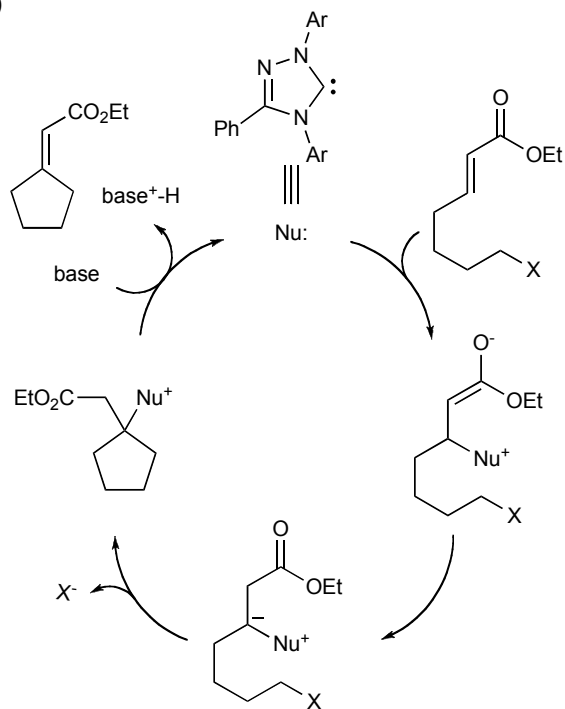
ICy - not reactive



enantioselective = (25 % ee)



Fu's extension to α , β -unsaturated esters: (*J. Am. Chem. Soc.* **2006**, *128*, 1472-1473)

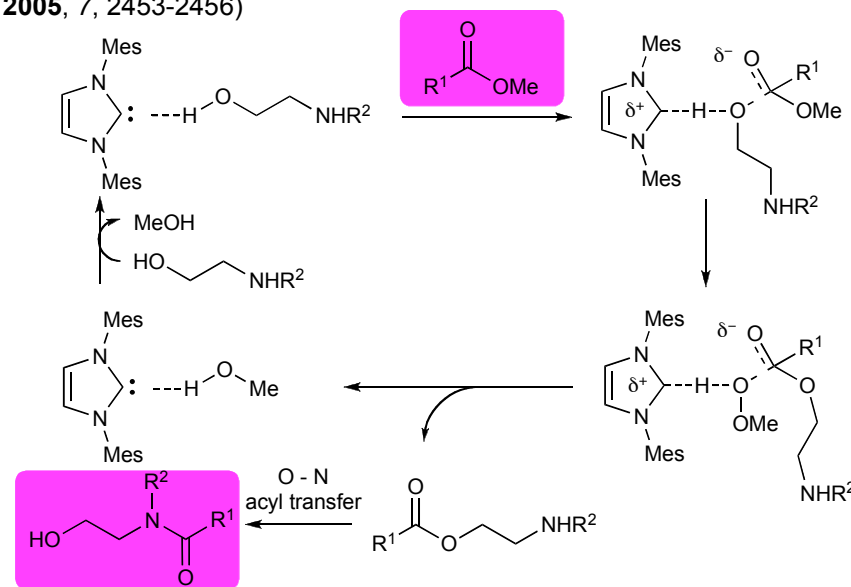


- interestingly neither the imidazolium or thiazolium NHCs worked
- phosphines also proved ineffective - this is in sharp contrast to their ability to cat. alkylation of unsaturated ketones (α -position)

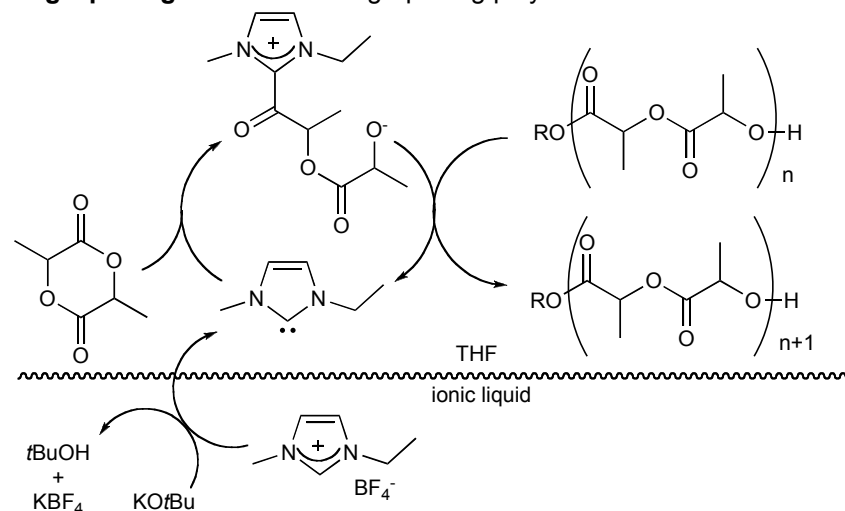
Transesterification and Acylation reactions:

- Nolan (*Org. Lett.* **2002**, *4*, 3583-3586) and independently Hendrick (*Org. Lett.* **2002**, *4*, 3587-3590) showed NHCs effectively catalyzed transesterification reactions
- Functional group tolerance, selectivity, and low catalyst loading are advantages of this approach
- this reaction has been extended to secondary alcohols (Nolan et al. *J. Org. Chem.* **2004**, *69*, 209-212)

Movassaghi's amidation of unactivated esters with amino alcohols: (*Org. Lett.* **2005**, *7*, 2453-2456)

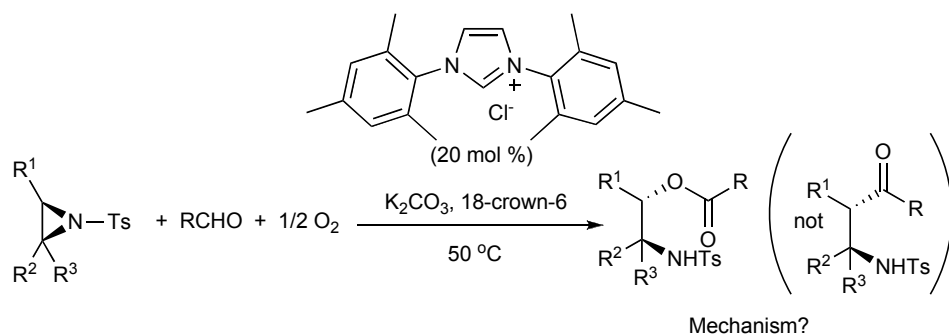


Ring Opening Reactions: Ring-opening polymerization:

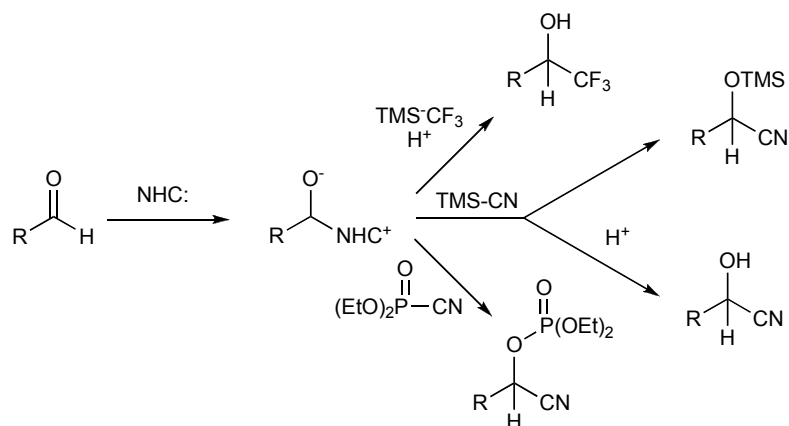
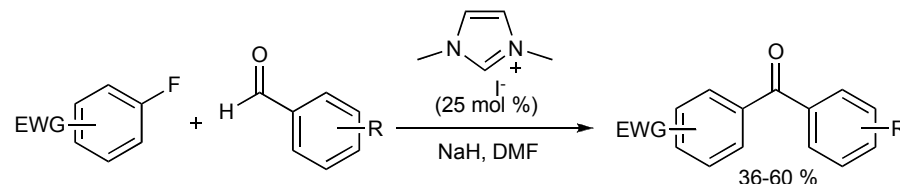


Ring-Opening Reactions of Three-Membered Rings:

- In 2001, Nguyen reported (*Org. Lett.* **2001**, 3, 2229-2231) that NHCs can promote the ring opening of epoxides by trialkylaluminum complexes
- In 2006, Wu established (*Tet. Lett.* **2006**, 47, 4813-4816) that NHCs are efficient catalysts for the ring opening of aziridines by silylated nucleophiles.
- Chen and co-workers have made a very interesting observation regarding the reaction of aziridines and aldehydes in the presence of an NHC cat. and oxygen (*Org. Lett.* **2006**, 8, 1521-1524)



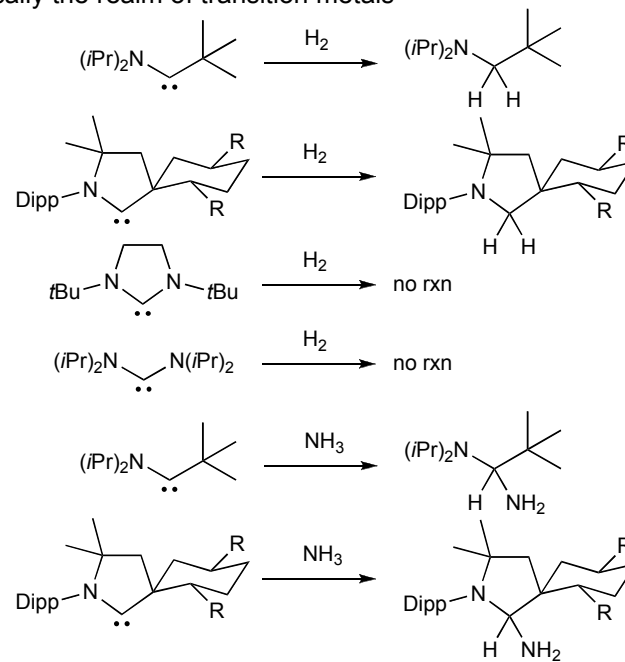
1,2-Addition reactions:

Nucleophilic benzoacylation: (Suzuki et al. *Chem. Commun.* **2003**, 1314-1315)

- moderate yields, but this cannot be accomplished via classic Friedel-Crafts reaction
- chloroarenes are inert under the reaction conditions

Facile splitting of hydrogen and ammonia: (Bertrand et al. *Science* **2007**, 316, 439-441)

- typically the realm of transition metals



Additional References:

- 1) Nolan et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988-3000
- 2) Nolan, S. P. *N-Heterocyclic Carbenes in Synthesis*; Wiley-VCH; Weinheim, 2006, pp 1-304
- 3) Glorius, F. *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Topics in Organometallic Chemistry; Springer-Verlag: Berlin Heidelberg, 2006, Vol. 21, pp 1-218