

The Other Side of NHCs: NHCs in Transition
Metal Catalysis

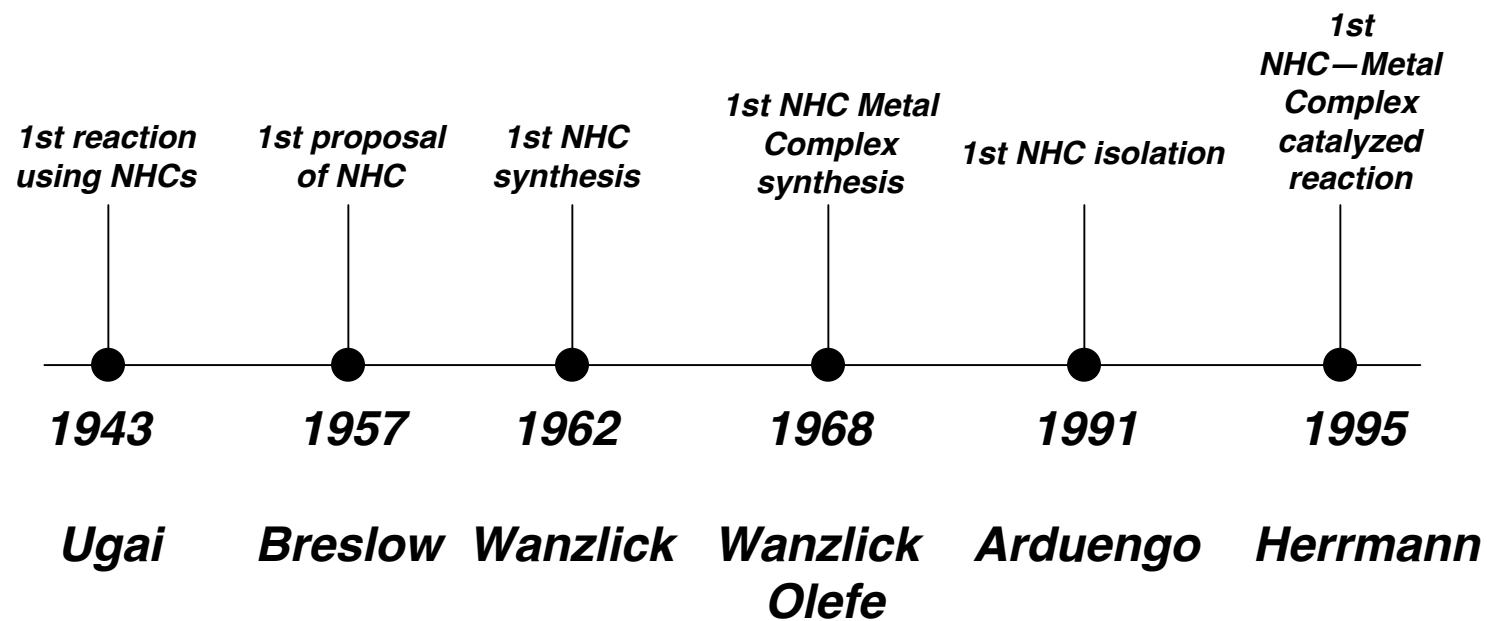
Long Lit 2-23-09

John Roberts

Outline of Long Lit.

- ***History of NHCs/Physical Properties***
- ***Formation of Metal Complexes/Comparison to Phosphines***
- ***Cross Couplings/Oxidation/Reduction***
- ***Metathesis/Conj. Addn./Applications Towards Clavirolide C***

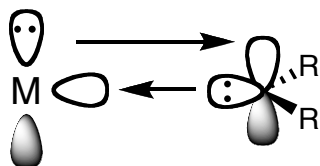
Timeline of NHCs in Synthesis



Types of Transition Metal Carbene Complexes

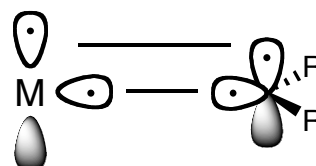
- **Historically, there have been two types of transition metal carbene complexes: Fischer and Schrock.**
- **NHC—Metal complexes represent a new class of complexes.**
- **Due to the NHCs poor π -backbonding capabilities a metal—NHC bond is usually represented as a single bond.**

Fischer Carbene



Carbene = Electrophilic
Low Ox. Metal
 π -Acceptor Ligands

Schrock Carbene

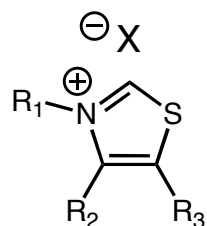


Carbene = Nucleophilic
High Ox. Metal
non π -Acceptor Ligands

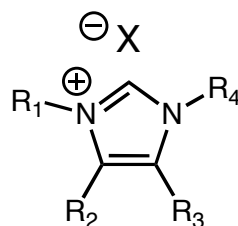
Types of N–Heterocyclic Carbenes

- *There are many types of NHC precursors, but thiazolium, triazolium, and imidazolium salts are the most important to catalysis.*
- *Imidazoles, saturated and unsaturated, are the most widely used NHCs as ligands.*
- *Four, six, and seven–membered NHCs also exist, but are not as widely used.*

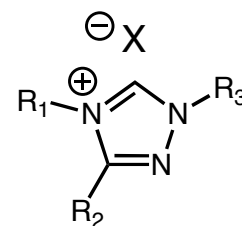
Thiazolium



Imidazolium

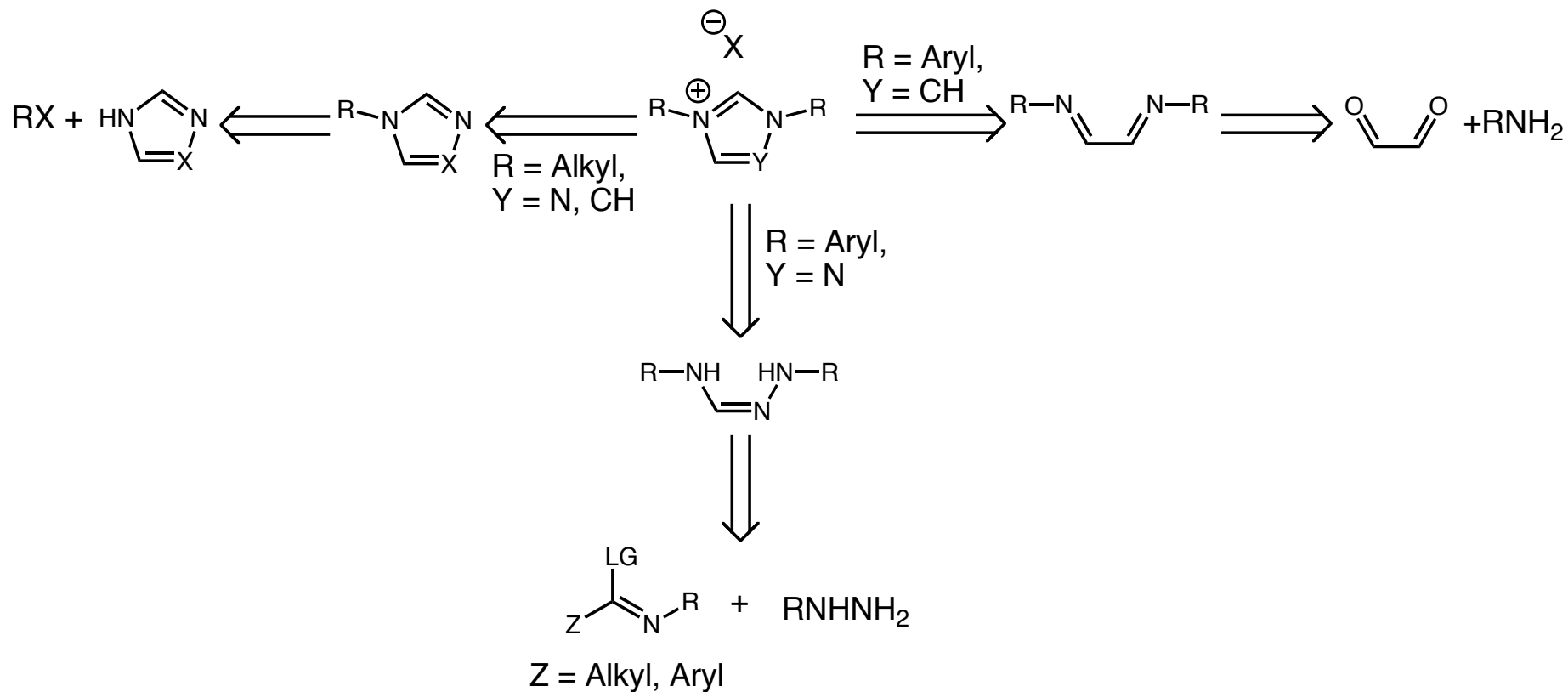


Triazolium



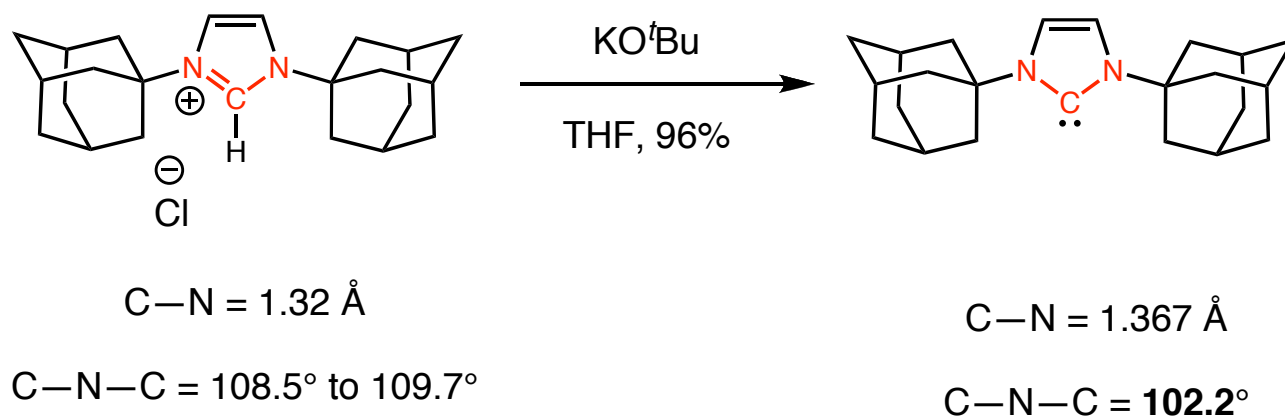
Routes to N–Heterocyclic Carbenes

- *Imidazolium and triazolium salts are the most prevalent ligands.*
- *Synthesis usually involves cyclizing a linear NHC precursor or alkylating the intact NHC core.*
- *Unsymmetrical/chiral NHCs involve more complex synthesis*



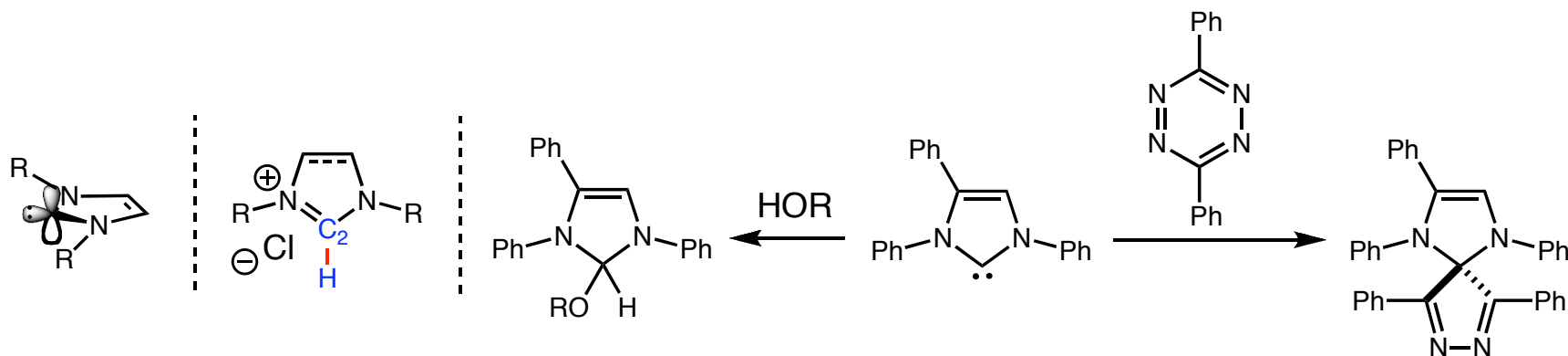
Arduengo's Breakthrough

- **Synthesized an adamantyl substituted imidazolium salt and rigorously characterized it.**
- **They were able to deprotonate and grow a crystal of the free carbene.**
- **NMR, Mass Spec., X-ray, and IR data unequivocally show the free carbene has been formed.**



Physical Characteristics of Carbenes

- **NHCs are singlet carbenes, with a filled σ orbital and an empty π orbital.**
- **The pK_a of the C_2 carbon is 24 (DMSO), making NHCs strongly basic.**
- **NHCs are nucleophilic, but they can also undergo cycloadditions and insertions like other carbenes.**



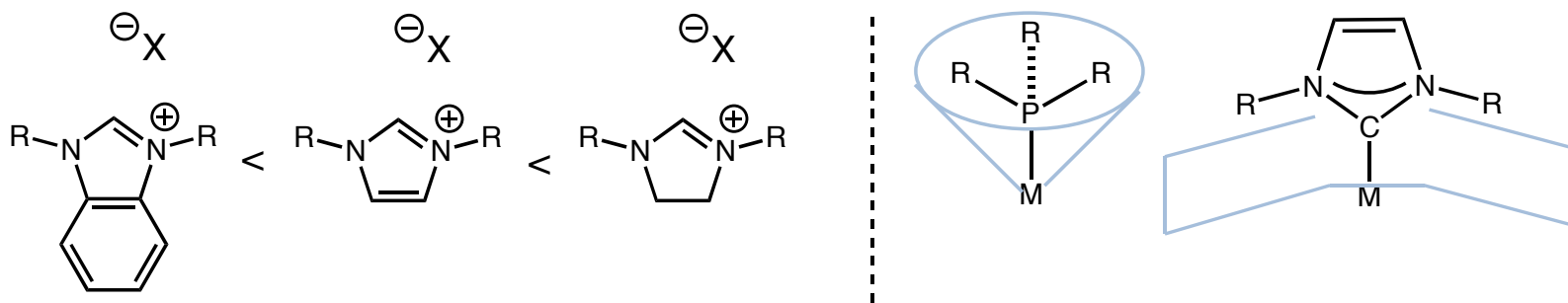
Bonding Characteristics to Metals

- ***NHCs are electron rich and strong σ donors. Their π back-bonding ability is the source of debate.***
- ***Substitution on the NHC, the metal complex, and the specific metal all affect the π back-bonding ability.***
- ***All NHCs have relatively similar donating ability, where as phosphines vary widely.***

<u>Ligand</u>	<u>Complex</u>	<u>$\nu_{\text{CO}}(\text{A}_1)$</u>
IMes	Ni(CO) ₃ (IMes)	2050.7
SIMes	Ni(CO) ₃ (SIMes)	2051.5
IPr	Ni(CO) ₃ (IPr)	2051.5
SIPr	Ni(CO) ₃ (SIPr)	2052.2
ICy	Ni(CO) ₃ (ICy)	2049.6
P ^t Bu ₃	Ni(CO) ₃ (P ^t Bu ₃)	2056.1
PCy ₃	Ni(CO) ₃ (PCy ₃)	2056.4
PPh ₃	Ni(CO) ₃ (PPh ₃)	2068.9

Stability/Shape of NHC Ligands

- **NHC ligands, in general, form more stable bonds with metals. Saturated NHCs bind more weakly than their unsaturated counterparts.**
- **The metal–NHC bond is not inert. Migratory insertion and reductive elimination are degradation pathways.**
- **NHC ligands have a different profile than phosphine ligands.**



Metals NHCs can Bind to

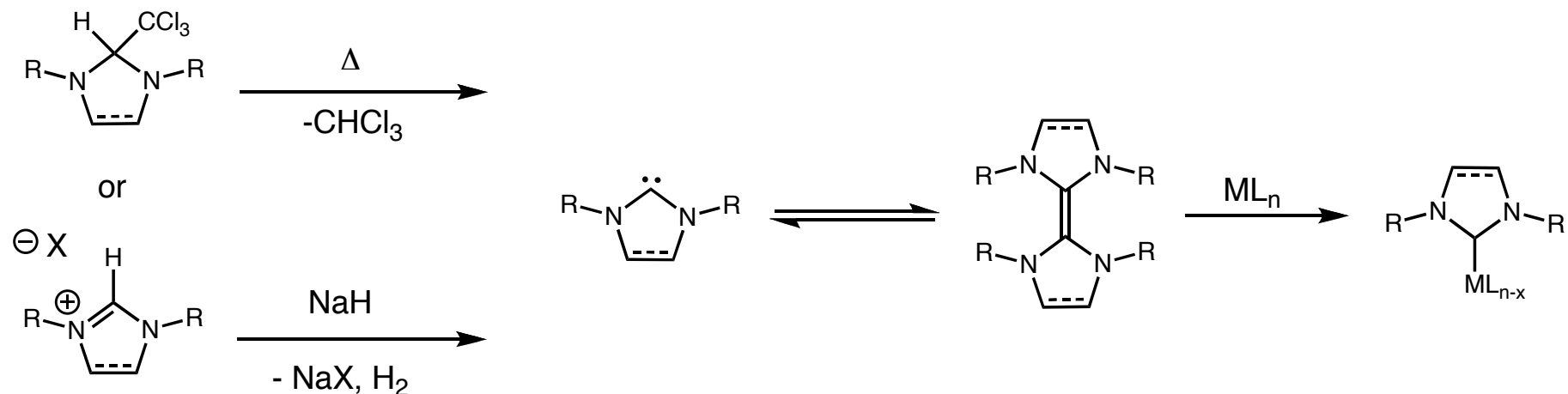
- *NHCs can form complexes with 52 elements, including every transition metal except Sc, Tc, and Cd.*
- *Most prevalent complexes are Group 6–9 transition metals.*
- *Strategies for forming NHC–metal complexes include transmetallation, oxidative addition, and deprotonation.*

H																	He						
Li	Be																	B	C	N	O	F	Ne
Na	Mg																	Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr						
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe						
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn						
Fr	Ra	Ac	Rf	Ha	Sg	Ns	Hs	Mt	Unn	Unu													

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

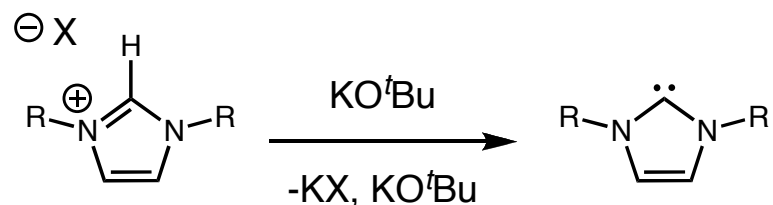
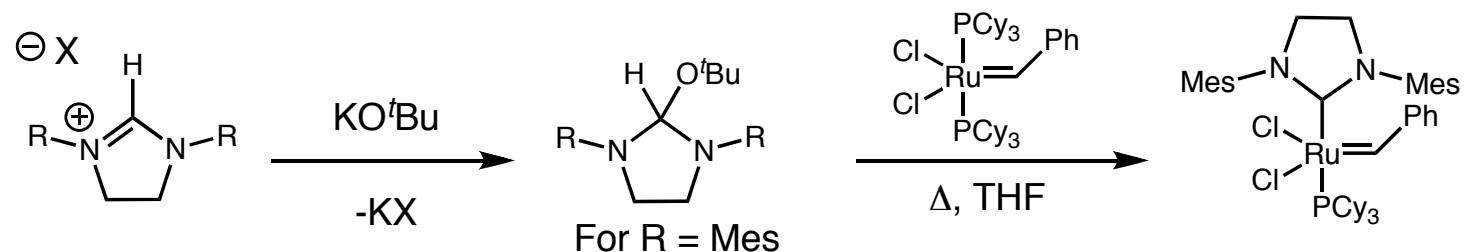
Insertion of Metal into NHC Dimer

- **There is an equilibrium between the free carbene and its dimer, known as the Wanzlick equilibrium.**
- **The free carbenes from the dimer can add to a metal or displace other ligands with heating.**
- **Dimers are synthesized by deprotonating the corresponding azolium salts.**



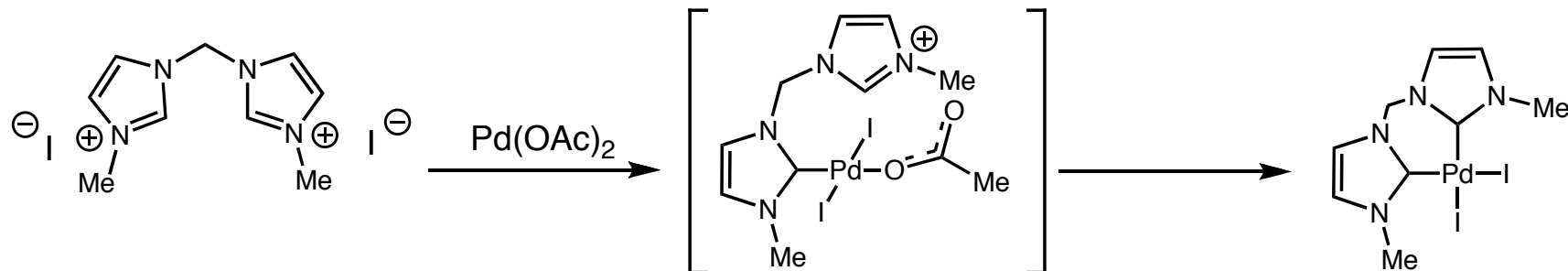
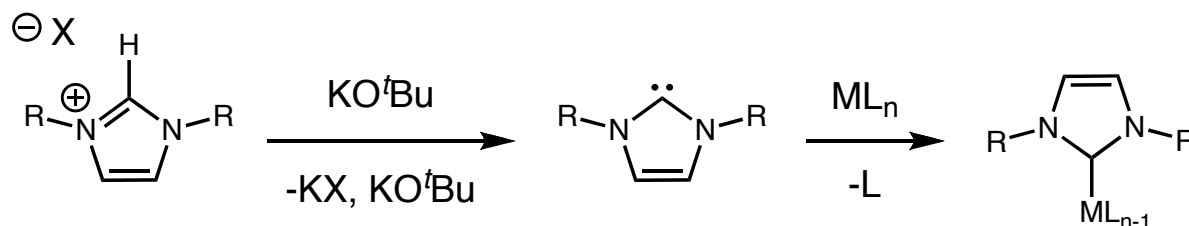
'Protected' NHCs

- **When forming air sensitive metal complexes, protecting the free carbene with an alcohol or chloroform proves useful.**
- **Not all azolium salts can be protected in this manner—unsaturated NHCs are deprotonated.**
- **Coordination to metal may involve carbene dimer and Wanzlick equilibrium.**



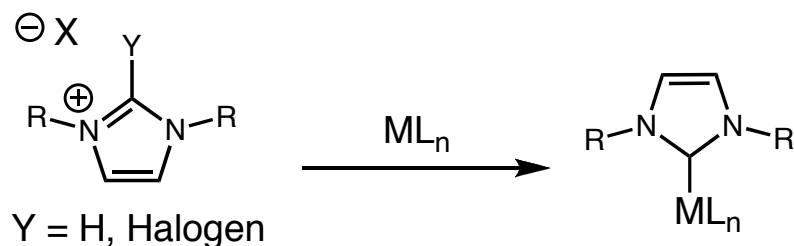
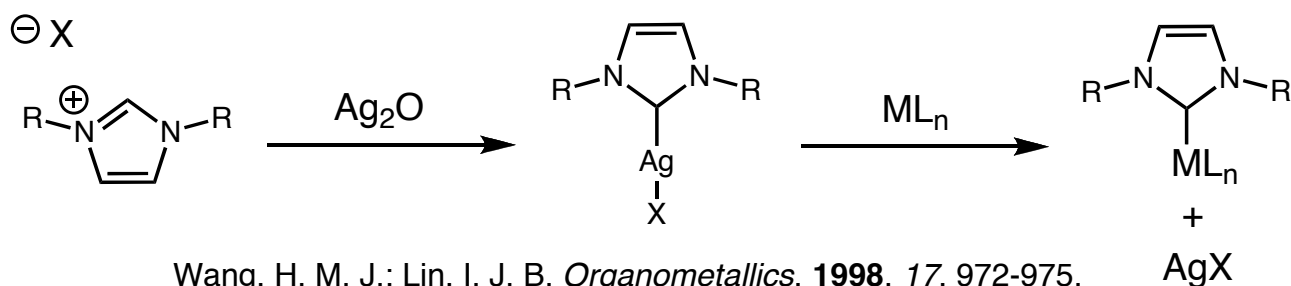
Preformed Carbenes/In situ Deprotonation

- **Exposing a metal complex to preformed carbenes or forming the carbene in situ with an irreversible base is the most straightforward process.**
- **The free carbene must be relatively stable.**
- **The base can be added to the reaction mixture or be part of the metal complex.**



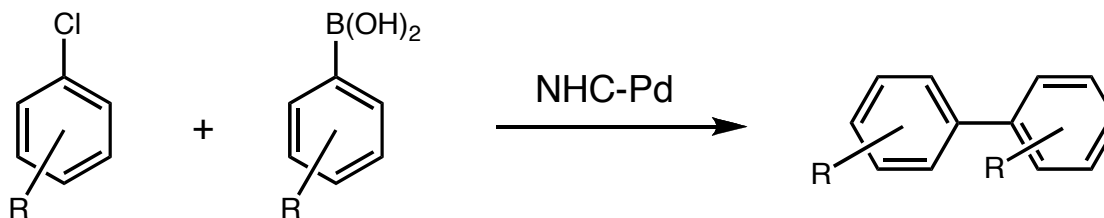
Transmetallation from NHC-Ag Complexes/Oxidative Addition

- **The lability of the Ag-NHC bond allows Ag-NHC complexes to be carbene transfer agents.**
- **NHCs can undergo oxidative addition at the C2 carbon when exposed to metal complexes.**
- **Oxidative addition works with $Y = H, X$, but low valent metals can only undergo it with hydrogen.**



Cross-Coupling Reactions : Suzuki Coupling

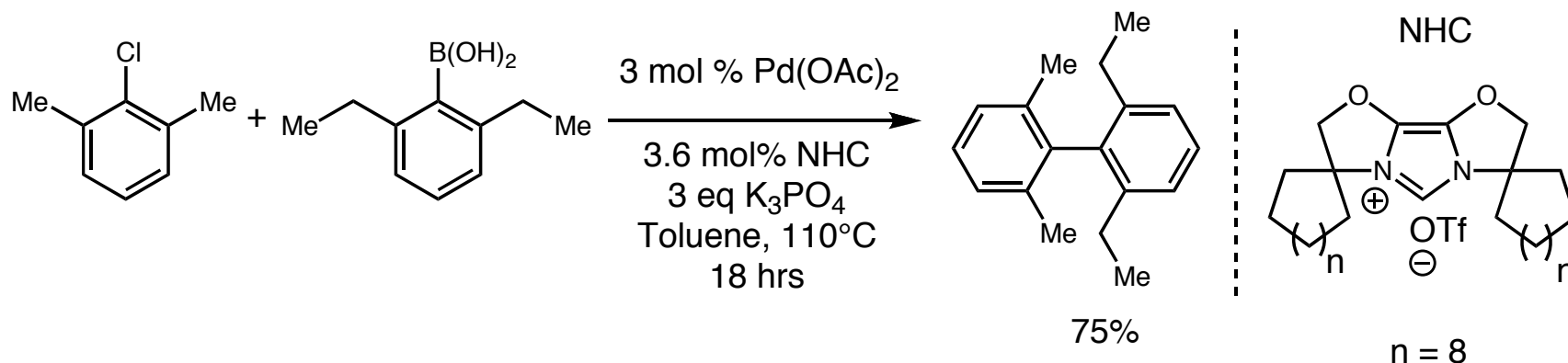
- **Employing NHCs as ligands for palladium in the Suzuki-Miyaura coupling reactions has several benefits.**
- **The electron donating properties of NHCs aids oxidative addition.**
- **NHC-palladium complexes can catalyze the coupling of unactivated aryl chlorides and or sterically encumbered coupling partners.**
- **Catalyst systems can be used with common solvents and mild reaction conditions.**



R = deactivating, ortho substitution

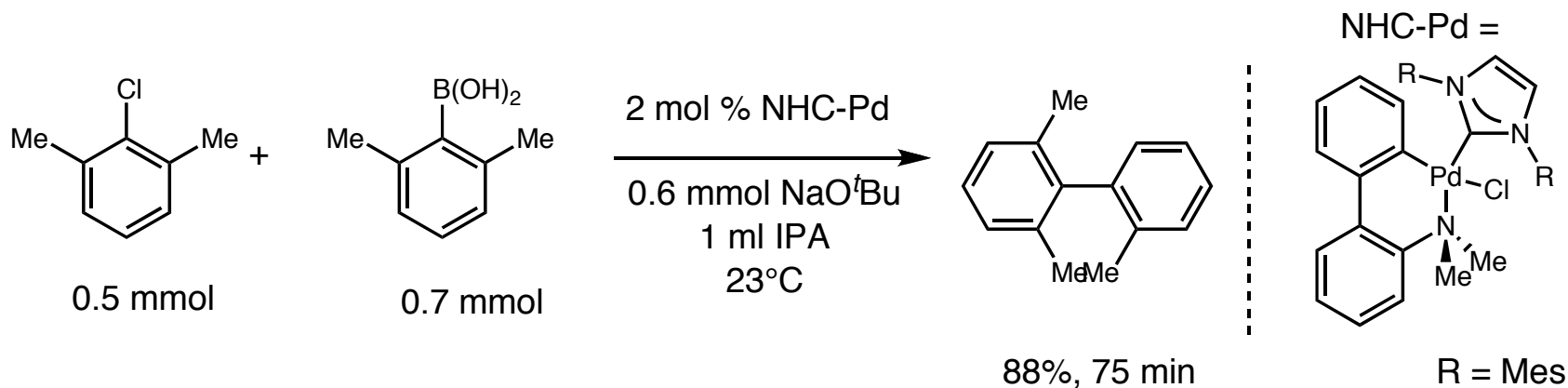
Cross-Coupling Reactions : Suzuki Coupling

- **Glorius has used electron rich NHCs as ligands to perform these difficult couplings.**



Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195-15196

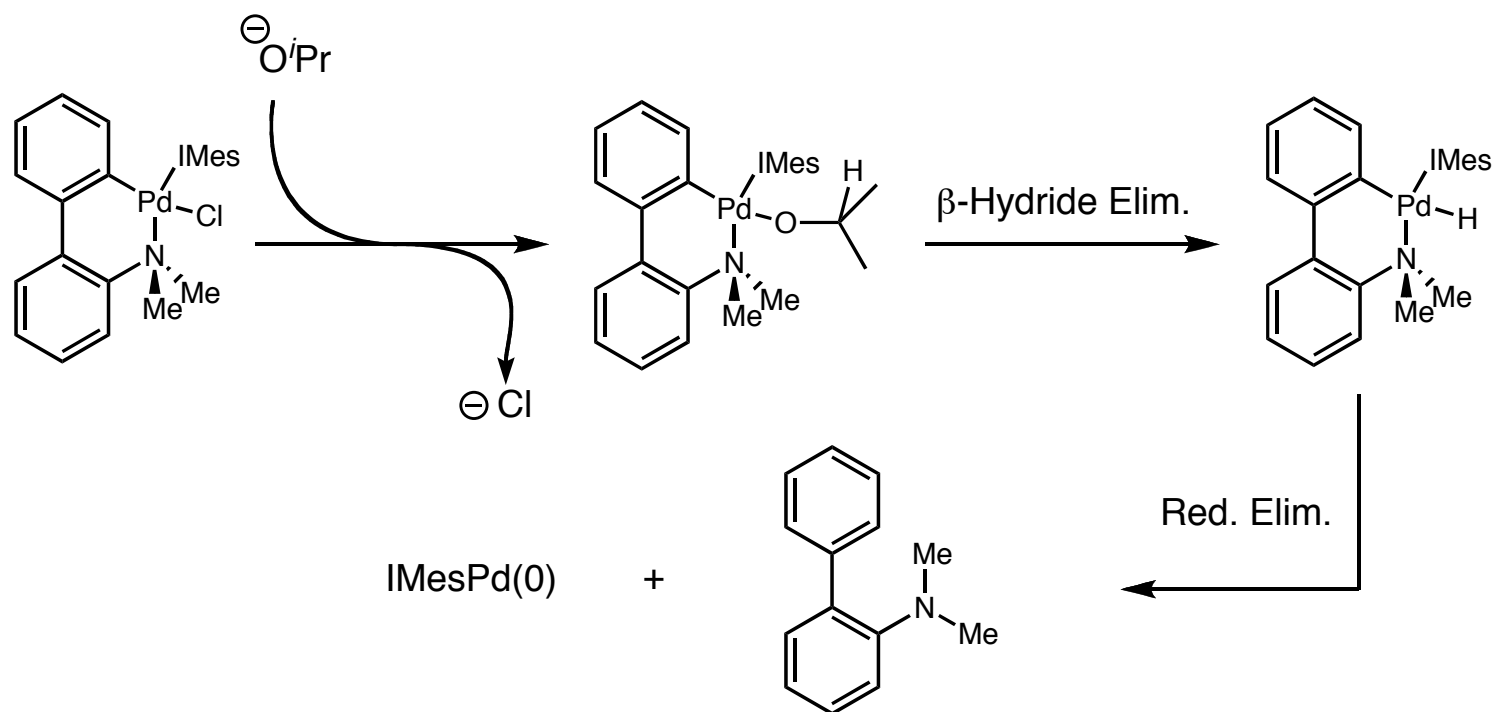
- **Nolan uses a NHC-palladium complex to perform couplings at room temp. using isopropanol in minutes.**



Navarro, O.; Kelly, R. A. II; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194-16195

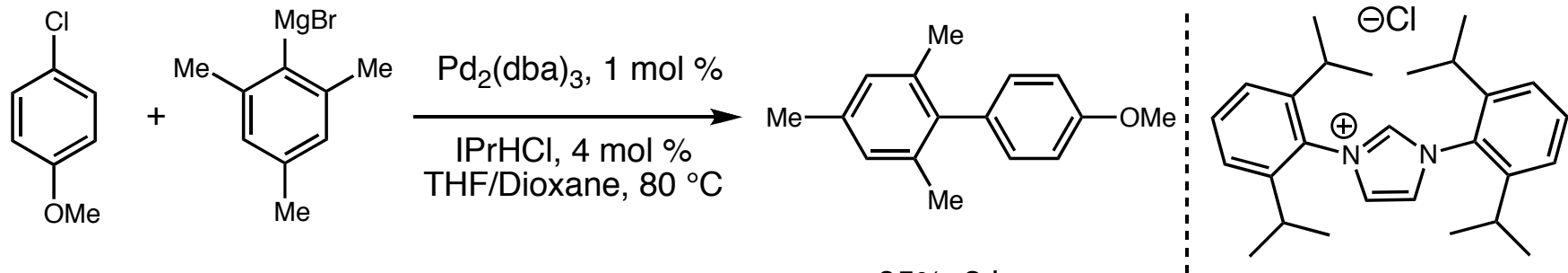
Cross-Coupling Reactions : Suzuki Coupling

- *The palladacycle Nolan uses is only the precatalyst.*
- *Palladium (0) must be generated for the coupling.*
- *Drawbacks are harsh conditions for forming palladacycle and mandatory slow addition of aryl chloride.*



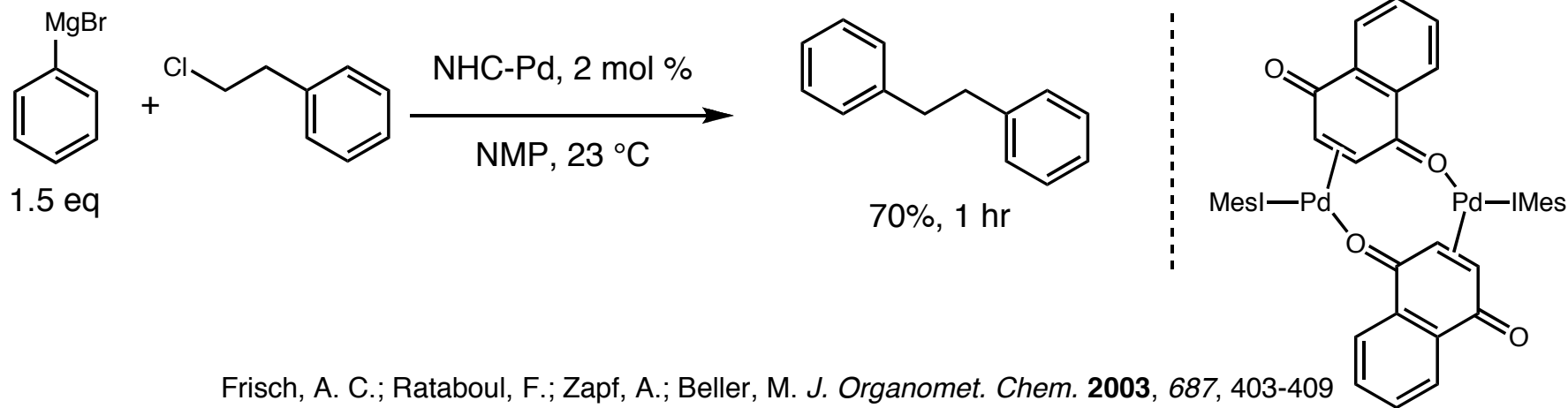
Cross Coupling: Kumada Coupling

- **Using NHCs as ligands once again allows for the use of unactivated aryl or alkyl chlorides.**
- **The mild reaction conditions and fast reaction times allow for greater functional group tolerance.**
- **Ortho substituents are also tolerated.**



Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, 121, 9889-9890

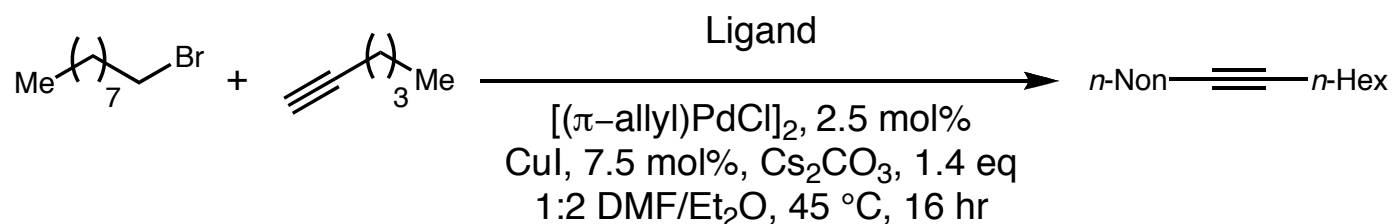
95%, 3 hrs



Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, 687, 403-409

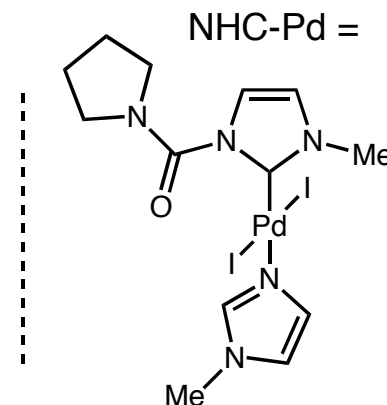
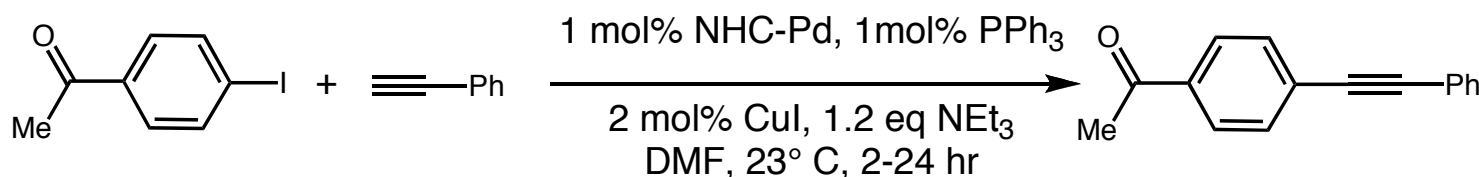
Cross Coupling: Sonogashira

- **NHC-Pd complexes cannot catalyze this reaction for aryl chlorides.**
- **NHC-Pd complexes catalyze the coupling of β hydrogen-containing alkyl electrophiles while phosphine-Pd complexes are ineffective.**
- **Coupling with aryl iodides can be accomplished at room temp.**



Ligand	% Yield
PPh ₃	< 5%
PCy ₃	< 5%
IPr·HCl	67%
IAd·HCl	80%

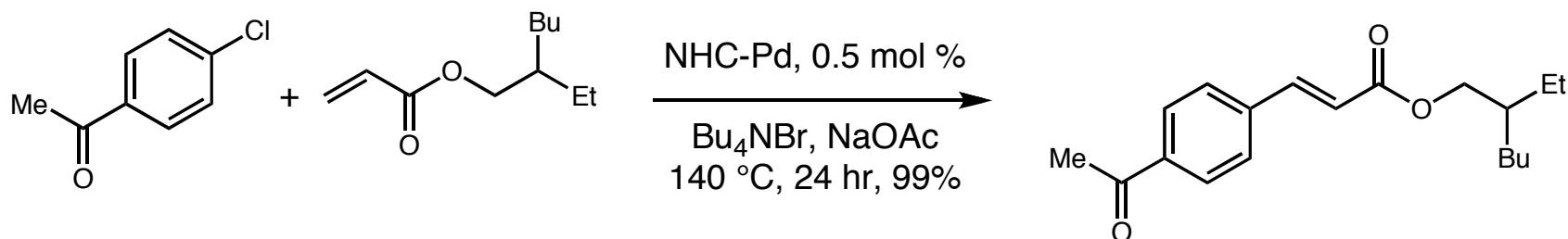
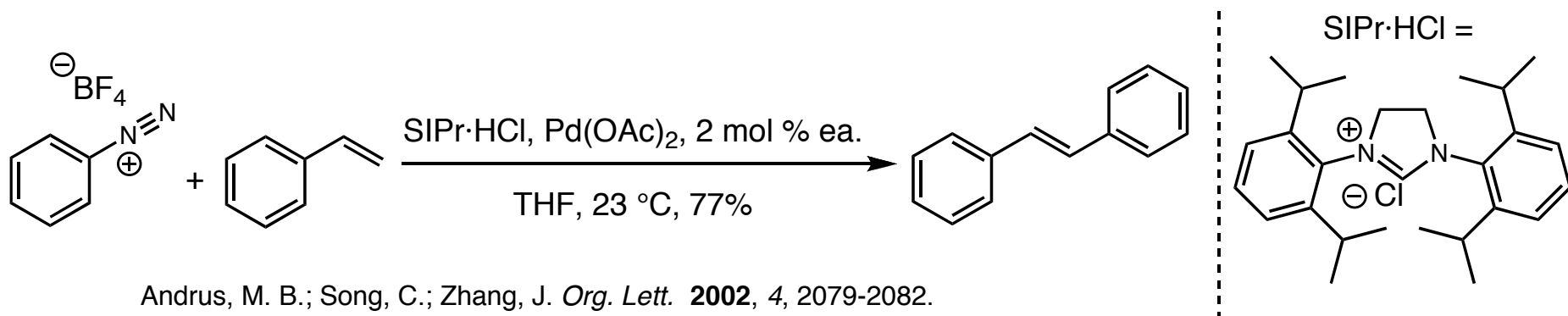
Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642-13643.



Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411-1414.

Cross Coupling: Heck

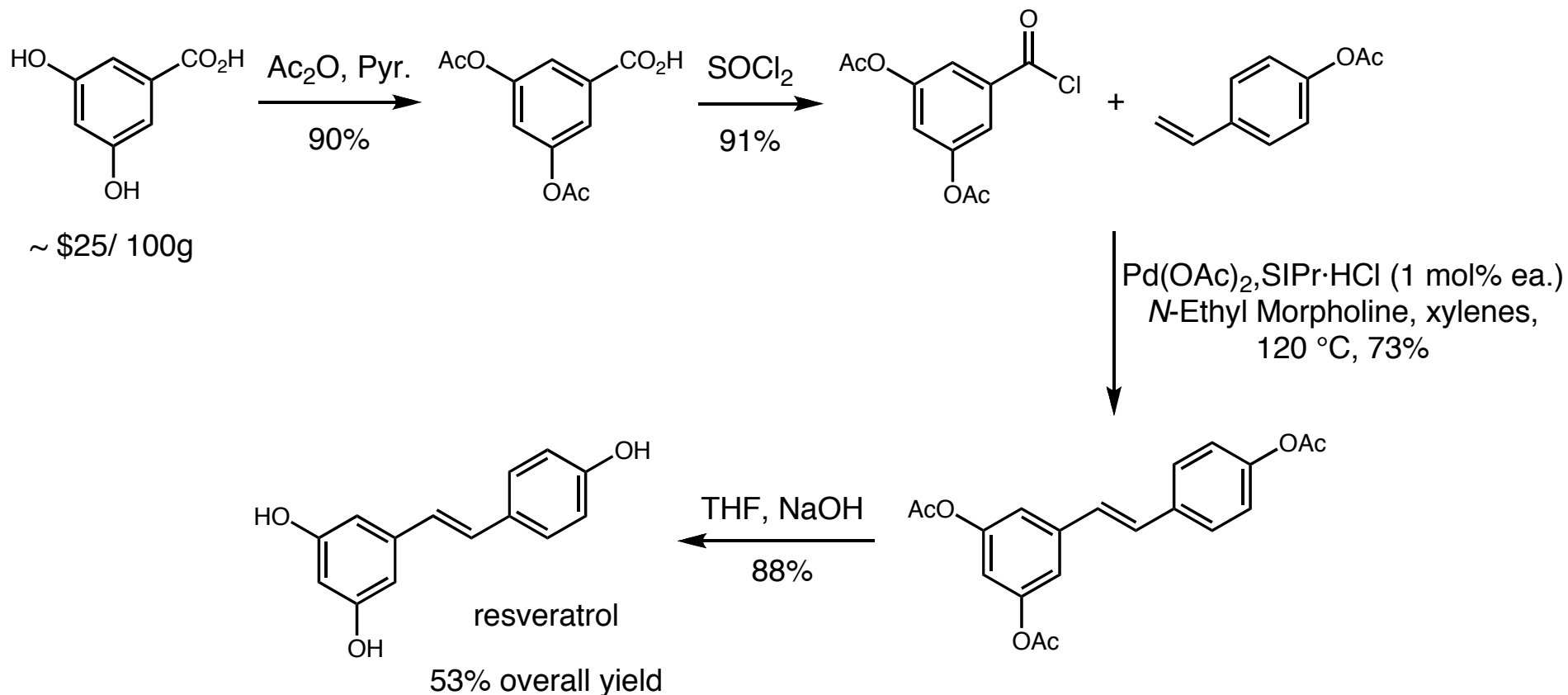
- **First report of transition metal catalysis using NHC ligand (Herrmann, 1995).**
- **The coupling of aryl chlorides can be carried out in ionic liquids.**
- **Mild reaction conditions can only be accessed when using diazonium salts**



Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, 4, 3031-3033.

Cross Coupling: Heck

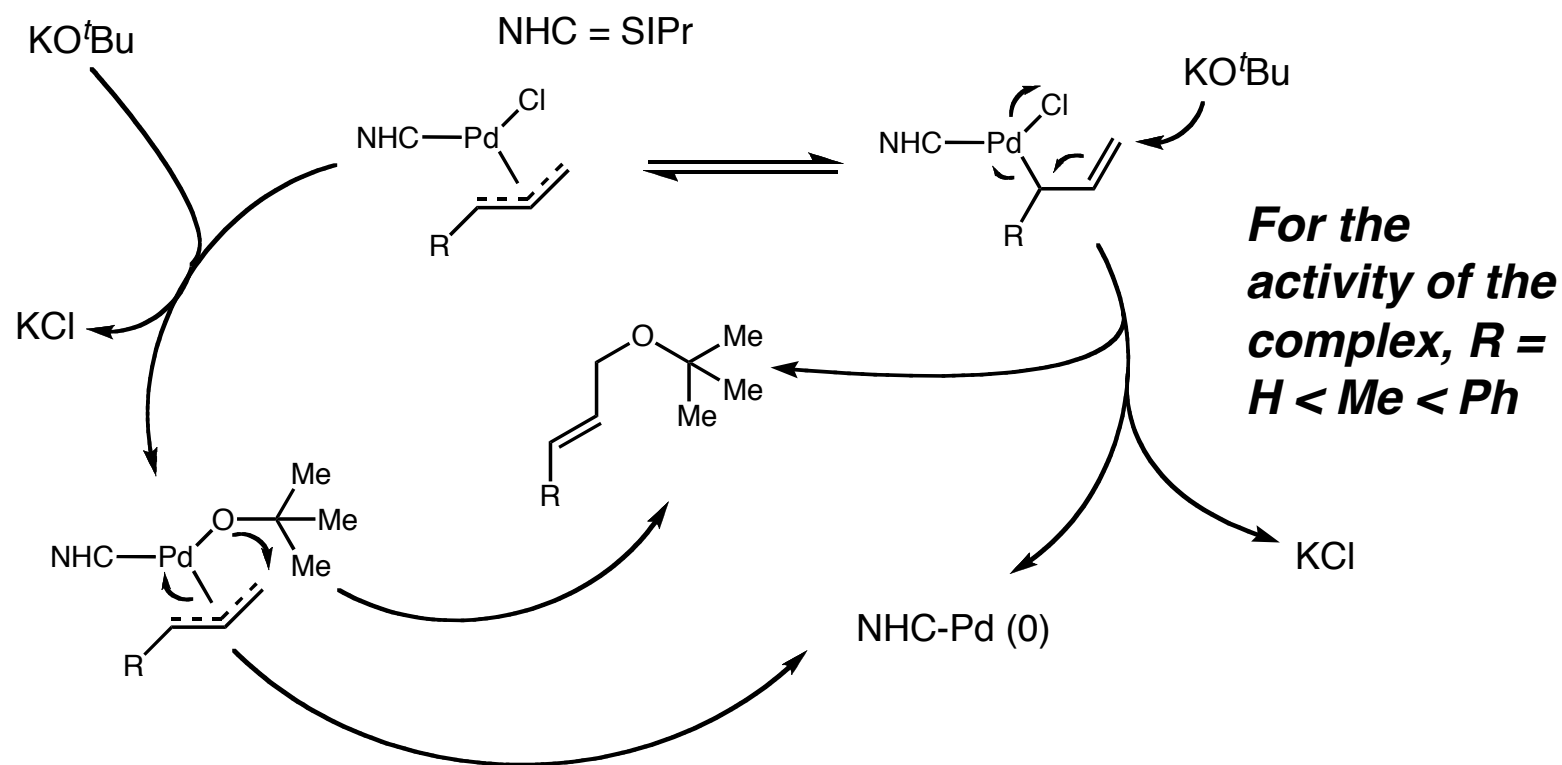
- **A NHC-Pd complex was employed in a recent cost effective synthesis of resveratrol.**
- **Other Heck couplings and an optimized HWE gave either longer routes or poor yields.**
- **There is speculation whether resveratrol is in part responsible for the 'French Paradox'.**



Andrus, M. B.; Liu, J. Meredith, E. L.; Nartey, E. *Tetrahedron Lett.* **2003**, 44, 4819-4822.

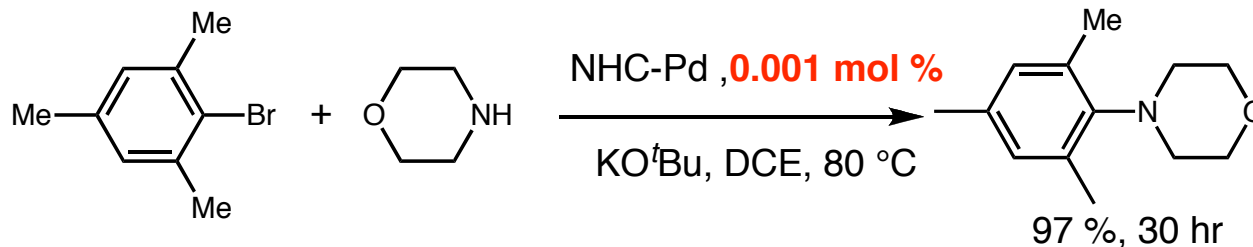
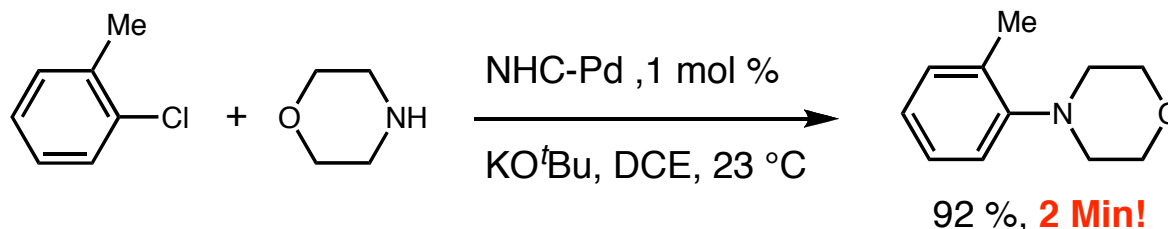
Cross Coupling: Buchwald-Hartwig Amination

- As with the Suzuki-Miyaura reaction, NHCs help catalyze the amination of unactivated aryl chlorides.
- Steric bulk on the NHC or around the palladium helps to generate the active catalyst more efficiently.
- NHC-Pd complexes can catalyze this reaction with very low catalyst loadings or mild reaction conditions.



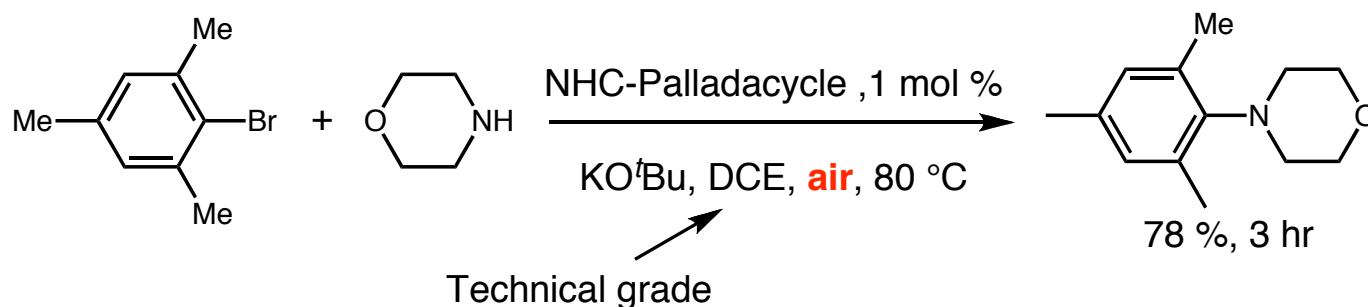
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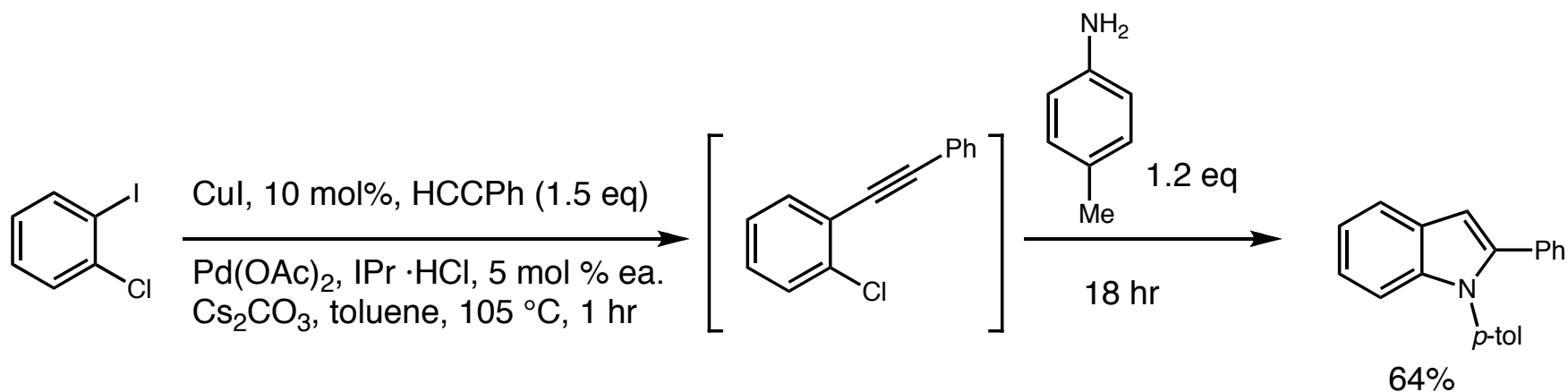


Cross Coupling: Buchwald-Hartwig Amination

- **NHC-Pd complexes can even catalyze the reaction in technical grade solvents under aerobic conditions.**
- **NHC-Pd complexes can also catalyze the related indole synthesis.**



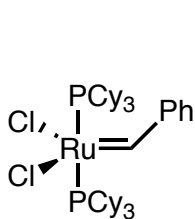
Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, 4, 2229-2231.



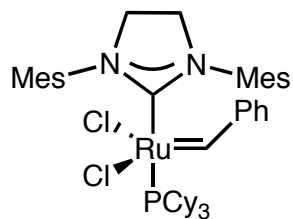
Altermann, L. *Org. Lett.* **2004**, 7, 439-442.

Olefin Metathesis

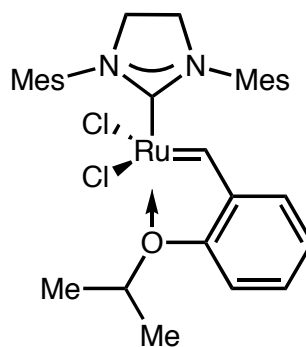
- **Olefin metathesis is a very powerful tool, both in natural product related synthesis and in polymer chemistry.**
- **The incorporation of a NHC ligand onto Grubbs' Ru based catalyst allowed for more widespread applications.**
- **Hoveyda's internal chelate modification allows for greater stability and recycling via chromatography.**
- **Ru based metathesis catalysts are generally more 'user-friendly' than Schock's Mo-alkylidene catalysts.**



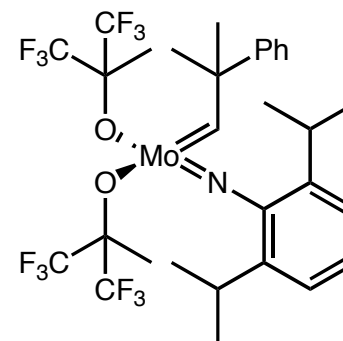
Grubbs I



Grubbs II



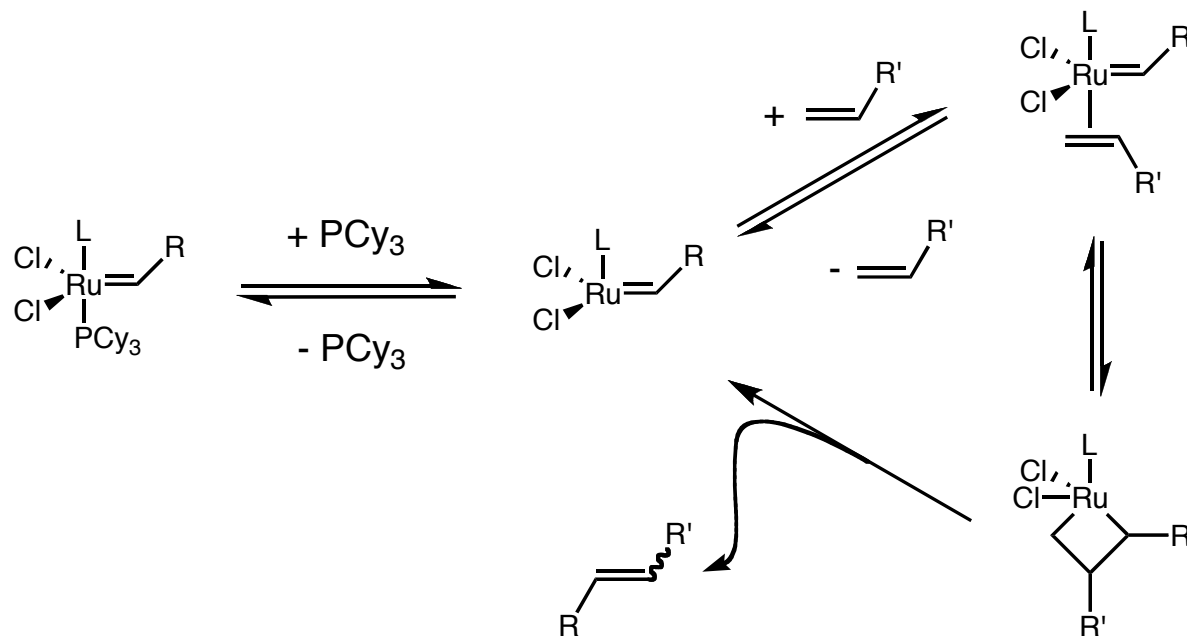
Hoveyda-Grubbs II



Schrock's catalyst

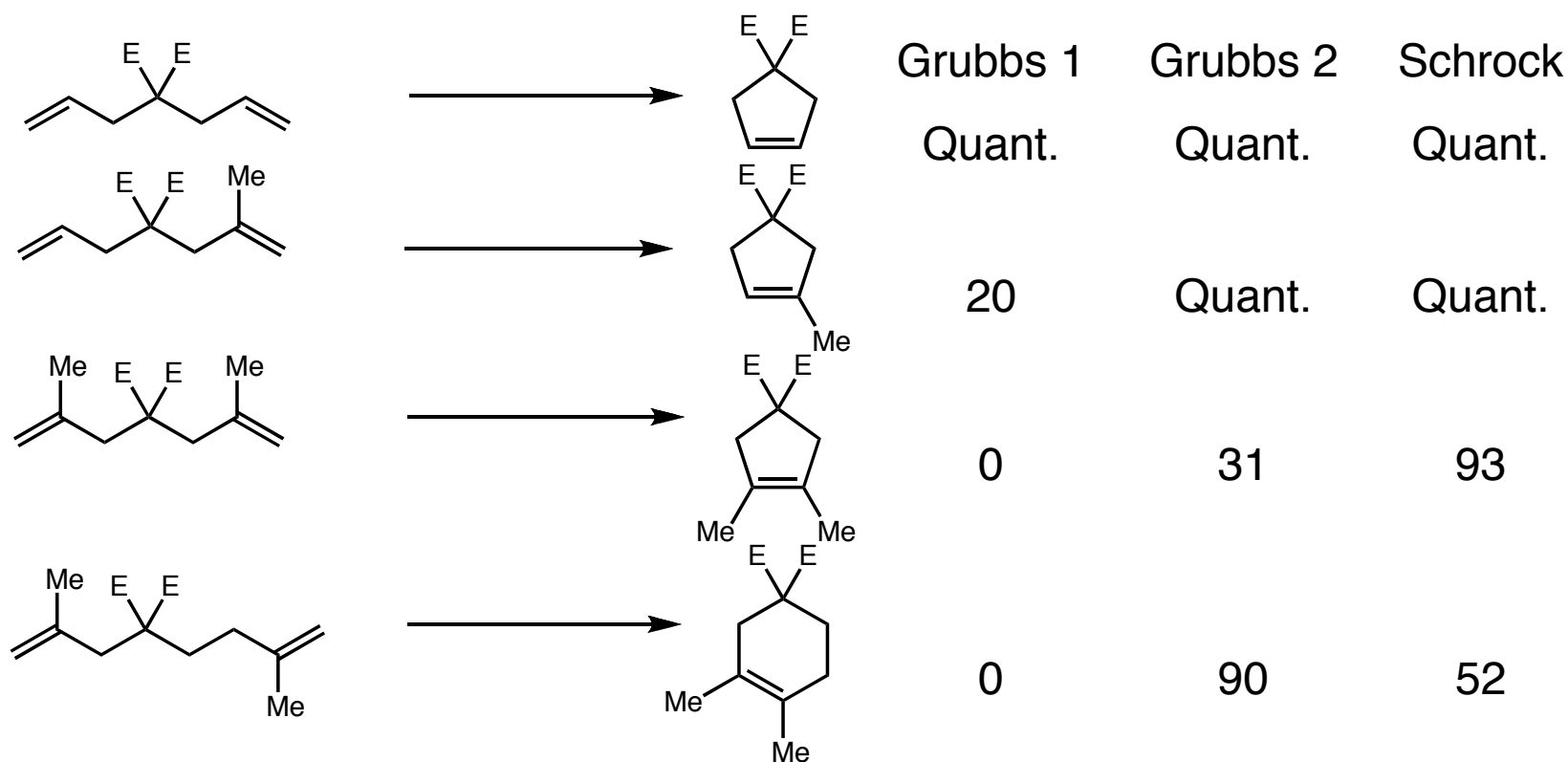
Olefin Metathesis: Mechanistic Insights

- **Grubbs I has more functional group tolerance and is less air sensitive than Schrock's catalyst.**
- **Low thermal stability, C–P bond degradation, and reduced activity all problems.**
- **Mechanism states phosphine dissociation and low reassociation essential for high turnover.**
- **Steric bulk and electron donating ability important factors for ligand.**



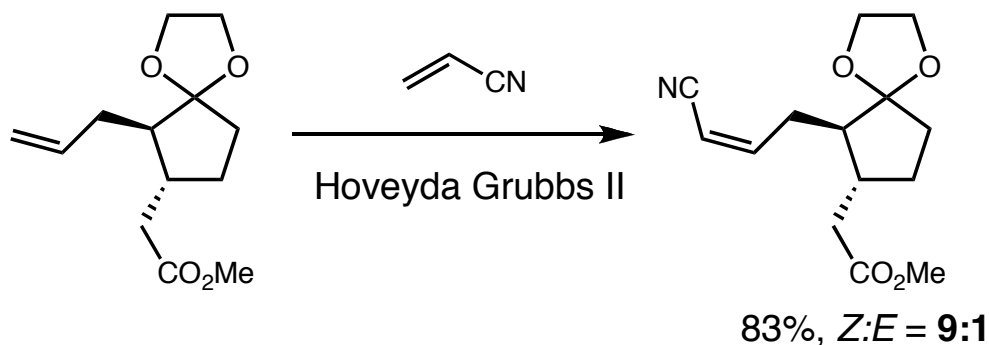
Olefin Metathesis: Incorporation of NHCs

- **NHCs are perfect candidates as ligands for Ru based metathesis.**
- **Strong σ donation and weak π acceptor character leads to strong NHC-Ru bonds (5 kcal/mol greater!)**
- **These factors, along with greater steric bulk, result in increased activity, more robust reaction conditions, and decreased reaction times.**

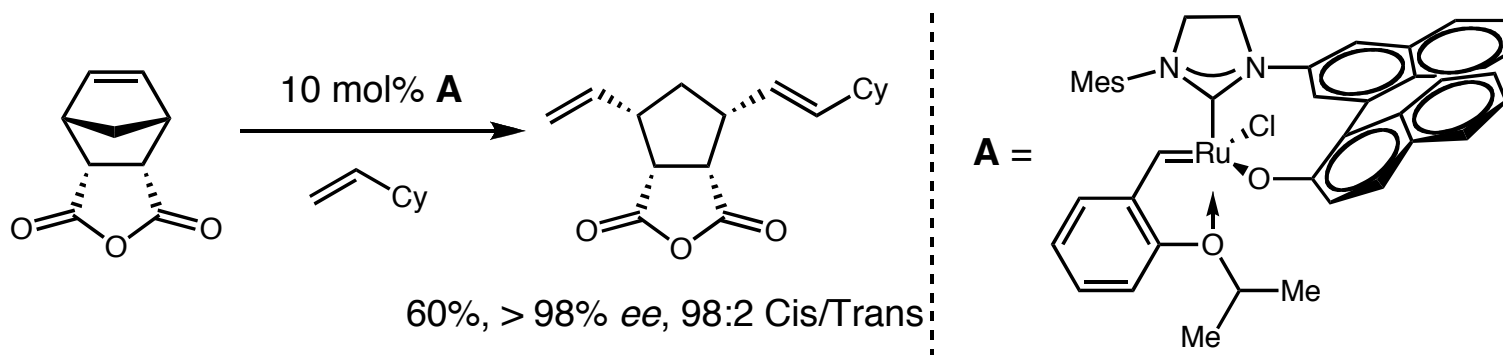


Olefin Metathesis: Phosphine-Free and Chiral Catalysts

- **Phosphine-free catalysts prepared by Hoveyda and Blechert groups independently.**
- **These catalysts improve cross metathesis and work with electron deficient olefins.**
- **Chiral metathesis catalysts carry out AROM/CM catalysis**



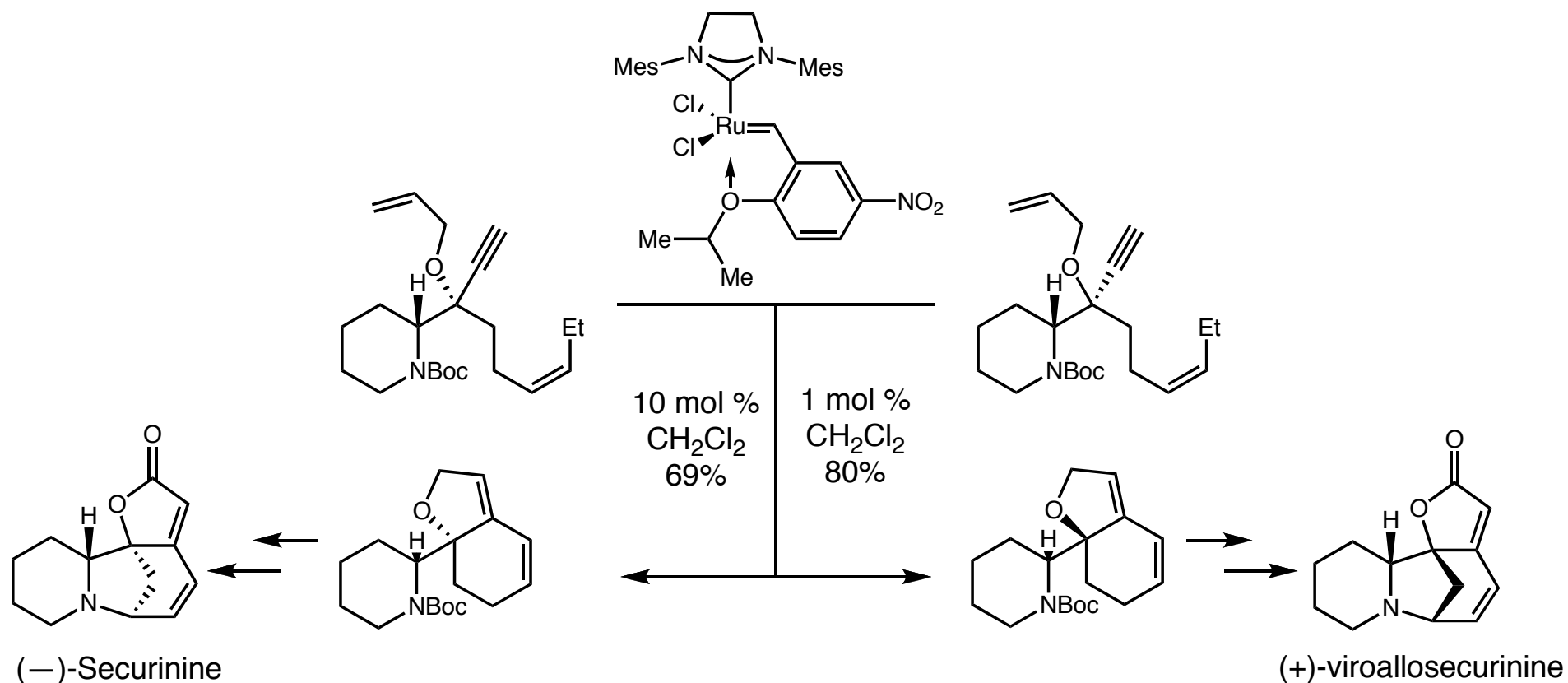
Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430-432.



Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, 124, 4954-4955.

Olefin Metathesis: Applications to Synthesis

- Aside from many applications in the polymer science field, RCM, cross-methasis, and enyne metathesis have found many applications in the total synthesis of natural products.

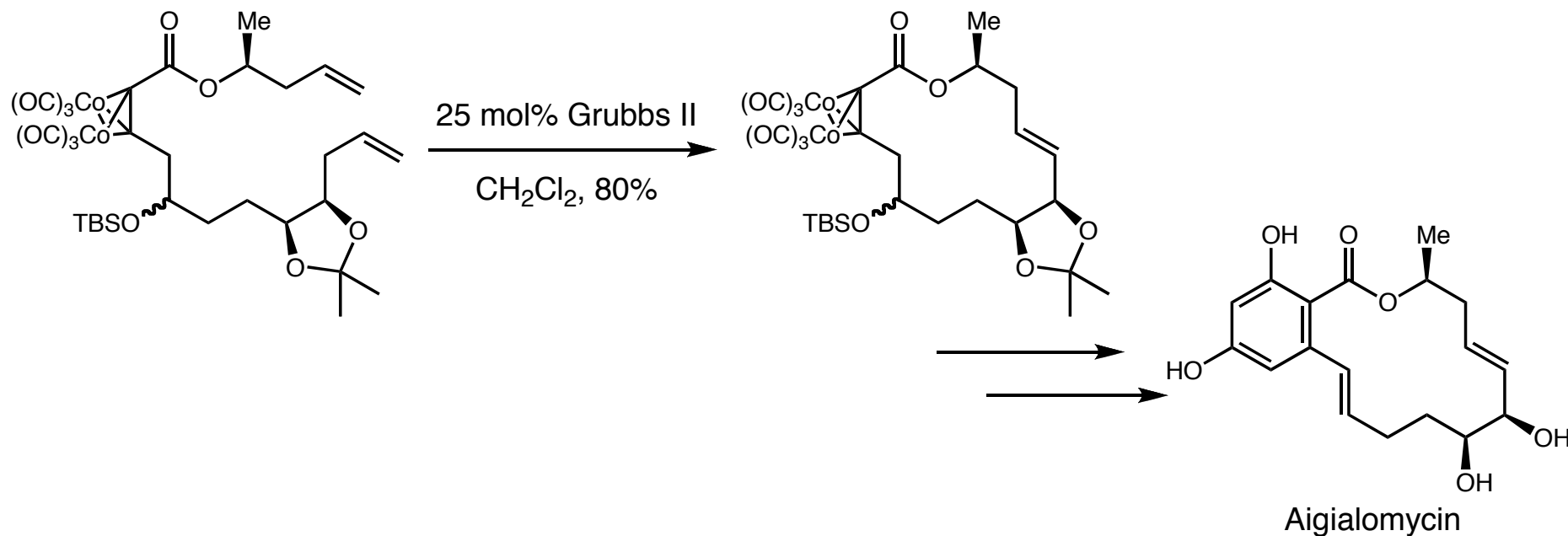


Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. *Org. Lett.* **2004**, *6*, 87-89.

Honda, T.; Namiki, H.; wantanabe, M.; Mizutani, H. *Tetrahedron. Lett.* **2004**, *45*, 5211-5213.

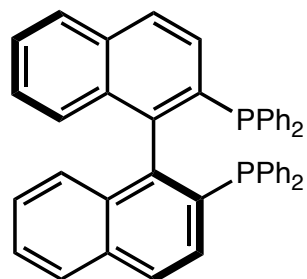
Olefin Metathesis: Applications to Synthesis

- **Aside from many applications in the polymer science field, RCM, cross-methasis, and enyne metathesis have found many applications in the total synthesis of natrual products.**

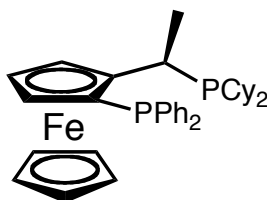


Asymmetric Additions with NHC-Metal Complexes

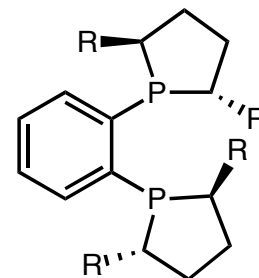
- **Chiral phosphine ligands are successful ligands for many asymmetric transition metal–mediated reactions.**
- **Could NHCs be successful ligands with their unique features?**
- **The profile of chiral NHC ligands differs significantly from chiral phosphine complexes. NHCs do not have an ‘edge-to-face’ orientation of their aryl groups like phosphines.**



BINAP



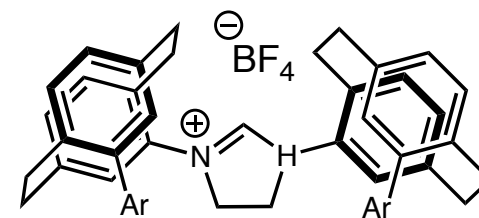
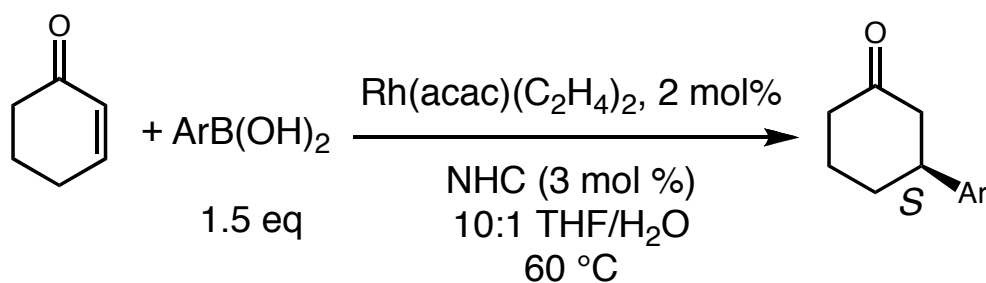
Josiphos



DuPhos

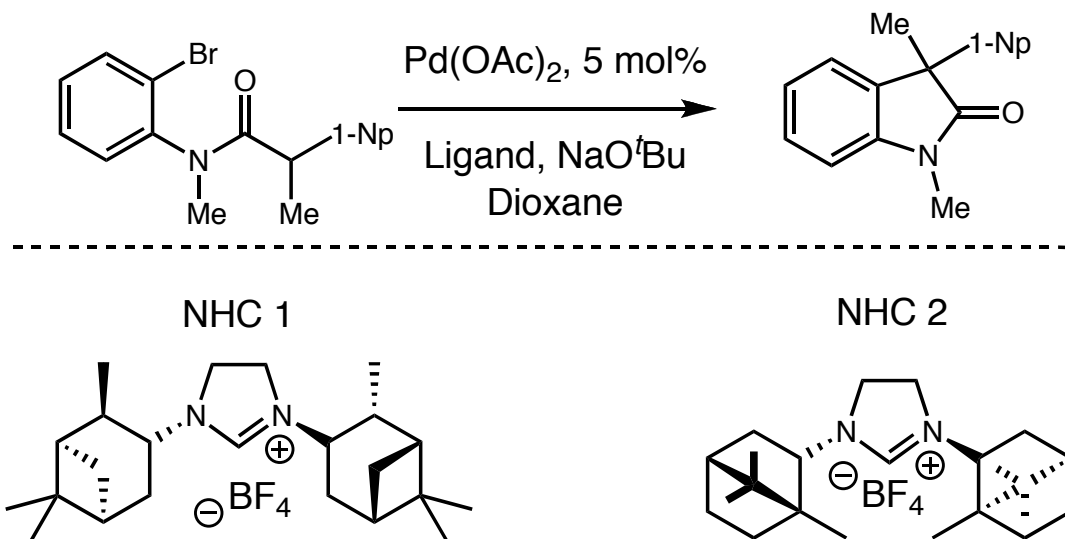
Asymmetric Additions with NHC-Metal Complexes: Conjugate Arylation

- **First investigated by Miyaura and Hayashi in 1998 using a Rh/BINAP complex.**
- **A system developed by Arduś using a NHC-paracyclophane ligand gives comparable yields and selectivity with more mild conditions.**
- **Bulky NHC ligands are essential, which was first shown by Fürstner.**



Asymmetric Additions with NHC-Metal Complexes: Asymmetric α -arylation

- Reaction reported in 1997 by Buchwald and Hartwig. Muratake and Natsume reported intramolecular version at the same time.
- Best ligand for the asymmetric intramolecular version is a NHC.
- This ligand better than workhorse phosphine ligands. Unfortunately, only modest selectivity is achievable at present time.



<i>Ligand</i>	<i>Temp. (°C)</i>	<i>Yield (%)</i>	<i>ee (%)</i>
<i>(R)-BINAP</i>	100	49	46
<i>Josiphos</i>	100	72	2
<i>DuPhos</i>	100	70	61
<i>NHC 1</i>	25	88	67
<i>NHC 2</i>	10	75	76