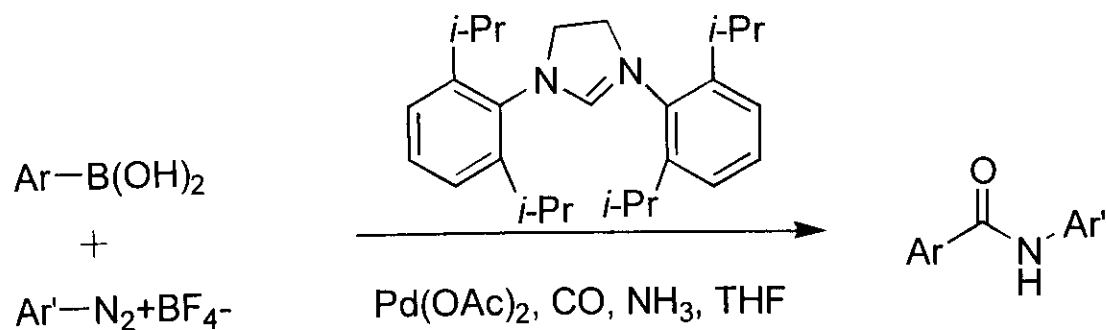


# Palladium-Imidazolium *N*-Heterocyclic Carbene-Catalyzed Carbonylative Amidation With Boronic Acids, Aryl Diazonium Ions and Ammonia

Yudao Ma, Chun Song, Qiang Chai, Changqin Ma,  
Merritt B. Andrus

*Synthesis*, **2003**, No.18, 2886

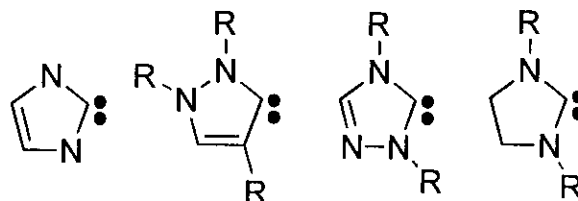


# Outline

- N-Heterocyclic Carbenes (NHC)
- History of NHC in Synthesis
- NHC vs. Phosphorous Containing Ligands
- Reactions Incorporating NHC Ligands
- Past NHC Work by Andrus
- Biological Activity of Aryl Amides
- Title Paper Methodology for Formation of Aryl Amides

# N-Heterocyclic Carbenes

*Examples of Some NHC*



N-Heterocyclic Carbenes possess a nucleophilic singlet carbene which acts as a 2 electron donor

NHC can substitute amines, ethers and phosphorous as metal ligands

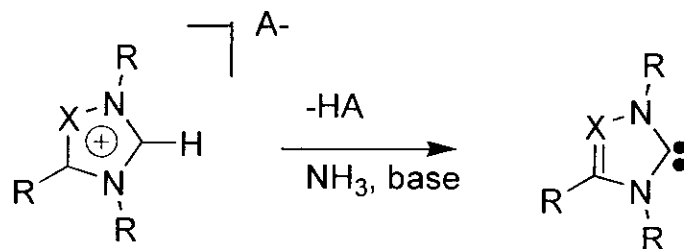
These ligands can coordinate to a wide variety of both low and high oxidation state metals (Pd, Ru, Ti, V, W, Re, and others)

*Angew.Chem.Int.Ed*, **2002**, 41, 1290

*Angew.Chem.Int.Ed*, **1997**,36, 2162

# Generation of N-Heterocyclic Carbenes

- One literature method for the generation of NHC:



*Chem. Eur. J.* **1996**, *2*, 162

- Many commonly used NHC are derived from imidazoles. These stable carbenes can be isolated and are relatively stable to both air and water
- The NHC-metal complex can be formed insitu when used for synthesis

# NHC vs. Phosphorous Ligands

- Similarities

- Both are 2 electron donors
- Both share similar coordination chemistry

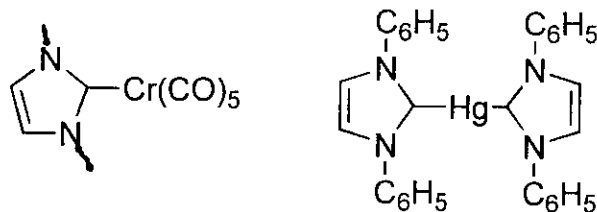
- Differences

- An excess of phosphorous ligand is frequently needed because of P-C bond cleavage.
- NHC ligands do not need to be used in excess
- P ligands are frequently water and air sensitive
- NHC ligands are stable to heat, oxygen and moisture
- With Pd coordination, NHC are arranged cis on the plane whereas P ligands are trans

*Angew.Chem.Int*, **1995**, 34, 2371

# History of NHC in synthesis

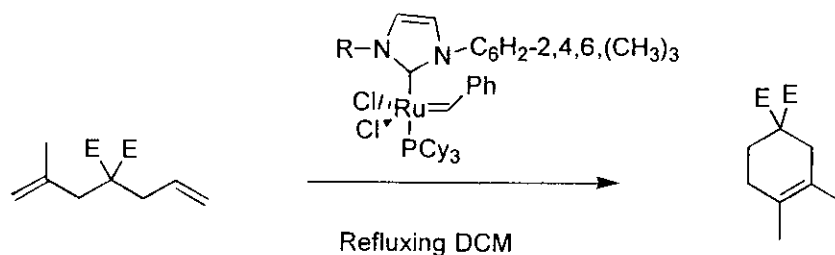
- Fischer and Students introduced carbenes into synthesis in 1964 (*Angew.Chem.* **1964**, 76, 645)
- In 1968 Ofele and Wanzlich described two new Metal-NHC complexes (*J.Organomet.Chem*, **1968**, 12, P42 and *Angew.Chem.Int.Ed*, **1968**, 7, 141)



- In 1991 Arduengo reported methods for the generation of free, isolable NHC (*J.A.C.S.* **1991**, 113, 361)
- The applications of NHC have increased dramatically since Arduengo's report

# Reactions using NHC Ligands

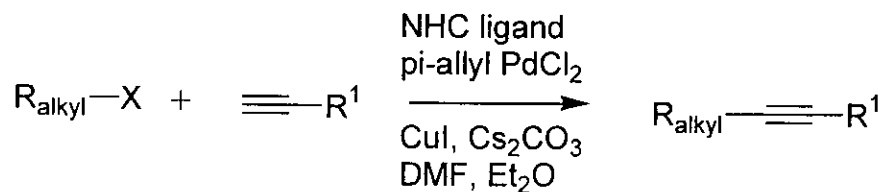
- Ring Closing Metathesis:



95% with NHC ligand  
 Replacing NHC with PCy<sub>3</sub> gives  
 No product

*Tet.Lett.* **1999**, 40, 2247

- Sonogashira with Alkyl Bromides:



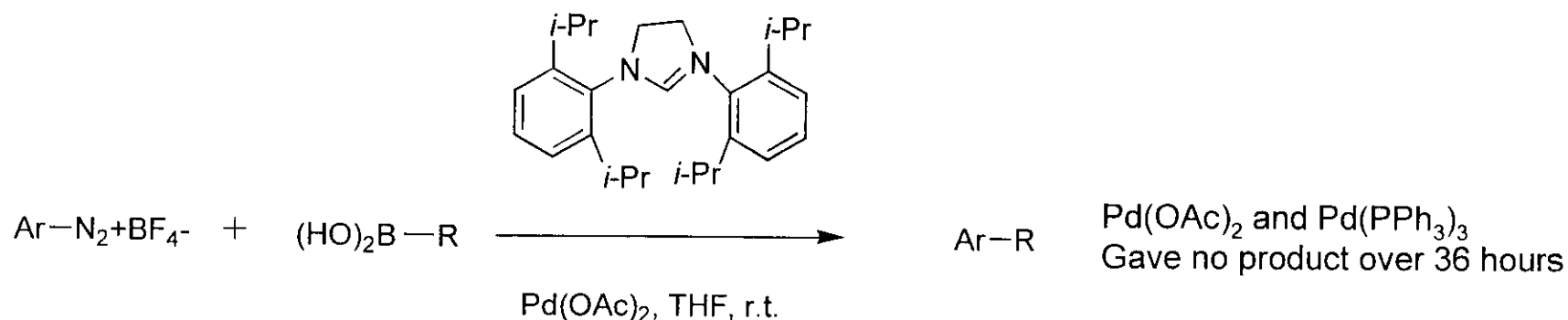
51-79 % yield for a variety  
 of substrates

Less than 5% with Phosphorous  
 ligands

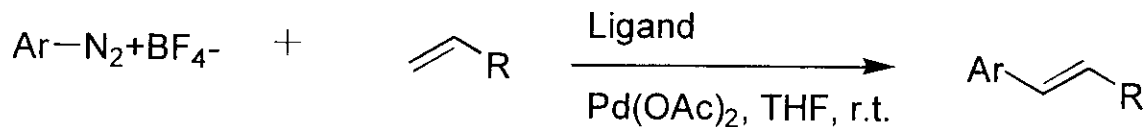
*J.A.C.S.* **2003**, 125, 13462

# Andrus Work with NHC Ligands

- Suzuki-Miyaura Reaction



- Mizuraki-Heck Reaction

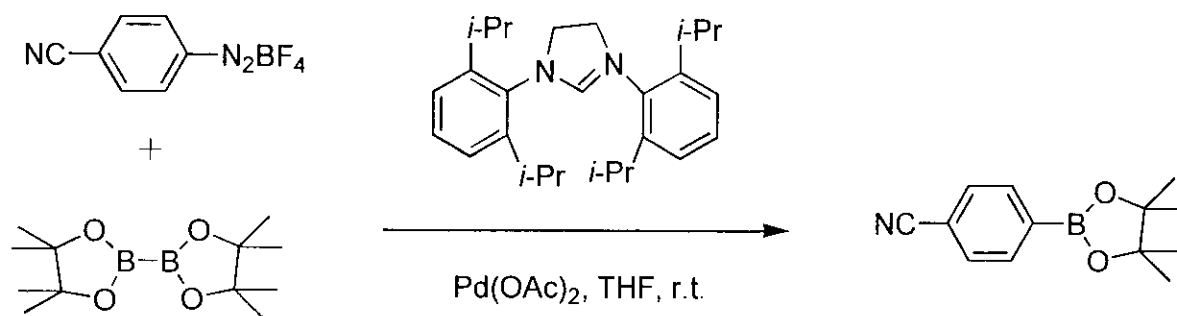


Stilbene example:      77%    with above conditions  
                                  21%    with Pd(OAc)<sub>2</sub> alone  
                                  n.r.     with Pd(PPh<sub>3</sub>)<sub>3</sub>



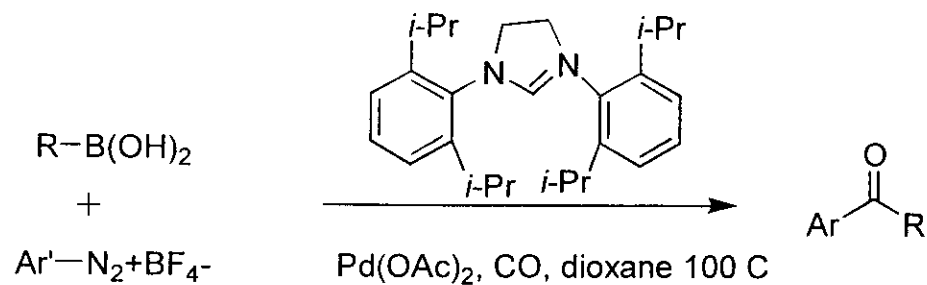
# Andrus Work with NHC (Cont)

- Borylation Reaction



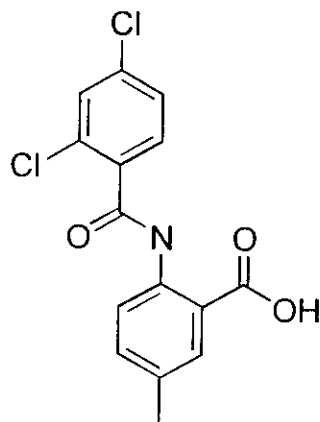
*Org.Lett.* **2003**, 5, 4635

- Carbonylative Coupling



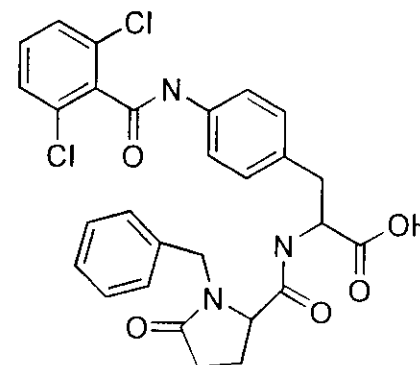
*Tet.Lett.*, **2002**, 43, 9137

# Biologically Active Aryl Amides:



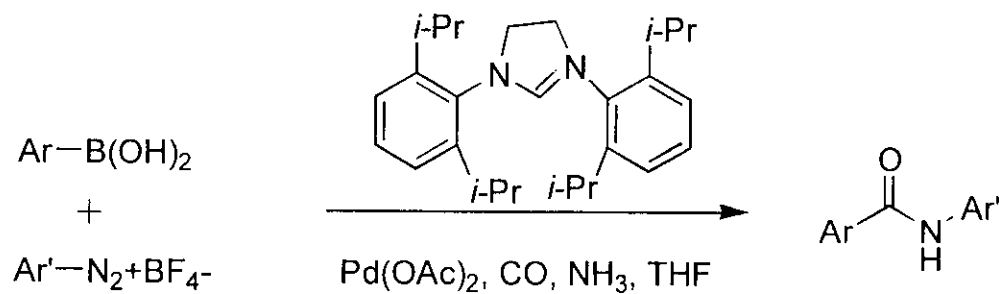
BVT 142

PPAR gamma agonist  
This compound and analogues  
Have shown modest to good activity  
In treatment of diabetes



Inhibitor of VCAM,  
This compound and analogues  
Are being investigated for the  
Treatment of inflammatory  
diseases

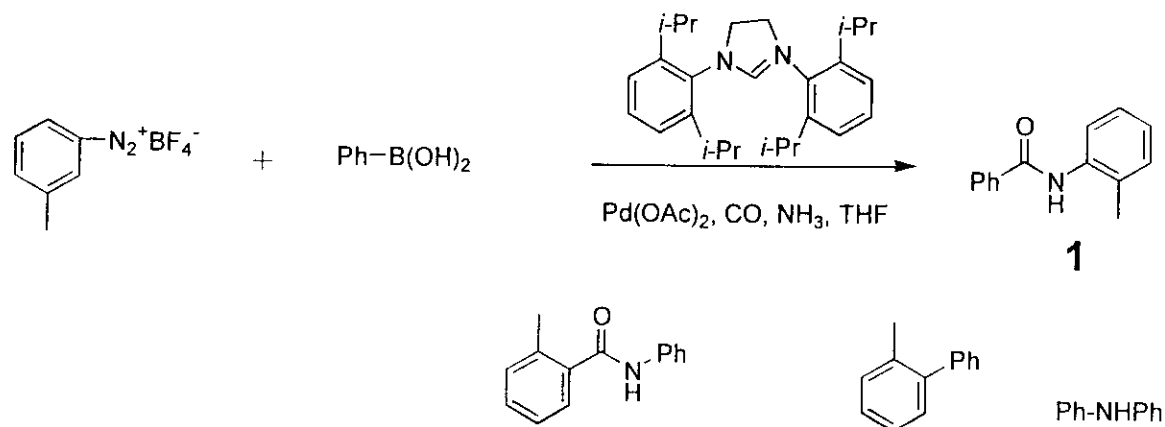
# Synthesis Paper Methodology for Preparation of Aryl Amides



Boronic Acid, Pd acetate, NHC and ammonia saturated THF were Combined and pressurized to 5 atm CO. 60 seconds later the diazonium salt was added

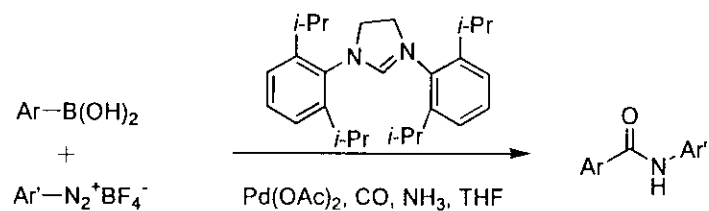
When the order of addition was reversed, reverse amide was also formed

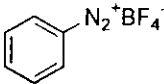
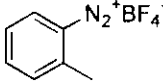
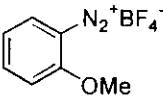
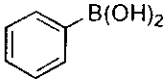
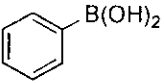
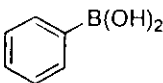
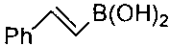
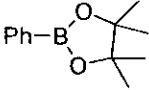
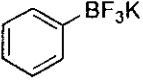
# Effects of CO Pressure on Product Distribution



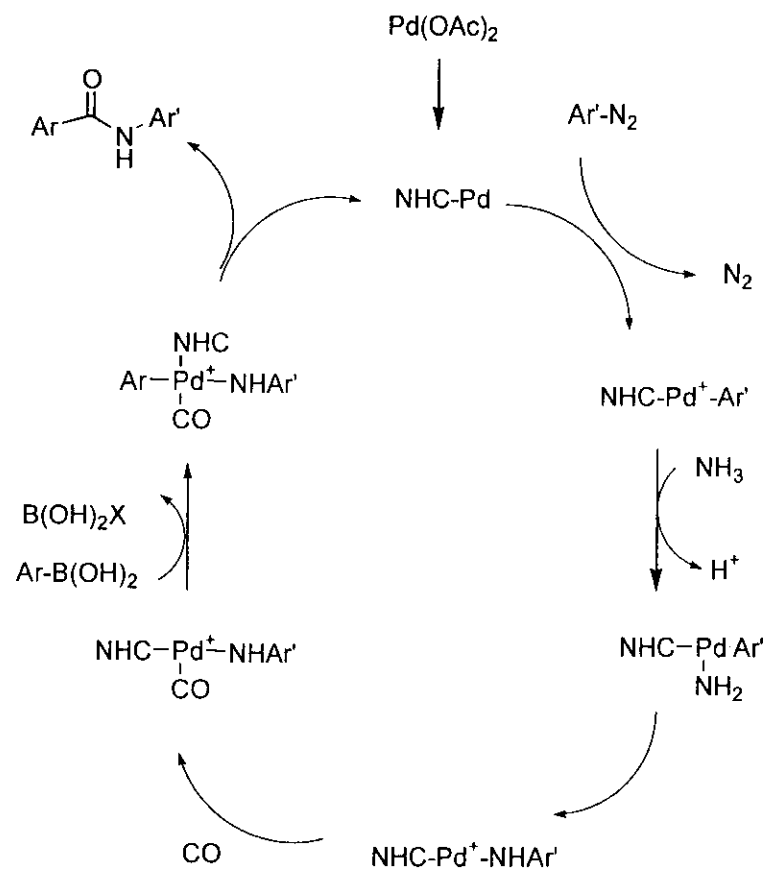
CO Atm	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
1	23	-	30	47
2	32	-	25	42
3	46	-	27	7
5	82	-	3	trace
10	83	-	trace	trace

# Substrate Variability and Yields



			
	83 (3 h)	82 (3 h)	64 (6 h)
	86 (3 h)	83 (4.5 h)	73 (5 h)
	80 (4.5 h)	87 (3 h)	80 (3.5 h)
	80 (4.5 h)	77 (5 h)	75 (6.5 h)
	67 (5.5 h)	62 (5.5 h)	58 (6 h)
	83 (3 h)	72 (3 h)	68 (6h)

# Mechanism



# Conclusions:

- The durable and relatively stable NHC ligands have been recently incorporated into a wide variety of reactions (metathesis and numerous coupling reactions)
- In some situations these ligands have been shown to greatly increase the yields and reactivity of reactions that commonly utilized phosphine and phosphate ligands
- The Andrus group has explored the use of NHC ligands in several commonly used coupling reactions (Suzuki, Heck)
- The recent four component aryl amidation is another example of the utility of these ligands