N-Heterocyclic Carbenes

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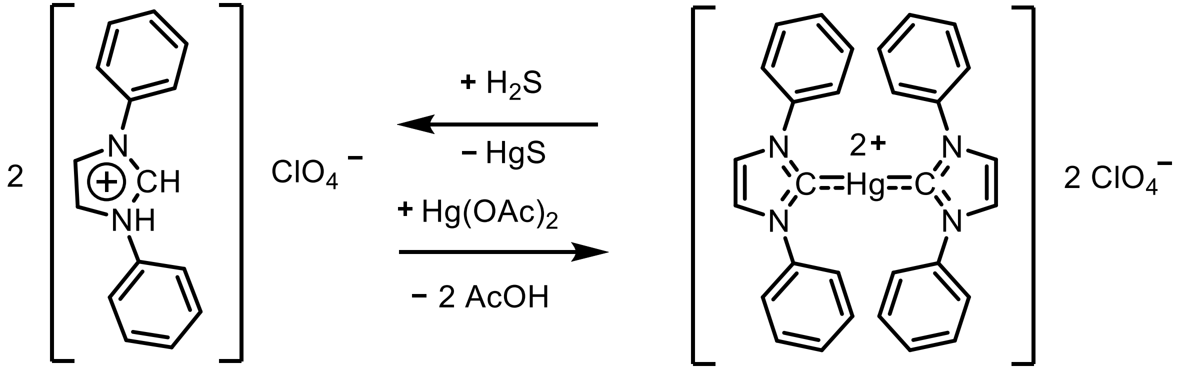
EAA 14/12/18

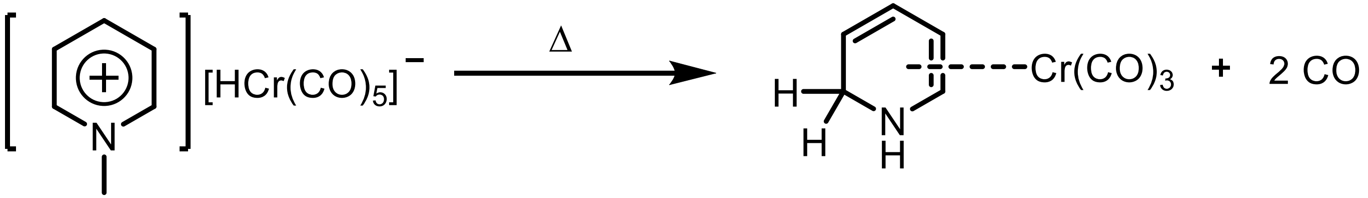
N-Heterocyclic Carbenes (NHC)

- Defined as heterocyclic species containing a carbene carbon and at least one nitrogen atom within the ring structure.[1]
- First investigated by Wanzlick in the 1960s and reported the first use as ligands for metal complexes

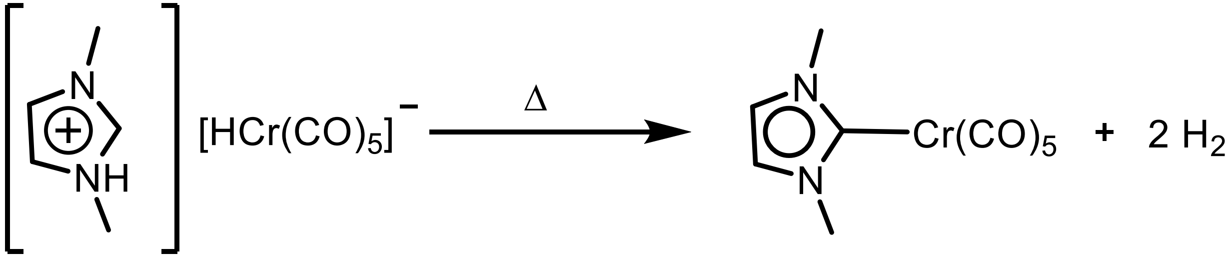


N-Heterocyclic Carbenes (NHC)

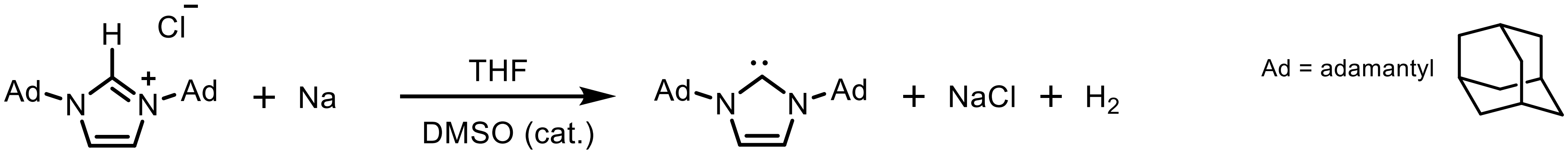
- Oefele in the same year was working on synthesising dihydro-complexes from heterocyclic salts[1]



- He observed a side reaction when using imidazolium salts[1]



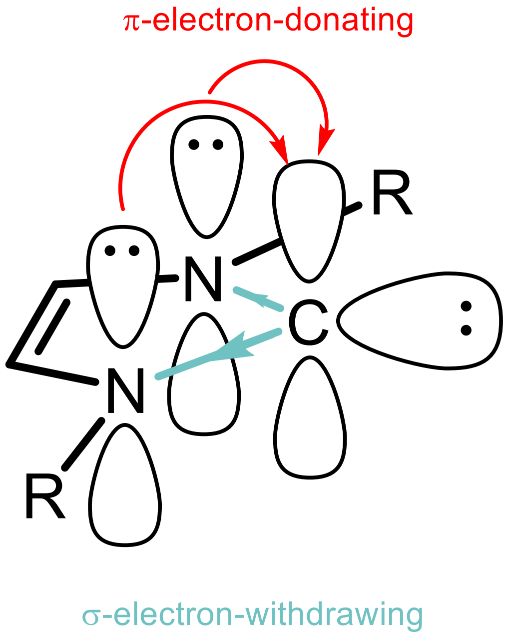
- NHC Isolated for crystalline structure in 1991 by Anthony Arduengo III[2]



1) Ofele, *J. Organomet. Chem*. **1968**, P42-43
2) Arduengo III *et al*, J. AM. CHEM. SOC., **1991**, *113* (1), PP 361–363

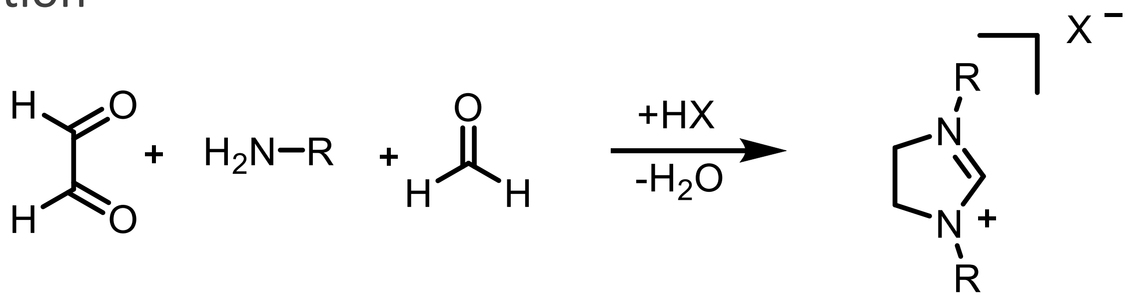
NHC Properties

- Generally feature bulky substituents adjacent to the carbene carbon
  - Help kinetically stabilise compound to sterically disfavour dimerization
- Electronic stabilisation from aromaticity
  - Substituents affect carbene electronics
- Cyclic structure favours bent singlet ground state
- Nitrogen's electronic influence stabilise the compound electronically
  - Posses some double bond character

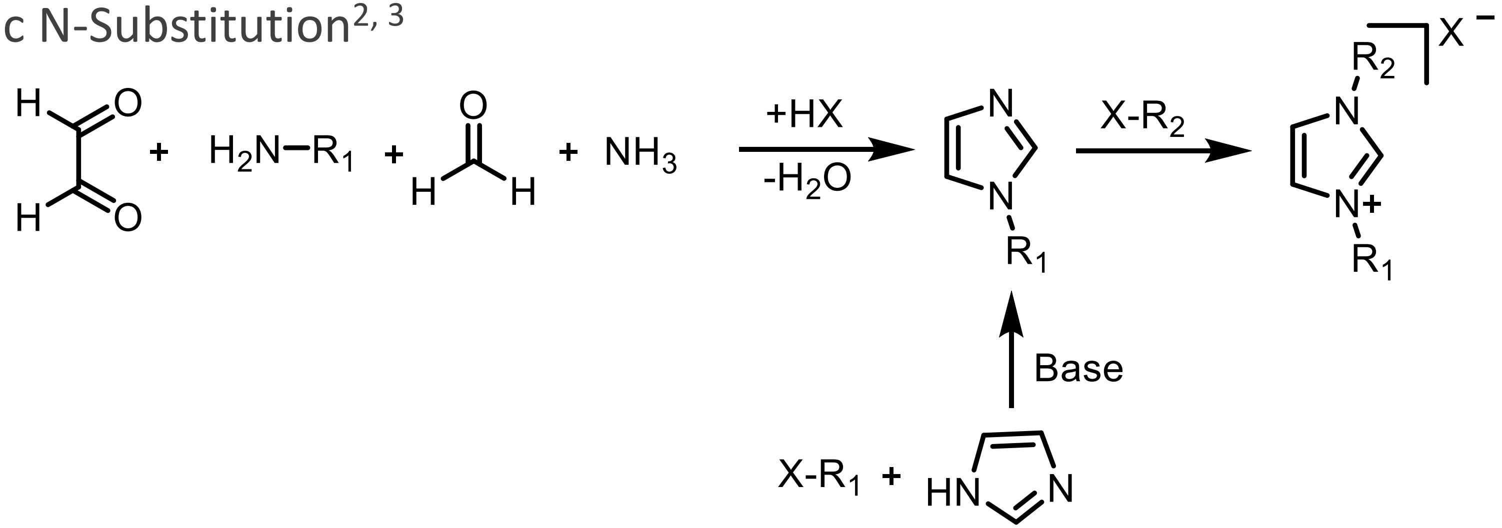


NHC Synthesis

- Symmetric N-Substitution[1]

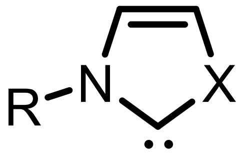


- Unsymmetric N-Substitution[2, 3]

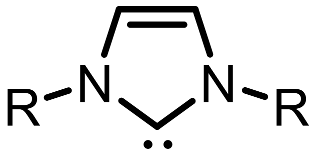


1) Wallach *et al.*. *Ber. Dtsch. Chem. Ges.*, **1925**, 15, 645.
2) E.I. Dupont de nemours & company, *US 5.077.414 a2*, **1992**.
3) Mihaltseva *et al.*, *Synth. Commun.* **1994**, 24, 1547

Heteroatom and other NHC Alternatives

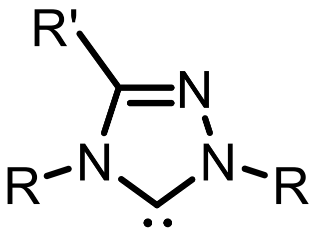


R = S, O

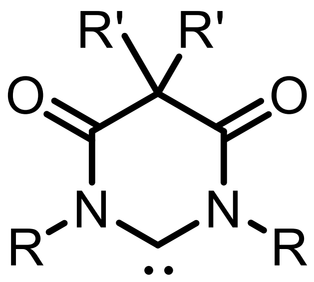


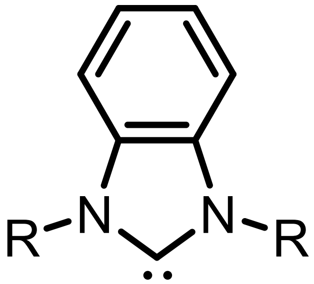
R = Mes

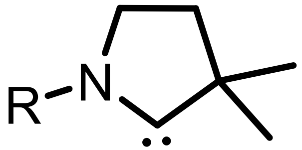
R = 2,6-(^{i}Pr)$_2$C$_6$H$_3$

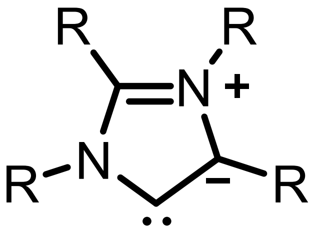


R = R' = Ph



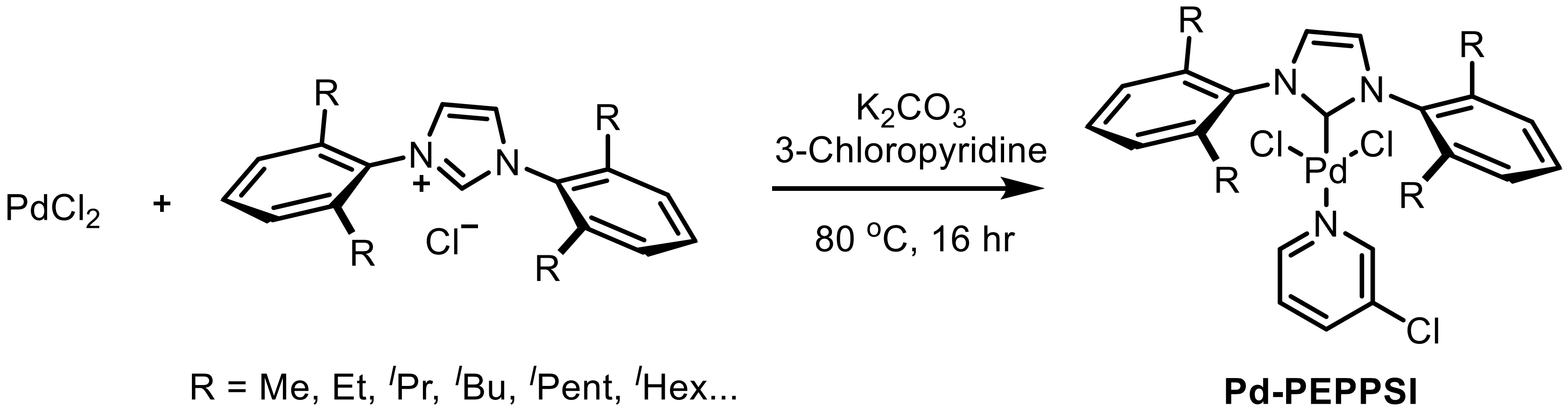






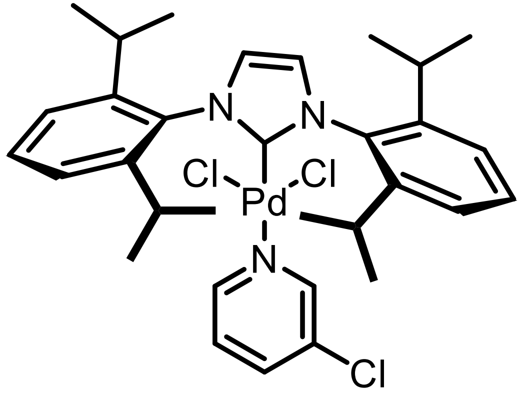
New Generation of NHCs- PEPPSI

- Pyridine Enhanced Precatalyst Preparation Stability and Initiation
- Simple synthesis
- Stable to air, heat, and moisture.

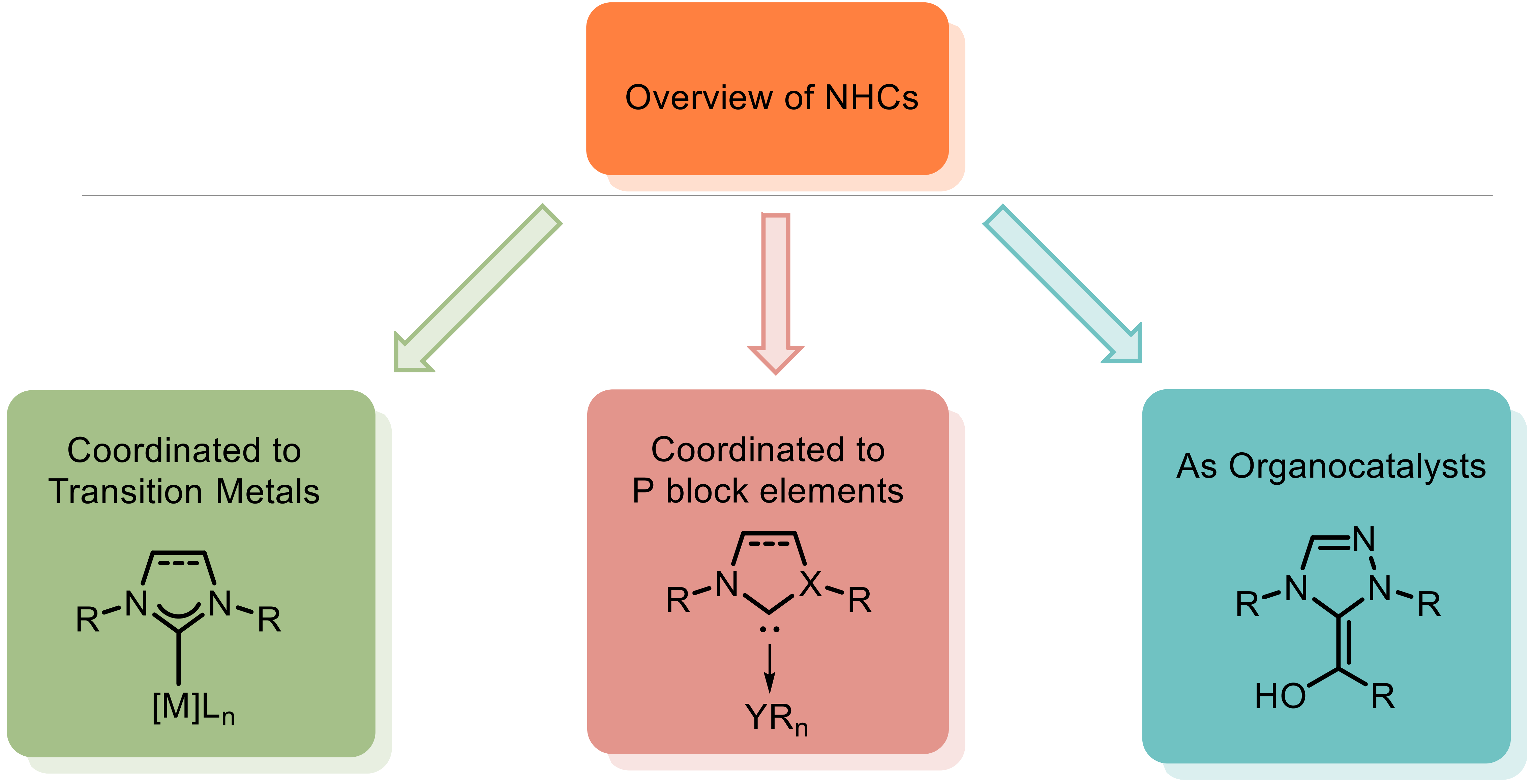


New Generation of NHCs - PEPPSI

- Aryl groups act as ‘paddles’ altering the steric topography around palladium
  - Facilitates various stages of the catalytic cycle
- Bulky alkyl substituents on the aryl group facilitate rapid reductive elimination
- NHC’s σ-donor allows for oxidative addition to readily take place
- Pd (II) species not air or moisture sensitive
- Pyridine ligand aids in preparation initiation and stability of complex
  - The chloride however has not been fully evaluated but has been theorised to assist in catalytic initiation.

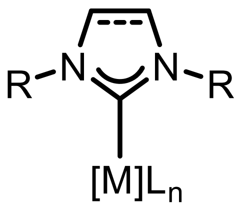


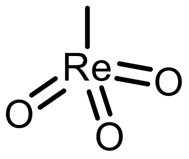
Pd-PEPPSI-IPr


Overview of NHCs
Coordinated to Transition Metals
R
N
N
R
[M]Ln
Coordinated to P block elements
R
N
X
R
YRn
As Organocatalysts
N
R
N
N
R
HO
R

Coordination of NHCs to Transition Metals

- NHCs have a σ-donor ability with a formal *sp*^{2}- hybridized lone pair available for donation into a σ-accepting orbital of the transition metal.[1]
  - π-back-bonding into the carbene *p*-orbital and π-donations account for 20% of the overall bond energy[2]
- Drawn with single bond, to show rotation around metal-carbon bond
- NHC not oxidised by MTO, while phosphine ligands are oxidised
- More electron donating than phosphine ligands[3]
  - Shorter bond lengths
  - Greater bond dissociation energies





MTO

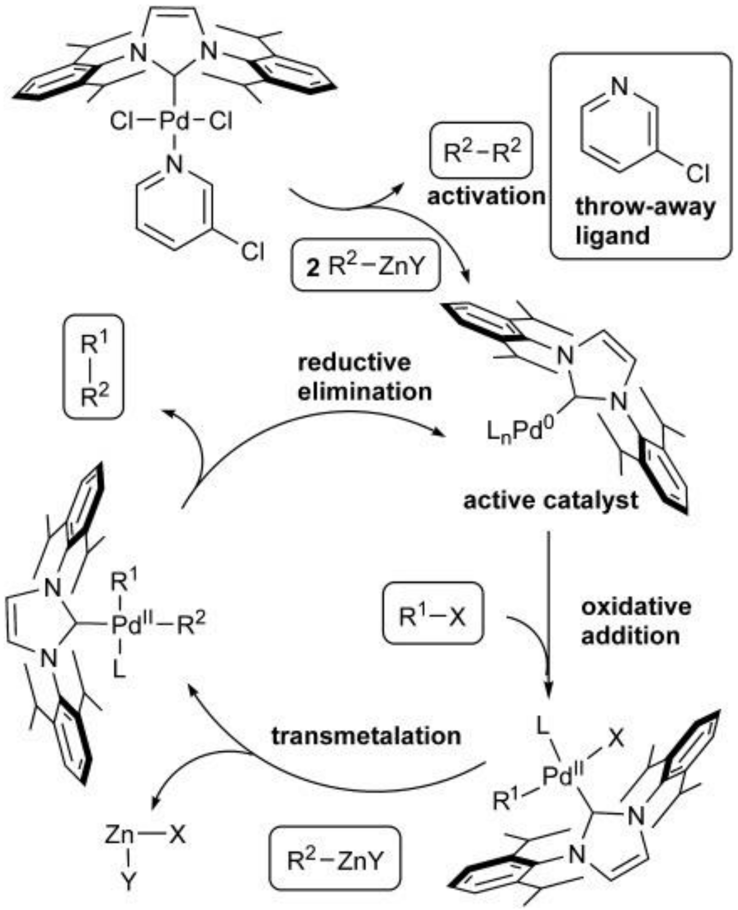
1) Cavallo *et al.*, *Coord. Chem. Rev.*, **2009**, 253, 687–703
2) Frenking *et al.*, *Organometallics*, **2004**, 23, 3640-3646
3) Hillier *et al.*, *Organometallics*, **2003**, 22, 4322–4326

Coordination of NHCs to Transition Metals

- 1. Cross-coupling
- 2. Metathesis
- 3. Hydrogenation
- 4. Different uses

Coordination of NHCs to Transition Metals – Cross-coupling

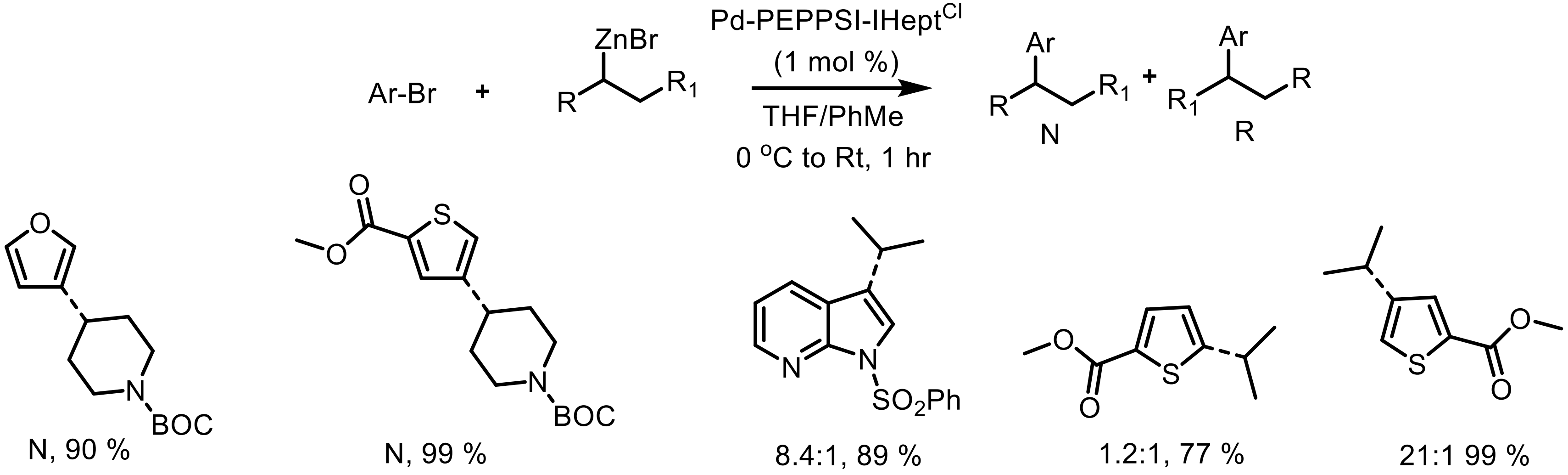
- Negishi Cross-coupling
  - Mechanism using PEPPSI
- Pyridine unlikely dissociated to activate catalyst
  - High complex stability
- Rapid reduction facilitated by organometallic reagent to Pd(0)



Organ *et al.*, *Chem. Eur. J.*, **2006**, 12, 4743 – 4748

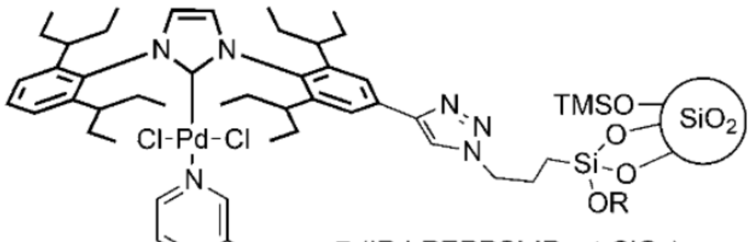
Coordination of NHCs to Transition Metals – Cross-coupling

- Negishi Cross-coupling
  - Esters, nitriles, amides, alkynes, and acetals
  - First coupling of secondary alkyl fragments to five-membered heterocycles where the site of oxidative addition is at the C2 or C3 in the heterocycle[1]

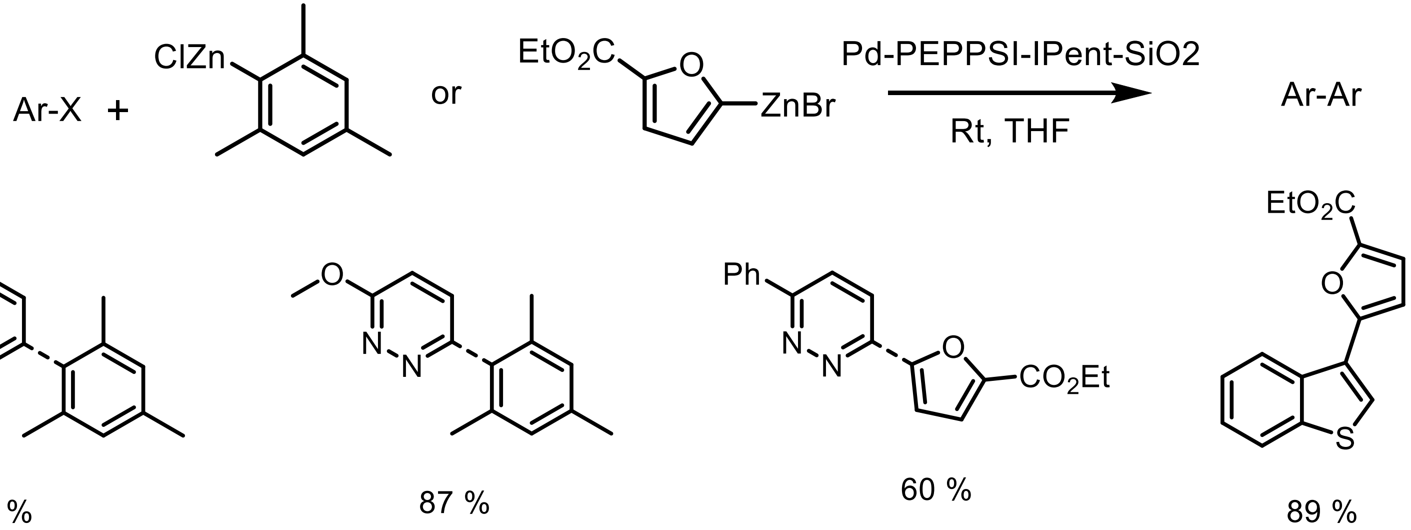


Coordination of NHCs to Transition Metals – Cross-coupling

- Negishi Cross-coupling
  - Used in Flow!

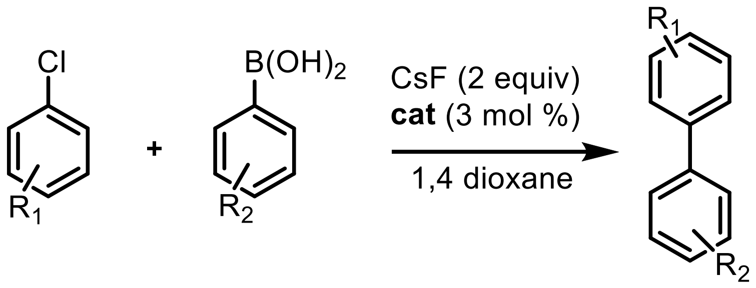


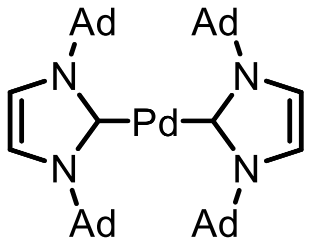
7 (IPd-PEPPSI-IPent-SiO_2)
(0.12 mmol/g loading)



Coordination of NHCs to Transition Metals – Cross-coupling

- Suzuki-Miyaura Cross-coupling
  - Previously, reactions proceeded slowly at room temperature using phosphine ligand





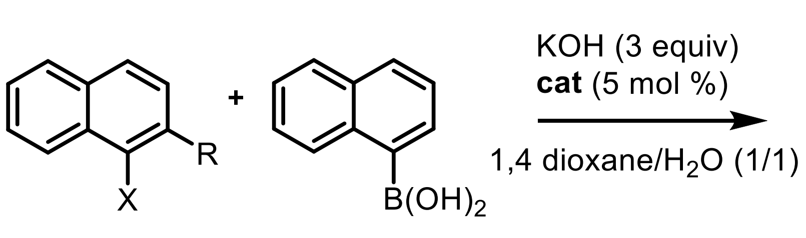
cat

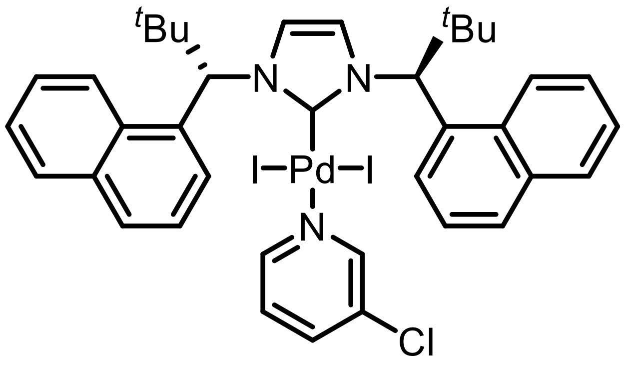
R_1	R_2	Yield (%)
4-CH_3	H	97
4-OCH_3	H	99
4-CF_3	H	95
3-CH_3	H	80
4-OCH_3	3-OCH_3	97
4-CH_3	3-OCH_3	80

1) Herrmann *et al.*, *Angew. Chem., Int. Ed.*, **2002**, 41, 1363–1365

Coordination of NHCs to Transition Metals – Cross-coupling

- Suzuki-Miyaura Cross-coupling
  - Assymetric Suzuki-Miyaura using Pyridine Enhanced Precatalyst Preparation Stabilisation and Initiation (PEPPSI)





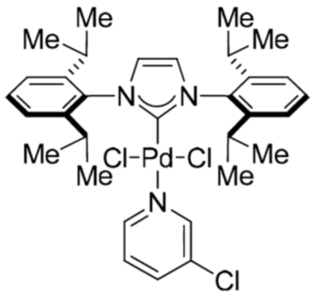
Cat.

X	R	Yield (%)	e.r.
Br	CH_3	85	90:10
Br	CH_3	42	88.5:11.5
Cl	CH_3	67	89:11
Br	OCH_3	90	81:19
Cl	OCH_3	44	81.5:18.5

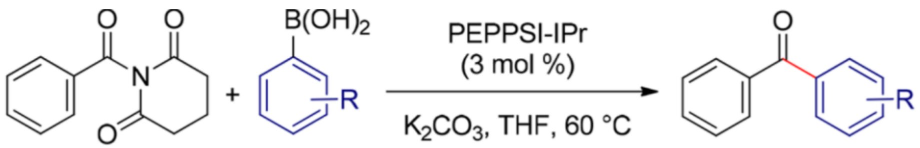
1) Kundig *et al.*, *Organometallics*, **2014**, 33, 260–266

Coordination of NHCs to Transition Metals – Cross-coupling

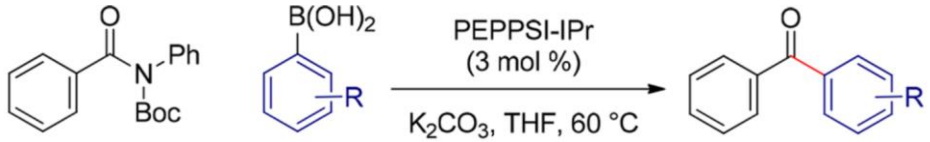
- Suzuki-Miyaura Cross-coupling
  - Recently been used to cross-couple amides



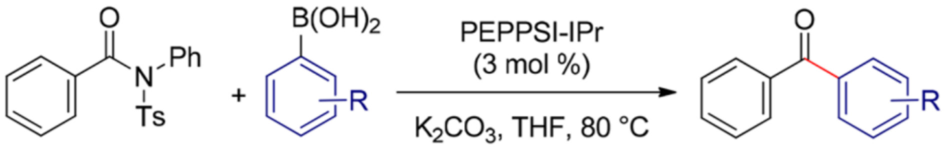
Pd-PEPPSI-IPr



R	Yield (%)
H	94
2-CH_3	97
4-CH_3	97
4-OCH_3	98
4-CO_2CH_3	90



R	Yield (%)
H	94
2-CH_3	90
4-CH_3	92
4-OCH_3	98
4-CO_2CH_3	90

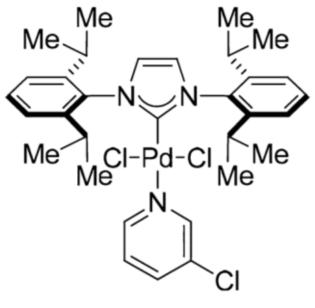


R	Yield (%)
H	92
2-CH_3	83
4-CH_3	83
4-OCH_3	85
4-CO_2CH_3	63

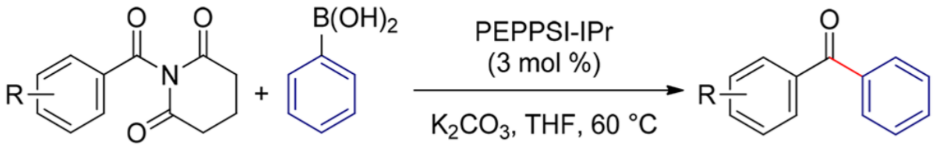
1) Szostak *et al.*, *J. Org. Chem.*, **2017**, 82, 6638–6646

Coordination of NHCs to Transition Metals – Cross-coupling

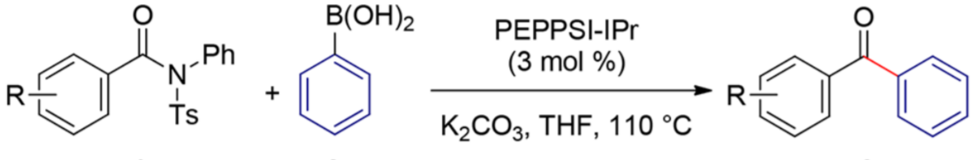
- Suzuki-Miyaura Cross-coupling
  - Recently been used to cross-couple amides



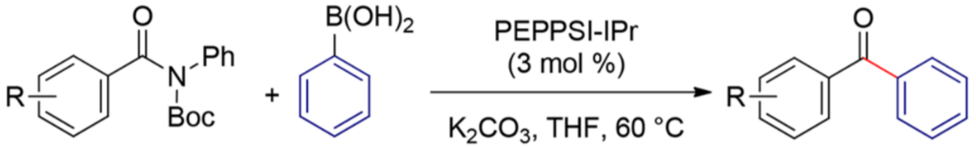
Pd-PEPPSI-IPr



R	Yield (%)
H	94
3-CH_3	98
3-OCH_3	96
4-CF_3	98
4-CN	82
4-CO_2CH_3	93
3,4-F,F	95



R	Yield (%)
4-Thiophene	76
2-CH_3	91
2-F	98

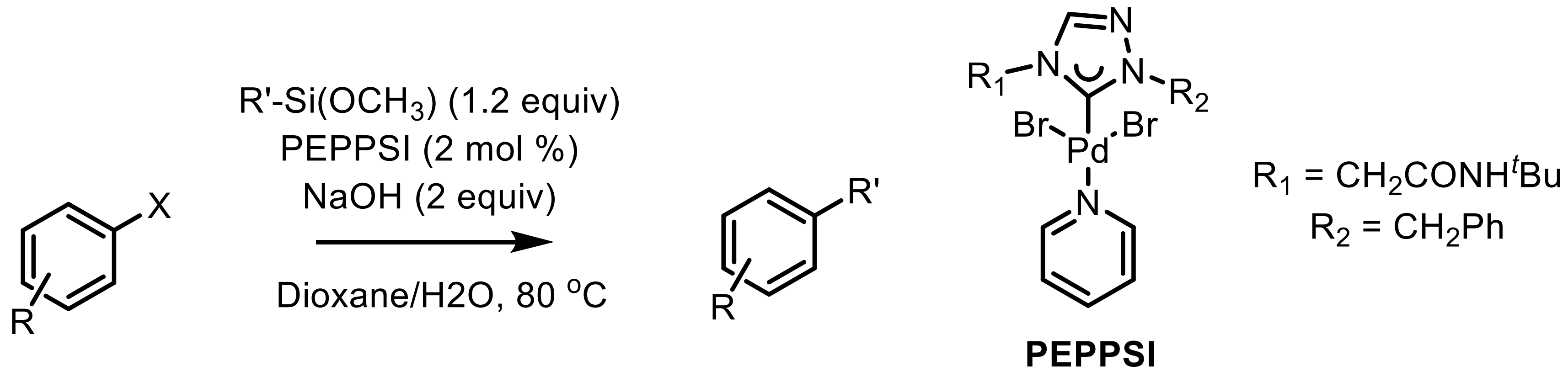


R	Yield (%)
4-Furan	92
4-CF_3	98
4-OCH_3	98

1) Szostak *et al.*, *J. Org. Chem.*, **2017**, 82, 6638–6646

Coordination of NHCs to Transition Metals – Cross-coupling

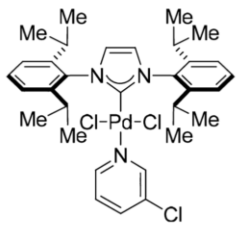
- Hiyama Cross-coupling
  - Fluoride free
  - strain release Lewis acidity

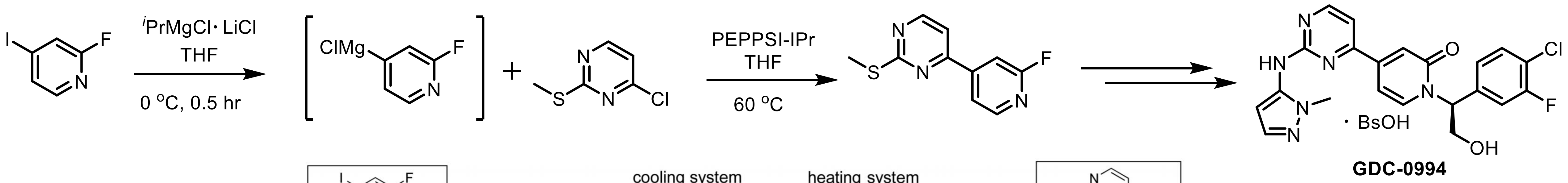


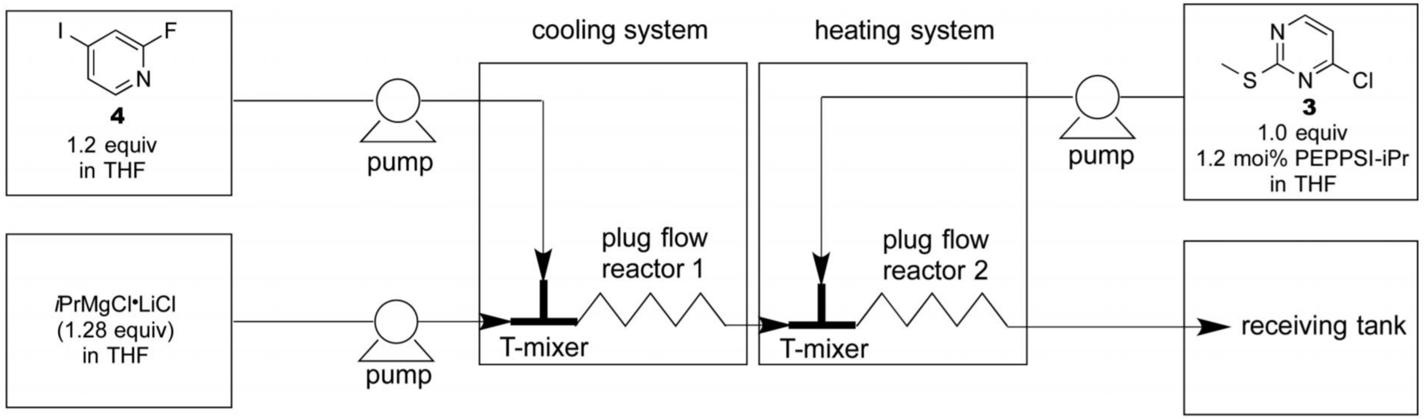
R	R’	Time (hr)	Yield (%)
4-$COCH_3$	Ph	4	96
4-OCH_3	Ph	4	99
2-OCH_3	Ph	4	93
2-NO_2	Ph	16	53
4-$COCH_3$	$CHCH_2$	16	22

Coordination of NHCs to Transition Metals – Cross-coupling

- Kumada Cross-coupling
  - Industrial application - Genentech
  - Higher yielding than phosphorous ligand

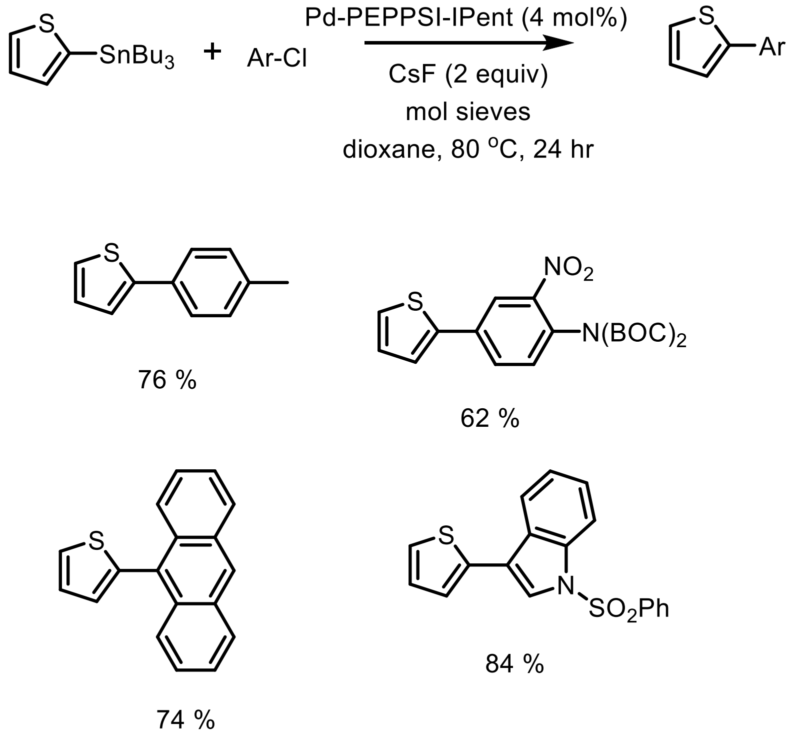


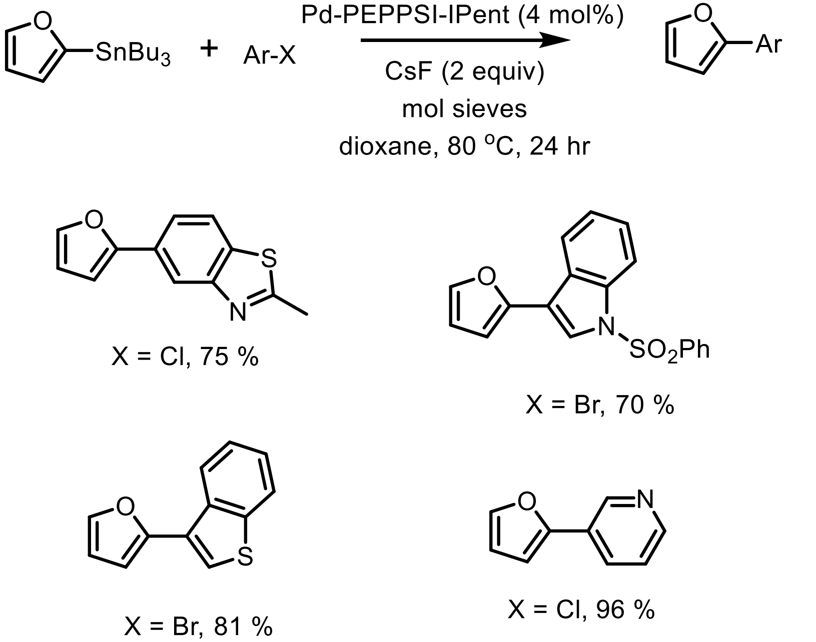


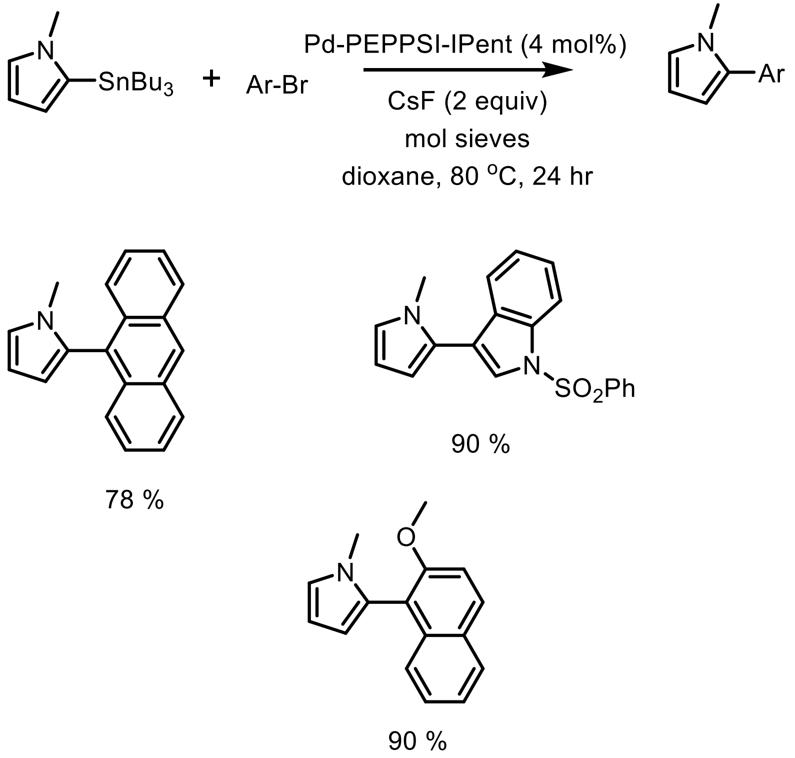


Coordination of NHCs to Transition Metals – Cross-coupling

- Stille Cross-coupling
  - Using PEPPSI catalyst allows temperature reduction from 100 °C or more





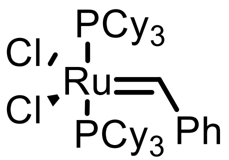


Coordination of NHCs to Transition Metals

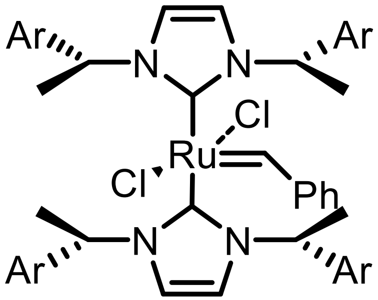
- 1. Cross-coupling
- 2. Metathesis
- 3. Hydrogenation
- 4. Different uses

Coordination of NHCs to Transition Metals – Metathesis

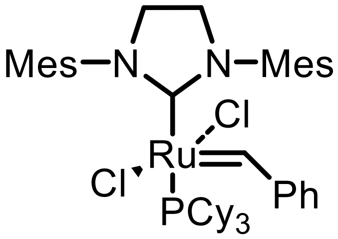
- Decreased lability of carbenes, compared to the phosphine ligands, is believed to be one of the reasons for the improved thermal and oxidative stability of the corresponding organometallic complexes
  - NHC-Ru bond is calculated to be 20-40 kcal/mol stronger than R_3P-Ru
- Grubbs I subject to oxidative decomposition
- Hermann proposed to use NHC to increase tolerance toward functional groups
  - Decreased activity
- Grubbs then proposed a labile phosphine ligand and a nonlabile NHC
  - Why?



Grubbs I



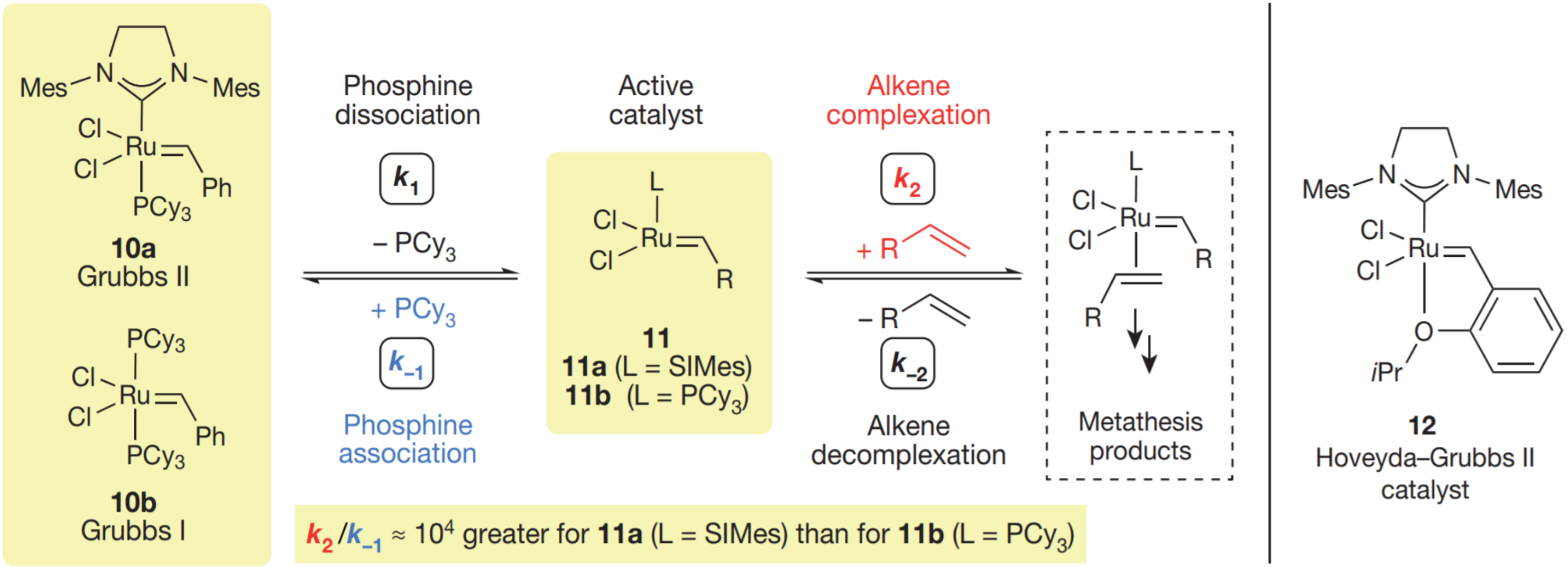
Hermann



Grubbs-Nolan

Grela et al., *Chemical reviews*, **2009**, VOL. 109, NO. 8

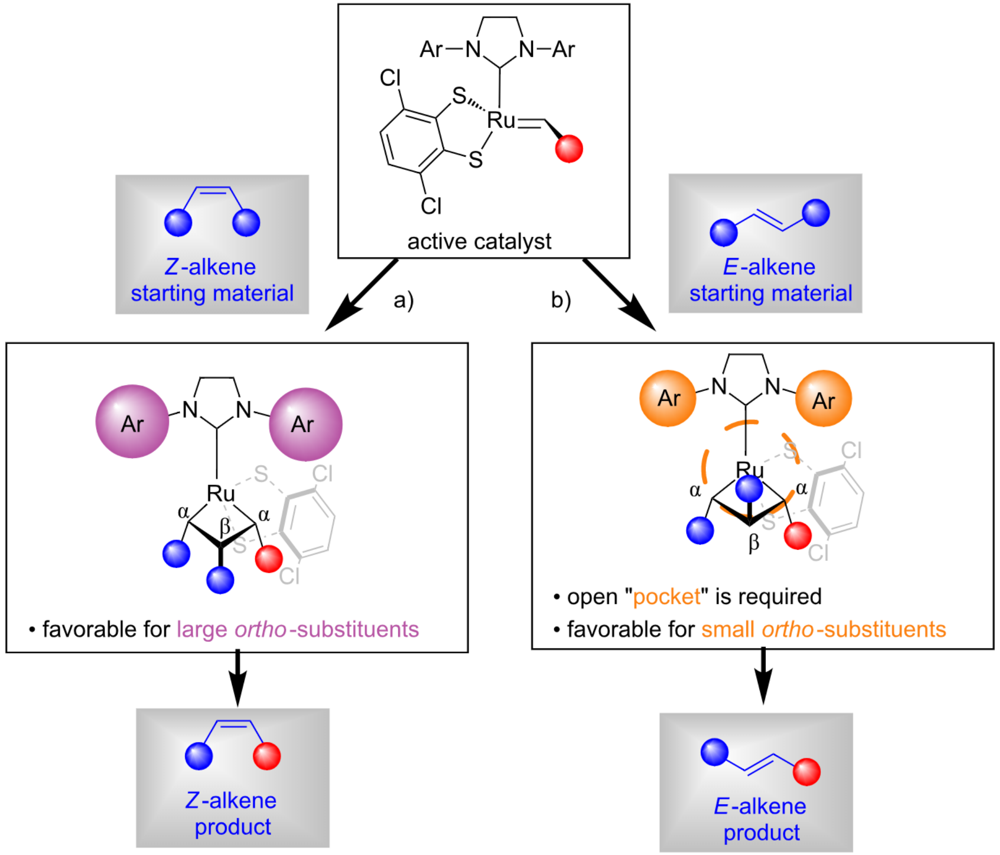
Coordination of NHCs to Transition Metals – Metathesis



- Hoveyda developed phosphine free
  - Robust
  - Improved activity towards electron deficient alkenes
  - Stabile to air and moisture

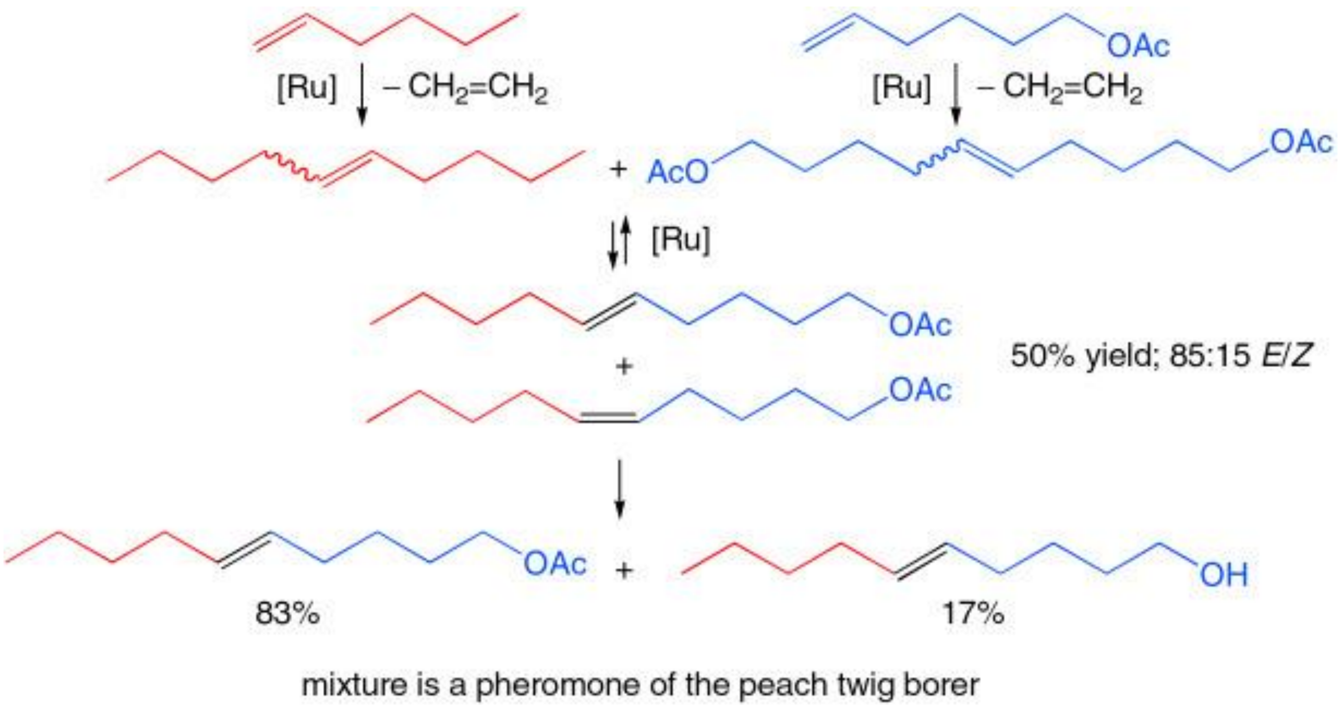
Coordination of NHCs to Transition Metals – Cross Metathesis

- Catalyst design influences E or Z alkenes
- Thermodynamic and kinetic control
  - Substrate and catalyst dependant



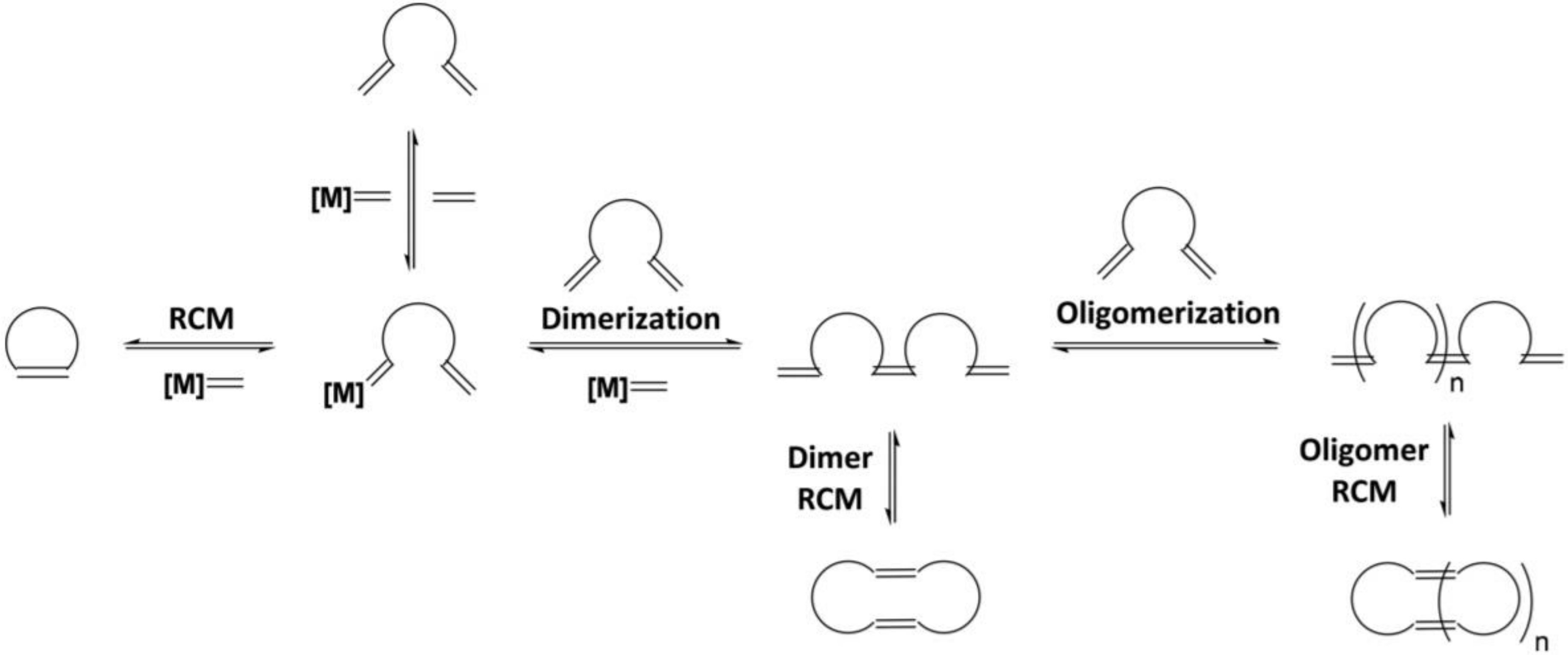
Coordination of NHCs to Transition Metals – Cross Metathesis

- Is used from small scale to large scale
  - Solvent free!



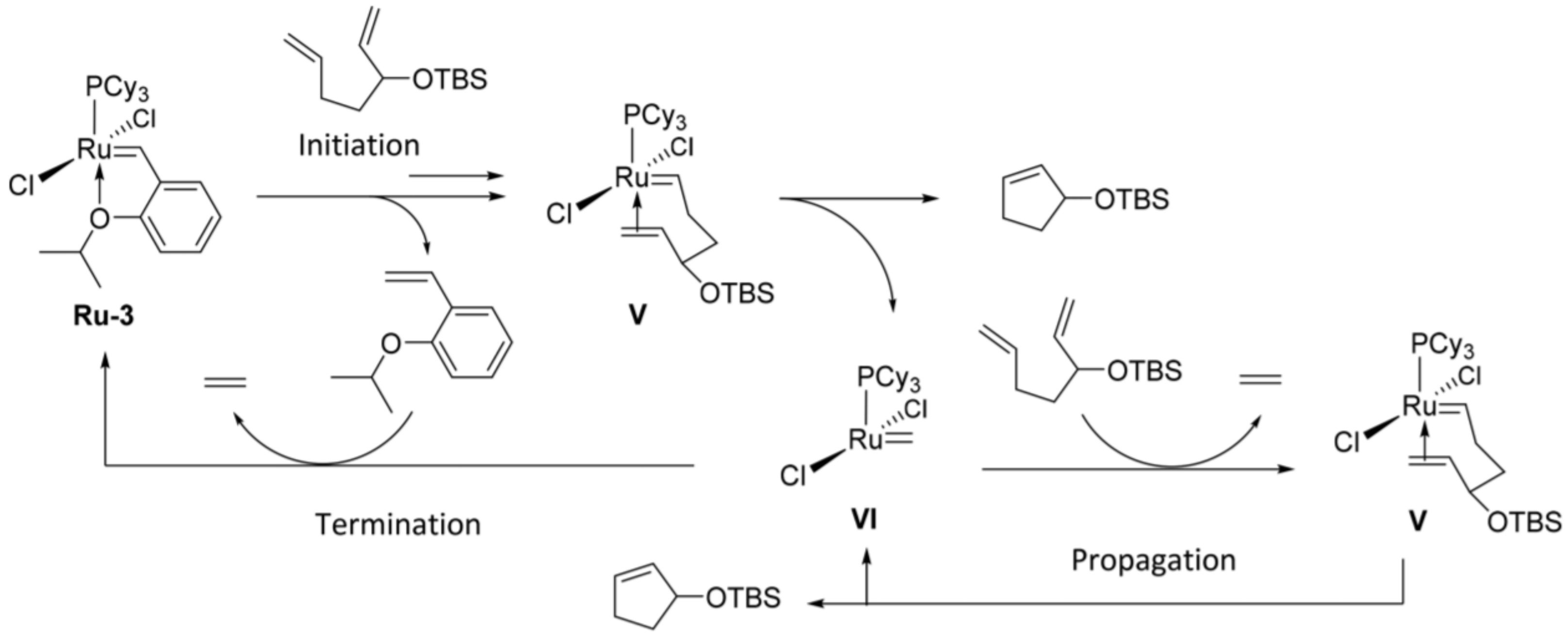
Coordination of NHCs to Transition Metals – Ring-closing Metathesis

- Possible pathways



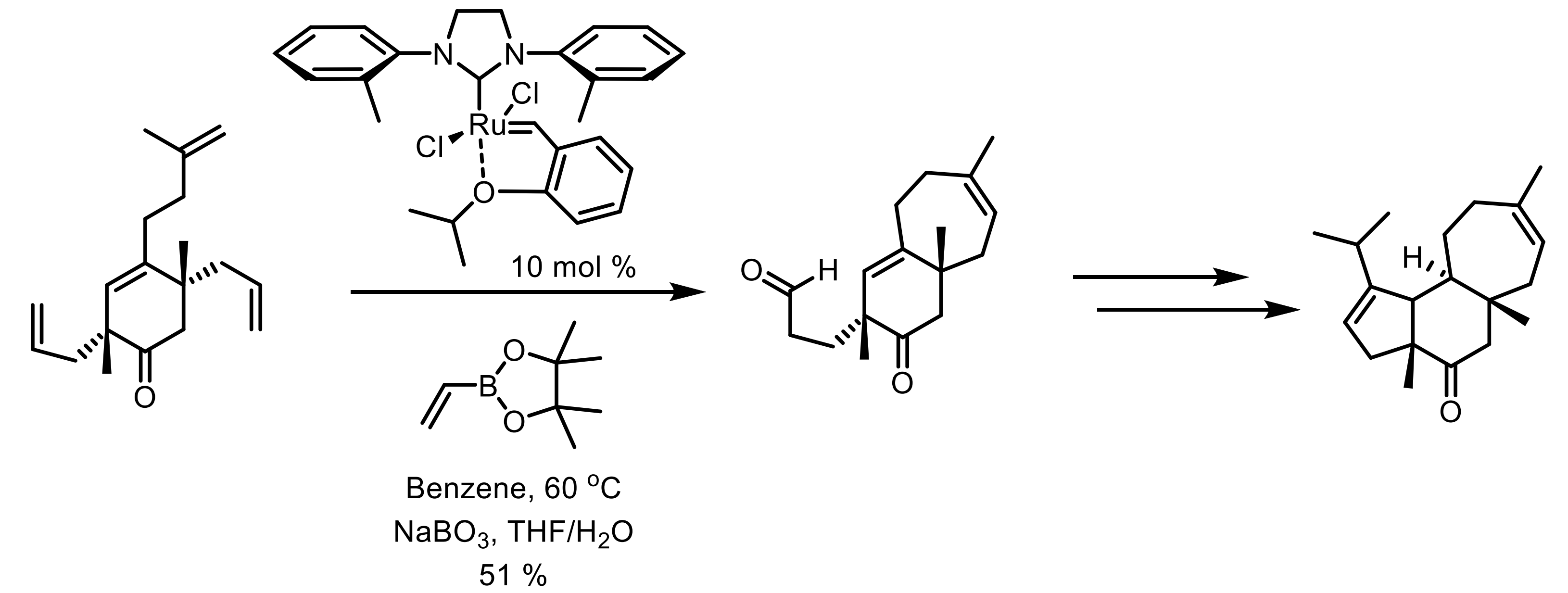
Coordination of NHCs to Transition Metals – Ring-closing Metathesis

- Making of small rings
  - increased yield from 84 % to greater than 90 % on industrial scale when switching to Grubbs II



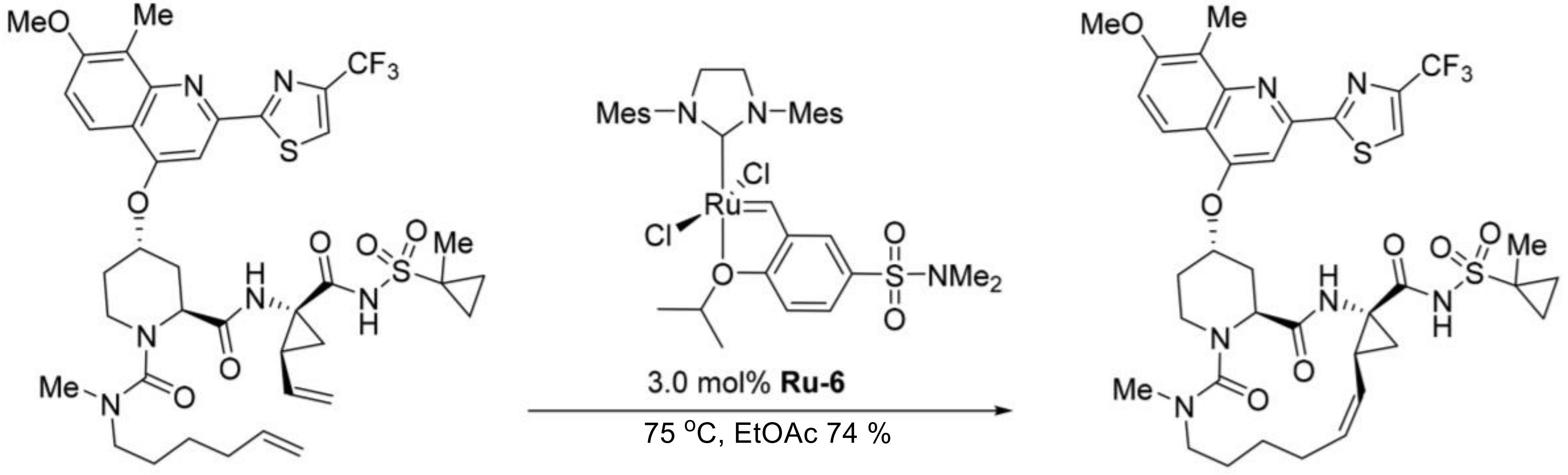
Coordination of NHCs to Transition Metals – Ring-closing Metathesis

- Making medium rings
- Used widely, especially in total synthesis
  - Cyanthiwigin F



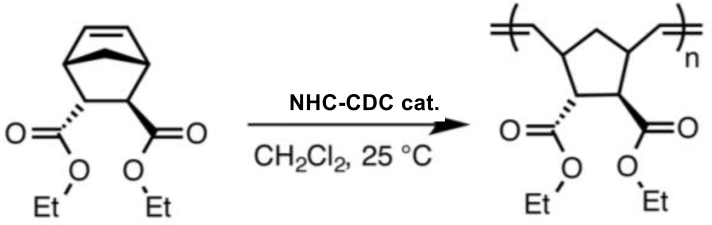
Coordination of NHCs to Transition Metals – Ring-closing Metathesis

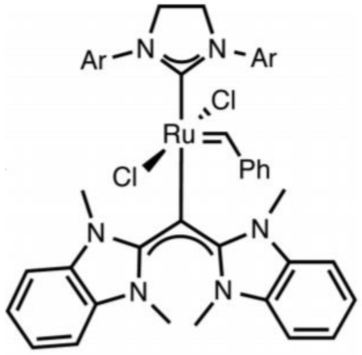
- Making large rings
- Some industrial APIs are made using RCM
- Charcoal treatment to remove ruthenium
  - Synthesis of IDX320 on 1.6 kg scale



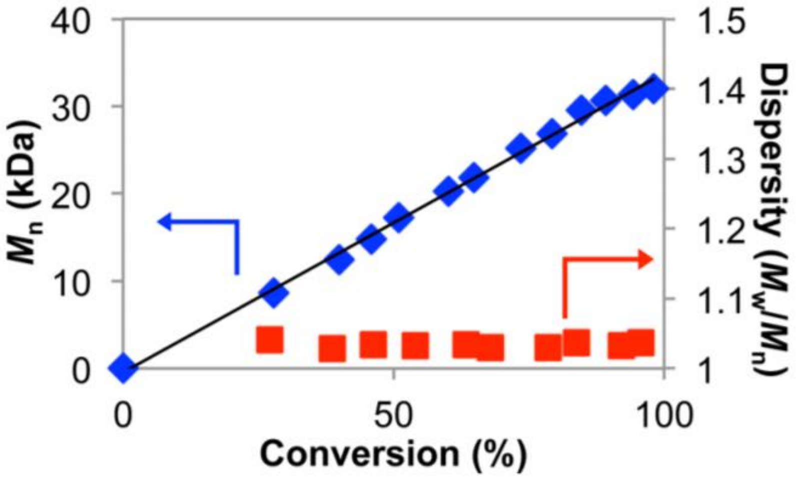
Coordination of NHCs to Transition Metals – Ring-opening Methathesis Polymerisation

- Driving force is release of ring strain
- Recently Grubbs has been investigating carbodicarbene (CDC) ligands due to strong donor ability
  - Bent allene
  - Double ylide
- Shows CDC ligand dissociates before NHC
- Rate of product formed to norbornenyl conversion





NHC-CDC cat.
Ar = Diisopropylphenyl

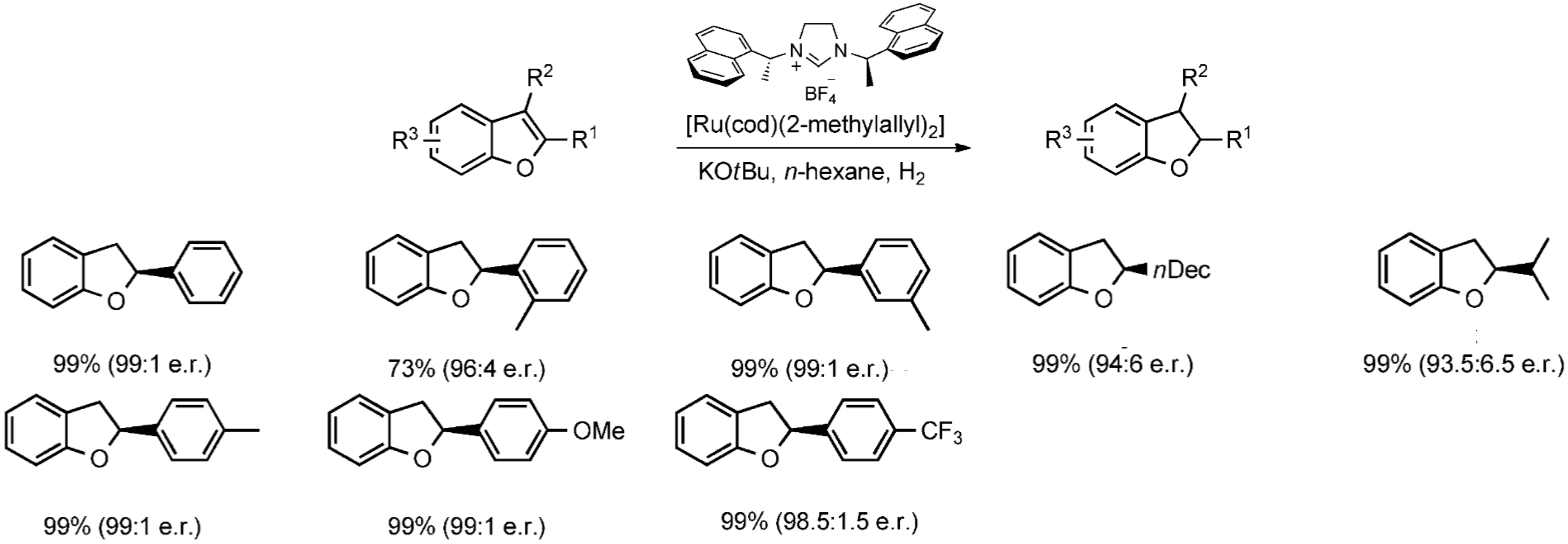


Coordination of NHCs to Transition Metals

- 1. Cross-coupling
- 2. Metathesis
- 3. Hydrogenation
- 4. Different uses

Coordination of NHCs to Transition Metals – Hydrogenation

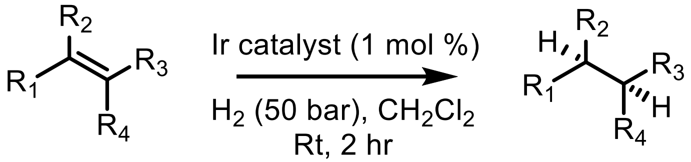
- Recent work to asymmetrically hydrogenate challenging compounds[1]
  - Benzofuran – previously Baiker using Pd/Al_2O_3/CD (29% conv, 50 % ee)[2]
  - This work does require 10 bar H_2



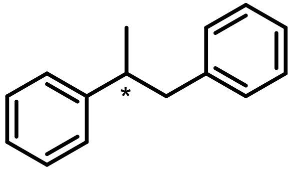
1) Glorius *Et al., Angew. Chem. Int. Ed.*, **2012**, 51, 1710 –1713
2) Baiker *et al., J. Catal.,* **2003**, 219, 52

Coordination of NHCs to Transition Metals – Hydrogenation

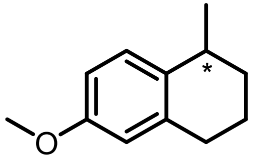
- Recent work to asymmetrically hydrogenate challenging compounds[1]
  - Benzofuran – previously Baiker using Pd/Al_2O_3/CD (29% conv, 50 % ee)[2]
  - Requires high pressure



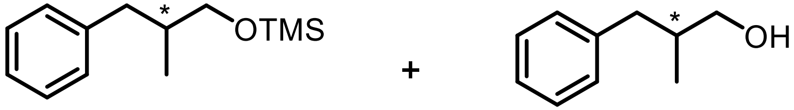
R = 2,6-diisopropylbenzene



(S) 99 %, 93 % ee

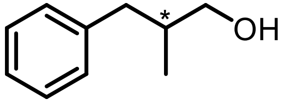


(S) 99 %, 95 % ee

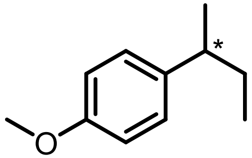


(S) 84 %, 83 % ee

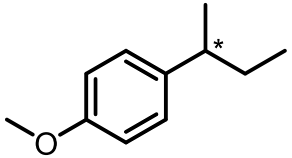
16 %



(S) 86 %, 93 % ee



(S) 99 %, 92 % ee

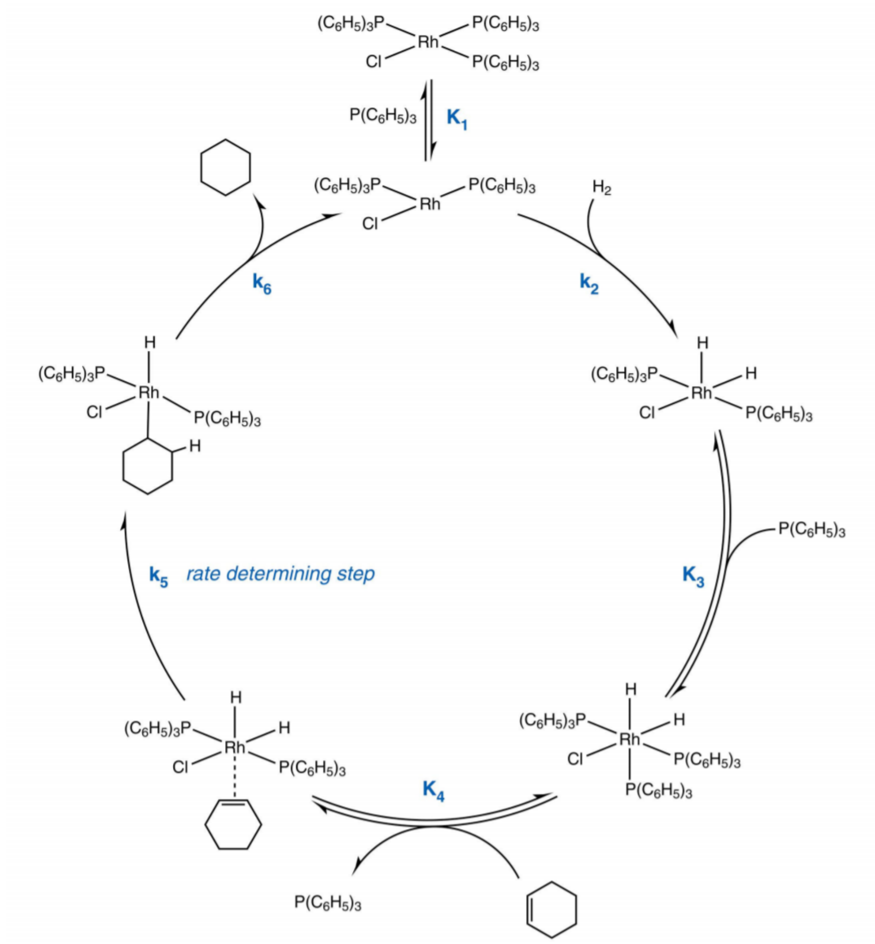


(S) 99 %, 97 % ee

1) Pfaltz *et al.*, Angew. Chem. Int. Ed., **2013**, 52, 7422 –7425

Coordination of NHCs to Transition Metals – Hydrogenation

- Proceeds similar to Wilkinson's complex

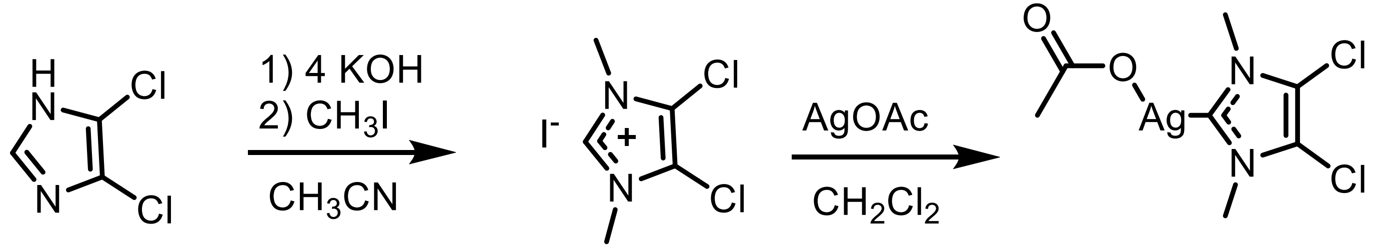


Coordination of NHCs to Transition Metals

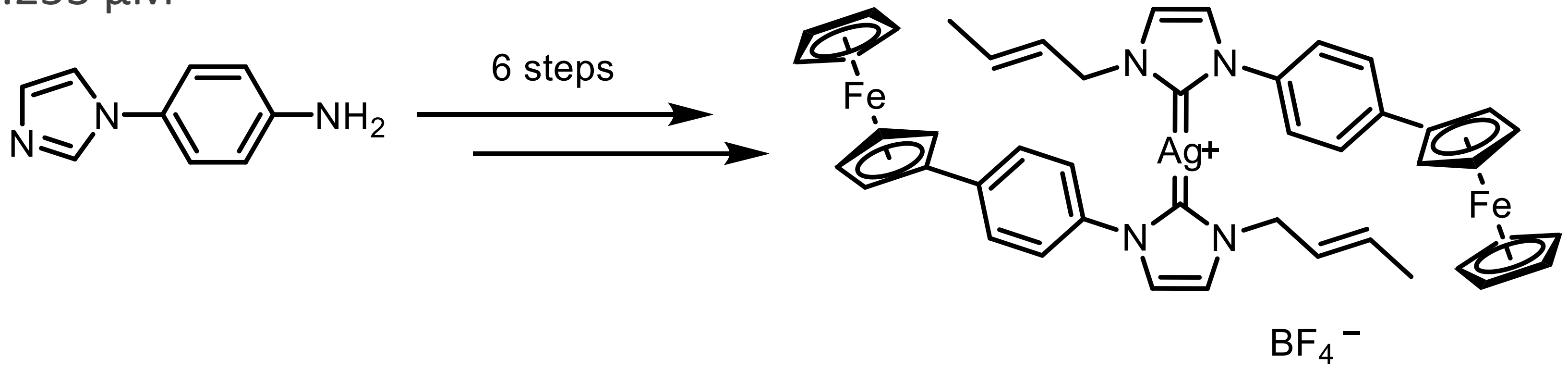
- 1. Cross-coupling
- 2. Metathesis
- 3. Hydrogenation
- 4. Different uses

Coordination of NHCs to Transition Metals - Metallopharmaceuticals

- Bactericidal
- MIC in $\mu g/ml$ for: *B. stabilis, P. aeruginosa, B. cepacian, B. pyrocina…*



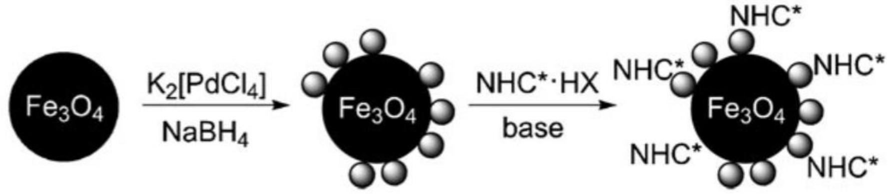
- Jurkat (leukemia) cells IC_{50} 0.253 µM
  - Cisplatin IC_{50} 0.783 µM
  - Attacks mitochondria
  - Selective



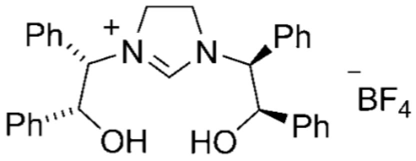
1) Hindi *et al.*, *Chemical reviews*, 2009, 109, 3859-3884

Coordination of NHCs to Transition Metals – Coordination to Surfaces

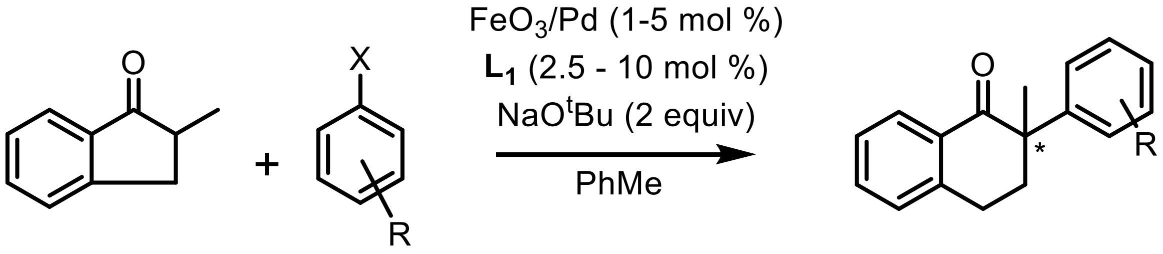
- Can bind to different metal nanoparticles
- Industrial applications in homogenous catalytic reactions[1]
  - Previous problems generating chiral heterogenous catalysts

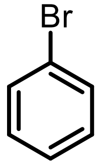


- Glorius group showed first asymmetric heterogeneous catalysis reaction using NHCs as chiral modifiers[2]

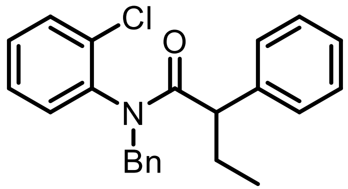


L1: 74% yield
53% *ee*

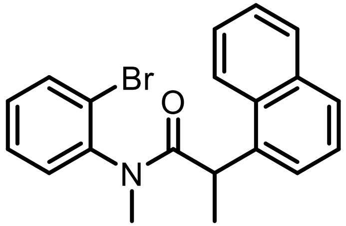




Yield 61 %
ee 35 %



Yield 91 %
ee 81 %



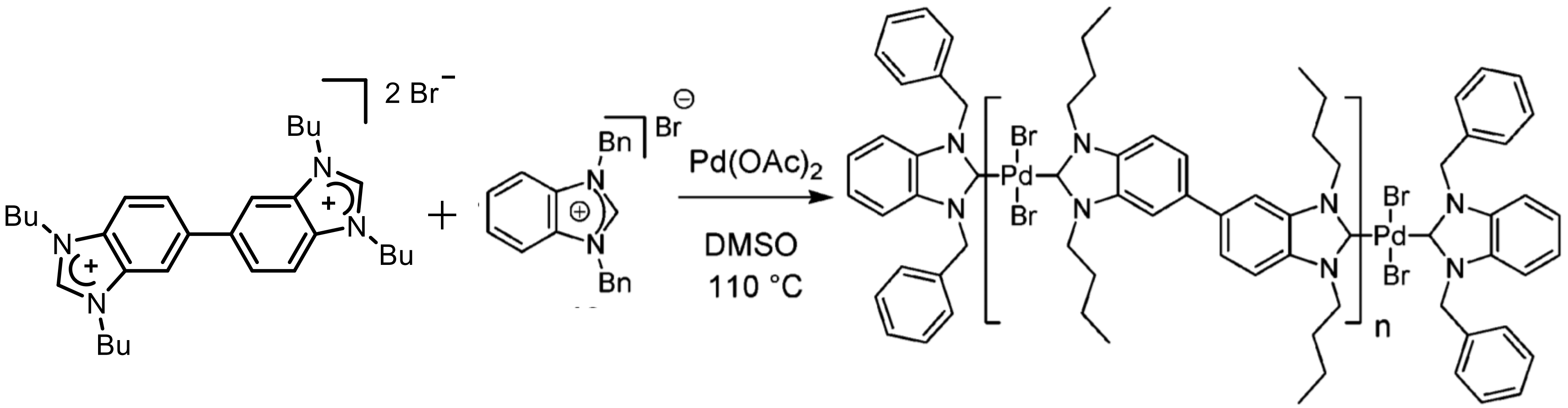
Yield 68 %
ee 85 %

- Magnet recovery!

1) Glorius *et al.*, *Angew.Chem.*, **2006**, 118, 4850 – 4881
2) Glorius *et al., Angew. Chem. Int. Ed.*, **2010** , 49, 7786 –7789

Coordination of NHCs to Transition Metals – Coordination Polymers

- Metal polymers are used in electronic devices and various nonlinear optics
  - Typically requires anhydrous conditions, inert atmospheres, and (sometimes) long syntheses
  - Bielawski group used NHCs built in 3 steps from commercial starting materials[1]



  - $n_{theoretical} = 10$, $n_{observed} = 8.9$

1) Bielawski *et al.*. *J. Am. Chem. Soc.*, **2005**, *127* (36), 12496–12497

Summary

- NHC ligands bind tighter to transition metals than phosphine ligands
- New developments for key reactions
  - Stille
  - Kumada
  - Hiyama
  - Suzuki
  - Negishi
- NHC and PEPPSI ligands are a powerful tool in total synthesis and are starting to be applied to industry